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Clinical Trial
In vivo - Ex vivo

dynamic quadripolar radiofrequency

UNIVERSITA' DEGLI STUDI DI PAVIA

SCIENTIFIC & TECHNICAL REPORT CONCERNING THE CLINICAL-PHYSICAL STUDY OF EFFECTIVENESS AND SAFETY OF "RADIO 4" EQUIPMENT

Purchaser: NOVAVISION Group

Date of issue: April 21st, 2011

UNIVERSITA' DEGLI STUDI DI PAVIA

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1 Introduction

The Centre has conducted a research study with the purpose of evaluating both the effectiveness and safety of RADIO4 equipment in relation to the operator's and customer's safety as requested by "Novavision Group s.r.l." Company. The Centre has been entrusted with this task by "Novavision Group s.r.l." Company, with their registered office in Milan, Via Aurelio Saffi 29, P. I. IT02164550960, following the signature of the regular agreement stipulated on 9.9.2010. This piece of equipment is a radiofrequency generator, classified as Class IIa equipment, to be used as indicated by the manufacturing company for the non-invasive treatment "of blemishes caused by wrinkles, of skin tension and cellulite reduction".

RADIO 4 relies on another worldwide patented technology from the Novavision Group Company, the so-called RSS ™ (Radiofrequency Safety System), that makes use of a group of 4 electrodes that are set up automatically and in a dynamic way by a control software in order to let the radiofrequency current circulate between them.

The variable configuration of the electrodes allows creating the creation of electric fields which, once set in the ideal combination, direct the energy deeply in the tissues by electrically overheating them.

In order to allow the above-mentioned evaluations to be carried out, Novavision company delivered a model of RADIO 4 to the Centre, the so-called RADIO4M, that is able to emit the maximum power (100%) of 55W; the Company also supplied a copy of the User Manual and an adequate quantity of aqueous gel to be regularly interposed between the skin and the radiofrequency generator handpieces during the treatments.

Clinical trials were carried out in two concurrent phases: a clinical-experimental phase and an evaluation phase of physical parameters for safety.

The clinical-experimental phase has been carried out under the guidance of Dr Antonia Icaro Cornaglia, tenured Researcher of Histology at the University of Pavia and permanent member of the Centre and under the guidance of Dr Silvia Scevola, Plastic Surgery Specialist and co-opted member of the Centre.

The evaluation phase of physical parameters for safety has been carried out under the guidance of Dr Antonio Coppola, Physicist Specialist in Environmental Health Physics, Qualified Expert (EQ III degree) in Radiation Protection (no. 418 on National Register) and co-opted member of the Centre.

CLINICAL RESEARCH & EXPERIMENTAL STUDIES

2 Experimental clinical study preliminary remarks

The study has been conducted in two stages:

- ***ex vivo* phase:** on body parts removed during surgery
- ***in vivo* phase:** on healthy volunteers.

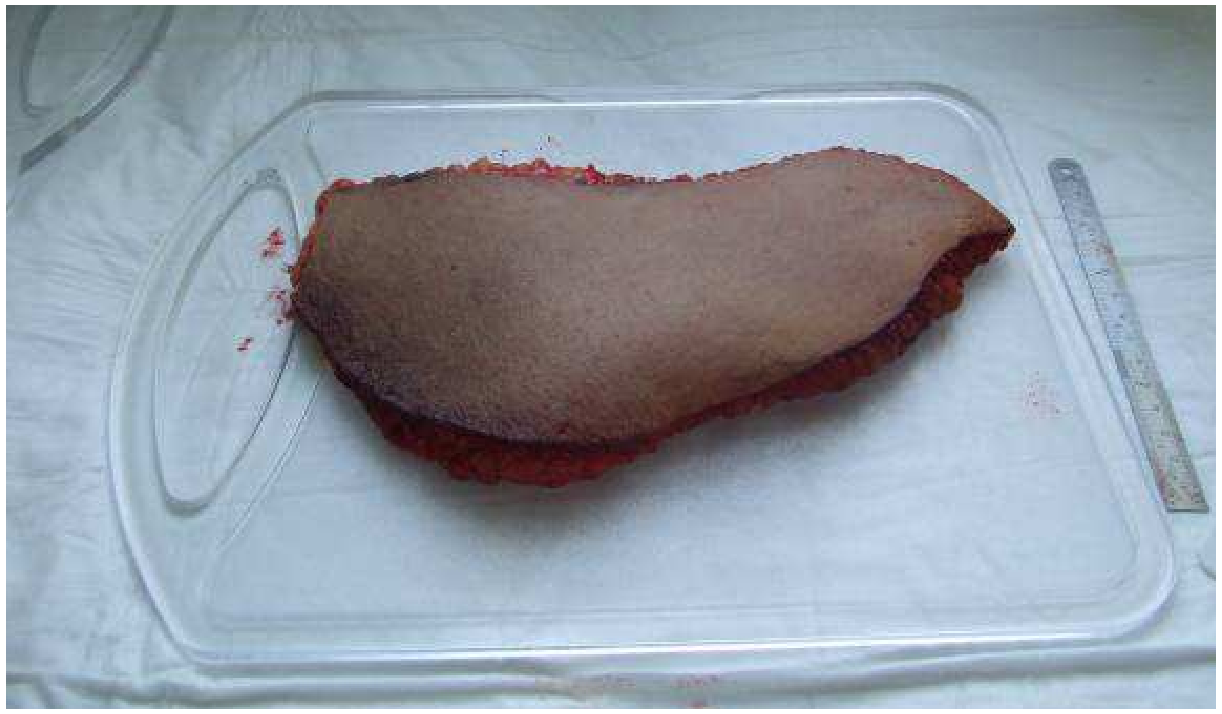
3 *Ex vivo* study

The purpose of the first leg of the study was to identify the safety limits of the equipment. Therefore its effects were tested by delivering power at different growing levels until the maximum bearable power and the maximum time of application in terms of safety of such amount of energy were tested. Being a test carried out on *ex vivo* samples, thus without thermoregulation, this procedure is to be considered as performed under the worst possible conditions.

3.1 First trial

3.1.1 Procedure

During dermolipectomy surgery four parts with a length of 11x13 cm and a maximum thickness of 3 cm were obtained from the proximal areas of the inner thighs of a 51-year-old female patient. (Picture 1).



Picture 1: body part removed from the inner thigh.

A full-thickness control sample (epidermis, dermis, subcutaneous adipose tissue) was taken by means of a scalpel for histological examination.

Then the 4 surgical parts – respectively named part no. 1, no. 2, no. 3, no. 4 – underwent Radio 4 treatment.

We specify once and for all that all treatments, both ex-vivo and in-vivo, are carried out by interposing a layer of aqueous gel, provided by the Company, between the skin and the various handpieces.

The medical software supplied by the Company was used. The body parts were treated by using the medium handpiece and following the same criteria as listed below for the whole length of the procedure (Picture 2).

3.1.2 Used Parameters

- General Program
- Mode RFS 3:1
- Time RFS 5 seconds
- Duty cycle 100% (timing on 1.000msec, timing off 0 msec)
- Maximum length of treatment: 4 minutes.

The only parameter that changes in the various parts is the power, as specified below:

- part no.1 power 25%
- part no.2 power 50%
- part no.3 power 75%
- part no.4 power 100%
-

Picture 2: ex vivo treatment by means of medium handpiece

During and immediately after treatment, visual controls concerning the macroscopic modifications of tissues were carried out. Temperature changes were recorded by means of a digital thermographic camera in the treated body parts as the power emitted by Radio 4 changed.
Biopsy samples were taken from each part near the points of maximum skin temperature recorded by the thermographic camera; samples were sent for histological examination.

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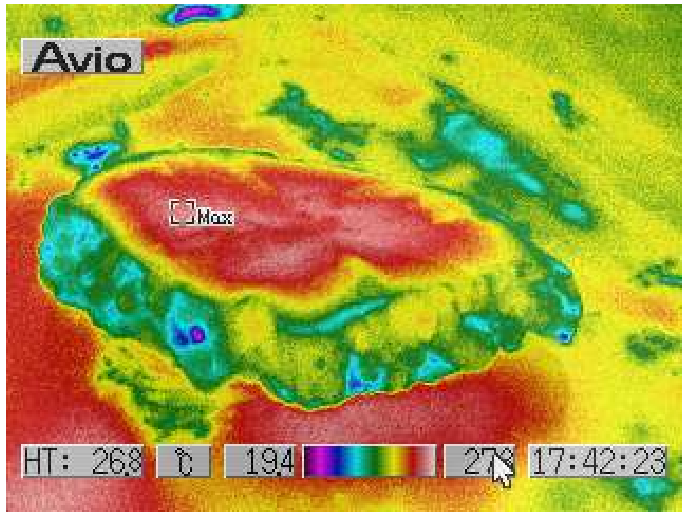
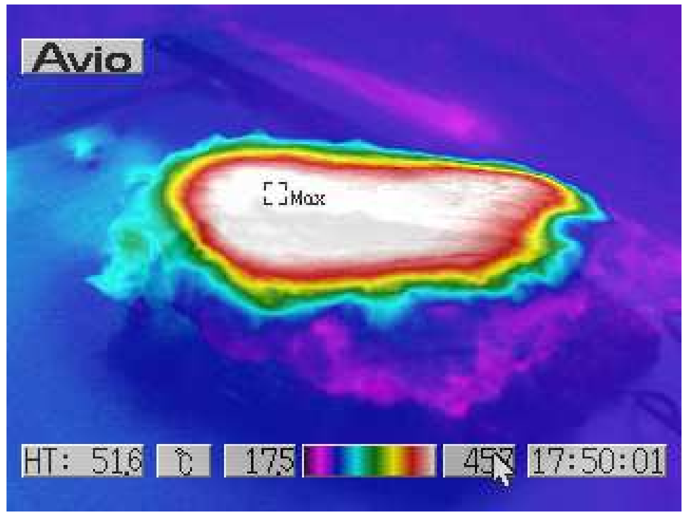
3.1.3 Results

Variations in temperature

The recorded temperatures are reported in detail in the enclosed table. It is worth pointing out that there is no correspondence between the temperature indicated by the thermographic camera and the temperature measured by the handpiece, because the built-in sensor of the handpiece computes the weighted average of its own movement; therefore the temperature detected by the thermographic camera always slightly exceeds the actual temperature recorded by the sensor of the handpiece by a few degrees.
Moreover, an increase in temperature can be seen in the surface layers. (Picture 3a, 3b).



Picture 3a: thermal image of the body part shown in picture 1 before the treatment



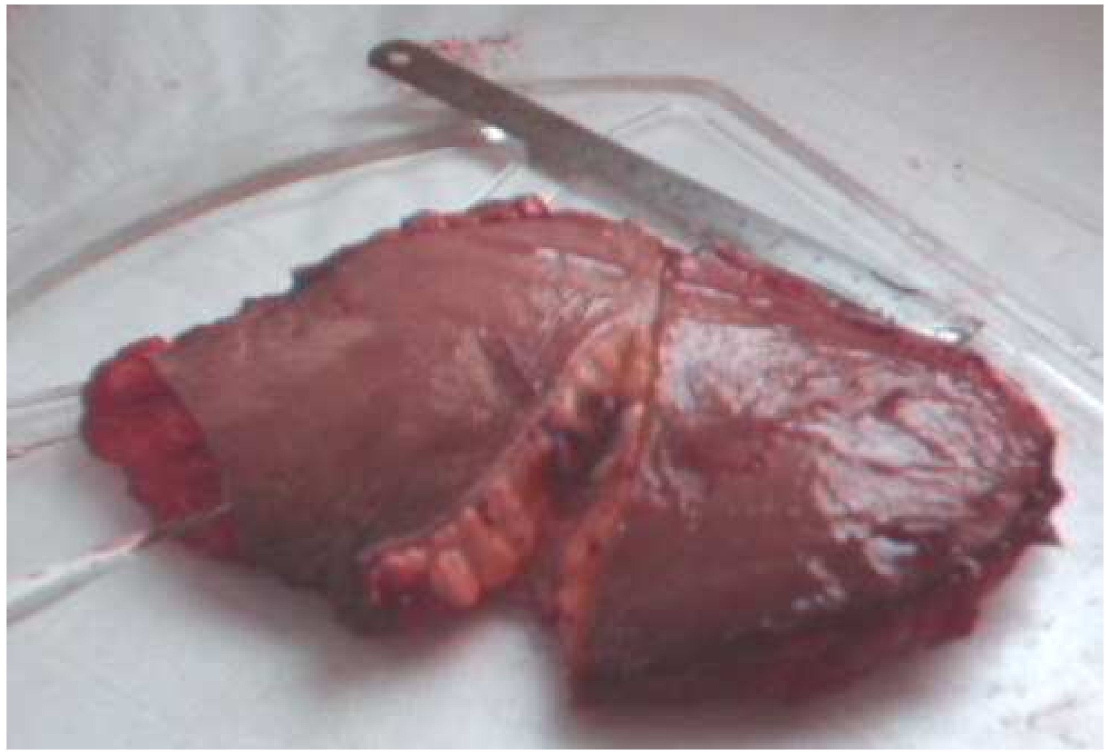
Picture 3b: thermal image of the body part shown in picture 1 at the end of the treatment. The rise in temperature of the surface layers is evident.

Macroscopic variations

Upon inspection of the body part treated to 25% of power, it does not show any macroscopic variations of the skin surface at the end of the treatment, while adipose tissue appears less supple and more wrinkled.

The body part treated to 50% of power shows the wrinkling of adipose tissue after 90 seconds of treatment. Cutis progressively starts coming unstuck, contracting and shrinking after 3 minutes of treatment. After 4 minutes, cutis looks burned. The body part treated to 75% of power shows the coming unstuck, the contraction and retraction of the entire cutis 90 seconds after the treatment: adipose tissue appears to be coagulated.

The body part treated to 100% of power shows signs of burn after a few seconds after the treatment (white, rigid cutis, unstuck from the underlying layers; coagulated adipose tissue) (Picture 4a,4b,4c).



Picture 4a: Macroscopic appearance of the body part of Picture I after a few seconds of treatment to 100% of power. It can be seen that epidermis came unstuck from dermis; adipose tissue appears compact and hardened in its surface layers while the deepest ones are intact.

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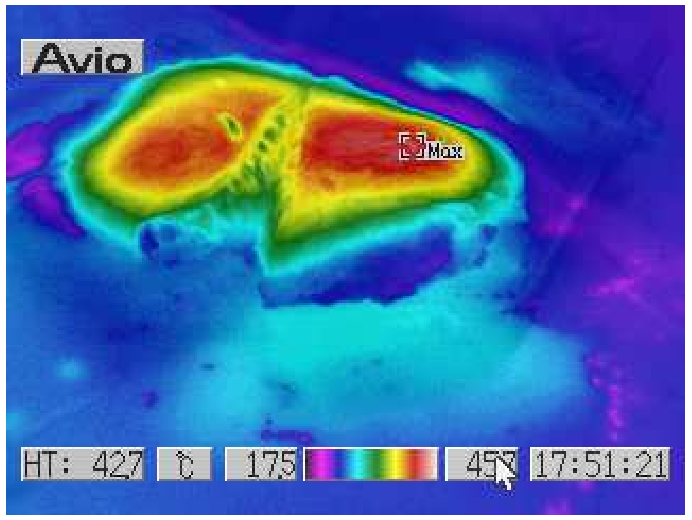
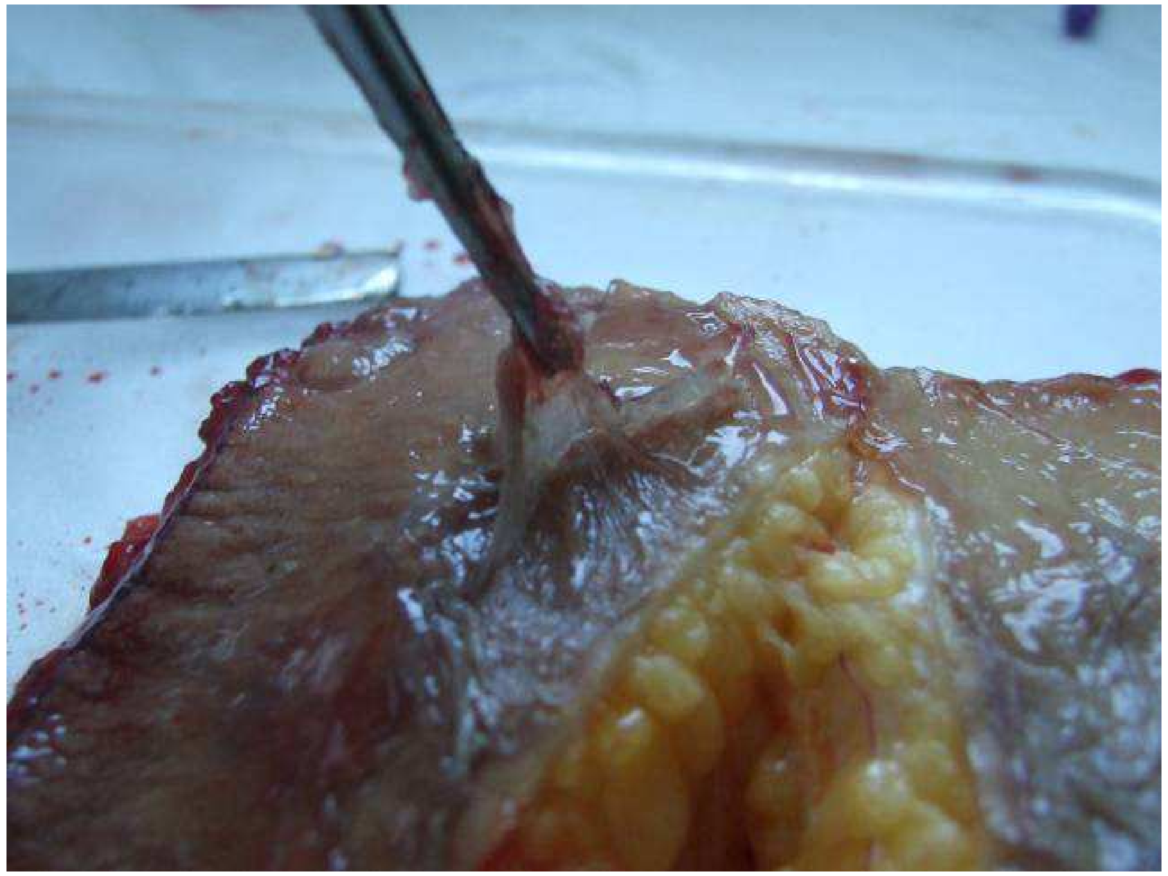


Picture 4b: thermal image of the body part shown in picture 4a. The increase in temperature is evident through the transmission of heat along the connective septa, with minimum effect on adipose tissue.



Picture 4c: In the same body part as the one shown in picture 4a the coming unstuck of epidermis from dermis can be seen.

3.2 Second trial

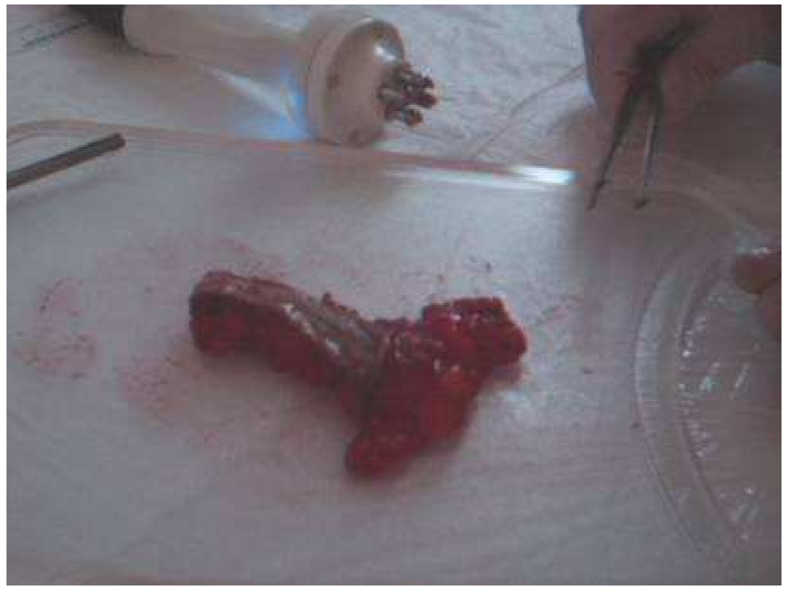
3.2.1 Procedure

During the dermolipectomy surgery of the proximal areas of inner thighs of a 52 year-old female patient, two body parts were removed. A sample was taken for control, while three portions underwent treatment.
The set parameters which were kept fixed throughout the procedure are the same as the first trial.

3.2.2 Used parameters

- General Program
- Mode RFS 3:1
- Time: RFS 5 seconds
- Duty cycle 100% (timing on 1.000 msec. timing off 0 msec)
- Maximum length of treatment: 4 min.

The small handpiece was used.
A body part with a size of 11 x 3 cm and a thickness of 1,5 cm was treated to 25% power for 3 minutes. Cutis became off-white and retracted (Picture 5a, 5b).



Picture 5a: Macroscopic appearance of the body part after the treatment to 25% of power for 3 minutes. It shows the retraction of cutis.

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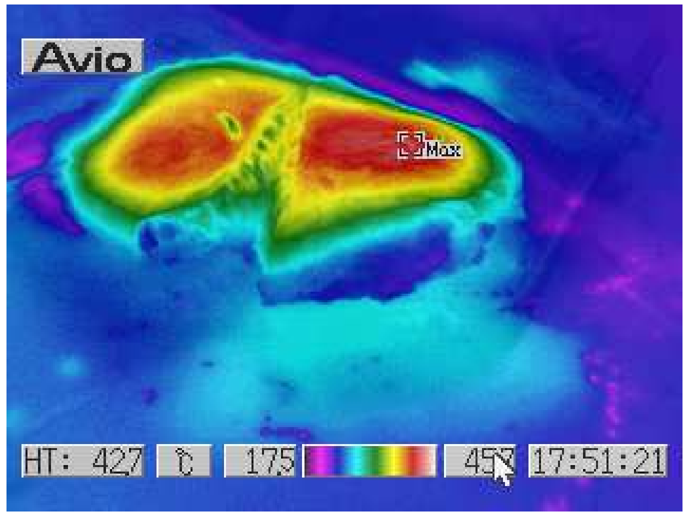

Picture 5b: thermal image of the body part shown in picture 5a

A body part with a size of 8 cm x 4,5 cm and a maximum thickness of 3 cm was treated to 10 % of power for 5 minutes.
Surface temperature went from 27,0° C to 49,5 °C.
A body part with a length of 7x3 cm and a maximum thickness of 2,5 cm was treated tor 5 % of power for 1 minute (temperature variation from 27,0° to 31,0°) .
After 5 minutes surface temperature went from 27.0°C to 40.7°C. Tissue consistency shrinks and cutis appears slightly retracted. Samples were taken from each body part for histological examination.

3.3 Synopsis of temperature variations

The recorded temperatures are reported in detail in the table 1 shown below.

POTENZA	T pre	T 30"	T 45"	T 60"	T 90"	T 2'	T 2'30"	T 3'	T 3'20"	T 4'	T 5'
Controllo (camp. 5)											
cute	30										
grasso	29										
Potenza 5% (camp. 9)											
cute	27			31			37,4				40,7
grasso	27										27
Potenza 10% (camp. 8)											
cute	27					42			45	48	49,5
grasso	27										27
Potenza 25% (camp. 1)											
cute	29,5 24,6									40 37	
grasso	28,8 29									28,8	
Potenza 25% (camp. 7)											
cute	26	42						67			
grasso	26							36			
Potenza 50% (camp. 2)											
cute	27 22,2				42					51 47,7	
grasso	27									27 22,2	
Potenza 75% (camip. 3)											
Cute	30 25,8							60 50		70 55	
grasso	27,2									35,5 27,2	
Potenza 100%											
Cute	27		27								
grasso		55									

TABLE 1: Temperature summarizing the temperatures recorded on ex-vivo samples. Temperatures recorded by the thermographic camera are written in black; temperatures recorded by the handpiece sensor are written in red. All the indicated values are expressed in Celsius degrees.

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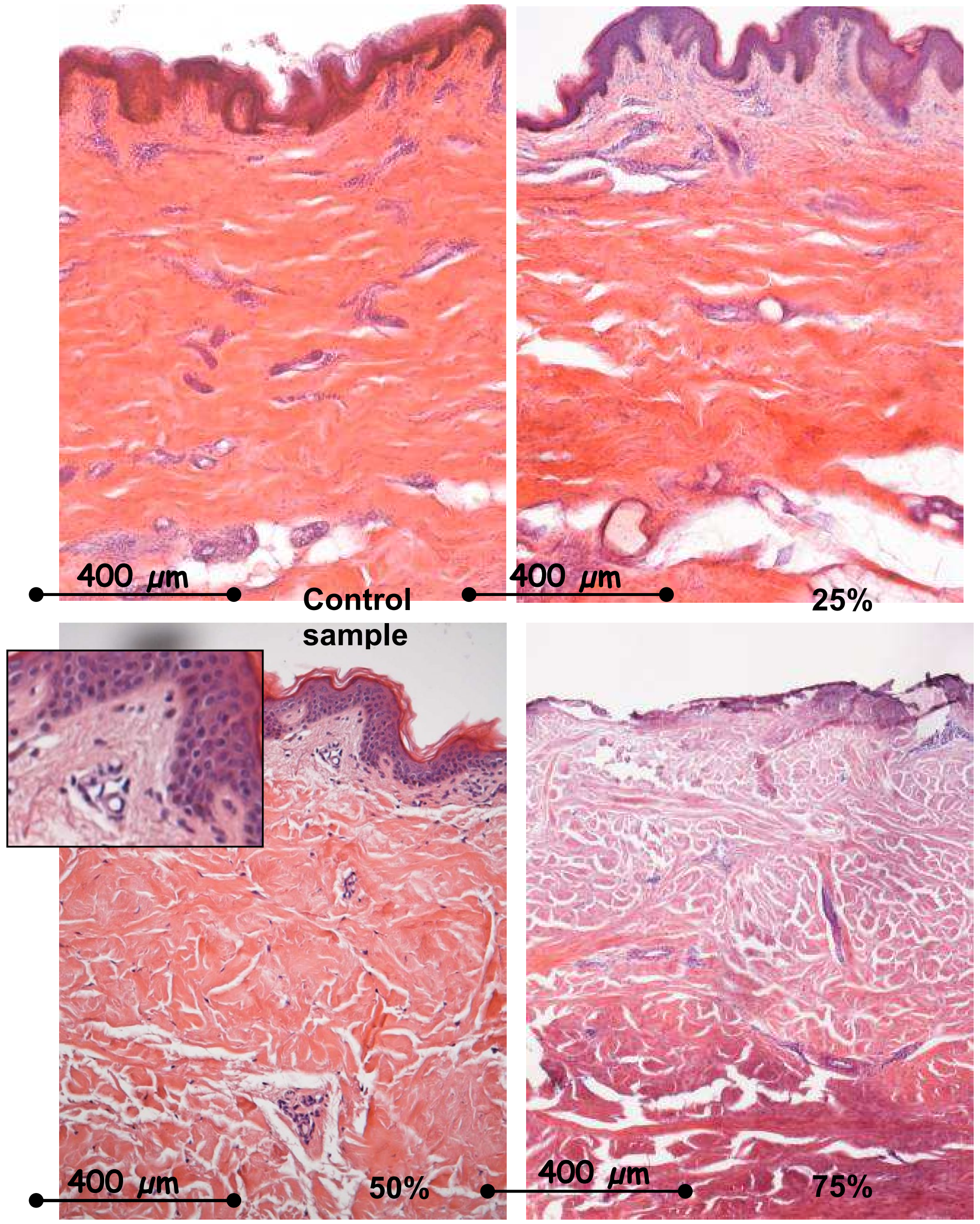
3.4 Histological corroboration

The 9 samples were examined by light microscopy using a fixative containing 4% paraformaldehyde in phosphate buffer.

Subsequently the samples were immersed in cryoprotectant (saturated solution of sucrose) for at least 6 hours, frozen in liquid nitrogen and dissected by cryostat sectioning in order to preserve the integrity of adipose tissues. Finally samples were dyed with hematoxylin and eosin stain. As shown in Table 1, all treated samples show bundles of disarranged collagenous fibers with immediate evident alterations of the dermis papillary layer (small clots) visible up to approximately 1,5 cm depth. "Damage" seems to be proportional to the intensity of treatment; epithelium is present and outwardly intact up to 50% of delivered power. The adipose tissue – endothelium - nerves and glands, instead, appear outwardly intact after using a 75% power (Table 2).

Table 1



Cutis and subcutis histological examination of *ex vivo* treated samples using different levels of power energy (25%, 50% and 75% of the total power delivered by this piece of equipment). Collagen fibers appear modified compared to the control sample: changes are evident on dermis papillary layer where small bundles of fibers coagulated into small clots can be found (see box); they affect the entire subcutaneous layer and seem to be proportional to the intensity of treatment. Epithelium is present, outwardly intact, up to 50% of power energy.

Samples are dissected by cryostat sectioning and dyed with haematoxylin and eosin stain.

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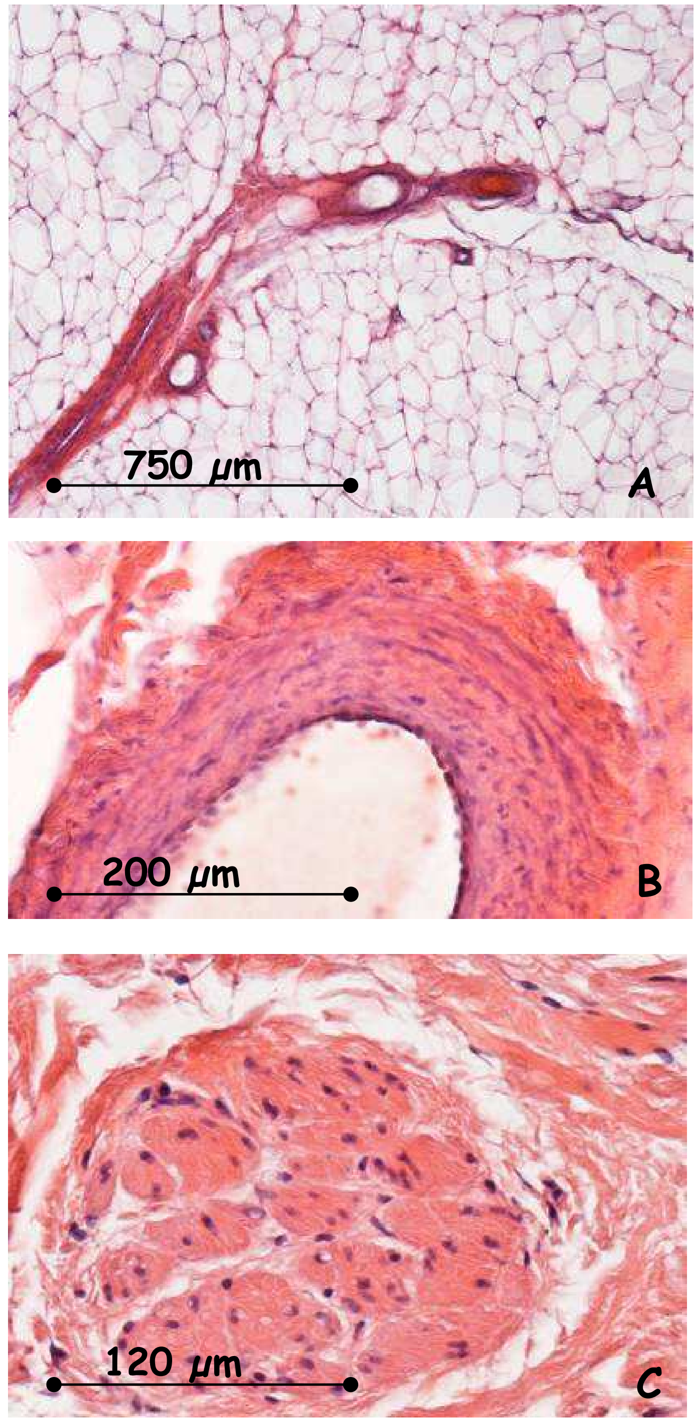
Table 2



Histological examination of the cutis and subcutis of *ex vivo* treated samples at energy power equalling 75%.

All treated samples preserve seemingly unaltered adipose tissue (A) and show perfectly preserved endothelium and vascular walls (B) and nerves (C).

4 In vivo study

We clarify that the purpose of the second leg of this study was to identify the safety limits of the equipment and therefore all possible scenarios of intolerance in the human subject in order to deduce correct use protocols in the current practice. Therefore its effects have been tested by first delivering the maximum power determined to be safe in the first leg - ex vivo – of the study and, in case, proceeding with decreasing levels of power energy and times until the maximum power and time of application subjectively tolerable in the various body areas have been identified.

4.1 First trial

A 48-year-old female volunteer was treated by means of RADIO 4 in the proximal areas of thigh root, on both sides according to the following modes.

4.1.1 I Treatment (28.05.2010)

Parameters: large handpiece, right thigh mode RFS 1:3, left thigh mode RFS 2:2 , duty cycle 100%, time RFS 5 sec, 20 minute duration for each thigh.

Right thigh: initial temperature 28°C. Initial power 50% which induces extremely painful sensations, similar to an electric shock. Power is progressively reduced reaching a tolerable sensation to 35% power, which is delivered without causing pain or inconvenience for 5 minutes, although the painful sensation is stronger in the medial areas. At that time the surface temperature recorded by the thermographic camera is 33° C. Afterward power is reduced still further, obtaining wide tolerability to 25% value, in which the patient only feels strong heat sensation and cutis appears erythematous in the more medial areas. Surface temperature detected by thermographic camera: 37,7°C .

Left thigh: initial power 50%; pain sensation more burning compared to the right thigh, but the electric shock sensation is absent. 50% power is tolerated for 1 minute; surface temperature recorded by the thermographic camera equals 34°C. Surface temperature recorded by the thermographic camera equals 34,8°C to 40% for 1 minute. The maximum tolerance exceeds 1 minute by a few seconds. At 35% the burning sensation is bearable and a stabbing pain occurred with a surface temperature peaks of 40°C. After 4 minutes the temperature rises to 43°C (37,6°C is the average temperature recorded by the handpiece). This treatment is extended to 35% for a total of 10 minutes in the most front area of the thigh; in the most medial area the treatment can be extended for 10 minutes to only 30% power.

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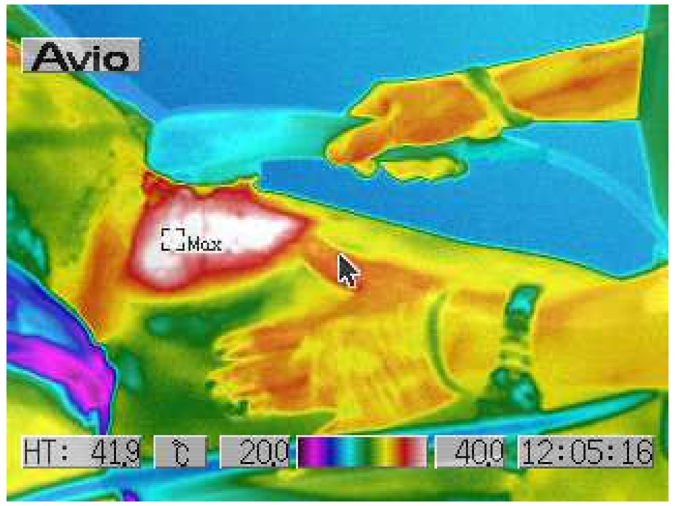
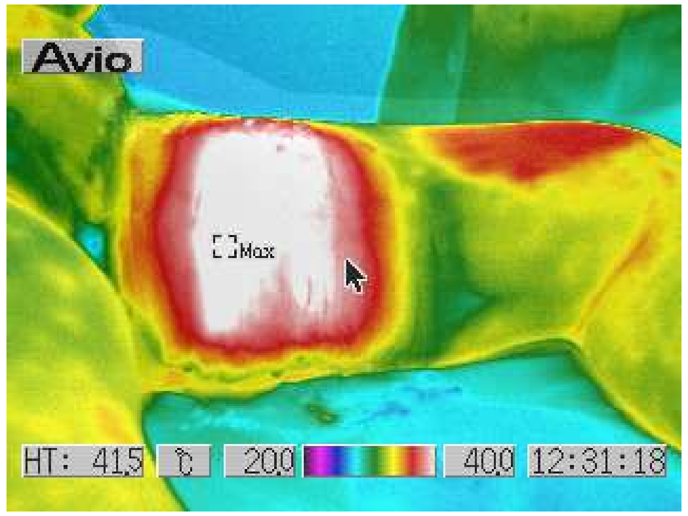
Temperature after 3 minutes of treatment: 38,4°C (thermographic camera) 36°C (handpiece).
Temperature after 16 minutes of treatment : 42°C (thermographic camera) 37°C (Handpiece) (Picture 6a, 6b, 7a, 7b).

Picture 6a: In vivo treatment of inner thigh with large handpiece



Picture 6b: thermal image of the treatment shown in picture 6a

Picture 7a : Appearance of the area of picture 6a at the end of treatment.



Picture 7b: thermal image of the area shown in picture 7a

There are not any skin lesions in both treated areas at the end of the treatment.

4.1.2 II treatment (11.06.2010)

Parameters: as the previous session. Total duration: 20 minutes.

Right: 25% power lowered to 20% in the most medial part for intolerance.

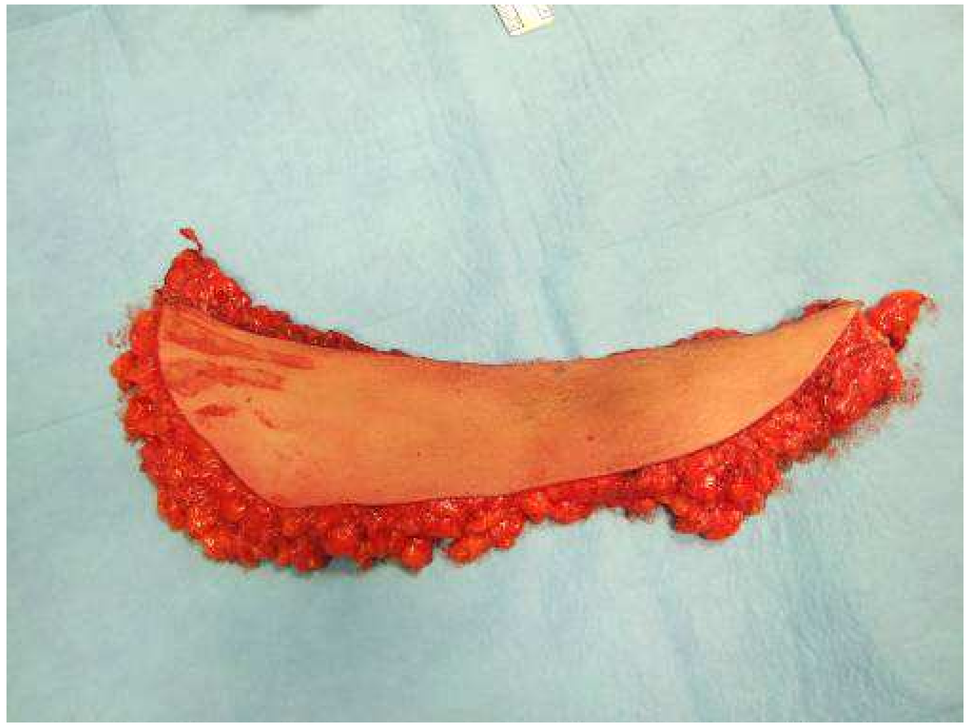
Left: 25% power in the whole area.

No skin lesions are observed.

During the first and the second treatment the most lateral body areas are treated for longer, and they turn out to be the less sensitive areas upon the passage of the handpiece.

4.1.3 Biopsies (21.06.2010)

During a dermolipectomy surgery, a few body parts previously treated (picture 8) were taken. 6 samples are obtained from them and sent for the histological examination.



Picture 8: body part taken from the inner thigh and previously subjected to two treatments

4.2 Second trial

42-year-old female patient waiting for abdominal dermolipectomy.

Subumbilical region.

Both right hemiabdomen and left hemiabdomen shall be considered as experimental unit.

Serial treatments with Radio 4 were scheduled: 20 minutes for each side, two week intervals between treatments.

These treatments were followed by dermal-adipose biopsies of the areas which were treated several times and sequenced in time in order to describe the histological effects after more treatments.

The right side shall be always treated with configuration 1:3, the left side with configuration 2x2.

4.2.1 I treatment (07.06.2010)

A control biopsy was performed using a punch of 6 mm diameter, and the first treatment was performed using the large handpiece (Picture 9).

Picture 9: right subumbilical region treatment. The picture shows skin erythema

Right Hemiabdomen:

RFS 1:3 duty cycle 100%, time RFS 5 seconds, duration 20 minutes. Initial temperature 36°C (thermographic camera), 29,1°C (handpiece sensor). Power is maintained to 45 % throughout treatment and temperature rises up during treatment reaching also maximum peaks of 39,0 °C .

Treatment turned out to be tolerable throughout the procedure, except in those areas where the handpiece had stayed for longer, causing intense heat, burning sensation and electric shock sensation.

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Left hemiabdomen:

RFS 2x2, duty Cycle 100%, time RFS 5 seconds, duration 20 minutes. Initial temperature: 35,9°C. Power to 50%, after 2 minutes the temperature values were: 43,3 °C (thermographic camera), 40,3° C (handpiece). Treatment is not tolerated by the patient using this amount of power energy. Therefore power was lowered to 40%; treatment became tolerable and temperature reached 44,0 °C after 11 minutes (thermographic camera).

At the end of treatment no skin lesions were observed (Picture 10a, 10b).

Picture 10a: appearance of left subumbilical area at the end of treatment.

Picture 10b: Thermal image of the subumbilical area shown in picture 10a

4.2.2 II treatment (23.06.2010)

Punch biopsy in the areas previously treated.

The parameters used were the same as the ones used on 07.06.10.

Temperature is measured only through the built-in sensor of the handpiece.

Right hemiabdomen:

Initial temperature 26,4°C. Tolerable power 45 % throughout the treatment.

Temperature at the end of treatment 38,7°C.

Left hemiabdomen:

Initial temperature 27°C. Power to 45% is tolerated for 8 minutes; treatment is completed using a power to 40%. After 9 minutes temperature reaches 47°C. The patient frequently reported her painful sensation of heat and burning.

4.2.3 III treatment (07.07.2011)

Punch biopsy in the areas previously treated (two treatments).

The parameters used were the same as the ones used on 06.23.2010.

Temperature is measured only through the built-in sensor of the handpiece.

Right hemiabdomen:

Initial temperature 28°C; power to 45%. After 4 minutes of treatment, the patient started feeling an intolerable burning sensation; temperature 34°C. Power was lowered to 40%. After a total of 8 minutes (that is 4 minutes to 40%), power was further lowered to 35%, which has been maintained until the end of treatment, recording a temperature of 37°C.

Left hemiabdomen:

Initial temperature 28,5°C. Initial power to 40%; after 5 minutes of treatment the patient felt a burning sensation, temperature was 39,3°C; power was lowered to 35%; the treatment has been tolerated for 12 minutes; power was lowered to 30%.

4.2.4 IV treatment (21.09.2010)

Biopsy performed in the areas previously treated (three treatments).

The parameters used were the same as the ones used earlier.

Right: power to 40% for 20 minutes, maximum temperature 38,5°C (handpiece).

Left: power to 20% for 20 minutes, maximum temperature 39,7°C (this power was reached after a series of attempts using higher levels of power energy).

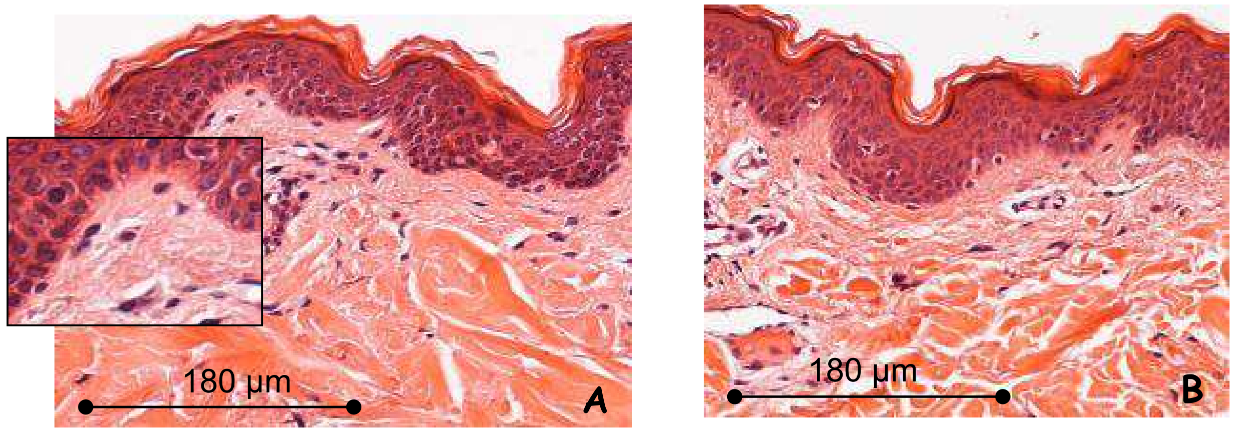
4.2.5 Histological corroboration

The bigger samples that were taken with the surgical scalpel were processed as ex vivo samples. The smaller samples, obtained using the *punch* method and featuring a lower amount of adipose tissue, were immersed in liquid paraffin and dissected using a microtome in order to obtain a better detail (the thickness of slices is thinner and more uniform).

The evidence fitted the results obtained after the same treatment in the ex-vivo samples for what concerns the epidermis and collagen fibers reaction: collagen appears constantly coagulated in small clots in the papillary layer of dermis and in larger clots in the underlying layers, whereas the epidermis is intact.

Quantity, arrangement and "behavior" of connective cells do not change in the treated samples compared to the control samples (Table 3).

Table 3

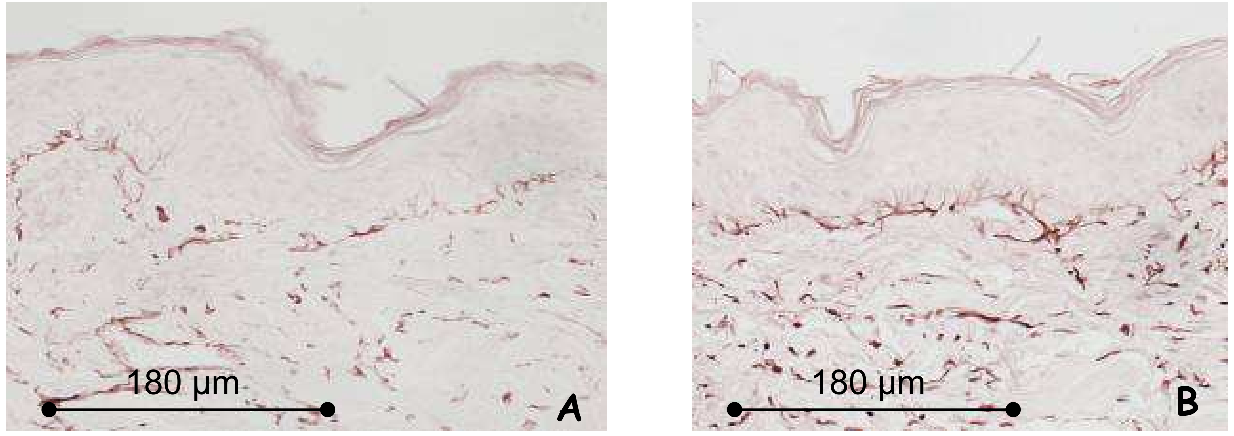


Samples taken using the *punch* method and immersed in liquid paraffin:

1. Control sample: collagen bundles appear thin, uncoiled, stretched out (hematoxylin and eosin stain).
2. Sample after 2 treatments using 45% power, one month after the first treatment: collagen appears coagulated in small clots in the papillary layer of dermis and in larger clots in the underlying layers. The epidermis is intact.

The changes that could be observed in the elastic fibers after the first two treatments are very interesting: they appear undoubtedly thicker and more evident in the treated samples than in the control samples. (Table 4)

Table 4



1. Control sample: the orcein stain highlights the elastic fibers which are finely branched in all dermis layers.
2. Sample after 2 treatments using 45% power, one month after the first treatment: elastic fibers became considerably thicker than the control samples in all the dermis layers. The perpendicular arrangement was emphasized in the papillary dermis in relation to the basal membrane.

Instead, a slight increase in the number and activity of macrophages was found after the treatments. This report indicated the presence of material that could be reabsorbed: such material likely consists of coagulated collagen fragments. (Table 5 a, b)

Table 5a

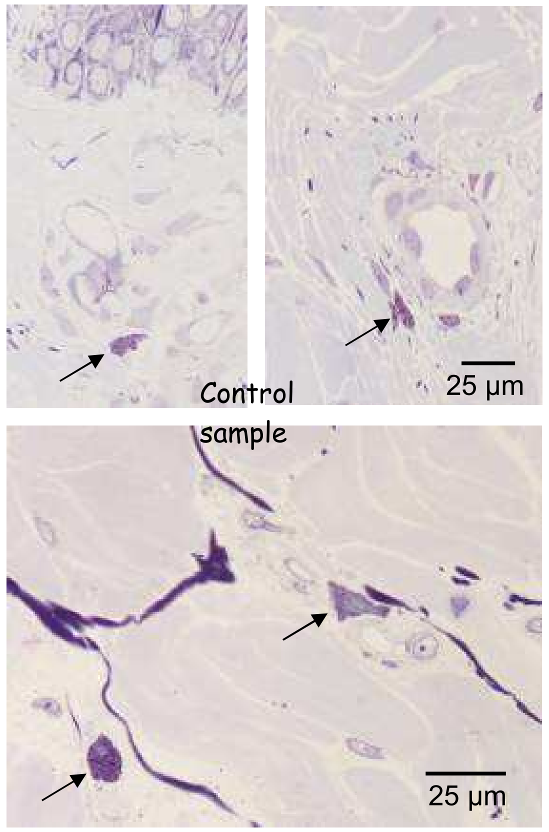


Table 5b

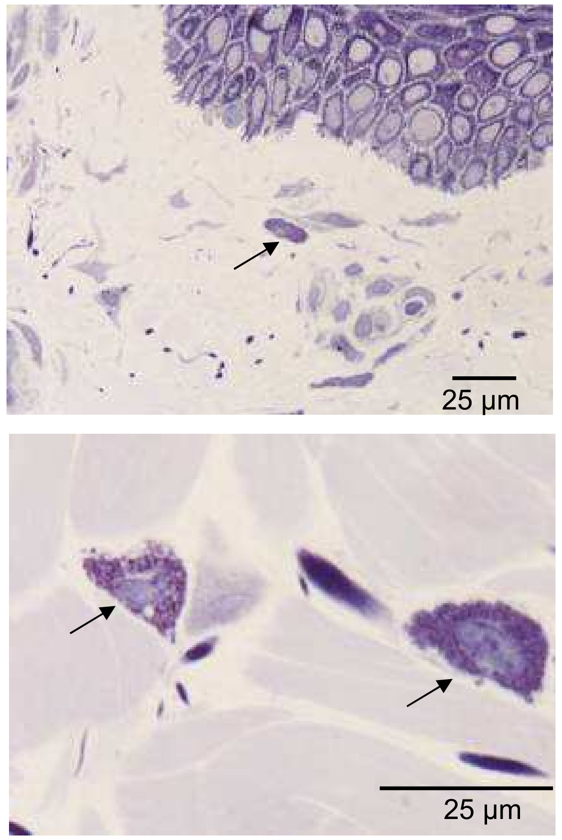


Table 5a: Control sample stained with toluidine blue: arrows highlight the macrophages that are mainly arranged in the perivascular area. This indicates a quiescent state.

Table 5b: Sample after 3 treatments using 45% power, stained with toluidine blue. Macrophages appear slightly more numerous than the ones in the control sample and they are not located in the perivascular area. This indicates an activity condition.

EVALUATION OF PHYSICAL PARAMETERS FOR SAFETY

(pursuant to Title VIII, Paragraph IV of the Legislative Decree no. 81/2008)

5 Preliminary remarks on the evaluation of physical parameters for safety

The aim of the study was to examine and assess the physical parameters that guarantee the safety of both the operator and customer/patient during the use of RADIO4 radiofrequency equipment.

The purposes of the evaluation were the following ones:

A. To identify the emission levels of the electromagnetic field that is generated by RADIO4 equipment in the environment at its maximum use power (for the two applicative fields: cosmetic and medical) and for the three supplied handpieces.
B. To measure the current induced in the operator's limbs under the maximum load conditions according to the different configurations of use.
C. To assess the operator's exposure – under the different conditions of use – and check the compliance with the limits provided for by the legislation in force.
D. To estimate the Specific Absorption Rate (SAR) of the radiofrequency field in the treated tissues, on the basis of the noticed thermal gradients (thermographic maps on ex vivo tissues or on their equivalent phantom) and of the electrical features of the tissues involved.
E. To evaluate the safety of customer/patient who undergoes radiofrequency treatment and to define the employment criteria of RADIO4 equipment in relation to the effects generated by the electromagnetic fields.

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6 Methods of measurement of physical sizes and evaluation criteria of exposure

Measurements were carried out in order to evaluate the intensity of the variable magnetic field (VMF) and of the current induced in the limbs according to the indications laid down in the ICNIRP 1998 guidelines defining the action values and the exposure limit values pursuant to Title IV of the Legislative Decree no. 81/08 waiting to be fully enforced as of April 2012.

However ICNIRP limits are currently in force for every exposure evaluation for people working in the presence of Electromagnetic Fields (CEM) from the entry into force of the obligations laid down in the Legislative Decree no. 81/08, that is January 1, 2009, as worldwide good practice.

The evaluation of the emission level of electromagnetic fields in the environment and the evaluation of the operator's exposure level with all the possible configurations of RADIO4 equipment were carried out in accordance with the technical regulations CEI 211-6:2001 and CEI 211-7:2001 by using the following measurement chain:

- Narda EHP-50C isotropic sensor analyzes selective, broadband measurements of low-frequency electric and magnetic fields from 5 Hz to 100kHz.
- Narda EHP-200 isotropic sensor analyzes selective, broadband measurements of low-frequency electric and magnetic fields from 9 kHz to 30MHz.

Measurements of the induced current in the limbs were carried out in accordance with the standard IEE C95.1 1991 by using the following measurement chain:

- ETS - Lindgren HI 4416 induced current meter with HI 3702 amperometric clamps from 9kHz to 110 MHz.

The electric field and magnetic field were measured on the various handpieces along the power supply cable by simulating the grip of the operator on the handpiece and around a hemisphere with a 30 cm radius (as shown in the following pictures) in order to find the maximum emission level.

Measurements were performed using phantoms to simulate the patient: this phantom had the same electromagnetic characteristics as the human body at the essential operating frequency of the equipment in a nearby unperturbed field.

Measurements of induced currents in limbs were performed under normal operating conditions of the equipment during both the treatment on a volunteer and on simulating phantoms.

H1 Big handpiece for body

H2 Medium handpiece for body

H3 Small handpiece for face

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7 Results of electric field and magnetic field measurements

Measurements along the power supply cables did not produce significant emission values. This indicates the presence of an efficient passive shielding. The following tables show the maximum levels of the electric field E(V/m) and of the magnetic field H(A/m) measured in proximity to the handpieces in the temperature interval ranging between 22°C and 42°C of the patient-mimicking phantom.

7.1 H1 Big handpiece

Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori = RFS 1-3** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	307,4	0,157
	@ 30 cm	31,9	0,014
P = 50%	@ contatto	150,5	0,133
	@ 30 cm	42,9	0,014
Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori = RFS 2x2** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	390	0,400
	@ 30 cm	30,2	0,014
P = 50%	@ contatto	396,3	0,300
	@ 30 cm	26,5	0,014
Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori: RFS 2=2** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	310,9	0,280
	@ 30 cm	22,9	0,014
P = 50%	@ contatto	281,6	0,130
	@ 30 cm	16,0	0,014

7.2 H2 medium handpiece

Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori = RFS 1-3** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	123,7	0,085
	@ 30 cm	1,9	0,013
P = 50%	@ contatto	114,9	0,079
	@ 30 cm	1,9	0,013
Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori = RFS 2x2** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	129,3	0,091
	@ 30 cm	3,0	0,013
P = 50%	@ contatto	122,8	0,090
	@ 30 cm	2,5	0,012
Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori: RFS 2=2** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	131,5	0,106
	@ 30 cm	2,1	0,013
P = 50%	@ contatto	132,0	0,091
	@ 30 cm	1,3	0,012

7.3 H3 small handpiece

Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori = RFS 1-3** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	49,5	0,130
	@ 30 cm	4,3	0,013
P = 50%	@ contatto	26,9	0,082
	@ 30 cm	1,9	0,013
Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori = RFS 2x2** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	85,0	0,130
	@ 30 cm	5,2	0,013
P = 50%	@ contatto	47,6	0,102
	@ 30 cm	1,4	0,013
Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori: RFS 2=2** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	44,6	0,240
	@ 30 cm	2,9	0,014
P = 50%	@ contatto	43,3	0,103
	@ 30 cm	2,2	0,013

7.4 Results of current measurements induced in the limbs

The measurements performed under the maximum load operating conditions – using all the handpieces and all the possible configurations – did not produce any significant values, and they always equalled the current pulse amplitude (< 0,01 mA).

7.5 Electric field and magnetic field measurements under the handpieces

In order to evaluate the level of the electric field and magnetic field the portion of treated tissue was exposed to during the RF treatment, the treatment by means of different handpieces perpendicularly placed on a Petri dish (diameter= 10cm; thickness= 1mm) evenly covered with about 5cm of conductive gel was simulated. The Petri dish containing the conductive gel and on which the handpiece was placed perpendicularly, was put in direct contact with the isotropic measurement sensor. The actual point of measurement is defined on the handpiece axis to 5 cm depth from the contact surface of electrodes.

The measurements of electric and magnetic fields were carried out by means of the Narda EHP-200 isotropic sensor for selective, broadband measurements of electric and magnetic fields (9 kHz ÷ 30 MHz) on the three handpieces coming with RADIO4 equipment.

The following tables show the maximum values of electric field E(V/m9) and magnetic field H(A/m) measured under the handpieces (by a contact sensor), in the temperature interval of the patient-mimicking phantom ranging between 22°C and 42°C.

7.6 H1 big handpiece

Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori = RFS 1-3** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	282,4	0,200
P = 50%	@ contatto	297,0	0,127
Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori = RFS 2x2** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	322,6	0,062
P = 50%	@ contatto	239,6	0,070
Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori: RFS 2=2** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	198,2	0,380
P = 50%	@ contatto	169,4	0,360

7.7 H2 medium handpiece

Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori = RFS 1-3** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	212,4	0,060
P = 50%	@ contatto	155,2	0,063
Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori = RFS 2x2** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	224,2	0,060
P = 50%	@ contatto	208,2	0,075
Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori: RFS 2=2** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	170,4	0,073
P = 50%	@ contatto	202,8	0,060

7.8 H3 small handpiece

Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori = RFS 1-3** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	98,2	0,218
P = 50%	@ contatto	104,5	0,101
Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori = RFS 2x2** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	78,4	0,120
P = 50%	@ contatto	86,7	0,097
Impostazioni	**duty cicle = 100%** **configurazione degli elettrodi trasmettitori/ricevitori: RFS 2=2** **tempo di rotazione RFS = 5 sec**		
Potenza	**p.to di misura**	**Campo Elettrico E (V/m)**	**Campo Magnetico H (A/m)**
P = 100%	@ contatto	121,6	0,120
P = 50%	@ contatto	95,2	0,160

8 Measurement analysis

Measurement data were compared with the INCIPRP 1998 action levels, which, if not exceeded, assure that the occupational exposure limit values are not exceeded. An excerpt of those values is shown in the following table.

Excerpt from INCNIRP 1998 table 6

Guidelines for limiting exposure to time-varying electric, magnetic, and electromagnetic fields ● ICNIRP GUIDELINES

Table 6. Reference levels for occupational exposure to time-varying electric and magnetic fields (unperturbed rms values).[a]

Frequency range	E-field strength ($V\ m^{-1}$)	H-field strength ($A\ m^{-1}$)	B-field (μT)	Equivalent plane wave power density S_{eq} ($W\ m^{-2}$)
up to 1 Hz	—	1.63×10^5	2×10^5	—
1–8 Hz	20,000	$1.63 \times 10^5/f^2$	$2 \times 10^5/f^2$	—
8–25 Hz	20,000	$2 \times 10^4/f$	$2.5 \times 10^4/f$	—
0.025–0.82 kHz	$500/f$	$20/f$	$25/f$	—
0.82–65 kHz	610	24.4	30.7	—
0.065–1 MHz	610	$1.6/f$	$2.0/f$	—
1–10 MHz	$610/f$	$1.6/f$	$2.0/f$	—
10–400 MHz	61	0.16	0.2	10
400–2,000 MHz	$3f^{1/2}$	$0.008f^{1/2}$	$0.01f^{1/2}$	$f/40$
2–300 GHz	137	0.36	0.45	50

Estratto dalla tabella 6 ICNIRP 1998		
Valori di azione (frequenza)	**Intensità di campo elettrico E (V/m)**	**Intensità di campo magnetico H (A/m)**
(0,065 - 1 MHz)	610	1,6

Valori massimi misurati ed in % rispetto ai valori di azione ICNIRP			
Manipolo (valori massimi a contatto)	**Intensità di campo elettrico E (V/m)**	**Intensità di campo magnetico H (A/m)**	**Configurazione manipolo**
H 1 (potenza 100%)	390 / **63,9 %**	0,400 / **25 %**	RFS 2 X 2
H 1 (potenza 50%)	396,5 / **65 %**	0,300 / **18,7 %**	RFS 2 X 2
H 2 (potenza 100%)	131,5 / **21,6 %**	0,106 / **6,12 %**	RFS 2 = 2
H 2 (potenza 50%)	132 / **21,6 %**	0,091 / **5,7 %**	RFS 2 = 2
H 3 (potenza 100%)	44,6 / **7,3 %**	0,240 / **15 %**	RFS 2 X 2
H 3 (potenza 50%)	43,3 / **7,1 %**	0,103 / **6,4 %**	RFS 2 X 2

The action values for the electric and magnetic field have never been exceeded, even in the most unfavourable conditions for the operator.

The most emissive working configuration for H1 and H3 handpieces is RFS 2x2, while for H2 handpiece is RFS 2 = 2. Such differences must be attributed to the various current tracks inside the phantom that simulates the *in vivo* treatment and is also linked to the distance and shape of the electrodes.

Measurements were carried out again in the same operating conditions and at different times in

9 Effects of "RADIO 4" radiofrequency treatment on tissues

In order to study the radiofrequency treatment effects by means of RADIO4 equipment on the treated tissues, it is necessary to consider the following factors:

1. The type of coupling between the handpiece electrodes and skin tissue affects the way in which the electromagnetic energy is transferred to the tissue. In particular, the conductive component as well as the radiative one of the RF electromagnetic field must be taken into consideration;
2. skin's electrical properties, which are subjected to significant differences between different people and body parts, greatly depend on the hydration of the horny layer, therefore on the absorption of the applied conductive gel for the RF treatment;
3. the peculiar structure of skin made up of multiple layers of epithelial tissues (epidermis, dermis, hypodermis) has a low thermal conductivity able to guarantee the body homeothermy;
4. the dermis and the hypodermis (containing collagen) elastin, blood and lymphatic vessels, nerves, hair and glands (entirely held in a gel rich in water), mucopolysaccharides and electrolytes make up a high-electrical conductivity system that depends all the same on the temperature and on the frequency of the applied current.

9.1 Interaction mode of RADIO4 equipment with the treated tissues

The radiofrequency treatment by means of RADIO4 equipment is performed through the contact between the hemispheric surface of handpiece electrodes and the patient's skin properly covered with the conductive gel to guarantee a proper electric coupling. The various configurations of active and neutral electrodes (1:3;2x2;2=2) that can be set entail different distributions of the radiofrequency current density in the points of skin-electrode contact. In addition to the radiofrequency current that runs between the active and neutral electrodes, there is also a radiofrequency electromagnetic field that hits the treated tissue. Its spectral shape in the frequency domain is shown in the following picture.

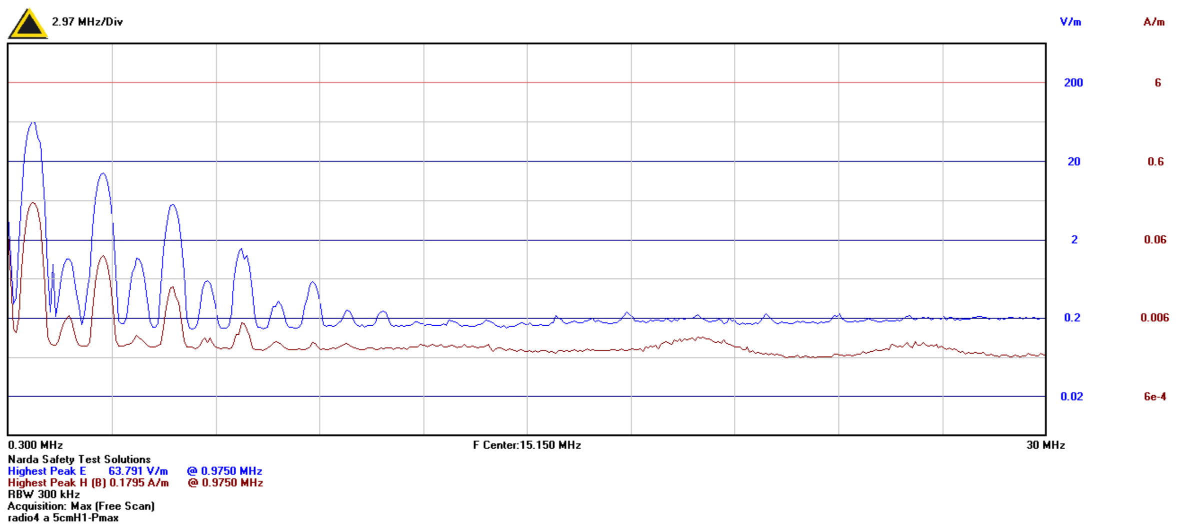

Table 1: Spectrum of electric field E(V/m) and magnetic field H(A/m) in proximity of the treatment handpieces

The peaks of the electric and magnetic fields having a frequency of 1MHz with the respective harmonics of superior level are recognized from the spectral shape. The conductive component is undoubtedly the prevailing one between the two modes by which energy is transferred to the treated tissue (conductive and radiative). In fact, for each configuration of active/neutral electrodes (1:3;2x2;2=2), the values of electric and magnetic field in proximity to the handpiece - both laterally and frontally to the electrodes – turn out to be of the same magnitude.

The presence of the inductive gel on skin assures a good electric coupling (electrode/skin), thus greatly reducing the formation of high current density contact points that cause considerable pain in the patient, but they also generate a high-conductivity substrate in which part of the radiofrequency current runs.

The radiofrequency current that runs between the active and neutral electrodes is distributed among the various substrates that are in contact with the electrodes depending on their conductibility. The main substrate tissue that is directly affected by the radiofrequency current is the dermis because it contains high levels of water and electrodes. The horny layer of skin contributes to transferring the RF current as well, following the hydration given by the conductive gel.

9.2 Analysis of thermal gradients and comments about SAR

In view of the complexity and variability of the phenomena taken into account, some significant parameters were singled out to be used as a valid reference to evaluate the effects of radiofrequency treatment on both "*ex vivo*" and "*in vivo*" tissue to be later compared to the histological results on the respective tissue samples subjected to RF.

These parameters, identified in the tissue temperature and in the electric field value under the handpiece, are linked to the specific absorption rate (SAR) within the tissue, and consequently to the amount of electromagnetic energy that is absorbed in the unit time per unit mass. In particular, only the SAR the operator may be exposed to must be evaluated in relation to the whole body and limbs, since it does not make sense to take into account this aspect in the subject to be treated as the heating effect is desired. Since the values of electric field emitted by RADIO 4 regarding the operator turned out to be below the action values defined by ICNIRP, it follows that SAR limits regarding the operator were not exceeded.

In order to analyze the thermal gradients between the cutaneous surface and the deepest levels of tissue after RF treatment on *ex vivo* tissue samples (without thermoregulation), the different surface thermographic maps were acquired in the different operating modes both on the treated skin and on the inner surface of the tissue dissected immediately after the treatment.
Despite the margin of error linked to the dissection operations of the tissue, limited by the low thermal conductivity of the tissue involved, the following observations were made:

- surface temperatures of the treated skin may be reached at the maximum set power equalling approximately 50°C after 30 seconds of treatment, while the temperature gradient in the deepest layers is scarcely significant (the rise in temperature concerns almost exclusively the skin surface);
- a surface temperature equalling approximately 50°C is reached at 50% of the set power for treatment times of about 5 minutes with a significant temperature gradient up to about 1,5 cm depth.

These results, besides confirming the scarce thermal conductivity of the tissues involved, can be directly correlated to the distribution of electromagnetic energy that is absorbed within the treated tissue, which is remarkably located on skin surface where the energy transfer through radiofrequency current that running in the gel-tissue surface substrates prevails.

10 Analysis of the results

The measurement data of the electric and magnetic field under the handpieces through contact measurement probe, being of the same magnitude as the values found around the corresponding handpieces and for each possible configuration of electrodes, indicate that the prevailing component of the electromagnetic field energy transfer to the tissue is conductive.

It is possible to identify some interaction mechanisms between RF currents, radiofrequency field and treated tissues that explain the corroborations found on the histological samples by analyzing the results related to the thermographic maps on the "*in vivo*" and "*ex vivo*" tissue samples that underwent the RF treatment and by assessing the effects of the radiofrequency currents and the electromagnetic fields that are generated by RADIO 4 handpieces.

In particular, both the trials performed on "*in vivo*" and on "*ex vivo*" samples and the effects noticed on the relevant histological samples highlighted how the thermal effect – mainly generated by radiofrequency currents – is located on the skin surface layer (in particular in the dermis).

The small clots found out in the reticular layer of the dermis are presumably due to local rises in RF current density, which may occur near the skin high-conductivity points, with the consequent increase in local temperature that changes its structure. It should be noted that literature shows that the coagulation effect on tissues and collagen denaturation occurs in the range between 60°C and 80 °C.

The collagen and elastin fibers of dermis, immersed in a matrix rich in water form a homogeneous structure that is clearly highlighted in the untreated biopsy samples. Elastin and collagen fibers are extremely hydrophobic and tend to cluster after the rise in local temperature of the aqueous matrix in which they are present. This would account for the rise in thickness of the elastic fibers found on the biobsy samples subjected to RF treatment. This phenomenon – which is responsible for the esthetic effect on the skin (smoothness and softness of the skin in the treated areas) seems to be favored also by the radiative component of the radiofrequency field that transfers the electromagnetic energy in particular to water, thus facilitating the mechanism described above.

11 Conclusions

The analysis of the values of the electric and magnetic field which were found, and the comparison with the respective action levels for workers as laid down in the INCIRP 1998 Guidelines show that Radio 4 equipment complies with the safety regulations currently in force for workers (Legislative Decree no. 81/08).

As far as patients are concerned, the need of using power levels < 50%, which seem to be the tolerable ones thanks to the *in vivo* clinical evaluation, seems to be also supported by the levels of electric and magnetic field emitted upon contact by H1 handpiece, which generates the highest values and for which a high accumulation of energy in the tissue (SAR) is expected and must therefore be assessed.

The electric field levels emitted at a distance of 30 cm from the handpieces show that people with pacemakers, neurostimulator implants and other implantable medical devices cannot be treated with this piece of equipment (as a precaution).

Another contraindication is the presence of tattoos on the area to be treated, since conductive substances that may favour the local generation of electric discharges on the skin may be used. They may generate a local burn due to "hot spots" formation.

In relation to the aspects concerning the electromagnetic field interaction generated by RADIO4 equipment on the skin in order to obtain a significant esthetic effect through the application of radiofrequency current by means of different handpieces and configurations of electrodes, it can be stated as follows:

1. skin treatment by means of RADIO4 allows a controlled, surface accumulation of electromagnetic energy capable of generating a heating of the first layers that leads to an evident increase in the smoothness and softness of the treated area due to the changes occurred in dermis structure;
2. the treatment turns out to be well tolerated if the power used is below 50% of the maximum set level and if the skin is properly prepared with the supplied conductive gel. Failure to comply with even a single condition may lead to the localized rise in current density on tissue and/or inside it, thus causing adverse effects that are scarcely tolerated (rash, redness, stabbing pain). Moreover, the study proved that the configuration of the electrodes "1-3" improves both the tolerability and efficacy of the treatment. This is presumably due to the current distribution all over a larger tissue surface, therefore to a more uniform distribution of thermal effect;
3. even though the absorption of radiofrequency electromagnetic energy occurs on the surface, the possibility of having adverse thermal effects that can hardly be controlled in proximity to critical organs must be taken into account.

12 Technical and normative references

1. 1999/519/EC: Council Recommendation of 12 July 1999 on "the limitation of exposure of the general public to electromagnetic fields (0 Hz to 300 GHz)" (Official Journal L199/59, 07/30/1999).
2. Directive 2004/40/EC on "the minimum health and safety requirements regarding the exposure of workers to the risks arising from physical agents (electromagnetic fields)".
3. Legislative Decree no. 81 of 9 April 2008 "Consolidation Act on health and safety in the workplace", published in the Official Journal no. 101 of 30 April 2008. Ordinary Supplement no. 108/L.
4. "Guidelines for limiting exposure tot ime-varying electric, magnetic and electromagnetic fields (up to 300 GHz)" ICNIRP, 1998.
5. CEI 211-6 Standard, "Guide for the measurement and the evaluation of electric and magnetic fields in the frequency range 0Hz-10kHz, with reference to the human exposure, 2001".
6. CEI 211-7 Standard, "Guide for measurements and the evaluation of electric and magnetic fields in the frequency range 10 KHz-300 GHz, with reference to the human exposure, 2001".
7. Electronic Communications Committee (ECC) Recommendation 04: Measuring non – ionising electromagnetic radiation (9 KHz – 300 GHz), 2007.
8. CEI 61-251 Standard, "Measurement methods of electromagnetic fields of household appliances and similar appliances with reference to the human exposure, 2008";
9. "IEEE Standards for Safety Level with Respect to Human Exposures to Radio Frequency Electromagnetic Fields, 3 kHz to 300 GHz" Std C95.1:1999.

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13 Summary conclusions

The following conclusions can be drawn from the analysis of the data found on *ex vivo* samples, during *in vivo* treatments and on histological preparations.

The power energy emitted by Radio 4 is delivered in the form of heat generation. The significant changes in temperature noticed in *ex vivo* samples are partially compensated *in vivo* by the thermoregulatory mechanism. Under no circumstances can power emissions ≥ 50% (values referred to the medical software) be used.

The biological effect of the temperature rise is proportional to the application time.
The tolerability shown by patients during *in vivo* trials faithfully reflects the anatomic-pathological effects noticed under the microscope.
Those areas with a greater sensitive innervation cannot tolerate higher levels of power energy for longer times.

With power emissions tolerated by the subjects, only the denser tissues seems to be affected (dermis, inter-adipose connective septa); while the epidermis does not seem to be damaged, it only appears erythematous at the end of the treatments. Any effects on the subcutaneous adipose tissue can be only related to the thickening and shortening of connective septa and not to a direct effect on adipocytes.
The 2 x 2 configuration of electrodes seems to be less tolerable - for the same power level, - in comparison with the 1:3 configuration.

In order to obtain more safe results, it would be advisable to increase the treatment time rather than to increase power emissions.
After only 2 treatments, the treated subjects report a smoother and softer skin in the treated areas, while the underlying panniculus adiposus did not show any changes even after 4 treatments.
Both *ex vivo* and *in vivo* histological corroborations show large disarranged bundles of collagen fibers, with more evident alterations of the dermis reticular layer (small clots), visible up to approximately 1,5 cm depth. These alterations seem to be proportional to the intensity of the treatment and to the number of applications. Adipose tissue, vascular endothelium, nerve endings and cutaneous annexes seem intact up to 75% of power. The epithelium seems present and intact up to 50% of power.

As regards the effects of the treatments on the *in vivo* response, a minimum cellular response can be detected even after 3 months from the beginning of treatment, after 3 applications during 1 month. It exclusively consisted in a moderate activation of the sole macrophages activity, which revealed the presence of material to be reabsorbed, that would most likely be represented by coagulated collagen fragments. No changes were detected either in other cells indicating an inflammatory response or in connective cells (fibrocytes and fibroblasts) whose qualitative and quantitative characteristics appear unchanged at the end of the cycle of the performed treatments.

As regards the described changes sustained by the elastic fibers – which can be already noticed one month after starting treatment, after 2 applications performed within 2 weeks, - the increase in fibers thickness, involving both the papillary dermis and the reticular dermis, is an event that can be usually observed in skin subject to photodamage after exposure to UV radiation. In a similar way, the increase in thickness of elastic fibers is a constant feature of skin aging, which corresponds, in clinical terms, to a loss of elasticity. On the other hand, it can be noticed that the elastic fibers thickened after the Radio 4 treatment maintain a reticular pattern, typically seen in young people: this ostensible contradiction could be probably interpreted by bearing in mind that Radiofrequency, as thoroughly described in the physical-medical part of this report, induces connective fibers to cluster together by means of a physical mechanism only, connected to the increase in energy potential of the aqueous environment where these highly hydrophobic structures were placed.

The comprehensive interpretation of the evidence involving connective fibers would lean toward a process of spatial rearrangement, without any signs of scar formation. Any clinical-esthetic relapses of these biologic processes in time, especially with regard to a possible stimulation of regenerative processes, cannot be determined on the basis of data collected until now.

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The results of the physical tests carried out until now show an overall substantial safety of the equipment, provided that it is used at a power not exceeding 50% using the medical software and sticking to the restrictions widely described above.

Moreover, the manufacturing Company guarantees that RADIO4 equipment is put on the market of non-surgical cosmetics supplied with a software that automatically limits the power to 25W (this corresponds to 45% of the power emitted by the medical equipment tested by us (RADIO4M), which has a maximum power of 55W).

Anyway, the operators working both in the medical field and in the cosmetic field shall pay utmost attention when they treat areas where the increase in temperature might induce adverse side effects. In particular, the application on the movable part of eyelids in direct contact with the eyeball should be banned, as any increase in heat of the eyeball causes opacity of the crystalline lens.

In witness thereof,
Prof. Angela FAGA
Director of the Interdepartmental Research Center "T.A.Me.Ri.Ci."
University of Pavia

Pavia, 21.4.2011

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The Biological Effects of Quadripolar Radiofrequency Sequential Application: A Human Experimental Study

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Angela Faga, MD, FICS,[1–3] and Silvia Scevola, MD, PhD[2]

Abstract

Objective: An experimental study was conducted to assess the effectiveness and safety of an innovative quadripolar variable electrode configuration radiofrequency device with objective measurements in an *ex vivo* and *in vivo* human experimental model. ***Background data:*** Nonablative radiofrequency applications are well-established anti-ageing procedures for cosmetic skin tightening. ***Methods:*** The study was performed in two steps: *ex vivo* and *in vivo* assessments. In the *ex vivo* assessments the radiofrequency applications were performed on human full-thickness skin and subcutaneous tissue specimens harvested during surgery for body contouring. In the *in vivo* assessments the applications were performed on two volunteer patients scheduled for body contouring surgery at the end of the study. The assessment methods were: clinical examination and medical photography, temperature measurement with thermal imaging scan, and light microscopy histological examination. ***Results:*** The *ex vivo* assessments allowed for identification of the effective safety range for human application. The *in vivo* assessments allowed for demonstration of the biological effects of sequential radiofrequency applications. After a course of radiofrequency applications, the collagen fibers underwent an immediate heat-induced rearrangement and were partially denaturated and progressively metabolized by the macrophages. An overall thickening and spatial rearrangement was appreciated both in the collagen and elastic fibers, the latter displaying a juvenile reticular pattern. A late onset in the macrophage activation after sequential radiofrequency applications was appreciated. ***Conclusions:*** Our data confirm the effectiveness of sequential radiofrequency applications in obtaining attenuation of the skin wrinkles by an overall skin tightening.

Introduction

Over the past decade, radiofrequency (RF) has become an important and frequently used technology in aesthetic medicine. The mechanism of action of RF is based on an oscillating electrical current (2,000,000–3,000,000 times/sec) forcing collisions between charged molecules and ions, which are then transformed into heat.[1] A further contribution to the increase in the local temperature is provided by the radiation component of the RF field, with electromagnetic energy transfer to the water-rich dermal matrix.

Noninvasive delivery of RF energy to collagen and subcutaneous tissues produces collagen remodelling, therefore, achieving noninvasive tightening of lax skin and body contouring.[2,3] RF-treated skin displays an immediate and temporary change in the helical structure of collagen, with fibrils showing a greater diameter than that of fibers pretreatment.[4]

It is also thought that RF thermal stimulation results in a microinflammatory stimulation of fibroblasts, which produces new collagen, new elastin, and other substances, to enhance dermal structure.[1,5]

The depth of penetration of RF energy is inversely proportional to the frequency. Consequently, lower frequencies of RF are able to penetrate more deeply. The currently available devices work with frequencies within the 1 Hz to 40.68 MHz range.

Two different forms of RF delivery have been developed so far: monopolar and bipolar. Monopolar systems deliver current through a single contact electrode with an

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accompanying grounding pad that serves as a low resistance path for current flow to complete the electrical circuit; the active electrode concentrates most of the energy near the point of contact, and energy rapidly diminishes as the current flows through the body toward the grounding electrode. As a result, the tissue in the treated area is heated rather deeply (usually up to 20 mm) and intensely.[2]

Bipolar devices pass electrical current between two electrodes closely positioned to the skin; no grounding pad is necessary with these systems because no current flows throughout the rest of the body. The depth of penetration is approximately half the distance between the two electrodes.[3]

As a result, the tissue in the treated area is heated less deeply (usually up to 2–4 mm in depth) and less intensely than with the monopolar RF devices.[6]

Despite its lesser absolute effectiveness, the bipolar technology is currently gaining an increasing popularity, as it allows fair outcomes with significantly less invasive applications.[7]

Nowadays, patients asking for cosmetic medical treatments expect perfect results, with a minimum of work and social downtime. Therefore, such innovative noninvasive treatments have been progressively replacing the traditional and time-honored surgical procedures for skin tightening.

The increasingly large number of technological innovations proposed on the global market require rigorous study protocols for the assessment of safety and effectiveness prior to authorization for human use. As a group of academic plastic surgeons actively involved in aesthetic surgery and medicine research, we were commissioned to assess the effectiveness and safety of an innovative quadripolar variable electrode configuration RF device.

Materials and Methods

The study was conducted at the Advanced Technologies for Regenerative Medicine and Inductive Surgery Research Center of the University of Pavia, Italy, in cooperation with the Plastic and Reconstructive Surgery Unit of the Salvatore Maugeri Research and Care Institute, Pavia, Italy, and the Histology and Embryology Unit, Department of Public Health, Neuroscience, Experimental and Forensic Medicine, University of Pavia, Pavia, Italy.

The study was approved by the University of Pavia Ethical Committee. A formal informed written consent was obtained from all of the patients and the study conformed to the Declaration of Helsinki.

A novel Class I RF generator, RADIO4™, produced by Novavision Group s.p.a., (Via dei Guasti 29, 20826 Misinto, Milan, Italy) was tested. RADIO4 is based on a four electrode system with software-controlled automatic dynamic configuration providing a 1 MHz RF current circulation. The variable electrode configuration allows for creation of custom-made electric fields promoting thermal energy transfer to the tissue from RF current circulation. The device allows three possible electrode configurations within the four electrodes (Fig. 1):

- 1–3: one transmitter electrode and three receiver electrodes
- 2×2: two transmitter electrodes and two receiver electrodes in a cross fashion

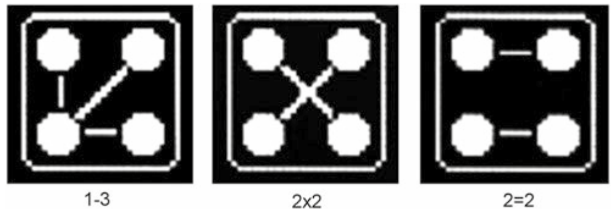

FIG. 1. The three electrode configuration options in the tested device: (1) 1–3, one transmitter electrode and three receiver electrodes; (2) 2×2, two transmitter electrodes and two receiver electrodes in a cross fashion; (3) 2=2, two transmitter electrodes and two receiver electrodes in a parallel fashion.

- 2=2: two transmitter electrodes and two receiver electrodes in a parallel fashion

The single electrode configuration is allowed to swap over at a time interval adjustable between 1 and 9 sec.

The maximum device working power is 55 W adjustable within a 5–100% delivery range. The device is equipped with an original patented safety technology, Radiofrequency Safety System (RSS™), and has been developed for noninvasive treatment of skin wrinkles and cellulite and for skin tightening.

The study was performed in two steps: *ex vivo* and *in vivo* assessments.

Ex vivo assessment

The ex vivo assessment was conducted on eight human anatomical specimens, including full thickness skin and subcutaneous tissue harvested from four female patients during sessions of abdominoplasty. The specimens underwent the experimental process after surgical harvesting, and the average time delay between harvesting the tissue and starting the experiment was 10 min. The tests were conducted in a dedicated air conditioned room at a temperature of 23°C. A control biopsy, including full thickness skin and adipose tissue, was harvested from each specimen before treatment.

FIG. 2. *Ex vivo* radiofrequency application with the device's probe.

FIG. 3. Areas of abdominal fat that were investigated on the two patients scheduled for abdominoplasty.

The effects of RFs on the specimens were assessed with the association of three different methods:

- Clinical full examination and medical photography
- Temperature measurement in the specimens before and after the treatments with thermal imaging scan using the AVIO Thermal Video System TVS 500 camera with an uncooled infrared sensor with a 8–14 μm spectrum sensitivity, 320×240 pixel thermal image resolution, and 0.1°C thermal resolution (Nippon Avionics Co., Ltd. Gotanda Kowa Bldg., 1–5, Nishi-Gotanda 8-chome, Shinagawa-ku, Tokyo, 141-0031 Japan).
- Histological examination at light microscopy. Tissue samples were fixed in a 4% paraformaldehyde solution in phosphate buffer for 6 h, cryoprotected by immersion in sucrose saturated solution, frozen in liquid nitrogen, and finally cut in a cryostat. Finally, tissue sections were routinely stained using hematoxylin and eosin.

A water gel was applied on the skin surface in order to allow an optimal delivery of the RFs from the probe to the tissues (Fig. 2). The gel was stored at room temperature (23°C).

The study was performed using the 1–3 electrode configuration modality, Radio Frequency System (RFS) 1–3, and the configuration swap over time (RFS time) was set at 5 sec.

The eight specimens were divided into four groups of two and the RF was delivered to each group at the following percentages of the maximum device working power: 25% (13.75 W), 50% (27.50 W), 75% (41.25 W), and 100% (55 W). The energy was delivered in continuous mode (duty cycle 100%, time on = 1.000 msec, time off = 0 msec). The scheduled maximum application time was 4 min. As the specimens treated with the maximum device working power displayed clinical evidence of full thickness burn after few seconds, the applications in this group were discontinued at this time.

At the end of the application, a full thickness skin and subcutaneous tissue biopsy was harvested in each specimen from the site of maximum tissue warming, as displayed by the thermocamera scan.

In vivo assessment

The *in vivo* investigations were conducted on two volunteer female patients scheduled for abdominoplasty at the end of the experimental study (Fig. 3). The assessments were performed on the lower abdominal skin area bounded above by the umbilicus, below by the pubis, and on each side by the anterior superior iliac spine. The applications were performed in the same dedicated air conditioned room at a temperature of 23°C, as in the *ex vivo* tests.

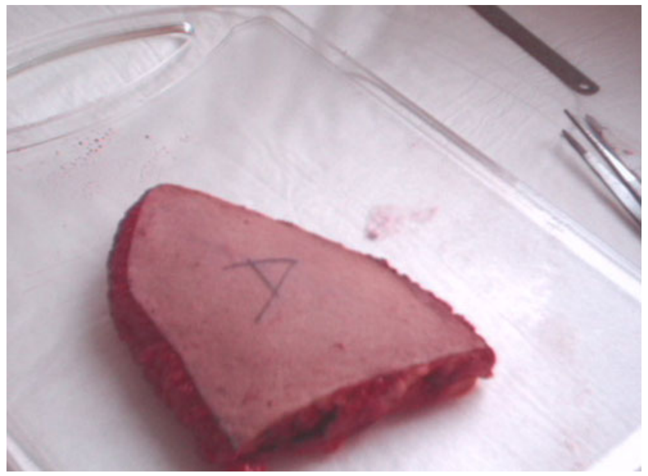

FIG. 4. Human *ex vivo* specimen before treatment: macroscopic view.

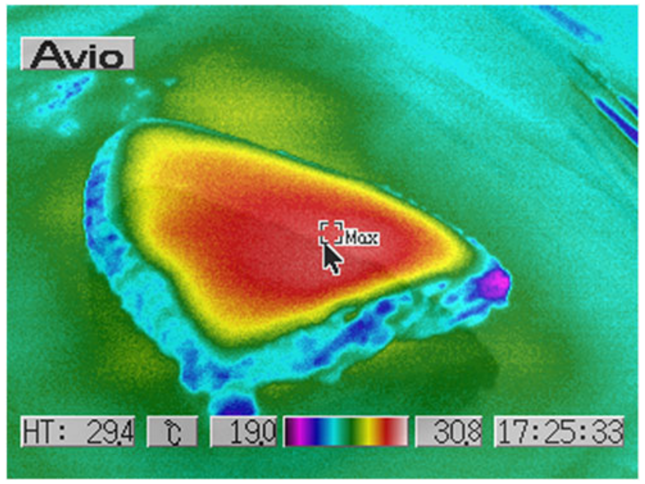

FIG. 5. Human *ex vivo* specimen before treatment: thermal imaging scan.

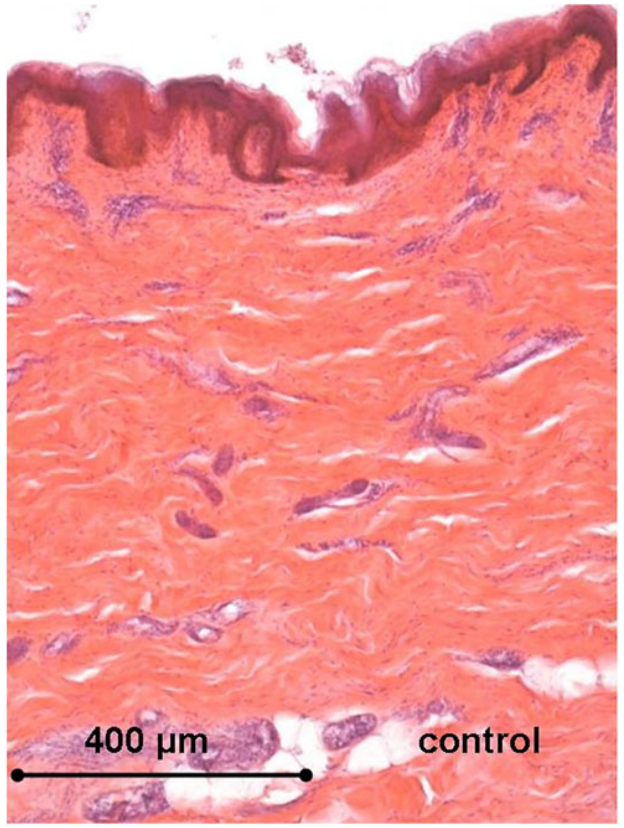

FIG. 6. Histology of the human *ex vivo* specimen before treatment: the epidermis displays a regular multilayered structure, the dermis shows regular dermal papillae with thin collagen fibers and thick collagen bundles in the reticular dermis. Light microscopy, hematoxylin and eosin staining, bar 400 μm.

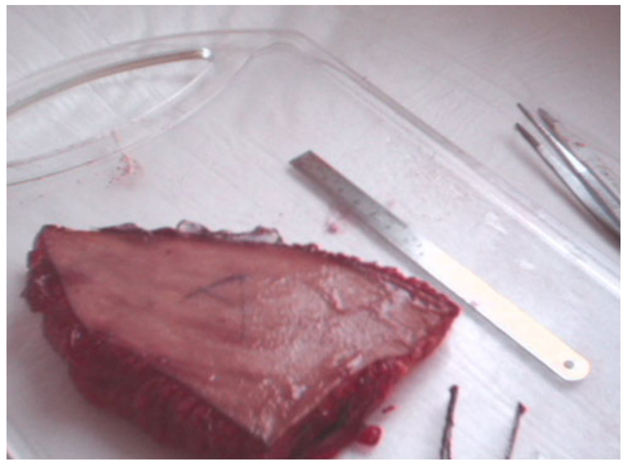

FIG. 7. Human *ex vivo* specimen after treatment with 25% of the maximum device working power (13.75 W): macroscopic view.

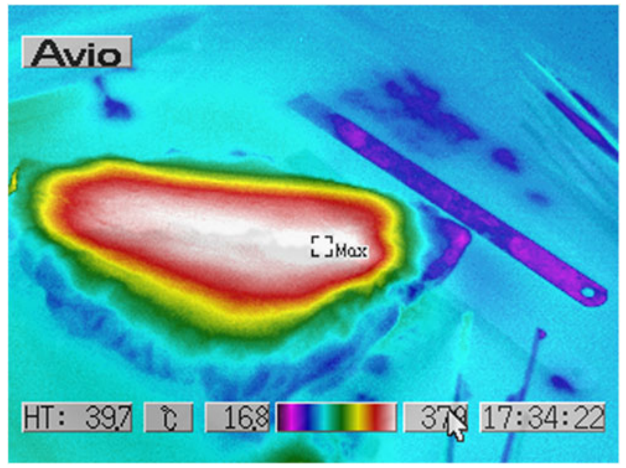

FIG. 8. Human *ex vivo* specimen after treatment with 25% of the maximum device working power (13.75 W): thermal imaging scan.

A control biopsy, including full thickness skin and adipose tissue, was harvested before the treatment. Three sequential treatments were performed with 2 weeks' interval. A water gel was applied on the skin surface in order to allow an optimal RF energy delivery from the probe to the tissues.

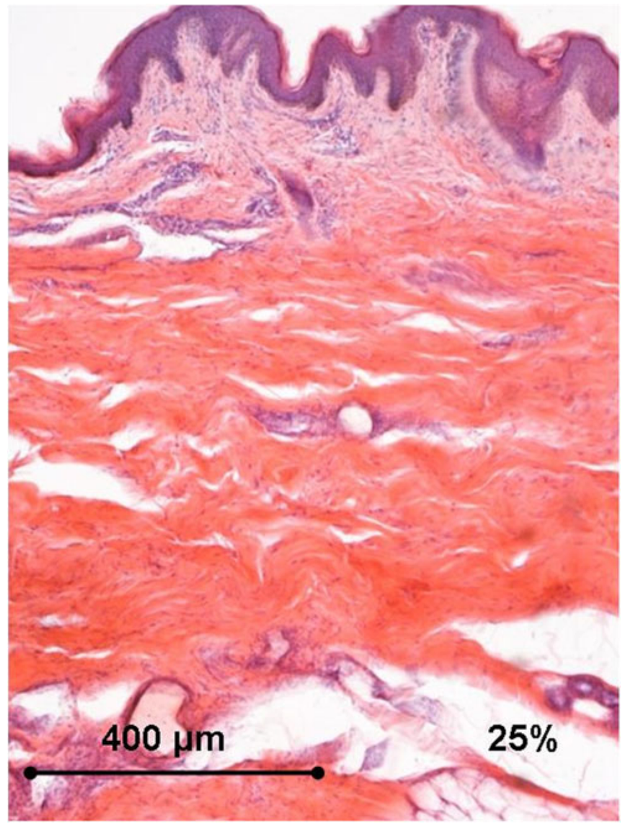

FIG. 9. Histology of the human *ex vivo* specimen after treatment with 25% of the maximum device working power (13.75 W): complete sparing of the epidermis that displays normal structure; an early thickening of the collagen bundles is appreciated in the deep dermal layers. Light microscopy, hematoxylin and eosin staining, bar 400 μm.

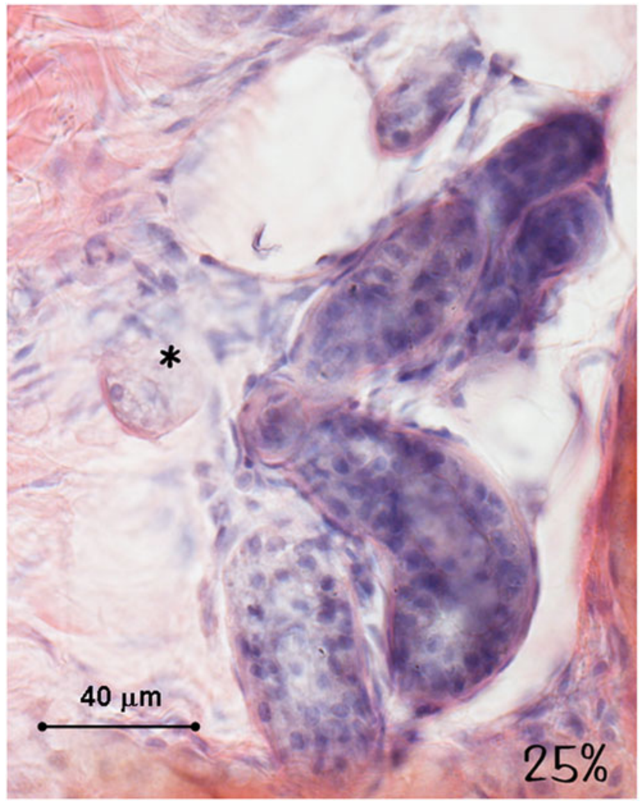

FIG. 10. Histology of the human *ex vivo* specimen after treatment with 25% of the maximum device working power (13.75 W): the sweat glands and the nerves (asterisk) display a normal structure and a regular staining. Light microscopy, hematoxylin and eosin staining, bar 40 μm.

The applied parameters were the same as in the *ex vivo* section of the study: RFS 1–3, duty cycle 100%, RFS time 5 sec.

Three sequential treatments were scheduled with 2 weeks' interval. Each treatment lasted 20 min.

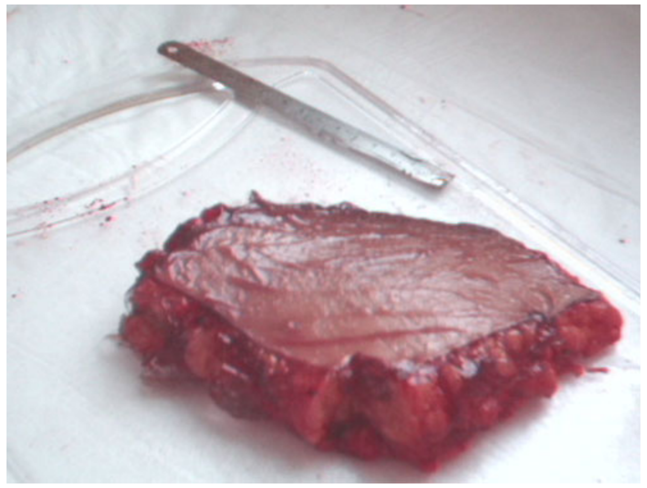

FIG. 11. Human *ex vivo* specimen after treatment with 50% of the maximum device working power (27.50 W): macroscopic view.

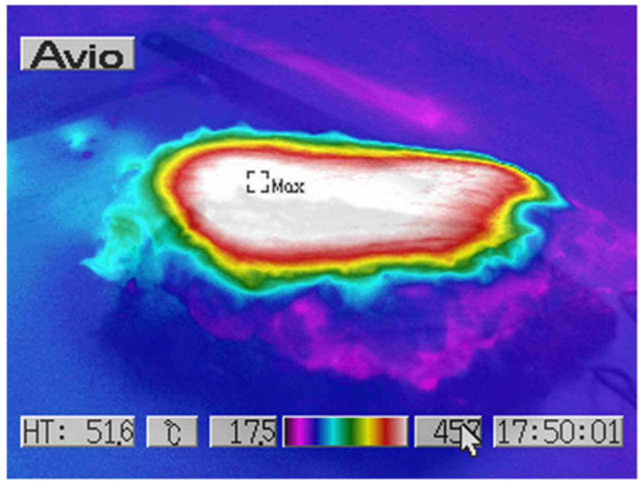

FIG. 12. Human *ex vivo* specimen after treatment with 50% of the maximum device working power (27.50 W): thermal imaging scan.

The initial working power was 45% (24.75 W); however, following a patient's consistent subjectively perceived discomfort, the energy delivery power was reduced to 35–40% (19.25–22 W) in all of the tests, and this level was comfortably tolerated. On occasion of the second treatment in

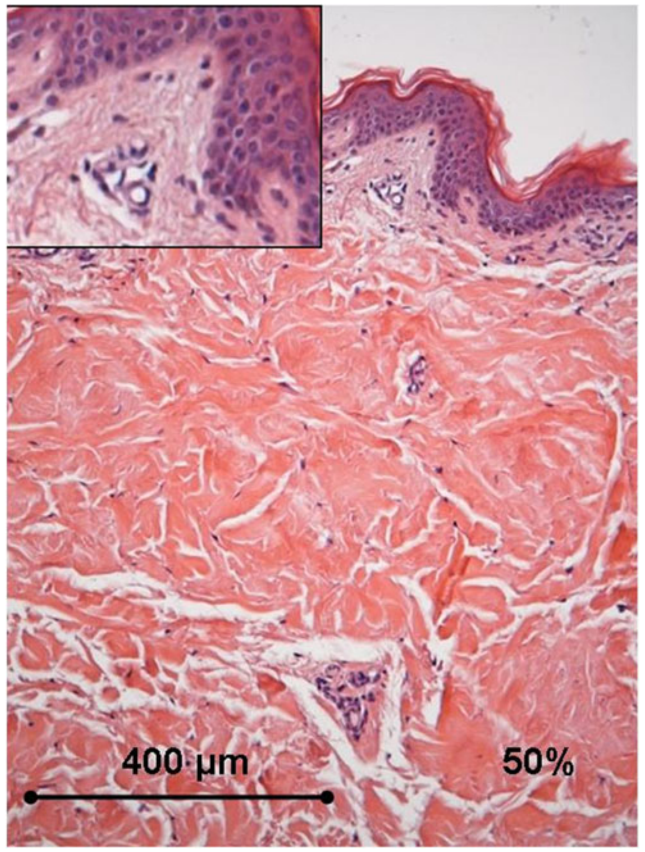

FIG. 13. Histology of the human *ex vivo* specimen after treatment with 50% of the maximum device working power (27.50 W): the thickening of the collagen fibers in the papillary dermis is appreciated, whereas the blood vessels in the dermal papillae do not display any alteration (box). Light microscopy, hematoxylin and eosin staining, bar 400 μm.

FIG. 14. Histology of the human *ex vivo* specimen after treatment with 50% of the maximum device working power (27.50 W): the sweat glands and the nerves (asterisk) display a normal structure and a regular staining. Light microscopy, hematoxylin and eosin staining, bar 40 μm.

one patient, the energy delivery power had to be reduced to 20% (11 W) in the last 8 min of application, because of severe subjective discomfort.

The effects of the RF applications on the patient were assessed with the same methods used in the *ex vivo* assessment: clinical examination, thermocamera scan, and histological examination of treated tissue biopsies. Three punch full thickness skin and subcutaneous tissue biopsies were harvested from each treated area. The first biopsy was harvested 2 weeks after the first treatment, the second one 2

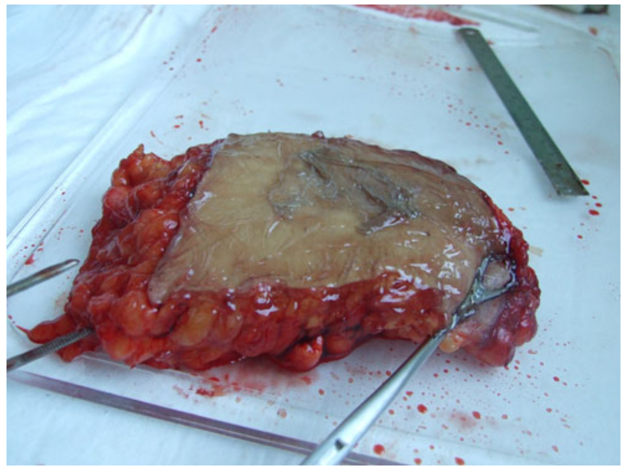

FIG. 15. Human *ex vivo* specimen after treatment with 75% of the maximum device working power (41.25 W): macroscopic view.

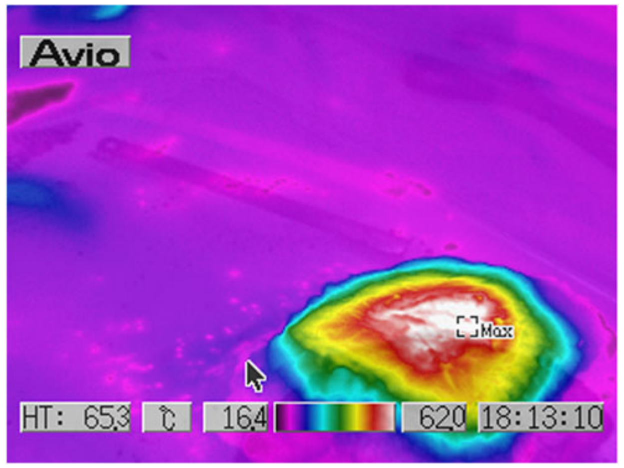

FIG. 16. Human *ex vivo* specimen after treatment with 75% of the maximum device working power (41.25 W): thermal imaging scan.

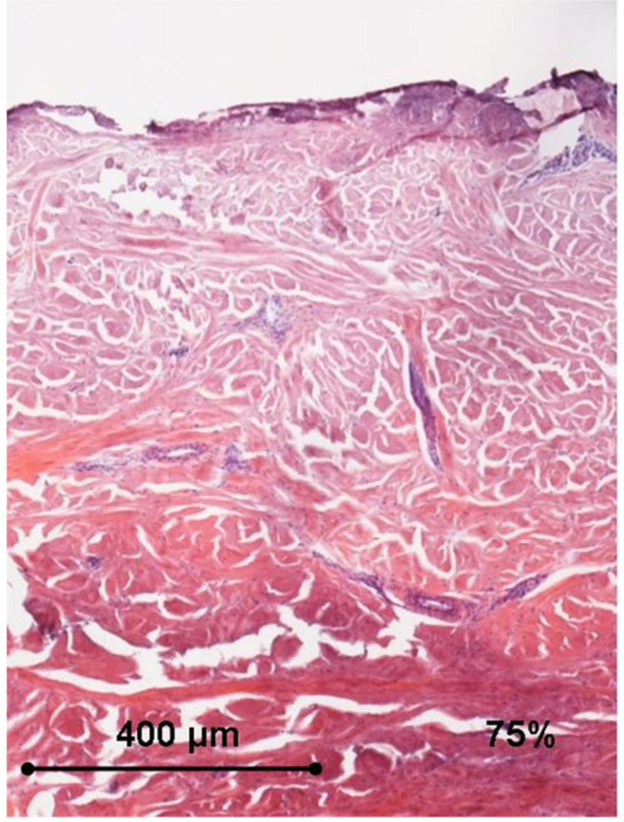

FIG. 17. Histology of the human *ex vivo* specimen after treatment with 75% of the maximum device working power (41.25 W): the epidermis is necrotic, and the collagen bundles display a remarkable diffuse thickening in the whole dermis. Light microscopy, hematoxylin and eosin staining, bar 400 μm.

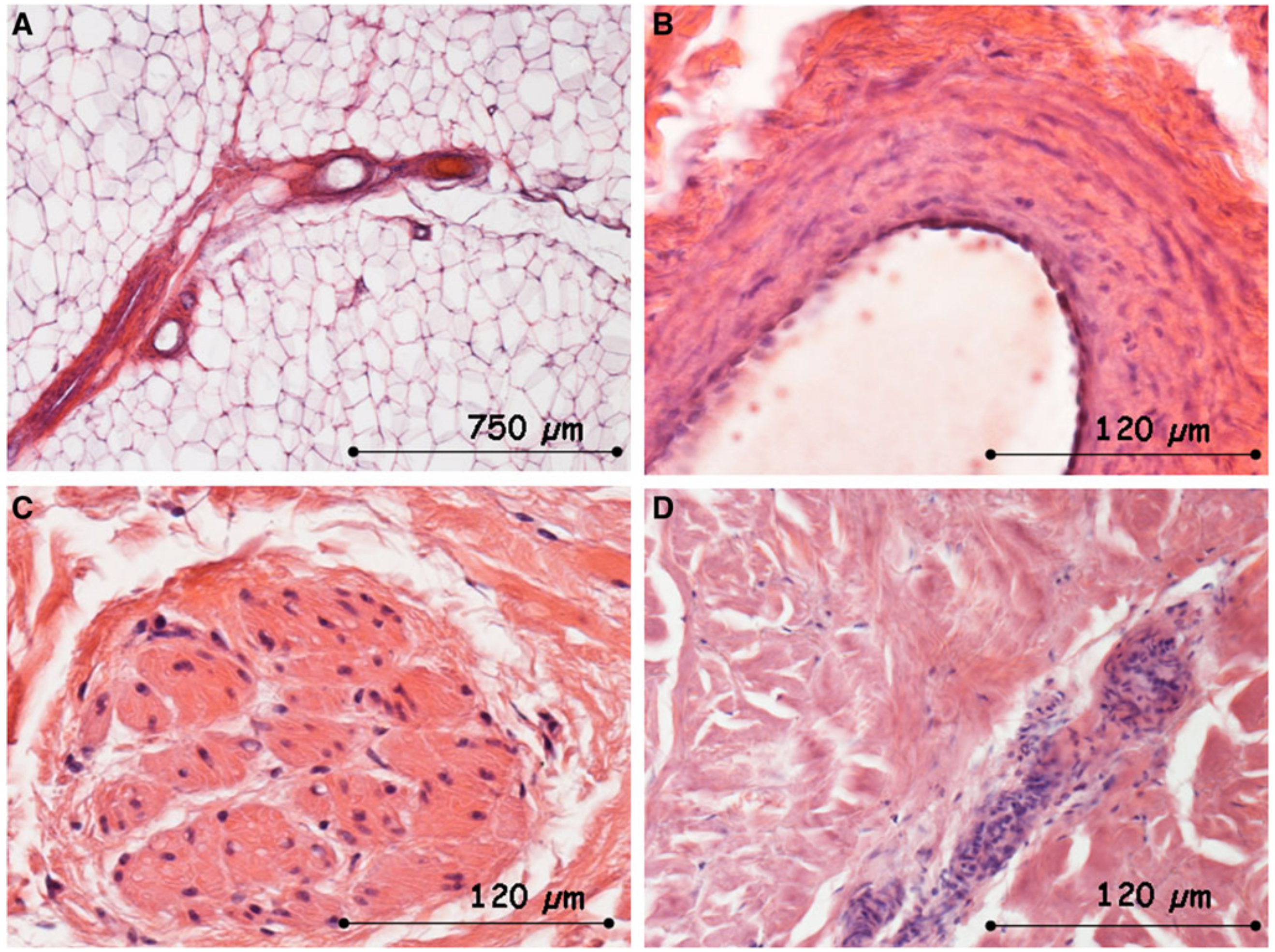

FIG. 18. Histology of the human *ex vivo* specimen after treatment with 75% of the maximum device working power (41.25 W): the subcutaneous tissue (**A**, bar 750 μm), the vascular wall with its endothelial lining (**B**, bar 120 μm), the nerves (**C**, bar 120 μm), and the sweat glands (**D**, bar 120 μm) appear intact. Light microscopy, hematoxylin and eosin staining.

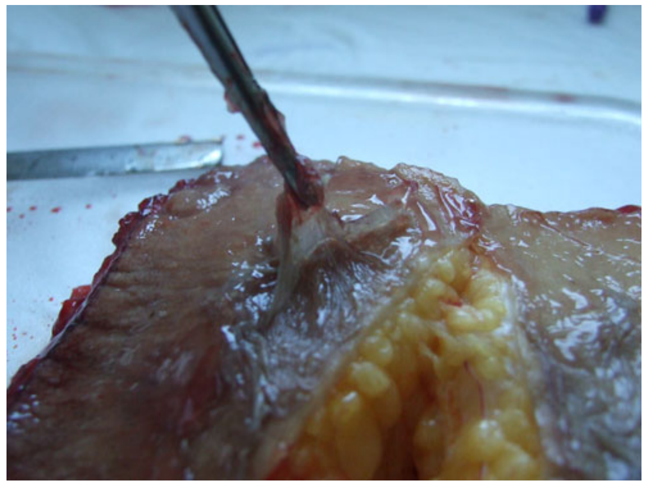

FIG. 19. Human *ex vivo* specimen after treatment with 100% of the maximum device working power (55 W): macroscopic view; after a few seconds of application, the epidermis displays separation from the dermis, and the subcutaneous tissue shows coagulative necrosis in the superficial layer while it appears intact in the deep layer.

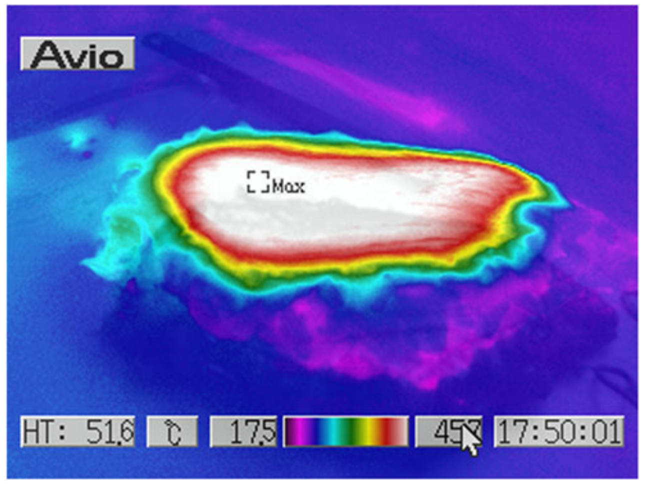

FIG. 20. Human *ex vivo* specimen after treatment with 100% of the maximum device working power (55 W): thermal imaging scan.

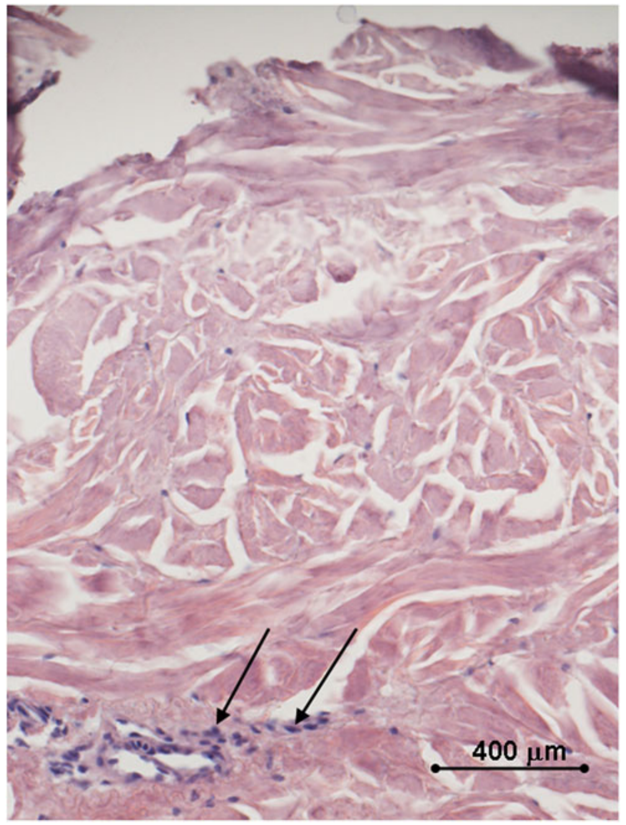

FIG. 21. Histology of the human *ex vivo* specimen after treatment with 100% of the maximum device working power (55 W): a complete loss of the epidermal lining and a massive coagulative dermal necrosis are appreciated; the sweat glands display early signs of necrosis (arrows). Light microscopy, hematoxylin and eosin staining, bar 400 μm.

weeks after the second treatment, and the third one 10 weeks after the last treatment.

Results

Ex vivo assessment (Figs. 4–21)

Clinical examination. At the end of the application, the specimen treated with 25% of the maximum working power did not display any macroscopic skin surface alterations, although the subcutaneous tissue was softer at palpation and displayed some degree of shrinkage.

The specimen treated with 50% of the maximum working power showed a significant wizening of the subcutaneous tissue after 90 sec, whereas the skin showed a remarkable retraction and separation from the subcutaneous tissue in 3 min; after 4 min, the overall appearance was as a deep skin and subcutaneous tissue burn.

The specimen treated with 75% of the maximum working power displayed a total skin retraction and separation from the subcutaneous tissue after 90 sec, with coagulative necrosis of the subcutaneous fat.

The specimen treated with full working power displayed a full thickness burn appearance in a few seconds.

Temperature report. The energy application was followed by an increase of the specimen temperature proportional to the application power and time, with a gradient decreasing from the surface to the subcutaneous adipose tissue (Table 1).

Histological examination. All of the specimens displayed scattering of the collagen bundles that was appreciated from the papillary dermis up to 1.5 cm in depth. Such an alteration was proportional to both time and energy power application. The epithelial superficial lining appeared intact up to the application of 50% of the maximum working power. The subcutaneous tissue, the nerves, and the skin glands appeared intact up to the application of 75% of the maximum working power.

In vivo assessment

Clinical examination. The treatments were well tolerated, and the patients occasionally referred to tolerable local heat sensation, burning pain, and electric shock sensation. At the end of the treatments, no skin lesions were appreciated. After two applications, the patients referred to improved local skin softness and smoothness.

Temperature report. The energy application was constantly followed by an increase of the skin surface temperature (Table 2, Fig. 22).

Histological examination (Figs. 23–29). The *in vivo* findings 2 weeks after the first treatment closely resemble those in the *ex vivo* specimens: the collagen bundles appeared diffusely scattered whereas the epithelial superficial lining, the subcutaneous tissue, the nerves, and the skin glands appeared intact.

Two weeks after the second application, the collagen bundles appeared coagulated in small grumes in the papillary dermis and in larger grumes in the underlying reticular dermis. The epidermis appeared normal. The overall connective cell count and general pattern did not differ from the

TABLE 1. AVERAGE *EX VIVO* SPECIMEN TEMPERATURE VALUES MEASURED AT DIFFERENT WORKING POWER APPLICATIONS

	T pre	*T post 4' 25%*	*T post 4' 50%*	*T post 4' 75%*	*T post 45'' 100%*
Skin surface	25.8°	37°Δ + 11.2°	47.7°Δ + 21.9°	55 Δ + 29.2°	60 Δ + 34.2°
Subcutaneous adipose tissue	27.5°	28.8°Δ + 1.3°	27.5°Δ 0	27.2 Δ − 0.3°	27 Δ − 0.5°

T, temperature in degrees Celsius; Δ, average temperature delta between pre- and post-treatment; ', minutes; '', seconds.

Table 2. Average Skin Surface Temperature Values Measured at the End of the *In Vivo* Treatment

	T pre	*T post*	Δ
Skin surface	29.6°	38.2°	+8.6°

T, temperature in degrees Celsius; Δ, average temperature delta between pre- and post-treatment.

control areas. A remarkable thickening in the elastic fibers with a regular reticular pattern and a definite orientation perpendicular to the basal membrane in the papillary dermis was appreciated in the treated areas versus the controls.

Ten weeks after the third application, the macrophages had moved from the perivascular niche and displayed a slight increase in their count, thus suggesting some sort of functional activation. Such a finding suggests the presence of coagulated collagen fragments and/or other tissue debris.

Discussion

The device used in our study is one of the innovative multipolar developments of the bipolar technology.[8]

As any technical innovation should undergo a rigorous assessment of both safety and effectiveness prior to clinical use, our study provided a prudent design with two different and sequential steps.

The *ex vivo* experimental assessments allowed for identification of the effective safety range for human application, which was established between 11 and 22 W.

We deliberately opted for a random choice of only one electrode configuration out of three potentially available in the device setting, as the rigorous compliance requirements substantially limited the number of patients recruited for the study.

As expected, the biological effects of RF application were related to the thermal energy transfer to the tissues, and were proportional to both local temperature and exposure time.[9] All of the possible typical macro- and microscopic tissue

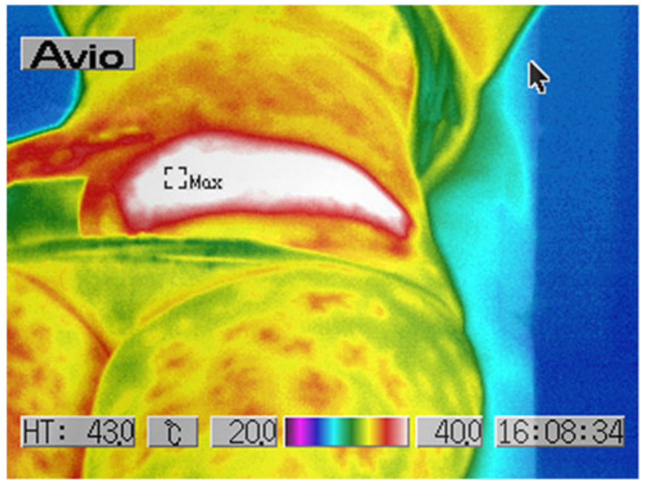

FIG. 22. Thermal imaging scan of the lower abdominal region after the *in vivo* treatment.

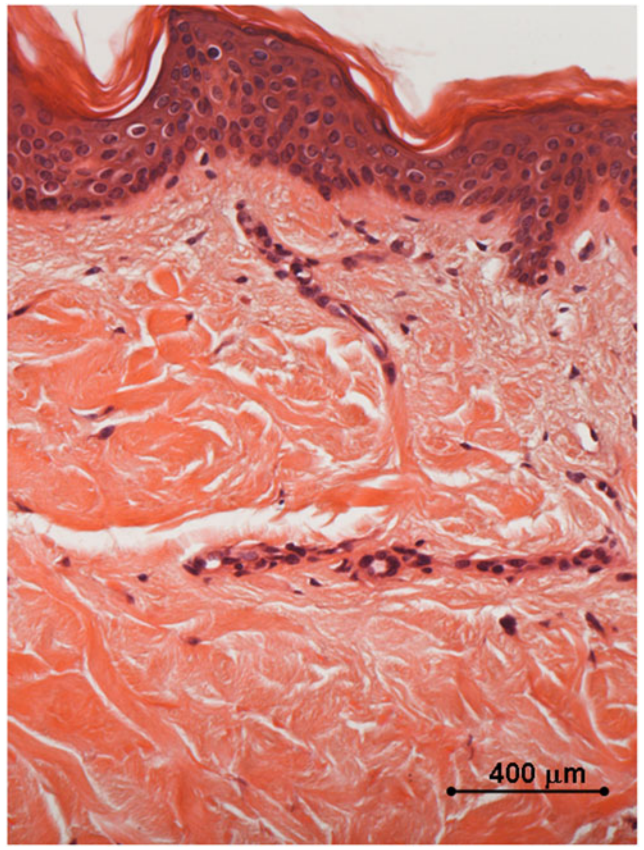

FIG. 23. Histology of *in vivo* control biopsy: the collagen fibers appear thin and outstretched. Light microscopy, hematoxylin and eosin staining, bar 400 μm.

burn features were observed in the *ex vivo* samples in relation to the different levels of applied energy. However, these effects were mainly appreciated in the dermis and subcutaneous tissue, with involvement of the overlying epidermis only for the highest applied energy levels. Such a figure is a peculiar advantage of RF technology that allows selective heat transfer to the dermis and subcutaneous tissue, yielding a controlled collagen alteration.

After accurate definition of the effective safety range of RF applications on human tissues, the trial proceeded with the *in vivo* assessments.

These tests allowed for demonstration of the biological effects of the device under study at different time intervals.

The temperature changes reported in the *ex vivo* samples were partially compensated *in vivo* by the active thermoregulation and the local temperature increase was proportional to the application time.

A selective effect was appreciated in the more dense and compact tissues, as the dermis and the connective septa of the adipose tissue. The temperature reports and the histological examinations, both *ex vivo* and *in vivo*, consistently demonstrated selective scattering of the collagen bundles in the dermis. The small grumes observed in the reticular dermis of the *in vivo* samples 2 weeks after the second application might have followed local increase of RF current density in sites of enhanced electric conductivity with eventual focal temperature rise.

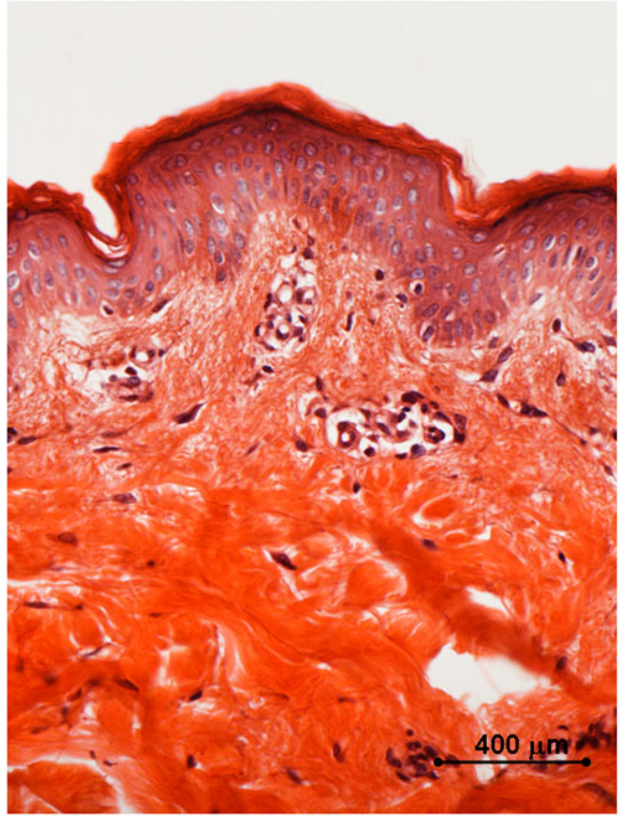

FIG. 24. Histology of *in vivo* sample harvested 2 weeks after the first treatment with 35–40% of the full device working power: early signs of coagulations are appreciated both in the papillary and in the reticular dermis. Light microscopy, hematoxylin and eosin staining, bar 400 μm.

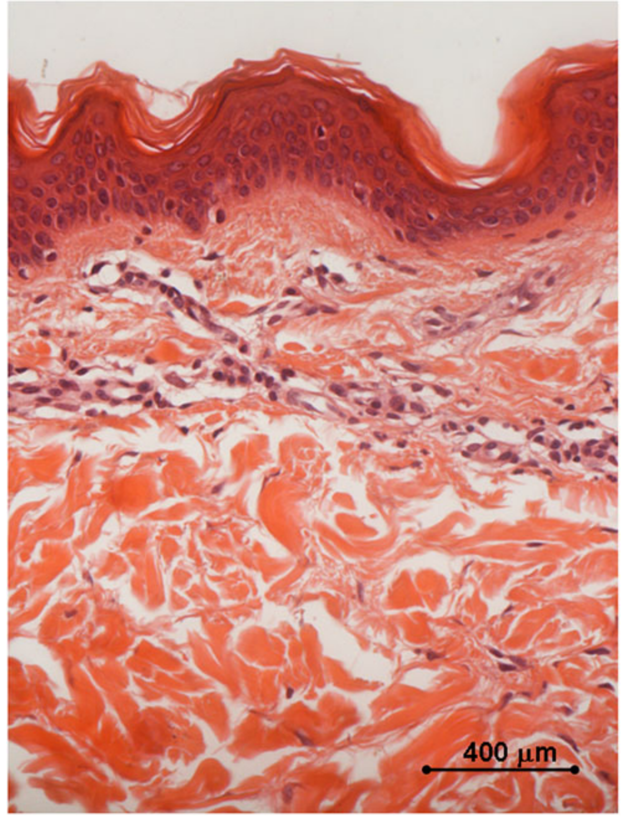

FIG. 25. Histology of *in vivo* sample harvested after two treatments with 35–40% of the full device working power, 1 month after the first treatment: the collagen fibers are coagulated in small grumes in the papillary dermis and in larger ones in the underlying layers; the epidermal lining is intact. Light microscopy, hematoxylin and eosin staining, bar 400 μm.

It is demonstrated that collagen fibers begin to curve at 52–55°C[10] and contract at 65°C,[11] and the denaturation threshold falls between 60° and 70°C.[12] According to the thermal imaging scan in our *ex vivo* and *in vivo* samples, such a temperature threshold was unlikely to have been approached, although it may be theoretically supposed that it occurred in very small and circumscribed tissue spots. We can, therefore, suppose that the observed structural changes of the collagen fibers were not related exclusively to the temperature rise.

The overall effects of the sequential *in vivo* RF applications observed on the connective fibers, both collagen and elastic, might suggest their spatial rearrangement in the absence of complete denaturation: actually, no signs of scarring were observed under the microscope in any of our samples. As the collagen and elastic fibers are highly hydrophobic and are invested by a highly electric conductive water rich matrix, they obviously tend to gather when the temperature in the investing highly hydrophilic matrix rises.

Some interesting changes were observed in the skin elastic fiber network after two sequential applications with 2 weeks' interval 1 month after the first treatment: the elastic fibers appeared thicker both in the papillary and the reticular dermis; however, although thick elastic fibers are a typical feature of skin photo- and chrono-ageing, in our samples their regular network pattern was found more similar to the juvenile one.

Such an interesting figure might also be explained by the shrinkage of the highly hydrophobic elastic fibers with exclusive physical mechanism after increase of the energetic potential in the local water rich environment. These data are consistent with the literature,[13] and are in favor of the bipolar technology, as the elastic fibers seem to significantly decrease after monopolar treatment. [2] The epidermis did not display any significant damage apart from a transient erythema at the end of the *in vivo* treatments.

Adipose tissue, endothelial cells, nerves, and skin adnexa appeared intact with power application up to 41.25 W (Figs. 10, 14, and 18). Such an evidence was consistent with the peculiar temperature gradient figure between the skin surface and the underlying adipose tissue where relevant temperature changes in the dermis were not transmitted to the underlying fat.

These data both confirmed the low thermal conductivity of the human skin and demonstrated the selective superficial distribution of the electromagnetic energy within the treated tissues.

The *in vivo* effects of the RF application included a slight macrophage activation after three sequential applications

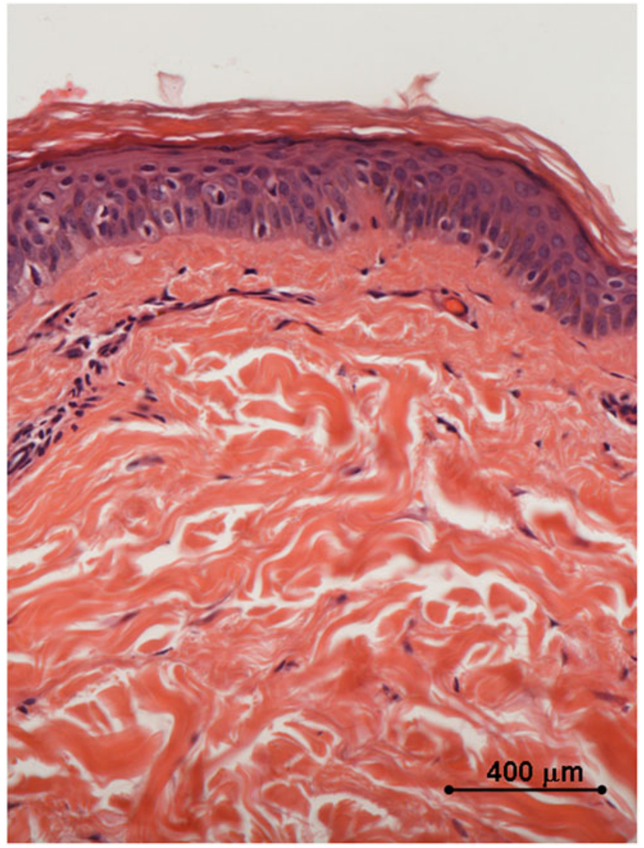

FIG. 26. Histology of *in vivo* sample harvested 10 weeks after the third treatment with 35–40% of the full device working power: the epidermis displays a normal differentiation and layer organization; a remarkable degree of collagen coagulation is appreciated in the papillary dermis, and the collagen bundles in the reticular dermis display a significant thickening as well. Light microscopy, hematoxylin and eosin staining, bar 400 μm.

with 2 weeks' interval, and might suggest the presence of tissue debris and/or coagulated collagen still being metabolized.

Nevertheless, no actual inflammatory cells or fibroblast response was appreciated.

However, a significant cellular response might be expected after further sequential applications, as suggested by the clinical protocols currently in use. The sequential application of RF for the treatment of skin wrinkling would definitely appear as a far different philosophy from the traditional surgical face and body lifting, as it would rely on a progressively induced and gently modulated body biological response. RF might, therefore, be considered an effective alternative for mild cases of skin laxity, and a useful completion of traditional surgical techniques.

Conclusions

The tested quadripolar variable electrode configuration RF equipment can provide selective and favorable changes in the dermal structure without side effects in the epidermis, vessels, and nerves when the energy delivery power ranges between 11 and 22 W.

After a course of RF application, the native collagen fibers underwent an immediate heat- induced rearrangement, and were just partially denaturated and progressively metabolized by the macrophages. Subsequently, an overall thickening and spatial rearrangement was appreciated both in the collagen and in the elastic fibers, the latter displaying a juvenile skin reticular pattern.

Our data demonstrated a late onset in the macrophage activation after sequential RF applications. It might be supposed that such a recruitment might be followed by a fibroblastic response at a later stage,[5] although such a hypothesis would suggest further investigations.

All of our data confirm the effectiveness of the RF applications in obtaining attenuation of the skin wrinkles by an overall skin tightening.

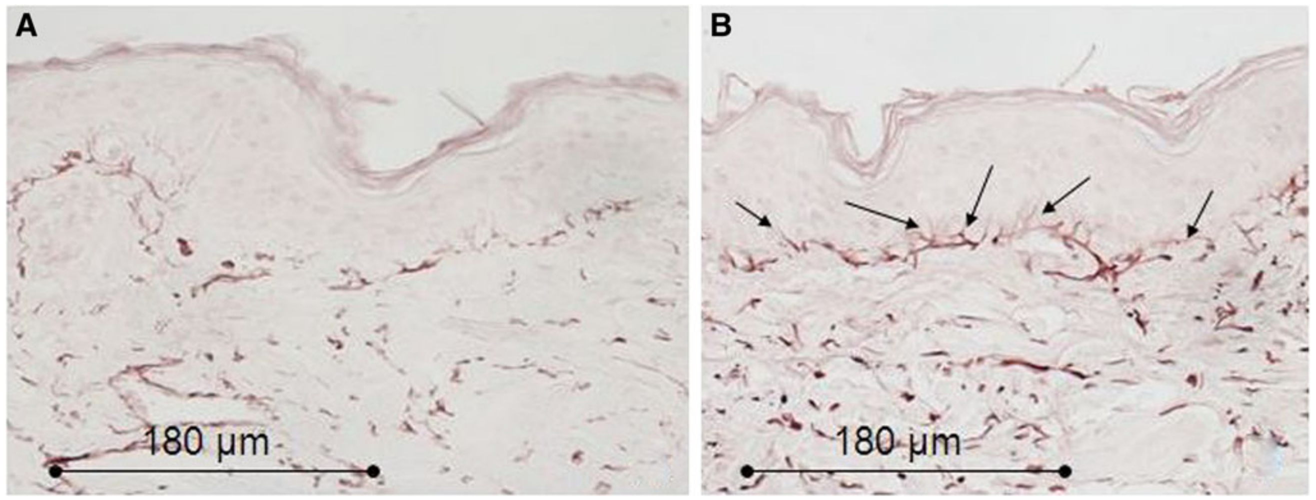

FIG. 27. Histology for elastic fibers of *in vivo* biopsies. **(A)** Control sample: the elastic fibers (purple-brown) show a regular distribution throughout the whole dermis. **(B)** Sample harvested after two treatments with 35–40% of the full device working power 1 month after the first treatment: the elastic fibers show a significant thickening throughout the whole dermis; in the papillary dermis the elastic fibers show a more definite perpendicular orientation to the basal membrane (arrows). Light microscopy, orcein staining, bar 180 μm.

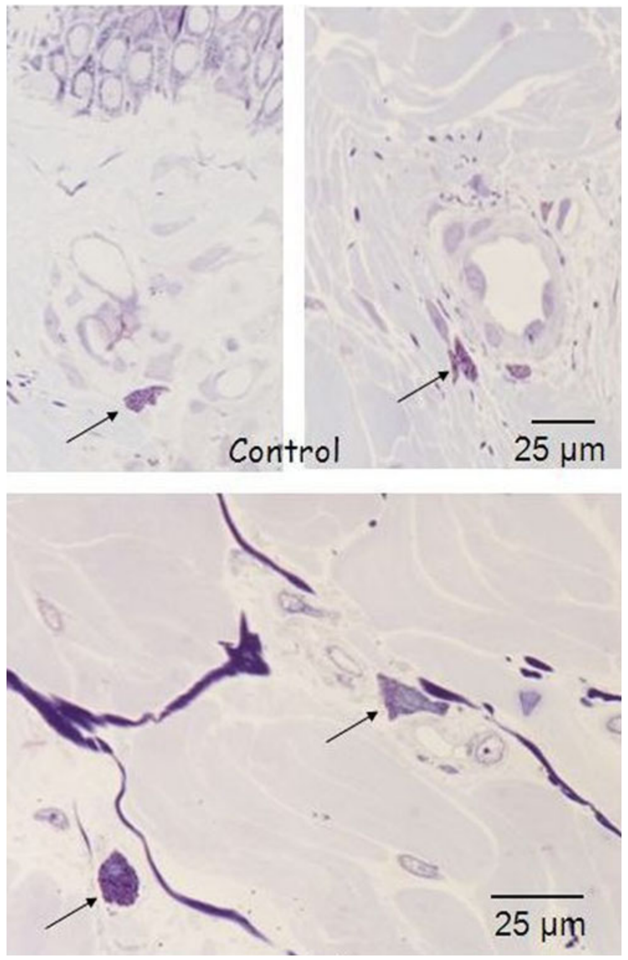

FIG. 28. Histology for macrophages of *in vivo* control biopsy: the arrows highlight the macrophages in quiescent status around the vessels. Light microscopy, toluidine blue staining, bar 25 μm.

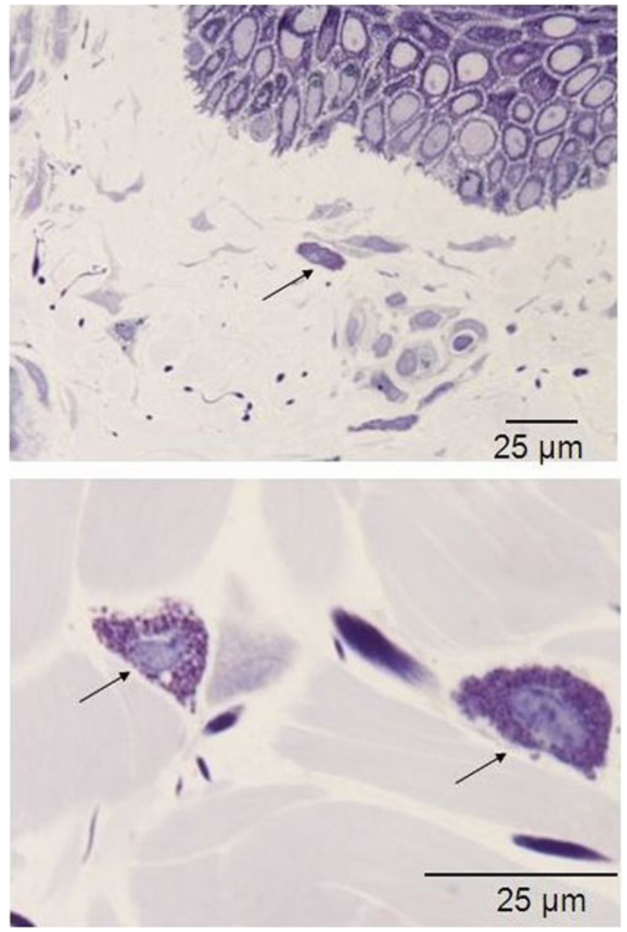

FIG. 29. Histology for macrophages of *in vivo* biopsy harvested after three treatments with 35–40% of the full device working power: the arrows highlight the macrophages that have moved from the perivascular niche, and display a slight increase in their count, thus suggesting an active status. Light microscopy, toluidine blue staining, bar 25 μm.

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Author Disclosure Statement

No competing financial interests exist.

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The Efficacy of Fractional Co2 Laser in Treatment of Post Acne Scars

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Abstract

One of the most common dermatological diseases is acne. Acne scars and pigmentation may have a dramatic psychological effect on people who suffer from severe breakouts. Laser, radiofrequency, chemical, surgical, microneedling, fillers, and/or fat injections are all current therapeutic methods. With less reported downtime than lasers or chemical peels, fractional radiofrequency-based treatments have lately been utilised to reduce acne scars with less risk of scarring or hyperpigmentation. Fractional Co2 Laser therapy of acne scars is the focus of this study. There were 15 individuals with post-acne scars who participated in this research. Fractional Co2 Laser was used on the right side of the patients. They had three monthly sessions of treatment. The sessions were completed in all instances. The mean pain score for the first session of fractional CO2 laser treatment was 60. Within two sessions, it dropped to 57.3 and then to 52.7, indicating a substantial reduction in discomfort with time (p=0.039). Mean improvement scores increased significantly over time (p0.001), according to the findings of this investigation. It was shown that there was a significant difference in the improvement grades across sessions when the improvement score was stratified into grades of moderate and outstanding. Erythema (100 percent) and edoema (20 percent) were the most common side effects of fractional CO2 laser treatment. There aren't any hyperpigmentation or scars to be seen here. Conclusion: Fractional Co2 improved the patient's score greatly, but it was also related with more severe pain and more erythema than usual.

Key words: Fractional Co2 Laser, Treatment, Post Acne Scars.

1. Introduction

Dermatologists encounter a lot of patients with acne, which is one of the most common skin problems. Acne scars and pigmentation may have a dramatic psychological effect on people who suffer from severe breakouts. Laser, radiofrequency, chemical, surgical, microneedling, fillers, and/or fat injections are all current therapeutic methods. More recently, fractional radiofrequency-based treatments have been utilised to relieve acne scars with less reported downtime than lasers or chemical peels and the capacity to treat darker or sensitive skin types with less risk of scarring or hyperpigmentation and [1].

It was established by Manstein and colleagues in 2004 as a way to bridge the gap between ablative and nonablative laser treatments, which are both effective. Resurfacing with fractional resurfacing uses a matrix of energy beams to create an array of small thermal wounds (microscopic treatment zones) in the dermis to induce a therapeutic response in the skin [2]. Tissue ablation induced by a brief, high-energy exposure is quick enough to minimise extracutaneous skin damage. Injuries caused by lasers may be quickly repaired because to the reservoir of skin that is saved [3]. Fractional resurfacing, although not as effective as complete ablative laser skin resurfacing, has fast become more popular than the latter due to the reduced side effects, dangers, and downtime of treatment, as well as the acceptable improvement in appearance [4].

Radiofrequency (RF) has seen a substantial rise in popularity in the last several years. It is possible to simulate skin regeneration processes with the application of high-frequency current, which causes oscillating migration of ions and causes an increase in temperature [5]. Their low risk of consequences and relatively high efficacy, their applicability for the face and body, painlessness, and the ability to conduct them at any time of the year and on any skin phototype are some of the features of these procedures [6].

Fractional Co2 Laser therapy of acne scars is the focus of this study.

2.Patients and Methods

This was an observational study conducted from August 2021 to November 2021. This study was carried out on 15 patients with Fitzpatrick skin types III-IV aged between 18-50 years who were presented with mild-to-severe atrophic facial acne scars. Their mean age was 30.5 years (± SD). They were 5 males (33.3%) and 10 females (66.7%). All patients were informed about the nature of the procedure and were requested to sign a written informed consent that was approved by the Ethics Committee of Human Research, Benha University. They were treated with fractional co2 on the right side and 4 plus on the left side at one month interval for 3 sessions.

2.1. Inclusion criteria:

Male or female patients with age 18-50 years, with post acne scars and skin type III-IV.

2.2. Exclusion criteria:

All patients presenting with any of the following conditions were excluded from the study:

- Previous treatment with oral retiniods within six months prior to study.
- Previous treatment of face with ablative laser.
- Hypertrophic scars or keloids.
- Pregnancy or breastfeeding.
- Photosensitivity.

Included patients underwent a detailed history and full clinical examination to determine the affected sites, Fitzpatrick skin type, and type of acne scar as proposed by **Jacob *et al.*** [7] (Table 1).Severity of acne scar was

assessed using qualitative scarring grading system, which was developed by **Goodman and Baron's** [8] qualitative global acne scarring grading system, 2006a in (Table 2).Those with mild-to-severe atrophic facial acne scars are included in this study.

The patients informed to stop topical creams one week before the session and to stop any cosmetic in between the sessions. Patients were explained about the outcome, side effects, and complications of the procedure. Before any procedure, the treatment area was cleansed of sebum and debris (including dirt, makeup, and powder) using a mild cleanser and 70% alcohol. A thick layer of anesthetic cream (Pridocaine) was then applied to the treatment site for 1 hour prior under occlusion. Before starting the procedure, the cream was removed with dry gauze and the treatment site was once more cleaned with an antiseptic solution. Both the patients and the operators wore safety goggles during the laser session. At each visit the severity of acne scars, patient satisfaction scores, visual analyze scores and side effects were assessed.

BX 300 is the fractional CO2 laser device used in this study. This fractional laser delivers a fine laser beam to minimize the damage done to the skin by heat and to shorten the recovery period this laser beam vaporizes the epidermis and part of the dermis promoting collagen contraction via its thermal effects, thereby inducing skin remodeling. D**i**fferent settings were used according to each individual case regarding the type of scar, severity and skin type fluence ranging from 36 to42 j/cm2 was used and pulse duration 1.8 ms . In an attempt to avoid common side effects that occur with fractional laser treatment, a lower fluence was used in the first session and depending on the results, the fluence was increased per treatment session.

4 PLUS ITALY is the quadripolar radiofrequency device used in this study. The dynamic quadripolar radiofrequency emission focus energy on the layer of the tissue that needs treating, reducing both power needed and risks dramatically fluence ranging from 20 to35 j/cm2 was used. The tissue is treated in a natural, safe, comfortable and effective way.

Postoperative care, sun protection 50 SPF was prescribed as well as topical anti-inflammatory cream twice daily for the next week after each session. All patients were strictly advised to avoid direct sunlight for 4-5 days post laser treatment.

Patients were treated with a total of three sessions at 1-month intervals. Follow up occurred one month after each treatment session. Post-treatment changes in erythema and pigmentation as well as improvements in texture, atrophy, and overall appearance were graded by the investigator on a quartile scale (mild, ≤25%; 26–50% = moderate improvement; good, 51–75% = marked improvement; and excellent, >75% = near-total improvement). Two blinded dermatologists assessed the treatment response by comparing pre treatment and post-treatment clinical images using the same quartile grading scale.

A subjective assessment was also performed by the patients in terms of their overall satisfaction with appearance using a five-point scale (grade 0, no improvement = dissatisfied; grade 1, 1–25% = slightly satisfied; grade 2, 26–50%= satisfied; grade 3, 51–75% = very satisfied; grade 4, 76–100% improvement =extremely satisfied). Patients were also asked to grade pain during the procedure on a four-point scale (0 = no pain; 1 = mild pain; 2 = moderate pain; and 3 = severe pain).

Acne scar classification [7]

Acne scars subtype	Clinical features
Ice-pick	Ice-pick scars are narrow (<2 mm), deep, sharply demarcated tracts that extend vertically to the deep dermis or subcutaneous tissue
Rolling	Rolling scars may reach ≥5 mm in diameter. They have a rolling or undulating appearance that occurs from fibrous tethering of the dermis to the subcutis
Boxcar	Boxcar scars are oval depressions with sharply demarcated vertical edges. They are wider at the surface than ice-pick scars and do not taper to a point at the base

3. Results

The present study was conducted on 15 cases with moderate-to-severe post acne scars on face. Their mean age was 30.5 years (± SD). They were 5 males (33.3%) and 10 females (66.7%).

Table (1) Age and gender distribution among all studied cases.

		Cases N=15	
Age (years)	**mean±SD**	30.5	±5.9
Male	**N, %**	5	33.3%
Female	**N, %**	10	66.7%

SD, standard deviation.

Among all studied cases, 26.7% were smokes, and 26.7% had positive family history of scar (Table 2).

Table (2) Relevant history of all studied cases.

	Cases N=15	
	N	%
History of smoking	4	26.7%
Positive family history of scar	4	26.7%

Most of studied cases (80%) were received previous treatment, all of them received topical treatment and 5 cases (33.3%) were received systemic treatment (Table 3).

Table (3) Previous treatment among all studied cases.

	Cases N=15	
	N	%
Not receiving any treatment	3	20%
Using topical and systemic	12	80%

Face was affected in all studied cases. Mean (±SD) disease duration was 7.7 (±2.2) years.Grade I was found in 26.7%, grade II in 40% and grade III in 33.3%. (Table 4).

Table (4) Features of AV scars in all studied cases.

			Cases N=15	
Duration (years)		**mean±SD**	7.7	±2.2
Grades	**I**	**N, %**	4	26.7%
	II	**N, %**	6	40%
	III	**N, %**	5	33.3%

Regarding fractional CO2 laser, mean pain score at the first session was 60. It decreased by the 2nd session to 57.3 and by the 3rd session to 52.7, with significant decrease in pain score across time (p=0.039) (table 5).

Table (5) Comparison of pain grades after fractional laser throughout 3 sessions.

		Fractional CO2 1st session		2nd session		3rd session		*p*
		mean	±SD	mean	±SD	mean	±SD	
Pain score		60	12.4	57.3	13.9	52.7	14.4	**0.039**
		N	**%**	**N**	**%**	**N**	**%**	
Pain grades	**No pain**	0	0%	0	0%	0	0%	0.276
	Mild	5	33.3%	6	40%	8	53.3%	
	Moderate	9	60%	7	46.7%	6	40%	
	Severe	1	6.7%	2	13.3%	1	6.7%	

Regarding fractional CO2 laser, mean improvement score at the first session was 32.3. It increased by the 2nd session to 45 and by the 3rd session to 63.3, with significant increase in improvement score across time (p<0.001) (Table 6).

Table (6) Comparison of improvement grades after fractional laser throughout 3 sessions.

		Fractional CO2 1st session		2nd session		3rd session		*p*
		Mean	±SD	mean	±SD	Mean	±SD	
improvement score		32.3	8.6	45.0	10.4	63.3	12.5	**<0.0·1**
		N	**%**	**N**	**%**	**N**	**%**	
Improvement grades	**No**	3	20%	1	6.7%	0	0%	**<0.0·1**
	Mild	12	80%	11	73.3%	4	26.7%	
	Moderate	0	0%	3	20%	8	53.3%	
	Excellent	0	0%	0	0%	3	20%	

Regarding fractional CO2 laser, all cases had erythema (100%, while 20% has edema. None had hyperpigmentation or scarring (Table 7).

Table (7) Frequency of side effects after fractional laser.

	Fractional CO2 N	%
Edema	3	20%
Hyperpigmentation	0	0%
Erythema	15	100%
Scarring	0	0%

4. Discussion

The mean pain score for the first session of fractional CO2 laser in this research was 60. Within two sessions, it dropped to 57.3 and then to 52.7, indicating a substantial reduction in discomfort with time (p=0.039).

Previous investigations, such as those by Bjrn et al. [9] and Manuskiatti et al. [10] have demonstrated that the average pain score decreases with each therapy session. Our findings support these earlier research. Tolerability to pain increased with consecutive laser treatments, according to Ochi et al.[11]. Similarly, each subsequent laser treatment reduced the amount of time patients had to deal with erythema afterward.

After the second and third treatments, Chapas et al. [12] found that stimulating the wound healing response resulted in quicker recovery and better tolerability. It's also possible that patients' pain was reduced because they were more accustomed with the therapy process [9].

Xu and Deng [13], showed that patients who received treatment with a greater density or higher fluence of lasers felt more discomfort or pain that lasted longer.

Mean improvement scores increased significantly over time (p0.001), according to the findings of this investigation.

It was shown that there was a significant difference in the improvement grades across sessions when the improvement score was stratified into grades of moderate and outstanding.

The findings of this research were consistent with those of previous investigations. There was a clinical improvement in all of the patients investigated by El-Taweel et al., Majid and Imran. [15], and Hedelund et al. [16] who used fractional CO2 lasers to treat atrophic scars, according to the evaluation of the investigator and the two blinded dermatologists. After each treatment session, the skin texture of the acne scar and depressed scar group improved. Both scar groups had a statistically significant improvement in skin texture between the three sessions of therapy, according to all dermatologists.

An ablative 10,600-nm wavelength is combined with the notion of fractional photothermolysis in the fractionated carbon dioxide (CO2) laser. Thermal ablation removes just a small portion of the skin, leaving behind healthy skin that quickly replaces the ablated areas. Histological signs of wound healing and new collagen synthesis may be seen [11]. When compared to standard laser resurfacing, fractionating the CO2 laser improves skin regeneration and scarring while requiring less downtime and having a far lower risk of adverse effects [17].

Erythema (100 percent) and edoema (20 percent) were the most common side effects of fractional CO2 laser treatment. With no scars or hyperpigmentation.

Majid and Imran [15] also found that the treatment regimen's side effects, such as erythema that lasted an average of 3-4 days, superficial crusting that lasted 4-6 days, and moderate transitory edoema, were all temporary. Some 6 people had transient acneiform lesions, and 2 needed oral therapy. In our research, only three patients had post-inflammatory hyperpigmentation, which was the only significant adverse impact. Over the course of two to three months, a course of topical medication cleared up the hyperpigmentation.

According to Hedelund et al. [16], all of the patients in their study had short-term side effects that resolved on their own, and none of them went on to have long-term or irreversible side effects.

Three patients in the research by Arsiwala et al., [18] had hyperpigmentation, while two patients each had discomfort, erythema, and acne, and one had secondary infection, while one patient had a secondary infection.

Adverse events occur more often as the number of therapy sessions rises, according to Ochi et al.[11]. Blistering (4.0 percent), crusting (2.9 percent), worsening of inflamed acne lesions (1.7 percent), and scarring are among the side effects, with 6.4% of patients reporting hyperpigmentation (0.6 percent). Hypopigmentation, bacterial or viral infection were not observed to have any negative side effects in this study. The most prevalent side effect of laser therapy, postinflammatory hyperpigmentation (PIH), was restricted to the regions that had been treated. It was brief, lasting anywhere from seven to fourteen days on average, until finally dissipating after 13.5 days.

5. Conclusion

Improvement scores increased considerably, but so did the incidence of higher pain grades and more erythema associated with fractional CO2.

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NOVAVISION GROUP
MAKING FUTURE

I
Dermatology

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White
Papers

DQRF
dynamic quadripolar radiofrequency

DYNAMIC QUADRIPOLAR RADIOFREQUENCY WITH BIOSTIMULATION

AESTHETIC MEDICINE HAS CHANGED A LOT IN THE LAST FEW YEARS.

This has happened because the approach, but above all the way of thinking of its interpreters, has changed and has affected the shift from a very limited as well as a bit unique view of things to a much broader one. There is no longer just the aesthetic aspect, and our attention to the patient moves from a curative medicine in the narrow sense of the word - that is certainly aesthetic - to a medicine that, in our opinion, will be the one of the future: the regenerative medicine.

This broader vision allows us to get much more satisfactory results in a much more natural way and, above all, in the respect of our patients.

The aesthetic physician can fight the signs of skin aging by means of many tools, whether they are injectable, pharmacological or instrumental materials, and each of them has specific usage instructions with specific targets, that are well known by the medical community and that have to be achieved.

Indeed, technology has widely contributed to this development and currently there are many companies that invested lots of time and money in order to develop high-technology tools to be used in the aesthetic medicine field.

This is the case of **NOVACLINICAL** which developed a series of equipment – such as radiofrequency - able to act on the skin quality; what we want to emphasize is that not all devices are the same. First of all, it is important to remember that there are purely aesthetic devices used in beauty centres by non-medical personnel and medical devices that have particular characteristics and that, therefore, require to be used, and above all managed, by people with a medical experience.

Any device produced by these companies is tested and cannot harm patients health; anyway, obviously, each of these devices will present side effects significantly different according to the device type and the patient's sensitivity.

Radiofrequency is a treatment that has been used for a long time in the fight against aging in dermatology and aesthetic medicine with the aim of creating a stimulus for tissue regeneration.

In particular, radiofrequency is a technology exploiting electromagnetic waves that are transferred from the device to the patient's tissue in a more or less deep way. The waves used have different features and vary according to their frequency, to the wavelength and to the power which can be adjusted by means of the device settings.

The target of the emitted waves is to stimulate specific parts of our cellular system through heat; these are fibroblasts that are simply responsible for the production of the elements that form the dermis and that provide the important substances necessary to maintain the cell viability. Hence fibroblasts, that have been dormant over the years, are stimulated by radiofrequency waves in order to produce collagen, glycoproteins, and hyaluronic acid. This triggers a system that is able to execute a skin tissue regeneration that results in a much brighter, rested and healthy appearance of the skin. Therefore, radiofrequency is able to give back tone and elasticity to the dermis, to redefine the features of the treated area, to reduce fine roughness and to improve the texture and thus to slow aging, at the same time.

RADIOFREQUENCY HAS DIFFERENT FORMS: NON- ABLATIVE AND ABLATIVE.

The ablative radiofrequency form is a bit more invasive because its usage causes a limited destruction of the top layer of the tissue on which it is applied, whereas the non-ablative form does not imply any relevant alteration

and it allows to create a stimulus by producing a controlled heat source which can act also at deep dermis level. This radiofrequency type is mainly used in aesthetic medicine with the aim of improving various anatomical areas of the face and body in order to tone and reshape them.

Depending on the device you use, the radiofrequency device can emit waves that can be monopolar, bipolar, three-polar or quadripolar. The monopolar form involves the usage of two electrodes: one placed on the handpiece and one on a plate applied to the patient, which becomes an integral part of the circuit. Obviously, the bipolar device includes two electrodes placed on the handpiece, therefore the area hit by waves will be very limited and superficial.

The latest jewel developed by **NOVACLINICAL** is a dynamic quadripolar radiofrequency with fractionated **4RFH** handpiece, i.e. a latest generation handpiece for dynamic fractionated quadripolar radiofrequency.

It is a non-invasive device mainly used for skin laxity and tissue rejuvenation. The treatment consists in moving a handpiece which originates electric arcs that are a few microns away from each other and that selectively vaporize some skin cells; this energy hits only some of them and leaves undamaged the surrounding ones.

The **4RFH** handpiece of **RADIO4** was developed so that the dynamism of the pins creates a matrix in the considered area of the dermis surface and stimulates the progressive reparative process of epidermis by favouring the production of healthy cells.

The 32 gold-plated pins with 12μNeedles allow to penetrate the stratum corneum through a pressure system calibrated for a more direct power, comfort and efficiency.

As stated above, it is a non–invasive procedure and the patient can resume his/her social activities immediately after the treatment that is not particularly painful. It is safe and it gives excellent results already after the first session with an overall rejuvenation and improvement of the skin quality, i.e. of the texture, of the superficial wrinkles and of the periorbital and perioral ones.

It therefore allows to fight Aging at face, neck and décolleté level, and to improve other imperfections such as stretch marks or scars.

There are no risks in using this device and, the RSS technology in the dynamic fractionated quadripolar radiofrequency 4RFH handpiece monitors the movement of the handpiece and constantly controls the position by ensuring a comfortable, safe and effective treatment.

What we really love and that, in our experience, has given and gives great results with regard to rejuvenation – i.e. the tissue bio-dermal regeneration - is the usage of a multidisciplinarity of techniques and biochemical principles to be introduced at tissue level.

Many scientific clinical studies have shown that cells attacked by free radicals and by the action of metalloproteinase send a message of help to survive and remain viable. This message of help is shown at receptor level through receptor units allowing the transductions of the signal that is the cornerstone of the intercellular communication.

In our opinion, what happens is that such cell condition is not homogenous since the action of aging is very slow and progressive.

The intuition was to create an external stimulus that enables a pathophysiological regeneration and that, through limited damages, allows to develop this message of help sent by the cells in a much stronger and homogeneous way.

Hence, for example, through a thermal stimulus, such as the one originated by radiofrequency, it is possible to stimulate the receptor system (CD44, RHAMM, icam-1) as well as different control systems at cellular level as the one provided by the heat shock proteins, a family of molecular chaperone proteins that are triggered when the cells subjected to thermal stress undergo a protein denaturation and their action allows the usual protein folding. This folding will be codified for new intracellular messages at nuclear level as well as at level of cytosol, endoplasmic reticulum, mitochondria and chloroplasts in addition to the request to activate cellular units that allow a secondary cell revitalization.

The synergy of a condition such as the one originated by radiofrequency, that enables to create the limited thermal damage which "triggers" all cells of the area treated with an endogenous stimulation carried out through nutrients such as hyaluronic acid, polynucleotides, amino acids or better through the platelet growth factors, is extremely successful and, at biochemical and aesthetic level, the result does not just increase, but it multiplies. In our studies, we draw up various protocols related to the tissue bio-dermal regeneration, and radiofrequency - together with injections of platelet rich plasma at intradermal level - is certainly the one on which we place great reliance in terms of achievable results because it directly stimulates the collagen fibers thanks to the thermal effect and it simultaneously prepares the cell receptivity for growth factors released by platelet elements prepared through specific sterile kits which enable an intensive repair and cell regeneration activity.

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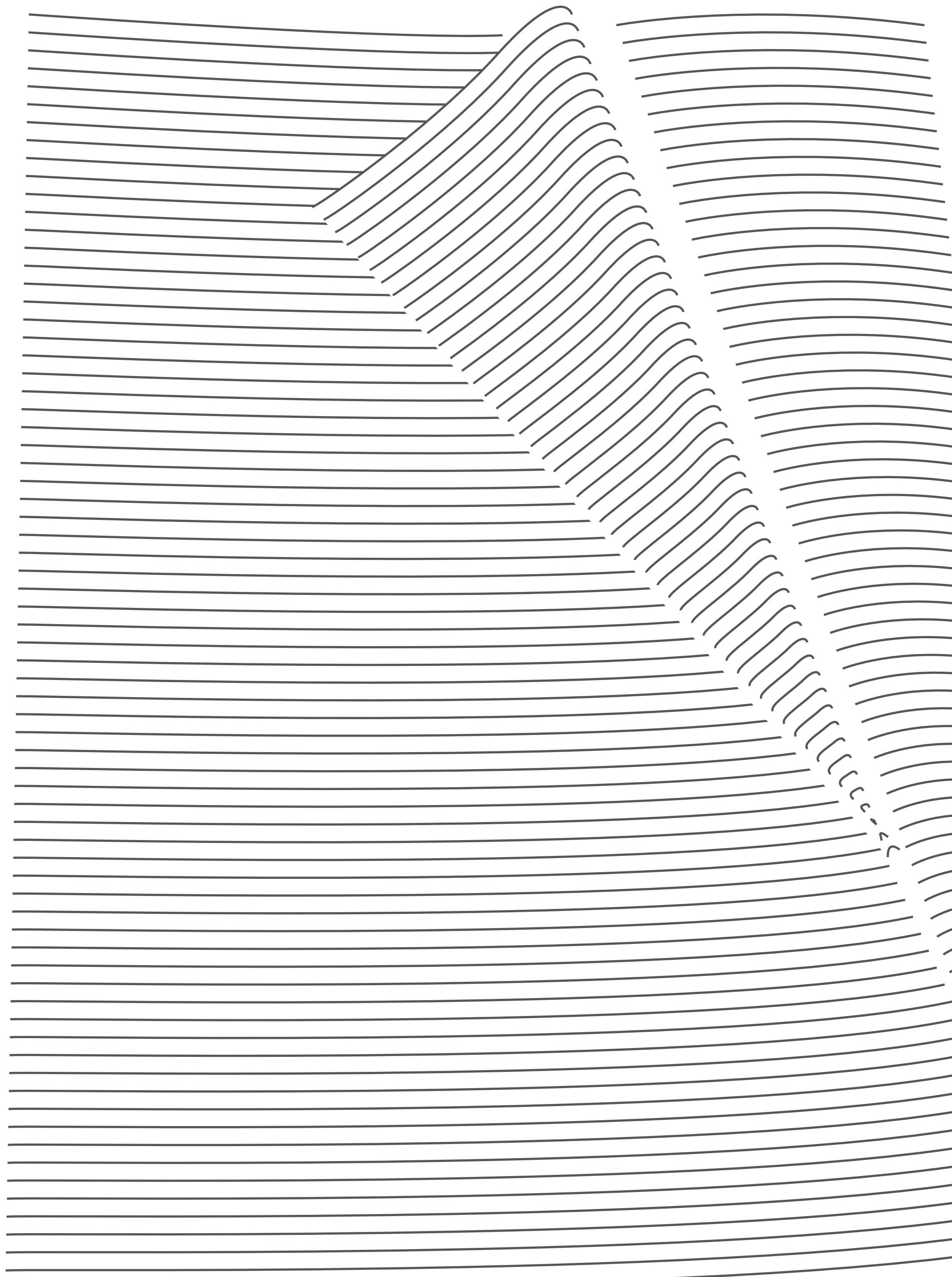


THE ROLE OF QUADRIPOLAR RADIOFREQUENCY IN AESTHETIC SURGERY AND MEDICINE

INTRODUCTION

Cosmetic surgery and medicine have undergone immense evolution over the last few years. Aesthetic medicine has expanded its horizons thanks to new methods, new devices and enhanced equipments, enabling us to achieve better and more lasting results.

Plastic surgery, instead, has improved the surgical techniques for face and body, making them less and less invasive; nowadays surgery is often combined with aesthetic medicine in order to allow a faster recovery and improve the overall aesthetic results.

Radiofrequency is a well known resource in aesthetic medicine, whose technical features can make it the ideal complement to surgical treatments as well.

Particularly relevant among the new-generation radiofrequency technology devices is the "Dynamic and Fractional Quadripolar Radiofrequency" exclusively property of Novavision Group.

AIM AND INDICATIONS

It's an absolutely painless treatment, no local anesthesia is required, whose side effects are minimal, in most cases the treated areas can just show mild redness for a few hours. This last generation emits specific electric flows in order to treat several face and body blemishes by generating **heat only in the concerned skin layer** – from the most outer superficial one, to the deepest one – thus triggering the **regeneration, tightening** or **lipolytic** required processes.

The primary advantage of the **Quadripolar Dynamic Radiofrequency** technology, is that we are able to deliver the heat only to the **targeted skin layer**: when working in depth, the epidermis remains completely untouched and safe, while it becomes vigorously stimulated when performing fractional radiofrequency resurfacing treatments.

Prior to treatment a layer of gel is applied in order to properly transfer heat to the tissues.

In case of lifting and firming treatments, heating the dermal layer not only involves proinflammatory cytokines release, it also causes collagen matrix contraction and stimulates the local fibroblasts to produce new collagen.

On the face, the immediate benefits of the treatment is a tighter and smoother-looking skin and wrinkles improvement; the long-term effect is an improvement of the skin tone and firmness, due to the production of new collagen in the deep layers of the skin.

Radiofrequency has positive effects on the micro circulation as well and performs a draining effect, therefore it is suitable for the treatment of cellulite, localized fat deposits, circulatory and lymphatic stasis. It can be used in all cases of skin laxity (lower limbs, abdomen, arms) to restore firmness to the treated areas, or tighten the face skin reducing wrinkles and laxity with the outcome of a non-surgical facelift.

RADIOFREQUENCY AND COSMETIC SURGERY

At Leonardo Clinic's Department of Plastic Aesthetic Surgery, radiofrequency is performed either as a stand-alone procedure, to improve ageing skin of the face and the body, or in combination with surgical procedures.

The average treatment protocol for an overall facial rejuvenation includes 5 sessions of radiofrequency, performed two months before a soft "thread face lift" and facial fat grafting, and 5 sessions one month later.

DYNAMIC QUADRIPOLAR RADIOFREQUENCY

NOVAVISION White Paper 11/2015

RADIOFREQUENCY

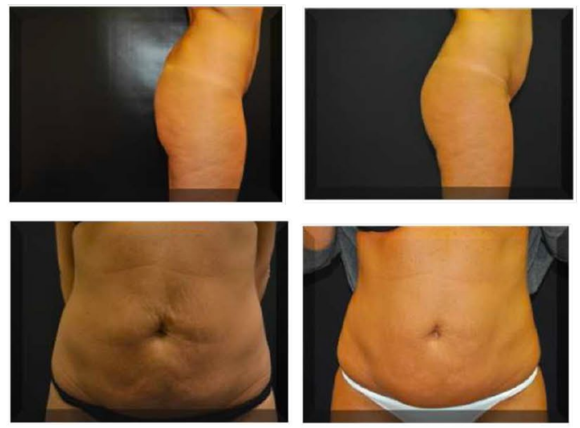
This enables us to obtain a non-surgical facelift which includes jaw line contouring, skin tone improvement and wrinkles reduction. (Pic 1-2)

In case a rhytidectomy (face lift surgery) is required, the treatment protocol still includes 5 sessions of radiofrequency performed two months before the surgery, that mainly focus on the lower part of the neck, in order to restore the dermal architecture of the skin and boost the deep healing process this surgery involves, owing to the facial soft tissue detachment.

During the post op recovery time 3 more radiofrequency sessions are performed, using the fractional handpiece 4RFH, to obtain a resurfacing of the periocular and perioral regions. (Pic 3-4-5)

As regards the body, we propose a series of radiofrequency treatments that prepare the abdominal area, the inner thigh, the buttocks and the arms to a successful suture suspension lift, allowing a better anchorage of the threads to the deep fascia and reducing the skin laxity.

In particular, the buttocks area involves: 8 intensive sessions of radiofrequency for toning the gluteus maximus before the thread suspension treatment, and 8 more one month later. This way we can achieve the best lifting result, emphasizing the traction effect of the sutures. (Pic 6 -7)



In case of liposculpture of abdomen or lower limbs, patients with sagging skin are treated with 8 radiofrequency sessions two months before the intervention, and 5 more sessions after.

This allows greater skin retraction both in the treated and the surrounding areas, therefore enhancing the aesthetic results.

The procedure takes about 30 minutes for the face and about 40 minutes for the body.

CONCLUSIONS

To conclude, our experience shows that the outcome of a cosmetic medicine or surgery treatment can be dramatically enhanced if we include a series of radiofrequency sessions both in the preoperative and the postoperative phases.

This global approach makes patients satisfied, as once they've been properly informed they are able to appreciate not only to the aesthetic outcome they have obtained but also its long lasting effectiveness over time.

4PLUS System Offers Novel Application of RF Technology

By Kevin A. Wilson, Contributing Editor

Applying radiofrequency (RF)-based technology in novel ways to address common skin improvement and body contouring indications, NOVACLINICAL 4PLUS™ from Novavision Group SpA (Misinto, Italy), is ideal for practices and medspas looking to provide patients with a variety of safe, comfortable and effective treatment options for the face and body.

Elena Fasola, M.D.
Director of GyPlast Medical Institute
Milano, Italy

"4PLUS treats signs of cutaneous aging such as skin laxity, striae distensae and wrinkles by stimulating fibroblasts and collagen production," said Elena Fasola, M.D., director of GyPlast Medical Institute in Milano, Italy. "Lipolytic effects can be initiated as well, depending on how it is used."

As its name suggests, 4PLUS features four integrated technologies harnessing the power of RF. Dynamic Quadripolar Radiofrequency (DQRF™) focuses RF energy at different levels in skin using a self-guided system that carefully manages emission to maximize efficacy and safety. "The energy reaches deep into tissue to enhance local cellular metabolism and stimulate lipolysis without burning because of how well energy transmission is managed," Dr. Fasola explained.

Variable Radiofrequency (VRF™) features a range of pre-set frequencies for focused deep thermal effects without epidermal heating, which can be used as a stand-alone therapy or synergistically with DQRF.

"Thanks to the continuous movement of electric charges between the poles, which behave as receivers and transmitters, the device uses relatively low energy with DQRF to deliver safe treatment, without any risk of burns. Nevertheless, it is very effective on the tissue layer that you want to treat, especially in combination with VRF technology, which enables you to selectively focus the action on the targeted tissue layer," Dr. Fasola stated.

With 32 gold-plated pins, each having 12 contact points, Radiofrequency Fractional Handle (4RFH™) has 384 possible transmission points whose action is configured by dedicated software. Each pin is pressure calibrated to send RF energy past the stratum corneum.

Needled Fractional Radiofrequency (4NFR™) also features 32 gold-plated pins and reaches deep to layers that usually require surgery to affect, Dr. Fasola noted. "These technologies are particularly good for facial wrinkles and stretch marks on the body." Removable tips for both handpieces are autoclavable.

Ultra Pulsed Radioporation (UPR™) is a modulation of DQRF that facilitates penetration of topicals, Dr. Fasola expressed. "The introduction of UPR represents an important upgrade, allowing infiltration of actives that normally cannot be absorbed by the skin easily, such as hyaluronic acid, lipolytic agents and vitamins. With this technology we can enhance results achieved with DQRF."

"Skin tone is visibly improved after the first session," Dr. Fasola reported. "Normally it is sufficient to treat skin laxity in four to seven sessions, localized fat in seven to ten sessions and wrinkles and striae in five to eight sessions with the fractional handpieces."

The 4PLUS Radiofrequency Safety System (RSS™) is what makes the device so safe. Onboard monitoring of electrodes, handpiece motion and skin temperature provides feedback used to automatically avoid overtreatment for safe, efficient energy transmission in any mode.

"This makes treatment safe and comfortable without anesthesia, and with no recovery time," Dr. Fasola shared.

4PLUS is also excellent in combination with other modalities. According to Dr. Fasola, "4PLUS can help treat skin after liposuction, address laxity more powerfully with LED photodynamic therapy, work as an adjunct to a facial rejuvenation protocol, or be used with fillers and botulinum toxin. It also works well with carboxytherapy for the treatment of localized fat and cellulite."

Localized fat on the abdomen before and after six weekly treatments with NOVACLINICAL 4PLUS
Photos courtesy of Novavision

II

Gynaecology

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Published *Studies*

DQRF
dynamic quadripolar radiofrequency

TECHNOLOGICAL EVOLUTION IN THE RADIOFRENCY TREATMENT OF VAGINAL LAXITY AND MENOPAUSAL VULVO-VAGINAL ATROPHY AND OTHER GENITOURINARY SYMPTOMS: FIRST EXPERIENCES WITH A NOVEL DYNAMIC QUADRIPOLAR DEVICE

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Franco VICARIOTTO, Mauro RAICHI

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ORIGINAL ARTICLE

Technological evolution in the radiofrequency treatment of vaginal laxity and menopausal vulvo-vaginal atrophy and other genitourinary symptoms: first experiences with a novel dynamic quadripolar device

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ABSTRACT

BACKGROUND: This paper was a spontaneous, non-sponsored exploratory study to investigate the safety and efficacy of two schedules of thermal treatment with a new low-energy dynamic quadripolar radiofrequency (DQRF) device in: A) premenopausal women referring perception of vaginal introital laxity and related symptoms, with special reference to dysuria and urinary incontinence and unsatisfactory sexual activity (vaginal laxity arm of the study); B) postmenopausal women with vaginal atrophy and dryness and other vulvo-vaginal atrophy and *genitourinary syndrome* of *menopause* (VVA/GSM) related symptoms (VVA/GSM arm of the study).
METHODS: As for the vaginal laxity arm of the study, 12 women with perception of very to slightly loose vaginal introital laxity underwent five 20-min DQRF thermal treatment sessions every 14±1 days. A Vaginal Laxity Questionnaire (VLQ, certified Italian translation) and short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12, Italian certified translation) were used to assess urinary incontinence, sexual gratification and the contribution of any concomitant pelvic organ prolapse. As for the VVA/GSM arm of the study, 13 women with objective evidence of VVA and vaginal dryness and/or dyspareunia rated as moderate/severe most bothersome symptoms underwent four 10-min DQRF sessions every 10±1 days. Specifically designed visual analogue scales (VAS) for VVA/GSM symptoms and overall satisfaction with sexual life were used.
RESULTS: No adverse effects, including thermal burns or injuries, were reported during or after treatments in either arm of the study. Eleven of the enrolled women completed the five planned DQRF treatment sessions in the vaginal laxity arm of the study; 12 women completed the four DQRF sessions planned in the VVA/GSM arm of the study. Clinically and statistically significant improvements in self-perceived sensation of looseness and symptoms like dysuria/urinary incontinence and sexual function in the vaginal laxity arm of the study as well as VVA/GSM symptoms and overall satisfaction with sexual life in the VVA/GSM arm of the study. Improvements were already reported at the first assessment visit before the end of the planned DQRF sessions of each arm of the study, after, respectively, 56±4 and 30±3 days.
CONCLUSIONS: The DQRF treatment was well tolerated, with no pain during the procedure and no untoward effect reported over the 2-month follow-up periods in both the vaginal laxity and VVA/GSM arms of the study. Improvements in self-reported VLQ and PISQ-12 scores (vaginal laxity arm) and VAS self-evaluation of VVA/GSM symptoms and overall satisfaction with sexual life (VVA/GSM arm of the study) were rapid and persistent. This suggests rapid and persistent vaginal rejuvenation as the basis of subjective improvement in symptoms and decreased sexual distress in both indications, including dysuria and urinary incontinence in menopausal women. Such promising exploratory findings deserve confirmation in larger studies.

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Key words: Pulsed radiofrequency treatment - Urinary incontinence - Menopause.

Well-defined clusters of events occur in all women in the weeks after vaginal childbirth and the months and years after menopause. The almost inevitable stretching during delivery of the dense connective tissue of the vaginal wall, introitus and labia majora, that then heals in varying degrees of laxity and worsen with each successive birth, may be considered physiological or quasi-physiological. Though distinct from vaginal and other genito-pelvic structures bulging into the vaginal canal and introitus more properly defined as prolapse, vulvovaginal laxity may seriously affect the woman's self-image, self-esteem and overall quality of life. This is due to compromised genital aesthetics and discomfort and irritation in everyday life, as well as to the negative impact on the woman's sexual experience and couple relationship. Much the same can be said of the menopausal estrogen drop associated with vulvar and vaginal involution and decreased circulatory engorgement, lubrication and elasticity, frequently leading to vulvo-vaginal atrophy (VVA) and related symptoms (dryness, irritation, itching, burning, discharge, dysuria).

Decreased genito-pelvic sensation during sexual activity is common in women with vaginal laxity. In a multinational survey of members of the International Urogynecological Association (IUGA), more than four out of five interviewed practitioners described vaginal laxity — mainly a delivery-related problem, though compounded by natural aging — as an under-reported and troubling condition that impacts the couple relationship. The interviewed IUGA members also described vaginal laxity as the most important change of body integrity experienced by women after vaginal delivery.[1]

As regards VVA and genitourinary syndrome of menopause (GSM), symptoms may trouble up to 50% of postmenopausal women.[2, 3] A 2015 survey in women with VVA symptoms found EQ-5D (EuroQol-5D) scores to be linearly related to symptom severity assessed with the Menopause Rating Scale. The decrements in EQ-5D scores associated with moderate to severe VVA symptoms were comparable to those observed in other serious conditions such as arthritis, chronic obstructive pulmonary disease, asthma, and irritable bowel syndrome.[4] The surveyed prevalence of VVA/GSM symptoms in the general menopausal population ranged between 40% (Germany) and 54.4% (Spain), with half of women reporting their symptoms as either moderate or severe.[4] Vaginal dryness is the most commonly reported VVA symptom in Europe (70%), with 32% of women in Italy, Germany, Spain and the UK naïve to any kind of treatment.[3, 5]

Besides impacting on the woman's quality of life and psychological wellbeing, introital and vaginal laxity after delivery and menopausal VVA/GSM frequently expose to unwelcome consequences in terms of long-term morbidity. Vaginal laxity is often detected in conjunction with atrophic vaginitis, stress incontinence and/or inappropriate micturition reflex with bladder instability. A lax vagina may in fact be the main determinant of both stress and urge female urinary incontinence.[6] As regards VVA and GSM, recent vaginal infections were much more likely in a survey of a selected population of 722 women diagnosed with GSM out of 913 looking for routine gynecological examinations in Italian menopause health centers (OR 2.48, 50% CI: 1.33-4.62, *vs.* non-GSM controls). Itching and dysuria as risk factors for further morbidity were also highly prevalent (56.6% and 36.1%, respectively).[7]

The paper illustrates the outcomes, with special reference to safety, of the first study with the last technological evolution of non-ablative radiofrequency treatment in women with either vaginal laxity or VVA/GSM (see Appendix). The study, designed as a spontaneous, non-sponsored, short-term exploratory investigation, was carried out in a private outpatient setting and targeted to women experiencing quite severe quality of life disruption because of significant GSM- and vaginal laxity-related symptoms. Emphasis was on safety and the medical value of the new technology as elective procedure when either condition is a serious problem for the woman's wellbeing and quality of life.

The paper also discusses how the efficacy and safety outcomes of the study relate to the

biophysics of dynamic quadripolar application of highly targeted heat-generating radiofrequency fields to vulvar and vaginal subepithelial tissue layers.

Materials and methods

Study goal and design and study population

A spontaneous, exploratory, open-label investigation was prospectively conducted in outpatient office-based subjects at the investigator's private practice to probe the safety and efficacy of a newly developed dynamic quadripolar device as non-surgical, non-laser radiofrequency treatment in: A) women with subjective perception of laxity of vaginal introitus and other laxity-associated symptoms with special reference to urinary incontinence; B) postmenopausal women with subjective perception of vaginal dryness and other VVA/GSM-related symptoms. All study materials were appropriately peer reviewed for ethical problems. All candidate women gave full informed consent.

Candidate women with vaginal laxity were screened from early January to mid-May 2015; candidate women with VVA/GSM for enrolment from late mid-February to late May 2015. A total of 12 women with vaginal laxity and 13 with VVA/GSM were enrolled; follow-up of the last subjects ended in July 2015. The dimensions of the two samples were defined without any clear-cut indications from either published papers or systematic clinical experience about the value and role of the new radiofrequency technology in the two indications. The two schedules of thermal dynamic quadripolar radiofrequency (DQRF) treatment were designed based on the evidences of preclinical experiences in animal vaginal models.

Activities specific to the vaginal laxity arm of the study

Screening and enrolment procedures

Candidate women were to be less than 54 years old and premenopausal. They were to have had at least one full-term vaginal delivery (more than 36 weeks gestation) completed at least one year before study enrolment and to currently have negative pregnancy tests and a normal Papanicolau Smear Cytology Test (obtained no more than two months before enrolment). Candidate women were to be in a stable monogamous heterosexual relationship, to have reasonable sexual activity (at least two vaginal intercourses per month using an acceptable method of birth control), and to have no evidence of significant pelvic organ prolapse (*i.e.*, beyond the hymenal ring). Dosage of any medication, such as antihypertensives and psychotropics, known to affect sexuality should have been stable for at least 1 month prior to treatment with no dosage change likely or planned in the forthcoming weeks. Candidates should not have been taking medications known to affect collagen metabolism and healing such as non-steroidal anti-inflammatory drugs and steroids for at least one month. The vaginal canal, introitus and vestibule were to be free of injuries and bleeding. Previous pelvic surgery within four years also prevented enrolment.

Candidates were fit for enrolment if they reported a perception of vaginal introital laxity that they defined as "very loose", "moderately loose", or "slightly loose" on a certified Italian translation of the Vaginal Laxity Questionnaire (VLQ), a Likert-type Scale with seven levels of response ("Very loose", "Moderately loose", "Slightly loose", "Neither loose nor tight", "Slightly tight", "Moderately tight", "Very tight").[8] Subjects with severe urinary incontinence with suspected intrinsic sphincteric deficiency (ISD) and positive empty bladder stress tests were excluded.

Outcome assessment

VLQ was the main outcome measure instrument; the short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12, Italian certified translation) was also used as a validated standard assessment instrument for symptoms like dysuria/urinary incontinence and for gratification with sexual life as well as to discriminate the contribution of any concomitant pelvic organ prolapse.[9] Categorical levels of response were translated into ordinal scores for statistical analysis (for the VLQ scale, for instance, "Very loose"=1, "Moderately loose"=2, "Slightly loose"=3, "Neither loose nor tight"=4, "Slightly tight"=5, "Moderately tight"=6, "Very tight"=7). After the first one, the 20-min DQRF sessions were repeated every 14±1 days for a total of 5 sessions.

Activities specific to the VVA/GSM arm of the study

Screening and enrolment procedures

Candidate women were to be more than 50 years old and to have experienced no menstruation for at least 12 months. A wish to maintain an active sexual life should have been coexisting with vaginal dryness and/or dyspareunia rated as moderate/severe most bothersome symptoms [10] and objective evidence of VVA (thinning/loss of vaginal rugae, mucosal pallor, friability and/or petechiae, low vaginal pH, low vaginal maturation index). Any systemic or local hormonal replacement therapy should have been stopped for at least six months and no vaginal moisturiser, lubricant or any other local preparations should have been used in the previous month. Prolapse staged ≥II according to the pelvic organ prolapse quantification system [11] also prevented enrolment.

Outcome assessment and timing of DQRF sessions

Clinical severity of VVA/GSM symptoms (vaginal dryness, burning and itching, dyspareunia, dysuria) was self-assessed by the enrolled subjects using 10-cm visual analogue scales (VAS) with "No symptom" at the left extreme of the scale and "Symptom as severe as it could be" at the right extreme as previously reported in several VVA studies including breast cancer survivors.[12] The overall satisfaction with sexual life was similarly assessed by enrolled women using a 10-cm VAS with "Worst level of satisfaction" at the left extreme of the scale and "Best level of satisfaction" at the right extreme. After the first one, the 10-min DQRF sessions were repeated every 10±1 days for a total of 4 sessions.

Screening and outcome assessment activities common to both arms of the study

Screening assessment included a physical and pelvic examination, demographics, and medical and obstetric/gynecological history. Exclusion criteria included pelvic surgery within four years of the study, acute or recurrent urinary tract infections, active genital infections, chronic vulvar pain or vulvar lesions or disease (dermatitis, human papillomavirus, herpes simplex, vulvar dystrophy), inadequate thickness of the recto-vaginal septum as assessed by pelvic examination. Any systemic condition or mood/psychiatric disorder interfering with informed consent and study compliance also prevented enrolment in either arm of the pilot study.

Basal assessment was performed immediately before the first DQRF procedure in both arms of the study immediately before the first DQRF session. Three office follow-up visits were planned: immediately before the last procedure (*i.e.*, after 56±4 days in women with vaginal laxity and after 30±3 in women with VVA/GSM) and after 30±1 and 60±1 days following this first follow-up assessment (Figure 1).

In-office safety assessment included recording of vital signs and adverse events with special reference to any experience of pain or discomfort during and after the procedure. Post-treatment safety assessments were carried out the next day by telephone calls and by questioning for any need of analgesics, anti-inflammatory drugs or other medications at the following DQRF session.

Statistical analysis

Descriptive statistics (means and standard deviations for continuous variables, frequency distributions and percentages for categorical

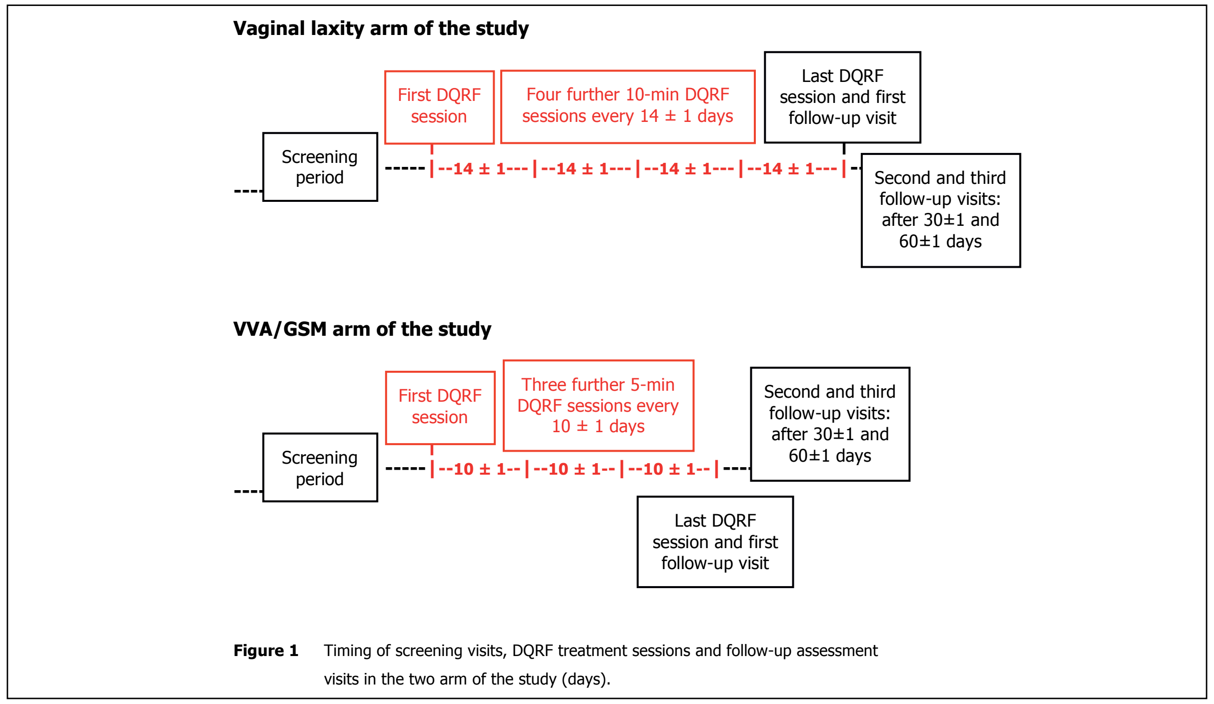


Figure 1.—Timing of screening visits, DQRF treatment sessions and follow-up assessment visits in the two arm of the study (days).

variables) were generated for demographics, medical history, and physical examination findings. The nonparametric Wilcoxon Signed Rank Test for repeated measurements on a single population was applied to both repeated measures of ordinal data (VLQ, PISQ-12 and SF-12 mean scores) and continuous variables (VAS mean scores); the McNemar Test was used to test for differences in ordinal mean scores. Two-sided 95% confidence levels were used with $p<0.05$ as cut-off for statistical significance.

Results

Eleven women completed the 5 planned sessions of DQRF treatment in the vaginal laxity arm of the study; 12 women completed the 4 planned sessions in the VVA/GSM arm of the study. One woman was lost to follow-up in each arm of the study without any further information. Table I illustrates the demographics and other characteristics relevant to the investigations of the two study populations at the screening visits immediately before the first treatment session.

Table I.—*Main characteristics of the two populations in the two arms of the study. SD, standard deviation; HRT, hormone replacement therapy.*

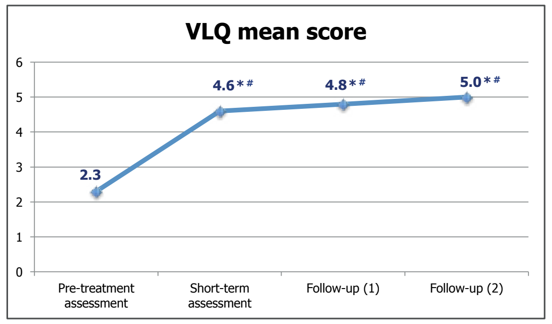
Vaginal laxity arm, study population	
Women completing the five planned DQRF sessions	11
Age (years, mean ± SD)	41.7 ± 5.5
Body Mass Index (kg/m², mean ± SD)	24.1 ± 2.0
Parity (n, %)	
0	1 (9%)
1	3 (27%)
2	4 (36%)
3	3 (27%)
Current sexual activity (n, %)	11 (100%)
Frequency of sexual activity per week	1-4
VVA/GSM arm, study population	
Women completing the four planned DQRF sessions	12
Age (years, mean ± SD)	60.4 ± 6.5
Body Mass Index (kg/m², mean ± SD)	23.0 ± 1.8
Previous live births (n, %)	9 (75%)
Parity	1.7 (1-3)
Current sexual activity (n, %)	7 (58%)
Previous systemic HRT (n, %)	3 (25%)
Months of systemic HRT (months, range)	31 (3-54)

As regards evaluation of safety as the main goal of this explorative study, no burns, blisters or other complication were reported during or after treatments in both arms of the study. All DQRF sessions were described as relaxing and comfortable in both arms of their study. All women were able to resume all everyday activities, including sexual life, immediately after each DQRF treatment session.

Vaginal laxity arm of the study

Secondary vaginal laxity-related conditions (orgasmic dysfunction, stress incontinence, atrophic vaginitis) were reported at the screening visit by 10 out of the 12 enrolled women with self-reported perception of vaginal laxity (9 out of the 11 subjects who actually completed the study).

Compared to basal assessment, VLQ mean scores as index of subjective perception of vaginal tightness significantly improved by at least one level in all women, as observed already at the first follow-up visit before the end of the five DQRF sessions. Six out of the 11 women who completed the five planned DQRF sessions reported VLQ scores that were 2-4 levels higher than before treatment at the first assessment visit. A marginally non-significant trend to further improvement was apparent during the 2-month post-treatment follow-up, with 9 women reporting VLQ scores that were 2-4 levels higher than basal assessment after 60±1 days (Figure 2A).



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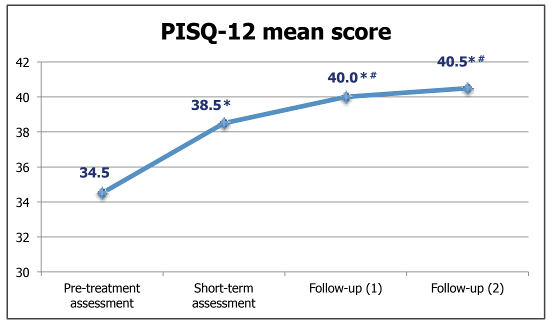

B

Figure 2.—Mean Vaginal Laxity Questionnaire (VLQ) scores (A), and mean Total Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) scores (B) immediately before the first DQRF procedure (Pretreatment assessment), immediately before the last planned DQRF procedure (Short-term assessment) and after 30±1 and 60±1 days of post-treatment follow-up (Follow-up (1) and Follow-up (2)). *P<0.05 *vs.* basal assessment; #non-significant *vs.* first assessment visit.

A statistically significant improvement in overall sexual function (mean Total PISQ-12 Score) could be demonstrated at the first evaluation visit, immediately before the last DQRF procedure, compared with basal assessment (34.5±6.8 *vs.* 38.5±6.1, P<0.05). Nine out of the 11 women who completed the five planned sessions showed an improvement of 2 to 4 points (Figure 2B).

Four individual PISQ-12 scores showed statistically significant improvements at the first assessment visit (Q2 or frequency of climax, Q6 or urinary incontinence related to sexual activity, Q7 or fear of urinary and stool incontinence, Q9 or emotional reactions during sex); four individual scores showed a tendency to improve (Q1 or sexual desire, Q3 or sexual excitation, Q4 or variety of sexual activities, Q8 or sense of vaginal bulging preventing sex,); for three PISQ-12 categories there was no change (Q5 or pain during intercourse, Q10 or partner's erection problems, Q11 or partner's premature ejaculation).

Similar mean total PISQ-12 scores were reported at the second and third assessment visit after 1 and 2 months of follow-up (40±5.5 and 40.5±5.6, not significant compared to the first assessment visit, P<0.05 compared with basal assessment.

Pain with intercourse subscores, already very low at screening, did not change over the follow-up period, meaning lack of even a very low-level of chronic inflammation induced, or anyway associated with the DQRF procedure. At the second visit, one woman missed more than two answers and was excluded from PISQ-12 assessment in accordance with PISQ-12 scoring instructions.[9]

VVA/GSM arm of the study

Before treatment, 8 out of the 13 screened and enrolled women (61.5%) and 7 out of the 12 women who completed the four planned sessions (58.3%) were sexually active; 5 of the screened women reported to have had no sexual intercourse for at least three months due to severe VVA/GSM symptoms. As regards VVA/GSM symptoms, vaginal dryness was reported by all 13 enrolled women before treatment, vaginal itching and vaginal burning by 10, dyspareunia by 11, and dysuria/incontinence by 8.

At the first assessment visit before the first DQRF session, 10 of the enrolled women reported to have resumed coital sexual activity (83.3%). At the last follow-up visit 11 women reported to be variably but anyway sexually active; only one woman reported physical and emotional discomfort during a few attempts at having intercourse and would not consider herself sexually active.

Compared to basal assessment, clinically and statistically significant improvements were observed for mean VAS scores of most VVA/GSM symptoms and for the overall satisfaction with sexual life at the first evaluation visit before the last DQRF session. Further improvements for all scored items, or at least a tendency to further improvement, could be appreciated at the two post-treatment visits during the follow-up period (Table II).

The mean VAS score for overall satisfaction with sexual life improved from 4.3±1.4 at baseline up to 7.0±2.0 after 30±3 days ("First assessment visit") and 7.7±2.4 at the last follow-up visit, 90±4 days after the first DQRF session (Figure 3).

Discussion

The radiofrequency technology for non-surgical thermal treatment and vaginal rejuvenation in women with either vaginal laxity or VVA/GSM is well established and widely considered safe and effective.[8, 13]

In spite of the relative paucity of enrolled women with vaginal laxity and VVA/GSM, this exploratory study suggests that the novel dynamic quadripolar evolution of radiofrequency treatment is safe and well tolerated in both indications of vaginal rejuvenation with an excellent 2-month follow-up safety profile.

Even minimally invasive technologies may expose to bleeding, pain and burning.[14] By minimizing the risk of thermal injuries, the new DQRF technology may offer further safety benefits over the current unipolar radiofrequency and laser technologies for non-surgical thermal treatment of introital and vaginal laxity and VVA/GSM.

Preclinical evidences provide convincing evidences of the biophysics of the DQRF concept. In infrared thermophotographs, the thermal effect in the treated genital areas appears to be highly localized onto the target mucosal surfaces and to rapidly dissipate after the end of the procedure without residual irritation or more severe injuries (Figure 4). The whole procedure has been usually reported by all women enrolled in the two arms of the study as painless and often devoid of any thermal sensation.

Table II.—*Detection and clinical severity of VVA/GSM symptoms in the study population of the VVA/GSM arm of the investigation. Mean scores (±standard deviation); data in cm assessed on 10-cm specifically designed visual analogue scales.*

	N.	Pre-treatment assessment	Short-term assessment	Follow-up (1)	Follow-up (2)
Vaginal dryness	12	8.8±2.4	4.3±1.8 **	3.4±1.7 ** °	3.2±1.9 ** °
Vaginal itching	10	7.5±2.7	3.7±1.9 **	3.0±1.6 ** °	2.6±1.3 ** °°
Vaginal burning	10	7.2±2.5	3.4±1.8 **	3.0±1.7 ** #	2.8±1.4 ** °
Dyspareunia	11	8.7±2.2	4.5±1.9 **	3.0±1.8 ** #	3.1±1.9 ** °
Dysuria/incontinence	8	5.5±2.6	3.0±1.9 *	2.9±1.6 * #	2.6±1.5 ** °

N.: women reporting symptom; *P<0.05 *vs*. basal assessment; **P<0.01 *vs*. basal assessment; °P<0.05 *vs*. first assessment visit; °°P<0.01 *vs*. first assessment visit; # non-significant *vs*. first assessment visit.

Preclinical investigations relating to the time course and spatial distribution of the thermal effect in the subepithelial layers also suggested the tentative treatment schedules adopted in this exploratory study. More formal dose-finding studies are warranted to fine-tune radiofrequency wavelengths and times of applications to maximize efficacy in both menopausal vaginal atrophy and laxity of the vaginal introitus and wall.

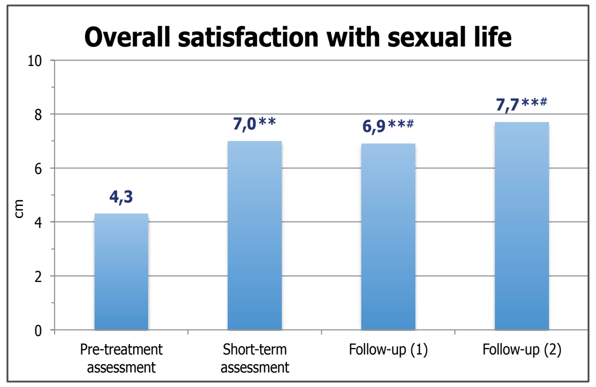

Figure 3.—Mean scores for overall satisfaction with sexual life (expressed as cm on a 10-cm visual analogue scale) before the first DQRF procedure (Pretreatment assessment) and at the first and second follow-up visit after 30±1 and 60±1 days of follow-up (Follow-up 1 and Follow-up 2). *P<0.05 *vs.* basal assessment; #non-significant *vs.* first assessment visit.

Somewhat different sets of biological effects should be pursued in the two conditions. As also suggested for other thermal therapy technologies, vaginal rejuvenation in introital and vaginal laxity implies re-activation of fibroblast and connective tissue function and development of new networks of collagen and elastin fibres in the subepithelial layers of introitus and vagina.[13, 15]

Collagen re-activation is also the goal in vaginal rejuvenation in VVA/GSM, but possibly an even more important goal is vasodilatation. Increases of local blood flow facilitate the diffusion of the inactive sex steroid precursor dehydroepiandrosterone (DHEA) to vulvo-vaginal cells for local intracrine estrogen production. Thermally induced vasodilatation also facilitates the diffusion of DHEA-derived estrogens produced in local adipose tissue to the atrophic vaginal mucosa. From the time of menopause, DHEA from the adrenal glands becomes the only significant source of sex steroids for all hormone-dependent female tissues except the uterus. Ease of diffusion of DHEA and DHEA-derived sex steroids to vulvo-vaginal target cells may be crucial to counteract menopausal symptoms such as osteoporosis, muscle loss, vaginal atrophy, fat accumulation and hot flashes.[16, 17]

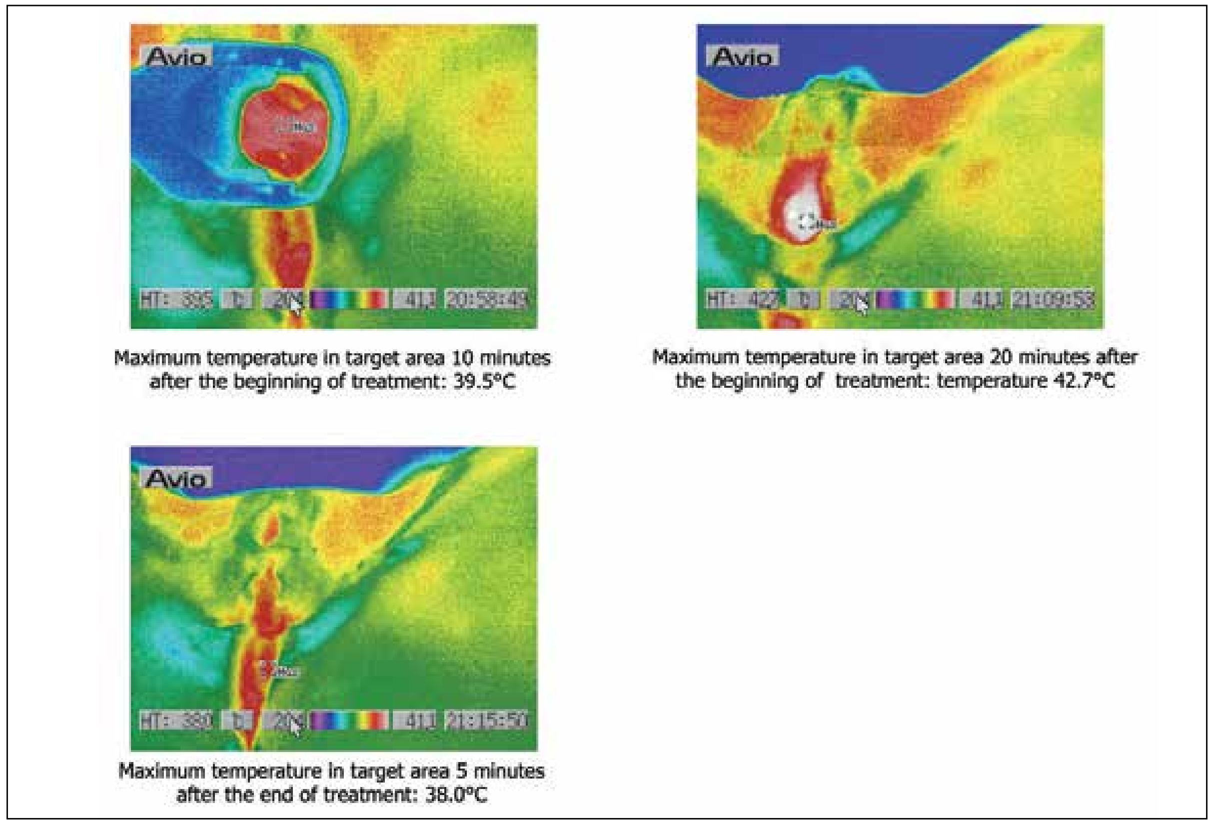

Figure 4.—Infrared temporised thermophotographs of the perineal, vulvar and vaginal areas of a woman enrolled in the vulvo-vaginal laxity arm of the study during her first 20-min DQRF session. Operational position: dorsal lithotomy position.

The women with introital and vaginal laxity enrolled in the study defined their perception as “very loose”, “moderately loose”, or “slightly loose” on an internationally recognized self-assessment instrument as the VLQ. However few, as it is usually the case in exploratory studies, these women were a faithful sample of the universe of women with subjective perception of vaginal laxity in the gynecologist’s everyday clinical practice.

Improvements were rapid for both mean VLQ scores as index of vaginal laxity and PISQ-12 scores as index of overall sexual function and ancillary VVA-related disturbances like sex-related urinary and stool incontinence. Statistical and clinical VLQ and PISQ-12 improvements could be already shown at the first assessment visit immediately before the last DQRF procedure, only about 40 days after the first one, suggesting rapid onset of clinical benefits.

Improvements in VLQ and PISQ-12 scores *vs.* pre-DQRF basal assessment were similar at the first, the second and the third follow-up visits, suggesting persistence of clinical benefits with a base in anatomical re-modelling. Individual scores for intensity of orgasms and emotional experience during intercourse improved similarly to scores for dysuria and incontinence, confirming that anatomical remodelling may be behind such ample benefits. Rapid and persistent improvement of vaginal laxity perception and laxity-related symptoms with DQRF treatment is in line with previous clinical evidences with highly effective unipolar radiofrequency and laser treatments.[8, 13, 14]

When informally questioned during follow-up visits, women with pre-treatment introital vaginal laxity were usually happy to confirm gratifying, even unexpected, improvements in self-perceived sense of looseness, reduction of orgasmic dysfunction, better overall sexual satisfaction with a more relaxed couple relationship, as well as more pleasing genital aesthetics and improvement or disappearance of sex-associated stool and urinary incontinence. The operator also commonly referred visual improvements in looseness of labia majora, introitus and vagina: even at the first visit before the last planned DQRF treatment session.

As regards the VVA/GSM arm of the study, consistent improvements of all symptoms, as well as of sexual gratification, were reported by almost the whole VVA/GSM sample. Once again, the improvement of symptoms and the benefits for the sexual life were rapid — already after about a month and even before the end of the planned DQRF programm — and persisted over the 2-month follow-up period.

The persistency of benefits once again suggests anatomical re-modelling and real correction of atrophy. Although no evaluation of thinning/loss of vaginal rugae, mucosal pallor and friability, low vaginal maturation index and other VVA-related symptoms was formally planned, anecdotic observations by investigators confirm anatomical rejuvenation. The menopausal fall of sex hormones, especially estrogens, impacts on mucosal elasticity by fusion, hyalinization and fragmentation of collagen and elastin fibers, and loss of highly hydrated matrix glycosaminoglycans.[18, 19] As a consequence, urogenital atrophy-related symptoms develop in 40-57% of post-menopausal women and even in 15% of pre-menopausal ones.[18]

The benefits for vaginal health in menopausal women suggested by this exploratory study could even be indirectly self-sustaining over the long time. By letting the woman resume and maintain an active sexual life, DQRF vaginal rejuvenation may activate a series of physiological protective mechanisms that help to counteract the loss of mucosal elasticity and hydration associated with sex hormone deprivation.[20]

However promising the results of this exploratory study with the new technologically advanced radiofrequency device in women with either vulvo-vaginal laxity or VVA/GSM, whether the benefits for wellbeing, self-esteem, sexual health and couple relationship are long-lasting remains an open question. Only further studies with a longer follow-up, hopefully in comparison with other effective non-surgical treatments, will be able to answer the question. Decreased sexual functioning in young breast cancer survivors as well as in pre-menopausal women with chemotherapy-related or surgical amenorrhea is another issue that this new technology could possibly contribute to relieve.[21]

Another field of application of non-surgical technologies for vaginal rejuvenation relates to the wish by many women, who have no real genitalia disorders, to obtain a more subjectively pleasing aesthetic appearance. This may indeed be the foremost field of application of non-surgical procedures for vaginal rejuvenation, and even for elective surgery.

Recent studies have shown that aesthetic reasons were behind the decision by 90% of patients to undergo elective surgery for vaginal tightening and perineal support.[22] Labial reduction surgical procedures performed in the UK have doubled in the current decade,[23] whilst vaginal rejuvenation procedures increased by almost 30% in just one year in the USA in the last decade, from 793 in 2005 up to 1030 in 2006, according to the American Society of Plastic Surgeons.[24] The dynamic quadripolar evolution of the established radiofrequency technology is likely to have brilliant future also in aesthetic medicine, if the dynamic quadripolar concept — "persistent rejuvenation whilst minimising the risk of thermal injuries" — will survive the test of time. Well-designed dose-finding studies are a must also for any development in aesthetic medicine.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Appendix.—DQRF device and procedure

The radiofrequency generator is driven by a patented dynamic quadripolar technology emitting radiofrequency DQRF with frequencies that vary between 1MHz and 1.3MHz and a maximum emitting power of 55W. The device is equipped with both a movement and a temperature detector sensor for high safety. Specifically designed treatment tips equipped with medically certified AISI Type 316 stainless steel dynamic quadripolar electrodes are mounted on anatomical probes used for intravaginal, introital and vulvar applications.

Procedures were office-performed with no need for previous preparations like analgesia or local anesthesia; subjects were placed on the examining table in dorsal lithotomy position. Vagina, perineum, and perianal area were cleansed using an alcohol-free cleanse. The treatment area, defined by a vaginal circumference at the hymenal ring of about 12 cm, was about 20 cm^2. The probe tipped by the dynamic quadripolar electrode system is applied onto the mucosa of the vaginal introitus starting behind the hymenal ring using a coupling gel to ensure the RF delivery. Radiofrequency energy is applied over the treatment area with circular and back-and-forth continuous movements, keeping the probe in contact with the vaginal mucosal walls. The target temperature is reached setting the power from 15% to 18% according to the patient's sensitivity. The target range in VVA/GSM subjects is lower (40° C to 42° C) and is reached by setting a power between 12-15% according to the patient's sensitivity.

The new DQRF technology does not need a grounding pad attached on the subject's upper thigh, thereby leading to current flows through the thigh tissues and delivery of heavy energy loads because of Ohm's resistances in tissues. Electric fields generate only within the electrodes area. The configuration of the four electrodes is continuously and electronically controlled between alternating receiver and transmitter states. This allows repelling electric fields to form that, once in the ideal combination, direct energy deep in the subepithelial layers of the introitus, vagina and vulva. The operator can fine-tune the low-energy thermal effect generated by the localized electric fields both volumetrically and in terms of depth. Such fine-tuning is facilitated by a complete set of anatomically designed probes and tips equipped with the dynamic quadripolar electrode system.

Genitourinary syndrome of menopause: an overview of clinical manifestations, pathophysiology, etiology, evaluation, and management

CrossMark

Jason Gandhi, MS; Andrew Chen, BA; Gautam Dagur, MS; Yiji Suh; Noel Smith, MD; Brianna Cali, BS; Sardar Ali Khan, MD

Genitourinary syndrome of menopause, a new term for a condition more renowned as atrophic vaginitis, is a hypoestrogenic condition with external genital, urological, and sexual implications that affects >50% of postmenopausal women. Due to sexual embarrassment and the sensitive nature of discussing symptoms, genitourinary syndrome of menopause is greatly underdiagnosed. The most up-to-date literature pertaining to clinical manifestations, pathophysiology, etiology, evaluation, and management of genitourinary syndrome of menopause is comprehensively reviewed. Early detection and individually tailored pharmacologic (eg, estrogen therapy, selective estrogen receptor modulator, synthetic steroid, oxytocin, and dehydroepiandrosterone) and/or nonpharmacologic (eg, laser therapies, moisturizers and lubricants, homeopathic remedies, and lifestyle modifications) treatment is paramount for not only improving quality of life but also for preventing exacerbation of symptoms in women with this condition.

Key words: atrophic vaginitis, dyspareunia, estrogen-progestin therapy, genitourinary syndrome of menopause, hypoestrogenism, menopausal hormone therapy, nonhormonal vaginal therapy, quality of life, urinary incontinence, urogenital atrophy, vaginal maturation index, vulvovaginal atrophy

Introduction

Genitourinary syndrome of menopause (GSM), previously known as vulvovaginal atrophy, atrophic vaginitis, or urogenital atrophy, is a chronic, progressive vulvovaginal, sexual, and lower urinary tract condition characterized by a host of symptoms secondary to a clinical state of hypoestrogenism after onset of menopause. In 2014, the International Society for the Study of Women's Sexual Health and the North American Menopause Society agreed that "genitourinary syndrome of menopause" is a more inclusive and accurate term to describe the conglomeration of external genital, urological, and sexual sequelae caused by hypoestrogenism during menopause.[1] They also agreed the new terminology would carry less social stigma thus making it easier for women to openly talk about it, especially to their care providers. GSM-like symptoms may also be mirrored in hypoestrogenic premenopausal women. The syndrome or its features manifest in some manner in approximately 15% of premenopausal women[2] and 40-54% of postmenopausal women.[3] Because women have a higher life expectancy than men, and approximately >17% of the population will be age >65 years by 2030, the consequences of declined endogenous estrogen levels in menopausal women should be of great interest to clinicians.[4]

GSM is often underdiagnosed due to sexual embarrassment[5] or general disregard due to associating it as a liability of natural aging. In a recent study, only 4% of women were able to attribute vulvovaginal symptoms to GSM.[6] Only around 25% of women with GSM go to a practitioner for consultation.[2] Another European study found that only 54% of women discuss their sexual health with practitioners when asked, and 33% of women do not discuss it at all.[7] Identifying postmenopausal women's profiles (eg, their tendency to be proactive or reserved) may help bypass the social taboo on discussing GSM, thus expediting evaluation and management.[8] In cases of abrupt estrogen deprivation, eg, surgical menopause, patients can experience significant sexual dysfunction and even poorer quality-of-life outcomes. We presently explore the signs, symptoms, and genitourinary manifestations of GSM; the importance of its early detection; as well as the crucial role of proper patient education in avoiding the long-term risks and complications that may severely compromise quality of life. Management of GSM must ideally be tailored to individual patient medical history, potential risks and benefits of exogenously administered estrogen therapy (ET), as well as patient lifestyle.

Clinical manifestations

Clinicians play a major role in recognizing the signs of GSM because many women are reluctant to report their symptoms due to personal reasons. Additionally, 50% of postmenopausal women with mild or moderate GSM are asymptomatic, making diagnosis particularly challenging. Only a weak correlation has been found between symptom score and physical examination of GSM.[9]

Manifestations of GSM are primarily divided into external genital and urological signs and symptoms (Table 1), which can be observed through physical examination.[1] Genitourinary complications experienced secondary to GSM are included in Table 1 to further guide clinicians and health care providers. There may be a linking of certain signs and complications, eg, vaginal vault prolapse and urinary incontinence. Introital stenosis to a width <2 fingers, decreased vaginal depth, and vaginal dryness must be diagnosed before insertion of the speculum, otherwise the pelvic examination will cause considerable pain. Vaginoscopy is an alternative if the practitioner is unable to perform a pelvic/vaginal examination.

GSM is most commonly diagnosed when the patient presents with dyspareunia secondary to vaginal dryness. Common signs and symptoms in order of prevalence and degree of atrophy include vaginal dryness (in 75% postmenopausal women), dyspareunia (38%) and vaginal itching, discharge, and pain (15%).[10,11] When the vulvovaginal epithelium is inadequately lubricated, ulceration and fissures can develop during intercourse, causing dyspareunia. Vaginismus, or painful spasm of vaginal muscles, can also occur as a physiological response when there is anxiety toward expected sexual pain. Sexual manifestations are an extension of those of the external genitalia (Table 1).

Pathophysiology

During female embryologic development, the urogenital sinus, müllerian ducts, and sinovaginal node (ie, Müller tubercle) form the vaginal vestibule and lower fifth of vagina, urinary bladder, trigone, and the entire urethra. Fused müllerian ducts form the uterus and upper four-fifths of the vagina. The genitalia and lower urinary tract share common estrogen receptor function. Due to the common embryological origin, hypoestrogenism has both vulvovaginal and urologic effects; urogenital tissue receptors are dependent on endogenous estrogen levels to maintain normal physiology.[12] During postmenopause, the number of estrogen receptors continue to decrease but never fully disappear. However, in the presence of exogenous administration of estrogen, one can replenish lost estrogen receptors.[2]

In the vulvovaginal tissue, estrogen receptor-α is predominantly present in premenopausal and postmenopausal women, whereas estrogen-β appears to only be expressed in premenopausal women.[13] Estrogen is a vasoactive hormone that increases blood flow.[11] Vaginal lubrication is caused by fluid transudation from blood vessels, and from endocervical and Bartholin glands. Activated estrogen receptors also encourage epithelial proliferation with redundant smooth muscle tissue layer. The formation of rugae aids in expandability, distensibility, and lubrication of the vagina during sexual stimulation. Vaginal secretions, lubrication, and improved blood flow of vaginal walls all help to increase vaginal mechanical

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TABLE 1
External genital, urological, and sexual manifestations of genitourinary syndrome of menopause

External genital		Urological		Sexual
Signs and symptoms	Complications	Signs and symptoms	Complications	Signs and symptoms
Vaginal/pelvic pain and pressure Dryness Irritation/burning Tenderness Pruritus vulvae Decreased turgor and elasticity Suprapubic pain Leukorrhea Ecchymosis Erythema Thinning/graying pubic hair Thinning/pallor of vaginal epithelium Pale vaginal mucous membrane Fusion of labia minora Labial shrinking Leukoplakic patches on vaginal mucosa Presence of petechiae Fewer vaginal rugae Increased vaginal friability	Labial atrophy Vulvar atrophy and lesions Atrophy of Bartholin glands Intravaginal retraction of urethra Alkaline pH (5—7) Reduced vaginal and cervical secretions Pelvic organ prolapse Vaginal vault prolapse Vaginal stenosis and shortening Introital stenosis	Frequency Urgency Postvoid dribbling Nocturia Stress/urgency incontinence Dysuria Hematuria Recurrent urinary tract infection	Ischemia of vesical trigone Meatal stenosis Cystocele and rectocele Urethral prolapse Urethral atrophy Retraction of urethral meatus inside vagina associated with vaginal voiding Uterine prolapse Urethral polyp or caruncle	Loss of libido Loss of arousal Lack of lubrication Dyspareunia Dysorgasmia Pelvic pain Bleeding or spotting during intercourse

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TABLE 2
Causes of estrogen deficiency in premenopausal women or due to factors unrelated to menopause

Type	Cause
Systemic	Hyperprolactinemia (during breast-feeding) Postpartum estrogen deficiency Hypoestrogenism (eg, due to autoimmune disorders affecting ovaries, pituitary tumors)
Pharmacological	Gonadotropin-releasing hormone agonist analogs Leuprolide Nafarelin Selective estrogen receptor modulators Tamoxifen Aromatase inhibitors Danazol Medroxyprogesterone
Iatrogenic	Bilateral oophorectomy (ie, surgical menopause) Ovarian failure secondary to pelvic radiation Chemotherapy Radiation therapy

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compliance.[2] In the advent of hypoestrogenism, these prolubricative and proelastic functions are lost due to diminished collagen, elastin, and hyaluronic acid content; thinned epithelium; impaired smooth muscle proliferation; denser connective tissue arrangement; and loss of vascularity, thus predisposing the woman to irritation and sexual trauma.[14]

The vaginal and urethral epithelium is comprised of nonkeratinized stratified squamous epithelium with superficial, intermediate, and basal cell layers that store glycogen in the presence of physiologic estrogen levels. The epithelium of the vaginal wall is constantly exfoliating and producing glycogen, which is hydrolyzed to glucose. A healthy vaginal flora is composed of a variety of aerobic and anaerobic, gram-positive and gram-negative bacteria. Predominant *Lactobacillus* metabolizes glucose into lactic acid and acetic acid, lowering the vaginal pH to a range of 3.5-4.5. The acidity of the vagina provides natural protection against urinary tract infections (UTI) and vaginitis, discouraging the growth of pathogenic bacteria and infection.[11] Estrogen is vital for modulating innate defenses of the urinary tract. Thus, knowledge of the association between GSM and recurrent UTI can help avoid unnecessary use of antibiotics and prevent antimicrobial resistance.[15]

Atrophy of urogenital tissue is identified with declined endogenous estrogen levels with vaginal epithelium appearing thin, pale, and less rugated. The loss of estrogen is responsible for the reduction of *Lactobacillus*, changing the vaginal fluid to an alkaline pH of $\geq$5.0. The higher pH impairs the viability of healthy vaginal flora[5] and promotes overgrowth of gram-negative rod fecal flora including group B streptococci, staphylococci, coliforms, and diphtheroids, inducing vaginal infection and UTI and inflammation.[16] In decreased levels of circulating estrogen, substantial vascularization is lost in the urogenital tract, making the tissue atrophic. Estrogen deficiency causes loss in dermal collagen in dense connective tissue of the vagina, bladder, and urethra, and then causes the vaginal wall to become thinner and less elastic. In consequence, the vagina becomes shortened and narrowed, which may lead to dyspareunia. The bladder and urethra also become atrophic, causing urinary incontinence and frequency.[2,11] One study reported that 20% of postmenopausal women experienced urge incontinence while roughly 50% experienced stress urinary incontinence.[17] It is thought that estrogen receptors in the bladder trigone and urethra aid in increasing the sensory threshold when the bladder becomes distended. Lack of estrogen decreases the threshold and impairs urethral closure pressure and Valsalva leak-point pressure, contributing to urinary urgency.[17] Research studies have also suggested that in postmenopausal women, the lack of estrogen impairs connective tissue and causes urethral sphincter dysfunction of stress urinary incontinence. In comparison, premenopausal women experience stress incontinence mainly due to anatomical changes.[18] GSM-related incontinence is a key cause of recurrent UTI in postmenopausal women, signifying the importance of GSM evaluation and management to avoid the repercussions of inessential antibiotic therapy.[15]

TABLE 3
Risk factors for genitourinary syndrome of menopause

Menopause
Nonmenopause hypoestrogenism
Bilateral oophorectomy
Cigarette smoking
Alcohol abuse
Decreased frequency and sexual abstinence
Ovarian failure
Lack of exercise
Absence of vaginal childbirth

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Etiology

The etiology of GSM is secondary to decreased levels of endogenous estrogen levels. In the female body, the 3 forms of estrogen produced mainly in the ovaries are estradiol, estrone, and estriol with estradiol being the most abundant in premenopausal women. During the transition between perimenopausal and postmenopausal years, estrone becomes the most prominent and is a less potent form of estrogen.[19]

Table 2 outlines nonmenopause-related causes of estrogen deficiency that may mimic GSM sequelae,[12,16] such as the hormonal therapies and chemotherapy from treating women with breast cancer. Table 3 lists risk factors for developing GSM such as cigarette smoking, which contributes to decreased circulation and impaired receptor function.[5,12] Table 4 distinguishes between development of superficial and deep dyspareunia.[20,21]

TABLE 4
Classifications, etiologies, and risk factors for superficial and deep dyspareunia

	Subtype	
	Superficial	Deep
Prevalence	More common	Less common
Location	Vulvar region, vaginal opening	Pelvic region, internal genitalia
Etiologies	Genitourinary syndrome of menopause, vulvitis, vulvovaginitis, vulvovestibulitis, genital herpes, urethritis, atrophic vulvitis, lack of lubrication, vaginal dryness, vaginal infection, episiotomy, radiotherapy, sexual trauma, and topical irritants	Pelvic inflammatory disease; gynecological, pelvic, or abdominal surgery; postoperative adhesions; endometriosis; genital or pelvic tumors; irritable bowel syndrome; urinary tract infections; and ovarian cysts
Risk factors	Age, menopause, hypoestrogenism, vaginal atrophy, lack of arousal and lubrication, and pelvis floor abnormalities	
Type of pain	Sharp, burning, itching	

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Evaluation

A full history should be performed on patients suspected to have GSM. Lubricants, powders, soaps, spermicides, and panty liners commonly contain irritants that could produce discomfort to the genitourinary region. Antiestrogen medications or a history of oophorectomy, radiation, or chemotherapy increases suspicion of GSM-like symptomology particularly in premenopausal women.

The cornerstone of evaluating menopausal women with sexual health symptoms is the pelvic examination. Atrophic vaginal epithelium appears pale and shiny, and patches of erythema may be present. One should check for any signs of lacerations or lesions, labial fusion, introital stenosis, and friable epithelium. Table 5 catalogs findings of cystoscopic and laparoscopic procedures.

Differential diagnoses that should be evaluated when a woman is thought to present with GSM include bacterial vaginosis, trichomoniasis, candidiasis, contact irritants, foreign bodies, and sexual trauma. Other diagnoses to consider include neoplasia and precancerous neoplasia of external or internal female genitalia, endocrine disorders, infections from body piercing, vaginal stenosis secondary to radiation, lichen sclerosus, and lichen planus.[12]

To aid in the diagnosis of GSM, several laboratory tests are useful. Cytology of the vaginal epithelium shows an increase in parabasal cells and a decrease in superficial cells. Ultrasound examination of the uterus is especially useful as a thin endometrial thickness of $\leq$5 mm indicates decreased estrogen stimulation. Vaginal pH, Pap test, and vaginal culture are also useful in assessing for genitourinary infection. Table 6 lists the diagnostic tests to perform after the initial clinical assessment.

Management

Management of GSM varies according to symptom severity. For moderate to severe symptoms, ET is reported to be the most successful treatment option in terms of increasing the vaginal maturation index (VMI). For milder symptoms, though nonhormonal therapies are subjectively effective, they are suitable for women at risk for estrogen-responsive neoplasia, and do not require prescriptions.[22,23] To assess the effectiveness of treatment, a pH test and cytologic analysis may be utilized. Since GSM is a chronic condition, life-long management is essential to prevent recurrence of symptoms.

Estrogen therapy

ET is the standard treatment for GSM. It has proven to be successful in rapidly restoring vaginal epithelium and associated vasculature, improving vaginal secretions, lowering vaginal pH to restore healthy vaginal flora, and alleviating overall vulvovaginal symptoms.[24] Both systemically (eg, oral or patch) and vaginally administered forms are effective in improving GSM. However, hormonal therapy is only considered after all risk factors and benefits have been thoroughly reviewed with the patient. The lowest effective dosage of systemic ET is always advisable, as the stimulatory effect of high estrogen levels on the endometrium can lead to proliferation, hyperplasia, or carcinoma. Local ET is the most accepted form of therapy for GSM; it also offers the fastest and most effective symptomatic relief. Although local ET does not reduce the risk of osteoporosis or effectively manage vasomotor symptoms, up to

TABLE 5
Physical findings of urogenital instrumentation in genitourinary syndrome of menopause

Cystoscopy	Laparoscopy
Squamous metaplasia of trigone Shortening of urethra Pale urethral mucous membrane Urinary sphincter dysfunction (eg, decreased contractility) Compliance Pale trigone	Atrophic uterus, fallopian tubes, and ovaries Supporting lax ligaments

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TABLE 6
Diagnostic tests to consider post–initial clinical assessment

Tests	Findings
Pelvic exam with speculum and bimanual palpation (with topical anesthesia); vaginoscopy	Loss of rugae
Rectal exam	Rectal mass; rectocele
Transvaginal ultrasound; hysteroscopy	Endometrial stripe <5 mm indicating loss of estrogenic stimulation; pelvic mass
pH test	Symptomatic pH: 5–7 (normal pH: 3.5–4.5)
Vaginal cytology	Basal epithelial cells predominate and decreased percentage of superficial cells
Wet mount	Presence of leukocytes and paucity of *Lactobacillus*
Pap test	Atrophy of cervix and stenosis of os
MRI/CT scan	Pelvic and adnexal abnormalities

CT, computed tomography; *MRI*, magnetic resonance imaging.
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90% of women report subjective improvement of their symptoms.[25]

As with all hormone replacement therapies, some risks accompany the benefits of treatment. Each woman should discuss her situation with her physician to determine the duration and severity of her series of symptoms. Women may prefer to avoid hormone therapy and approach the option of over-the-counter vaginal creams for symptomatic relief.

Although side effects are uncommon, systemic ET is associated with breast tenderness and/or enlargement, vaginal bleeding or spotting, nausea, and modest weight gain. In cases where the patch is used, some irritation at application sites may occur. The most common side effect of hormone replacement therapy is increased systemic estrogen. Additionally, some women might experience headache, back pain, abdominal pain, and vaginal yeast infections. Breast tenderness most often decreases with time, and taking oral estrogen with food can prevent nausea. Common side effects of intravaginal products include vaginal secretion, vaginal spotting, and genital pruritus. To avoid any harmful long-term side effects of hormone replacement therapy, many physicians advise patients to use the cream or gel for 6 months, discontinue temporarily, and then resume treatment.

Contraindications to the use of ET include known or suspected cases of breast cancer, estrogen-dependent cancers, undiagnosed vaginal bleeding, history of thromboembolism (ie, blood clotting disorders), endometrial hyperplasia or cancer, hypertension, hyperlipidemia, liver disease, hypersensitivity to active compounds in ET, history of stroke, venothrombotic events, coronary heart disease, pregnancy, smoking in those age >35 years, migraines with neurologic symptoms, and acute cholecystitis/cholangitis.

Systemic. Systemic hormone replacement therapy is suggested to patients who seek relief from GSM symptoms in addition to relief from hot flashes and protection from osteoporosis.[26] Due to concomitant use of progestin in women with a uterus, systemic ET is associated with adverse effects such as endometrial bleeding, breast tenderness, increased risk of stroke, venous thromboembolism, and breast cancer. Potential adverse effects of estrogen-progestin therapy may cause the therapy to be contraindicated and unacceptable to some women. Women taking systemic hormone therapy with unresolved symptoms should also take continuous or intermittent topical ET.

Topical. Topical estrogens alone supply sufficient estrogen to reduce symptoms and reverse atrophic vaginal epithelial conditions. The treatment limits systemic absorption by avoidance of hepatic metabolism. Thus, additional progestin is not necessary to prevent endometrial hyperplasia or cancer. Topical treatment is advised to patients who seek relief solely from vaginal atrophy symptoms, as the low dose of estrogen may not be enough to alleviate other menopausal symptoms. In contrast to systemic estrogen, topical estrogens do not solve vasomotor symptoms associated with menopause or reduce the risks of osteoporosis. According to the North American Menopause Society, low-dose vaginal estrogens decrease vaginal pH, increase the number of vaginal lactobacilli, improve vaginal and urethral cytology, and prevent frequent UTI.[11] Vaginal ET trials have also demonstrated relief of urinary symptoms of urgency, frequency, nocturia, and stress/urgency urinary incontinence.[23] Vaginal tablets, creams, and rings are the routes of low-dose local estrogen; the 2006 Cochrane Database of Systematic Reviews stated that all types are equally effective in resolution of dyspareunia, vaginal itching, and dryness.[27]

Women should choose the option of low-dose vaginal ET based on their personal preference and lifestyle. Women may select the tablet over the cream due to reduction in mess. Creams are currently the most common choice of vaginal product for the treatment of GSM and provide flexibility of dosage and frequency of administration. Advantages of estradiol-releasing vaginal rings are that they are long-acting over a period of 3 months and require less sustained effort to use. However, there are reports of occasional vaginal ring expulsion so adequate dexterity is required for insertion and removal. Cystoceles or rectoceles may also cause the ring to become displaced and fall out.

Roughly 80-90% of women on local ET report subjective improvement

and relief from GSM.[12,16,22] Care and monitoring are often customized depending on a woman's medical history and symptoms. Relevant factors include whether a woman is premenopausal or postmenopausal, whether she has a uterus, and whether she has had hormone-dependent cancer (eg, breast or endometrial). In asymptomatic women using topical estrogens, there are currently insufficient data to recommend annual endometrial surveillance.[28]

Selective estrogen receptor modulator

Another oral treatment option for GSM are selective estrogen receptor modulators (SERM). Ospemifene was approved by the Food and Drug Administration in 2013. Ospemifene provides a therapeutic pharmacologic treatment option for patients who are not candidates for ET. The current literature shows that it is both efficacious and safe in treating vulvovaginal atrophy and dyspareunia by improving vaginal structure and pH.[29] Double-blind placebo-controlled studies have shown that it remains efficacious and safe up to 52 weeks while providing greater symptomatic relief than vaginal lubricants. There were no cases of endometrial cancer and <1% of patients experienced endometrial hyperplasia with treatment.[30] Similar to ET, ospemifene increases the incidence of thromboembolism and should be avoided in patients with increased risk of venous thromboembolism.

Lasofoxifene is another SERM that binds to both estrogen receptor types and has high oral bioavailability. Three phase III clinical trials showed that lasofoxifene is effective in increasing bone mineral density.[31-33] Additionally, the drug has been shown to have many other beneficial effects such as decreased coronary disease, stroke, vaginal pH, and vaginal dryness.[34]

A newer therapy, tissue-specific estrogen complex, involves combining a SERM with a conjugated estrogen. Studies show that pairing bazedoxifene, a SERM, with estrogens is associated with higher safety and better tolerability than estrogen-progestin therapy.[35,36]

Laser therapies

Recently, the use of laser treatment has become an innovative treatment option for GSM. In 2014, the Food and Drug Administration approved the use of fractional microablative carbon-dioxide laser therapy for genitourinary surgery. At specific diode parameters, laser therapy stimulates improved vascularity; improved glycogen storage, collagen, and extracellular matrix production; as well as cellular proliferation to increase the thickness of the squamous epithelium with the formation of new papilla, thus enhancing the viability of the vaginal epithelium.[37-39] One study reported that improvement of vaginal dryness, pruritus, dysuria, and dyspareunia was maintained at 12 weeks' follow-up posttherapy.[40] This study included 50 women and reported an 84% satisfaction rate with the laser treatment. In addition, no adverse events were reported during the study period. Additional research has shown that the microablative therapy also significantly improves quality of life and sexual function.[38] In all, 85% of women who were previously not sexually active due to GSM symptoms regained a normal sexual life at 12 weeks following therapy.[41]

Novel nonablative laser therapies are also being studied for use in the treatment vulvovaginal symptoms. Pilot studies have found that vaginal erbium laser treatment significantly improves both vaginal dryness and dyspareunia up to 24 weeks after treatment.[42] Precise impulses are released to raise the temperature of vaginal tissue, stimulating remodeling of collagen in the introitus and vaginal canal. Novel low-energy dynamic quadripolar radiofrequency (DQRF) lasers are now also being used for vulvovaginal treatment. Previous ex vivo and in vivo studies demonstrated that DQRF thermal treatment could produce thickening and rearrangement of collagen and elastin fibers without side effects in the epidermis, nerves, or blood vessels.[43] A study conducted by Vicariotto and Raichi[44] demonstrated that in women with vaginal laxity, DQRF produced subjective improvement in laxity, sexual satisfaction, dysuria, and incontinence. As an attractive novel nonhormonal therapy for GSM, additional studies are needed to explore the long-term safety and efficacy of various laser therapies on genitourinary symptoms.

Synthetic steroid

Tibolone, a synthetic steroid, has been found not only to improve the VMI but also increase sex drive through its part-androgenic properties. Moreover, urinary incontinence problems of nocturia and urgency were found to be minimized.[45]

Oxytocin

Oxytocin, the neuropeptide released by the posterior pituitary gland, has also been studied amidst concerns over ET. A randomized double-blind controlled trial conducted in Stockholm reported that application of oxytocin gel produced healthier and more normalized vaginal epithelium. Treated participants reported significant reduction in their most bothersome symptom. Additionally, vaginal pH decreased with use of oxytocin and no increase in endometrial thickness was observed.[46]

Intravaginal dehydroepiandrosterone

Dehydroepiandrosterone (ie, prasterone) is a steroid hormone intermediate in the biosynthesis pathway for androgen and estrogen synthesis. A recent randomized, double-blind, placebo-controlled phase III trial showed that daily intravaginal application of 0.5% dehydroepiandrosterone increased superficial cell percentage and decreased parabasal cell in the vaginal epithelium, decreased vaginal pH, and decreased sexual pain. At gynecological examination, dehydroepiandrosterone application improved vaginal secretions, epithelial thickness, and color in comparison to placebo.[47] As a promising novel therapy, more research is needed to assess the long-term efficacy and safety of dehydroepiandrosterone.

Moisturizers and lubricants

Moisturizers and lubricants are used for temporary relief of vaginal dryness and itching during sexual intercourse. These therapy options do not reverse most vaginal atrophic effects and have effectiveness length of <24 hours. Hence, they are more useful and recommended to women with mild symptoms, or should be used in conjunction with systemic or topical ET. Moisturizers may contain polycarbophil-based polymers that adhere to the epithelial and mucin cells on the vaginal wall to preserve moisture levels.[24] When selecting a lubricant or moisturizer, it is advised that the product should mimic vaginal secretions in terms of osmolality, pH, and composition.[48]

Homeopathic remedies

It is estimated that 10% of women experiencing vaginal symptoms of GSM are using herbal therapies such as black cohosh, dong quai, phytomedicines, nettle (250 mL infusion/d), comfrey root, motherwort, soy foods, and chaste tree extract. Other alternatives and complementary therapies are chickweed tincture, wild yam, and acidophilus capsules. Although homeopathic remedies show improvement in vaginal tissue flexibility, studies show that there is no proven efficacy on the vaginal epithelium and treatment of GSM.[16] Some vitamins such as vitamin E and D have been used for GSM therapy; vitamin D may help generate keratinocyte proliferation and differentiation in the vaginal epithelium.[24]

Lifestyle modifications

Increased sexual activity is advised for maintaining robust vaginal muscle condition. There is a positive link between sexual activity and maintenance of vaginal elasticity and pliability as well as lubricative response to sexual stimulation. Sexual intercourse improves blood circulation to the vagina and seminal fluid also contains sexual steroids, prostaglandins, and essential fatty acids, which serve to maintain vaginal tissue. Vulvovaginal tissue stretching also helps to promote vaginal elasticity. Masturbation or sex devices are options for patients without a partner.[22] Stress-reduction therapy and psychological counseling may benefit women with nonorganic causes of vaginal dryness. Cessation of smoking can help relieve symptoms. Lastly, wearing looser undergarments and legwear may improve air circulation, discouraging growth of microorganisms.

Conclusion

"Genitourinary syndrome of menopause" is the latest terminology instated to increase awareness and reduce social stigma of the genitourinary sequelae and sexual dysfunction associated with postmenopausal hypoestrogenism. ET is the mainstay of medical treatment but the risks and benefits should be thoroughly discussed with each patient. More importantly the physician and patient should work together to find the optimal combination of lifestyle changes and management options. Global assessment scales for GSM are currently seeing development; a proposed tool rates elasticity, lubrication, and tissue integrity; state and color of individual vulvovaginal and urethral anatomy; as well as pH and VMI.[49] Such assessment tools may help a physician to tailor treatment based on the objective and subjective severity of signs and symptoms. Newer treatments such as laser therapy are promising but require further studies to prove long-term efficacy. ■

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ORIGINAL ARTICLE

Dynamic quadripolar radiofrequency treatment of vaginal laxity/menopausal vulvo-vaginal atrophy: 12-month efficacy and safety

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ABSTRACT

BACKGROUND: Twelve-month extension of a previous spontaneous exploratory study investigating safety and efficacy of a new low-energy dynamic quadripolar radiofrequency (DQRF) device in: A) premenopausal women with symptoms of vaginal laxity, with special reference to dysuria, urinary incontinence and unsatisfactory sexual life (vaginal laxity arm of the study); B) postmenopausal women with vulvovaginal atrophy/genitourinary syndrome of menopause (VVA/GSM) and VVA/GSM-related symptoms (VVA/GSM arm of the study). DQRF treatment schedule in both study arms: 4 to 6 procedures of 15 to 20 min every 14 days (vaginal laxity, range 12-17 days; VVA/GSM, range 13-16). Operative temperatures in vaginal target tissues during procedure: vaginal laxity, 42 °C (range 40-43 °C); VVA/GSM, 40 °C (range 40-42 °C).

METHODS: In the vaginal laxity arm of the study, 25 women with subjective sensation of vaginal introital laxity (very to slightly loose). Assessment of urinary incontinence, satisfaction with sexual relationship and contribution of pelvic organ prolapse: Vaginal Laxity Questionnaire (VLQ, Italian certified translation) and short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12, Italian certified translation). Further evaluation of sexual gratification: Sexual Satisfaction Questionnaire (SSQ). In the VVA/GSM arm of the study, 32 women with objective evidence of VVA and vaginal dryness and/or dyspareunia as most bothersome symptoms. Assessment of VVA/GSM symptoms and overall satisfaction with sexual life: specifically designed 10-cm visual analogue scales.

RESULTS: All 4 to 6 planned DQRF sessions were well tolerated in both the vaginal laxity and VVA/GSM arms of the study, with no troubling pain, thermal injury or other immediate adverse effects during all the procedures. All screened women completed the planned DQRF treatment sessions in both arms of the extension study. There was no participant attrition with only a few occasionally missing visits over the 12-month follow-up period. Improvements were rapid in self-perception of introital looseness and related symptoms like dysuria/urinary incontinence and unrewarding sexual relationship (vaginal laxity patients) and atrophy-related symptoms including painful and unsatisfactory sexual activity (VVA/GSM patients). Participating women consistently reported wide-spectrum strong clinical improvements by the end of the planned DQRF sessions. Clinical improvements remained steady for the whole follow-up period in postmenopausal women; a statistically non-significant tendency to slight deterioration in VLQ, PISQ-12 and SSQ mean scores was detected after 6 to 9 months of follow-up in the vaginal laxity arm of the study.

CONCLUSIONS: Safety was excellent during all DQRF procedures and over the 12 months following the end of the treatment sessions. VLQ, PISQ-12 and SSQ scores (women with vaginal laxity), VAS self-evaluation of VVA/GSM symptoms and overall satisfaction with sexual life (women with VVA/GSM symptoms) improved rapidly, reaching almost normal levels by the last DQRF session and suggesting rapid, but also persistent, vaginal rejuvenation in both indications. A late tendency to some slight deterioration in women treated for vaginal laxity suggests such women might benefit from new DQRF treatments 6 to 9 months after the previous cycle.

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Key words: Vulva - Vagina - Atrophy - Urinary incontinence - Rejuvenation.

The radiofrequency technology for non-surgical thermal treatment and vaginal rejuvenation in women with either vaginal laxity or VVA/GSM is well established and widely considered safe and effective.[1, 2] Increased awareness of these undertreated conditions and technological advances stimulate a steady flow of new surveys and high-level studies.[3-5] A previous paper in 2016 in this journal described for the first time the efficacy and safety of a new technologically advanced low-energy radiofrequency device (EVA™, technology patented by Novavision Group S.p.A., Misinto, Monza-Brianza, Italy) in women experiencing severe quality of life disruption because of either postpartum vaginal laxity or vulvo-vaginal atrophy/genitourinary syndrome of menopause (VVA/GSM). This pioneer short-term investigation was carried out in a private outpatient setting as a spontaneous non-sponsored study.[6]

The 2016 paper also discussed the biophysics leveraged by the patented VDR™ (Vaginal Dynamic Radiofrequency) quadripolar 1.0-1.3 MHz radiofrequency technology of the new device (maximum emitting power, 55 W) to generate radiofrequency fields with high spatial precision in vulvar and vaginal subepithelial layers. Movement and temperature detector sensors specifically designed for high safety (RSS™, Radiofrequency Safety System technology) eliminate any need for systemic analgesia or local anesthesia in the target area — usually a circle of some 12 cm around the hymenal ring.[6]

The herein described two-arm study is the 12-month open-label extension of the previous one with a substantial increase of evaluated women in both indications. In the pioneering office-based pilot study that led to the current extension, 11 women with vaginal laxity and 12 women with VVA/GSM completed a total of, respectively, 5 treatment sessions and 4 sessions every 14±1 and 10±1 days. In this long-term extension, new enrolments have complemented the few participants of the exploratory study up to more than double women with vaginal laxity and almost three times more in the VVA/GSM arm of the study. As the previous investigation, this 12-month extension was also conducted in a private outpatient setting.

Materials and methods

Candidate women with vaginal laxity were screened and treated since early January 2015 and the follow-up was over by mid-January 2017; the total period for candidate women with VVA/GSM was since mid-February 2015 to early February 2017, for both indications within the pool of outpatients regularly attending the investigator's private practice. All candidate women referred either subjective perception of laxity of vaginal introitus and other laxity-associated symptoms or postmenopausal vaginal dryness and other VVA/GSM-related symptoms. All pelvic organ prolapses beyond the hymenal ring, chronic vulvar pain, vulvar lesions (dermatitis, human papillomavirus, herpes simplex, vulvar dystrophy) and poor thickness of the recto-vaginal septum at pelvic examination led to exclusion of candidates. Any active genital or urinary tract infection required treatment before enrolment. All study materials were peer-reviewed for ethical problems and all candidates gave informed consent.

Vaginal laxity arm of the study

Screening criteria

As in the previous short-term exploratory study, the last full-term vaginal delivery (more than 36 weeks gestation) of all premenopausal candidates should have occurred at least one year before study enrollment with currently negative pregnancy tests; candidates should also be reporting a sensation of introital laxity defined as "very loose", "moderately loose", or "slightly loose" — first three categorical levels of response out of the seven of the Likert-type Scale Vaginal Laxity Questionnaire or VLQ in a certified Italian translation.[7] Ancillary screening criteria included age less than 54 years, a normal Papanicolau smear cytology assay obtained no more than 2 months before enrolment, a stable monogamous heterosexual

relationship with at least two vaginal intercourses per month using an acceptable birth control method, and stable doses of any medication known to affect sexuality such as antihypertensives and psychotropics for at least one month. Treatment with medications known to affect collagen metabolism and healing such as non-steroidal anti-inflammatory drugs and steroids, as well as injuries and bleeding of vaginal canal, introitus and vestibule, pelvic surgery in the last 4 years, and severe urinary incontinence with suspected intrinsic sphincteric deficiency and positive empty bladder stress tests also prevented enrollment.

Outcome evaluation

The Italian certified translation of VLQ was the main evaluation instrument; the 12-question short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12, Italian certified translation) was also useful to discriminate the contribution of any concomitant pelvic organ prolapse to vaginal laxity symptoms like dysuria, urinary incontinence and poor sexual satisfaction with couple relationship.[8] An Italian translation of the Sexual Satisfaction Questionnaire (SSQ, 6-level ordered responses: none, poor, fair, good, very good, excellent) was also used to evaluate sexual satisfaction from vaginal intercourse. Categorical responses were translated into ordinal scores for statistical analysis (for instance for the VLQ Scale, very loose=1, moderately loose=2, slightly loose=3, …, moderately tight=6, very tight=7).

VVA/GSM arm of the study

Screening criteria

As in the previous short-term exploratory study, in all postmenopausal candidates (no menstruation for at least 12 months and currently no hormonal replacement therapy) a desire for a still active sexual life should have been coexisting with vaginal dryness, dyspareunia and other VVA/GSM symptoms and/or objective evidence of mucosal atrophy (thinning or loss of vaginal rugae, mucosal pallor, etc.).

Outcome evaluation

Clinical severity of VVA/GSM symptoms (vaginal dryness, burning and itching, dyspareunia, dysuria) was self-assessed by participants at each visit using 10-cm visual analogue scales (VAS) with "no symptom" at the left extreme of the scale and "symptom as severe as it could be" at the right extreme, as in several previous VVA studies including in breast cancer survivors.[9] The overall satisfaction with sexual life was also evaluated by VAS ("worst level of satisfaction" at the left extreme of the 10-cm scale and "best level of satisfaction" at the right extreme).

An overall basal evaluation was performed immediately before the first DQRF procedure in all enrolled women participating in either arm of the study. On the same occasion, all women were asked for a judgement about how they remembered to have felt, compared with their current situation, before either delivery and development of vaginal laxity or development of VVA/GSM.

DQRF operative procedure

Four to six treatment sessions were planned every 14±2 days for both indications. Power was applied, using a coupling gel, for 15 to 20 minutes starting behind the hymenal ring, with circular back-and-forth continuous movements and keeping the tip probe in contact with the vaginal mucosa. Power settings were 14% to 20% of the device maximum power (55 W) to treat vaginal laxity and 12% to 18% to treat VVA/GSM. Follow-up appointments were planned after 1, 2, 6, 9 and 12 months. Safety, with special attention to pain and discomfort, was assessed in all women at each study visit and by telephone calls over the following days.

Statistical analysis

Descriptive statistics (means and standard errors of the mean for continuous variables, frequency distributions and percentages for categorical variables) were generated for demographics, medical history, and physical examination findings. The nonparametric Wilcoxon Signed Rank Test for repeated measurements on single populations was applied to both repeated measures of ordinal data (VLQ, PISQ-12 and SSQ mean scores) and continuous variables (VAS mean scores); the McNemar test was used to test for differences in ordinal scores. Two-sided 95% confidence levels were used with P<0.05 as cut-off for statistical significance.

Results

All women in both arms of the study completed their planned DQRF treatment sessions with only some occasional missing visits. Table I illustrates the demographics of the two study populations as recorded before the first DQRF session. All DQRF sessions were described as comfortable and no burns or other complications were reported. All women resumed their everyday activities, including sexual couple relationship, immediately after all DQRF treatment sessions.

Table I.—*Demographics and characteristics of study participants.*

Vaginal laxity arm, demographics	
Women completing the planned DQRF sessions	25
Age (years, mean±SD)	41.4±5.8
BMI (kg/m², mean±SD)	24.5±5.0
Parity (N., %)	
0	1 (4%)
1	5 (20%)
2	10 (40%)
3	6 (24%)
≥4	3 (12%)
Current sexual activity (N., %)	24 (96%)
Frequency of sexual activity per week	1-4
VVA/GSM arm, demographics	
Women completing the planned DQRF sessions	32
Age (years, mean±SD)	61.1±6.9
BMI (kg/m², mean±SD)	23.9±4.6
Previous live births (N., %)	23 (72%)
Mean parity (range)	1.7 (1-4)
Current sexual activity (N., %)	18 (56%)
Previous HRT (N., %)	9 (28%)

SD: standard deviation; HRT: hormone replacement therapy.

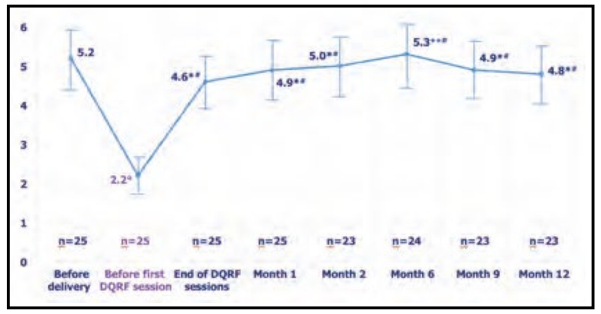

Figure 1.—Vaginal Laxity Questionnaire (VLQ) 7-level rating scale (very loose=1 to very tight=7), mean scores±SEM. Women's estimate before developing vaginal laxity ("before delivery") and evaluations immediately before the first and the last DQRF treatments ("before first DQRF session", "end of DQRF sessions"), and at follow-up visits 1, 2, 6, 9 and 12 months after the last DQRF session.
°P<0.01 *vs.* "before delivery". *P<0.05 *vs.* "before first DQRF session"; #non-significant *vs.* "before delivery"; ++P<0.01 *vs.* "before first DQRF session" and P<0.05 *vs.* "end of DQRF sessions".

Vaginal laxity arm of the study

One or more disorders associated with vaginal laxity such as orgasmic dysfunction and stress incontinence were reported before starting the DQRF treatment sessions by 21 out of the 25 women (84%) participating to the study. Before the last DQRF session 17 women (68%) already reported VLQ scores as index of subjective perception of vaginal tightness that were at least 3 levels higher than before the first DQRF session (4.6±1.8 *vs.* 2.2±0.9; P<0.05). VLQ scores slowly yet steadily improved over the 6 months after the last DQRF treatment session, with 21 women (84%) reporting VLQ scores at "month 6" visit that were at least 3 levels higher than before the first DQRF session (VLQ mean score, 5.3±2.0; P<0.01 *vs.* basal assessment, P<0.05 *vs.* last DQRF session). Subjective perception of tightness showed a slow trend towards some deterioration at "month 9" and "month 12" visits with 19 women (76%) reporting VLQ scores at the "month 12" visit at least 3 levels higher than before the first DQRF session (VLQ mean Score, 4.8±1.9; non-significant *vs.* last DQRF treatment session) (Figure 1).

The overall sexual function and sexual satisfaction from vaginal intercourse also showed marked improvements at the first evaluation

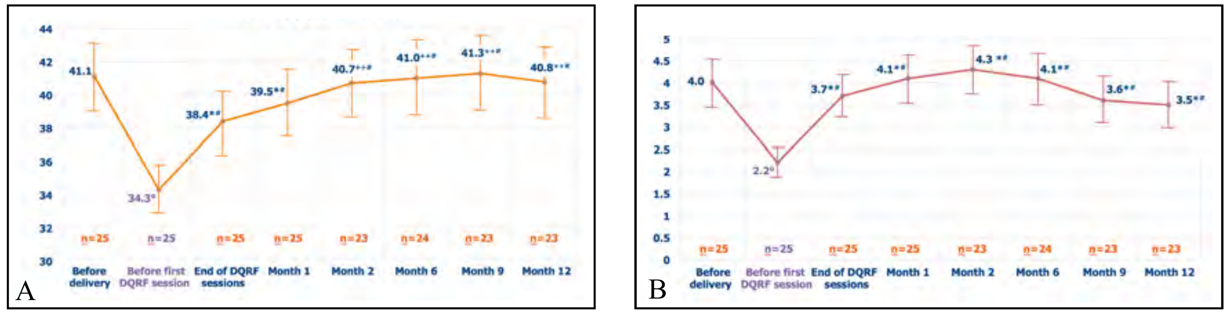

Figure 2.—A) Pelvic Organ Prolapse/Incontinence Sexual Questionnaire, short form (PISQ-12) and (B) Sexual Satisfaction Questionnaire (SSQ) 6-point rating scale (none=1 to excellent=6), mean scores±SEM. Women's estimate before developing vaginal laxity ("before delivery") and evaluations immediately before the first and the last DQRF treatments ("before first DQRF session", "end of DQRF sessions"), and at follow-up visits 1, 2, 6, 9 and 12 months after the last DQRF session.
°P<0.01 *vs.* "before delivery". *P<0.05 *vs.* "before first DQRF session"; #non-significant *vs.* "before delivery"; ++P<0.01 *vs.* "before first DQRF session" and P<0.05 *vs.* "end of DQRF sessions".

visit with, respectively, mean total PISQ-12 and SSQ scores ("end of DQRF sessions" *vs.* "before first DQRF session") of 38.4±6.5 *vs.* 34.3±5.8 and 3.7±1.6 *vs.* 2.2±0.9, P<0.05 (Figures 2A, 2B). Twenty and 19 women out of 25 showed a short-term improvement (before the last DQRF session) of at least 3 points in, respectively, PISQ-12 and SSQ scores.

VVA/GSM arm of the study

Clinically significant improvements were observed for all VVA/GSM symptoms at the first evaluation visit ("end of DQRF sessions") compared with the overall clinical picture at basal assessment ("before first DQRF session"). A steady progress of all scored symptoms towards the premenopausal situation, estimated by the "before VVA/GSM" VAS scores, was apparent over the whole follow-up period (Table II).

Ten of the 32 screened women (31.2%) reported being forced to renounce any attempt at sexual intercourse during the three months before the first DQRF treatment visit because of severe VVA/GSM symptoms. Only 25 women reported at least some sexual activity, often unwillingly. All women reported vaginal dryness before treatment while 27 reported vaginal itching and burning, 29 dyspareunia, and 17 dysuria/incontinence.

At the first short-term assessment before the first DQRF session, 27 women out of 32 reported to have resumed having intercourse (84.4%); all women but four had resumed coital activity by the "month 2" visit (87.5%). Only two women reported strong physical and emotional discomfort during attempts at intercourse at

Table II.—*Clinical severity of VVA/GSM symptoms, self-assessed mean scores±SEM (10-cm visual analogue scales). Women's estimate before developing VVA/GSM ("before VVA/GSM") and evaluations immediately before the first and the last DQRF treatments ("before first DQRF session", "end of DQRF sessions") and at follow-up visits 1, 2, 6, 9 and 12 months after the last DQRF session.*

	Vaginal dryness	Vaginal itching	Vaginal burning	Dyspareunia	Dysuria/incontinence
Before VVA/GSM (N.=25)	2.9±1.4	2.1±0.9	2.5±1.1	2.1±0.9	2.4±1.0
Before first DQRF session	8.9±2.4 °	7.6±2.8 °	7.2±2.5 °	8.8±2.2 °	5.9±2.5 °
End of DQRF sessions	4.3±1.9 * #	3.8±1.8 *	3.5±1.8 * #	4.4±1.7 *	2.9±1.9 * #
Month 1 (N.=25)	3.4±1.7 * #	3.0±1.7 * #	3.0±1.8 * #	2.9±1.8 * #	2.8±1.5 * #
Month 2 (N.=23)	3.2±1.6 * #	2.6±1.8 * #	2.9±1.6 * #	2.8±1.8 * #	2.7±1.6 * #
Month 6 (N.=24)	3.0±1.5 * #	2.4±1.6 * #	2.6±1.7 * #	2.4±1.5 * #	2.5±1.8 * #
Month 9 (N.=23)	3.1±1.1 * #	2.3±1.3 * #	2.5±1.2 * #	2.4±1.3 * #	2.4±1.4 * #
Month 12 (N.=23)	3.1±1.3 * #	2.3±1.2 * #	2.6±1.1 * #	2.3±1.2 * #	2.5±1.3 * #

°P<0.01 *vs.* "before VVA/GSM"; *P<0.05 *vs.* "before first DQRF session"; #non-significant *vs.* "before VVA/GSM".

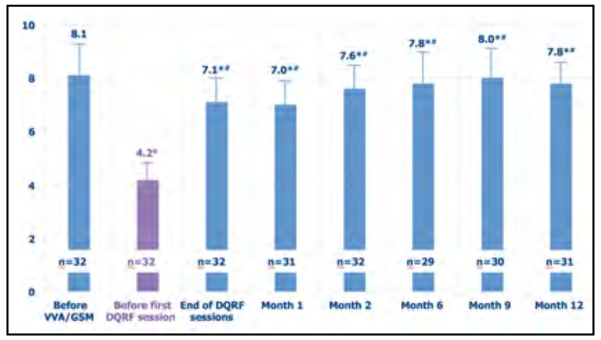

Figure 3.—Overall satisfaction with sexual life, self-assessed mean scores±SEM (10-cm VAS). Women's estimate before developing VVA/GSM ("before VVA/GSM") and evaluations immediately before the first and the last DQRF treatments ("before first DQRF session", "end of DQRF sessions") and at follow-up visits 1, 2, 6, 9 and 12 months after the last DQRF session.
°P<0.01 *vs.* "before VVA/GSM"; *P<0.05 *vs.* "before first DQRF session"; #non-significant *vs.* "before VVA/GSM".

the "month 6" through "month 12" follow-up visits. Mean VAS scores for overall satisfaction with sexual life improved from 4.2±1.2 at baseline ("before first DQRF session") to 7.0±2.1 before the end of the DQRF program ("end of DQRF sessions") and up to 7.6-8.0 after the sixth month of follow-up (Figure 3).

Discussion

The 12-month extension of the previous exploratory investigation of the new dynamic quadripolar evolution of radiofrequency treatment for vaginal rejuvenation confirms the new DQRF technology as most effective in both investigated indications postdelivery: vaginal laxity and postmenopausal atrophy of female genital tissues with associated genitourinary symptoms. The 12-month safety follow-up was also excellent. The long-term clinical benefits of the new technology are in line with the previous evidences with highly effective unipolar radiofrequency and laser devices.[1, 10, 11]

No disturbing thermal injury or pain occurred during all the many performed procedures and, according to treated women, the procedure was painless and often free of any thermal sensation. The new DQRF technology might well be a safety advance over laser technologies that, even if minimally invasive, may cause bleeding, pain and burning.[10] It might also be an advance over available unipolar radiofrequency system because the new DQRF device does not need a grounding pad on the subject's upper thigh, thus avoiding all risk of current flows triggering Ohm's resistances in crossed tissues.

The technological trick is generating electric fields only within the medically certified stainless steel dynamic quadripolar electrodes tipping the anatomically designed probes. After the probes are applied to the vaginal, introital and vulvar mucosa, the configuration of the four electrodes is continuously and electronically controlled between alternating receiver and transmitter states. This allows repelling electric fields to be generated that concentrate energy in topographically localized electric fields in the subepithelial layers of the introitus, vagina and vulva. The operator can thus fine-tune the thermal effect associated with these low-energy electric fields in terms of both tissue volume and mucosal depth. Clinical pharmacology investigations with infrared thermophotographs of treated genital areas confirmed the thermal effect to be highly localized at the desired mucosal depth, and to dissipate rapidly without residual irritation.[6]

VLQ scores as main index of vaginal laxity, and PISQ-12 and SSQ scores as index of overall sexual function and ancillary VVA-related disturbances like sex-related urinary and stool incontinence, rapidly improved in participant women with introital and vaginal laxity even before the end of the planned DQRF sessions. Rapidly improved genital aesthetics and control of sex-associated stool and urinary incontinence were both reported as most gratifying by many women independently of the more relaxed couple relationship. Aside from any real medical consideration and remembering that aesthetic reasons were behind the decision by 90% of patients to undergo elective surgery for vaginal tightening and perineal support,[12] obtaining a more subjectively pleasing aesthetic appearance thanks to non-surgical techniques of cosmetic genitoplasty may even become the foremost field of application of vaginal rejuvenation.

Anatomical re-modeling defines vaginal rejuvenation. Anatomical re-modeling is most likely associated with thermal re-activation of fibroblasts and development of new networks of collagen and elastin fibers in the subepithelial layers of introitus and vagina.[11, 13] The program of 4 to 6 DQRF sessions was over in less than two months, yet the vaginal rejuvenation effect persisted for a whole year after the last treatment. A few participant women reported some slight deterioration in perceived vaginal laxity and sexual satisfaction from vaginal intercourse (VLQ and SSQ mean scores), though there was no deterioration of improved ancillary symptoms like dysuria and urinary incontinence (PISQ-12 mean scores). This suggests consolidating the re-modelling and symptomatic benefits of the previous DQRF vaginal rejuvenation program with some further sessions after 6 to 9-12 months.

The Women's EMPOWER Survey most recently showed that women's awareness and understanding of VVA/GSM is still poor in spite of quite a lot of VVA surveys and wide media coverage of the problem over recent years.[14-16]

Vaginal rejuvenation as an option in VVA/GSM also benefits from direct thermal re-activation of fibroblasts and collagen, elastin, and matrix neosynthesis, but thermal vasodilatation is also a goal. The peri- and postmenopausal fall of estrogens impacts on mucosal elasticity by matrix glycosaminoglycans depletion and by hyalinization, fragmentation and fusion of collagen and elastin fibres.[17,18] These events are associated with urogenital atrophic symptoms even in 15% of premenopausal women.[17] Facilitating diffusion to the atrophic vaginal mucosa of adrenal dehydroepiandrosterone (DHEA) and DHEA-derived estrogens produced in local adipose tissue is likely to counteract vaginal atrophy, and possibly even postmenopausal osteoporosis, muscle loss, fat accumulation and hot flashes.[19, 20] All women but two in the VVA/GSM arm of the study reported control of dyspareunia and resumption of coital activity and gratifying couple relationship at the end of the 12-month follow-up period, but benefits were already impressive before the last treatment session, no later than one month and a half or two months after beginning the DQRF program.

Conclusions

The study data suggest there is no tendency to clinical deterioration even after one year since the last DQRF treatment session. This observation suggests persistent anatomical remodeling and real counteracting of atrophy. As in the pioneer exploratory study, no formal evaluations of thinning/loss of vaginal rugae, mucosal pallor and friability and low vaginal maturation index were formally planned, yet anecdotal observations by the investigator confirmed anatomical rejuvenation.

The follow-up of this office-based investigation is still going on with the goal of further defining the clinical and safety profile of the new DQRF device in both indications with the forthcoming evidences after 18 and 24 months.

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Efficacy and safety of Dynamic Quadripolar Radio-Frequency, a new high-tech, high-safety option for vulvar rejuvenation

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Abstract

Background: The flow of papers about surgical and non-surgical vulvar rejuvenation techniques parallels the steadily increasing interest by the general public and the market. All vulvar rejuvenation procedures share the goal of correcting vulvar aesthetic imperfections and alleviating the related physical and psychological burden experienced by the woman in her everyday life (irritations, discomfort, possibly unrewarding couple relationship). Dynamic Quadripolar RadioFrequency (DQRF) is the latest-born technology in the evolving world of light- and energy-based therapies as effective alternative options to traditional techniques of aesthetic and cosmetic surgery.

Methods: More than 500 complete DQRF vulvar rejuvenation cycles were performed between March 2016 and June 2017 according to the proprietary "EVA™ Vulvar Rejuvenation" treatment protocol in an advanced international centre of plastic and aesthetic medicine and surgery. The evolution of vulvar aesthetics and the subjective level of gratification of women for aesthetic and daily life benefits were retrospectively evaluated in a random sample of 25 DQRF cycles by the same EVA™ operator. As regards efficacy, for each woman the authors retrospectively scored, on 10-cm visual analogue scales (VAS), the photographic documentation of the vulvar area before and at the end of the DQRF rejuvenation cycle and after 3 months of follow-up without further treatments. While scoring, authors were blind to the history and demographic details of women.

The outcomes (VAS scores) of standardised-format interviews conducted by the EVA™ operator at the end of each vulvar rejuvenation session were also analysed. Investigated issues: wellbeing during the procedure and aesthetic and functional benefits experienced by the woman up to that moment of the vulvar rejuvenation cycle.

Results: Improvements of vulvar aesthetics were objectively apparent in all women at the end of the DQRF rejuvenation sessions, often after the first one. Mean scores attributed to the photographic documentation of the vulvar area significantly improved between the beginning and the end of treatments (4.1 vs. 7.8; $p<0.05$). Aesthetic objective improvements persisted over the following months (score at the end of the no-treatment follow-up: 7.6). The level of individual gratification of treated women, already significantly increased before the second DQRF session, steadily increased over the following weeks and after the end of their vulvar rejuvenation cycle. No woman experienced clinically significant adverse effects; only a slight degree of transitory hyperaemia was commonly reported.

Conclusions: A short vulvar rejuvenation cycle of four 10-min sessions based on the new DQRF technology significantly improves vulvar aesthetics and helps to suppress the problems and discomfort in the woman's everyday life that are commonly related to her vulvar atrophy. Aesthetic and functional progress is seen in all treated women; relief of discomfort and irritations was often reported even before the end of the DQRF sessions. The procedure is comfortably office-based, technically simple and devoid of disturbing adverse effects. Development of the DQRF technology in the next future will have to focus on cytological and histological studies to deepen understanding of biological effects, as well as on expanding the number of treated women and the documented follow-up period (so far, one year in published clinical studies). Validated questionnaires will have to be used to assess the subjective level of gratification of treated women.

Introduction

According to the American College of Obstetricians and Gynecologists, aesthetic and cosmetic surgery over the vulvar area is experiencing double-digit growth in the United States, even in young and sometimes adolescent women [1]. This is no more than one example of the growing interest that aesthetic (cosmetic) gynaecology is currently enjoying all over the world from both technical and scientific perspectives and the business point of view.

This booming world is borderline with the technologies and procedures aimed at relieving the symptoms and discomfort associated with the genitourinary syndrome of menopause - postmenopausal vaginal dryness, pain, burning and itching, dyspareunia, slight urinary incontinence and recurrent urinary tract infections - and, in younger women, with post-delivery vaginal laxity. Both these conditions impact

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on the woman's self-perception and self-confidence, and severely challenge the holistic quality of life of affected women [2,3]. However, it is mainly aesthetic gynaecology that at present enjoys centre stage in terms of attention by the general public and media. Two more examples coming from the two shores of the Atlantic: according to a 2010 American survey, looking for improved aesthetics was the only reason leading 90% of patients to undergo elective surgery for vaginal tightening, vaginoplasty and perineal support [4], whilst elective reductive labiaplasty procedures doubled in the United Kingdom in the decade around the turn of the century [5].

Much the same is true in Italy. According to the 2014 data of the Italian Association for Aesthetic Plastic Surgery (Italian acronym, AICPE), more and more Italian women undergo intimate plastic surgery (3,300 in 2014 or 1.3% of all aesthetic surgery procedures, +13% compared with 2013) [6]. Labiaplasty techniques, autologous adipose tissue transplantation (lipofilling) and office injections of hyaluronic acid fillers are some of the options that are at present available to plastic surgery and aesthetic gynaecology practitioners [7-9].

Attention is also dramatically surging for light- and energy-based technologies such as monochromatic laser radiation and radiofrequency thanks to their non-invasive nature, simpler logistics, and reduced costs. Emission of electromagnetic energy of variable wavelength aims at anatomical re-modelling and rejuvenation of extra-introital and extra-vaginal tissues through thermal re-activation of fibroblasts [10-12]. Immunohistochemical and electron microscope observations are steadily accumulating that correlate fibroblast re-activation and deposition of new networks of collagen and elastin fibres in the subepithelial layers of the vulva. Increasing tissue levels of profibrotic cytokine TGF-β1 and persistent activation of heat shock proteins are also markers of connective tissue matrix re-modelling [12].

"EVA™ Vulvar Rejuvenation" treatment protocol

- Four 10-min sessions, spaced 14-16 days
- Setting of the radiofrequency generator: 1 Mhz
- Operating Power: 8-14% of the maximum device power (55 W)
- Target temperature in vulvar tissues during procedures: 42°C (range 40-43 °C)

The innovative Dynamic Quadripolar RadioFrequency (DQRF) technology is based on advanced research by the Italian company Novavision Group S.p.A. (Misinto, Monza-Brianza, Italy). Together with the low-energy DQRF-based EVA™ device and the proprietary "EVA™ Vulvar Rejuvenation" treatment protocol, DQRF is the most recent technology designed to trigger anatomical re-modelling in vulvar tissues.

The core of DQRF innovation is in the peculiar interaction between the subepithelial layers of the vulva and the energy emitted by the radiofrequency generator. DQRF biophysics allows the operator to define the depth and volume of the target vulvar area and drastically reduce administered energy; electronically controlled movement and temperature sensors in the EVA™ device (RSS™, Radiofrequency Safety System, technology) allow rigid control of tissue temperature [13]. The ongoing clinical studies programme begins to suggest that the DQRF technology might in fact overcome the unwieldiness and safety problems of conventional light- and energy-based vulvar rejuvenation devices [13,14].

The herein presented study was designed with a double goal: evaluating the objective evolution of vulvar morphology in a random sample of women with vulvar atrophy treated with the DQRF technology and monitoring the treated women's subjective gratification for the perceived aesthetic and functional benefits in their everyday life.

Material and Methods

More than 500 DQRF vulvar rejuvenation cycles were performed between March 2016 and May 2017 at the international centre for plastic and aesthetic medicine and surgery "Naturade Women's Clinic" (Guangzhou, Guangdong, PRC).

All treatments followed the "EVA™ Vulvar Rejuvenation" protocol, developed from preclinical data by the DQRF patents holder and producer of the EVA™ device and validated in the present study. Rigid standardized procedures allowed collection of comparable data ready for statistical analysis. The first author personally supervised all activities of local operators.

The study was carried out in a retrospective random sample of 25 women who had completed their 4-session DQRF vulvar rejuvenation cycle. The sample was selected with the help of a random numbers generator within all women who had completed their DQRF rejuvenation cycle in the centre and had been treated by the same operator (randomly chosen).

All women showing evidence of vulvar dystrophy, acute or chronic vulvar disorders including dermatitis, condylomata and herpes simplex, or considered at high risk for human Papillomavirus infections were excluded from the sample; some visible laxity of labia minora or referred vulvar and/or vestibular dryness did not prevent sampling. Women poorly sensitive to pain or heat or showing areas of vulvovaginal ischemia as well as unrepaired wounds, mucosal or vulvar irritations or signs of infection in the treatment area were similarly excluded. A short standardised interview by the operator had already identified women (retrospectively excluded from sampling) with symptoms related to, or arising suspicion of, immune depression, uncontrolled diabetes mellitus, urinary tract or sexually transmitted infections, moderate or severe pelvic organ prolapse and bleeding diathesis. Women being treated with anti-coagulant or immunosuppressive drugs or radiant therapy had also been preliminarily screened.

Objective aesthetic efficacy was assessed by independent retrospective scoring by authors of the photographic documentation of the vulvar area of each sampled woman before and at the end of the DQRF rejuvenation cycle and after 3 months of follow-up without further treatments; 10cm Visual Analogue Scales (VAS) were used for scoring. Evaluators were blind to the history and demographic details of sampled women as well as to the outcomes of past interviews by the operator (see below). Individual author-attributed VAS scores were then averaged to monitor the mean evolution of vulvar aesthetics at each assessment time and compared with a non-parametric test (Wilcoxon Signed Rank Test).

As regards the assessment of subjective benefits perceived by treated women, the analysis was based on first-hand information prospectively collected by the local operator with short standardised interviews before each DQRF treatment session. The operator's standardised questions had focused on both the woman's subjective perception of any improvement of her vulvar aesthetics and the benefits the woman had the sensation to experience in her daily life due to irritation and discomfort (associated for instance with tight trousers and lingerie), loss of self-esteem, difficulties in social interactions, and problems with sexual life and couple relationship. At the end of the interview, the operator had asked the woman for an overall categorical assessment of both her subjective aesthetic gratification and perceived functional benefits ("Not at all satisfied", "Poorly satisfied", "Fairly satisfied", "Highly satisfied"; retrospective analysis of the distribution of subjective women's assessments over time: chi-square test).

In those interviews, women were also questioned about co-morbilities (see above) and any side effects experienced after the previous DQRF session. Two-sided 95% confidence levels were used for all statistical tests with p<0.05 as cut-off for significance. All study materials were peer-reviewed for ethical problems; all women had given informed consent to anonymous collection of their data before the first DQRF session.

Results

The mean age of sampled women was 34.3 years (range, 25-44); in 8 women there was a slight degree of labia minor laxity, in 11 vulvar and/or vestibular dryness. The photographic documentation of a selection of vulvar atrophy cases before and at different steps during the DQRF "EVA™ Vulvar Rejuvenation" programme demonstrates with visual evidence the tightening efficacy of the new DQRF technology over the vulvar area even before the final session. On average, the VAS scores related to the overall aesthetic vulvar appearance significantly improved between the beginning and the end of the vulvar rejuvenation program (Figures 1-8).

Follow-up information for the 3-following no-treatment months was available for 22 of the sampled women (88%); 3 women were lost to follow-up. No significant objective worsening of vulvar aesthetics occurred during the follow-up period in spite of lack of further rejuvenation sessions (Figure 9).

Figure 1. Baseline situation (left): quite severe 3-year vulvar atrophy; at right (marked with "1"): evolution of atrophy after the first DQRF session. Woman's age: 41; operational power: 8-10%.

Figure 2: Baseline situation (at left, marked with "0"): 1-year yet rapidly evolving vulvar atrophy; at right (marked with "1"): evolution of atrophy after the first DQRF session. Woman's age: 35; operational power: 8-11%.

Figure 3. Baseline situation (left, marked with "0"): moderate yet steadily worsening 2-year vulvar atrophy; at right (marked with "1"), evolution of atrophy after the first DQRF session. Woman's age: 29; operational power: 10%.

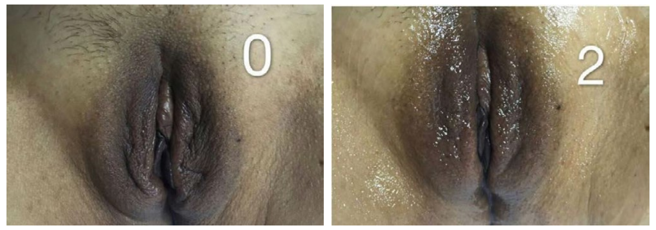

Figure 4. Baseline situation (left, marked with "0"): moderate vulvar 2.5-year atrophy; at right (marked with "2"), evolution of atrophy after the second DQRF session. Woman's age: 36; operational power: 9-12%.

Figure 5. Baseline situation (left, marked with "0"): recent yet quite severe vulvar atrophy; at right (marked with "2"): evolution of atrophy after the second DQRF session. Woman's age: 31; operational power: 10-13%.

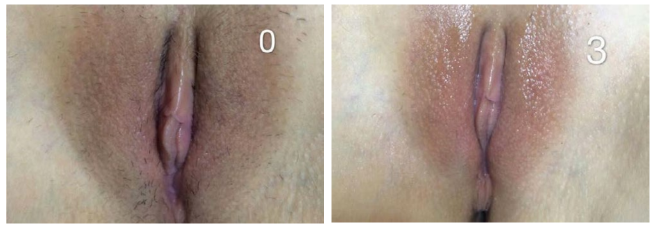

Figure 6. Baseline situation (left, marked with "0"): quite severe 1-year vulvar atrophy; at right (marked with "3"), evolution of atrophy after the third DQRF session. Woman's age: 37; operational power: 8-12%.

Table 1 (subjective appreciation of current vulvar aesthetics) and Table 2 (discomfort and self-esteem and couple-relationship problems incurred in daily life) illustrate the perceived levels of gratification reported by the sampled women before each of the four DQRF sessions and at follow-up interview. The distribution of categorical assessments showed a statistically significant shift compared with baseline towards more subjective satisfaction before the second rejuvenation session; the

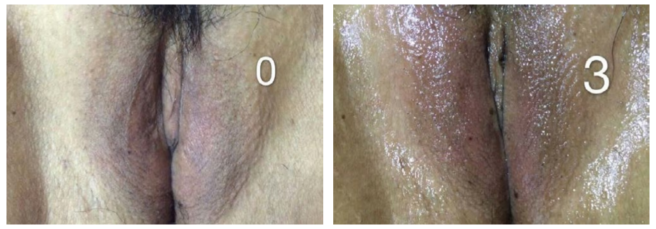

Figure 7. Baseline situation (left, marked with "0"): quite severe 3-years vulvar atrophy; at right (marked with "3"), evolution of atrophy after the third DQRF session. Woman's age: 40; operational power: 8-12%.

Figure 8. Baseline situation (left, marked with "0"): moderate to severe 2-year vulvar atrophy; at right (marked with "4"), evolution of atrophy 2 weeks after the fourth DQRF session. Woman's age: 34; operational power: 8-13%

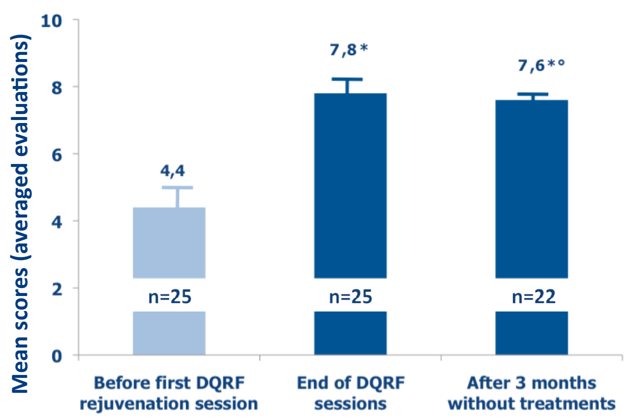

Figure 9. Mean averaged VAS scores (± SEM) attributed to the aesthetic vulvar appearance before the first DQRF rejuvenation session (baseline), before the fourth and last DQRF session and 3 months after the end of the treatment cycle (* p< 0,05 vs. baseline situation; ° no statistically significant difference vs. end of treatments).

Table 1. Distribution of women's VAS scores (subjectively perceived vulvar aesthetics) over the DQRF vulvar rejuvenation treatment cycle up to the last session (n=25) and after 3 months without further treatments (n=22).

	Not at all satisfied	Poorly satisfied	Fairly satisfied	Highly satisfied
Before first session	16	9	0	0
Before second session*	5	9	8	3
Before third session	0	2	8	15
Before last session**	0	1	8	16
Follow-up (3 months)**	0	0	7	15

* p <0.05, ** p <0.01, Chi-square test.

Table 2. Distribution of women's VAS scores (discomfort in everyday life, loss of self-esteem, problems with sexual life and couple relationship and other difficulties) over the DQRF vulvar rejuvenation treatment cycle up to the last session (n=25) and after 3 months without further treatments (n=22). Overall distribution, * p <0.05; ** p <0.01 vs. baseline (Chi-square test).

	Not at all satisfied	Poorly satisfied	Fairly satisfied	Highly satisfied
Before first session	14	11	0	0
Before second session*	4	9	11	1
Before third session	0	1	15	9
Before last session**	0	0	8	17
Follow-up (3 months)**	0	1	5	16

women's perceived satisfaction reached high statistical significance vs. baseline at the end of the DQRF cycle without appreciable deterioration over the following no-treatment months.

No treated woman reported any clinically significant or disturbing side effect or discomfort during the procedures. The operator reported, in almost all women, only a slight degree of hyperaemia and a subjectively pleasant, or at least undisturbing, warm sensation that largely resolved within 30 minutes and completely in a few hours.

Discussion

The physical effect of exposure to radiofrequency fields is induction of oscillating electrical currents in target tissues with translational motion of charged atoms and molecules and re-orientation of permanent dipole moments of water molecules. Viscosity of water translates into resistance (impedance) to molecular movements and rotations, leading to dissipation of motion energy and heat generation in female tissues [12].

Contraction due to breakage of intra-molecular hydrogen bonds and partial denaturation of collagen by radiofrequency fields is first seen at a tissue temperature of about 60°C; collagen denaturation at about 67°C correlates with maximal signal to fibroblasts for neocollagenesis and it is frequently sought in dermatological medical procedures. Lower levels of tissue temperature (40-45°C) are instead ideal for tightening and rejuvenation effects in skin and vulvar areas thanks to the long thermal relaxation time (about 225 msec) of collagen and other subepithelial vulvar structures [12,15]. A target temperature of 42°C in vulvar tissues as induced by the "EVA™ Vulvar Rejuvenation" protocol avoids triggering the pain threshold of vulvar nociceptors. Compared with laser technologies, deposition of new elastin is relatively unique to radiofrequency devices and gives peculiar mechanical strength and tightness, but also elasticity, to vulvar tissues [12,15,16].

The 1.0-1.3 MHz DQRF generator is equipped with four stainless steel dynamic electrodes on anatomical probes (maximum emitting power, 55 W). These quadripolar electrodes are continuously and electronically cycled between receiver and transmitter states. This high-tech trick allows repelling electric fields to form that, when in the ideal combination, convey energy with high tridimensional precision to the subepithelial layers of the vulva.

This allows the operator to fine-tune the vulvar thermal effect in terms both of tissue volumes and depth, with the further benefits that the grounding pad on the upper thigh and the need for heavy energy burdens because of Ohm's resistances in tissues are eliminated. Low-energy vulvar rejuvenation is often pleasant with no downtime period and the risk of burns is virtually eliminated as shown in clinical studies in women with vaginal laxity and genitourinary syndrome of menopause carried out so far [13,14].

As regards Aesthetic and Functional Gynaecology, a relatively new discipline for gynaecologists in spite of some dissenting opinion that is being occasionally heard [17,18] and more and more practiced by plastic surgeons and specialists of aesthetic medicine[9], the present study demonstrates the efficacy of new DQRF technology also when applied to vulvar rejuvenation. The photographic documentation visually shows that a tightening effect, even in women with quite severe vulvar atrophy, is clearly apparent already after the first or second treatment session. Objective VAS scores blindly attributed by authors almost doubled between the beginning and the end of the vulvar rejuvenation treatment sessions (from 4.2 ± 0.45 to 7.8 ± 0.31, $p < 0.05$ vs. baseline), strongly supporting the qualitative observation. Lack of a control group is a limit of the study design, yet dramatic aesthetic improvements look quite real.

The benefits experienced at the end of the DQRF rejuvenation cycle showed no appreciable tendency to dissipate over the following 3 months without further treatments, neither objectively nor in the subjective judgement of treated women. Noticeably, women's gratification for improved vulvar aesthetics, perceived psychological benefits, and reduced daily-life discomfort improved rapidly in the two weeks between the first and the second DQRF session and in the following two weeks before the third session. Subjective satisfaction of women steadily progressed until the end of the DQRF sessions and even in the following no-treatment period. The percent of women reporting to be fairly or highly satisfied increased from 92% after the third DQRF session to 96% after the fourth and last session and up to 100% after 3 months without further treatments ("Highly satisfied" women were 60%, 64% and 68%, respectively). The trend was similar for self-perception and self-esteem, psychological consequences and impact on daily life and activities. Once again, lack of a control group may be another weak point of the study, but it does not invalidate its objective and subjective favourable outcomes.

Our results encourage us to look more in depth into the potential of a new technology that is easy to master and to practice in any private office, is free of any serious or disturbing complications and, as demonstrated retrospectively in this study, seems to reward treated women's expectations both in terms of subjective aesthetic gratification and self-esteem and impact on daily life. More studies are warranted about the cytological, histological and overall biological effects of the DQRF technology; expanding the number of women exposed to new technology should also be a goal. A similar goal should be providing more data related to very long-term follow-up periods: so far, safety and efficacy outcomes from clinical studies are available for one year [13,14]. Validated questionnaires will have to be used to assess the subjective level of gratification of treated women.

Conflict of Interest Disclosures

Gianluca Benincà, David Bosoni and Franco Vicariotto are Medical Consultants and members of the Scientific Board of Novavision Group S.p.A. (Misinto, Monza-Brianza, Italy), manufacturer of the DQRF technology used during the investigation. Mauro Raichi is a Medical Research Consultant for Novavision Group S.p.A. (Misinto, Monza-Brianza, Italy).

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Research Article

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Dynamic quadripolar RadioFrequency and vulvodynia

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Abstract

Background: Among the several subtypes of vulvodynia or idiopathic vulvar pain lasting for at least 3 months, Localised Provoked Vulvodynia (LPV) is the most highly prevalent clinical variant identified by the "2015 classification". The pathophysiology underlying LPV is still elusive and unclear. The association with recurrent vulvovaginal candidiasis and aerobic vaginitis is most likely prominent in leading to the vestibular nociceptive hypersensitivity that is a distinctive diagnostic marker of LPV. The exploratory non-randomised study herein described was designed to investigate if the demonstrated vulvar remodelling and rejuvenating properties of DQRF (Dynamic Quadripolar RadioFrequency) treatment might be of benefit to control the vestibular pain of LPV. The working hypothesis behind the study was that correcting the mucosal hypotrophy frequent in many LPV women would restore a thriving vestibular and vaginal microorganism ecosystem and break the vicious cycle of recurrent yeast and aerobic infections that leads to exaggerated nociceptive response and LPV hyperesthesia, hyperalgesia, and dyspareunia.

Methods: Prospective cohort of 30 consecutively enrolled premenopausal women with vestibulitis and/or moderate to severe hyperesthesia and pain, dyspareunia or pelvic floor hypercontractility related to recurrent vulvovaginal candidiasis and/or aerobic vaginitis. The first 20 women were treated with four 10-min DQRF sessions (EVA™ device) spaced at least 7 to 10 days; the last 10 women, acting as controls, underwent a standard 4-week program of pelvic floor rehabilitation. After the baseline clinical, microbiologic and microscopic assessment, a second follow-up visit was planned no more than 15 days after the fourth (last) DQRF treatment session. Assessed parameters included *Lactobacillus* and aerobic microflora, polymorphonuclear and clue cells, pH, Nugent score, provoked pain (Swab Test), and severity of vaginal atrophy (Vaginal Health Index).

Results: All women completed the planned four DQRF/EVA™ or physical therapy sessions without adverse effects. Both treatment strategies significantly reduced the Swab Test provoked pain. The reduction in pain severity seemed to be more marked at the follow-up visit in the DQRF treatment group (mean pain score difference, -3,55) compared with control women (mean pain score difference, -3,20), although with only marginal statistical significance ($p \approx 0.054$). Both treatment strategies improved the vestibular and vaginal environment and mucosal hypotrophy, though more definitely in the DQRF-treated women, as observed for the Vaginal Health Index (DQRF vs. physical therapy pre/post score difference: +5.50 vs. +5.0, $p < 0.05$) and for the microbiologic and microscopic markers of deranged intimate ecology (lactobacilli, Nugent score, polymorphonuclear and clue cells, etc.).

Conclusions: The endoderm-derived vestibule, embriologically distinct from the ectoderm-derived external vulva and the mesoderm-derived vagina, may have a quite peculiar inflammatory and immune reactivity compared with contiguous areas. The outcomes of this preliminary pilot study seem to support the working hypothesis that DQRF-induced subepithelial remodelling in the vestibular areas of hyperesthesia and adjoining mucosa may help to restore the normal *Lactobacillus*-dominated ecology of these areas and to normalise the nociceptive responsiveness of the vestibule. The observed clinical benefits were at least comparable to those of pelvic floor rehabilitation and might have been possibly greater if study cohorts had been larger and statistical power higher in a well-controlled study. Further randomised studies are warranted to validate the working hypothesis and quantitatively estimate the symptomatic benefits and impact on quality of life compared to established vulvodynia therapies.

Introduction

Surprisingly, the origin of the highly prevalent and disabling painful condition that is known as vulvodynia is poorly understood and vulvodynia is still an under-studied and under-diagnosed woman's health issue. Vulvodynia affects up to 28% of women, often of childbearing age, as estimated in U.S. surveys [1], with an overall direct and indirect pharmacoeconomic burden that has been estimated to rise to 31 to 72 billion dollars per year [2]. According to the new nomenclature of vulvar pain, referred to as the "2015 classification" because agreed on at a consensus conference organised in that year by the International Society for the Study of Vulvovaginal Disease, the International Society for the Study of Women's Sexual Health and the International Pelvic Pain Society, vulvodynia is defined as idiopathic vulvar pain lasting for at least 3 months and is classified into several clinical subtypes (localized, generalized, or mixed; upon contact, spontaneous, or mixed; intermittent or constant; primary or secondary). The "2015 classification" also acknowledges that vulvodynia is unlikely to be a single nosological entity rather than a constellation of symptoms of several disease processes with extensive overlappings [1].

The most common clinical presentation and diagnostic category, Localised Provoked Vulvodynia (LPV) - acute vestibular knife-like or burning pain, or a combination of both, lastingly evoked by even light pressure - has been estimated to affect about 16% of women over their lifetime; almost 7% of surveyed women were experiencing unexplained localised pain when interviewed [3]. A recent survey put at 30-48% the

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women with vulvar burning or pain upon contact lasting for at least 3 months and impacting on sexual activity who never sought care; the same survey put at more than half the women experiencing vestibular pain and looking for a diagnosis who never received it [4].

Though the labia minora, labia majora, the mons pubis, and the perineum are relatively pain-free to pressure and touch, the impact on the woman's sexual life and couple relationship, self-esteem, and mood can be devastating; even such an everyday task as inserting a tampon can be excruciating in severe cases, and dysuria is frequent [5].

Proliferation of vulvar nociceptors and co-morbid conditions, as well as central nervous system, hormonal, myofascial and muscular factors, have all been implicated in the genesis of vulvodynia. Genetic, embryological and congenital factors have also been deemed to be important, possibly with a leading role for inflammation. All these pathophysiological determinants variably contribute in different situations and are interdependent, but the paucity of prospective longitudinal studies still prevents to define a clear flow of causality [2].

Treatment of vulvodynia is at present difficult and poorly codified. The progression of therapeutic strategies in women with vulvodynia is usually consecutive, from non-invasive attempts (psychological support, physical therapy) to drug treatments (e.g., topical hormones, gabapentin, antimycotics and antibiotics) up to surgery, with the latter effective in up to more than 80% of affected women. However, though complications like pruritus, bleeding, infection, Bartholin duct stenosis and vaginismus are frequent [6]. The whole process is empirically based on trial and error, although algorithms have been proposed based on physical examination findings and laboratory tests [6,7]. The efficacy of psychological interventions, pelvic floor physical therapy, and vestibulectomy for provoked vestibulodynia are quite supported in the international literature; conversely, empirical evidence is still sparse for other treatment options like anti-inflammatory agents, hormones and anticonvulsant medications [8].

The herein discussed non-invasive strategy based on the innovative Dynamic Quadripolar RadioFrequency (DQRF) technology, developed by the Italian biotechnology company Novavision Group S.p.A. (Misinto, Monza-Brianza, Italy) and integrated into the low-energy DQRF-based EVA™ device, may be a novel treatment option of vulvodynia.

DQRF is the most recent technology, based on a biophysical approach, aimed at anatomical re-modelling of vulvar tissues and, indirectly, restoration of the vestibular and vaginal ecosystem. The interaction between the reduced flow of energy emitted by the DQRF radio frequency generator and the vestibular subepithelial tissues is biophysically quite peculiar in terms of depth and volume of the target subepithelial vulvar areas and administered energy; the electronically controlled movement and temperature sensors of the EVA™ device (RSS™, Radiofrequency Safety System, technology) allow an easy control of the vestibular subepithelial temperatures [9-11].

The herein presented exploratory non-randomised study in a relatively small sample of LPV women of childbearing age was designed to investigate if the vulvar remodelling properties of the DQRF technology, shown in previous studies, might also be of benefit to control the vestibular LPV pain [9,10]. The working hypothesis that guided the study was that remodelling of vestibular and vaginal tissues, beyond its established aesthetic value in women with variable degrees of vulvovaginal hypotrophy [11], could also help to restore a more physiological vestibular and vaginal ecology and the *Lactobacillus* microflora to its normal role as gatekeeper of the vaginal ecosystem. This could break the self-sustaining cycle, more extensively discussed in the last section of the paper, of recurrent yeast and aerobic eukaryote infections, dysregulation of vestibular fibroblasts with hyper-expression of proinflammatory cytokines, and nociceptive pain that is thought to be at the core of the most prevalent vulvodynia subtype [12].

Methods

A prospective cohort of 30 premenopausal women with signs and symptoms of vestibulitis and moderate to severe hyperesthesia and pain, dyspareunia, and/or pelvic floor hypercontractility, was consecutively enrolled in the study between January and October 2017. Candidate women routinely attended the Ambulatory Gynaecology Unit at the University of Trieste as outpatients. Vulvodynia followed Recurrent Vulvovaginal Candidiasis (RVVC) and/or Recurrent Aerobic Vaginitis (RAV) in all women.

To be included in the study, candidate women with vulvodynia should not be undergoing any local or systemic therapy, with special reference to hormone therapies, and should not be pregnant. All women referring a history of atopy or showing evidence of vulvar dystrophy or vulvoperineal unrepaired tears and wounds, acute or chronic vulvar disorders including dermatitis, condylomata and herpes simplex, or considered at high risk for human *Papillomavirus* infections, were excluded. Any confirmed or unconfirmed suspicion of neurological, endocrinological or dermatologic disorder similarly led to exclusion. All selected women provided written informed consent to anonymous collection of their data before the first DQRF session, and all study materials were peer-reviewed for ethical problems.

The first 20 women consecutively enrolled in the study were treated according to the EVA™/DQRF vulvovaginal treatment protocol illustrated in the text box.

The 1.0-1.3 MHz DQRF generator in the standard EVA™ device that was used in the study is equipped with four stainless steel dynamic electrodes on anatomical probes. The maximum emitting power is 55 W, with the four electrodes continuously cycled between receiver and transmitter state. When in the ideal combination, these electrodes convey energy with high precision in the subepithelial layers of the vulva and allow to fine tune the vulvar thermal effect in terms both of tissue volumes and depth. The new technology also eliminates the need for a grounding pad and the need to administer heavy energy burdens with the related risk of burns, as already demonstrated in clinical studies [9-11].

Vulvodynia was associated with RVVC in 15 DQRF-treated women and with RAV in 5 women. The last 10 consecutively enrolled women (controls) underwent 4 weekly sessions of standard pelvic floor rehabilitation.

A baseline assessment before the first DQRF treatment session and a follow-up visit after the end of the treatment program were planned to evaluate the microbiological and phase-contrast (x400 magnification) microscopic health of the vestibular and vaginal

- Four 10-min sessions, spaced at least 7 to 10 days
- Setting of the radio frequency generator: 1 MHz
- Operating power: 8-14% of the maximum device power (55 W)
- Target temperature in vulvovaginal tissues during procedure: 42°C (range 40-43°C)

EVA™/DQRF vulvovaginal treatment protocol ecosystem. These included *Lactobacillus* microflora and pH; Nugent score (identification and scoring of large *Lactobacillus*-like rods, small *G. vaginalis*-like Gram-positive rods, and curved *Mobiluncus* spp.-like Gram-variable rods); polymorphonuclear and *Gardnerella*-specific "clue cells" in vaginal secretions; diagnostic evidence of partial bacterial vaginosis (no woman with Nugent score >7 out of 10 was enrolled); Group-B streptococci, other aerobic bacilli and cocci (e.g., *E. coli*, *S. aureus*, *S. faecalis*), and evidence of aerobic vaginitis. Diagnosis of aerobic vaginitis was based on Donders' scores (0 to 10) based on *Lactobacillus* grade, number of leukocytes, proportion of toxic leukocytes, background flora and proportion of parabasal epitheliocytes, with all parameters attributed partial scores 0 to 2 (slight signs of aerobic vaginitis: summed-up score between 3 and 4; moderate AV: summed-up score between 5 and 6; severe AV: summed-up score between 6 and 10) [13]. Semi-quantitative subjective ordinal scores were applied to microbiological assessments (0 to +++). Provoked pain (Swab Test, score 0 to 10) and severity of vaginal atrophy (Vaginal Health Index: vaginal elasticity, fluid volume, pH, epithelial integrity, and moisture scored 1 to 5; maximum total score 25) were also assessed at the baseline and the follow-up visits. The second clinical and microbiological follow-up assessment was performed within 2 months of the first DQRF treatment session and no more than 15 days after the fourth DQRF session.

A non-parametric test, the Wilcoxon Signed Rank Test, was applied to the means of the Swab Test pain scores, Nugent scores, pH, and Vaginal Health Index scores of the DQRF-treated and pelvic floor rehabilitation sub-cohorts (follow-up vs. baseline visits). Due to the low numbers involved, outcomes related to the incidence of partial bacterial vaginosis and aerobic vaginitis, as well as microbiologic assays (incidence of lactobacilli, Group-B streptococci, yeasts, etc.) were simply tabulated for qualitative discussion; variations of median values were also qualitatively discussed. Two-sided 95% confidence levels were used for all statistical tests on means with p<0.05 as cut-off for significance.

Results

The mean age of enrolled women was 34.0 years in the DQRF group and 33.1 in the pelvic floor rehabilitation group; all women completed the planned four DQRF or physical therapy sessions. No woman of the prospective cohort reported side effects.

Figure 1 illustrates the efficacy of the two treatments as controlling strategies of the provoked pain. The severity of the Swab Test pain significantly improved in both treatment groups over the about 2 months of the study (highly significantly in the DQRF-treated women). The reduction in pain severity at the follow-up visit was more marked in the DQRF treatment group (mean pain score difference, -3,55) compared with control women (mean pain score difference, -3,20), though the difference approached only marginal statistical significance (p≈0.054). The provoked pain median scores improved from 7.0 to 3.5 in the DQRF group, and from 7.0 to 4.0 in the pelvic floor rehabilitation group.

Figure 2 summarises the evolution of the mean Vaginal Health Index scores in the two treatment groups. At baseline assessment, the composite index described a significantly more severe hypotrophy in the DQRF group compared with control women (16.15 vs. 16.60, respectively; p<0.05). Conversely, the vestibular and vaginal hypotrophy improved at the follow-up visit to very similar levels in both treatment groups (21.65 vs. 21.60, mean Vaginal Health Index pre/post score difference, +5,5 vs. +5.0, p <0,05). The corresponding

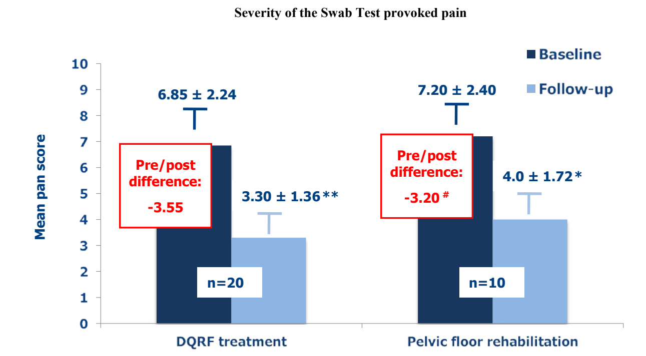

Figure 1. Mean Swab Test provoked pain scores (± SEM) before the first DQRF or pelvic floor rehabilitation session (baseline) and at the follow-up visit within 15 days after the end of the 4-session treatment cycle (* p< 0.05 vs. baseline visit; ** p< 0.01 vs. baseline visit; # pre- vs. post-difference, p≈0.054).

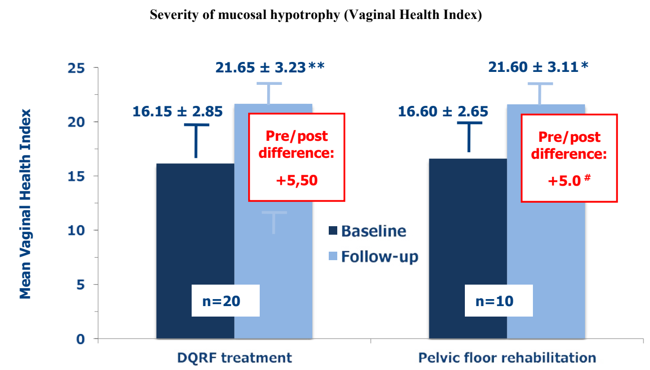

Figure 2. Mean Swab Test provoked pain scores (± SEM) before the first DQRF or pelvic floor rehabilitation session (baseline) and at the follow-up visit within 15 days after the end of the 4-session treatment cycle (* p< 0.05 vs. baseline visit; ** p< 0.01 vs. baseline visit; # pre- vs. post-difference, p< 0.05).

median values improved from 16.0 to 21.5 in the DQRF group, and from 16.5 to 21.5 in control women treated with physical therapy.

As regards microbiologic and microscopic evaluations, all five women in the DQRF treatment group that fulfilled t he c lue c ells criteria for partial bacterial vaginosis at baseline assessment were negative at the follow-up visit; the same was true for women with aerobic vaginitis. Conversely, only one of the five women diagnosed with partial bacterial vaginosis at baseline in the physical therapy group was negative at follow-up. Aerobic vaginitis persisted in both women with that diagnosis at the baseline visit. Group-B streptococci cultures, positive at baseline assessment in the two women of the DQRF group with aerobic vaginitis, were both negative at follow-up, while Group-B streptococci persisted in the two control women with unresolved aerobic vaginitis. The median count of polymorphonuclear cells per optical field in the vaginal swab fell in the DQRF group (from + to 0) but showed no change in the control group (+ at both visits).

Vaginal swab lactobacilli increased at follow-up compared with the baseline visit in the DQRF group (subjective ordinal-score assessment from + to ++), but they did not change in the physical therapy group (+ at both visits); the evolution in the mean vestibular and vaginal pH reflected these changes in the lactobacilli populations (DQRF group: from 4.15 to 3.45, p<0.05; control group: from 4.15 to 3.65, not significant). The median intimate pH changed from 4.0 to 3.5 in both groups. Table 1 illustrates the descriptive tabulation of the vaginal swab counts of polymorphonuclear cells and lactobacilli per optical field in the treatment groups at the baseline and follow-up visits.

The observed changes in the Nugent score reflected the pattern of changes in the diagnosis of partial bacterial vaginosis in the two treatment groups (DQRF group: from 3.55 to 2.25, p <0.001; control group: from 3.8 to 3.4, marginally non-significant). The corresponding median values changed from 4.0 to 3.0 in the DQRF group and remained stable at 4.0 in control women (Table 1).

Discussion

Localised provoked vestibulodynia has long been linked with inflammation, yet failure is almost the rule with treatments aimed at controlling local inflammation.

A careful review of 1,619 studies up to November 2015 failed to support a consistent association between LPV and unambiguous evidence of steady background inflammation [14]. Increased number of mast cells are very frequent in LPV subepithelial areas and activated mast cells produce nerve growth factors and proinflammatory cytokines that are known to induce hyperplasia and sensitisation of the peripheral nociceptive C-fibres. A speculative basis for allodynia might thus be envisioned, yet the authors failed to highlight any steady increase in background proinflammatory cytokines in vestibular tissues of affected women. Conversely, some low degree of inflammatory infiltration of the subepithelial part of the lamina propria is quite normal in healthy women due to the environmental conditions of the vulva, which facilitate proliferation of eukaryotes and yeasts [14]. Steady background inflammation definitely seems a blind alley to explain vulvodynia.

Some clues about LPV pathophysiology are provided by the strong association between vulvodynia and several other pain conditions, e.g., interstitial cystitis, fibromyalgia and irritable bowel syndrome, as well as autoimmune diseases, psoriasis, and atopy [2,15,16]. As a consequence, the emphasis has shifted over the last decade to local regulation of immunity and the role of genetics and epigenetics [12,17,18]. For instance, natural killer cells are significantly less in LPV women compared with healthy controls [14], in good correlation with the history of previous chronic and recurring *Candida* infections (known to occur in up to 70-80% of LPV women) [5,14]. Toll-like surface receptors 4, activated in situation of damage or danger and important in the priming of immune cells, are known to be activated by *Candida* infections, further reinforcing the correlation between recurrent candidiasis and vestibulodynia without obvious baseline inflammation [19-21]. Similarly, activation of the immune system can probably be documented in up to three quarters of LPV women, with most instances of abundant mast cell infiltration being in fact a secondary mast cell disorder [14]. The role of immune activation in provoked vestibulodynia is further supported by the association between epithelial nerve hyperplasia and increased B-cell infiltration and germinal centres [22].

Table 1. Vaginal swab polymorphonuclear cells and lactobacilli, counts per optical field; semiquantitative assessments and median scoring at baseline and follow-up visit. Colums 1 and 3: DQRF treatment group (n=20); Colums 2 and 4: pelvic floor rehabilitation group (n=10).

Polymorphonuclear cells (baseline/ follow-up)		Lactobacilli (baseline/follow-up)	
+/0	+++/0	+/++	+/++
++/+	+/+	+/++	+/+
++/++	++/+	+/+	+/+
++/0	++/+	+/+++	+/+
0/0	+/+	+/++	+/+
0/0	++/++	+/+++	+/+
+/+	0/0	+/+	+/+
+/O 0/0	+/+	+/+++	+/+
	+/+	++/++	+/+
0/0	+/+	++/++	+/+
+/0		+/+++	
+/0		+/+++	
0/0		+/++	
++/+		+/++	
+/O 0/0		+/+++	
		+/+++	
++/+		+/++	
0/0		+/+	
0/0		+/+	
0/0		+/+	
Median: +/0	**Median: +/+**	**Median: +/++**	**Median: +/ +**

These observations could explain the correlation between bacterial vaginosis and trichosomiasis and vestibular pain that has also been documented [23,24], possibly even more strongly than the association with recurrent candidiasis (according to Smith et al, the odds ratio is 9.4 for physician-reported bacterial vaginosis vs. 5.7 for *Candida* infections and 20.6 for trichosomiasis) [23].

Yet more evidences: although there may be little baseline inflammation, the vestibular fibroblasts from LPV women express more proinflammatory cytokines such as IL-1ß, IL-6 and IL-8 compared with healthy women after *in-vitro* stimulation [12,14,18]; likewise, inflammation-triggered control mechanisms, e.g., expression of the IL-1 receptor antagonist, appear genetically less efficient in LPV women [14]. Vestibular fibroblasts from painful areas of LPV women also strongly express Dectin-1, a transmembrane pattern-recognition receptor with high binding affinity for the *C. albicans* cell wall glucan and an important role in anti-fungal innate immunity [5,17]. Dectin-1 expression in areas of hyperalgesia is significantly higher compared with expression from fibroblasts from non-painful external vulvar areas at a short distance: blocking the function or expression of Dectin-1 - e.g., via the NFκB pathway - is associated with a reduced expression of inflammatory cytokines. Inhibition of the NFκB pathway has already been targeted clinically, almost eliminating proinflammatory mediator secretion in vulvar fibroblasts [5,17,25]. Finally, the very short endoderm-derived vestibule, interposed between the ectoderm of the external vulva and the vaginal mesoderm, is embriologically, and possibly functionally, quite peculiar. A tendency to local cytokine dysregulation and ineffective control of induced inflammation might contribute to local nociceptor sensitisation in vulvodynia-afflicted women [12,18].

Summarising, a growing body of evidence seems to suggest a mechanistic connection among the described actors: proinflammatory stimulants triggering fibroblast activation in the vestibular region even with low or nil baseline inflammation, peculiarly responsive fibroblasts, enhanced expression of proinflammatory cytokines, and nociceptive pain. In the words of Foster et al, vulvodynia should not even be considered a real disorder, rather than "an extreme but natural phenomenon" in an embriologically unique tiny area, the inch or so of the vulvar vestibule, extensively exposed to trauma and foreign proteins during reproduction and thus prone to "unique inflammatory/immunologic responsiveness" [12].

Neurobiological factors are also quite likely to influence vulvodynia. Generalized hyperalgesia, meaning lower local and remote pain thresholds (i.e., after vulvar, and after thumb deltoid and shin pressure, respectively) is definitely a factor in vulvodynia. This is well highlighted by functional magnetic resonance imaging (fMRI) during vulvar and thumb stimulation, which shows enhanced brain activation within the insula, the thalamus and the dorsal mid-cingulate and posterior cingulate cortex of LPV women compared with age-matched pain-free controls. Neural fMRI activation correlates with pain severity; different levels of neural activation are also specific of the recognised vulvodynia subgroups, meaning primary versus secondary and provoked versus unprovoked subgroups, as further hint that several heterogeneous disorders actually coexist under the label of vulvodynia [26]. However, it is still unclear whether the increased central pain processing and generalised hyperalgesia, exemplified by the pain stimulated at sites remote from the vulva like the thumb, are secondary to a primary vestibular disorder of pain control, or whether the augmented neural activity is in fact driving the perceived pain. Few are the accepted facts: for instance, that remission of vulvodynia symptoms is frequent, but relapses are likewise common whilst persistence without remission is quite exceptional rather than the rule [27].

In this far from clear pathophysiological background, this exploratory study supports the working hypothesis that guided its design: the vestibular and vaginal microflora ecology improves as a consequence of remodelling and rejuvenation of the vulvovaginal mucosa. Most likely, this helps to break the self-sustaining flow of events that leads to the enhanced inflammatory responsiveness of the LPV vestibule, even with no or minimal evidence of background inflammation, and excruciating nociceptive pain [12]. The recently developed DQRF/EVA™ technology has shown a peculiarly strong remodelling efficacy of the vulvovaginal anatomy in a variety of conditions [9-11]. This novel radiofrequency technology was thus chosen to test the working hypothesis in comparison with pelvic floor physical therapy, which is known to be of benefit in most LPV patients [28].

Only in 2013 did the first report appear of successful use of pulsed radiofrequency in the treatment of severe refractory (neuropathic) vulvodynia-i.e., nosologically distinct from LPV according to the "2015 classification" [2,29]. Since then, pulsed radiofrequency has been widely used with no clear rationale in this frankly neuropathic indication. Another 2016 pilot study described the efficacy of fractional CO_2 laser treatment of the vestibule in women with idiopathic vulvodynia and vestibular pain associated with the genitourinary syndrome of menopause. Some benefits were observed - possibly because, in the vulva and vagina, the loss of oestrogens is associated with increased density of sensory nerve fibres per unit area - yet once again not in LPV [30]; without forgetting that painful scars and vulvodynia may follow CO_2 laser treatment [31]. As far as we know, this may well be the first study applying a radiofrequency technology to the treatment of LPV.

Both the DQRF/ EVA™ device and the standard pelvic physical therapy both appeared to control the Swab Test provoked pain and to improve the mucosal hypotrophy. The outcomes of the study seem to suggest that the DQRF/ EVA™ technology could have an overall higher efficacy, yet the data cannot suggest at the moment anything more than a tendency due to the non-randomised design of the study. A non-randomised design is justified in an exploratory study, but further randomised evidences are warranted. However, there is at least a revealing clue, the microbiologic changes of the vestibular and vaginal microflora, which might suggest a significant efficacy of the new radiofrequency technology. The DQRF technology was definitely more efficient that physical therapy in restoring a healthy *Lactobacillus* population and in suppressing the polymorphonuclear and clue cells infiltration. That goes hand in hand with its high efficacy in almost normalising the Vaginal Health Index though starting from a situation of comparatively worse mucosal hypotrophy (final mean score in DQRF-treated women - 21.65 out of a maximum of 25).

The effect on pain was most unlikely to be a placebo effect. A most recent small metanalysis of topical medications as monotherapy of vulvodynia showed placebo to be as effective as any medication [32]. This does not seem the case for the DQRF/ EVA™ technology. First of all, the study was limited to women with localised provoked vulvodynia and did not include women with the less frequent idiopathic clinical subtype, which as a neuropathic disorder is liable to placebo effects. Secondly, reduction of pain with the DQRF physical treatment was associated with a shift towards normality of the depleted *Lactobacillus* vestibular microflora as well as other signs of ecological and microscopic improvement. Such improvements seem unlikely to be a mere placebo effect.

In conclusion, the outcomes of this ground breaking exploratory study suggest that the new DQRF technology might be a promising new strategy to control provoked vulvodynia and the severe impact on female self-esteem that is all too often associated with this poorly recognised disorder. Any final judgement must wait for new soundly designed trials.

Conflicts of Interest

The authors were in the past consultants to Novavision Group S.p.A. They certify to have no current conflict of interest with any financial or commercial organization regarding the content of this manuscript.

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Ultra-Pulsed Radioporation further enhances the efficacy of Dynamic Quadripolar RadioFrequency in women with post-menopausal vulvo-vaginal atrophy

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Abstract

Background: A growing body of evidence illustrates the benefits experienced by women with vulvo-vaginal atrophy/genitourinary syndrome of menopause (VVA/GSM) undergoing vaginal rejuvenation with the very recent low-energy Dynamic Quadripolar RadioFrequency (DQRF™) technology. Twelve-month follow-up data describe significant improvement from both a clinical (relief of VVA/GSM symptoms) and psychological perspective (women's self-esteem and satisfaction from sexual life and couple relationship). The proprietary Ultra-Pulsed Radioporation (UPR™) technology is intended to associate the anti-atrophic benefits of both the DQRF™ technology and any topical agent with anti-atrophic properties. UPR™ acts by opening aqueous channels in cell membranes and further modulating DQRF™ performance. UPR™ helps any active principle with useful properties to penetrate the deep layers of vulvar skin and vaginal mucosa. Topical hyaluronic acid (HA) is increasingly used, based on solid biological rationale, to help slow and reverse the menopause-related loss of elasticity and volume of vulvo-vaginal tissues. This pilot study was designed to verify if the novel UPR™ technology, applied to a test anti-atrophic topical agent like HA in combination with standard DQRF procedures, could indeed enhance the already established anti-atrophic efficacy of the DQRF™ technology.

Methods: Prospective, randomised, open-label study; two parallel groups of 30 women with evidence of vaginal atrophy and dryness and other postmenopausal VVA/GSM symptoms. Radiofrequency treatment schedule in both the Dynamic Quadripolar RadioFrequency ("DQRF™") and Dynamic Quadripolar RadioFrequency/Ultra-Pulsed Radioporation ("DQRF™ + UPR™") study arms: five 15-min sessions every 14-16 days following application of either standard or UPR coupling gel. Operative temperatures in target tissues during procedure: 42°C (range 40-43°C). Self-administered evaluation tools (before and at the end of the treatment sessions): 10-cm visual analogue scales (VAS) for VVA/GSM symptoms (vaginal dryness, itching and burning, dyspareunia, dysuria/incontinence), 13-item Female Sexual Distress Scale-Revised (FSDS-R) questionnaire (multi-perspective assessment of the woman's personal distress related to sexual dysfunction), Sexual Satisfaction Questionnaire (SSQ) (sexual gratification.) Non-parametric statistical analysis (Wilcoxon Signed Rank and McNemar tests).

Results: On average, all the assessed parameters (VAS symptom scores, FSDS-R and SSQ scores related to the sexual sphere) underwent statistically significant or highly significant improvements in both the "DQRF™ + UPR™" active group and "DQRF™" controls over the about two months of the treatment program. The observed improvements, though always very strong, were somewhat less impressive for at least some parameters in the control "DQRF™" group compared with the active "DQRF™ + UPR™" treatment group. That was distinctively the case for vaginal itching, dyspareunia and dysuria/incontinence among VVA/GSM symptoms ("DQRF™ + UPR™" vs. "DQRF™" VAS scores: -60.9% vs. -49.2%, -63.8% vs. -50.5%, and -59.3% vs. -44.9%, respectively), and for sexual satisfaction from intercourse activity ("DQRF™ + UPR™" vs. "DQRF™" SSQ scores: + 96.4% vs. + 85.8%, $p < 0.05$).

Discussion: The novel UPR™ technology was devised to modify the performance of the DQRF™ EVA™ device to facilitate the deep penetration of any topical active principle that has demonstrated to have a favourable impact on the atrophy of female post-menopausal intimate tissues. The idea behind the UPR™ concept was to enhance the established rejuvenation effect of the DQRF™ technology thanks to the synergy between the biological effect of the radiofrequency treatment and that of the topical active principle. In the current short-term pilot study, low-molecular weight HA was chosen as the model topical active principle to test the UPR™ concept. This short-term pilot study confirmed the high vaginal rejuvenation efficacy over a short time of the established DQRF™ technology in post-menopausal women. Moreover, the study suggested that the novel UPR™ technology is likely to further enhance the DQRF™ clinical benefits. Long-term studies are warranted to confirm these preliminary encouraging results.

Introduction

Low-energy Dynamic Quadripolar RadioFrequency (DQRF™) technology is one of the most recent evolutions in the field of light- and energy-based technologies. DQRF™ has already shown its potential for vulvo-vaginal rejuvenation in postmenopausal women experiencing vulvo-vaginal atrophy and related symptoms of genitourinary syndrome of menopause (VVA/GSM) with, often, severe disruption of quality of life [1-3]. The proprietary DQRF™ technology is patented all over the world by Novavision Group S.p.A. (Misinto, Monza-Brianza, Italy). An extensive clinical research programme with the DQRF™-based device, EVA™, is in progress, and follow-up has reached one year with encouraging safety and efficacy data [1].

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There is some indication from all these data that the new DQRF™ technology might overcome the problems of low manageability and safety sometimes experienced with other light- and energy-based vulvo-vaginal rejuvenation strategies [3]. At the core of the new high-tech EVA™ device is the VDR™ (Vaginal Dynamic Radiofrequency™) quadripolar 1.0-1.3 MHz radiofrequency technology. VDR™ is based on four stainless steel, electronically controlled dynamic electrodes on anatomical probes with a maximum emitting power of 55 W. All happens within the four radiofrequency electrodes that continuously cycle, under electronic control, between receiver and transmitter states eliminating the need for grounding pads on the upper thigh. In the ideal configuration, the repelling electric fields that are generated concentrate the thermal effect with high tridimensional precision in the target vulvo-vaginal subepithelial layers. This allows respect of surrounding tissues and reduces the administered energy by almost eliminating Ohm's resistances in tissues. Electronically controlled movement and temperature sensors (RSS™, Radiofrequency Safety System™ technology) allow rigid control of tissue temperature, eliminating all needs for systemic analgesia or local anaesthesia in the treated area. This area has usually a diameter of some 12 cm, or about 4 inches, centred on the hymenal ring. Women can pause the session at will thanks to a feedback button [3].

A further very recent development of the DQRF™ concept is the proprietary Ultra-Pulsed Radioporation™ (UPR™) technology. The cue for developing the UPR™ technology was taken from radiofrequency electroporation techniques long used in genetic engineering to allow high-efficiency gene transfection and transfer of biological macromolecules into cells [4,5]. UPR™ acts by opening aqueous channels in cell membranes through modulation of the radiofrequency effects of the DQRF™ technology. This is useful to allow the massive transfer of any active principle with useful properties down to the deep layers of vulvar skin and vaginal mucosa. Speculatively, the effect on post-menopausal vulvo-vaginal hypotrophy and loss of tissue elasticity by DQRF™ could sinergise with the anti-atrophic properties of the topical active principles. Always speculatively, the biophysics behind the UPR™ technology could facilitate the efficient penetration of topical active principles into vulvo-vaginal tissues, further enhancing the DQRF™ anti-atrophic efficacy.

Cross-linked HA restores the extracellular matrix needed for fibroblast activation and collagen and elastin production [6]. A small yet increasing number of papers over the last few years has investigated the role of hyaluronic acid (HA) to counteract the age-related loss of elasticity and volume of female external genitalia. The aesthetic perspective was dominant in some of these studies, carried out with HA dermal fillers in women with mild to moderate labia majora hypotrophy [7,8]. Other studies with topical HA formulations were more focused on the VVA/GSM symptoms of vaginal dryness, burning and itching, dyspareunia and dysuria/incontinence. Outcomes, both in terms of symptom relief and respected ecology of the vaginal microenvironment, were similar for topical HA and estriol or conjugated oestrogen formulations [9-12].

All these evidences support topical HA as a fine active principle to test the value of the novel UPR™ technology. A coupling gel additioned with low-molecular weight HA (about 290 kDa) was developed to test in a pilot study whether combining the DQRF™ and UPR™ technologies could further enhance the established benefits of DQRF™ rejuvenation in post-menopausal women.

The herein described double-blind pilot study was designed to compare the short-term evolution of VVA/GSM symptoms and women's gratification and satisfaction with sexual life in two random samples of post-menopausal women randomised to rejuvenation with either the established DQRF™ technology or the novel DQRF™ + UPR™ approach. In the five planned sessions, a standard coupling gel and the HA-additioned gel were respectively used. The two coupling gels could not be identified.

Materials and methods

Screening and randomisation

Sixty VVA/GSM women reporting no menstruation for at least 12 months were screened and randomised, after giving informed consent, between January and July 2017 within the pool of more than 150 outpatients regularly attending a specialist department for post-menopausal disorders in a private clinic. All screened women referred postmenopausal vaginal dryness, evidence of mucosal atrophy (thinning or loss of vaginal rugae, mucosal pallor, etc.), and other VVA/GSM-related symptoms; an explicit wish for a still active sexual life was also a must. Hormonal replacement therapy, any pelvic organ prolapse beyond the hymenal ring, chronic vulvar pain, vulvar dermatitis or dystrophy, viral lesions, including high risk for human Papillomavirus infections, and poor thickness of the recto-vaginal septum at pelvic examination led to exclusion of candidates. Any active genital or urinary tract infection required treatment before enrolment.

The randomisation log to the two double-blind treatment groups ("DQRF™" as controls, "DQRF™ + UPR™" as active group; 30 women per group) was generated with the help of a random numbers generator. All study materials, including informed consent forms, study protocol and electronic case report forms, were peer-reviewed for ethical problems and authorised by the clinic authorities. All women gave informed consent to anonymous collection of their data before the first treatment session.

Outcome evaluation

The clinical severity of VVA/GSM symptoms (vaginal dryness, burning and itching, dyspareunia, dysuria/incontinence) was self-assessed by participants immediately before each of the five treatment sessions using the same 10-cm visual analogue scales (VAS) used in previous DQRF™ studies ("No symptom" at the left VAS extreme and "Symptom as severe as it could be" at the right extreme) [1,3]. The self-administered Female Sexual Distress Scale-Revised (FSDS-R) questionnaire was used to assess the main factors related to sexual dysfunction affecting the women's personal distress. The FSDS-R responses are based on the frequency with which each problem has caused distress to the woman within the recall periods (for this study, the previous 7 days) [13]. An Italian translation of the Sexual Satisfaction Questionnaire (SSQ — 6-level ordinal responses: none, poor, fair, good, very good, excellent) was also used to evaluate sexual satisfaction from vaginal intercourse. All categorical responses were translated into ordinal scores for statistical analysis (for instance for the SSQ scale, none=0, poor=1, fair=2, …, excellent=5).

DQRF™ and DQRF™/UPR™ treatment protocol

- Five 15-min sessions, spaced 14-16 days
- Setting of the radiofrequency generator: 1 MHz
- Operating power: 25% of the maximum device power (55 W)
- Target temperature in vulvo-vaginal tissues during procedure: 42°C (range 40-43°C)

Operative procedures

Five treatment sessions were planned spaced 14-16 days. Power was applied for 15 minutes using either the DQRF™ or DQRF™ + UPR™ coupling gels starting behind the hymenal ring, with circular back-and-forth continuous movements and always keeping contact between the tip probe and the mucosa. The DQRF™ power was set at 25% of the device maximum power (55 W). A standard coupling gel was applied before each DQRF™-only session to the control women of the "DQRF™" treatment group. The HA-supplemented coupling gel used in women of the "DQRF™ + UPR™" treatment group (combining the established DQRF™ and novel UPR™ technologies) was indistinguishable from the DQRF™ coupling gel and was pre-prepared by adding 5 grams of HA to the usual dose of standard coupling gel. Neither the operator nor the treated woman knew which coupling gel was being applied. The operator and the treated woman were similarly unaware if a DQRF™-alone or a DQRF™ + UPR™ modified EVA™ device were being used and all procedures were double blind. Safety, with special attention to pain and discomfort, was assessed in all women at each study visit and by telephone calls over the following days.

Statistical analysis

Descriptive statistics were generated for demographics and physical examination findings. The nonparametric Wilcoxon Signed Rank Test for repeated measurements on single populations was applied to both repeated measures of ordinal data (converted FSDS-R and SSQ mean scores) and continuous variables (VAS mean scores); the McNemar test was used to test for differences in ordinal scores. The Wilcoxon Signed Rank Test will also be instrumental in the forthcoming morphological assessment. Two-sided 95% confidence levels were used for all statistical tests with p<0.05 as cut-off for significance.

Results

All randomised women completed their double-blind treatment program as planned without missing visits. Table 1 illustrates the comparable demographics of the two study groups before the first treatment session. All participant women described their treatment sessions as comfortable; no burns or other complications were reported. All women resumed their everyday and sexual activities immediately after the end of their treatment program.

Figure 1 illustrates the evolution of the VVA/GSM symptoms over the about two months of the "DQRF™ + UPR™" and "DQRF™" treatment programs. On average, all the assessed VVA/GSM symptoms underwent statistically significant or highly significant improvements in both treatment groups. Compared with the basal situation, VAS mean scores were at least halved (p <0.01) after the end of the treatment program in the "DQRF™ + UPR™" group (vaginal dryness −59.0%, vaginal itching −60.9%, vaginal burning −59.4%, dyspareunia −63.8%, dysuria/incontinence −59.3%). The basal mean scores were also at least halved (p <0.01) in the control group at the end of the "DQRF™" program for vaginal dryness (−51.4%), vaginal burning (−59.4%) and dyspareunia −50.5%), but the registered symptomatic improvement was somewhat less for vaginal itching (−49.2%, p <0.01) and dysuria/incontinence (−44.9%, p <0.05). There was no statistically significant difference in the evolution of VVA/GSM symptoms between the "DQRF™ + UPR™" and the "DQRF™" treatment groups for vaginal burning (−59.4% in both treatment groups), while there was a borderline non-significant difference for vaginal dryness (−59.0% vs. -51.4%, p ≈0.06), and a highly significant difference (p <0.01) for vaginal itching (−60.9% vs. -49.2%), dyspareunia (−63.8% vs. −50.5%) and dysuria/incontinence (−59.3% vs. −44.9%).

Table 1. Demographics of the "DQRF™+UPR™" and "DQRF™" treatment groups. SD, standard deviation; HRT, hormone replacement therapy

ACTIVE GROUP ("DQRF+UPR")	
Age (years, mean ± SD)	58.1 ± 5.7
Body Mass Index (kg/m², mean ± SD)	23.6 ± 2.5
Previous live births (n, %)	25 (83%)
Mean parity (range)	1.3 (1-4)
Current sexual activity (n, %)	25 (83%)
Previous HRT (n, %)	10 (33%)
CONTROL GROUP ("DQRF")	
Age (years, mean ± SD)	57.9 ± 6.8
Body Mass Index (kg/m², mean ± SD)	24.2 ± 3.1
Previous live births (n, %)	27 (90%)
Mean parity (range)	1.7 (1-4)
Current sexual activity (n, %)	23 (77%)
Previous HRT (n, %)	12 (40%)

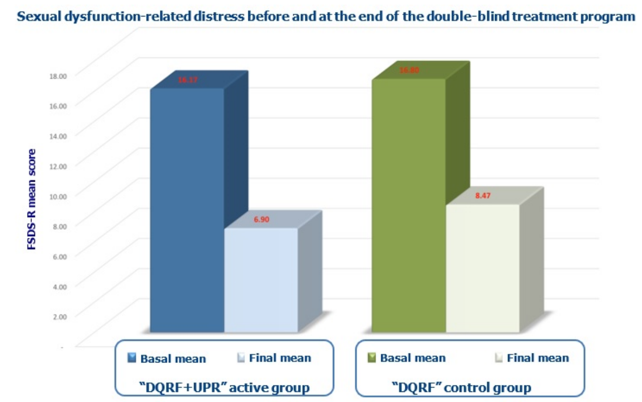

Figure 1. VAS mean scores for the VVA/GSM symptoms in the active "DQRF™ + UPR™" treatment group compared with the control "DQRF™" treatment group

Figure 2 illustrates how the women's personal distress related to sexual dysfunction evolved in the "DQRF™ + UPR™" treatment group and in the "DQRF™" control group. FSDS-R basal mean scores more than halved in the active group (−57.3%, p <0.01); the women of the "DQRF™" control group showed a tendency towards a somewhat less dramatic improvement of sexual distress (−49.6% vs. mean basal score, p <0.01), with a marginally significant difference between the two treatment groups (p ≈0.054).

Figure 3 illustrates the women's experience with vaginal intercourse and how the related sexual satisfaction evolved in the "DQRF™ + UPR™" active group and in the "DQRF™" control women. The improvement of SSQ mean scores was highly significant in both treatment groups (+96.4% and +85.8%, respectively; p <0.01 vs. mean basal score for both groups), but the final SSQ improvement was significantly higher in the "DQRF™ + UPR™" treatment group (p <0.05).

Discussion

Radiofrequency fields induce oscillating electrical currents in target tissues with steady re-orientation of dipole moments like water molecules. Water viscosity means resistance (impedance) and attrition to movements of other biomolecules under the influence of the variable electrical fields in female intimate tissues. That results in dissipation of biomolecular kinetic energy into heat [2]. More and more accumulating evidences suggest that the DQRF™ technology could be an advance, most likely in terms of safety, over other light- and energy-based technologies. Laser devices may especially cause bleeding, pain,

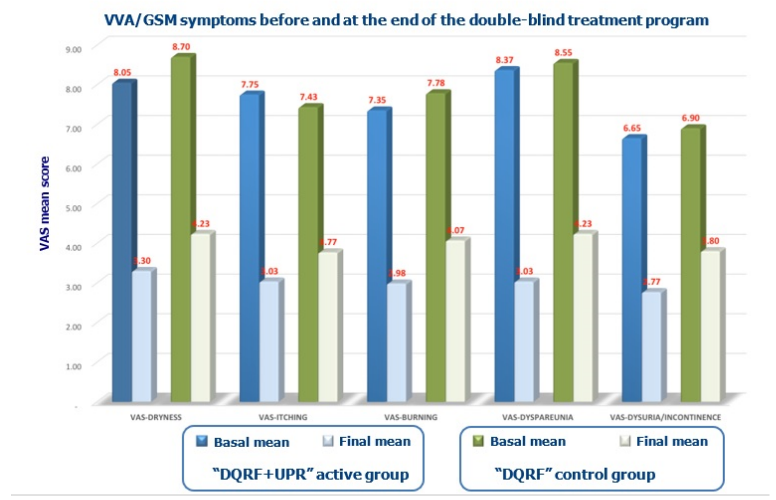

Figure 2. FSDS-R mean scores (main factors affecting the women's personal distress due to sexual dysfunction) in the active "DQRF™ + UPR™" treatment group compared with the control "DQRF™" treatment group

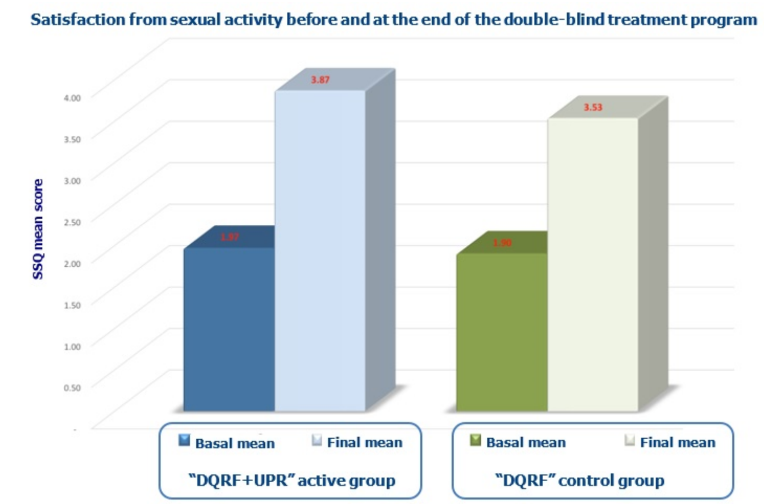

Figure 3. SSQ mean scores (sexual satisfaction from vaginal intercourse) in the active "DQRF™ + UPR™" treatment group compared with the control "DQRF™" treatment group

and burning [14]. Induction of new elastogenesis is also relatively unique to radiofrequency technologies, helping to restore mechanical strength, tightness, and elasticity to atrophic external genitalia of post-menopausal women [2,15,16].

The novel UPR™ technology was devised to modify the performance of the DQRF™ EVA™ device so as to facilitate the penetration of any topical active principle applied to the treated vulvo-vaginal area. The idea behind the UPR™ concept is to enhance the established rejuvenation effect of the DQRF™ technology thanks to synergy between the biological effect of the radiofrequency treatment and that of the topical agents that were shown to improve the atrophy of female post-menopausal intimate tissues. Available evidence led to choose low-molecular weight HA as the model topical active principle to test the UPR™ concept in the current short-term pilot study [9-12]. The DQRF™ technology has once again confirmed its rapid efficacy on the often troubling VVA/GSM symptoms as well as on other problems relating to the woman's sexual life and self-esteem. Outcomes were in line with those observed in previous studies in post-menopausal women. A general tendency was apparent in the "DQRF™" treatment group to about halve the severity of symptoms and the disruption of intimate life over the about two months of the five-session treatment program [1,3]. The UPR™ concept tested in this double-blind pilot study also seems validated thanks to a global enhancement of the DQRF™ clinical benefits with special reference to VVA/GSM symptoms like vaginal itching and dysuria/incontinence. Interestingly, the score differences between the "DQRF™ + UPR™" active group and the "DQRF™" control women that support the UPR™ concept were especially strong in the area of the women's everyday sexual life: dyspareunia, distress related to sexual dysfunction, gratification directly related to sexual activity. Of course, long-term studies are warranted to confirm these preliminary encouraging results.

Conflicts of interest

The authors were in the past consultants to Novavision Group S.p.A. They certify to have no current conflict of interest with any financial or commercial organization regarding the content of this manuscript.

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Genital Rejuvenation

Dynamic Quadripolar Radiofrequency: Pilot Study of a New High-Tech Strategy for Prevention and Treatment of Vulvar Atrophy

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Abstract

Background: The well-being of the vulva and a woman's quality of life are strongly correlated. Dynamic quadripolar radiofrequency (DQRF), one of the newest nonsurgical light- and energy-based vulvar rejuvenation technologies, has been demonstrated to be an effective option in aesthetic gynecology.

Objectives: The aim of this study was to perform qualitative and semiquantitative evaluations of short-term changes in vulvar aesthetics to illustrate the efficacy of an accelerated DQRF vulvar rejuvenation program in women with mild to moderate vulvar atrophy.

Methods: Twenty women with mild to moderate vulvar atrophy were prospectively screened and evaluated. Serial photographs documented the aesthetic impact of DQRF on the vulvar area over the 2-month study period. The overall aesthetic improvement was rated on a Global Aesthetic Improvement Scale modified to create a 10-point semiquantitative rating tool. Complications and side effects were recorded.

Results: All women successfully underwent 3 planned DQRF procedures spaced 7-10 days apart. Signs and symptoms of vulvar atrophy and the range of aesthetic judgments of the vulvar area were improved in most women after the first DQRF session, and improvements in vulvar aesthetics were persistently highly significant 1 month after the end of the DQRF rejuvenation program. No complications or side effects occurred.

Conclusions: Improvements in the signs and symptoms of vulvar atrophy by DQRF rejuvenation of the labia majora confirm the efficacy and safety of this technically simple outpatient procedure. In women with mild to moderate atrophy, a rapid rejuvenation program of closely spaced sessions achieved significant improvements.

Level of Evidence: 4

Therapeutic

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The vulva is a complex organ, and thus an in-depth understanding of the functional anatomy of this complicated area is crucial.[1] The labia majora are prominent paired cutaneous lateral folds of hair-bearing skin and adipose tissue that extend inferiorly from the mons pubis and merge with neighboring skin to form a ridge overlying the perineal body, also known as the posterior fourchette.[1] In addition to adipose tissue, the labia majora also contain the distal ends of the round ligaments, hair follicles, and a rich supply of sebaceous, apocrine, and eccrine sweat glands.[1] The labia majora resemble the anterior abdominal wall in their underlying composition, which comprises the superficially located Camper's fascia with a predominance of fat; and the thicker Colles' fascia that forms the deeper layer and corresponds to Scarpa's fascia in the abdominal wall.[1] The

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labia minora are pigmented, hairless folds of skin, devoid of fat, but rich in nerve endings and sensory receptors. They are located medial to the labia majora, immediately adjacent to the vestibule. Anteriorly, each labia minora separates into 2 folds that run over and under the glans of the clitoris. The superior folds unite in the midline to form the prepuce, or clitoral hood. The inferior folds insert into the underside of the clitoris to form the frenulum. The posterior aspects of both labia minora merge with the labia majora at the posterior fourchette. Hart's line demarcates the transition between the keratinized epithelium of the labia majora (embryologically deriving from the ectoderm) and the nonkeratinized epithelium of the vestibule of the vagina (embryologically deriving from the endoderm). The dermis of the labia minora is composed of thick connective tissue containing elastic fibers and small blood vessels.[1]

Vulvar atrophy is an age-related condition affecting different parts of the vulva, including the mons pubis, labia majora, and labia minora; women's external genitalia need steady estrogen stimulation to maintain their normal structure and function. α- and β-estrogen receptors, widely distributed throughout the vulva during reproductive life, decline with aging.[2] A lack of estrogen in dermal layers contributes to the loss of elasticity by inducing fusion and hyalinization of collagen and the fragmentation of elastic fibers;[3,4] mucosal hydration is also negatively affected by the reduction of matrix mucopolysaccharides and hyaluronic acid.[5,6] Macroscopically, the mucosa of the introitus and labia minora becomes thin and pale, and the reduced vascularization, quite evident microscopically, translates into a decreased volume of transudates and other secretions.[7,8]

Intimate trophic modifications profoundly affect a woman's sexual life, self-esteem, and quality of life, as shown in several recent studies.[9–11] Awareness of these problems is growing; indeed, what the authors of the International Vagina Dialogue Survey predicted almost 10 years ago is happening today: many women are no longer ashamed to discuss and acquire information about their intimate trophic problems.[12] The social impact of aging-related vulvar problems will be even more severe in the future: by 2025 there will be 1.1 billion women > 50 years of age in the world (in 2009 they were less than 700 millions).[13] Thus, it is crucial for gynecologists, aesthetic physicians, and plastic surgeons to be up to date with the latest developments in vulvar rejuvenation technologies.

Interest in vulvar rejuvenation procedures is indeed rising.[14] According to the American College of Obstetricians and Gynecologists, aesthetic and cosmetic procedures of the vulvar area have been showing double-digit growth in the United States in recent years, even in young and sometimes adolescent women.[15] The American Society for Aesthetic Plastic Surgery reported a total of 8745 labiaplasty procedures performed in 2015, a 15% increase over the previous year.[16] Most techniques—wedge resections,[17,18] edge resections, Z-plasties, or modified resections[19]—target skin redundancy (hypertrophy) of the labia minora. Fewer techniques have been developed for vulvar skin atrophy: augmentation of the labia majora through the grafting of adipose tissue[20,21] or hyaluronic acid fillers[22,23] are some examples.

Due to their noninvasive nature and simpler management, increasing attention is being paid to light- and energy-based technologies such as monochromatic laser radiation and radiofrequencies.[24] The key to rejuvenation is the thermal activation of fibroblasts, leading to anatomic remodeling of the vulvar and vaginal tissues as shown with both electromagnetic and laser radiation.[24–26]

Low-energy dynamic quadripolar radiofrequency (DQRF) is the most recent in a large group of emerging biophysical technologies aimed at the rejuvenation of vulvar tissues. Developed by the Italian company Novavision Group SpA (Misinto, Monza-Brianza, Italy), innovative DQRF technology is at the core of Novavision's EVA device.

The DQRF approach relies on the particular interaction between the subepithelial layers of the vulva and the energy emitted by the 4 electronically controlled dynamic electrodes of the radiofrequency generator. These electrodes sequentially act as receivers and transmitters and continuously generate variably repelling electrical fields. DQRF biophysics allows the operator to define with high 3-dimensional (3D) precision the subepithelial vulvar volume that receives the energy. The overall energy administered is much reduced due to the lack of dispersion into tissues adjoining the target area; electronically controlled movement and temperature sensors (RSS, Radiofrequency Safety System technology) facilitate accurate control of tissue temperature when using the DQRF-based EVA device.[27–29] Clinical studies have already demonstrated the safety and efficacy of the DQRF technology in relieving bothersome intimate symptoms in women with post-delivery vaginal laxity and postmenopausal vulvovaginal atrophy and genitourinary syndrome; other studies are currently being published and planned.[27–29]

Regarding age-related vulvar atrophy and a more aesthetic and cosmetic gynecology perspective, a proprietary 4-session "EVA Vulvar Rejuvenation" protocol has already been validated in women with mild to severe vulvar atrophy[27] (four 10-min sessions, spaced 14–16 days apart, setting of the radiofrequency generator 1 MHz, operating power 8%–14% of the maximum device power 55 W, target temperature in vulvar tissues during procedure 42°C, range 40–43°C) in women with mild to moderate atrophy. This further pilot study was designed to evaluate the efficacy of a program of 3 DQRF vulvar rejuvenation sessions with a more compressed time frame.

METHODS

A prospective cohort of 20 Caucasian women with signs and symptoms of mild to moderate vulvar atrophy was

Table 1. Classification of Labial Hypotrophy/Atrophy[23]

	Subcutaneous layers	Cutaneous layers	Symptoms
Stage I: mild (early)	Mild hypotrophy/atrophy; distribution of adipose tissue is usually symmetrical	None to mild cutaneous hypotrophy/atrophy; thin wrinkles may be visible	Usually asymptomatic, may follow a weight loss
Stage II: moderate	Moderate hypotrophy/atrophy; distribution of adipose tissue may be asymmetrical	Moderate cutaneous laxity, dermatochalasis; visible wrinkles	Dryness, dyspareunia, and soreness may be observed
Stage III: severe	Severe hypotrophy/atrophy; adipose tissue is frequently distributed asymmetrically	Severe dermatochalasis and deep wrinkles	Usually associated with symptoms such as dryness, dyspareunia, and soreness

screened and enrolled in the study between June 2016 and September 2017. At screening, each candidate woman's atrophy was staged through a clinical examination according to our classification into 3 grades (mild or early, moderate, and severe) considering both the adipose tissue and the cutaneous layer (Table 1).[23] This staging classification takes into consideration both the skin layers and the subcutaneous adipose tissue.

All patients included in the study provided written informed consent for the anonymous collection of their data before the first DQRF session, and all study materials were peer reviewed to check for any ethical issues. The procedures conformed to the ethical guidelines of the Declaration of Helsinki. Inclusion criteria at screening were signs and symptoms of mild to moderate vulvar atrophy (Stages I and II), premenopausal age, normal body mass index (BMI) (18.5–24.9 kg/m^2), regular sexual activity, and cosmetic indications for treatment. The premenopausal status was determined by asking to our women (who were all older than 41 years) their menstrual rate (everyone of them had regular/irregular periods, nobody was in amenorrhea from more than 1 year). Moreover, they all had signs (and someone of them also symptoms) of climateric syndrome as vulvar atrophy. Exclusion criteria were severe Stage III vulvar atrophy, any previous aesthetic procedures or previous surgery on the external genitalia, history of vulvar cancer, acute or chronic vulvar disorders including dermatitis and sexually transmitted viral infections, poor sensitivity to pain or heat, immune depression, autoimmune diseases, uncontrolled diabetes mellitus, urinary tract or sexually transmitted infections, moderate or severe pelvic organ prolapse, and bleeding diathesis. Candidate women being treated with anticoagulant and immunosuppressive drugs or radiotherapy were also excluded. Dysmorphic syndrome was excluded based on a clinical interview performed during the screening visit. Demographic data including pharmacologic treatments and evidence of premenopausal syndrome were recorded; we enrolled premenopausal women because this is the life stage at which the majority of our patients start to report symptoms related to vulvar atrophy, but at the same time still desire a satisfactory sexual and intimate life, and because this

Table 2. Accelerated Rejuvenation Program in Mild to Moderate Vulvar Atrophy Evaluated and Validated in this Study (3 DQRF sessions, spaced 7-10 days apart, with the same device settings)

Three 10-min sessions, spaced 7-10 days apart
Setting of the radiofrequency generator: 1 MHz
Operating power: 8%–14% of the maximum device power (55 W)
Target temperature in vulvar tissues during procedure: 42°C (range 40–43°C)

kind of patient is our main professional focus and expertise. All women were treated according to the accelerated EVA Vulvar Rejuvenation protocol that is being validated in this pilot study (Table 2).

Accelerated DQRF "EVA Vulvar Rejuvenation" Treatment Protocol

This outpatient procedure requires the application of a glycerin-based gel to the vulvar area, after which the treatment is carried out by slow circular movements, 5 minutes for each side, with all 4 of the electrodes in contact with the skin of the labia majora. No anesthesia or cooling system is required due to the DQRF biophysics, which as described above reduces the amount of energy involved in the process.

Aesthetic improvement was documented photographically before the first DQRF™ session (Figures 2A, 3A, and 4A, and Supplemental Figures 1A and 2A), and before the second DQRF™ session (Figures 2B and Supplemental Figure 1B); a last photographic documentation was collected at a follow-up visit programmed 30 days after the last treatment session (Figures 2C, 3B, and 4B, Supplemental Figures 1C and 2B). The treated women and an independent medical evaluator, a specialist in aesthetic gynecology who was unaware of the history and demographic details of the cohort women, rated the aesthetic improvement on a Global Aesthetic Improvement Scale (GAIS) modified to give a semiquantitative rating tool based on 10 scores, ranging from 1-2 ("Worse") and 3 ("No change") to 9-10 ("Very much improved"). The assessments were performed before the first DQRF treatment session (baseline), before the second DQRF treatment session (i.e., 7-10 days after the first session), and 30 days after the

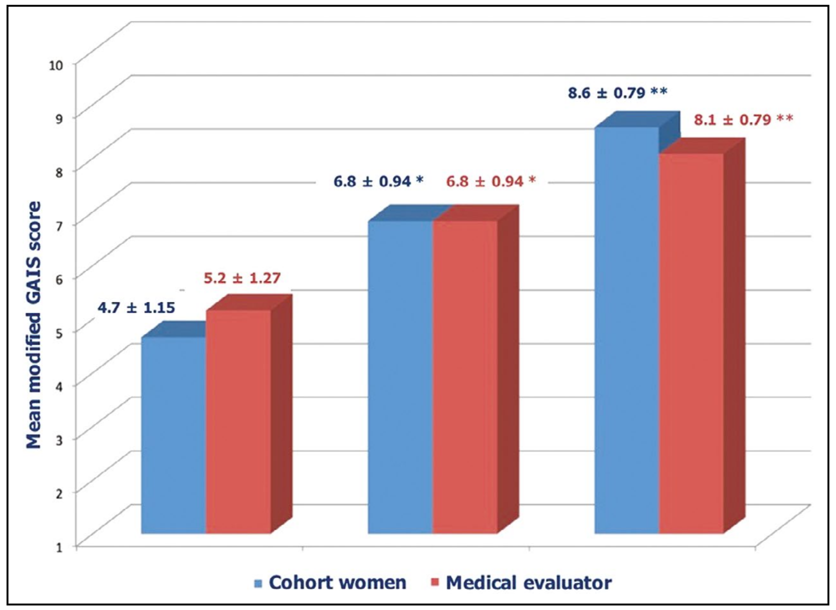

Figure 1. Mean modified GAIS scores assigned by the women of the study cohort and an aesthetic gynecology specialist acting as blind evaluator who was unaware of the clinical history of the cohort women.

third and last treatment of the accelerated DQRF rejuvenation program (follow-up visit). Each woman was identified by a serial number in order to allow anonymous scoring and comparisons of the photographic documentations. Statistical analysis consisted of the nonparametric Wilcoxon signed-rank test, with $P < 0.05$ being regarded as significant. Both systemic and local adverse reactions and complications were recorded through a clinical interview before and after every session and at the follow-up visit.

RESULTS

The mean age of the screened women was 47.3 ± 3.5 years (range 41–51 years). In line with the inclusion criteria, all enrolled women had Stage I or Stage II atrophy (12 and 8 women, respectively), were not satisfied with their vulvar aesthetics, and had cosmetic indication for treatment. Seven women, all of whom had moderate atrophy, subjectively complained about occasional dyspareunia and/or dryness. All women were premenopausal, of normal BMI (mean 23.1 ± 1.5 kg/m^2, range 18.7–24.9 kg/m^2), and reported having regular sexual activity. None of these women was taking any medications that might influence the outcome. All women returned for their planned follow-up visits 30 days after their last DQRF session.

The photographic documentation of the vulvar area provides objective evidence of the rapid efficacy of the accelerated EVA Vulvar Rejuvenation program in women with mild to moderate atrophy. The mean GAIS scores reported by both the evaluator and the treated women improved even after the first DQRF session. Improvements in vulvar aesthetics were persistently highly significant 1 month after the end of the DQRF rejuvenation program—evaluator's scores: 5.2 ± 1.27 (baseline) vs 6.8 ± 0.94 (before second treatment session, $P < 0.05$ vs baseline) and 8.1 ± 0.79 (follow-up, $P < 0.01$ vs baseline); cohort women's scores: 4.7 ± 1.15 (baseline) vs 6.8 ± 0.94 (before second treatment session, $P < 0.05$ vs baseline) and 8.6 ± 0.79 (follow-up, $P < 0.01$ vs baseline) (Figure 1). The subgroup of women with bothersome symptoms of dryness or dyspareunia reported subjectively significant improvements in vulvar skin hydration and pain during intercourse; all treated women informally expressed satisfaction with their final aesthetic outcome. No clinically significant side effects or discomfort were reported during the procedures. A slight degree of hyperaemia that lasted about 30 minutes was observed in almost all women after the treatment sessions. All women referred to the warm sensation experienced during the procedure as pleasant or at least definitely not troubling.

DISCUSSION

The last few years have seen steadily growing academic and practical interest in the aging vulva in aesthetic medicine, aesthetic gynecology, and plastic surgery, as well as a steady expansion of clinical research. This is in line with the burgeoning interest in all the gynecological conditions that impact the aesthetic self-perception, body image, and quality of life of women, such as the genitourinary syndrome of menopause, with its bothersome vulvar, vaginal,

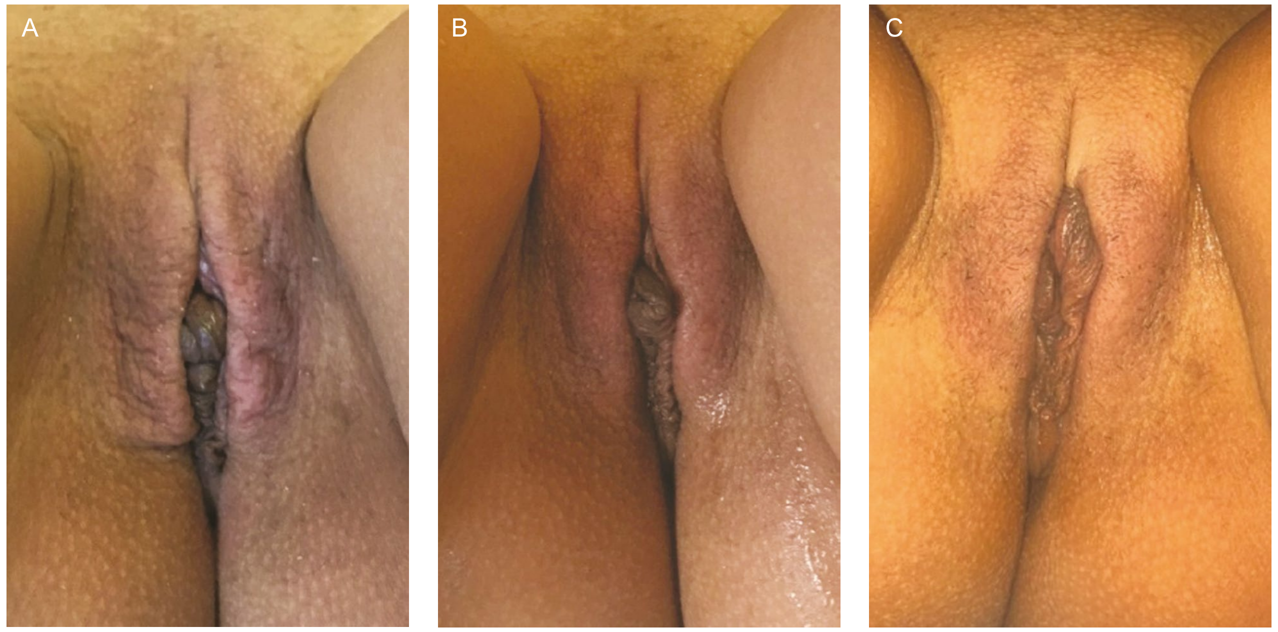

Figure 2. A 41-year-old woman with moderate vulvar atrophy (stage II). (A) T0: baseline, before the first DQRF session. (B) T1: before the second DQRF session (10 days after the first session). (C) T3: at the follow-up visit (30 days after the third session).

Figure 3. A 41-year-old woman with moderate vulvar atrophy (stage II). (A) T0: baseline, before the first DQRF session. (B) T3: at the follow-up visit (30 days after the third session)

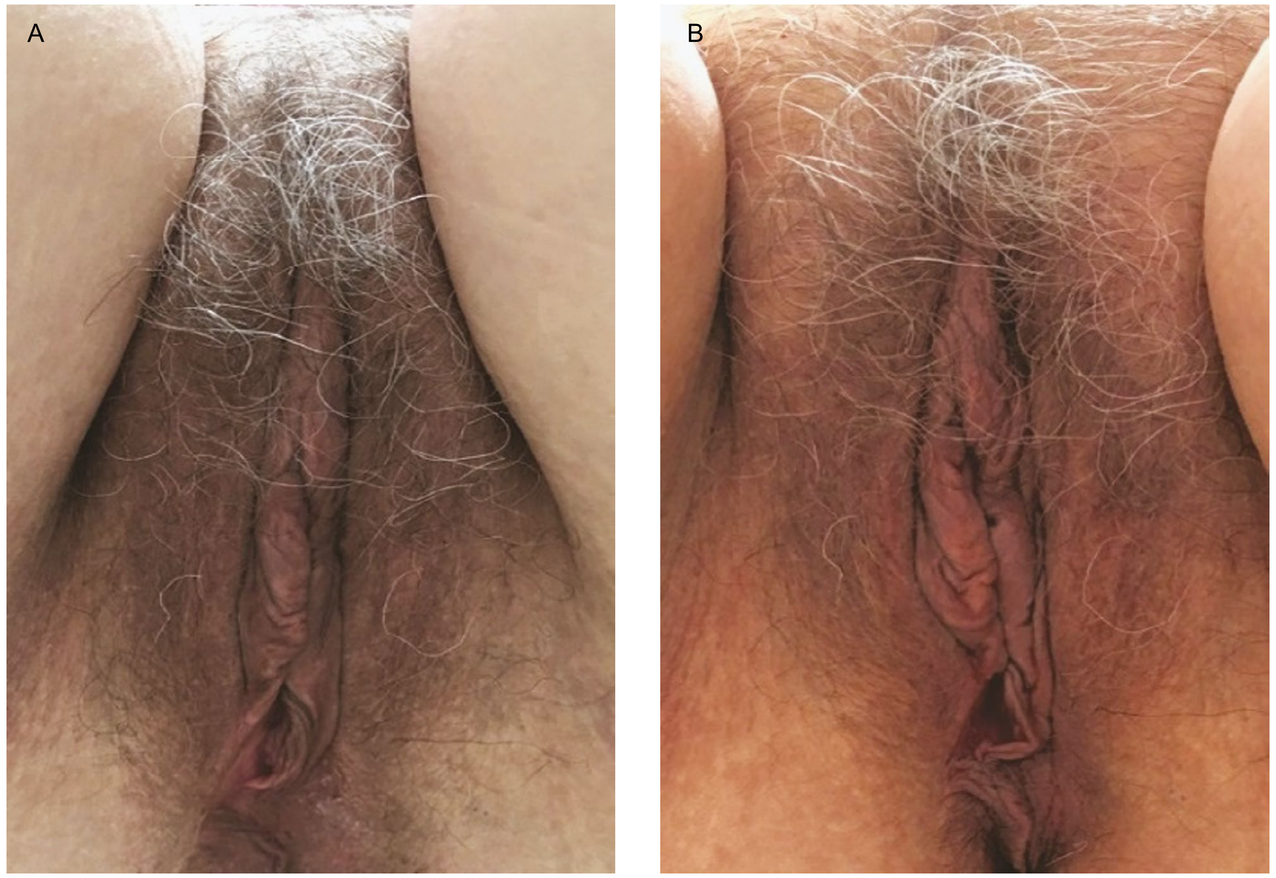

Figure 4. A 51-year-old woman with moderate vulvar atrophy (stage II). (A) T0: baseline, before the first DQRF session. (B) T3: at the follow-up visit (30 days after the third session)

and urinary symptoms, and vaginal laxity.[30,31] In addition to these symptoms, all these chronic vulvar conditions frequently also affect sexual function,[32] justifying the ongoing dramatic surge in the number of surgical and nonsurgical vulvar rejuvenation procedures that are being performed worldwide, and the growing academic interest in these procedures and technologies.[14,16,19]

Light- and energy-based devices, based on laser and radiofrequency technologies, offer the opportunity for noninvasive rejuvenation procedures and simpler logistics.[24] Radiofrequency technologies might indeed prove to have the brightest future in aesthetic gynecology. Radiofrequency waves generate electrical fields that streamline the spontaneously random translational motions and rotations of polar biomolecules in vulvar and vaginal tissues.[24,33] Steric and electrical interactions and attritions mean that local tissue temperature increases as a function of the intensity of currents and exposure time. This has been shown to lead to a biological effect in intimate tissues due to fibroblasts causing neocollagenesis and neoelastogenesis.[34,35] At tissue temperatures of 40–45°C, radiofrequency can induce collagen production by fibroblasts through the activation of heat shock proteins and the initiation of the inflammatory cascade, and radiofrequency is effective in skin tightening.[36,37]

Radiofrequency energy is dispersed in 3D volumes of tissue at controlled depths. The creation of new dermal volume in response to radiofrequency treatment has been extensively reported, and has been shown to improve skin laxity and the mechanical characteristics of the skin.[24,38] Both neocollagenesis and elastogenesis are induced with improved skin elasticity, which correlates with elastometry.[37,38] Collagen fibers are composed of a triple helix of protein chains linked through interchain bonds to form a highly organized structure. When collagen fibers are heated to specific temperatures, they contract due to breakage of intramolecular hydrogen bonds. This contraction causes the triple-helix structure to fold, creating thicker and shorter collagen fibers, a process that is thought to be responsible for the immediate tissue tightening seen after skin-resurfacing procedures. The partially denatured collagen serves as a signal for neocollagenesis.[24,39] The creation of new elastin, a process almost unique to radiofrequency, may play a role in the effectiveness of this approach in treating skin laxity.[24,38,39] Specifically, DQRF technology has been proven to be effective based on objective measurements in an ex vivo and in vivo human experimental model: after a course of DQRF application, native collagen fibers underwent an immediate heat-induced rearrangement, and were partially denatured and progressively metabolized by macrophages. Subsequently, an overall thickening and spatial rearrangement was observed both in the collagen and in the elastic fibers, the latter displaying a skin reticular pattern characteristic of juveniles.[40]

In the EVA DQRF device, the high-tech trick of cycling the 4 dynamic electrodes between receiving and transmitting configurations eliminates all electric current flows through tissues and allows low levels of energy to be administered to precisely defined vulvar areas and layers. The gentle heating of the vulvar region is subjectively well tolerated, and virtually all risks of overheating and burning are eliminated. Women can control and pause treatment at will.

Due to the lack of a control group, this pilot study does not provide any reliable quantitative estimation of the aesthetic improvements to the vulvar achieved with the DQRF device and the accelerated EVA Vulvar Rejuvenation program; however, the women who received the treatment objectively experienced and subjectively reported significant improvements in their vulvar aesthetics. The GAIS scores assigned by both the evaluator and cohort women were significantly improved even after the first DQRF treatment session. The aesthetic benefit seemed to increase during the follow-up period, or at least showed no short-term reversal, up to scores of > 8 out of a maximum of 10, in the higher range of the "Much improved" standard GAIS assessment. Interestingly, the dispersion of aesthetic judgments seemed to converge with the progression of treatments, as shown by the steady reduction in standard deviations. This may mean that the worst degrees of basal vulvar atrophy showed the strongest aesthetic improvements compared with milder basal situations. It may also mean that all such improvements progress up to a more or less maximum plateau that is subjectively and objectively judged as very satisfactory compared with the ideally normal situation without atrophy.

This interpretation is in good agreement with evidence from immunohistochemistry and electron microscopy about the biological effects of thermal stimulation in vulvovaginal tissues associated with the emission of electromagnetic energy. Reactivation of fibroblasts leads to the deposition of new collagen and elastin fibers in the subepithelial layers of the vulva;[24–26] increased tissue levels of the profibrotic cytokine transforming growth factor β1 and persistent activation of heat shock proteins are markers of connective matrix remodeling.[24] Tissue temperatures in the range 40-45°C are ideal for the tightening and rejuvenation of vulvar areas because of the long thermal relaxation time of collagen in subepithelial vulvar structures (about 225 msec).[24,35] In line with morphological outcomes, women with moderate atrophy seemed to experience especially rapid relief from bothersome symptoms such as dryness and dyspareunia. The high scores given by the DQRF-treated women at the follow-up visit bear testimony of their satisfaction with the functional outcomes (quality of life, sexual and relationship well-being) even well after the end of the vulvar rejuvenation program.

Even though this was conceived as a pilot study, the relatively small size of the prospective cohort of treated women is admittedly a limitation. More serious limitations of the study are the short 1-month follow-up period after the end of the vulvar rejuvenation sessions and the lack of a control group. Another possible limitation is the evaluation method, a version of the GAIS modified from a 5-point to a 10-point scale that rates the global aesthetic improvement compared to pretreatment, although without formal scoring of the baseline aesthetic situation, and the exposure shown in some of our photographs. Also, the use of a single independent evaluator may be considered a limitation.

Increasing the size of the cohort, prolonging the follow-up period, adding a control group in order to evaluate the placebo effect, increasing the number of independent evaluators, and utilizing validated questionnaires to assess subjective efficacy will be crucial in future studies of DQRF devices in aesthetic gynecology. We are currently intending to conduct a long-term follow-up to the short-term data presented in this pilot study. More studies are warranted to investigate the cytological, histological, and overall biological effects of DQRF technology, and this is in line with the current position of the latest reviews regarding nonsurgical vulvovaginal rejuvenation.[37]

CONCLUSIONS

This pilot study strongly suggests that the 3-session "Accelerated EVA Vulvar Rejuvenation" protocol is highly efficacious in women with mild to moderate vulvar tissue atrophy. Qualitatively, the photographic documentation after 3 sessions shows a persistent tightening and volumizing effect in all treated women, often after the first DQRF treatment session; quantitatively, the mean modified GAIS scores assigned by both the specialist evaluator and the treated women improved significantly, up to > 8 out of 10. Aesthetic and functional improvements were achieved with an easy-to-master and pleasant outpatient procedure that is virtually devoid of side effects. Interestingly, subjective relief from some symptoms, such as dryness and dyspareunia, was especially rapid in women with moderate atrophy.

Supplementary Material

This article contains supplementary material located online at www.aestheticsurgeryjournal.com.

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Disclosures

Dr Bosoni is a medical consultant and member of the Novavision Scientific Board. Novavision Group SpA is the patent-holder of the DQRF technology and the manufacturer of the EVA device used in the investigation. Dr Fasola declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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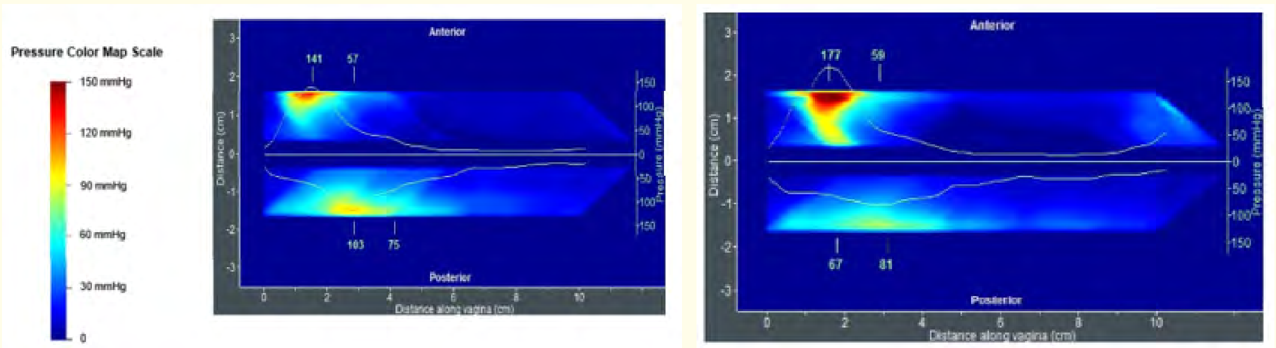
A Standard Vaginal Laxity Questionnaire (VLQ) translated in French was also used. It obtains perceptions on level of vaginal laxity/tightness assessed with 7-level ordered responses (very loose, moderately loose, slightly loose, neither loose nor tight, slightly tight, moderately tight, or very tight).

The patient was successfully treated with 4 consecutive DQRF treatments with 15 days interval.

The non-parametric Wilcoxon Signed Rank Test for repeated measurements on single populations was applied to both repeated measures in Improvement in Elasticity and Pelvic Floor Muscles Strength after treatment, and average calculation of vaginal elasticity. Two-sided levels were used for all statistical tests with $p < 0.01$ as cut-off for significance.

Results

The vaginal tissues elasticity improved from a VLQ score of 1 (very lose) to 6 (moderately tight), and improved in pressure and calculated pressure gradients with color map going wider in yellow and red colours for pressure in test 1 (Figure 1), gradient and pressure in test 2 (Figure 2) and pressure in test 3 (Figure 3). There are statistically significant improvements in pressure at test 1 by 100%, from 20% to 500% in gradient in test 2, and 60% in test 3 (Table 1). The PFM strength for voluntary muscle contractions (Figure 4) and PFM strength for involuntary contractions (contraction with a cough, figure 5) showed higher peak pressures after treatment. PFM increased respectively by 242% and 172% (Table 1).



Before Treatment *After 4 sessions of treatment*

***Figure 1:** Pressure patterns for vaginal tactile imaging probe elevation (test 1) and calculated pressure along the anterior and posterior compartments before and after radiofrequency treatment.*

Citation: Hichem Bensmail. "Evolutions in Diagnosis and Treatment of Vaginal Laxity". *EC Gynaecology* 7.8 (2018): 321-327.

Standardized instruments for assessing biomechanical conditions of the pelvic floor and all urogynecologic aspects of female sexual dysfunction are lacking. In the last decade, a new modality for tissue characterization termed Elasticity Imaging (EI) or Elastography has emerged. EI allows visualization and assessment of mechanical properties of soft tissue. Mechanical properties of tissues (elastic modulus, viscosity), are highly sensitive to tissue structural changes in several physiological and pathological processes. Evaluating the biomechanical properties of the vaginal wall and its immediate surrounding connective tissue has been particularly difficult. The specific goal of VTI is to provide a reproducible and quantifiable means to visualize and measure vaginal tissue elasticity. VTI most closely mimics manual palpation because the TI probe, with a pressure sensor array, acts like human fingers during a clinical examination. The probe slightly compresses soft tissue and detects changes in the pressure pattern ("stress imaging," "computerized palpation," or "mechanical imaging").

Case Report

Methods

In January 2017, a 42-year-old Caucasian Patient was treated for vaginal laxity. She had given birth to three children, the most recent being six years before vaginal rejuvenation was performed. She had no previous non-surgical vaginal rejuvenation treatments and no past medical history that would be significant to this procedure such as recent surgical labiaplasty, etc., no known drug allergies, no sexual health history, until the procedure, and cervical smears has never shown any abnormalities. DQRF procedures were performed at 2 week intervals for 4 consecutive treatments.

The Vaginal Tactile Imager (VTI) developed by Egorov., *et al.* [3] was used to assess the vaginal walls, pelvic floor support structures and pelvic floor muscle (PFM) contractions before and two weeks after the final DQRF treatment.

VTI is performed on a patient the dorsal lithotomy position with empty bladder and rectum. The full VTI examination takes 2 to 3 minutes to complete. The VTI probe is calibrated before every clinical application. The VTI procedure consists of 3 independent parts: (i) probe insertion, (ii) probe rotation, and (iii) muscle contractions, with 8 different tests listed below.

VTI allows the acquisition of pressures applied to the vaginal walls and the acquisition of probe location to visualize vaginal and pelvic floor support structures and to record pelvic floor muscle contractions. The VTI software provides visualization, analysis, information, and reporting tools. The acquired data and analysis information can be used for quantitative assessment of the vaginal and pelvic floor conditions. The VTI device is associated with a movable computer display cart. The VTI probe is equipped with 96 pressure sensors along both sides of the probe, an orientation sensor, and temperature sensors with micro-heaters. During the patient examination procedure, data are sampled from the probe sensors and displayed on the VTI computer display in real time. The probe surfaces that contact the vaginal walls are preheated to human body temperature. A lubricating jelly is used for patient comfort and to provide reproducible boundary-contact conditions with deformed vaginal tissue.

The VTI probe allows for an estimation of: a) vaginal tissue elasticity as a pressure gradient under vaginal wall deformation, (test 1 and 2), b) pelvic floor support conditions as pressure gradient under a deformation of the posterior compartment (test 3), and c) PFM strength as a pressure feedback under voluntary and involuntary (cough) contractions (tests 4 to 8). Orthogonal cross-sections of the 3-D tactile image allow visualization of anatomy and elasticity distributions. Tactile imaging reveals not only the elasticity conditions of vaginal wall itself, but the elasticity distribution of underlying tissue structures. These images may be considered as documentation of the current elasticity state of the vaginal walls and surrounding support tissues. 8 VTI parameters were proposed to characterize vaginal conditions (2): Test 1 allows the calculation of: 1. Maximum resistance force to insertion (Flmax in newtons, N); 2. Insertion work (Wl in millijoules, mJ); 3. Maximum stress-to-strain ratio, i.e. gradient, elasticity (Glmax kilopascals per millimeter, kPa/mm). Test 2 allows the calculation of: 1.Maximum intravaginal pressure at rest (kilopascals, kPa); 2. Anterior vs posterior force at rest (newtons, N); 3. Left vs right force at rest (newtons, N). Test 3 allows the calculation of: 1. Maximum intravaginal pressure at pelvic muscle contraction (kilopascals, kPa); 2. Muscle contraction force (newtons, N).

Citation: Hichem Bensmail. "Evolutions in Diagnosis and Treatment of Vaginal Laxity". *EC Gynaecology* 7.8 (2018): 321-327.

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Case Report

Evolutions in Diagnosis and Treatment of Vaginal Laxity

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Abstract

Introduction: The use of Dynamic Quadripolar Radiofrequency (DQRF) is a new therapy for the treatment of vulvovaginal conditions such as laxity and sexual dysfunctions, while Vaginal tactile imaging allows biomechanical assessment of vaginal tissues and pelvic floor muscles.

Purpose: The purpose of this study is to explore changes in vaginal tissue elasticity, pelvic floor support and muscle strength after applied vaginal radiofrequency treatments.

Case Report: In January 2017, a 42-year-old Caucasian Patient was treated for vaginal laxity. She had given birth to three children, the most recent being six years before vaginal rejuvenation was performed. She had experienced no previous non-surgical vaginal rejuvenation treatments and no past medical history that would be significant to this procedure such as recent surgical labiaplasty, etc. no known drug allergies, no sexual health history until the procedure, and cervical smears has never shown any abnormalities. DQRF procedures were performed at 2 week intervals for 4 consecutive treatments. The Vaginal Tactile Imager (VTI) was used to assess the vaginal walls, pelvic floor support structures and pelvic floor muscle (PFM) contractions before and two weeks after the final DQRF treatment. The VTI probe allows for an estimation of: a) vaginal tissue elasticity as a pressure gradient under vaginal wall deformation, b) pelvic floor support conditions as a pressure gradient under deformation of the posterior compartment, and c) PFM strength as a pressure feedback under voluntary and involuntary (cough) contractions.

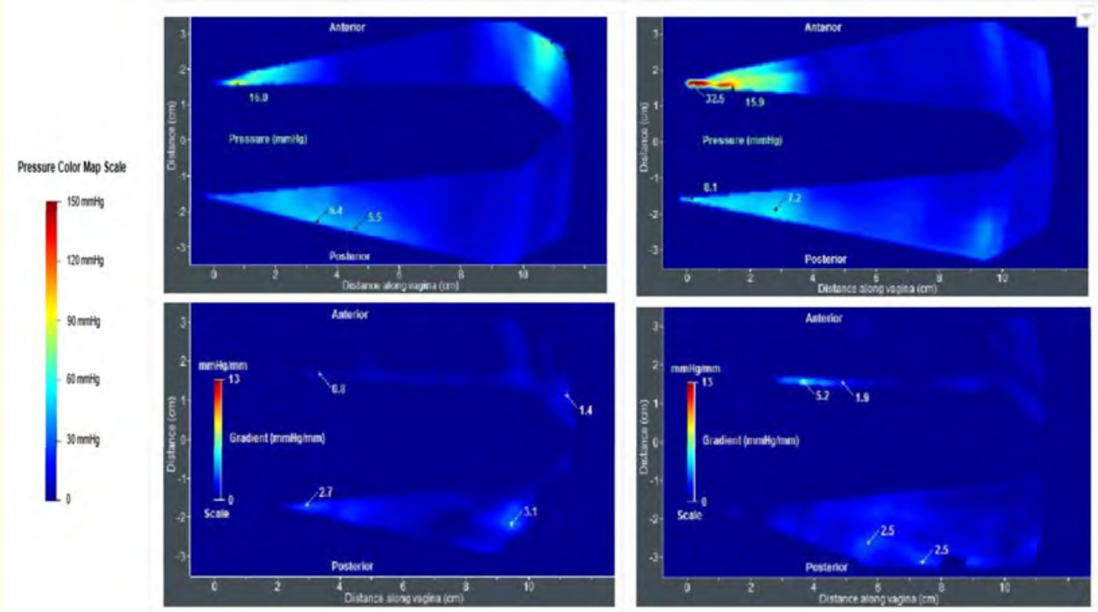
Conclusion: Dynamic Quadripolar Radiofrequency treatment is a promising novel technology with clinical results improving tissue elasticity, pelvic floor support and PFM strength upon assessment with tactile imaging. VTI allows monitoring of biomechanical transformation of tissues before and after the radiofrequency treatment and may predict the effectiveness of therapy for individual patients.

Keywords: *Vaginal Tactile Imaging; Radiofrequency; Vaginal Laxity; Vaginal Rejuvenation*

Introduction

The use of Dynamic Quadripolar Radiofrequency (DQRF) is a new therapy [1,2]. for the treatment of vulvovaginal conditions, while Vaginal tactile imaging (VTI) allows biomechanical assessment of vaginal tissues and pelvic floor muscles [3-5].

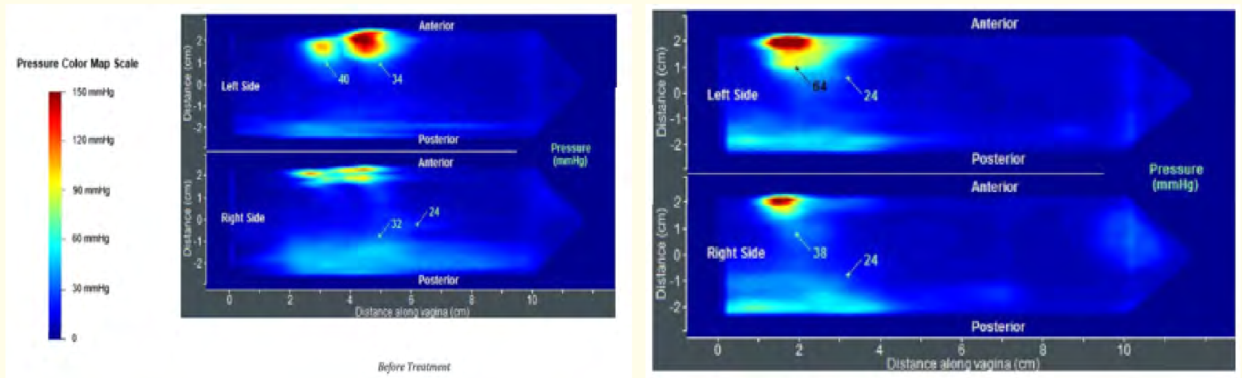
The purpose of this study is to explore changes in vaginal tissue elasticity, pelvic floor support and muscle strength after vaginal DQRF treatments upon assessment with tactile imaging.



Before Treatment

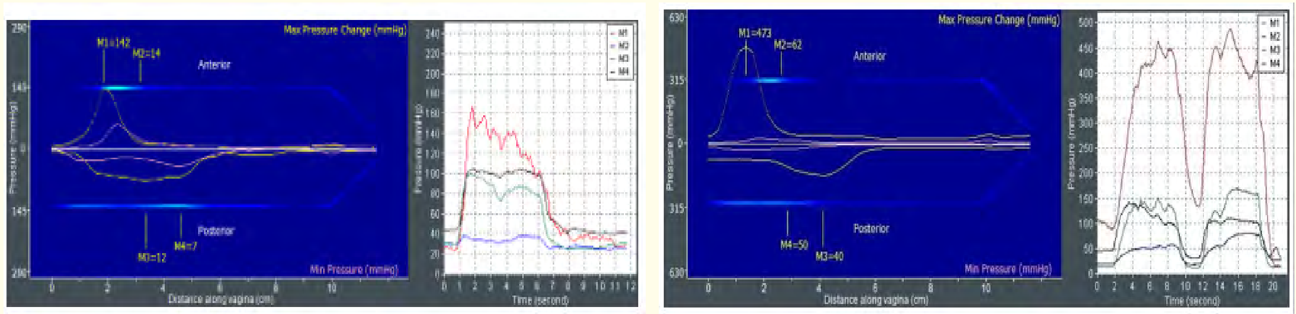
After 4 sessions of treatment

Figure 2: *Pressure patterns for vaginal tactile imaging probe elevation (test 2) and calculated pressure and pressure gradients along the anterior and posterior compartments before and after radiofrequency treatment*



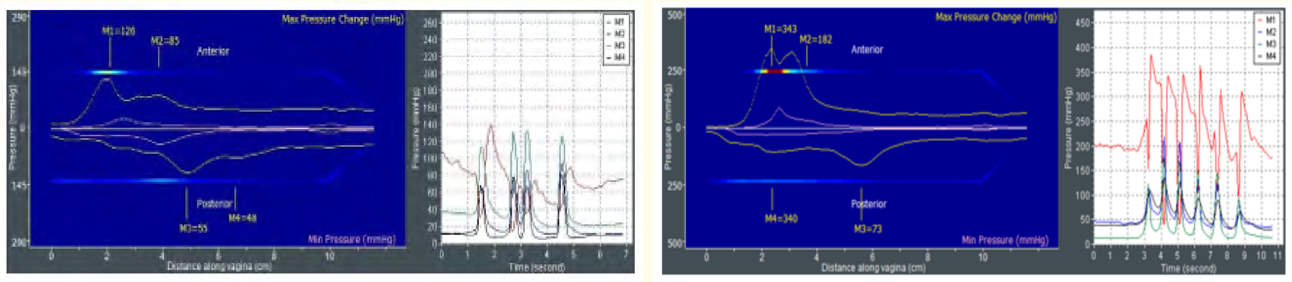
Before Treatment *After 4 sessions of treatment*

Figure 3: *Pressure patterns for vaginal tactile imaging probe rotation (test 3) and calculated pressure along the vaginal walls before and after radiofrequency treatment.*



Before Treatment *After 4 sessions of treatment*

Figure 4: *Pelvic Floor muscles strength for voluntary contraction (test 5).*



Before Treatment *After 4 sessions of treatment*

Figure 5: *Pelvic Floor muscles strength for involuntary contraction (test 5).*

	Before treatment	After 4 sessions of treatment
Pressure at VTI Test 1	141	177
Pressure at VTI Test 2	16	32.5
Gradient at VTI Test 2	0.8	5.2
Pressure at VTI Test 3	40	64
PFM strength voluntary contraction	142	473
PFM strength involuntary contraction	126	343

Table 1: *Improvement in Elasticity and Pelvic Floor Muscles Strength after treatment Numbers in red shows statistical significance (p < 0.01).*

The measurement of elasticity (Gradient in kPa/mm in test 1) of the underlying tissues surrounding the vagina, significantly improved by 88%. Maximum intravaginal pressure at pelvic muscle contraction (kPa) increased by 10.5% and muscle contraction force (N) increased by 8.3% (Table 2).

	F_{max} (N)		W (mJ)		Gradient (kPa/mm)	
	Before	After	Before	After	Before	After
Test 1	0.665	0.928	32.9	39.9	098	1.84

	P_{max} at rest (N)		F (N) at rest vert		F (N) at rest horiz	
	Before	After	Before	After	Before	After
Test 3	23.76	26.24	1.56	1.69	0.69	0.68

Table 2: *Average calculation of Vaginal Tissue Elasticity Numbers in red show statistical significance (p < 0.01).*

Comfort level of the VTI examination procedure was classified as more comfortable as manual palpation; No report for the VTI exam as painful.

Discussion

Increasingly, thermal non-invasive treatments are used for vaginal modification. However, objective assessment of vaginal conditions before and after the applied treatment does not exist yet. Objective anatomic measures, biomechanical, and functional characterization are essential to understand the difference between normal and abnormal conditions. The VTI approach resembles soft tissue palpation, which has been the most prevalent medical diagnostic technique for accessible human organs and the musculoskeletal system. but clinical examination cannot be translated into objective and comprehensive information for a medical report for other clinicians. And that's where tactile imaging acquisition with stored data has a great interest in translating the sense of touch into a digital image [4].

Tactile imaging displays tissue anatomy and elasticity distribution by keeping the stress-strain relation for deformed tissue. The 3-dimensional tactile image can be transformed into an elasticity image with the use of a linear transformation for a region of interest. Functional tactile imaging is a translation of muscle activity into a dynamic pressure pattern. VTI allowed in our report better comprehension of vaginal walls and pelvic floor muscle changes, when Vagina Laxity Questionnaire (or other questionnaires) is not enough accurate for detailed analysis. It is always useful to have reproductible, stored DATA for comparison and further studies [5].

Vaginal laxity is common symptom in urogynecology everyday practice. It is often associated with younger age, vaginal parity, symptoms of prolapse. Vaginal laxity occurs in all women in the weeks after vaginal childbirth and after menopause. The stretching of the dense connective tissue of the vaginal walls and introitus during delivery varies in degrees of laxity and can worsen with successive deliveries. Although it may be considered physiological vulvovaginal laxity may deeply affect self-esteem and quality of life, due to discomfort in everyday life, and to negative impact on sexual relationships [6]. Then, loss of sensation is common in women with vaginal laxity. and vaginal laxity is described my practitioners as the most important change of body integrity experienced by women after vaginal childbirth.

Radiofrequency (RF) used for medical treatments [7] is an advanced technology based on converting the energy of an electromagnetic wave into heat: radiofrequency waves interact with the tissues, generating controlled thermal change. Unlike lasers, which produce heat by selectively targeting a specific chromophore, non-ablative radiofrequency generates heat as a result of the tissue's resistance to movement of the electrons subject to the RF field.

As also suggested for other thermal therapy technologies, DQRF vaginal rejuvenation in introital and vaginal laxity implies re- activation of fibroblast and connective tissue function and development of new networks of collagen and elastin fibers in the subepithelial layers of introitus and vagina [2].

One of the current gold standard treatments for after childbirth abnormal conditions are daily sessions of pelvic floor training (PFT). Significant improvement are mostly noticed after 2 months. However, the cost-effectiveness of is not well known. Population approaches (recruiting antenatal women regardless of continence status) may have a smaller effect on urinary incontinence, although the reasons for this are unclear. It is uncertain whether a population-based approach for delivering postnatal PFT is effective in reducing urinary incontinence. The new DQRF technique can bring valuable clinical outcomes for patients because of less discomfort for women and less disruption of their daily life and routine. This may require further investigations to compare both methods.

DQRF seems to hold advantage regarding its non-ablative characteristics compared to CO2 lasers, and deeper effects in the dermis compared to Erbium Lasers. Comparative studies could be interesting to conduct to assess these differences [8].

Conclusion

Dynamic Quadripolar Radiofrequency treatment seems promising to improve tissue elasticity, pelvic floor support and PFM strength upon assessment with tactile imaging. VTI allows monitoring of biomechanical transformation of tissues before and after the radiofrequency treatment and may predict the effectiveness the therapy for individual patients.

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Review

Vaginal Health in Menopausal Women

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Abstract: The aim of this review is to provide an overview of genitourinary health in peri- and postmenopause, particularly of vulvovaginal atrophy (VVA), which is part of genitourinary syndrome (GSM). This condition has a high prevalence among post-menopausal women and negatively affects a woman's quality of life. Epidemiology, signs, symptoms, diagnostic criteria of VVA and target treatments for restoring vaginal health are discussed in light of the most recent literature. Issues related to this condition in menopausal women are under-diagnosed, lack objective diagnostic criteria, and consequently under-treated. Over the years, many treatments have been developed but their long-term effectiveness and safety have yet to be clearly defined. Patients are often dissatisfied and stop treatment, suggesting the need for a more personalized and tailored approach to achieve better compliance and thereby effectiveness. The aim of this paper is to provide an overview of the most recent literature on VVA in order to help the gynecologist in the management of this condition.

Keywords: vaginal health; menopausal women; vulvovaginal atrophy; genitourinary syndrome

1. Introduction

The condition of hypoestrogenism related to menopause has a strong negative impact on vaginal and urinary health, often leading to a condition called genitourinary syndrome (GSM), a term introduced by the International Society for the Study of Women's Sexual Health and the North American Menopause Society in 2014 [1]. GSM is associated with genital signs and symptoms such as dryness, burning, irritation, and sexual symptoms such as discomfort or pain, and impaired sexual function. This condition, previously known as vulvovaginal atrophy (VVA), may also be accompanied by urinary signs and symptoms such as urinary incontinence, dysuria, stranguria, and frequent urinary tract infections [2]. Unlike other menopausal symptoms, VVA is a chronic condition that tends to worsen throughout the years after menopause. It therefore requires prompt and long-term therapy to achieve good results and to avoid the recurrence of symptoms when treatment is stopped.

The aim of this paper is to provide an overview of the most recent literature on VVA that would help to sensitize the clinician toward the diagnosis and treatment of this condition [3,4]. This condition has important consequences in the daily life of post-menopausal women and in their relationships [5,6]. Considering that women spend a third of their life in menopause, it is essential to recognize and treat this syndrome in order to restore the vaginal and vulvar epithelium and ultimately improve quality of life.

The rationale of treatment is the restoration of normal vaginal and vulvar physiology that leads to the alleviation of symptoms. Many options have been developed over the years such as local, systemic hormonal, and non-hormonal treatments or energy-based treatments that could potentially fulfill most women's needs and preferences, thus improving the quality of post-menopausal women's lives (Figures A1 and A2).

2. Epidemiology of Vulvovaginal Atrophy

VVA affects most peri- and postmenopausal women with a prevalence ranging from 36% to almost 90%, according to the most recent surveys. It has recently been reported that this condition is also already present in pre-menopausal years with a prevalence of 19% in women aged 40–45 (Table A1) [7–13].

In spite of its high prevalence, VVA is still under-diagnosed and under-treated. Most women do not discuss their symptoms with their gynecologist for various reasons; often because they believe it is just a natural part of aging or because they are uncomfortable talking about it. Often they are unaware that there is treatment for the syndrome, or because of time constrains and/or perceived lack of interest of their healthcare provider. Whatever the reason, the lack of diagnosis still remains one of the major issues in the care of this condition [10,14].

Women tend to self-medicate using over-the-counter drugs that are sometimes ineffective or not effective enough and are therefore stopped, leaving the woman to live with the condition untreated [14].

3. Clinical Signs and Symptoms of Vulvovaginal Atrophy

The drop in circulating hormone levels, especially estrogens, represents the main trigger determining vulvovaginal atrophy. The vaginal epithelia of post-menopausal women display flattened epithelial surfaces with features of keratinization and the absence of papillae. Multiple layers of parabasal cells with higher nucleus to cytoplasm ratio and few intermediate and superficial cells are present in which glycogen stores are reduced. This leads to a decrease in the number of Lactobacilli resulting in an increase in vaginal pH [15]. The low percentage of Lactobacilli and the increase in the relative proportion of anaerobic bacteria found in post-menopausal women may predispose symptomatic VVA, although not all studies consistently report this association [16–18].

Hypo estrogenic vaginal states typically also include changes in the connective tissue composition with decreased type I/III collagen ratio, which leads to reduced tissue strength [19]. Thinning of the vaginal epithelium increases susceptibility to trauma, resulting in bleeding, petechiae, and ulceration with any type of pressure including sexual activity or a simple gynecological maneuver. Thinning also exposes the underlying connective tissue, which is more vulnerable to inflammation or infection.

Due to these histological changes, clinical signs at the vaginal level include anything from dryness and insufficient hydration, redness, loss of elasticity, petechiae, ulceration, inflammation, atypical secretions, to fibrosis and vaginal obliteration. The most frequent signs at a vulvar level include reduction in tissue thickness, labia agglutination, loss of pubic hair, and scratching lesions due to itching. Consequent symptoms include vaginal dryness and superficial dyspareunia with a prevalence of 78% and 76%, respectively [20], which can be associated with itching, a burning sensation, and susceptibility to mechanical insults, leucorrhoea, or atypical secretions. At a vulvar level, the most frequent symptoms are burning, pain, increased susceptibility to physical and chemical irritants, and mechanical insults [21].

All of these changes have a great impact on women's sexuality and relationships [22]. The REVIVE study suggested that VVA symptoms have a significant impact on the patients' ability to achieve pleasurable relations (74%) and spontaneity (70%). Seventy-five percent of sexually active post-menopausal women with VVA were reported to have a significantly reduced sex drive as a direct consequence of the symptoms related to this condition [20]. A 2014 study, showed that most women were worried that vaginal discomfort could have long-term effects on their relationship [23].

4. Diagnosis of Vulvovaginal Atrophy

The diagnosis of vulvovaginal atrophy is based on clinical assessment: anamnesis, evaluation of the patient's symptoms, and gynecological examination with the evaluation of clinical signs. In addition, standardized scores and laboratory tests can be used such as the evaluation of vaginal pH and the vaginal maturation index (VMI). The anamnesis should also include questions about sexual function, the presence of decreased libido, and of dyspareunia. It is important to differentiate superficial dyspareunia, typical of vulvovaginal atrophy, from deep dyspareunia, typical of endometriosis. Moreover, the sexual life of the couple should be investigated from the perspective of the new paradigm of couplepause [24]. Avoiding sexual intercourse can exacerbate VVA as sexual activity can preserve the vaginal epithelium by increasing blood flow and elasticity.

However, there is not always a correlation between clinical signs, laboratory data, and symptoms and this represents an important limitation for diagnosis. Another issue is the subjectivity of the diagnosis. One of the most commonly used scores is the vaginal health index (VHI) [25] for the evaluation of vaginal elasticity, secretions, pH, the presence of petechiae on the epithelial mucosa, and hydration. The score can vary between five and 25, with a cut-off < 15 index of atrophic vagina. The vulvar health index can be used to evaluate the vulva including vulvar inflammation, musculature contraction, pain at speculum insertion, and epithelial integrity. The score can vary from zero to 24, with a cut-off > 8 index of atrophic vulva.

The VMI indicates the degree of tissue maturation, measuring the percentage of superficial, intermediate, and parabasal cells. The maturation value (MV) is calculated with the following formula: MV = % surface cells + (0.5 × % intermediate cells) [26].

A pilot study proposed the use of trans-abdominal ultrasound to measure vaginal wall thickness and total vaginal mucosal thickness at the bladder trigone [27]. Although the study is still preliminary, this could represent a valuable tool for obtaining an objective evaluation of vaginal health and to quantify the response to therapeutic interventions.

5. Treatment Options for Vulvovaginal Atrophy

5.1. Lubricants and Moisturizers

Various non-hormonal, non-prescription treatments exist for vaginal atrophy (VA), namely increased coital activity, cessation of smoking, pelvic-floor physiotherapy (PT), and lubricants or moisturizers [22]. Many women with VVA use over-the-counter (OTC) products such as vaginal lubricants and moisturizers. International guidelines consider these to be the first line of therapy in the treatment of VVA being free from significant contraindications and side effects [28]. They can be used alone or in combination with hormonal therapies as needed. This treatment option is also recommended for women for whom the use of vaginal estrogen preparations is unacceptable. It is important that osmolality, pH, and the composition of these products, either lubricants or moisturizers, are similar to vaginal secretion [29].

The main difference between vaginal lubricants and moisturizers is the timing of application. Vaginal lubricants are particularly indicated for women whose main concern is vaginal dryness during intercourse. Lubricants provide short-term relief from dryness and reduce dyspareunia. They can be water-based, which are water-soluble and have a tendency to dry out; oil based, which are more durable, but with a lower lubricating effect; or silicone-based. Some lubricants contain glycerin, propylene glycol, sweeteners and parabens, which may have an impact on the pH and osmolality of water-based products [29].

Vaginal moisturizers are insoluble hydrophilic cross-linked polymers with a characteristic bio-adhesiveness that is able to adhere to the epithelium of the vaginal wall by retaining water. They can also contain a large amount of excipients that influence the pH and the osmolality of the formulation. They can be used more regularly, rather than just in association with sexual activity, and have a longer lasting effect, improving the moisture of the vaginal mucosa and reducing the pH. The

frequency of use is directly proportional to the severity of VVA [29]. The posology of the acute phase consists in local applications in the evening, before going to bed, for seven to ten consecutive days, so that they can act throughout the night, followed by two local applications per week to maintain the beneficial effects. The most commonly used moisturizers are based on hyaluronic acid (HA), a glycosaminoglycan produced by fibroblasts, which is the main component of the extracellular matrix. The possible action mechanism of hyaluronic acid is cell migration because it has a very high capacity to bind water, which may facilitate cellular movement [30]. Thus, in the case of tissue damage, HA may stimulate the migration and proliferation of fibroblasts and therefore the deposition of collagen fibers, in addition to stimulating neo-angiogenesis and re-epithelialization. If used on a regular basis, daily or every 2–3 days, HA based products improve symptoms of vaginal dryness, with an effect that has been compared with the effect of topical estrogen therapy [31]. Some adverse effects have been reported with the use of HA [32], but most have occurred after injections. They include local reactions namely bruising, erythema, swelling, and, rarely, more severe events such as tissue necrosis, infection, or pulmonary complications. To the best of our knowledge, no severe adverse effects have been reported with the use of HA-based vaginal moisturizers.

Other possible components of vaginal moisturizers are ozonides, intermediate products of ozone, which act as a biological reservoir preserving the therapeutic power of the molecule. In contact with biological tissue, ozonides activate quickly, stimulating the local microcirculation to induce neo-angiogenesis, promoting tissue repair, and inhibiting pro-inflammatory prostaglandins [33].

Oral vitamin D and vaginal vitamin E have been proposed for the treatment of VVA, but efficacy data are limited and sometimes discordant. Vitamin D stimulates the proliferation of the vaginal epithelium by activating the vitamin D receptor (VDR). Vaginal vitamin E is involved in the metabolism of all cells and prevents tissue damage caused by oxidants. This facilitates blood circulation, which consequently increases the metabolism of vaginal connective tissues and enhances the moisture and flexibility of vaginal walls [34–36].

Oral and vaginal probiotics for improving vaginal microbiota may be beneficial for the treatment of VVA symptoms, however, placebo-controlled trials that prove their effectiveness are lacking [37].

Oral phytoestrogens are not effective [38] while topical phytoestrogens seems to have a beneficial effect on VVA, improving genital symptoms, maturation index, vaginal pH, morphology, and expression of estrogen receptors in the vaginal epithelium [39], however, these are preliminary investigations that need to be verified in larger, prospective studies.

5.2. Hormonal Treatments

Hormone treatments of menopause (HTM), the association of estrogen-progestins, estrogen-bazedoxifene, tibolone, or exclusively estrogens in hysterectomized women, have a beneficial effect on many symptoms related to menopause including VVA. According to international guidelines, they are not recommended in women who suffer only from vaginal and vulvar symptoms, however, when they are used for primary indications, the evidence shows that HTM are able to restore the physiological vaginal pH, the maturation index, and the thickness of the vaginal epithelium, its vascularization and lubrication [40].

Tibolone is converted into metabolites that have tissue-specific agonistic estrogenic (3-alpha and 3-beta-hydroxytibolone) and progestogenic/androgenic (delta-4 tibolone) properties [41]. In post-menopausal women, tibolone normalizes the maturation index, alleviates atrophic vaginitis symptoms [42], and increases vaginal elasticity. Due to its androgenic activity, it has also been reported to have positive effects on sexual function [43].

The association of bazedoxifene with conjugated estrogens (BZA/CE), called tissue selective estrogen complex (TSEC), has also been reported to be effective in the treatment of moderate to severe VVA and its symptoms. At week 12, the BZA/CE combination increased superficial cells, decreased parabasal cells, decreased vaginal pH, and improved the most bothersome symptoms such as vaginal dryness or dyspareunia [39].

International guidelines recommend local hormonal therapy as a second step in the event of the ineffectiveness of vaginal lubricants and moisturizers [40]. Options available include estradiol, estriol, conjugated estrogens or promestriene gels, creams, ovules, tablets, or rings. These are specifically indicated for the treatment of VVA including dyspareunia. All estrogen-based vaginal products are more effective than a placebo for VVA. Vaginal estrogens are superior to lubricants and moisturizers in studies lasting at least six to twelve months [44,45].

The recommended dose is commonly a local daily application for two weeks as an attack therapy, and then application twice a week as maintenance therapy [30].

Estrogen absorption is limited to low doses, but it is not eliminated, especially in the early phases of treatment [45]. If the prescribed doses are taken, it is not necessary to associate a progestin for endometrial protection. Clinical evidence from large observational studies such as the Women's Health Initiative Observational Study (WHI-OS) and the Nurse's Health Study cohort did not find an increased risk of endometrial cancer in women who used vaginal estrogens [46]. However, observational studies have limitations and prospective, randomized controlled studies of long duration are lacking. The placement site inside the vagina is important as this has been suggested to affect the amount of estrogens reaching the endometrium [47]. The risks of stroke, breast cancer, pulmonary embolism, and deep vein thrombosis were not significantly different between vaginal estrogen users and non-users [46]. No significant differences in the safety profile of estradiol and estriol have been reported, while data on promestriene are scarce [48].

5.3. Selective Estrogen Receptor Modulator (SERM): Ospemifene

Ospemifene is the only selective estrogen receptor modulator (SERM) to be indicated for the treatment of VVA. It has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate to severe dyspareunia and by the European Medical Agency (EMA) for the treatment of moderate to severe VVA in women, with or without a uterus, who are not candidates for local estrogen therapy [49]. It exerts a positive effect on the vaginal epithelium while having, at the same time, a neutral or minimal effect on the other estrogen-dependent organs. In particular, it seems to have a neutral effect on the endometrium and the cardiovascular system, and an anti-estrogenic effect in pre-clinical studies on the breast. It is used at a dose of 60 mg daily.

The effects on the signs of VVA are visible after four weeks of treatment such as the increase of superficial cells, the reduction of basal cells, and the reduction of vaginal pH [50]. A significant effect on symptoms such as dryness and dyspareunia has been demonstrated to occur after 12 weeks of treatment [51]. Recently, the efficacy of ospemifene at a histological level in both vaginal and vulvar tissue has been demonstrated by observing increases in vaginal and vulvar epithelial thickness, glycogen content, proliferation index, and an increase in vaginal estrogen receptor alfa (ERα) [50,52]. Ospemifene has also been shown to improve atrophy of the vulvar vestibule and to normalize vestibular sensitivity by increasing the perception threshold at a vulvar level [53]. In a short-term study, it has also been shown to increase ratio type I and type III collagen at the vaginal level, suggesting possible beneficial long-term effects on vaginal connective tissue [52].

A current or previous thromboembolic event, vaginal bleeding of unknown origin, presence of signs or symptoms of endometrial hyperplasia, malignant tumor dependent on sex hormones, and ongoing breast carcinoma represent contra-indications. The EMA has also approved its administration in women with a previous breast cancer after the completion of treatment including adjuvant therapy and after performance of a control mammogram. The safety of this SERM on vaginal mucosa was first demonstrated in phase II and III clinical studies and has now been on the market for six years in the U.S. and for four years in some European countries including Italy. Ospemifene has an excellent safety profile that has been demonstrated by both randomized, double-blind, multicenter phase II and III placebo-controlled studies on a large number of patients, by the adverse event (AE) report and by the Post-Authorization Safety Study (PASS). The thromboembolic risk appears to be lower than with other SERMs. The incidence of cerebrovascular events was also lower in the cohort treated with

ospemifene when compared to controls and in the cohort treated with other SERMs. Data on lipid and coagulative profiles were just as good, therefore the cardiovascular risk seems to be limited. Observed results regarding the risk of endometrial carcinoma meet the FDA criteria for endometrial safety. As with other compounds in this class, ospemifene seems to be safe on the breast in in vitro studies, in pre-clinical studies in animals, and in the surrogate parameters of breast safety [54–56].

5.4. Dehydroepiandrosterone (Prasterone)

Prasterone (dehydroepiandrosterone) has recently been introduced to the market for the treatment of VVA. It acts as a precursor of intracellular sex steroid androgens and estrogens. Since the conversion happens inside the cells, serum estradiol remains within the normal values for postmenopausal women, thereby probably avoiding the risk of systemic effects [57]. The efficacy of dehydroepiandrosterone (DHEA) has been demonstrated in a prospective, randomized, double-blind, placebo-controlled phase III clinical trial that examined the effects of daily intravaginal prasterone (6.5 mg) on four co–primary objectives, namely, the percentage of vaginal parabasal cells, percentage of vaginal superficial cells, vaginal pH, and moderate to severe dyspareunia, identified by women as the most bothersome VVA symptom. It may also be effective on the reduction of libido with a possible action on nerve endings, however, more scientific evidence is needed on this aspect [58].

Although data are limited to short-term studies on a relatively small number of patients, prasterone seems to be very safe. The endometrium is not affected by DHEA because the enzymes required to transform DHEA into estrogens are absent in the endometrium. Although no systemic increase of estrogen level has been reported, a history of breast cancer remains a contraindication.

5.5. Treatment Using Energy-Based Devices

5.5.1. Laser Therapy

A new trend gaining in popularity in the treatment of VVA is the advent of energy-based devices. The most widely used are fractional microablative CO_2 laser, non-ablative photothermal erbium: yttrium aluminum garnet (YAG) laser, and radiofrequency (RF)-based energy devices.

Laser or RF waves act by heating the connective tissue of the vaginal wall to 40 °C to 42 °C. In this way, they induce collagen contraction, neocollagenesis, vascularization, and growth factor infiltration that ultimately revitalizes and restores the elasticity and moisture of the vaginal mucosa. The proposed mechanism is the activation of heat shock proteins and tissue growth factors to stimulate new collagen synthesis and epithelial remodeling [59].

Recent reviews have suggested some potential benefits with the use of this technology in treating patients with VVA [60]. The efficacy of laser therapy in the treatment of VVA has been suggested by the improvement of GSM symptoms, VHI scores, and female sexual function index (FSFI) in many studies with its effectiveness at least as good as that of local estrogen based treatments [61,62]. However, none of these studies were sham or placebo controlled and the lack of sufficient information, especially concerning long-term safety, prompted the FDA in 2018 to warn against the indiscriminate marketing of laser treatments [63].

Although authors generally suggest that the procedure is well tolerated, being rapid and painless, increased vaginal pain, scarring, fibrosis, and vaginal wall lacerations have been reported [64].

The suggested treatment schedule involves three cycles at a distance of 30–40 days from each other as an attack therapy, with one cycle per year as maintenance therapy. Studies do not show how long the effects persist if the treatment is stopped and how often the treatment can be repeated.

5.5.2. Radiofrequency Devices

Radiofrequency devices most commonly used by gynecologists are the transcutaneous temperature-controlled radiofrequency (TTCRF), and more recently, the low-energy dynamic quadripolar radiofrequency (DQRF). The mechanism of treatment is to trigger anatomical remodeling in the vaginal and vulvar tissues. There have been some small studies that prove its effectiveness on vaginal symptoms, sexual function as well as urinary symptoms, but again they have been small, non-randomized studies [65–67].

5.5.3. Options for Treatment of Breast Cancer Survivors

In the case of women with previous or ongoing breast cancer, the options for treatment for VVA are unfortunately limited. All hormone-based therapies are contraindicated including vaginal isoflavone-based soy therapies, as there have been no studies on their safety in this cohort of women. Non-hormonal approaches are the first-line choices during or after breast cancer [68]. The options therefore are to offer these women moisturizers and vaginal lubricants, laser or radiofrequency treatments.

Another treatment that could be discussed with these women is ospemifene. Indeed, this SERM has been approved by the FDA for its use in women with previous breast cancer who have completed adjuvant therapy and have regular negative follow-ups. In cultured human breast tissue, ospemifene has been shown to induce a downregulation of ERα expression and decrease the proliferation of the cells, an effect that is consistent with the proposed anti-estrogenic activity of this SERM at the breast level [69]. In a recent small post-hoc analysis, a previous history of breast cancer did not appear to affect the efficacy or safety of ospemifene [54].

Finally, in this cohort of women, vaginal estrogen should be reserved for those patients who are unresponsive to non-hormonal remedies. The decision to use vaginal estrogen should be made in coordination with the woman's oncologist. Importantly, an informed decision-making and consent process in which the woman is provided with the information and resources to consider the benefits and potential risks of vaginal estrogen administration should precede this decision [61]. Vaginally administered estrogen can be absorbed in small amounts without raising blood levels, however, it may potentially stimulate occult breast cancer and could interfere with tamoxifen or aromatase inhibitors (AI) [70]. DHEA seems to be safe on breast tissue as it maintains serum estradiol within normal post-menopausal values, thus avoiding the risk of systemic effects. However, there have been no studies in a cohort of breast cancer survivors.

6. Conclusions

VVA is still an under-addressed, under-diagnosed, and consequently under-treated condition. It affects the quality of life of millions of postmenopausal women. Although many treatment approaches have been developed over the past decade, many still lack proper efficacy data and, more importantly, safety data are still insufficient. More safety data are also needed for the treatment of this condition in hormone-dependent breast cancer patients. Ospemifene, DHEA, and laser treatments seem to be promising alternatives for patients who cannot use hormones; however, their safety needs further research.

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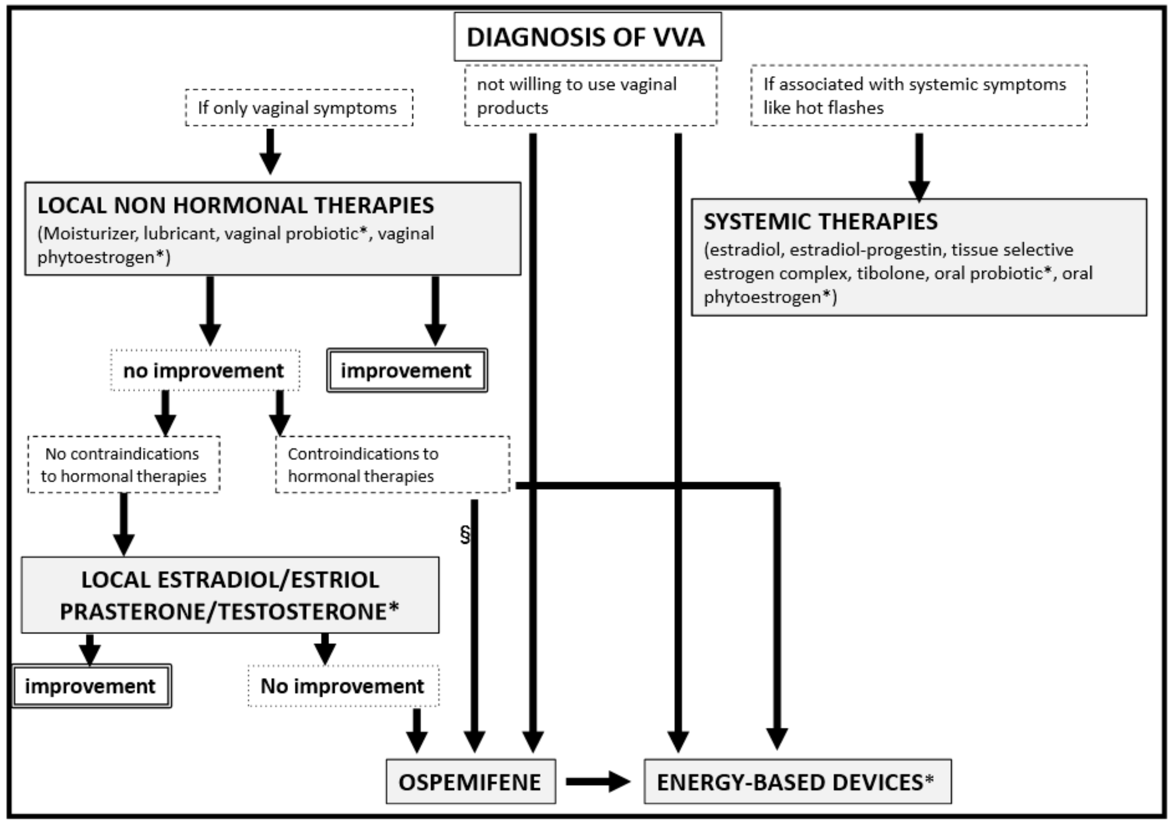
Appendix A

SYSTEMIC THERAPIES	LOCAL THERAPIES
Estradiol (E2) / Estradiol -Progestin (E2/P)	**Non hormonal therapy**
Estetrol (E4) *(still experimental)*	Lubricants and moisturizers
Bazedoxifene+conjugated estrogens (Tissue Selective Estrogen Complex TSEC)	Vaginal probiotics*
Tibolone	Vaginal phytoestrogen*
Ospemifene (Selective Estrogen Receptor Modulator SERM)	Energy based-devices*
Oral probiotics*	
Oral phytoestrogen*	**Hormonal therapy**
	Estradiol (E2) / Estriol (E3 *still experimental*)
	Prasterone (Dehydroepiandrosterone DHEA)
	Testosterone *

* no enough data to prove efficacy and safety

Figure A1. Possible treatment options for vulvovaginal atrophy.



* No enough data to prove efficacy § not approved to use before end of oncological treatment

Figure A2. Flow-chart of the management of vulvovaginal atrophy.

Table A1. Prevalence of vulvovaginal atrophy according to the most recent surveys and studies.

Study	Author	Year	Women's Age Range	Method of Study	Prevalence
"Women's voices in the menopause" survey	Nappi et al. [7]	2010	55–65 years	Computer-assisted web interviews	39%
VIVA survey	Nappi et al. [8]	2012	55–65 years	Online survey	45%
AGATA study	Palma et al. [9]	2016	59 years (average)	Interview and gynecological examination	79%
The Women's EMPOWER Survey	Kingsberg et al. [10]	2017	45–90 years	Online survey	39–51%
EVES study	Palacios et al. [5]	2018	45–75 years	Questionnaires and gynecological examination	90%
GENISSE study	Moral et al. [12]	2018	30–75 years	Interview and gynecological examination	70%
ANGEL study	Cagnacci et al. [13]	2019	40–55 years	Interview and gynecological examination	36.8%

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SOCIETY POSITION STATEMENTS

Radiofrequency-Based Devices for Female Genito-Urinary Indications: Position Statements From the European Society of Sexual Medicine

Check for updates

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ABSTRACT

Introduction: Radiofrequency (RF)-based treatment has been introduced as an esthetic alternative treatment for various medical indications without the scientific backup of a satisfactory body of evidence. Furthermore, the United States Food and Drug Administration issued a warning regarding the safety of energy-based technologies for indications such as vaginal "rejuvenation," cosmetic vaginal treatment, vaginal conditions related to menopause, and symptoms of urinary incontinence and sexual function on July 30, 2018.

Aim: To perform a thorough review of the existing literature regarding RF-based vaginal devices for the treatment of female genitourinary indications and summarize the evidence available in a few short statements.

Methods: A thorough review of the literature regarding RF treatments for gynecological indications was performed based on several databases. Studies that included at least 15 patients were eligible for analysis.

Main Outcome Measure: Efficacy of RF devices for different genitourinary indications.

Results: Although a high level of heterogeneity of studies poses a serious challenge, the committee reached a decision on several statements related to the use of RF-based devices for genitourinary indications.

Clinical Implications: RF-based vaginal treatments have not been studied thoroughly enough in order to establish decisive recommendations regarding their safety and efficacy.

Strength & Limitations: These position statements have been established by a group of experts. The lack of strong evidence makes it difficult to give decisive recommendations.

Conclusions: Further randomized controlled trials with proper methodology and design are required to establish both benefits and possible harm these treatments may have in both short and long term for all the different indications studied. **Otero JR, Lauterbach R, Aversa A, et al. Radiofrequency-Based Devices for Female Genito-Urinary Indications: Position Statements From the European Society of Sexual Medicine. J Sex Med 2020;17:393–399.**

Key Words: Efficacy; Genitourinary Indications; Radiofrequency; Safety

INTRODUCTION

Radiofrequency (RF) treatments have become increasingly popular during the last several years as alternative nonsurgical tissue remodeling treatment modalities in the field of sexual and gynecological medicine. These techniques have been commercially promoted as effective for various gynecological indications including alleviation of genitourinary syndrome of menopause (GSM) symptoms and treatment of stress urinary incontinence (SUI) and vaginal laxity.[1–3]

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When it comes to vaginal laxity treatment, physicians have frequently recommended pelvic floor physical therapy and/or Kegel exercises, with low compliance and conflicting results.[4,5] Topical, nonprescription vaginal tightening products have been suggested as alternative treatments, but these may cause severe disruption of the vaginal ecosystem, resulting in vaginal mucosal erosion, increased vaginal discharge, and an increased rate of infections.[6] Furthermore, both safety and efficacy of these products for the treatment of vaginal laxity have not been established scientifically. Surgery may also be performed to tighten the introitus if alternative treatments fail. Although some studies have demonstrated improvement in sexual function,[7–10] surgery is considered an invasive approach, with potentially serious adverse effects such as suburethral trauma and scar tissue formation that in turn may lead to dispareunia in addition to the need for a postoperative recovery period.[11]

There are currently several minimally invasive, RF-based devices that are being used to treat vaginal laxity, none of which have Food and Drug Administration (FDA) or European Medicines Agency (EMA) clearance or approval for vaginal laxity treatment.

RF is typically deeper than laser in its penetrative capacity within the tissues using a lower frequency and longer wavelengths. RF penetration depth is also dependent on modality, with monopolar systems penetrating most deeply. Unlike unipolar RF systems, other RF systems with bipolar, monopolar, and multipolar configurations (with or without a cooling feature) can deliver energy externally to the vulva as well as to the vaginal mucosal epithelium and lamina propria.[12–14]

Despite the histological rationale for the use of RF for vaginal rejuvenation, the efficacy and safety of this treatment modality have been scarcely assessed. Furthermore, while a few RF-based devices have been previously commercially marketed as possible treatments of vaginal laxity and SUI, the FDA recently issued a warning regarding false marketing claims made by several companies. In addition, the FDA emphasized the need for caution when considering energy-based procedures for the treatment of vaginal rejuvenation and cosmetic procedures.[15] The promotion of these procedures has reached beyond the setting of medical treatment and is currently part of the service catalog introduced by many esthetic treatment centers, with no regard to the level of clinical evidence. Health-care professionals including plastic surgeons, dermatologists, urologists, and others, although underequipped and undertrained, are offering various vaginal and vulvar health procedures.

In light of this situation, the aim of the present study is to provide the European Society for Sexual Medicine (ESSM) position statement on this topic, laying down the current evidence, the possible conflicting issues, and the need for further clarifications.

METHODS

A comprehensive PubMed, Web of Science, Embase, Medline, and Cochrane Library search was conducted based on the following keywords: radiofrequency vaginal application, genitourinary symptoms, genitourinary syndrome of menopause, vaginal laxity, urinary incontinence or sexual dysfunction, and rejuvenation. Studies from January 1, 1969, up to July 30, 2018, were included.

Owing to the limited presence of ramdomized clinical trials, studies including a minimum of 15 patients were included in the review. The search was also restricted to full-text articles written in English.

Owing to the limited level of evidence and a lack of good study quality and design, recommendations as per the Oxford 2011 Levels of Evidence criteria were not possible. However, specific statements on each topic are provided, summarizing the ESSM position based on long deliberations among a board of experts comprising clinicians from the ESSM board and scientific council, aiming at taking the first step in developing a coherent evidence base and treatment protocol.

PRECLINICAL RESEARCH

Limited evidence suggests that RF-based applications may affect cellular changes in the connective tissue layer of the vagina (statement 1).

Evidence

Cooling monopolar RF (CMRF) has been demonstrated to induce fibroblast activation and new collagen production in several tissues.[16] However, no data regarding vaginal mucosal epithelium has been published thus far. Based on this study, CMRF-proposed mechanism of action is cellular changes in the connective tissue layer elicited by energy-related heating of the tissue. This results in fibroblastic activation, collagen formation and restoration, and likely innervation and neovascularization. The restorative process occurs over time, possibly up to 90 days, and improves the overall integrity and function of the tissue.

Expert Opinion

Although preliminary results suggest that CMRF can result in positive outcomes in different tissues, the results should be replicated in vaginal tissues.

VULVOVAGINAL SYMPTOMS OF GSM

Currently, there is insufficient evidence to support the use of RF-based vaginal applications for the treatment of GSM (statement 2).

GSM Definition

As per the International Society for the Study of Women's Sexual Health/North American Menopause Society Consensus Conference, GSM is defined as a collection of symptoms and signs in association with a decreased estrogen and additional sex steroid levels causing changes in the labia majora/minora, clitoris,

Table 1. Evidence table-RF treatment

Indication	No. of patients	Follow-up (months)	Observed effects	Energy	References
Genitourinary syndrome of menopause					
Objective evidence of VVA, vaginal dryness, and/or dyspareunia; VAS VVA/GSM	32	12	Improvement in self-perception of atrophy-related symptoms	DQRF	19
VHI	20	3	Improvement in vaginal health scores	RF	18
VAS for dyspareunia					
Sexual function assessment					
FSFI	159	6	Significant improvement in sexual function	RF	10,26,31
FSFI/FSDS-R	164	6	Significant improvement in sexual function, decreased distress	CMRF	11
FSFImv/FSDS-R	24	6	Improvement in sexual function, decreased distress	CMRF	20
FSFI	20	12	Significant improvement in sexual function	CMRF	24
FSDS-R					
SSQ					
SSQ	25	12	Improvement in overall sexual satisfaction	DQRF	19
ICIQ-VS	30	2	Significant improvement noted	RF	23
PFIQ-7					
IIQ-7					
ICIQ-UI-SF					
Photos (also included external treatment)					
External labial treatment					
FSFI; VAS	17	1	Improvement in FSFI Improvement in VAS	RF	25
FSFI	43	12	Overall FSFI sexual function scores increased	RF	28
Vaginal laxity					
FSFI	79	6	Significant improvement in sexual function		10
VLQ	164	6	Statistically significant Improvement	CMRF	11
FSFI mv/FSDS-R	49	6	Self-reported improvement	CMRF	20,31
Vaginal laxity and SSQ/self-reported vaginal tightness					
VLQ	30	12	Self-reported improvement	CMRF	24
VVLQ	27	1	Statistically significant Improvement	RF	22
Combined intravaginal and labial treatment					
VLQ	25	12	Improvement in self-perception of vaginal looseness Statistically nonsignificant tendency to slight deterioration in VLQ, PISQ, and SSQ at 6-9 months	DQRF	19
Labial laxity	17	1	Vulvar improvement in appearance	RF	29
Vulvar appearance photo					
Stress urinary incontinence					
ICIQ-UI-SF	241	12	Statistically significant improvement	RF	22,24,25

(continued)

Table 1. Continued

Indication	No. of patients	Follow-up (months)	Observed effects	Energy	References
Combined intravaginal and labial treatment					
PISQ-12	119	12	Improvement	DQRF	19,25
ICIQ-VS	280	2	Significant improvement	RF	23,25,26,27
PFIQ-7					
ICIQ-UI-SF					
Photographs					
IIQ-7 (also included external treatment)					
UDI-6	390	12	Statistically significant improvement	RF	18,24,25,26,27
ICIQ-UI-SF					
Cough Test					
Urodynamic testing					

CMRF = cooling monopolar radiofrequency; DQRF = Dynamic Quadripolar Radiofrequency; FSDS-R = Female Sexual Distress Scale- Revised; FSFI = Female Sexual Function Index; FSFImv = Female sexual Function index modified version; ICIQ-UI-SF = International Consultation on Incontinence Questionnaire- Urinary Incontinence Short Form; ICIQ-VS = International Consultation on Incontinence Questionnaire- Vaginal Symptom; PFIQ-7 = Pelvic Floor Impact Questionnaire; PISQ-12 = Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionaire-12; RF = radiofrequency; SSQ = Sexual Satisfaction Questionnaire; UDI-6 = Urogenital Distress Inventory; VAS = visual analogue scales; VHI = Vaginal Health Index; VLQ = vaginal laxity scale; VVLQ = vulvovaginal laxity questionnaire.

vestibule/introitus, vagina, urethra, and urinary bladder.[17] The syndrome may include genital dryness, burning, and irritation sensations; sexual symptoms include lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms include urgency, frequency, dysuria, and recurrent UTIs.[13]

Evidence

The literature on GSM and RF is scant (Table 1). The Vaginal Health Index and a visual analogue scale for dryness and dyspareunia were used, and both measures were noted to be improved at the follow-up visit. Positive histological vaginal changes were noted.[18] The use of dynamic quadripolar RF was in a 12-month efficacy trial, in women with objective evidence of vulvovaginal atrophy, dryness or painful intercourse as the most bothersome symptom, reported rapid self-perception improvement in atrophy-related symptoms.[19]

Expert Opinion

Evidence regarding the use of RF treatment of GSM symptoms is lacking. Although reported positive outcomes in the aforementioned studies, large scale studies are required including comparative trials between RF and the other known medically approved pharmacological treatments for GSM.

VAGINAL LAXITY

Owing to the lack of a uniformly accepted definition of vaginal laxity, we cannot draw any specific recommendations regarding the role of RF-based vaginal application devices in treating this condition (statement 3).

Laxity Definition

Vaginal laxity is commonly considered a patient-reported condition lacking standardized criteria for diagnosis and severity grading. Furthermore, no expert consensus or scientific data exist on the subjective and objective parameters that are to be used for clinical characterization of this condition.

Evidence

Several articles have reported the use of RF in women complaining of symptoms related to vaginal laxity (Table 1). Results from case series demonstrate that RF may be a suitable noninvasive procedure for the treatment of vaginal laxity. Follow-up time varied between 1 and 12 months after RF treatment. All studies reported subjective improvement in either laxity symptoms or sexual function parameters. The longer follow-up studies that examined tolerability and safety found RF treatment for vaginal laxity to be safe and well tolerated.[19,20]

Expert Opinion

While preliminary data are promising, with respect to treatment efficacy of genitopelvic laxity, energy-based devices and accompanying procedures differ substantially with respect to treatment modality, protocols, study design, patient population, duration of procedure, and reporting efficacy and safety parameters, making the results difficult to interpret and determine consistent effects. Each RF system and its published scientific data should be examined individually. Future larger randomized controlled trial (RCT)/sham-controlled data are necessary.[21] Finally, as stated previously, the lack or general agreement on vaginal laxity definition limits the validity of the available results.

STRESS URINARY INCONTINENCE

Preliminary data suggest that the use of RF-based vaginal applications may improve mild to moderate subjective and objective symptoms of SUI, but the available data do not allow drawing any firm recommendation (statement 4).

Evidence

Several prospective observational studies have assessed the efficacy of RF vaginal treatments for SUI[18,19,22−27] (Table 1). These studies included a follow-up period of between 1 and 12 months. Only a single clinical RCT compared RF treatment with sham treatment.

Between 57 and 78% of patients reported substantial improvement in symptoms after RF treatment. The treatments were reported to be well tolerated with no serious adverse events.

In addition, to the patient-reported outcomes, one RCT reported results from punch biopsies at the urethra-vesicle junction before and after the treatments were performed, showing positive histologic changes.[18]

Expert Opinion

The number of patients included and the available studies is too small to draw final conclusions. Larger patient numbers, longer follow-up, and additional sham-controlled RCTs, in carefully delineated populations, are necessary to make further recommendations, concerning the validity, efficacy, and safety of RF use for this conditions.

SEXUAL HEALTH

Preliminary evidence, derived from secondary end points, suggests that RF-based vaginal applications may mainly improve arousal and orgasm domains. There is urgent need for well-designed studies before recommendation for the use of RF devices for treatment of sexual complains (statement 5).

Evidence

Few studies examined the effect of RF treatment on sexual health (Table 1).[10,11,20,28−31] Most studies reported pretreatment and post-treatment Female Sexual Function Index scores revealed improvement in both the orgasm domain and the arousal domain after treatment. CMRF is the only treatment modality which has been investigated with sham-controlled RCT study, which demonstrated domain changes as measured by the Female Sexual Function Index.[11]

Patients were treated both externally and internally with no difference between the 2 modalities in reported effect and treatment consequences in short (1 month) and long (12 months) follow-up periods.[10,11,20,28−31]

Expert Opinion

Studies are very heterogeneous and include both premenopausal and postmenopausal women who suffer a decrease in sexual health from different factors, thus making it difficult to draw absolute recommendations regarding the population of choice that would best benefit of RF treatment.

SAFETY

Adequate safety profile of RF-based vaginal applications needs to be further assessed through well-designed short- and long-term sham-controlled RCTs (statement 6).

Evidence

The medical device reports based on global clinical commercial experience have not revealed any serious adverse events or safety concerns of use of the device. Overall, the CMRF is safe and well tolerated. RCT safety results[11] report that in both treated and control populations, similar rates of treatment-emergent adverse events were documented. Therefore, the treatment was found to be safe and well tolerated as assessed by adverse events and patient reports.

Mild pain and bleeding (which could be due to the treatment of the entire canal) are the most frequent adverse events reported.

Expert Opinion

While most commercial data support that RF is safe and effective for vaginal treatment, only one trial followed patients prospectively and reported incidence of both sham and treatment intervention arms in a prospective fashion. Further RCT data are necessary to reinforce the long-term safety profile of RF with cooling and those without.

CONCLUSIONS

Clinical research in this setting remains poor, and the impact of the for mentioned histological changes on vaginal signs and symptoms has not been clearly established. In light of this scenario, we have identified a number of unmet needs that require addressing before evidence-based recommendations regarding the use of these treatment modalities for vaginal treatments may be reached. First, a consensus should be reached regarding uniform terminology regarding these interventions. Although the term "rejuvenation" has been adopted by some authors, it appears to be a trademarked commercial term which lacks a standardized definition of signs, symptoms, indications, and treatment criteria.[27] The need for

standardized terms includes commonly claimed conditions that are arguably indications for intervention such as vaginal laxity and relaxation. Second, RCTs are imperative for determining the efficacy of these interventions. In addition, owing to the fact that some of the studies are based on patient-reported outcomes regarding symptom improvement, a dummy blinded control group is essential to prevent biases related to patients' expectations of therapy. Finally, efficacy assessments of vaginal RF-based applications should be based on validated and homogeneous measurement tools which may allow comparisons between studies.

With regard to the safety of RF-based applications, all of the studies consistently reported no serious adverse events and a low rate of mild to moderate adverse events aside mechanical discomfort during interventions. Nevertheless, these findings must be taken cautiously considering the lack of RCTs and long-term follow-up on the effects of these therapies. Furthermore, the FDA has recently issued a warning regarding the limited evidence supporting the use of RF treatment of vulvovaginal atrophy.[15]

The limitations of this statement document may include the search strategy and information sources. As a result, although the search terms included in this review are widely used, the search might have ruled out studies assessing RF efficacy in vaginal conditions that were not reported as "rejuvenation." It is noteworthy, however, that various narrative reviews have been examined for individual studies, which have been added to the evidence pool. Unpublished studies until July 30, 2018, if exist, were not included in this statement document.

In summary, RF-based applications have demonstrated some beneficial effect in short-term efficacy for treatment of symptoms associated with genitourinary complaints. Safety-wise, only a number of studies have reported adverse events, and most studies did not aim to evaluate safety at all, but rather treatment efficacy alone. Thus, the effects of RF-based applications for various vaginal conditions require further confirmation in well-designed RCTs with long-term follow-up periods and emphasis on short- and long-term safety before proper evidence-based recommendations can be reached.

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Research Article

DQRF™ (Dynamic Quadripolar Radiofrequency) and UPR™ (Ultra-Pulsed Radioporation) 12-Month Synergy in Postmenopausal Vulvovaginal Atrophy

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Abstract

Introduction: The low-energy Dynamic Quadripolar Radiofrequency or DQRF™ vaginal technology overcomes several problems of manageability and safety experienced with other energy-based vulvovaginal energy-providing technologies by postmenopausal women with symptoms of vulvovaginal atrophy. The proprietary Ultra-Pulsed Radioporation or UPR™ technology has already shown to accrue the benefits of the new radiofrequency technology by facilitating penetration of active principles into the deep layers of vulvar skin and vaginal mucosa and enhancing hydration and trophism. Evaluating the impact on vulvovaginal atrophy symptoms, with vaginal dryness expected to benefit the most from the DQRF/UPR™ synergy, is the goal of this interim study.

Methods: Prospective real-life cohort study on 106 ambulatory women (mean age, 56.8 ± 8.61 years old) with vaginal atrophy and dryness. VVA treatment: four to five 25-min sessions every 14-16 days (coupling gel with hyaluronic acid); one more DQRF/UPR™ maintenance session after six months and a final visit (only assessment, no treatment) after 12 months. Operative temperatures in target tissues during the procedure: 42°C (range 40-43°C). Assessments (baseline and at the end of the treatment cycle): vaginal dryness (primary efficacy parameter, 10-cm impromptu Visual Analogue Scale); dyspareunia, burning and itching (4-score impromptu Likert-like scale) and photographic documentation at baseline at the end of the DQRF/UPR™ treatment cycle.

Results: Vaginal dryness rapidly improved vs baseline (T0), with a highly significant reduction (−83.1%) at the end of the treatment cycle (T1) that steadily persisted after 6 and 12 months (T2 and T3; −79.2% and −64.9%, respectively). All other symptoms similarly improved vs baseline over the year of follow-up: dyspareunia −81.5% (T1) and −70.4% (T3); burning −87.0% (T1) and −65.2% (T3); itching −89.5% (T1) and −68.4% (T3). All treatments were well tolerated, with no troubling pain or other side effects during or after the procedures.

Conclusion: The study confirms, over a one-year follow-up, the previously demonstrated benefits of the Dynamic Quadripolar Radiofrequency (DQRF™) in synergy with Ultra-Pulsed Radioporation (UPR™) as an innovative treatment option of vulvovaginal atrophy/genitourinary syndrome of the menopause symptoms. The novel UPR™ technology facilitates the deep penetration of active topical principles favourably acting on postmenopausal atrophic tissues. The DQRF/UPR™ concept aims to enhance the effects of the DQRF™ technology exploiting the synergy between the double biological effects-by the energy-based DQRF™ and the UPR™ active principle. Long-term studies will confi.

Keywords: *Electroporation, Genitourinary syndrome of menopause, Dynamic quadripolar radiofrequency, DQRF™, Ultra-Pulsed Radioporation, UPR™, Vulvovaginal atrophy*

Abbreviations

DQRF™: Dynamic Quadripolar Radiofrequency; GSM: Genitourinary Syndrome of Menopause; HA: Hyaluronic Acid; MDa: x10^6 Dalton; MHz: Megahertz or x10^6 Hertz; RSS™: Radiofrequency Safety System; SEM: Standard Error of the Mean; UPR™: Ultra-Pulsed Radioporation; VAS: Visual Analogue Scale; VDR™: Vaginal Dynamic Radiofrequency; VVA: Vulvovaginal Atrophy; W: Watt;

Introduction

Energy-based vulvovaginal treatment technologies often show manageability and safety difficulties in postmenopausal women with life-disrupting Vulvovaginal Atrophy (VVA) and Genitourinary Syndrome of Menopause (GSM). The low-energy DQRF™ (Dynamic Quadripolar Radiofrequency) technology candidates to overcome such problems in VVA women [1,2]. The four algorithmically controlled radiofrequency electrodes, continuously cycling between receiver and transmitter states (VDR™ or Vaginal Dynamic Radiofrequency™ technology), generate repelling electric fields within the closed electrode system and concentrate their low-energy thermal effects with high topographical precision in precise subepithelial areas without the need for grounding pads.

In addition, the treated area - usually a 4-inch area centred on the hymenal ring -need no systemic analgesia or local anaesthesia thanks to the integrated RSS™ (Radiofrequency Safety System) proprietary technology that steadily tracks the tip movements and local tissue temperature [1,2]. The Novavision Group S.p.A. (Misinto, Monza-

Brianza, Italy) holds worldwide rights for the patented DQRF™, VDR™, and RSS™ technologies.

Since 2018, integrating the DQRF™ concept with the proprietary UPR™ (Ultra-Pulsed Radioporation) radiofrequency electroporation technology has been a second technological jump forward. UPR™ modulates the DQRF™ radiofrequency effects and facilitates the transfer of biologically active principles through aqueous channels in vulvar skin and vaginal mucosa cell membranes [3]. The DQRF™ effects on vulvovaginal hypotrophy thus synergise with those of the UPR™-mobilised active principles-for instance, highly hydrating and pro-trophic Hyaluronic Acid (HA) [4]. Counteracting the postmenopausal loss of elasticity and volume with topical HA formulations and HA dermal fillers in women with labia majora hypotrophy has long been a common cosmetic gynaecology practice [5,6]. A double-blind pilot study compared VVA/GSM symptoms and women's satisfaction with their sexual and couple lives in two random samples of postmenopausal women randomised to either DQRF™ and DQRF/ UPR™ vulvovaginal treatment [3]. The low-molecular-weight HA was interspersed in the coupling gel in the DQRF/ UPR™ treatment group; the study established the DQRF/ UPR™ superior benefits [3].

The interim 12-month DQRF/ UPR™ outcomes on VVA symptoms herein illustrated aim to confirm the previous favourable outcomes over a more extended follow-up period and a more ample postmenopausal women cohort. Vaginal dryness, expected to benefit the most from the UPR™ synergy with DQRF™, was the primary efficacy parameter. The interim DQRF/ UPR™ cohort study herein described is currently being expanded to identify the characteristics of VVA women who will most likely benefit from the advanced DQRF/ UPR™ technology.

Methods

Real-life Study Design, Cohort Selection Criteria and Interim Cohort Demographics

All VVA/GSM women enrolled in the prospective DQRF/UPR™ cohort attended specialist departments for postmenopausal disorders in the authors' private health facilities. Candidate participants in the 45 to 66 years old age range with moderate to severe VVA symptoms (vaginal dryness, itching, burning and dyspareunia) and negative recent Papanicolau and mammography tests should not have reported menstruations for at least 12 months. In addition, they should not have participated in other clinical studies for the last six months. After giving informed consent to the anonymous collection of their data and photographic evidence before the first treatment session, the 106 women underwent their planned DQRF/UPR™ treatment cycle between January 2020 and March 2021. All women had objective evidence of moderate to severe mucosal atrophy with thinning or loss of vaginal rugae and mucosal pallor; an explicit wish for a still-active sexual life was also a must.

Hormonal replacement therapy, pelvic organ prolapses beyond the hymenal ring, vulvodynia or chronic vulvar pain, vulvar dermatitis or dystrophy, viral lesions, including a high risk for human Papillomavirus infections, vaginal infections in the last two months, a Sjögren syndrome diagnosis, and inadequate thickness of the recto-vaginal septum at the pelvic examination-all were exclusion criteria from the study.

All study materials, including informed consent forms and study protocol and case report forms, were peer-reviewed for ethical problems, and the authors always safeguarded the full respect of the ethical standards laid down in the Declaration of Helsinki as revised in Brazil 2013. Participant women also agreed to the publication of the study outcomes.

Operative Procedures

The DQRF™-based EVA™ device (Novavision Group S.p.A., Misinto, Monza-Brianza, Italy) and the proprietary UPR™ technology were previously described [1-3]. The protocol foresaw 4 to 5 treatment sessions spaced 14-16 days as a treatment cycle. First, power was applied for 15 minutes to the vaginal mucosa with hyaluronic acid (1.5 to 2.0 MDa, 0, 2% concentration) mixed with the coupling gel, starting behind the hymenal ring with circular back-and-forth continuous movements and always keeping contact between the tip probe and the mucosa. Then followed another 10 minutes of DQRF™ application for vulvar treatment: in both steps with the power of the EVA™ device set at 20% to 27% of the 55-W maximum emitting power. Previous preparation was limited to an alcohol-free cleanse; all procedures were performed with the woman on the examining table in the dorsal lithotomy position.

DQRF/UPR™ treatment protocol
Treatment cycle: four to five 25-min sessions spaced 14-16 days-15-min over the vaginal mucosa (device equipped with the vaginal tip), 10 min over the vulvar areas with the vulvar tip.
One DQRF/UPR™ maintenance session (same procedure) after six months and one assessment-only visit after 12 months.
Radiofrequency generator: set at 1 MHz.
EVA™ operating power: variable between 20% and 27% of the maximum device emitting power (55 W).
Target temperature in vulvovaginal tissues during the procedure: 42°C (range 40-43°C).

With particular attention to pain and discomfort, safety was investigated in all women at each study visit and by telephone over the following days. The treatment protocol foresaw a further DQRF/ UPR™ maintenance session after six months and a final visit (only assessment, no treatment) after 12 months. Figure 1 illustrates the sterilisable vaginal and vulvar DQRF™ tips with their medically

Figure 1: *On the left:* the EVA™ vaginal tip with the four emitters/receivers DQRF™ electrodes distributed longitudinally to adapt to the vaginal anatomy. *On the right:* the EVA™ vulvar tip with the four DQRF™ electrodes distributed on the terminal tip plane to adapt ergonomically to the vulvar areas.

certified AISI 316 stainless steel dynamic quadripolar electrodes. The electrodes continuously cycle between receiver and transmitter states; the generated active electric fields in subepithelial tissues minimise the delivered energy (only 11 to 15 W), tissue Ohm's resistances and untoward thermal side effects with the help of the RSS™ safety technology.

Assessments

Vaginal dryness was assessed before the first treatment session (baseline, T0) and at the end of the treatment cycle (T1), together with baseline and end-of-treatment photographs, with the help of a 10-cm impromptu Visual Analogue Scale (VAS). Assessments of itching, burning, and dyspareunia made use of impromptu 4-score Likert-like scales (0=none; 1=mild; 2=moderate; 3= severe), with semi-quantitative score assessments repeated at the two follow-up visits: after 6 and 12 months (T2 and T3, respectively). In addition, all participant women received a Pap-test and a transvaginal echography as further safety control at all visits up to T3.

Statistics

Descriptive data were tabulated as means ± standard errors of the mean. The non-continuous nature of the VAS (vaginal dryness) and Likert-like (other VVA symptoms) semi-quantitative scores and the lack of assumptions about the normal distribution of baseline and final data justified a conservative approach. The general linear model for repeated measures or Kruskal-Wallis test for independent samples (nonparametric one-way ANOVA test) was applied to scores, after correction of means for age and Body Mass Index, to assess for any DQRF/UPR™ effect, with two-sided 95% confidence levels and p <0.05 as a cut-off for significance. Using the nonparametric one-way ANOVA test was justified because the score variances were homogeneous at the Levene's test. After detecting a significant DQRF/UPR™ effect, pairwise post-hoc Sidak multiple comparisons identified the exact time points of score trend divergence vs baseline during the T1 to T3 period.

Table 1: DQRF/UPR™ cohort demographics and baseline symptom profile. SEM, standard error of the mean.

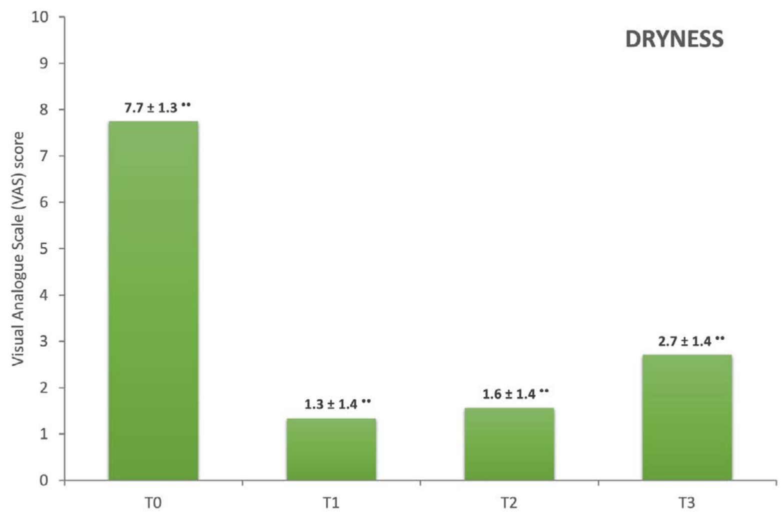
Baseline Prospective Cohort Data				
Postmenopausal women (N)	106			
Age (years, mean ± SEM)	56.8 ± 8.61			
Vaginal dryness (VAS scale ± SEM)	7.7 ± 1.35			
Other VVA symptoms	Absent	Mild	Moderate	Severe
Dyspareunia (cohort per cent)	0	5	22	74
Burning (cohort per cent)	1	14	39	46
Itching (cohort per cent)	4	32	34	30

Results

Table 1 illustrates the cohort demographics before the first treatment session. The clinical severity of the mail efficacy parameter, vaginal dryness, was alarming for most of the cohort VVA women (56.8 ± 8.61 years old), as highlighted by the high baseline VAS score and the low dispersion of baseline VAS scores (mean ± SEM, 7.7 ± 0.49). All other VVA symptoms were also quite troubling, as shown by the concentration of baseline scores for dyspareunia, but also burning and itching, in the "Moderate" (score 2) and "Severe" (score 3) groups. The baseline scores for dyspareunia and vaginal burning and itching were 2.7 ± 0.56, 2.3 ± 0.475 and 1.9 ± 0.88, respectively, in an impromptu 0-3 Likert-like scale. All women reported dyspareunia at baseline, and almost all intimate burning and itching.

Sixty-three women underwent four DQRF/UPR™ sessions, 43 women five treatment sessions. All participant women completed their DQRF/UPR™ treatment program as planned without missing visits and described their experience as always comfortable. All treatments were well tolerated, with no troubling pain, burns or blisters or other fastidious side effects or complications during or after the procedures. All women also resumed their everyday activities and sexual life immediately after the end of their treatment program.

The primary efficacy parameter, vaginal dryness, markedly improved



** p <0.001 vs baseline.

Figure 2: Vaginal dryness VAS scores at T0 (baseline), T1 (after the end of the DQRF/UPR™ treatment cycle), T2 (maintenance and assessment visit after six months), T3 (assessment visit after 12 months); means ± standard errors of the mean.

at the end of the DQRF/UPR™ treatment cycle with the relevant VAS score already diverging from the null hypothesis of no-effect trend (mean ± SEM, 1.3 ± 1.35, −83.1% and p <0.001 vs baseline), with 41 women reporting total subjective relief with a zero score for dryness. Furthermore, the benefits for vaginal dryness steadily persisted six months after the end of the treatment cycle (median VAS score 1.0; mean 1.6 ± 1.41, −79.2% and p <0.001 vs baseline) and only slightly deteriorated after 12 months of no DQRF/UPR™ sessions (median 3.0; mean 2.7 ± 1.44, −64.9% and p <0.001 vs baseline) (Figure 2). However, after 12 months, five women still reported no vaginal dryness and 15 only a mild dryness (Figures 3 and 4).

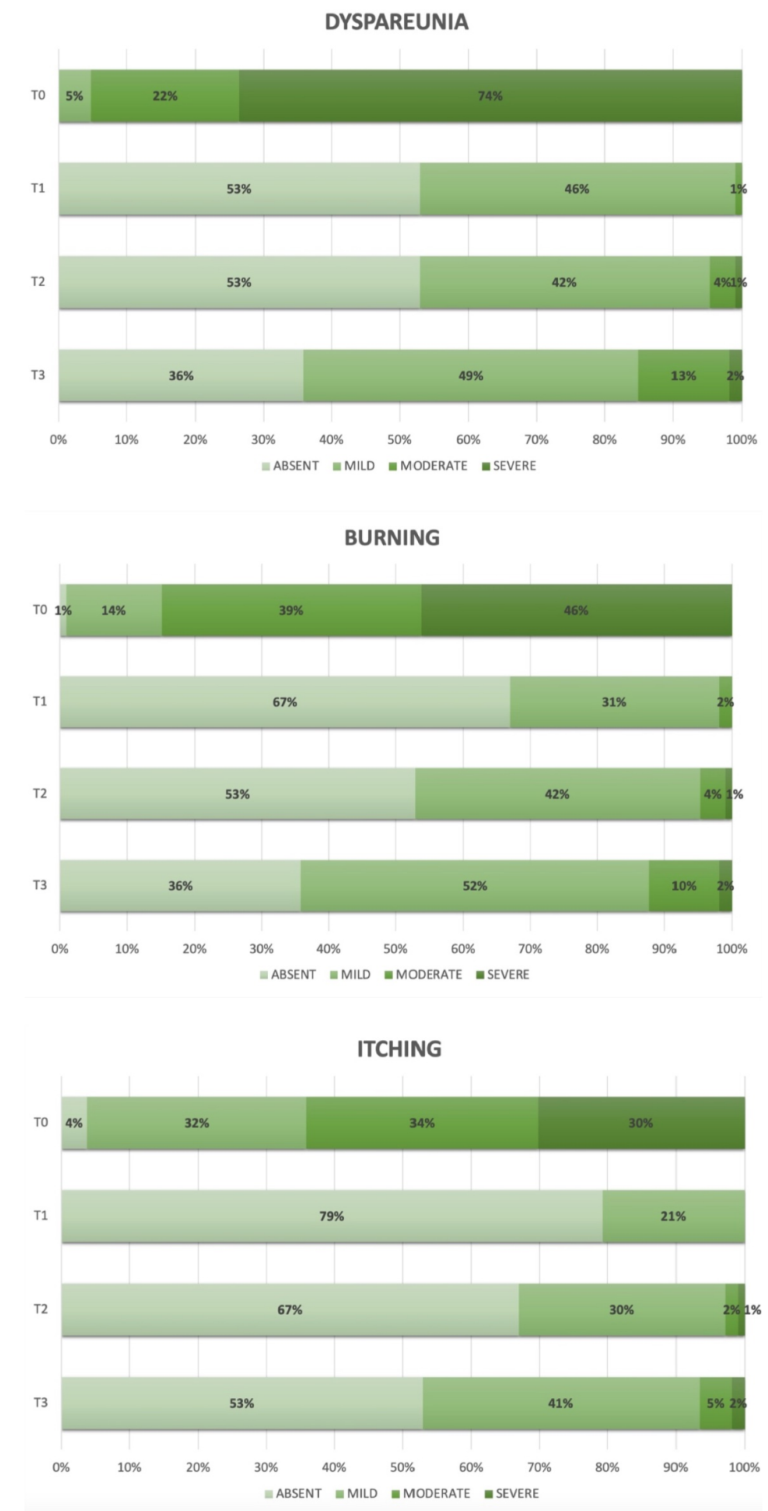


Figure 3: Per cent distribution of the symptom severity scores at baseline (T0), end of the DQRF/UPR™ treatment cycle (T1), and follow-up visits after 6 and 12 months (T2 and T3, respectively).

Figure 4: Vestibular atrophy at the end of the DQRF/UPR™ cycle, with the evidence of new vestibular rugae as morphological markers of the treatment benefits.

The benefits at T1 were similar for other VVA symptoms (Table 2): dyspareunia −81.5%, burning −87.0%, itching −89.5% vs baseline, all of them already diverging at T1 with high significance from the null hypothesis of no-effect trend.

The dyspareunia, burning and itching scores also remained steady at the maintenance visit after six months and only marginally deteriorated after 12 months (Table 3). However, the vaginal dryness VAS score was still 64.9% lower than baseline after one year, whilst the dyspareunia and vaginal burning and itching subjective scores were 70.4%, 65.2% and 68.4% lower.

Table 2: Dyspareunia, burning and itching scores (0-3 Likert-like scales) after the 4-5 DQRF/UPR™ treatment sessions. **p<0.001 vs. baseline; means ± standard errors of the mean.

VVA Symptom	End of the DQRF/UPR™ treatment cycle (T1)	
Dyspareunia	0.5 ± 0.52** (median 0)	56 women reporting no dyspareunia
Burning	0.3 ± 0.52** (median 0)	70 women reporting no vulvovaginal burning
Itching	0.2 ± 0.41** (median 0)	84 women reporting no vulvovaginal itching

Table 3: VVA severity scores (0-3 Likert-like scales) at the maintenance/assessment visit six months after the end of the DQRF/UPT™ treatment cycle (T2) and the final assessment follow-up after 12 months. **p<0.001 vs. baseline; means ± standard errors of the mean.

VVA symptom	T2	T3
Dyspareunia	0.5 ± 0.62** (median 0)	0.8 ± 0.73** (median 1)
Burning	0.5 ± 0.62** (median 0)	0.8 ± 0.70** (median 1)
Itching	0.4 ± 0.57** (median 0)	0.6 ± 0.68** (median 0)

Vincenzo Prestia, et al. (2021) DQRF™ (Dynamic Quadripolar Radiofrequency) and UPR™ (Ultra-Pulsed Radioporation) 12-Month Synergy in Postmenopausal Vulvovaginal Atrophy

Discussion

The DQRF™-induced variable electrical currents continuously re-orient dipole moments like water molecules in target vulvovaginal tissues. Other biomolecules, facing variable electric impedance and mechanical attrition due to the water viscosity, dissipate their Brownian kinetic energy into heat [7].

Over the years, more and more evidence has highlighted how thermal energy conveyed to vulvovaginal tissue may help reverse the natural ageing processes by stimulating the proliferation of glycogen-enriched epithelium new vessels and collagen formation in the lamina propria and by improving natural lubrication and urination control [7]. The 40°C to 43°C temperature range is critical to activate neocollagenesis by tissue fibroblasts [8].

The burden of bleeding, pain and burning problems may be severe for laser devices [9]. The digitally controlled DQRF™ technology helps to reduce the related discomfort, while the synergy with the UPR™ technology helps the in-depth penetration of hydrating and pro-trophic agents in treated vulvovaginal areas [3].

The study confirms the short-term outcomes of the first DQRF/UPR™ double-blind study over a longer one-year follow-up. The double-blind study already established the UPR™ contribution acting in synergy with the DQRF™ technology [3].

Although the baseline vaginal dryness and overall cohort VVA symptom profile appeared quite severe, most cohort women reported T1 reductions of baseline symptom scores between -81.5% and -89.5%-quite impressive after the relatively short DQRF/UPR™ treatment cycle, at most no more than about 80 days. Indeed, some caution is justified: together with the uncontrolled design, assessing symptom relief from VVA symptoms only through impromptu, non-validated VAS and Likert-like subjective scales is a weak point that deserves consideration before hasty conclusions.

Besides physical discomfort, VVA symptoms may severely affect the postmenopausal woman's self-perception [10-12]. In clinical situations where even minor clinical improvements may translate into significant perceived relief, benefits may appear magnified due to the placebo effect. Psychological and self-rated measures, mainly if assessed via subjective semi-quantitative scores, are primarily liable to placebo effects-as in this study.

However, the study intended only to confirm the benefits of the DQRF/UPR™ VVA treatment option, which the double-blind trial demonstrated [3], over a one-year follow-up, and its value is unaffected. On the contrary, the study provides new clinically significant information-the subjective VVA benefits persist for one year after a relatively short, four-to-five session treatment cycle, with VVA symptom severity scores still -64.9% and -70.4% vs baseline after twelve months. Interestingly, dyspareunia showed the most remarkable long-term improvement, indirectly highlighting the importance of a gratifying sexual life for the cohort's postmenopausal women. The open-label nature of the study cannot contribute to defining the contributing role of in-depth radioporation of the lenitive and possibly pro-trophic glucose-hyaluronic acid gel. However, the previous double-blind investigation already demonstrated the DQRF™ and UPR™ synergy [3].

Of course, further long-term studies will confirm these preliminary encouraging results.

Conclusion

The study confirms, over a one-year follow-up, the benefits, previously demonstrated in a double-blind trial, of the Dynamic Quadripolar Radiofrequency (DQRF™) in synergy with Ultra-Pulsed Radioporation (UPR™) of hydrating and pro-trophic hyaluronic acid as an innovative treatment option of the vulvovaginal atrophy, and in the general genitourinary syndrome of the menopause symptoms.

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The authors declare they have no financial or any other conflict of interest related to the study or the issues discussed in the paper.

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Non-invasive delivery of radiofrequency energy in women with faecal incontinence, the new era. The new-generation DQRF™ device

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Abstract

Introduction: With at least one humiliating episode per month, faecal incontinence, variable from undergarment soiling to urge and passive incontinence, is a vexing problem for no less than one adult woman out of ten. The efficacy and impact on the quality of life of temperature/movement-controlled radiofrequency energy delivery to the sphincter complex with invasive needles are actual but rapidly wane. An innovative device is a candidate to overcome previous radiofrequency technologies' limitations and discomfort in faecal incontinence. It is equipped with an anatomical probe and the non-invasive Dynamic Quadripolar RadioFrequency™ technology and exploits the in-depth penetration of active principles via Ultra-Pulsed Radioporation™. A careful study of the anatomically and functionally delicate anal sphincter complex was the basis for the device design.

Methods: Explorative cohort study in 25 unselected ambulatory women 30 to 71 years old, nulliparous to multiparous, with medium-severity faecal incontinence and quality of life disruption. Wexner score assessment before the first session and at the end of the radiofrequency treatment cycle; further follow-up control after about one more month.

Results: At the end of the treatment cycle (5.8 ± 0,91 mean sessions; median, 6.0), Wexner scores (overall baseline mean, 8.6 ± 2.65; overall final mean, 0.4 ± 0.58) decreased to zero in fifteen women with occasional solid, liquid and gas incontinence in one, five and four women, respectively, all under control at the final follow-up visit, with no immediate or later side effects and total compliance.

Conclusions: The non-invasive device effectiveness in daily life was satisfactory. The benefit of eliminating invasiveness in radiofrequency energy delivery needs confirmation in well-designed incontinence studies, yet it already looks like a definite plus.

Abbreviations: CCF-FI" Cleveland Clinic Florida Fecal Incontinence (score); DQRF™: Dynamic Quadripolar RadioFrequency™; FI: Faecal incontinence; FIQLS: Fecal Incontinence-related Quality of Life Score; MDa: $x10^6$ dalton; MHz: Megahertz; SEM: Standard error of the mean; UPR™: Ultra-Pulsed Radioporation™

Introduction

Beginning with the baby boomer generation, the sight of a highly educated woman waiting for her first baby in her early to mid-thirties is ever more frequent in Western countries. Will she experience the humiliating symptoms of the involuntary loss of solid or liquid stool in the future?

The question may seem whimsical; she now looks so radiantly happy, but it is not: obstetric trauma has always been the leading cause of anal sphincter disruption, although often much deferred in time. Obstetric injuries may directly cause pudendal neuropathy but are usually unlikely to evolve into faecal incontinence (FI) before the woman is in her fifties: an observation that has long pointed to FI determinants as multifactorial [1]. Unsurprisingly, although 27.6% of women with index delivery complicated by anal sphincter disruption and 25.8% of women with episiotomy experienced troublesome FI, so did 15.2% of women who had a caesarean section, according to a landmark 30-year retrospective study [2].

Coming back to our imminent mother in her thirties, forecasting her FI future in twenty years is hard. Obstetric advances and the steady decrease of mean parity per woman will continue to scale back two leading risk factors—direct damage to the sphincter complex and pudendal nerves. However, her likely long life will increase the risks of many conditions impacting the pelvic muscle tone and sphincter function—diabetic neuropathy, demyelinating and inflammatory bowel diseases, and rectal or perianal surgery or radiotherapy. Prolonged survival will also increase her lifelong burden of unfavourably acting drugs like antidepressants, anticholinergics, and laxatives [1].

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***Key words:** anal sphincter, faecal incontinence, dynamic quadripolar radiofrequency, DQRF™, ultra-pulsed radioporation™, UPR™*

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Advancing age is by itself a risk factor also because of the increasingly blunted rectal sensation and reflexes. The tendency for the sphincter and pudendal nerve efficiency is to worsen with ageing. Even if they do not, at least some progressions to lazy stool evacuation is likely, leading sequentially to delayed rectal stool retention and faecal impaction, prolonged relaxation of the internal anal sphincter, and possibly escape of liquid stool in the anal canal around the impacted faecal material, seepage, and undergarment staining [3].

FI is primarily a female problem, with about 9% of adult women experiencing episodes at least monthly, with urge FI and soiling the most frequent FI phenotypes due to pudendal neuropathy and diminished conscious contraction of the external anal sphincter [4,5]. Passive FI is the least common phenotype, probably due to unconscious and inefficient contractions by the external sphincter [5]. A population-based study in adult American women even suggested an incidence of up to 18.8%; in all cases, less than 30% of women seek care [6]. FI does not spare adult men, if only because 74% of inflammatory bowel disease patients experience FI at least once in their life and because of the expanding diabetic epidemic [6].

Even with severe FI (Wexner score 15 to 20), few patients progress to surgery while diet and drugs remain the mainstay treatments [7]. Mini-invasive, temperature-controlled radiofrequency energy delivery to the sphincter complex with nickel needles has complemented FI management for several years [8-10]. With a limit: the short-term moderate efficacy of the mini-invasive needle procedure completely wanes over the long-term, with no significant changes after five years in functional incontinence scales and the Fecal Incontinence-related Quality of Life Score (FIQLS), as well as in anorectal manometry and endoanal ultrasound imaging [9,10]. The efficacy of the mini-invasive radiofrequency technique, as measured by the Cleveland Clinic Florida Fecal Incontinence score (CCF-FI) or the Vaizey score, is already crumbling down to 10% of treated patients after only one year of follow-up [8,11].

The new non-invasive anatomical tip of the EVA™ device, based on the Dynamic Quadripolar RadioFrequency™ (DQRF™) technology, could change such disappointing outcomes in synergy with the Ultra-Pulsed Radioporation™ (UPR™) technology to facilitate the in-depth penetration of active principles. The paper illustrates the outcomes of the first study that explored the real-life FI effectiveness of the novel non-invasive radiofrequency technology.

Methods

Real-life study design, exploratory rationale, and cohort women's incontinence profile

A simple, prospective open design based on a small office-based cohort of 25 consecutive unselected women with faecal incontinence problems, nulliparous to multiparous, was deemed adequate for the first exploratory investigation of the DQRF™-based device designed explicitly for FI. The exploratory study, because of its intended real-life dimension, targeted a female population that experience medium-severity FI and everyday life disruption—the largest share of the ambulatory patients attending FI institutions and private practices. Candidate women should not have been taking medications known to affect collagen metabolism and neocollagenesis, such as non-steroidal anti-inflammatory drugs and corticosteroids, for at least one month.

Due to the preliminary and exploratory nature of the study, the investigators did not try to distinguish between incontinence variants such as soiling (accidental passage of small amounts of faeces with staining or soiling of underpants), urge FI (urge to rush to the toilet to prevent FI or unavoidable defecation within 5 min after the first urge sensation), and passive FI (accidental passage of large amounts of solid stool with no urge sensation).

All study materials were peer-reviewed for ethical problems, and all enrolled women gave full written informed consent. Table 1 analytically illustrates the cohort women's baseline FI severity based on Jorge-Wexner categories and overall score and subscores. As usual, calculating individual scores meant cross-tabulating frequencies versus anal incontinence symptoms and consequences for daily life and summing up all individual subscores (score range extremes: zero for perfect continence and twenty for complete incontinence) [12,13].

The DQRF™ device

The non-invasive DQRF™ device derives from the DQRF™-based EVA™ device (Novavision Group S.p.A., Misinto, Monza-Brianza, Italy) and its advanced technology of algorithmically controlled radiofrequency energy delivery to gynaecological tissues [14,15]. The DQRF™ device incorporates a novel flat anatomical probe, ergonomically designed to adapt without trouble to the endorectal environment (Figure 1).

The four stainless steel electrodes on the elongated anatomical probe are the core of the proprietary 1.0-1.3 MHz DQRF™ technology. The DQRF™ device's maximum emitting power is 55 watts. The electrodes continuously cycle, under algorithmic control, between radio wave receiver and transmitter status, thus eliminating the grounding pad indispensable with standard radiofrequency technologies. In the ideal configuration and with the help of self-guided automatisms, the

Table 1. Baseline FI severity based on the Continence Grading Scale as described by Jorge and Wexner [12]. 0 ("never"); 1 ("less than one per month"); 2 ("less than one per week but more than once per month"); 3 ("less than one per day but more than once per week"); 4 ("more than once per day"). "Wears pad" category: needing disposable and reusable incontinence body-worn products (diaper-type garments or pads) with superabsorbent materials or disposable and reusable under-pads or bed-pads — and mean Wexner category subscores ± standard error of the mean (SEM).

Jorge-Wexner categories	Baseline mean subscores ± SEM
Solid	1.4 ± 0.65
Liquid	2.3 ± 0.63
Gas	2.6 ± 0.64
Wears pad	0.9 ± 0.91
Lifestyle alteration	1.2 ± 0.60
Wexner overall scores	**8.6 ± 2.65**

Figure 1. The novel probe of the non-invasive DQRF™ IF device, equipped with the dynamic quadripolar electrode system, is specifically designed to concentrate the radiofrequency energy in the anorectal sphincter complex area with high topographic precision and without invasive needles penetrating the sphincter muscle fibres.

repelling electric fields, generated within the four DQRF™ electrodes, concentrate the radiofrequency energy and its thermal effect with high tridimensional and layer precision in the 2 to 4 cm of the muscular anal tube and within the 0.3-cm to 0.5-cm thick, slow-twitch, fatigue-resistant smooth muscle expansion of the internal anal sphincter and the 0.6-cm to the 1.0-cm expansion of the levator ani muscles known as external anal sphincter.

By strongly reducing Ohm's resistances in tissues, the DQRF™ technology maximises the intended goal of the radiofrequency treatment, thermal induction of neocollagenesis, while minimising the energy delivered and virtually eliminating all burn risk. Electronic movement and temperature sensors (RSS™, Radiofrequency Safety System technology) control the temperature in treated sphincter areas without systemic or local anaesthesia.

The FI DQRF™ device also exploits the previously described proprietary Ultra-Pulsed Radioporation™ (UPR™) technology to deliver a lenitive and pro-trophic mixture of two-third glucogel and one-third hyaluronic acid (molecular weight, 1.5 to 2.2 MDa, concentration 0.2%), previously spread on the tip, to the target sphincter complex areas [16]. UPR™ acts by opening aqueous channels in cell membranes through modulation of the DQRF™ radiofrequency effects. Genetic engineering has long exploited radiofrequency electroporation techniques to maximise gene transfection efficiency and macromolecule penetration into cells [17,18].

The DQRF™ and pelvic floor exercise program

Preclinical investigations with the DQRF™ device in animal FI models and clinical experiences with other DQRF™-based devices in the female pelvic areas were crucial for designing the ideal radiofrequency IF treatment programs. The individually planned FI treatment cycles varied between five and eight weekly DQRF™ sessions performed according to the ethical standards laid down in the Declaration of Helsinki as revised in Brazil 2013.

Before each session, the device power was set at 20-25% of its maximum (no more than 13.75 watts) to reach tissue temperatures of 39-41°C in the target sphincter complex areas. Each "passive" DQRF™ session lasted 10 minutes, with the probe steadily inserted in the rectum.

An "active" office program of tone-enhancing pelvic floor exercises without abdominal contraction followed each weekly "passive" DQRF™ session to train the smooth and somatic sphincter fibres (Figure 2). The women also performed thirty slow to rapid active muscle contractions at home twice daily during the non-invasive radiofrequency treatment program and were asked to repeat the program at least once every year.

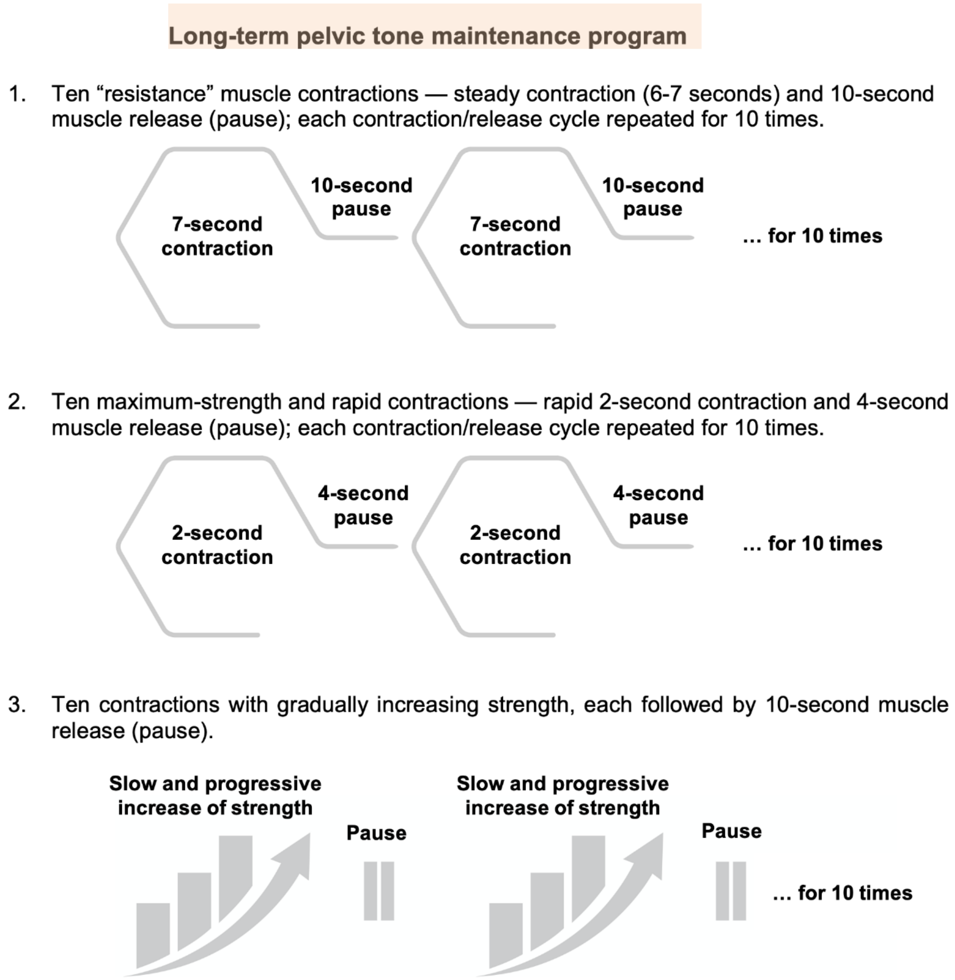

Figure 2. Pelvic floor exercises performed in the office after each DQRF™ treatment session and at home twice daily; program ideally repeated every year for long-term maintenance.

Wexner score assessments

Before the first DQRF™ + UPR™ session and after a pelvic exam, the investigators assessed the individual overall Jorge-Wexner scores and Wexner category subscores for each cohort woman; they repeated the complete assessment during the individual treatment cycle's last session. Follow-up control visit after about one more month.

Results

The 25 women included in the cohort had a mean age of 58.5 ± 9.89 years (median, 60.0 years; range, 30 to 71), with three women nulliparous and a mean cohort parity of 1.6 ± 0.87 (median, 2.0). The delivery had been natural in 18 women and caesarean in seven; all post-menopausal women had first experienced gas and stool incontinence only after menopause. Two women had systemic sclerosis; six had undergone haemorrhoidectomy and rectal surgery for cancer. Twelve women out of 25 underwent the shortest five-session DQRF™ + UPR™ program; seven women required six sessions, five women required seven sessions, and only one woman needed to undergo eight treatments. The overall mean number of non-invasive DQRF™ + UPR™ sessions was 5.8 ± 0.91.

At the end of the individualised radiofrequency treatment cycles, the overall Wexner scores (final mean, 0.4 ± 0.58, $p < 0.01$) had fallen to zero in fifteen cohort women and all women no longer needed incontinence body-worn products. One, five and four women still lamented occasional losses of, respectively, solid, and liquid stool and gas, and only one woman still referred some occasional impact on everyday life due to some occasional loss of gas. Even those residual liquid and gas incontinence appeared under control at the follow-up visit after one more month. Figure 3 illustrates the overall reported outcomes at the end of the DQRF™ + UPR™ cycle.

Discussion and conclusion

Within the anal sphincter complex, experimental physiology points to the 0.6- to 1.0-cm thick expansion of the levator ani muscle known as external anal sphincter as the crucial target for all non-surgical options that complement the dietary, drug, and pelvic training mainstay FI management. The pressures developed within the anal canal are consistently higher than the pressures simultaneously measured endorectally during defecation [19]. Concomitant rectal radiographic imaging and anal electromyogram recording confirm the external sphincter and the puborectalis muscle as the main continence actors. The flap valve mechanism, exerting pressure on the anterior rectal wall and the puborectalis muscle and suggested in the seventies to have a leading role, appears less critical [19,20].

The new DQRF™-based technique correctly targets the crucial dysfunctional anal external sphincter. As documented in other districts prone to muscle laxities like the perineum and the vaginal vestibule, in the radiofrequency range 200 kHz to 3.3 MHz, the impedance-controlled energy delivered to tissue water molecules increases their Brownian random motion and frictional energy dispersion as heat (Figure 4) [14]. The rapid, controlled temperature rise triggers the deposition of new collagen and elastin networks, with tissue remodelling and local biomechanics improvements [14].

The same cascade of biophysical events applies to the remodelling of the sphincter complex scaffolding [21]. When applied to the anal canal up to 2.5 cm from the dentate line, the final morphological changes evoke the typical sphincter structure [21]. Only chronic conditions like anal Crohn's disease and distal ulcerative colitis contraindicate the radiofrequency energy delivery to the sphincter complex; the same applies to previous local radiotherapy.

The study has several weak points: the not so high number of cohort women, the open, uncontrolled design, the short follow-up, and assessing relief from stool or gas incontinence only through questionnaires, subjective and liable to a placebo effect. The bias linked to the uncontrolled placebo effect might be most disruptive, as it is likely with any condition that severely impacts everyday life. Baseline FI clinical severity was also not dramatic. However, the study in no way claims to demonstrate efficacy once for all and to establish a new FI

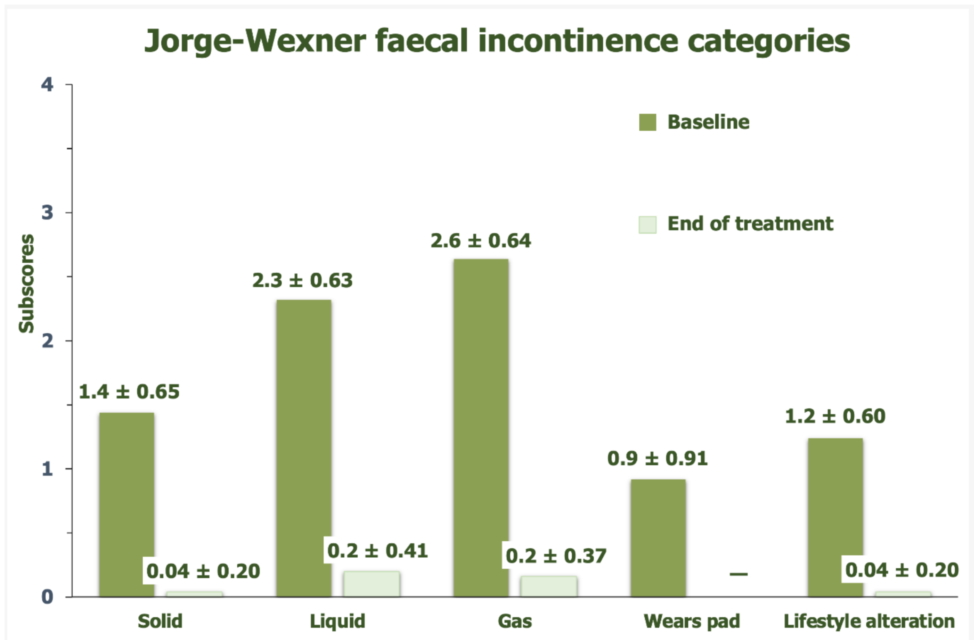

Figure 3. Jorge-Wexner FI category subscores at the end of the individual DQRF™ + UPR™ treatment cycles, mean ± SEM; p <0.01 vs baseline for all five category subscores.

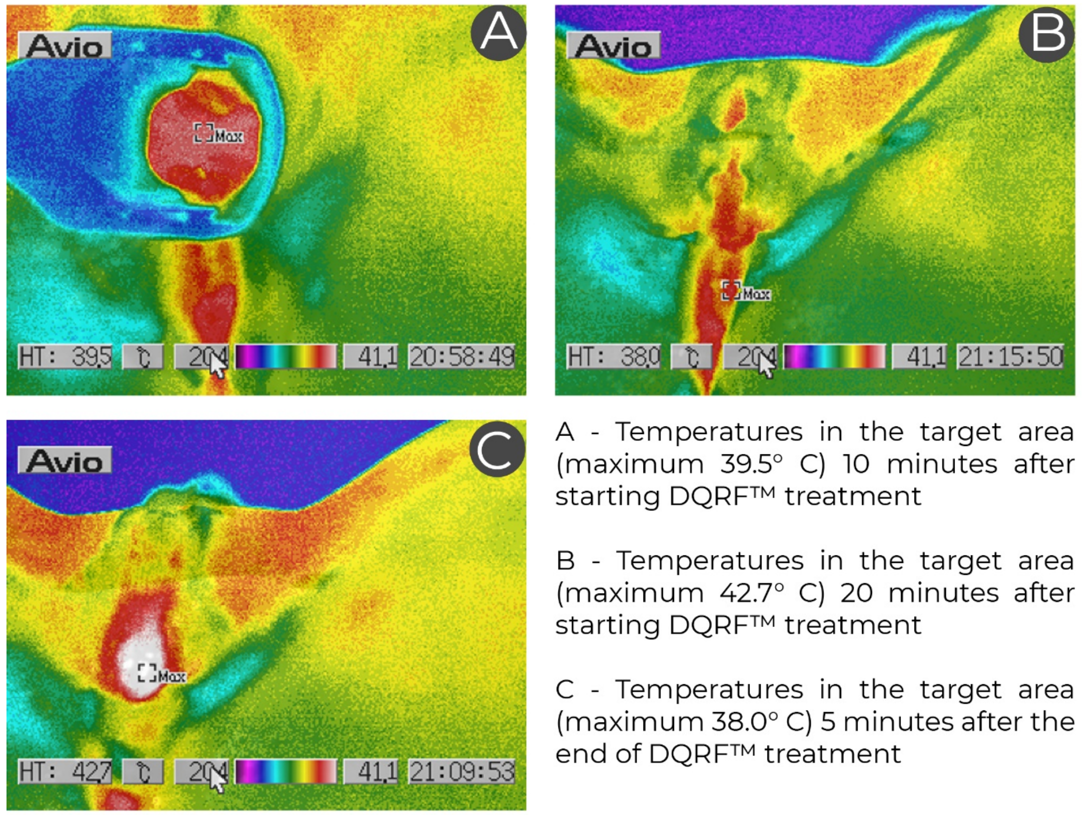

Figure 4. Sequential infrared photographs over 20 minutes in the perineal and vulvovaginal areas during a DQRF™ remodelling session (dorsal lithotomy position), Source: Novavision Group Spa Research & Development.

management standard. Exploring how sound is the rationale of non-invasively delivering radiofrequency energy to the sphincter complex was the sole aim—successfully reached, with 60% cohort women reporting complete FI control without untoward effects on the end of the DQRF™ + UPR™ sessions. The tendency for the residual, occasional (grade 1) loss of stool or gas in a few women at the end of the treatment cycle waned further at the follow-up visit after one more month.

Although needing caution because possibly prone to placebo effects and because coming from a small cohort, these exploratory outcomes will be most helpful to dimension the future trials that will give the definitive answer about how much effective is DQRF™ + UPR™ in faecal incontinence. Hopefully, future, well-designed studies will confirm the highly favourable subjective outcomes of this exploratory study over the long term. At least as significantly, well-designed studies will demonstrate that anal manometry and anorectal ultrasound improvements are steady over time. According to the most respected international scientific societies like the American Society of Colon and Rectal Surgeons and the American College of Gastroenterology, those crucial requirements are still unfulfilled by the currently available, minimally invasive radiofrequency technologies [22]. For the moment and waiting for more strong support, the DQRF™-based device lack of invasiveness looks like a definite benefit over existing radiofrequency technologies in FI management.

Acknowledgements

Novavision Group SpA, Italy, is the worldwide patent holder of the DQRF™ and UPR™ technologies and the DQRF™-based devices. The authors wish to acknowledge Novavision Group SpA for their support with the publication costs.

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Pilot experience of non-invasive delivery of radiofrequency energy in patients with pelvic hypertonia. A novel second-generation technology

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Abstract

Introduction: The pelvic floor dysfunction leading to muscle hypertonia is often idiopathic, but sometimes recognisable disorders may explain the steadily increased pelvic muscle tone in women and men. If tissue temperatures remain below 42°C, radiofrequency technologies induce pain relief and muscle relaxation, probably through neuromodulation, without heat-induced tissue damage. The Dynamic Quadripolar Radiofrequency™ (DQRF™) technology has the further benefit of being non-invasive. The paper reports on the outcomes of the first real-life exploratory study with the DQRF™ technology, combined with radioporation of lenitive and pro-trophic agents (UPR™), in subjects with pelvic floor muscle hypertonia.

Methods: Office-based, prospective pilot cohort study in 31 subjects with painful posterior pelvic floor muscle hypertonia, 20 women and 11 men 23 to 60 years old, without discriminating between idiopathic or secondary pelvic floor hypertonia. The DQRF™ device incorporates a novel flat probe ergonomically designed for the radiofrequency treatment of the posterior pelvic floor and anorectal areas. Assessments, at baseline (first treatment session) and end of treatment (last treatment session): carried out according to the validated criteria for pelvic floor dysfunction (IUGA/ICS Joint Report on the Terminology for Female Pelvic Floor Dysfunction); 10-cm VAS for pain; yes/no for evidence of constipation.

Results: Normal voluntarily and involuntarily muscle contraction and relaxation at the end of the planned DQRF™ treatment cycle; no loss of benefits over the following weeks and months thanks to the satisfactory compliance to the prescribed at-home exercise and massage program. Pain at the end of the treatment cycle: –83.9% vs baseline.

Conclusions: A short cycle of weekly, non-invasive DQRF™ + UPR™ sessions controls pain and the obstructed defecation syndrome effectively in subjects with idiopathic and non-idiopathic pelvic floor muscle hypertonia. The preliminary DQRF™ + UPR™ relaxation of pelvic muscles also facilitates all following physiokinetic therapies.

Abbreviations: ATF3: Activating Transcription Factor 3; DQRF™: Dynamic Quadripolar Radiofrequency™; MDa: x10^6 dalton; MHz: Megahertz; PRF: Pulsed RadioFrequency; SEM: Standard error of the mean; UPR™: Ultra-Pulsed Radioporation™; VAS: Visual Analogue Scale

Introduction

The factory production line has its times: has the long habit of self-imposed prolonged holding of urine or stool and the stress to avoid involuntary bowel or bladder incontinence led to Mary's current nonrelaxing pain dysfunction? Alternatively, the fault may have been Mary's longstanding atrophic vaginitis: she never wants to displease her partner, but more and more frequently, she has felt dyspareunia to trigger the involuntary muscle contraction of the pelvic floor. Perhaps, those painful moments of intimacy have perfidiously led to her current persistent pelvic hypertonia and chronic pain [1,2].

Jane's and Elizabeth's cases are seemingly less ambiguous: a transvaginal mesh kit placement a few years ago to correct Jane's urinary incontinence and endometriosis for Elizabeth [3]. Similarly, Helen's pelvic floor hypertonicity seems related to her interstitial cystitis/bladder pain syndrome [4]. Somehow all those conditions lower nociceptive thresholds and led to neuropathic up-regulation, hypersensitivity, and allodynia [5].

What about Richard's similar syndrome? The insidiously developing non relaxing pelvic floor dysfunction, with variable pain and voiding associated with anorectal and sexual dysfunctions, is not a female monopoly. The legs, the hips, the pelvis, and the spine are a single kinetic unit, and possibly Richard's car accident and lumbar spine injury some months ago triggered muscle overcompensation despite his strengthening physiotherapy sessions and his current, chronic and painful non relaxing pelvic floor dysfunction [6].

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***Key words:** pelvic floor muscle hypertonia, dynamic quadripolar radiofrequency™, DQRF™, ultra-pulsed radioporation™, UPR™*

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Often the inciting cause or event remains foggy, and even more so because those factors that often perpetuate chronic pain-depression, anxiety, sleep disorders-often settle in and contribute to the fog [2].

Radiofrequency techniques like mini-invasive Pulsed RadioFrequency (PRF) and non-invasive Dynamic Quadripolar Radiofrequency™ (DQRF™) avoid temperatures in the targeted tissues to rise beyond 42°C, the critical threshold for neuronal damage, and induce pain relief without thermal tissue damage [7]. A neuromodulatory effect might be the underlying analgesic mechanism. Revealing are the increased expression of the early gene c-Fos in pain-transmitting small-diameter axons (C and A-delta fibres) in the dorsal spinal horn, a marker of enhanced neuronal activity, and the Activating Transcription Factor 3 (ATF3) gene, a marker of cellular stress [8]. Electromagnetic waves in the frequency range 3 to 6 MHz, generating electric fields that oscillate at frequencies of two to three thousand per second, also have a relaxant effect on somatic muscles like the masseter and so, presumably, also on the anal sphincter complex and pelvic floor muscles [9].

However useful, PRF requires mini-invasive needles. The new non-invasive anatomical tip of the EVA™ device, based on the Dynamic Quadripolar RadioFrequency™ (DQRF™) technology, could obviate such limitation, possibly in synergy with the in-depth tissue penetration of active principles via Ultra-Pulsed Radioporation™ (UPR™). The paper illustrates the outcomes of the first study that explored the real-life effectiveness of the novel non-invasive DQRF™ technology in relieving the pain and muscle spasm associated with pelvic floor hypertonia.

Methods

Real-life study design, exploratory rationale, and cohort profile

In the authors' opinion, a small exploratory cohort of subjects with painful posterior pelvic floor muscle hypertonia, prospectively selected among those attending the authors' office, could give a first idea of how effective the non-invasive DQRF™ technology may be in real-world clinical practice. Even if preliminary, the outcomes in such a small uncontrolled cohort could also usefully help to dimension the future well-controlled studies.

Attenuating the muscle hypertonia and related pain was the DQRF™ treatment goal: in fact, a pre-condition to make the following individualised physiotherapy sessions tolerable. Due to the study's preliminary and exploratory nature, the investigators did not discriminate whether the idiopathic forms of pelvic floor hypertonia and the variants associated with recognisable causes answered differently to the radiofrequency treatment. The study remained at a purely symptomatic level.

All study materials were peer-reviewed for ethical problems, and all enrolled subjects gave full written informed consent.

The DQRF™ device

The DQRF™ device used in the study is an adaptation of the DQRF™-based EVA™ device (Novavision Group S.p.A., Misinto, Monza-Brianza, Italy) extensively used to deliver radiofrequency energy non-invasively to gynaecological tissues [10-12]. The DQRF™ device incorporates a flat probe of novel design, ergonomically suited to the posterior pelvic floor and anorectal anatomical areas (Figure 1).

The DQRF™ technology, centred on four stainless steel ring electrodes on the probe, operates at radio wave frequencies between 1.0 to 1.3 MHz and has a maximum emitting power of 55 watts. The DQRF™ device's electrodes steadily cycle between radio wave receiver and transmitter status. The cycling electromagnetic fields confined within the four electrodes and the electric current flows thus generated in pelvic floor tissues eliminate the need for an external grounding pad on thighs or buttocks as required by other radiofrequency technologies.

Figure 1. Evidence of the four-ring quadripolar electrode system and the flat-tipped DQRF™ probe. The system continuously generates variable and dynamically controlled electromagnetic fields within the four electrodes that allows the associated diathermic effect to concentrate in the posterior pelvic floor areas without the need for invasive needles penetrating tissues.

In the ideal configuration controlled by self-regulating automatisms, the confined electric fields so generated concentrate the pain-relieving and muscle-relaxant thermal effect with high topographical precision in the hypertonic posterior pelvic floor muscles and the anal tube while minimising the total energy burden delivered to target tissues and eliminating burn risks. Electronic movement and temperature sensors (RSS™, Radiofrequency Safety System technology) rigidly control temperatures in the targeted muscles and eliminates the need for systemic or local anaesthesia.

The proprietary Ultra-Pulsed Radioporation™ (UPR™) technology [12], used in combination with DQRF™ in the same session, deliver a lenitive and pro-trophic mixture of two-third glucogel and one-third hyaluronic acid (molecular weight, 1.5 to 2.2 MDa, concentration 0.2%), previously spread on the rectal flat tip, to the target pelvic skin and mucosal areas below and above the dentate line. UPR™ acts by opening aqueous channels in cell membranes through modulation of the DQRF™ effects [12].

DQRF™ and pelvic floor massage sessions

The data already available from preclinical investigations with the DQRF™ device in laboratory animals and clinical experiences with other pelvic DQRF™ devices helped identify the DQRF™ program fixed points.

Before each DQRF™ session, the device power was set at 18-20% of its maximum emitting power (about 10 watts) to reach tissue temperatures of 38-39°C in the target pelvic floor muscles. Each DQRF™ weekly session lasted 10 minutes, with the subject in the left lateral decubitus position and the probe steadily inserted in the rectum. The "Tenesmus" proprietary software controlled the 10-min radiofrequency energy delivery to the target hypertonic muscles. The treatment cycles were individually planned between five and ten weekly DQRF™ sessions, always performed according to the ethical standards laid down in the Declaration of Helsinki as revised in Brazil 2013.

To further relieve muscle tension and pain, a massage session by the anal route of the hypertonic pelvic floor muscles followed each DQRF™

sessions. A regular program of at-home respiration and relaxing exercises complemented the office DQRF™ and massage sessions; the regular at-home use of a footstool helped relieve the tension in the puborectalis muscle sling and pubococcygeus muscle during defecation.

Assessments

Muscle tone, trophism, and pelvic floor muscle function-baseline (first treatment session) and end of treatment (last treatment session)

Procedure: digitally in the vaginal introitus to assess the right and left aspects of the levator ani muscle and intra-anally to assess the external anal sphincter and then the puborectalis muscle—the latter distinguishable from other pelvic floor muscles thanks to its insertion on the inferior aspect of the os pubis. According to the International Urogynecological Association (IUGA)/International Continence Society (ICS) Joint Report on the Terminology for Female Pelvic Floor Dysfunction, the following four validated statements define the pelvic floor muscle function (tone at rest and strength of a voluntary contraction) [13]:

"Normal pelvic floor muscles" — Pelvic floor muscles which can voluntarily and involuntarily contract and relax.

"Overactive pelvic floor muscles" — Pelvic floor muscles which do not relax or may even contract when relaxation is functionally needed, for example, during micturition or defecation.

"Underactive pelvic floor muscles" — Pelvic floor muscles, which cannot voluntarily contract when this is appropriate.

"Non-functioning pelvic floor muscles" — Pelvic floor muscles where there is no action palpable.

Always according to IUGA/ICS Joint Report on the Terminology for Female Pelvic Floor Dysfunction, the strength of a voluntary contraction was rated as *"strong"*, *"normal"*, *"weak"* or *"absent"*, and voluntary muscle relaxation as *"absent"*, *"partial"* or *"complete"* [13].

Pain baseline and end of treatment

Standard 10-cm Visual Analogue Scale (VAS) - 0, no pain; 1 to 3, mild pain; 4 to 6, moderate pain; 7 to 10, severe pain.

Constipation associated with the pelvic floor hypertonia baseline and end of treatment

Binary assessment-Yes / No.

Results

The exploratory cohort of ambulatory subjects with painful posterior pelvic floor muscle hypertonia, 20 women and 11 men 23 to 60 years old (mean, 42.3 ± 9.92; median 44.0), was prospectively selected from September to December 2020. At baseline, all subjects showed a picture of *"overactive pelvic floor muscles"* and *"weak"* strength of the voluntary contraction. The posterior pelvic floor muscle hypertonia appeared purely dysfunctional in most subjects (29 out of 31 or 93.6%) with no evidence of anatomical disorders in the pelvic floor region like anal lesions, rectocoele or enterocoele and rectal intussusception or prolapse. Conversely, there was evidence of haemorrhoids and linear fissures in the remaining two subjects.

Voluntary muscle relaxation was *"absent"* at baseline in 20 subjects (64.5%) and *"partial"* in 11 (35.5%). An overall 22 out of 31 cohort subjects reported constipation, or a more correctly defined general obstructed defecation syndrome with specific reference to the two subjects with anal lesions. The mean VAS pain score at baseline was 6.2 ± 1.43 (median, 6.0).

The cohort subjects underwent a mean of 7.4 ± 1.91 DQRF™ plus massage sessions (median, 7.0; range, 5 to 10).

At the end of the individual treatment program, all cohort subjects showed a picture of regular voluntarily and involuntarily muscle contraction and relaxation *("normal pelvic floor muscles")*; the strength of a voluntary contraction was *"normal"* in all subjects but one, who showed a *"strong"* voluntary contraction. The end-of-treatment voluntary pelvic muscle relaxation was *"complete"* in most subjects (Figure 2), whilst no cohort subject reported an obstructed defecation syndrome, including the two subjects with anal lesions at baseline. No subject reported any clinically troublesome worsening of defecation control over the following weeks and months, provided they continued to comply with their at-home plan of self-administered massages and exercises and acceptable defecation practices in daily life. Figure 3 compares the mean pain VAS scores at baseline and end of treatment; 18 cohort subjects (58.1%) reached full pain control (zero pain VAS score) at the last treatment session. No subjects reported discomfort during and after the endocavitary DQRF™ rectal treatment.

Discussion

Subjects with pelvic floor muscle hypertonia frequently show a lost, or at least reduced, control of the levator ani muscle, with uncertain or impossible voluntary contraction and muscle relaxation. Pain is likely to contribute to poor levator ani control. All treatments, including kinesitherapy, aim to eliminate the pelvic pain that impedes daily activities and restore the normal tone and voluntary control of pelvic floor muscles [1,2].

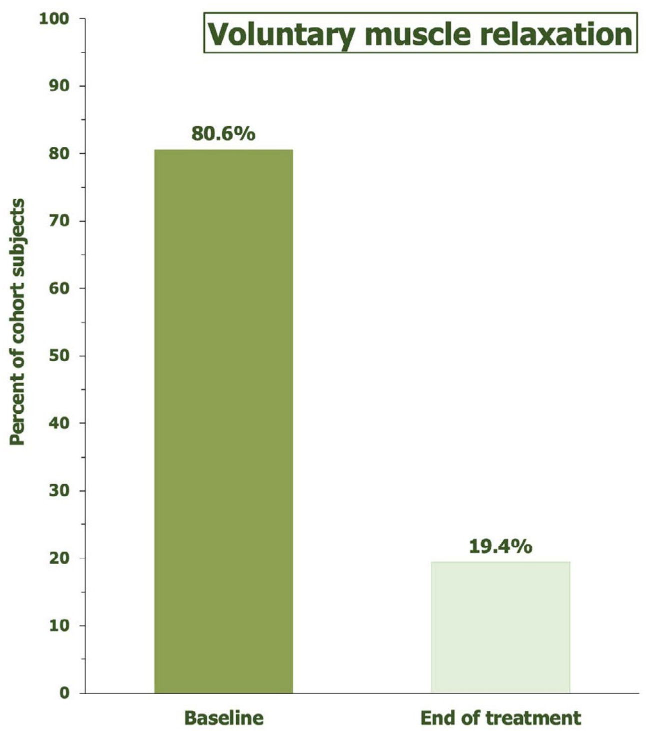

Figure 2. Voluntary pelvic floor muscle relaxation, end of treatment cycle vs baseline **p <0.01 vs baseline.

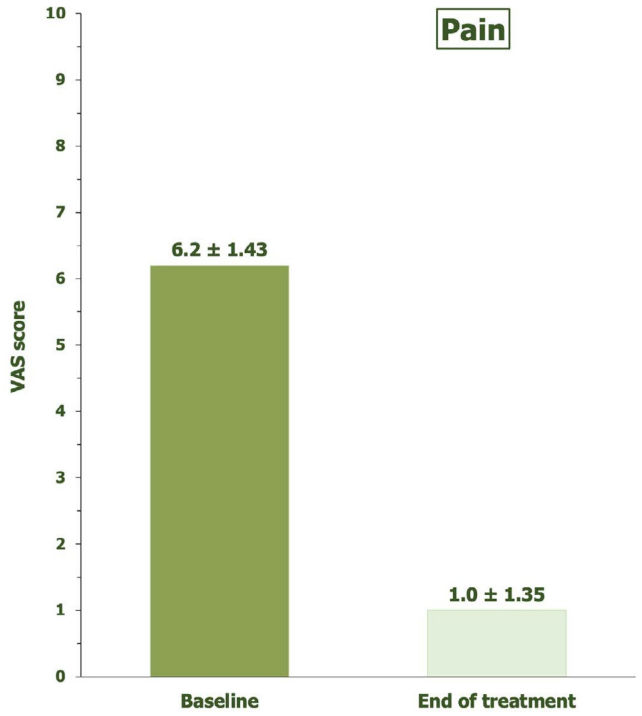

Figure 3. Pelvic pain, end of treatment cycle vs baseline, 10-cm VAS, ** p <0.01 vs baseline.

As a subtype of obstructed defecation syndrome, constipation is also frequent-for instance, in 20 out of the 29 cohort subjects with purely dysfunctional posterior pelvic floor muscle hypertonia. In subjects with dysfunctional constipation, barium defecography could quickly reveal the anorectal angle's failure to increase beyond the resting 90 degrees during defecation straining; standard manometry and electromyography at rest and during squeezing could confirm the functional nature of the pelvic floor musculature dysfunction [14]. In everyday clinical practice, procedures are more straightforward, as happened in the prospective cohort subjects.

The baseline at-rest muscle tone was "overactive", according to the IUGA/ICS Joint Report on the Terminology for Female Pelvic Floor Dysfunction classification, in all cohort subjects. Voluntary pelvic muscle relaxation was also "absent" in more than one-third of subjects; in no case, relaxation was more than "partial", meaning difficulties and shame whenever prompt muscle relaxation is crucial, like during micturition or defecation [13]. The end of the DQRF™ + UPR™ individualised treatment cycle saw a picture largely reversed, with only 24% of subjects still reporting a "partial" voluntary muscle relaxation and no report of constipation or, in general, obstructed defecation syndrome. The pain had also disappeared in more than half cohort subjects.

Quite impressive results indeed, that raise the placebo effect issue. The lack of a (sham-treated?) control group is acceptable in a probing study like this one, conceived as introductory to well-designed and adequately controlled clinical trials, but any outcome is only provisional and aimed at giving an idea of what to expect.

At present, we can definitively say the DQRF™ + UPR™ idea is non-invasive and innovative. We might also say that will it likely benefit subjects with a miserable life because of pelvic floor muscle hypertonia, be it idiopathic and purely functional or secondary to haemorrhoids or similar conditions. Only future well-designed studies compared with the therapies currently accepted as gold standard will define how much useful. Although possibly overestimated by the placebo effect bias, this exploratory cohort study's outcomes will be useful to dimension the future trials that will give the definitive answer about how effectively can DQRF™ + UPR™ counteract pelvic floor muscle hypertonia.

Conclusions

A short cycle of weekly DQRF™ + UPR™ sessions is likely to control pain and the obstructed defecation syndrome very effectively in subjects with idiopathic and non-idiopathic pelvic floor muscle hypertonia, with the benefit of non-invasiveness already firmly established. The preliminary DQRF™ + UPR™ relaxation of pelvic muscles also facilitates all following physiokinetic therapies.

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An exploratory, prospective cohort study of non-invasive dynamic quadripolar radiofrequency energy in vulvar lichen management. The new-generation DQRF™ option

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Abstract

Introduction: The main vulvar lichen treatment goal is itch reduction; improving and preserving the skin integrity and texture, healing the fissures and erosions, and preventing the later disfiguring fibrosis are the other crucial treatment goals. The side effect burden of high-potency topical corticosteroids, the current gold standard, can be heavy and alternative options are welcome. The paper illustrates the first exploratory outcomes in vulvar lichen planus and lichen sclerosus by the latest low-energy technological evolution of radiofrequency treatments, Dynamic Quadripolar RadioFrequency™, in synergistic combination with in-depth penetration of active principles via Ultra-Pulsed Radioporation™.

Methods: Explorative cohort study in 58 ambulatory women 27 to 80 years old, eighteen nulliparous and 26 uniparous, 53.4% in the postmenopausal period. The DQRF™ treatment program mainly aimed at symptom control, with four weekly sessions - 10 minutes over the lichenified vulvar areas and 10 minutes of vaginal rejuvenation even without evidence of lichen vaginal extension. Assessments (baseline and at the end of the treatment cycle): pain and dyspareunia (10-cm impromptu Visual Analogue Scales), vulvar burning (4-score Likert-like impromptu scale), vulvar lesions (binary evaluation - Yes / No).

Results: After a month, vulvar lichen inflammation appeared cooled down, and all cohort women reported dramatic improvements in daily and sexual symptoms - variable between -81.2% and -92% for pain, burning and itching, and -83% for dyspareunia.

Conclusions: Control of lichen inflammation, as documented by sequential photographs, is likely the rationale behind the very favourable outcomes after DQRF™ + UPR™ treatment. Well-designed comparative studies are critical to defining the role of the novel radiofrequency technology in vulvar lichen management.

Abbreviations: IFNγ: Interferon-gamma; CCL4, CCL5, CXCL9, CXCL10, CXCL11: Members of the 28-strong CC or ß class of chemokines; CXCR3, CCR5: Members of the ten known chemokine receptors (CCR1-10); CD4(+): T helper cells; CD8(+): Cytotoxic T cells, suppressor T cells; DQRF™: Dynamic QuadripolarRadioFrequency™; FOXP3: Forkhead box P3 (or scurfin, immune-tolerance related protein); IL-8: Interleukin-8; MDa: x106 dalton; mRNA: messenger ribonucleic acid; NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells; SEM: Standard error of the mean; TGFβ: Transforming Growth Factor beta; Th1: Type 1 T helper (Th1) cells; UPR™: Ultra-Pulsed Radioporation™; VAS: Visual Analogue Scales; VLP: Vulvar Lichen Planus; VLS: Vulvar Lichen Sclerosus

Introduction

Chronic (≥6 weeks) skin pruritus troubles about 20% of Europeans; in 5% to 10% of them, the itching involves the vulva and female genitalia [1]. After candidiasis, the most common causes of vulvar pruritus are chronic dermatoses, including vulvar lichen sclerosus (VLS), vulvar lichen planus (VLP), and vulvar eczema [1]. VLS may account for up to one in 70 diagnoses by general gynaecology practitioners with diagnostic experience in VLP and VLS, yet the lag between symptoms and diagnosis, ranging from 5 to 15 years, suggests VLS is underdiagnosed or misdiagnosed for years [2,3].

The link joining VLS and VLP is histopathology—the combination of a closely applied, band-like lymphocytic infiltrate and basal layer degeneration seen as apoptotic bodies, vacuolar change and squamatisation, which goes under the name of lichenoid reaction [4]. If the lichenoid reaction is associated with sawtooth-like rete ridges or acanthosis, the clinical variant is classic VLP; the clinical phenotype is erosive VLP if there is also a thinned or eroded epithelium. When the acanthosis is marked and associated with parakeratosis or hypergranulosis, the lichen variant is hypertrophic VLP. The evidence of multifocal or diffuse homogenised collagen in the papillary dermis signals VLS [4].

The well-demarcated, glazed erythematous lesions of erosive VLP, possibly with hyperkeratotic borders, usually distribute on the non-keratinised squamous epithelium of labia minora and vestibule, but vaginal extensions and even vaginal scarring and adhesions are not unusual. The keratinised vulvar skin is the site of the spontaneously

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resolving, pruritic and multicolour papules and plaques of classic VLP and the thick violaceous plaques of hypertrophic VLP [4].

Conversely, the patchy, thin, glistening, ivory-white lesions, showing the Koebner phenomenon, of early VLS distribute over the labial, perineal, and perianal areas but spares all mucosal areas beyond the hymenal ring. Progressive pruritus is the leading symptom of a symptom cohort quite extended even in the early phases - vulvar burning, dyspareunia, apareunia, anorgasmia, dysuria, and genital bleeding [5]. The longer-term evolution is devastating: bleeding skin cracks and painful sore areas with secondary infections, scarring and narrowing of the vaginal introitus with flattening and loss of labia minora, burying of the clitoris up to clitoral phimosis and loss of all chances of gratifying intimacy, urinary retention with overactive bladder and stress urinary incontinence, and anal stenosis, obstruction, and constipation [5].

The first goal of therapy is reducing the itch; the second one is improving skin integrity and texture. Fissures and erosions must heal for the woman to resume everyday activities and enjoy once again a gratifying sexual life; unfortunately, the disappearance of all whitening is impossible and cannot be an explicit therapy goal. Preserving the vulvar architecture and preventing disfiguring changes are the third therapy goal [6]. Early and aggressive treatment with super-potent clobetasol propionate-like or potent mometasone furoate-like topical steroids, the usual therapeutic gold standards, may halt the progression and even induce regression, but local and systemic steroid side effects may be troublesome. Moreover, only about two-thirds of VLP and VLS patients comply with topical steroid therapy recommendations [7].

A new advanced radiofrequency-based vulvar remodelling strategy could overcome such side effect and compliance problems. The paper illustrates the first outcomes in a real-life exploratory pilot study in VLP/VLS patients with the latest technological evolution of radiofrequency treatments - Dynamic Quadripolar RadioFrequency™ (DQRF™) combined with glucose gel/hyaluronic acid Ultra-Pulsed Radioporation™ (UPR™).

Methods

Real-life study design, exploratory rationale, and vulvar lichen cohort

The study, aimed at symptom control and quality of life improvement in everyday life, including dyspareunia and overall discomfort during sexual activity, was carried out between November 2019 and November 2020 in an ambulatory setting, under the authors' responsibility and insurance coverage, in a prospective cohort of 58 successively enrolled women 27 to 80 years old. To improve the women's intimate life and control any vaginal lichen extension, the DQRF™ treatment, using a coupling gel, also extended to the vaginal mucosa behind the hymenal ring, onto an area of about 20 cm^2 as previously described [8,9].

In the investigators' opinion, the study nature as the first exploratory assessment of the DQRF™ and UPR™ technologies in treating vulvar lichen allowed for an uncontrolled prospective cohort design and simplified clinical scoring.

Inclusion criteria were a negative Papanicolau test and a VLP or VLP diagnosis certified by vulvoscopy and vulvar biopsy of sclerotic areas. Women candidate for enrolment should not have co-morbidities, including neoplasia, nor should have received conservative or invasive treatments including vulvectomy, cryosurgery and laser ablation. All enrolled women agreed, by signing an individual informed consent form, to the anonymous collection of their data and photographic evidence; they also agreed to the publication of study outcomes. All study materials were peer-reviewed for ethical problems, and the authors always safeguarded the full respect of the ethical standards laid down in the Declaration of Helsinki as revised in Brazil 2013.

DQRF™ and UPR™ technologies and vulvar lichen

The DQRF™-based EVA™ device (Novavision Group S.p.A., Misinto, Monza-Brianza, Italy), with its patented dynamic quadripolar technology and algorithmically controlled energy delivery to the gynaecological target areas, was previously described [8-10]. The four medically certified AISI 316 stainless steel dynamic quadripolar electrodes, mounted on the ergonomic probes of the DQRF™ devices, steadily alternate between radio wave receiver and transmitter states with emitted frequencies in the range 1.0 to 1.3 MHz. The repelling electric fields so generated, when in the ideal configuration, concentrate the radiofrequency energy and the low-energy thermal effect in the subepithelial structures of the vulva and vaginal mucosa with high topographical and tridimensional precision. There is no need for a grounding pad because electric fields arise only within the closed and electronically controlled electrode system.

The energy emission settings were different to allow the control of local tissue temperatures in the vulvar lichen areas and the vaginal mucosa - between 8% and 10% of the device maximum, or no more than 5.5 watts out of a maximum of 55 W, onto the vulvar target areas leading to subepithelial vulvar temperatures of 38 to 39° C, and between 10% and 14% of the maximum, or no more than 7.7 watts, onto the vaginal mucosa leading to subepithelial vaginal temperatures of 39 to 41° C. The back and forth and circular movements over the vestibule, labia minora, and the commissure were rapid to avoid pain; the total DQRF™ energy delivery lasted 10 minutes onto the lichen vulvar areas, 10 minutes onto the vaginal mucosa.

Before the procedure, the only preparation was an alcohol-free cleanse with no analgesia or local anaesthesia (the DQRF™ technology distinctly reduces Ohm's resistances in tissues). Figure 1 illustrates the EVA™ device and its vaginal and vulvar probes with DQRF™ electrodes. The procedure is performed with the woman on the examining table in the dorsal lithotomy position.

Patented movement and temperature sensors (RSS™, Radiofrequency Safety System, proprietary technology) equip the

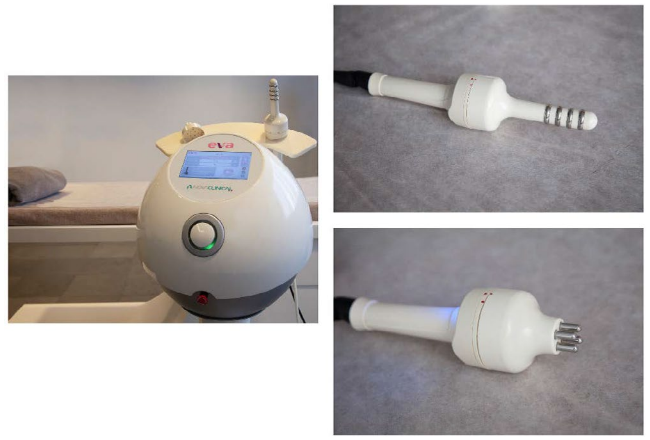

Figure 1. On the left: the EVA™ device with its double set of DQRF™ tips. Right upper photograph: evidence of the handpiece with the elongated, anatomical vaginal probe and its four stainless steel ring electrodes; right lower photograph: handpiece and vulvar probe; the electrodes are in a planar configuration

device to maximise safety. The device also exploits the proprietary UPR™ technology to deliver a lenitive and pro-trophic mixture of two-third glucose gel and one-third hyaluronic acid (molecular weight, 1.5 to 2.0 MDa, overall concentration 0.2%), previously spread on the probe tip, to the target vulvovaginal areas [9].

Timing of DRRF™ + UPR™ sessions and lichen assessments

The cohort women underwent four weekly DQRF™ + UPR™ sessions, complemented by at-home self-administered perineal massage sessions.

Lichen assessments, performed before the first treatment session (baseline, T0) and at the end of the treatment cycle (T1), used 10-cm impromptu Visual Analogue Scales (VAS) for pain and dyspareunia, impromptu 4-score Likert-like scale for vulvar burning, and baseline and end-of-treatment photographs to highlight lichen lesions and their persistence.

A consolidation program (a monthly DQRF™ + UPR™ session repeated for three months) and a long-term maintenance program (cycles of four DQRF™ + UPR™ sessions repeated every six months) followed the end of the treatment cycle.

Results

On average, the 58 cohort women were 49.4 ± 14.75 years old (range 27-80 years old, median 50; 31 or 53.4% postmenopausal women), and the mean parity was 0.95 with 18 nulliparous, 26 uniparous, and 14 multiparous women. Forty-five women exhibited VLP or VLS lesions at baseline, with an overall heavy symptom burden—mean subjectively assessed pain score of 8.5 ± 1.65 out of 10 (median, 9), and burning and itching scores of, respectively, 2.5 ± 0.63 and 2.3 ± 0.69 out of 3 (medians, 3.0 and 2.0, respectively). The emotional impact on sexual life was also severe, with a mean baseline dyspareunia score of 8.8 ± 1.55 out of 10 (median, 9.5). Figure 2 illustrates the subjectively reported improvements of symptoms and dyspareunia after the DQRF™ + UPR™ treatment cycle; Figure 3 some representative documentation of the VLP and VLS evolution between baseline and the end of the DQRF™ + UPR™ treatment cycle.

When informally questioned during follow-up visits, most women reported a less troublesome daily life and gratifying subjective sensations of more hydration and more tissue elasticity already after the first DQRF™ + UPR™ treatment session. Vulvar inflammation, visible in 45 cohort women out of 58 at baseline, had disappeared in all

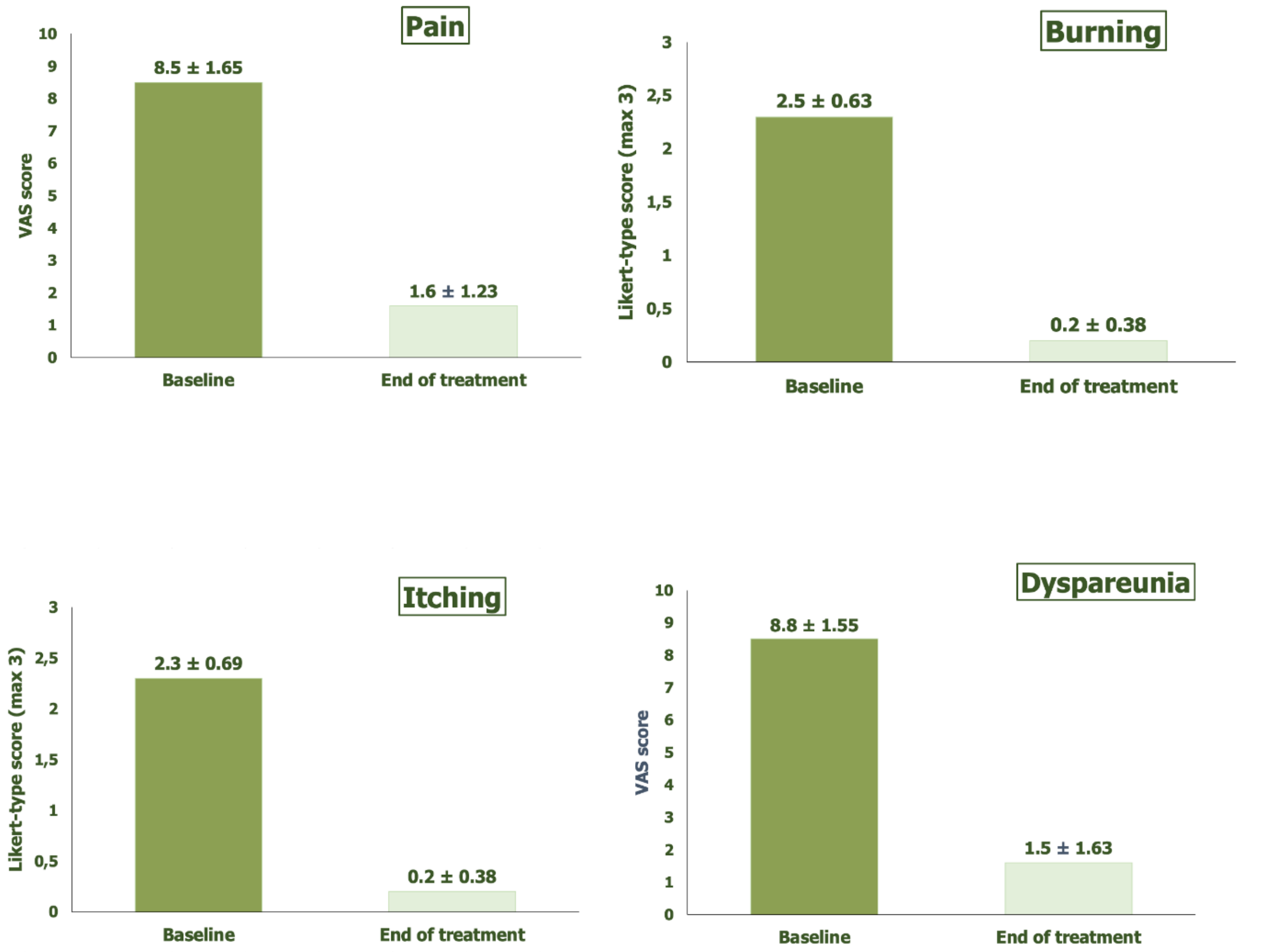

Figure 2. VLP and VLS symptom scores, end of treatment cycle vs baseline. Pain and dyspareunia: 10-cm VAS, burning and itching: impromptu 0-3 scale; for all comparisons: $p < 0.01$ vs baseline)

Figure 3. Representative examples of the vulvar morphology at baseline (photographs on the left) and the end of the DQRF™ + UPR™ treatment cycle (photographs on the right) with marked reduction of inflammation (VLS, vulvar lichen sclerosus; VLP, vulvar lichen planus)

women at the end of the treatment cycle. No woman reported burns, blisters or other fastidious side effects, neither during the ambulatory treatment sessions, always described as relaxing and comfortable, nor over the following days or weeks.

Discussion

Both VLP and VLS are T-cell-mediated chronic skin disorders and show a typical autoimmune phenotype, with a profile of increased pro-inflammatory cytokines - IFNγ, CXCR3, CXCL9, CXCL10, CXCL11, CCR5, CCL4, and CCL5 - signalling an IFNγ-induced Th1 immune response. Immunohistochemistry, showing a high density of CD4(+), CD8(+), and FOXP3(+) cells in the band-like lichenoid reaction in both conditions, confirms the strong T-lymphocyte response [11].

Symptom control and improvements in life quality rather than the impossible definitive cure are the treatment goals, exemplified by topical corticosteroids as still the therapeutic gold standard [6]. Many factors influence the compliance with topical steroid therapy—the greasy feeling and inaesthetic nature of ointments and creams, the trouble and confusions possibly associated with the variable dosing regimen over the early weeks and the shift to twice-weekly maintenance. Likewise, the ambiguous dosing instructions such as the vague "apply sparingly", the complicated application technique on medial labia majora, inter-labial folds, both sides of labia minora and the perineum and not only "white" areas do not help compliance. Prompt relapses and flare-ups in most women, when overlooking the twice-per-week routine, are also liabilities of the gold standard topical steroid therapy [7]. All these are potent inducers to find alternatives to control VLP and VLS symptoms - effective and well-tolerated over an indefinite long term.

As known since 2004, thermal changes in collagen conformation and collagen denaturation induces neocollagenesis in the deep layers of the skin and subcutaneous tissues, signalled by the increased steady-state expression of collagen type I messenger RNA [12]. In the frequency range used in this exploratory study, radiofrequency may have other, possibly non-thermal effects of more prominence in lichen-like chronic inflammatory conditions—reduced keratinocyte proliferation and decreased expressions of TGFβ, NF-κB, IL-8, other pro-inflammatory cytokines and chemokines, and angiogenesis-related inflammatory factors. These other effects are most likely the basis of the improvements observed after radiofrequency treatments in rosacea and acne lesions and scars [13,14].

This study tentatively suggests the combined DQRF™ + UPR™ treatment strategy might indeed be a safe and effective alternative to the corticosteroid gold standard in vulvar lichen. The side effect and discomfort profiles were nil; the same is true for the women's compliance to complete the treatment cycle with no recorded drop-off.

In terms of efficacy, a few DQRF™ + UPR™ sessions cooled down lichen inflammation in all women, as reported by the investigators and documented by sequential photographs; concomitantly, all cohort women scored dramatic improvements in their heavy baseline symptom burden and sexual lives—possibly too dramatic. Together with the open, uncontrolled design and the short follow-up, assessing relief from lichen symptoms only through impromptu, non-validated VAS and Likert-like scales is a critical study weak point with the need for a strong caveat against too hasty conclusions.

Lichen symptoms severely disrupt the daily life and self-image of affected women. However dramatic were improvements over the few study weeks, all reported symptom reliefs were subjective and thus liable to an uncontrolled placebo effect—the main reason why the study can in no way claim to establish a new vulvar lichen management standard. As an exploratory study, it has the only ambition to suggest a rationale for the DQRF™ + UPR™ treatment option. The contributing role of in-depth radioporation of the lenitive and possibly pro-trophic glucose gel and hyaluronic acid is also unclear, whilst there seem to be few doubts about the value of at-home perineal massage sessions as frequently as possible to maintain tissue elasticity.

Well-designed studies must confirm this exploratory study's subjective outcomes over the long term; correctly designed "dose-finding" studies are also critical to define the ideal DQRF™ + UPR™ schedule and how frequently repeat the treatment cycles—yearly? More frequently? Still a question mark. Future studies will also have to explore the biophysics of the DQRF™ anti-inflammatory effect, which presumably is the basis of the rapid and dramatic relief from daily and sexual lichen symptoms enthusiastically hailed by the DQRF™ treated women.

Conclusions

Control of lichen inflammation is likely the rationale behind the favourable outcomes after DQRF™ + UPR™ treatment. Well-designed studies are warranted to define the role of the new non-invasive radiofrequency technology in vulvar lichen management.

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Publishable conflict of interest statement

The authors declare that they have no competing or conflicts of interest relating to what described in the paper.

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Institutional Review board status - Not relevant. The manuscript reports on the real-life prospective treatment of unselected ambulatory subjects (no formal inclusion or exclusion criteria) freely seeking radiofrequency relief from vulvar lichen symptoms and attendant disruption of everyday quality of life. The Clinical Report Form and Informed Consent Forms were discussed and reviewed by peers at the National Health Service territorial facility, where the first author, Dr Vincenzo Prestia, works. The authors performed the study in complete agreement with the Declaration of Helsinki. No unusual risk was reasonably foreseeable in participating subjects other than those incurred with the usual ambulatory radiofrequency procedures routinely performed for vulvar lichen management. In any case, the authors' professional malpractice insurance coverage during private practice activities lawfully protected the subjects from all risks.

Authors' contribution statement

All authors sought and got informed consents from the women subjects seeking radiofrequency treatment because of vulvar lichen problems and enrolled in the study. All women received informed consents about the benefits and risks they could reasonably expect from the DQRF™ procedure. All authors performed all vulvar lichen procedures. All authors are accountable for the clinical and editorial work's accuracy and integrity, leading to the manuscript's submission to Obstetrics and Gynaecology Reports, including all comments on outcomes.

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2 - Cicatrici perineali dolorose: trattamento riabilitativo con RFQD, radiofrequenza frazionata associata al trattamento manuale.

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INTRODUZIONE E SCOPO DELLO STUDIO

Le lacerazioni perineali durante il parto sono eventi piuttosto frequenti, possono verificarsi in modo spontaneo con il passaggio del neonato oppure tramite incisione chirurgica per facilitare il parto. Queste lacerazioni perineali possono esitare in cicatrici fibrotiche, dure, anelastiche e possono trasformarsi in aderenze, formazioni di tessuto fibrotico che uniscono in maniera anomala due tessuti distinti rendendo le cicatrici ipomobili e adese al tessuto sottostante; sono causa di sintomatologia dolorosa e dispareunia. L'obiettivo di questo studio è quello di valutare l'efficacia e la validità del protocollo di trattamento proposto per le cicatrici perineali applicando la terapia manuale sulle cicatrici, associata con l'uso di un dispositivo che sfrutta la radiofrequenza quadripolare dinamica, la radiofrequenza frazionata e la porazione di acido ialuronico.

MATERIALI E METODI

Lo studio è stato condotto su 20 pazienti con lacerazioni spontanee di II e III grado in seguito a parto e conseguente cicatrice dolorosa, rigida e ipomobile. Le pazienti sono state prese in carico a distanza di almeno due mesi dal parto con una media di inizio della terapia riabilitativa a 5 mesi dal parto. Tutte le donne presentavano in anamnesi dispareunia, difficoltà o impossibilità di toccarsi la zona per ipersensibilità e dolore. Il 20% del campione esaminato aveva subito un parto operativo con manovre di Kristeller, tutte le donne presentano una cicatrice vulvare e vaginale. Per la valutazione sono state utilizzate delle scale di valutazione per il dolore, lo stato delle cicatrici e la qualità della sessualità: Vancouver scar scale (VSS), scala NRS (Numerical Rating scale), test Female Sexual Function Index.

Il protocollo di trattamento si è basato sull'uso della radiofrequenza quadripolare dinamica con manipolo interno vaginale ed esterno vulvare associata alla porazione di acido ialuronico, radiofrequenza frazionata sulla cicatrice vulvare associata al trattamento manuale della cicatrice e insegnamento del massaggio per il domicilio. Questo protocollo viene eseguito a cadenza settimanale, con un'applicazione di RFQD di 10 minuti vaginale, 5 minuti vulvare e 15 applicazioni statiche di RFF. È stato valutato a inizio e fine trattamento lo stato delle cicatrici in termini di elasticità e mobilità e il dolore.

RISULTATI

Il trattamento riabilitativo è stato svolto in 5 sedute da un'ora a cadenza settimanale, sono state effettuate valutazioni pretrattamento e alla quinta seduta; sono stati valutati i parametri delle cicatrici, del dolore e del funzionamento sessuale. La radiofrequenza è stata usata allo scopo di migliorare le cicatrici in termini di ossigenazione del tessuto, colore, morbidezza al tatto, la porazione ha contribuito all'elasticità del tessuto fibrotico e alla riduzione dell'ipertrofia cicatriziale, la terapia manuale è stata fondamentale per lo scollamento delle aderenze e per migliorare la mobilità cicatriziale. Il trattamento ha dato ottimi risultati nella riduzione dell'intensità di dolore percepito dalle pazienti in particolare durante le attività quotidiane. È stato osservato un miglioramento in termini di colore, pigmentazione, mobilità e spessore delle cicatrici, abbassando il punteggio della scala VSS da 8 a 3 in sole cinque sedute. La funzionalità sessuale è migliorata notevolmente.

DISCUSSIONE

Grazie alle tecniche di massaggio la cicatrice fin dal primo trattamento risultava più mobile, meno adesa al tessuto circostante. La radiofrequenza e la porazione hanno contribuito ad ottimizzare il processo di guarigione e a rendere la cicatrice più elastica e morbida al tatto, con un aumento della lubrificazione.

CONCLUSIONI

La dispareunia causata dalla cicatrice è molto frequente nel postparto, è importante poter offrire delle strategie per una guarigione veloce di questi sintomi. Questo protocollo di trattamento è stato bene accettato dalle pazienti perché totalmente indolore e confortevole.

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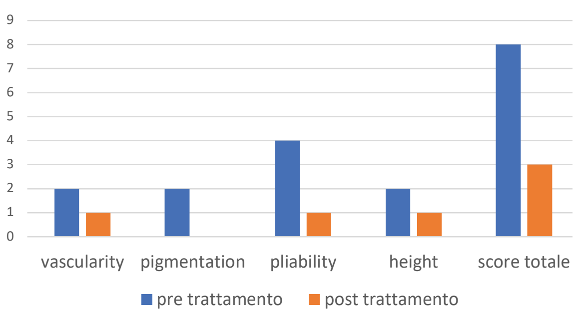
Grafico 1. Miglioramento dello stato delle cicatrici prendendo in considerazione la scala VSS



INTRODUCTION AND AIM

During the delivery perineal lacerations are frequent; The lacerations can be due by the delivery of newborn or surgical incision to facilitate the delivery. These lacerations can evolve into fibrotic, hard, inelastic scars, and then they can evolve into adherens, fibrotic skin tissues that link separated tissues to hypomobile and adherent to the underlying tissue that cause pain and dispareunia;

The goal of the study is to evaluate the effectiveness and protocol validity proposed for the perineal scars: manual therapy on the scars associated to use of dynamic quadripolar radiofrequency, fractioned radiofrequency and poration of hyaluronic acid.

METHODS

20 women with spontaneous lacerations of I and II degrees, caused by delivery, and with painful hypomobile scars. The rehabilitation therapy started average 5 months after delivery. All women suffered from dispaurenia, difficulty/impossibility to touch the interessed area for pain and ipersensitivity.

20% of women had undergone kristeller maneuvers during childbirth and all women had a vulvar and vaginal scar. They are used pain, scar condition and sex quality rating scales: VSS, NRS (Numerical Rating Scale), test Female Sexual Function Index. The protocol of treatment is based on the use of dynamic quadripolar radiofrequency with vaginal and vulval handpieces in association with porated yaluronic acid, fractioned radiofrequency on the vulvar scar associated to manual treatment of scar and home massage instruction. The protocol consists in 1 treatment of dynamic quadripolar radiofrequency per week: 10 minutes with internal vaginal tip, 5 minutes with vuvar tip; then 15 static application with fractioned radiofrequency.

RESULTS

5 sessions of 1 hour per week and evaluations pretreatment and at fifth session were performed; the parameters of scars, pain and sexual function have been evaluated. In relation to scars, the radiofrequency is be used to improve it the oxygenation, the colour, the sensation to the touch. The poration has be use to improve the elasticity of fibrotic tissues, to reduce hypertrophy of scars; the manual therapy has been important to loosening of adhesions and to improve scar mobility. The patients reported a decrease in pain intensity mainly during daily activities. Colour, pigmentation, mobility and thick of scars are improved by lowering the scale score from 8 to 3 in five sessions. Sexual function is much improved.

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Lypidome analysis of cervicovaginal fluid (CVF) in patients with vulvovaginal atrophy under exposure to dynamic quadripolar radiofrequency

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Objective: To study specific features of cervicovaginal fluid lipidome in patients with vulvovaginal atrophy (VVA) in postmenopause under exposure to dynamic quadripolar radiofrequency (DQRF).
Materials and methods: The study included 60 patients aged 46–65 years (the mean age 54.8 (5.1) years) with the symptoms of VVA. All patients underwent treatment: dynamic quadripolar radiofrequency was used in the area of vulva and vagina in group 1 (4 procedures with 2-week intervals); DQRF with radioporation technique with application of cream containing 0.5 mg estriol was used in group 2 (4 procedures with 2-week intervals); and local hormonal treatment with cream containing 0.5 mg estriol was used in group 3 (8 weeks of treatment). Lipid extraction from cervicovaginal fluid was performed using modified Folch method at two-time points – before and 1 month after treatment.
Results: Lipidome analysis compared 3 groups of samples of cervicovaginal fluid– in 40 patients before and after exposure to DQRF and in 20 patients before and after treatment with local estrogens according to treatment regimen. 6 compounds were isolated. Their levels were statistically significantly higher in the group of patients who were exposed only to radiofrequency – Anandamide (18:2, n-6), DG 18:0/18:0/0:0, DG 18:0/16: 0/0:0, LTB4-dimethylamide, N-hydroxy arachidonoilamine, Virodhamin. The levels of Anandamide (18:2, n-6), LTB4-dimethylamide, N-hydroxy arachidonoilamine and Virodhamin were statistically significantly lower in patients who were exposed to radiofrequency in combination with estrogens for treatment of VVA in postmenopause.
Conclusion: This article describes an innovative approach to alternative treatment of women with VVA in postmenopause using DQRF. The results of lipidome analysis of cervicovaginal fluid after exposure to DQRF are published for the first time. Further study and research in the field of high energy methods for VVA treatment are necessary to assess the effectiveness and safety of long term radio wave exposure.

Keywords

vulvovaginal atrophy · genitourinary syndrome of menopause · menopause · radio wave exposure · dynamic quadripolar radiofrequency · lipidome analysis · cervicovaginal fluid

Vulvovaginal atrophy (VVA) is one of the most well-known and widespread physiological processes of reproductive aging. Estrogen deficiency that occurs during the menopause can lead to changes and loss of elasticity of the vaginal wall along with decreased cervical secretions and thinning of the vaginal epithelium [1]. Urogenital atrophy symptoms including vaginal dryness, itching, discomfort, burning worsen with the decreased estrogen levels [2]. VVA is accompanied by painful intercourse and leads to the symptoms and conditions, such as urinary incontinence, urinary urgency, atrophic cystourethritis. Among the patients with VVA, urogenital infections [3], dyspareunia and vaginal bleeding during sexual intercourse are most common, and significantly reduce quality of life for socially active category of women.

VVA is most common in postmenopausal women. Given the fact that the number of women of this age is steadily increasing in modern society, especially in the developed countries, there is a reason to assume that the issue of treatment of VVA will become more and more relevant over time.

According to the study in North America, most women spend approximately 30% of their lives in menopause [4], but there is still no a clear awareness of patients about feasibility and treatment effects of this condition.

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Due to the use of special software for controlled temperature regulation during DQRF exposure, the procedure did not cause burns and other undesirable outcomes.

In our study we suggested that DQRF exposure to the vaginal and vulvar mucosa could change the vaginal metabolome in postmenopausal women with VVA.

The purpose of the study was to investigate specific features of cervicovaginal fluid (CVF) lipidome in postmenopausal patients with VVA under e dynamic quadripolar radiofrequency (DQRF) exposure.

Materials and methods

This prospective interventional study included 60 women.

Inclusion criteria were: the age of women from 45 to 65 years (the average age 54±4.2 years), the length of the time spent in menopause more than 1 year. Exclusion criteria were: unsatisfactory state of the skin and mucosa after previous procedures with laser, pulsed and low-frequency and RF devices used for treatment of fibrosis, thinning skin (parchment-like skin), systemic diseases of the connective tissue, urogenital infections, skin and mucosal injuries in the affected area, current oncological diseases or in the past medical history, precancerous conditions of the vulva, the use of cardiac pacemaker, taking painkillers on the day of the procedure.

The patients with the symptoms of VVA were recruited upon referral to the Department of Aesthetic Gynecology and Rehabilitation of the National Medical Research Center for Obstetrics, Gynecology and Perinatology named after Academician V.I. Kulakov of the Ministry of Health of Russia (further referred to as "the Center") from September 2019 to August 2021. All patients have signed informed consent to participate in the study. The approval of the Ethics Committee for Biomedical Research of the Center was obtained before starting the study.

The women were divided into three groups divided into three groups using spreadsheets of random numbers:

Group 1 received treatment using DQRF exposure to the area of vulva and vagina (4 procedures with 2-week intervals);

Group 2 received treatment using DQRF and Ultra-pulsed Radioporation and application of cream containing 0.5 mg estriol (4 procedures with 2-week intervals);

Group 3 received local hormonal treatment with cream containing 1mg/1g estriol. Dose regimen was vaginal administration of 0.5 mg estriol every other day during 2 weeks (up to 8 weeks).

The patients participating in the study underwent clinical laboratory testing in total test volume.

CVF samples were obtained from all patients before commencing the study and one month after completion of treatment.

Lipids extraction from CVF was performed with modified Folch method: 1000 μL of $CHCl_3$/MeOH 2/1 v/v was added to 200 μl of CVF and kept in ultrasonic bath for 10 minutes. The sample was mixed by Vortex for 10 seconds, then centrifuged for 5 minutes at 15000 rpm. The bottom organic layer (100 μl) was transferred to a separate vial. $CHCl_3$/MeOH 2/1(500 μl) was added to the remaining mixture and centrifuged for 5 minutes at 15000 rpm. The bottom organic layer (100 μl) was transferred to the previosly selected layer and dried by blowing a stream of nitrogen, then redissolved in 200 μl IPA/ACN 1/1 v/v. The purity of chemicals used for extraction was evaluated by LC-MS (Sigma Aldrich, USA).

Lipid extracts were analyzed by using liquid chromatography Dionex UltiMate 3000 (Thermo Scientific, Germany) system, which was connected to Maxis Impact qTOF mass analyzer with an ESI ion source (Bruker Daltonics, Germany). The samples were separated by reversed-phase high performance liquid chromatography using Zorbax SB-C18 column (150×2.1 mm, 5 μm, Agilent, USA) with a linear gradient from 30% to 90% eluent B (solution of acetonitrile/isopropanol/water, 90/8/ 2 o/o /o, with adding 0.1% formic acid and 10 mmol/L ammonium formate) for 20 minutes. Solution of acetonitrile/water (60:40, v:v) with adding 0.1% formic acid and 10 mmol/L ammonium formate were used as eluent A. Eluent flow rate was 40 μL/min, injection volume was 3 μL. Mass spectra were obtained in n positive ion mode (m/z in the range of 100-1700 uma) with the following settings : 4.1 kV capillary voltage in positive ion mode spray gas pressure 0.7 bar, drying gas flow rate 6 L/min, drying gas temperature 200°C.

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Data processing was carried out using software MzMine 3.1 with lipid identification was performed using LIPID MAPS Structure |Database (LMSD). Comparison between the lipid profile by one and two time points using the Wilcoxon test. Comparison of changes in lipid levels after treatment in each group was performed using Mann-Whitney U test. The threshold value for statistical significance was 0.05. Median (Me) and quartiles Q1 and Q3 (Q1; Q3) were used to describe lipid levels, where Me was a median value, Q1 – the value of the first quartile, Q3 – the value of the third quartile. Statistical data processing was performed using R 4.3.1 for Windows (R: A Language and Environment for Statistical Computing) with a set of tools Rstudio (R Studio: Integrated Development for R).

Results

The age of patients included in the study varied from 46 to 65 years and on average was 54.8 (5.1) years. The duration of menopause in patients was from 1 to 18 years and on average was 5.4 (3.3) years. The clinical and anamnestic data of patients is shown in Table 1.

The use of Dynamic Quadripolar Radiofrequency (DQRF) exposure (group 1), the differences in the level of PG 12:0/18:4(6Z,9Z,12Z,15Z) were found in positive ion mode (Table 2).

With combination of DQRF and Ultra-Pulsed Radioporation (UPR) with extragens (group 2), the differences were in the levels of 4 lipids: Anandamide (18:2, n-6), LTB4 dimethylamide, N-hydroxy arachidonylamine, Virodamine) in positive ion mode (Table 4).

Table 1. The clinical and anamnestic characteristics of patients

The groups of patients	Age, years	Body mass index, kg/m²	Duration of menopause (years)
Group 1 (*n*=20)	53.9 (5.1)	23.1 (1.4)	5.3 (3.1)
Group 2 (*n*=20)	55.8 (5.5)	22.1 (1.2)	5.7 (3.5)
Group 3 (*n*=20)	54.9 (4.8)	22.4 (1.1)	5.2 (3.4)

Table 2. The changes in the lipid profile of CVF in exposure to RF in positive ion mode

Lipid	Before treatment	1 month after treatment	*P*
PG 12:0/18:4(6Z,9Z,12Z,15Z)	4.22*10^5 (3.76*10^5;4.57*10^5)	4.61*10^5 (4.06*10^5;5.27*10^5)	0.02

P-value was assessed using the Wilcoxon test.

Table 3. The changes in the lipid profile of CVF in exposure to RF exposure in positive ion mode

Lipids	Before treatment	One month after treatment	*P*
Anandamide (18:2, *n*-6)	4.79*10^5 (2.27*10^5;6.52*10^5)	2.63*10^5 (2.34*10^5;2.84*10^5)	0.03
LTB4 dimethylamide	1.85*10^6 (1.26*10^6;2.76*10^6)	1.23*10^6 (1.17*10^6;1.39*106)	0.005
N-hydroxy arachidonylamine	1.54*10^6 (8.72*10^5;2.53*10^6)	9.05*10^5 (8.55*10^5;9.78*105)	0.006
Virodamine	1.36*10^6 (1.00*10^6;2.95*10^6)	9.85*10^5 (9.38*10^5;1.08*10^6)	0.005

P-value was assessed using the Wilcoxon test.

Table 4. Changes in the lipid profile of CVF in exposure to (DQRF) and UPR radioporation (UPR) with extragens in negative ion mode.

Lipid	Before treatment	One month after treatment	*P*
13E,15E,18Z,20Z- pentacosatetraen-11-ynyl acetate	1.34*10^4 (1.00*10^2;3.12*10^4)	3.26*10^4 (1.00*10^2;3.19*10^5)	0.04

P-value was assessed using the Wilcoxon test.

Table 5. Changes in the lipid profile of CVF in exposure to local extragens in positive ion mode

Lipid	Before treatment	One month after treatment	*P*
LTB4 dimethylamide	1.37*10^6 (1.34*106;1.50*10^6)	1.34*10^6 (1.24*10^6;1.43*10^6)	0.04

P-value was assessed using the Wilcoxon test.

Table 6. Significant difference in lipid levels between group 1 and group 3 after treatment in positive ion mode

Lipids	Changes in group 1 (DQRF)	Group 3 (local estragens)	*P*
DG 18:0/16:0/0:0	-9.27*10^4 (-1.94*10^5; -4.81*10^4)	-1.39*10^4 (-2.60*10^4; -7.89*10^2)	0.03
LTB4 dimethylamide	-6.28*10^5 (-9.42*10^5; -3.30*10^5)	-1.12*10^5 (-1.31*10^5; -3.81*10^4)	0.03
PC 12:0/14:1(9Z)	-1.73*10^7 (-2.47*10^7; -6.45*10^6)	5.36*106 (-6.17*10^6; 1.32*10^7)	0.04

At the same time, in group 3, which was exposed only to extrogens, the differences were in the levels of LTB4 dimethylamide. Also, reduced level of LTB4 dimethylamide was in group 2 (Table 5).

Comparison of treatment results in women in group 1 (DQRF) and group 3 (local estrogens) showed that 3 lipids (DG 18:0/16:0/0:0; LTB4- LTB4 dimethylamid; PC 12:0/14:1(9Z)) were identified in positive ion mode. In group 3, their levels did not change significantly (Table 6). At the same time, the level of PC 12:0/14:1(9Z) changed significantly in group 3 versus group 1.

Comparison of treatment results between group 1 and group 2 showed that 1 lipid – Anandamide (18:2, n-6) was identified in positive ion mode (Table 7), the level of which increased after treatment in group 1.

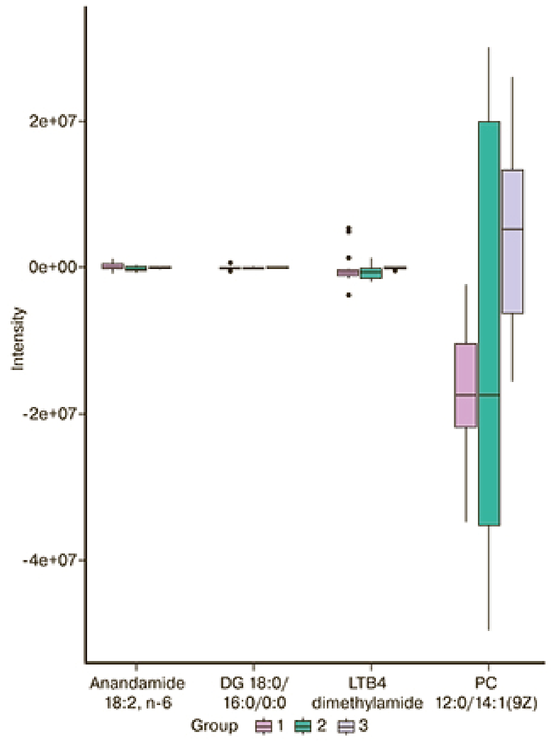
Table 7. Statistically significan changes in the levels of lipids between groups 1 and group 2 after treatment in positive ion mode

Lipids	Changes in group 1 (DQRF)	Changes in group 2 (DQRF + UPR)	*P*
Анандамид 18:2, *n*-6	5.64*10^4 (-1.19*10^4;4.59*10^5)	-2.29*10^5 (-4.14*10^4;4.89*10^5)	0.02

P-value was assessed using Mann-Whitney test.

The boxplot (Fig.) shows that the metabolomic profile after treatment in group 1 differed from the profiles in group 2 and group 3.

Figure. The range of the box plot of changes in the levels of lipids in CVF shows the differences between the groups after treatment in positive ion mode. Interquartile range Q1-1.5 IQR, Q1, Me, Q3, Q3+1.5 IQR



Duscussion

In this study, the differences in the lipid composition of cervicocaginal fluid in women with VVA, who underwent DQRF treatment we found and described for the first time.

Anandamide and virodamine in the lipid profile are of special interest. Significantly increased levels of these lipid were found in patients in patient in group 1, who received DQRF treatment as monotherapy. These substances are derivatives of arachidonic acid, endogenous cannabinoid neurotransmitters, biologically active lipids that activate cannabinoid receptors CB1, CB2.

The cannabinoid-1 receptor (CB1) was primarily indentified in 1990 г., then the cannabinoid-2 receptor 2 (CB2) was identified in 1993 г. The first isolated endocannabinoid was ethanolamide of arachidonic acid, also known as anandamide or arachidonoylethanolamine (AEA), (the word formed from the word "ananda", a Sanskrit word meaning "bliss"). Current data show that the cannabinoid receptors are expressed in cells of the reproductive system, including endometrial stromal cells, vaginal epithelium, ovaries, and spermatozoa. [15]. Intracellular signaling from interaction with the cannabinoid CB1 and CB2 receptors subsequently lead to the regulation of cell growth, proliferation and/or tissue differentiation. Thus, we suggest that improvement of vaginal tissue trophism and increased sexual satisfaction in women, who underwent treatment on the background of reduced incidence of VVA symptoms, among other things, are associated with activation of the CB1 and CB2 receptors. Interesting is the fact that this effect was lower in the groups with the use of local estrogens (estriol).

With the development of evidence-based medicine, it has become clear that the efficacy and safety of systemic hormonal therapy for VVA /GSM is overestimated. First of all, such therapy is not indicated for a number of categories of patients, for example, the patients with hormone-dependent cancer of the reproductive system and breast cancer (including in anamnesis), with normal estrogen levels at high risk of thrombosis, acute or chronic liver failure, myocardial infarction in history and other conditions [16].

Conclusion

The therapy for GSM/VVA by exposure of DQRF is an effective and safe treatment option for women, when hormone therapy cannot be used for one reason or another. Currently, the study is ongoing to assess the safety and duration of the achieved clinical effect.

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PROTOCOL: THERMAL TREATMENT OF VULVO-VAGINAL ATROPHY (VVA) USING NOVEL LOW-ENERGY DYNAMIC QUADRIPOLAR RADIOFREQUENCY (DQRF)

P21

Protocol: thermal treatment of vulvo-vaginal atrophy (VVA) using novel low-energy dynamic quadripolar radiofrequency (DQRF)

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Background: VVA affects 50%–70% of women in their sixties. The treatment includes, administration of topical estrogen (ET). Other treatments that may relieve VVA have emerged such as DQRF using small probes with thermal energy.

Aim: To evaluate safety and efficacy of DQRF for the treatment of VVA in postmenopausal women.

Material and method: Prospective randomized multi- centric study evaluating PH gel (control group) therapy versus DQRF.

Population: Postmenopausal women (40 and 75 years of age) suffering of VVA, defined as vaginal dryness, irritation, itching, pain associated with sexual activity and confirmed by at least one of the following criteria: superficial cells $\leq$5% in the vaginal Maturation Index, vaginal pH > 5. The patient either present contra-indication for ET, or are not willing to use ET or have failed to be helped using ET.

Procedure: Inclusion and exclusion criteria. Information and consent - Ph measurement, description, picture, and smear. At screening & week 10.

Randomization by 3rd party: *Group I*: treated first with a ph gel (self-administrated twice/week) for 10 weeks (control group).Group II: treated with DQRF (VDR™ (Vaginal Dynamic Radio-frequency) and RSS™ (Radio-frequency Safety System) for 8 weeks (+/− 2 weeks) (*n* = 4 sessions Provided that the results are satisfactory and show an improvement of DQRF over ph-gel, the latter treatment will be proposed also to group 1 but delayed by 10 weeks.

Evaluation primary outcome: Co-primary endpoints: change from screening to week 10 of the most bothersome symptoms (recorded as none, mild, moderate or severe), change of vaginal cell maturation, change of vaginal pH. Secondary Outcome Measures: Change from baseline to week 10 of each of the four following signs of atrophy, which constitute together the "vaginal health index", and of the "female sexual function index (FSFI).Statistical analysis Differences between groups will be tested by t test and Mann-Whithney. A sample calculation. We hypothesize an effect size between the two groups of 0.6. The calculated sample size is *n* = 112 (effect size between the groups = 0.6, type I error 2%, power 80%).

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P22

Higher levels of circulating androgens are associated with greater extent of liver fibrosis in postmenopausal women

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Introduction: Ovarian senescence during the menopausal transition is associated with fluctuating estrogen levels, which result into a proatherogenic lipid profile with adverse implication in metabolic function and tendency for central accumulation of weight. Fib4 score is a novel parameter, easily reproducible, which has been shown to predict the extent of liver fibrosis in general population and diabetic patients. We aimed to evaluate potential biochemical and hormonal predictors of liver fibrosis in a large sample of postmenopausal women.

Methods: This cross-sectional study included a total of 996 postmenopausal women, retrieved from the Menopause Clinic of the 2nd Department of Obstetrics and Gynecology, University of Athens, Aretaieio Hospital. The Fibrosis 4 score (Fib4) was used to evaluate the extent of hepatic fibrosis. Fasting blood samples were obtained for biochemical and hormonal assessment. We evaluated the association between Fib4 score values and anthropometric parameters as well as levels as free and total levels of sex hormones.

Results: Women aged 56.8 ± 6.4 years (menopausal age, YSM 1–39 years) with an average body mass index (BMI) of 27.9 ± 4.9 kg/m^2. Fib score values ranged from 0.02 to 4.70. Fib score values correlated with age (r = 0.420, p-value < 0.001), YSM (r = 0.320, p-value < 0.001), waist circumference (r = −0.124, p-value < 0.001), BMI (r = −0.151, p-value < 0.001). Levels of SHBG correlated positively with Fib4 score values (r = 0.200, p-value < 0.001), while an adverse link was observed with FAI (r = −0.146, p-value < 0.001) and FEI (r = −0.207, p-value < 0.001). Multivariate regression analysis showed that Fib4 score values were predicted by FAI levels adjusted (Model R^2 18.3%; FAI, b-coefficient = −0.106, p-value = 0.025), in combination with age and BMI. Similarly, SHBG predicted Fib4 values (Model R^2 19.2%; SHBG, b-coefficient = 0.164, p-value < 0.001), in combination with age and BMI. However, FEI values did not predict Fib4 scores in the multivariate analysis. All multivariate models were also adjusted for YSM, lipids, HOMA-IR, BMI and waist circumference.

Conclusion: We observed an inverse association between androgenicity and liver fibrosis in a large sample of apparently healthy postmenopausal women. Higher levels of circulating androgens and lower levels of SHBG predicted lower fibrosis score.

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Gynaecology

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DQRF
dynamic quadripolar radiofrequency

New Vaginal Rejuvenation Procedure Features Novel Use of RF Energy

By Jeffrey Frentzen, Executive Editor

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As non-surgical, energy-based vaginal rejuvenation procedures explode in popularity worldwide, European practitioners now have a versatile choice in the EVA™ system from Novavision Group S.p.A. (Misinto, Milano, Italy). This unique device employs innovative Dynamic Quadripolar Radiofrequency (DQRF) energy designed to trigger anatomical remodeling in vulvar tissues.

Compared with other non-invasive modalities, the EVA treatment offers a new approach to feminine rejuvenation. "Low-energy DQRF technology provides a novel interaction between the subepithelial layers of the vulva and the energy emitted by the system's RF generator," stated Gianluca Benincà, M.D., a plastic and cosmetic surgeon and professor at L.U.de.S. University of Lugano, Switzerland.

"This procedure is technologically superior," Dr. Benincà continued, noting the system's quadripolar 1.0 MHz to 1.3 MHz DQRF generator. "The four electrodes are continuously electronically cycled between receiver and transmitter states. This high-tech feature conveys energy with solid tri-dimensional precision in the subepithelial layers of the vulva. This is why low-energy vulvar rejuvenation is often pleasant with no downtime. In addition, the risk of burns is virtually eliminated." Furthermore, the EVA's electronically controlled movement and temperature sensors allow the operator to fine tune the vulvar thermal effect in terms of both tissue volumes and depth.

> "As demonstrated retrospectively in my study, this therapy seems to meet or exceed patients' expectations both in terms of subjective aesthetic gratification, as well as self-esteem and impact on daily life."

35-year-old patient with vulvar atrophy before and after one EVA treatment session

To test outcomes, Dr. Benincà conducted a recent clinical study following 25 healthy women that completed four treatment sessions of EVA, with a three month follow-up assessment.

"Working above all on collagen and elastin fibers as we know from the scientific literature, this simple procedure guarantees visible and perceived tightening and rejuvenation effects," Dr. Benincà stated. "It demonstrates the efficacy of new DQRF technology when applied to vulvar rejuvenation. Clinical images show the tightening effect is clearly apparent after the first or second treatment session."

In considering the overall biological effects of DQRF technology on patients, Dr. Benincà noted, "The subjectively perceived vulvar aesthetics and the discomfort in everyday life – such as loss of self-esteem, problems with intimate relationships and sex life – are deeply related, and both have been improved by the EVA treatments. Patients expressed gratification for superior vulvar aesthetics, perceived psychological benefits, and the discomfort that improved greatly. The results were both aesthetically and functionally pleasing."

This system is also easy to learn and use, Dr. Benincà expressed. "Additionally, the procedure is free of any serious or disturbing complications," he said. "None of my EVA patients have reported any clinically significant side effects, such as inflammatory states or discomfort during the procedures. As demonstrated retrospectively in my study, this therapy seems to meet or exceed patients' expectations both in terms of subjective aesthetic gratification, as well as self-esteem and impact on daily life."

The EVA vaginal rejuvenation therapy is safe, comfortable and effective, Dr. Benincà reiterated. "DQRF technology overcomes the unwieldiness and safety problems of conventional light and energy-based vulvar rejuvenation devices. That's why I chose EVA."

Dynamic Quadripolar RadioFrequency
New high-tech, high-benefit strategy for rejuvenation of the hypotrophic ageing vulva

ABSTRACT

Background The wellbeing of the vulva, under heavy influence by sexual hormones during the whole woman's lifespan, and several aspects of the woman's life, including self-esteem, sexual gratification and overall quality of life, are distinctly correlated. The last years have seen an increasing flow of papers and opinions about surgical and non-surgical vulvar rejuvenation techniques. Over the last two years, technologically innovative Dynamic Quadripolar RadioFrequency (DQRF), one of the newest light- and energy-based vulvar rejuvenation technologies, has showed to be an effective option in aesthetic and cosmetic gynaecology that may offer distinct benefits compared with other current technologies.

Objective Qualitative and semi-quantitative evaluation of the short-term vulvar aesthetics efficacy, based on serial photographic documentation, of an accelerated DQRF vulvar rejuvenation program in women with age-related mild to moderate vulvar hypotrophy.

Methods Twenty women with mild to moderate vulvar hypotrophy were prospectively screened and evaluated from June 2016 to September 2017 in the validation study of an accelerated DQRF vulvar rejuvenation program. Serial photographs documented the DQRF aesthetic impact on the treated vulvar area over the 2-month study period. A specialist in aesthetic gynaecology, unaware of the history and demographic details of treated women, rated the overall aesthetic improvement compared with the baseline visual documentation. Assessment times: before the first DQRF treatment session (baseline), before the second DQRF treatment session and 30 days after the third and last treatment of the accelerated DQRF rejuvenation program (follow-up). Assessment tool: Global Aesthetic Improvement Scale (GAIS) modified as a semi-quantitative rating tool (10 scores); the baseline visual documentation was also scored. Complication and side effects were recorded.

Results All women successfully underwent the three planned DQRF procedures spaced 7 to 10 days. Symptoms of vulvar hypotrophy and aesthetics of the vulvar area were already improving in most women after the first DQRF session and improvements in vulvar aesthetics were persistently highly significant one month after the end of the DQRF rejuvenation program — evaluator's GAIS scores: 2.6 ± 0.63 (baseline) vs. 3.4 ± 0.94 (before second treatment session, $p < 0.05$ vs. baseline) and 8.1 ± 0.79 (follow-up assessment, $p < 0.01$ vs. baseline); treated women's scores: 4.7 ± 1.15 (baseline) vs. 6.8 ± 0.94 (before second treatment session, $p < 0.05$ vs. baseline) and 8.6 ± 0.79 (follow-up assessment, $p < 0.01$ vs. baseline). No complications or side effects occurred.

Conclusions DQRF rejuvenation of labia majora and surrounding areas has confirmed to benefit vulvar aesthetics with a technically simple outpatient procedure and virtually no complication or side effect. In women with mild to moderate hypotrophy, this is possible with a rapid rejuvenation program of shortly spaced sessions.

Key words Ageing vulva, radiofrequency, vulvar rejuvenation, aesthetic gynaecology.

INTRODUCTION

Vulva is a complex organ and an in-depth appreciation of the functional anatomy of this interesting area is crucial.[1] Women's external genitalia need steady oestrogen stimulation to maintain their normal structure and function. Alpha- and beta-oestrogen receptors, widely distributed all over the vulva during reproductive life, decline with ageing.[2] Lack of oestrogens in dermal layers contributes to loss of elasticity by inducing fusion and hyalinisation of collagen and fragmentation of elastic fibres; [3,4] mucosal hydration is also negatively affected by reduction of matrix mucopolysaccharides and hyaluronic acid.[5,6] Macroscopically, the mucosa of introitus and labia minora becomes thin and pale, while the reduced vascularisation, quite evident microscopically, translates into decreased volume of transudates and other secretions.[7,8]

Intimate trophic modifications deeply impact on the woman's sexual life, self-esteem and quality of life, as shown in several recent studies.[9-11] Awareness of these problems is growing; indeed it is happening today what the authors of the International Vagina Dialogue Survey predicted almost ten years ago — women are no longer shameful to discuss and get information about their intimate trophic problems.[12] The social impact of ageing-related vulvar problems will be even more severe in the next future. The world in 2025 will host 1.1 billion women older than fifty:[13] it is crucial for gynaecologists, aesthetic physicians and plastic surgeons to be up to date with the latest developments in vulvar rejuvenation technologies.

The interest about vulvar rejuvenation procedures is indeed rising.[14] According to the American College of Obstetricians and Gynecologists, aesthetic and cosmetic procedures aimed at the vulvar area have been showing double-digit growth in the United States over the last years, even in young and sometimes adolescent women.[15] The American Society for Aesthetic Plastic Surgery reported a total of 8,745 labiaplasty procedures performed in 2015, or 15% more than the previous year.[16] Most techniques — wedge resections [17,18], edge resections, Z-plasties or modified resections [19] — target the skin redundancy (hypertrophy) of labia minora. Fewer techniques have been developed for vulvar skin hypotrophy: augmentation of labia majora through grafting of adipose tissue [20,21] or hyaluronic acid fillers [22,23] are but some of the few examples.

Due to non-invasive nature and simpler management, more and more attention is being devoted to light- and energy-based technologies like monochromatic laser radiation and radiofrequencies.[24] The rejuvenation key is thermal activation of fibroblasts, leading to anatomical remodelling of vulvar and vaginal tissues as shown with both electromagnetic and laser radiation.[24-26]

Low-energy Dynamic Quadripolar RadioFrequency (DQRF) is the most recent in a large group of emerging biophysical technologies aimed at rejuvenation of vulvar tissues. Developed by the Italian company Novavision Group S.p.A. (Misinto, Monza-Brianza, Italy), the DQRF innovative technology is at the core of the EVA™ device.

The DQRF innovation revolves around the peculiar interaction between the subepithelial layers of the vulva and the energy emitted by the four electronically controlled dynamic electrodes of the radio frequency generator. These electrodes sequentially act as receivers and transmitters and continuously generate variably repelling electrical fields. DQRF biophysics allows the operator to define with high three-dimensional precision the subepithelial vulvar volume that should receive energy. The burden of administered energy is strongly reduced thanks to lack of dispersion in tissues adjoining the target area; electronically controlled movement and temperature sensors (RSS™, Radiofrequency Safety System, technology) facilitate the rigid control of tissue temperature when the DQRF-based EVA™ device is operative.[28,29] Clinical studies have already demonstrated the safety and efficacy of the DQRF technology in relieving bothersome intimate symptoms in women with post-delivery vaginal laxity and post-menopausal vulvo-vaginal atrophy and genitourinary syndrome; other studies are currently being published and planned.[27-29]

As regards age-related vulvar hypotrophy and a more aesthetic and cosmetic gynaecology perspective, a proprietary four-session "EVA™ Vulvar Rejuvenation" protocol is already validated in women with mild to severe vulvar hypotrophy.[27] This further pilot study was designed to evaluate the efficacy of a program of DQRF vulvar rejuvenation sessions with a more compressed time frame in women with mild to moderate hypotrophy.

MATERIALS AND METHODS

A prospective cohort of 20 women with signs and symptoms of mild to moderate vulvar hypotrophy were screened and enrolled in the study between June 2016 and September 2017. At screening, the candidate women's hypotrophy was staged according to the clinical classification used in the authors' department (mild or early, moderate and severe; Table 1).[23] This staging classification takes into consideration both the skin layers and the subcutaneous adipose tissue.

	Subcutaneous Layers	Cutaneous Layers	Symptoms
Stage I Mild (Early)	Mild hypotrophy; distribution of adipose tissue is usually symmetrical	None to mild cutaneous hypotrophy; thin wrinkles may be visible	Usually asymptomatic, may follow a weight loss
Stage II Moderate	Moderate hypotrophy; distribution of adipose tissue may be asymmetrical	Moderate cutaneous laxity, dermatochalasis; visible wrinkles	Dryness, dyspareunia and soreness may be observed
Stage III Severe	Severe hypotrophy; adipose tissue is frequently distributed asymmetrically	Severe dermatochalasis and deep wrinkles	Usually associated to symptoms like dryness, dyspareunia and soreness

Table 1 Classification of labial hypotrophy adopted in the authors' department.[23]

All patients included in the study provided written informed consent to anonymous collection of their data before the first DQRF session and all study materials were peer-reviewed for ethical problems. Inclusion criteria at screening: signs and symptoms of mild to moderate vulvar hypotrophy (Stage I and II), premenopausal age, normal BMI (18.5 to 24.9 kg/m^2), regular sexual activity, cosmetic indication to treatment. Exclusion criteria: severe Stage-III vulvar hypotrophy, previous surgery on external genitalia, history of vulvar cancer, acute or chronic vulvar disorders including dermatitis and sexually transmitted viral infections, poor sensitivity to pain or heat, immune depression, uncontrolled diabetes mellitus, urinary tract or sexually transmitted infections, moderate or severe pelvic organ prolapse, bleeding diathesis. Candidate women being treated with anti-coagulant and immunosuppressive drugs or radiant therapy were also excluded. Demographic data including evidence of premenopausal syndrome and pharmacologic treatments were recorded. All women were treated according to the accelerated EVA™ Vulvar Rejuvenation protocol that is being validated in this pilot study (Table 2B).

DQRF "EVA™ VULVAR REJUVENATION" TRREATMENT PROTOCOLS

(A) Validated proprietary protocol [27]

- Four 10-min sessions, spaced 14-16 days
- Setting of the radiofrequency generator: 1 MHz
- Operating power: 8-14% of the max power (55W)
- Target temperature in vulvar tissues during procedure: 42°C (range 40-43°C)

(B) Accelerated protocol undergoing validation

- Three 10-min sessions, spaced 7-10 days
- Setting of the radiofrequency generator: 1 MHz
- Operating power: 8-14% of the max power (55W)
- Target temperature in vulvar tissues during procedure: 42°C (range 40-43°C)

Table 2 Comparison between **(A)** the longer EVA™ Vulvar Rejuvenation program (four DQRF sessions) already validated in mild to severe vulvar hypotrophy [27] and **(B)** the accelerated rejuvenation program in mild to moderate vulvar hypotrophy evaluated and validated in this study (three DQRF sessions with the same operative settings)

Aesthetic improvement was documented photographically before every DQRF session; a last photographic documentation was collected at a follow-up visit programmed 30 days after the last treatment session. Treated women and an independent medical evaluator, a specialist in aesthetic gynaecology unaware of the history and demographic details of the cohort women, rated the aesthetic improvement on an ordinal version of the standard categorical Global Aesthetic Improvement Scale (GAIS) modified as a semi-quantitative rating tool—10 scores ranging from 1-2 ("Worse") and 3 ("No change") to 9-10 ("Very much improved"). Assessment times: before the first DQRF treatment session (baseline), before the second DQRF treatment session (i.e., 7 to 10 days after the first session) and 30 days after the third and last treatment of the accelerated DQRF rejuvenation program (follow-up visit). Each woman was identified by a serial number so that to allow anonymous scoring and comparisons of the photographic documentations. Statistical analysis: non-parametric Wilcoxon Signed Rank Test; cut-off for significance, $p < 0.05$. Adverse reactions and complications were recorded before and after every session and at the follow-up visit.

RESULTS

The mean age of screened women was 47.3 ± 3.5 years (range, 41 to 51). In line with inclusion criteria, all enrolled women had Stage-I or Stage-II hypotrophy (12 and 8 women, respectively), were not satisfied with their vulvar aesthetics and had cosmetic indication to vulvar rejuvenation. Seven women, all of them with moderate hypotrophy, complained about occasional dyspareunia and/or dryness. All women were premenopausal, with regular BMI (18.5 to 24.9 kg/m^2), and reported a regular sexual activity. None of them was taking any medications that might influence outcome. All women returned for their planned follow-up visits 30 days after their last DQRF session.

The photographic documentation of the vulvar area (see ANNEX at the end of the paper for some examples) demonstrates with visual evidence the rapid efficacy of the accelerated EVA™ Vulvar Rejuvenation program in women with mild to moderate hypotrophy. The mean modified GAIS scores attributed by both the evaluator and treated women were already improving after the first DQRF session; improvements in vulvar aesthetics were persistently highly significant one month after the end of the DQRF rejuvenation program — evaluator's scores: 5.2 ± 1.27 (baseline) vs. 6.8 ± 0.94 (before second treatment session, $p < 0.05$ vs. baseline) and 8.1 ± 0.79 (follow-up, $p < 0.01$ vs. baseline); cohort women's scores: 4.7 ± 1.15 (baseline) vs. 6.8 ± 0.94 (before second treatment session, $p < 0.05$ vs. baseline) and 8.6 ± 0.79 (follow-up, $p < 0.01$ vs. baseline) (Figure 1). The subgroup of women with disturbing dryness or dyspareunia reported significant improvements in vulvar skin hydration and pain during intercourse; all treated women informally expressed satisfaction with their final aesthetic outcome. No clinically significant side effects or discomfort were reported during the procedures. A slight degree of hyperaemia that lasted about 30 minutes was observed in almost all women after the treatment sessions. All women referred to the warm sensation experienced during the procedure as pleasant or at least definitely not troubling.

Aesthetic assessments during and after the accelerated vulvar rejuvenation programme

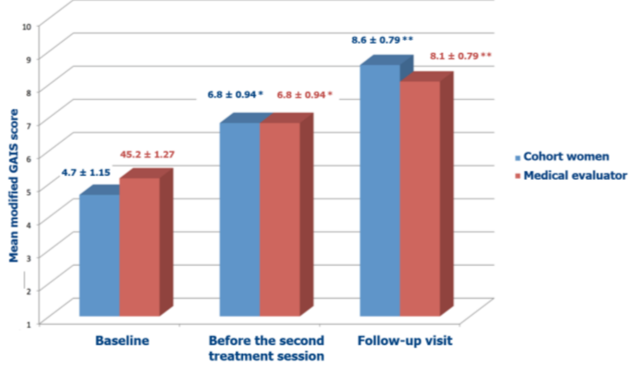

Figure 1 Mean modified GAIS scores attributed by the women of the study cohort and the aesthetic gynaecology specialist unaware of the clinical history of the cohort women acting as blind evaluator.

DISCUSSION

The last few years have seen a steadily growing academic and practical attention for the ageing vulva in aesthetic medicine, aesthetic gynaecology and plastic surgery, as well as a steady expansion of clinical research. This is in line with the surging interest for all the gynaecological conditions that impact the aesthetic self-perception, body image and quality of life of women such as the genitourinary syndrome of menopause, with its bothersomevulvar, vaginal and urinary symptoms, and vaginal laxity [30,31]. Apart from symptoms, all these chronic vulvar conditions frequently also affect the sexual function,[32] justifying the dramatic surge, year after year, of the number of surgical and non-surgical vulvar rejuvenation procedures that are being performed all over the world and the wide academic interest for these procedures and technologies.[14,16,19]

Light- and energy-based devices, based on laser and radiofrequency technologies, offer the opportunity for non-invasive rejuvenation procedures and simpler logistics.[24]

Radiofrequency technologies might indeed have the brightest future in aesthetic gynaecology. Radiofrequency waves generate electrical fields that streamline the spontaneously random translational motions and rotations of polar biomolecules in vulvar and vaginal tissues.[24,33]

Steric and electrical interactions and attritions mean that local tissue temperature increases as a function of intensity of currents and exposure time. This has been shown to lead as biological effect in intimate tissues to neocollagenesis and neoelastogenesis by fibroblasts.[34,35]

In the DQRF device EVA™, the high-tech trick of cycling the four dynamic electrodes between the receiver and transmitter configurations eliminates all electric current flows through tissues and allows the administration of low burdens of energy to precisely defined vulvar areas and layers. The gentle heating of the vulvar region is subjectively well tolerated, and all risks of overheating and burning are virtually suppressed. Anyhow, women can control and pause treatment at will.

Due to the lack of a control group, this pilot study does not allow any reliable quantitative estimation of the vulvar aesthetic improvement with the DQRF device and the accelerated EVA™ Vulvar Rejuvenation programme, yet treated women objectively experienced and subjectively reported strong improvements of their vulvar aesthetics. The modified GAIS scores attributed by both the evaluator and cohort women were already significantly improving after the first DQRF treatment session. The aesthetic benefit seemed to progress even during the follow-up period, or at least showed no short-term reversal, up to scores of more than 8 out of a maximum of 10, in the higher range of the "Much improved" standard GAIS assessment. Interestingly, the dispersion of aesthetic judgements seemed to converge with the progression of treatments, as shown by the steady reduction of standard deviations. This may mean that the worst degrees of basal vulvar hypotrophy showed the strongest aesthetic improvements compared with milder basal situations. It may also mean that all such improvements progress in treated women up to a more or less maximum plateau that is subjectively and objectively judged as very satisfactory compared with the ideally normal situation without hypotrophy.

Such interpretation is in good agreement with the evidences of immunohistochemistry and the electron microscope about the biological effects of thermal stimulation in vulvo-vaginal tissues associated with emission of electromagnetic energy. Re-activation of fibroblasts leads to deposition of new collagen and elastin fibres in the subepithelial layers of the vulva;[24-26] increased tissue levels of the profibrotic cytokine TGF-ß1 and persistent activation of the heat shock proteins are markers of connective matrix re-modelling.[24]

Tissue temperature in the range 40-45°C are ideal for tightening and rejuvenation of vulvar areas thanks to the long thermal relaxation time of collagen in subepithelial vulvar structures (about 225 msec).[24,35] In line with morphological outcomes, women with moderate hypotrophy seemed to experience especially rapid relief from troubling symptoms like dryness and dyspareunia. The high scores attributed by treated women at the follow-up visit bear testimony of the women's gratification for aesthetic outcomes even some time after the end of the vulvar rejuvenation program.

Although conceived as a pilot study, the relatively small size of the prospective cohort of treated women is admittedly a limitation; more serious limitations of the study are the short one-month follow-up period after the end of the rejuvenation sessions, the lack of a control group, and possibly the evaluation method, a modified version of the validated 5-point Global Aesthetic Improvement Scale that rates the global aesthetic improvement compared to pre-treatment, although without formal scoring of the baseline aesthetic situation.

Increasing the number of treated women, prolonging the follow-up period, and using validated questionnaires to assess subjective efficacy will be crucial in future studies with DQRF devices in aesthetic gynaecology.

CONCLUSIONS

This pilot study is strongly suggestive of the high efficacy of the 3-session “Accelerated EVA™ Vulvar Rejuvenation protocol in women with mild to moderate vulvar tissue hypotrophy. Qualitatively, the photographic documentation after three sessions shows a persistent tightening and volumising effect in all treated women, often after the first DQRF treatment session; quantitatively, the mean modified GAIS scores attributed by both the specialist evaluator and treated women improved strongly, up to more than 8 out of a maximum of 10. Aesthetic improvements were achieved with an easy-to-master and pleasant outpatient procedure virtually devoid of side effects. Interestingly, relief from some symptoms like dryness and dyspareunia was especially rapid in women with moderate hypotrophy.

DISCLOSURES AND FUNDING

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EVA Feminine Rejuvenation Device

Features Novel RF Technology

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"Patients are satisfied with the comfortable procedure and also happy because there is no downtime and they don't have to stop their daily activities, such as exercise, after treatment."

By Jeffrey Frentzen, Executive Editor

As an innovative energy-based device for performing vaginal rejuvenation, EVA™ from Novavision Group SpA (Milan, Italy), represents an advanced medical solution for feminine intimate care. This system employs a proprietary version of radiofrequency (RF) to address vaginal atrophy and laxity, external vulvar rejuvenation, genitourinary syndrome of menopause (GSM) and mild stress urinary incontinence (SUI).

According to Franco Vicariotto, M.D., a gynecologist in the department of vulvovaginal diseases at Buzzi Hospital, the University of Milan, Italy, the EVA device safely and comfortably treats vaginal pathologies. "Patients are asking more and more for solutions to these kinds of conditions. For physicians, we appreciate that the EVA procedure is effective, painless for the patient, and a safe technology."

This non-ablative system uses a series of four software-controlled electrodes that dynamically circulate RF energy to focus selectively on target tissue layers, leaving the surrounding areas unaltered. In Dr. Vicariotto's practice, patients have reported an improvement in laxity, as well as reduction in vulvovaginal atrophy and GSM symptoms, such as dryness, dyspareunia and atrophic vaginitis.

Two proprietary technologies are employed to make EVA safer for patients and easy to use for practitioners: Vaginal Dynamic Radiofrequency™ (VDR™) and Radiofrequency Safety System™ (RSS™). VDR is based on Dynamic Quadripolar energy emission, which uses a self-guided system to concentrate its action on vaginal tissue. This approach significantly reduces EVA's power usage compared with traditional RF-based devices, and eliminates any risk of burns.

RSS technology enables the operator to use VDR's full potential in a harmless, controlled way. For instance, the EVA applicator's electrodes constantly monitor the temperature simultaneously at four different points. "The movement sensor and temperature detectors are continually monitoring the way in which you perform the procedure," said Dr. Vicariotto. "The operator can always check the display to determine when they've reached the desired temperature."

Before treatment

After one EVA treatment
Photos courtesy of Franco Vicariotto, M.D.

Following the application of Dynamic Quadripolar RF-based energy, the EVA procedure initiates a collagen response with tissue remodeling and the activation of fibroblasts. After a cycle of five sessions in which no anesthesia is needed, results can also include improvement in the firmness of the genital tissue, as well as enhanced intimate satisfaction.

Patient approval is quite high, noted Dr. Vicariotto. "They are satisfied with the comfortable procedure and also happy because there is no downtime and they don't have to stop their daily activities, such as exercise, after treatment. A great number of them reported improvement in their condition, in particular regarding vaginal dryness, after just the first application. Another positive was that they needed only a handful of sessions to see good results."

Dr. Vicariotto has noticed an increasing number of people willing to ask for feminine rejuvenation procedures. "More and more women are considering their overall well-being during the different periods of their lives. In our society, there is also a growing number of menopausal women that want to maintain an active lifestyle. They want solutions to protect and improve their quality of life," he expressed.

Improved RF Technology Enhances EVA Feminine Rejuvenation Device

By Jeffrey Frentzen, Executive Editor

> "The EVA is all about improving the quality of a woman's personal life and sexual relationship. We recognize that the patient's quality of life is very important."

Rossella Nappi, M.D., Ph.D.
Associate Professor of Obstetrics and Gynecology
Research Center for Reproductive Medicine
Director
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IRCCS San Matteo Foundation
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Italy

Non-surgical vaginal rejuvenation treatments continue to advance with innovative technologies that effectively treat the most important vaginal pathologies. EVA™ from Novavision Group S.p.A. (Misinto, Italy) is one such next-generation offering, combining novel radiofrequency (RF)-based technology with distinctive features and benefits.

EVA employs proprietary Vaginal Dynamic Radiofrequency (VDR™) technology, in which fractionated quadripolar RF emissions focus energy on specific, targeted layers of the vaginal tissue via a self-guided temperature control called Radiofrequency Safety System (RSS™) to achieve non-invasive treatments. This enables the operator to modulate energy with much less power usage compared to traditional devices, virtually eliminating the risk of burns.

Indications include genitourinary problems typical in both fertile and menopausal women, including vaginal dryness; dyspareunia; vulvodynia; itching and intimate burning; vulvovaginal atrophy; vaginitis and recurrent cystitis; mild stress urinary incontinence; reduced sensitivity from post-birth vaginal laxity; and imperfections of the vulva.

This painless treatment requires no anesthesia or adjunctive cooling, and has no patient downtime, stated Rossella Nappi, M.D., Ph.D., associate professor of Obstetrics and Gynecology at the Research Center for Reproductive Medicine, and director of the Gynecological Endocrinology & Menopause Unit, IRCCS San Matteo Foundation, University of Pavia, Italy.

"EVA's selective heating improves microcirculation and epithelial hydration of the vaginal mucosa, reducing the degree of vulvovaginal atrophy and its main symptoms," said Dr. Nappi. "Treatment stimulates the collagen synthesis processes, and restores normal tissue development as well as bacterial flora balance, giving a more youthful appearance and aesthetically balanced female external genital organ."

In addition, in only a few sessions the thermic effect of EVA provides new urethra support and strengthens the pelvic region walls, without irritation or side effects, Dr. Nappi explained.

The EVA handpiece is equipped with a movement sensor system, which allows the operator to avoid harmful administration of heat to the tissue and provides consistent clinical results. "Four electrodes located on the handle constantly monitor the temperature and can automatically shut down the energy emission to avoid any possible risks," Dr. Nappi shared. "By exerting an automatic control on electrodes and movement sensors, the treatment is safe and comfortable. In my hospital, four EVA sessions are sufficient in the majority of cases to relieve the symptoms of vaginal atrophy. The technology has been shown to be effective and completely painless, letting patients immediately resume all activities post treatment."

Patient satisfaction has been very good, as well. "All the women we have treated with four session cycles – one treatment given every two weeks – have been quite satisfied with the results," Dr. Nappi added.

Moreover, the introduction of VDR technology represents an important upgrade in the ability of the physician to take care of their patients in full safety, Dr. Nappi stated. "The EVA is all about improving the quality of a woman's personal life and sexual relationship. We recognize that the patient's quality of life is very important in this changing world, where women wish to preserve their physical and psychological integrity."

Before and after four EVA treatment sessions

Data Proves Efficacy of DQRF Technology for Women's Intimate Health

In the fast-growing field of light- and energy-based devices for feminine intimate care, one of the most recent evolutions includes low-energy Dynamic Quadripolar Radiofrequency (DQRF) technology. For three years, an extensive program of clinical research regarding the DQRF-based EVA™ from Novavision Group S.p.A. (Misinto, Monza-Brianza, Italy) has been underway, and the device is now widely considered a complete and versatile choice for the treatment of several gynecological conditions.

Claudio Catalisano, M.D.
Gynecologist
Cerba HealthCare
Italy

According to Claudio Catalisano, M.D., a gynecologist at Cerba HealthCare (Italy), and member of EVA's scientific board, a growing body of evidence clearly demonstrates the benefits experienced by women with vulvovaginal atrophy (VVA)/ genitourinary syndrome of menopause (GSM) who received vulvar and vaginal treatment with EVA.

"In fact, the twelve-month follow-up data illustrates significant improvement from both a clinical (relief of VVA / GSM symptoms) and biopsychosocial perspective (women's self-esteem, sexual satisfaction and intimate relationships)," he reported. "From all of the data we strongly believe that the new DQRF technology may overcome the issues of low manageability and safety that have been experienced with some other light- and energy-based devices."

The core of the high-tech EVA device is the Vaginal Dynamic Radiofrequency (VDR™) technology. VDR is comprised of four electronically controlled electrodes on anatomical probes with a maximum emitting power of 55 W. The four RF electrodes continuously cycle, under electronic control, between receiver and transmitter states. In the ideal configuration, the repelling electric fields being generated are able to concentrate the thermal effect with high tridimensional precision into the targeted vulvovaginal layers. This mechanism of action leaves surrounding tissues unaffected and reduces the administered energy, guaranteeing a safe, comfortable and effective treatment.

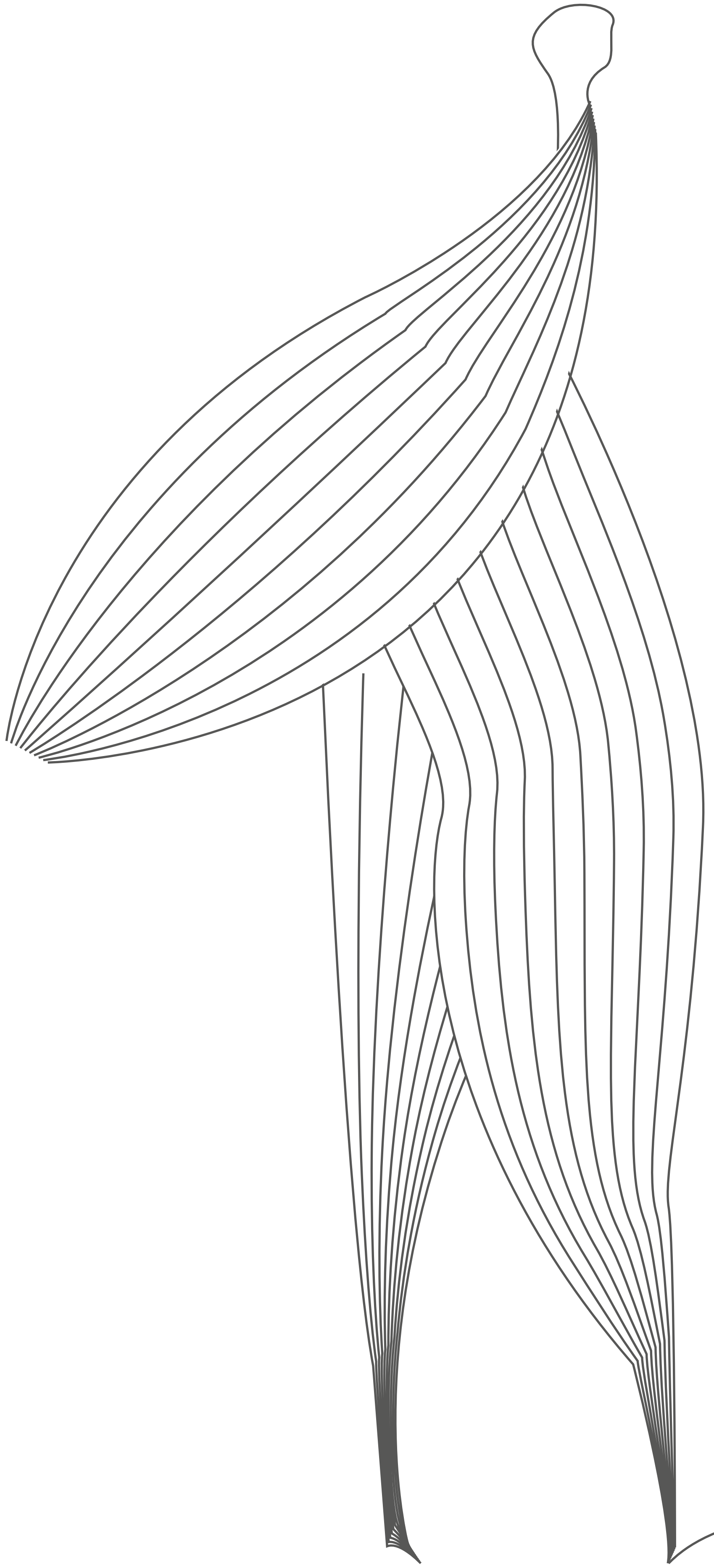
A more recent development of the DQRF concept is the proprietary Ultra-Pulsed Radioporation (UPR™) technology. "The idea behind UPR technology was taken from RF electroporation techniques long used in genetic engineering, which enables high-efficiency gene transfection and transfer of biological macromolecules into cells," Dr. Catalisano explained. UPR opens the aqueous channels in cell membranes by further modulating DQRF performance without having to change the handpiece or treatment program. This can be useful to facilitate the transfer of any active principle with appropriate properties down to the deep layers of the vaginal mucosa.

"The effect on post-menopausal vulvovaginal hypotrophy and loss of elasticity by either DQRF- or UPR-delivered active principles with anti-atrophic properties prove synergistic," Dr. Catalisano noted.

In order to test outcomes, the Novavision Group Scientific Board, made up of professors and key opinion leaders from around the world, conducted a double-blind pilot study on 60 patients, vehiculating low-molecular weight hyaluronic acid (about 290 kDa) in order to test whether combining the DQRF and UPR technologies could further enhance the benefits of DQRF treatment in post-menopausal women.

"The study will be published soon (currently in submission), but I can say that the results are noticeable," Dr. Catalisano stated. "The novel UPR technology seems to afford a general enhancement of DQRF's clinical benefits, specifically in the matter of women's sexual lives (dyspareunia, distress related to sexual dysfunction). Of course, further long-term studies are warranted to confirm these preliminary encouraging results, however we have an expansive pathway in front of us, with a very simple but effective outpatient procedure."

> "The twelve month follow-up data illustrates significant improvement from both a clinical (relief of VVA / GSM symptoms) and biopsychosocial perspective (women's self-esteem, sexual satisfaction and intimate relationships)."



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DQRF
dynamic quadripolar radiofrequency

USE OF A NEW LOW-ENERGY DYNAMIC QUADRIPOLAR RADIOFREQUENCY (DQRF™) DEVICE IN THE TREATMENT OF SYMPTOMS OF VULVOVAGINAL ATROPHY (VVA) IN NATURAL MENOPAUSAL WOMEN AND BREAST CANCER SURVIVORS

PROF. ROSSELLA E. NAPPI, MD, PhD

member of NOVAVISION GROUP Scientific Board

Full Professor of Obstetrics and Gynaecology, University of Pavia, Department of Clinical, Surgical, Diagnostic and Paediatric Sciences, Centre for Reproductive Medicine, Unit of Gynaecological Endocrinology and Menopause, IRCCS Policlinico San Matteo Foundation, Pavia (Italy). Member of the Board of IMS (International Menopause Society) and of ISGE (International Society of Gynecological Endocrinology), nominated in the Group "Top Italian Women Scientists" from 2017.

DQRF™ is a PATENTED TECHNOLOGY of NOVAVISION GROUP.
Presented at 16 WORLD CONGRESS OF MENOPAUSE - Vancouver 6,9 June 2018.

NOVAVISION GROUP
MAKING FUTURE

PRELIMINARY STUDY

USE OF **A NEW LOW-ENERGY DYNAMIC QUADRIPOLAR** RADIOFREQUENCY (**DQRF™**) DEVICE IN THE TREATMENT OF SYMPTOMS OF VULVO-VAGINAL ATROPHY (**VVA**) IN NATURAL MENOPAUSAL WOMEN AND BREAST CANCER SURVIVORS.

FEASIBILITY OF TREATING SYMPTOMS OF VULVO-VAGINAL ATROPHY (**VVA**) WITH A NEW LOW-ENERGY DYNAMIC QUADRIPOLAR RADIOFREQUENCY (**DQRF™**) DEVICE IN NATURAL MENOPAUSAL WOMEN AND BREAST CANCER SURVIVORS.

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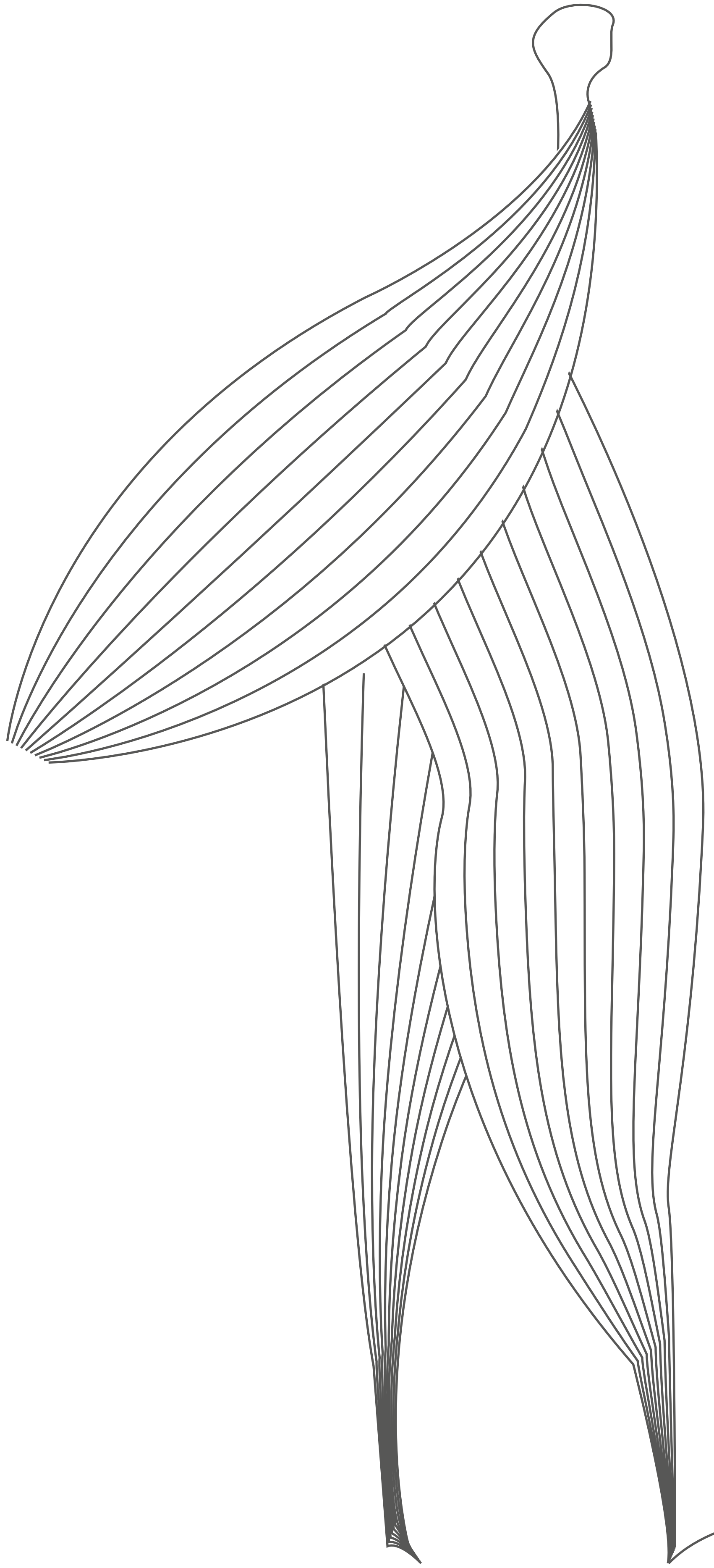

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Gynaecology

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Systematic
Review and Meta

Systematic Review and Meta-Analysis

Medicine

OPEN

The effect of dynamic quadripolar radiofrequency on genitourinary atrophy and sexual satisfaction

A systematic review and meta-analysis

Hassan Mohamed Elbiss, MD, MRCOG, CCT, FRCOG[a,*], Wardah Rafaqat, MBBS[b], Khalid Saeed Khan, MBBS, MSc[c]

Abstract

Background: Physiologic processes such as childbirth and menopause can alter vulvovaginal aesthetic appearance, reduce sexual satisfaction, and cause symptoms of vulvovaginal atrophy which affects a woman's quality of life. There is debate about whether dynamic quadripolar radiofrequency (DQRF) can be used to improve such conditions. We conducted a meta-analysis of studies among patients undergoing treatment with DQRF.

Methods: We conducted a literature search without language or article type restriction in PubMed, Cochrane library and Web of Science from inception to June 1, 2022. We included studies that reported outcomes of DQRF treatment. Article selection and data extraction in a predesigned data extraction form were conducted in duplicate. Individual studies reported outcomes in terms of the pre- and post-intervention repeated measures. Meta-analysis combined results across studies to produce effect sizes using random effects model with 95% confidence intervals (CI) taking into account sampling variance to adjust the estimated precision. PROSPERO: CRD42021227752.

Results: The search yielded 781 articles, from which 4 case series (127 participants) were included. Two studies reported a significant improvement in patient and medical evaluation assessments of vulvovaginal aesthetic appearance. Significant improvements were reported by three studies for patient assessed sexual satisfaction/discomfort, vaginal laxity and symptoms of genitourinary syndrome of menopause. Meta-analysis showed a trend towards improvement in aesthetic appearance (4 studies; 0.89; 95% CI –0.15 to 1.93; I^2 75.0%) and sexual satisfaction (2 studies; 0.62; 95% CI –0.03 to 1.27; I^2 0.0%).

Conclusion: Dynamic quaripolar radiofrequency is a potentially promising intervention to improve vaginal laxity, appearance and sexual satisfaction, as observed in four monocentric case series. Further studies with a control group, well-defined methods of patient selection and longer follow-up periods are necessary to reach a definitive conclusion.

Abbreviations: CI = confidence intervals, DQRF = dynamic quadripolar radiofrequency, GSM = genitourinary syndrome of menopause.

Keywords: DQRF, dynamic quadripolar radiofrequency, genitourinary syndrome of menopause, vaginal laxity, vulvovaginal atrophy

1. Introduction

Physiologic changes in a woman's life, such as childbirth may alter the laxity of the vaginal canal, damage the pelvic floor, and devitalize the mucosal tone of the vaginal wall.[1,2] Perimenopausal changes caused by estrogen deficiency may further alter vaginal tone and vulvovaginal appearance due to a decrease in the content of collagen and elastin in tissues, leading to thinning of the epithelium and disappearance of the superficial layer, leading to smooth muscle dysfunction and connective tissue degradation.[1,2] These events often lead to genitourinary symptoms including stress urinary incontinence, vaginal atrophy, dryness, pain, itching, dyspareunia and may cause distress affecting a woman's quality of life, self-confidence, and sexuality.[3]

Various treatment modalities are currently available to manage these indications including surgical procedures, hormone replacement therapy and radiofrequency treatment. Among these radiofrequency treatments are gaining importance due to their noninvasive nature. The radiofrequency device emits focused electromagnetic waves generating heat upon meeting tissue impedance. It generates temperatures between 40 °C and 45 °C which induces collagen production through fibroblasts via the activation of heat-shock proteins and initiation of the inflammatory cascade.[4] Among radiofrequency devices, the most novel is the dynamic quadripolar radiofrequency (DQRF) device. DQRF biophysics allow the operator to define the depth and volume of the target vulvar area and drastically reduce administered energy. It also allows electronic control of movements and temperature sensors in the radiofrequency device to allow rigid control of tissue temperature.[5]

To the best of our knowledge, currently no reviews exist that exclusively focus on summarizing evidence on the outcomes of DQRF. Reviews that examine noninvasive procedures for vulvar rejuvenation mix up different therapies making it difficult to decipher the unique effect of each treatment. We conducted a systematic review among patients undergoing treatment with DQRF for genitourinary atrophy and improvement in sexual satisfaction.

The authors have no funding and conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Ethical review was not necessary for this study as there was no patient interaction required or identifiable patient data present.

Supplemental Digital Content is available for this article.

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2. Materials and Methods

This systematic review was conducted after protocol registration in PROSPERO and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. PROSPERO: CRD42021227752.[6]

2.1. Search and selection

Randomized controlled trials, cohort studies, case series and case reports that reported patient outcomes following DQRF for the treatment of pelvic floor dysfunction were included. Inclusion of a variety of study designs ensured that all the available evidence on the topic was included and reviewed. The comparison group consisted of no treatment, other types of radiofrequency treatment, surgery, medication, pelvic floor exercises. Articles without a comparison group were also included. No restrictions regarding year of publication or language of the article were applied. The exclusion criteria consisted of articles that only existed in registries as protocols only.

On June 1, 2022, the databases of PubMed, Web of Science, and Cochrane Library were systematically searched. The following keywords were used: "female", "girl', "woman", "vulvar", "vaginal', "vulvovaginal", "genitourinary", "genital", "genitourinary syndrome of menopause", "Genitourinary syndrome of menopause (GSM)", "atrophy", "laxity", "dryness", "dysuria", "incontinence", "sexual activity", "sexual function", "sexual satisfaction", "altered sensation", "aesthetic improvement", "pelvic floor dysfunction", "pelvic organ prolapse", "low-energy DQRF", "DQRF", "radiofrequency", "energy-based", "thermal energy", "low-energy" and "multipolar radiofrequency" (Table S1, Supplemental Digital Content, http://links.lww.com/MD/H514). Duplicate citations were removed electronically from the records retrieved from the databases. References of the included studies were checked to find possible relevant articles and a citation search was also performed. Titles and abstracts of the articles were reviewed independently by two reviewers (WR and MHE) and the full texts of the articles that either reviewer found relevant were acquired with the input of a library consultant. Full texts were then assessed independently by two reviewers (WR and MHE) for relevancy and disagreements were settled by discussion with the third author (KSK).

2.2. Data extraction and study quality assessment

Data was extracted independently by two reviewers. Any disagreements were resolved by discussion between the two reviewers. Data on the following variables were extracted: study population (number, age, indication for treatment), details of the procedure, study design, funding sources, conflict of interest and outcomes (data extraction forms available from authors on request). Primary outcomes consisted of improvement in sexual satisfaction, vulvovaginal aesthetic appearance and symptoms of vulvovaginal atrophy. These outcomes were defined and measured according to published tools.

The methodological quality of the case series was evaluated using the tool for evaluating the methodological quality of case series and case reports.[7] It consists of eight items, categorized into four domains: selection, ascertainment, causality and reporting. Five items pertinent to this review were selected by the authors. Each item was given 1 point and measured as "Yes" (low risk of bias) or "No" (high risk of bias). The total score was then calculated by adding the score allotted to each item. Disagreements between the two reviewers (WR and MHE) in judgement of the quality of the study were settled by discussion with the third author (KSK). The conflict of interest and source of funding reported by all the studies included was also recorded.

2.3. Data synthesis

Mean and standard deviation of the outcomes reported in the included studies was summarized in a table and the significance of the differences was recorded. Individual studies reported outcomes in terms of the pre- and post-intervention repeated measures. Meta-analysis combined results across studies that had similar outcomes measured at the same follow-up visit after baseline using random effects model to produce effect sizes (standardized mean difference from baseline) with 95% confidence intervals (CI) taking into account sampling variance to adjust the estimated precision considering moderate correlation (pre-post $R = 0.5$).[8] A sensitivity analysis was carried to perform meta-analysis with adjustment for low correlation (pre-post $R = 0.1$). Heterogeneity was examined in a forest plot visually and estimated using I^2 statistic to capture the variations of results beyond chance.

3. Results

3.1. Study selection

A total of 781 articles were identified from literature databases and through reference and citation searches. After exclusion of duplicates, there were 672 remaining, which were assessed for relevance by reviewing the title and abstract. Thirty-eight articles were found relevant and were in English and German. After the exclusion criteria were applied, a total of 4 articles were included in the final systematic review[5,9–11] (Fig. 1).

3.2. Study characteristics

A total of 127 subjects were undergoing treatment with DQRF in the four included case series.[5,9–11] There were no cohort studies. The patients were undergoing treatment for vaginal laxity and vulvovaginal atrophy/GSM with symptoms consisting of sexual dissatisfaction, discomfort, low self-esteem. The DQRF was used with a setting of 55 W and 42 °C in all studies with varying duration of the session ranging from 5 to 20 minutes. The mean follow-up time was 6.5 months. (Table 1) Mean age of the patients ranged from 34 to 61.1 years. BMI and menopause status of the women was reported by three studies. BMI ranged from 23.1 to 24.5 kg/m^2 and two studies included an arm of women with menopause. (Table S2, Supplemental Digital Content, http://links.lww.com/MD/H515)

3.3. Risk of bias within studies

The case series received a score of 5 to 4 according to the tool for evaluating the methodological quality of case series and case

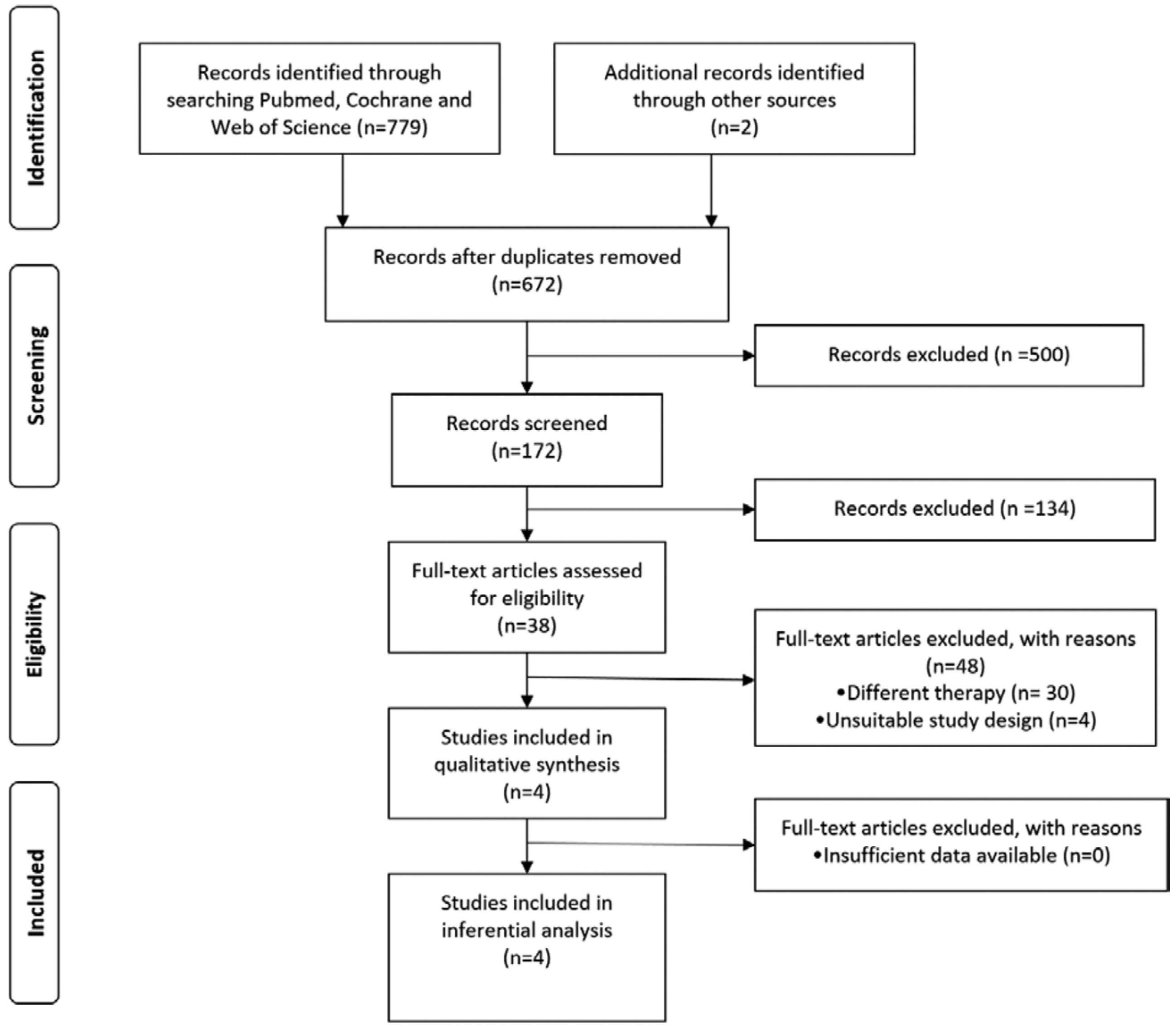

Figure 1. Flow chart for selection of studies for the meta-analysis.

reports, indicating good quality. There were some concerns present, however, in the domain of selection as three studies did not outline the technique for selecting the population included[5,10,11] (Table 2).

One study reported that no funding had not been received and declared no conflict of interest.[10] One study confirmed that no conflict of interest was present but did not report funding sources.[5] One study declared a conflict of interest.[9] Finally, one study did not report sources of funding or conflict of interest.[11]

3.4. Vulvovaginal aesthetic appearance

Vulvovaginal aesthetic appearance was reported in two studies.[9,10] It was assessed by the patient as well as by a medical evaluator/author who was blinded to the demographic details of the patient using tools such as the visual analogue scale and the global aesthetic improvement scale. A significant improvement was reported in the patient's and evaluator's assessment of vulvar aesthetics in both studies. Fasola et al reported a significant improvement after the first session and at the follow-up visit.[10] Beninca et al reported a significant improvement in patient's assessment of vulvar aesthetic appearance after the first session, the third session and subsequent follow-up visits.[9] The medical evaluator assessed appearance before the final session and at the 3-month follow-up visit and reported significant improvement. (Table 3) Meta-analysis showed a trend towards improvement in aesthetic appearance (4 studies; 0.89; 95% CI –0.15 to 1.93; I^2 75.0%) (Fig. 2). The sensitivity analysis showed that at the lower level of correlation, the meta-analytic summary was consistent (0.69; 95% CI –0.11 to 1.49).

3.5. Sexual satisfaction

Sexual satisfaction and patient discomfort were reported in three studies.[5,9,11] Patient reported outcomes including the visual analogue scale, vaginal laxity questionnaire, sexual satisfaction questionnaire and the pelvic organ prolapse/urinary incontinence sexual questionnaire were used for assessment (Table 3). A significant improvement was reported by Fasola et al at the first session and at the follow-up session[10] while Beninca et al reported a significant improvement after the first session, the third session and subsequent follow-up visits (Table 3).[9] Meta-analysis showed a trend towards improvement in sexual satisfaction (2 studies; 0.62; 95% CI –0.03 to 1.27; I^2 0.0%) (Fig. 3). The sensitivity analysis showed that at the lower level

Table 1

Characteristics of studies included in systematic review on the effect of DQRF on genitourinary atrophy and sexual satisfaction.

			DQRF treatment details						Sample size; loss to FU		
Study details	**Study type**	**Disease**	**No. of sessions**	**Duration (min)**	**Interval* (d ± SD)**	**Setting (Mhz)**	**Temp. (°C)**	**Power (W)**	**Group A**	**Group B**	**FU time (mo)**
Benincà et al[9]	Case series	labia minor laxity, vulvar/ vestibular dryness	4	10	14 ± 1	1	42	55	25; 3	NA	5
Fasola et al[10]	Case series	Stage I/II vulvar hypotrophy†	3	10	7-10	1	42	55	20; 0	NA	2
Vicariotto et al[5]	Case series	Group A: vaginal laxity Group B: VVA/GSM‡	Group A: 5 Group B: 4	Group A: 20 Group B: 10	Group A:14 ± 1 Group B:10 ± 1	1	42	55	12; 1	13; 1	Group A: 4 Group B: 3
Vicariotto et al[11]	Case series	Group A: vaginal laxity Group B: VVA/GSM‡	4–6	15–20	14 ± 1	1	42	55	25; 2	32; 0	12

DQRF = dynamic quadripolar radiofrequency, FU = follow up, GSM = genitourinary syndrome of menopause, No. = number, Mhz = MegaHertz, min = minute, SD = Standard Deviation, temp. = temperature, W = Watt.
*Interval between sessions.
†Classification of vulvar hypotrophy: Stage 1 (mild) hypotrophy consists of symmetrical distribution of adipose tissue, none to mild cutaneous hypotrophy, usually asymptomatic or any follow weight loss; Stage II (moderate) hypotrophy consists of asymmetrical distribution of adipose tissue, moderate cutaneous laxity, dryness, dyspareunia and soreness.
‡Vaginal dryness, Vaginal itching, Vaginal burning, Dyspareunia, Dysuria/incontinence.

Table 2

Quality assessment of studies included in review on the effect of dynamic quadripolar radiofrequency on genitourinary atrophy and sexual satisfaction.

	Study	Beninca et al[9]	Fasola et al[10]	Vicariotto et al[5]	Vicariotto et al[11]
	Selection				
1.	Representative population	1	0	0	0
	Ascertainment				
2.	Exposure ascertainment	1	1	1	1
3.	Outcome ascertainment	1	1	1	1
	Causality				
4.	Alternative causes	NA	NA	NA	NA
5.	Challenge/re-challenge	NA	NA	NA	NA
6.	Dose-response effect	NA	NA	NA	NA
7.	Length of follow-up	1	1	1	1
	Reporting				
8.	Replication	1	1	1	1
	Total score	5	4	4	4

NA: not applicable.
Selection: 1. Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?
Ascertainment: 2. Was the exposure adequately ascertained? 3. Was the outcome adequately ascertained?
Causality: 4. Were other alternative causes that may explain the observation ruled out? 5. Was there a challenge/re-challenge phenomenon? 6. Was there a dose-response effect? 7. Was follow-up long enough for outcomes to occur?
Reporting: 8. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?

of correlation, the meta-analytic summary was consistent (0.48; 95% CI –0.17 to 1.14).

3.6. Severity of vulvovaginal atrophy

Severity of vulvovaginal atrophy/genitourinary syndrome of menopause was reported in two studies.[5,11] It was further categorized into vaginal dryness, vaginal itching, vaginal burning, dyspareunia and dysuria and assessed at 1 month[5] and at 12 months.[11] The studies reported a significant improvement in all parameters at all follow-up visits. (Table 3)

4. Discussion

Our review showed that treatment with DQRF significantly improves vulvovaginal aesthetic appearance, sexual satisfaction, and symptoms of vulvovaginal atrophy. This is the first systematic review and meta-analysis focused exclusively on summarizing evidence on the novel, DQRF. Summarizing evidence on the effectiveness of DQRF helps to provide guidance on the adequate radiofrequency device to be selected for a patient and to determine the direction of further research for the assessment of the effectiveness of treatment with DQRF.

We conducted the systematic review using a prospective protocol, an exhaustive search and study quality assessment, limiting risk of bias in the evidence synthesis. Our review captured the conflict-of-interest thoroughly, even when it was not mentioned in the individual studies. It was seen that the studies included in the review were conducted by individuals who are members of Novavision Group, manufacturer of the DQRF technology. This is a possible cause of bias that should be considered when interpreting the significant improvements in the outcomes, particularly because the studies were too few to formally assess the effect of missing studies in funnel plot analysis. The criteria for selection of patients in the included studies excluded patients who were in late stages of their respective disease considering only stage I and II of

Table 3

Outcomes measured in studies included on review on the effect of dynamic quadripolar radiofrequency on genitourinary atrophy and sexual satisfaction.

Study details and time point	Outcome/ Outcome tool	Score ± SD	P value*	Outcome/Outcome tool	Score ± SD	P value*	Outcome/Outcome tool	Score ± SD	P value*
Beninca et al[8]									
	Discomfort† (pt. assessed)/ VAS-NS, PS, FS, HS	NS PS FS HS		Vulvar aesthetic imp. (pt. assessed)/VAS-NS, PS, FS, HS	NS PS FS HS		Vulvar aesthetics (evaluator assessed)/VAS		
Baseline		14 11 0 0			16 9 0 0			4 ± 4	
Bef. 2nd session		4 9 11 1	<.05		5 9 8 3	<.05			
Bef. 3rd session		0 1 15 9			0 2 8 15				
Bef. 4th session		0 0 8 17	<.01		0 1 8 16	<.01		7 ± 8	<.05
3-mo FU		0 1 5 16	<.01		0 0 7 15	<.01		7 ± 6	<.05
Fasola et al[9]									
Baseline	Vulvar aesthetic imp./GAIS score (pt. assessed)	4.7 ± 1.15		Vulvar aesthetic imp./GAIS score (evaluator assessed)	5.2 ± 1.27				
Bef. 2nd session		6.8 ± 0.94	.05		6.8 ± 0.94	.05			
1-mo FU		8.6 ± 0.79	.01		8.1 ± 0.79	.01			
Vicariotto et al[5]									
Baseline	Vaginal introital laxity (Group A)/VLQ	2 ± 3		Overall sexual satisfaction (Group A)/VAS	4 ± 3		VVA and GSM severity Group B)/VAS‡	34 ± 5	
Bef. 5th session		4 ± 6	<.05		7 ± 0	<.05		38 ± 5	<.05
1-mo FU		4 ± 8	<.05		6 ± 9	<.05		40 ± 0	<.05
2-mo FU		5 ± 0	<.05		7 ± 7	<.05		40 ± 5	<.05
	Severity of VVA and GSM (Group B)/VAS: VD, VI	VD VI		Severity of VVA and GSM (Group B)/VAS: VB, DP	VB DP		Severity of VVA and GSM (Group B)/VAS: DU	DU	
Baseline		8.8 ± 2.4 7.5 ± 2.7			7.2 ± 2.5 8.7 ± 2.2			5.5 ± 2.6	
Bef. 5th session		4.3 ± 1.8 3.7 ± 1.9	<.01		3.4 ± 1.8 4.5 ± 1.9	<.01		3.0 ± 1.9	<.01
1-mo FU		3.4 ± 1.7 3.0 ± 1.6	<.01		3.0 ± 1.7 3.0 ± 1.8	<.01		2.9 ± 1.6	<.01
2-mo FU		3.2 ± 1.9 2.6 ± 1.3	<.01		2.8 ± 1.4 3.1 ± 1.9	<.01		2.6 ± 1.5	<.01
Vicariotto et al[10]									
Baseline	Vaginal introital laxity (Group A)/VLQ	2 ± 2		Sexual satisfaction (Group A)/ SSQ	2 ± 2		Pelvic organ prolapse (Group A)/ PISQ-12	34 ± 3	
post last session		4 ± 6	<.05		3 ± 7	<.05		38 ± 4	<.05
1-mo FU		4 ± 9	<.05		4 ± 3	<.05		39 ± 5	<.05
2-mo FU		5 ± 0	<.05		4 ± 3	<.05		40 ± 7	<.01
6-mo FU		5 ± 3	n.s.		4 ± 1	<.05		41 ± 0	<.01
9-mo FU		4 ± 9	n.s.		3 ± 6	<.05		43 ± 3	<.01
12-mo FU		4 ± 8	n.s.		3 ± 5	<.05		40 ± 8	<.01
Vicariotto et al[10]					Outcome				
					VD VI VB DP			DU	
Baseline	Overall sexual function (Group B)/VAS	4 ± 2		Severity of VVA and GSM (Group B)/VAS: VD, VI, VB, DP, DU	8.9 ± 2.4 7.6 ± 2.8 7.2 ± 2.5 8.8 ± 2.2			5.9 ± 2.5	
post last session		7 ± 1	<.05		4.3 ± 1.9 3.8 ± 1.8 3.5 ± 1.8 4.4 ± 1.7			2.9 ± 1.9	<.05
1-mo FU		7 ± 0	<.05		3.4 ± 1.7 3.0 ± 1.7 3.0 ± 1.8 2.9 ± 1.8			2.8 ± 1.5	<.05
2-mo FU		7 ± 6	<.05		3.2 ± 1.6 2.6 ± 1.8 2.9 ± 1.6 2.8 ± 1.8			2.7 ± 1.6	<.05
6-mo FU		7 ± 8	<.05		3.0 ± 1.5 2.4 ± 1.6 2.6 ± 1.7 2.4 ± 1.5			2.5 ± 1.8	<.05
9-mo FU		8 ± 0	<.05		3.1 ± 1.1 2.3 ± 1.3 2.5 ± 1.2 2.4 ± 1.3			2.4 ± 1.4	<.05
12-mo FU		7 ± 8	<.05		3.1 ± 1.3 2.3 ± 1.2 2.6 ± 1.1 2.3 ± 1.2			2.5 ± 1.3	<.05

Bef.= before, DP = Dyspareunia, DU = Dysuria, FS = fairly satisfied, FU = follow-up, GAIS = Global Aesthetic Improvement Scale, HS = highly satisfied, NS = not satisfied, PISQ-12 = Pelvic Organ Prolapse/Incontinence Sexual Questionnaire, short form, PS = poorly satisfied, SSQ = Sexual Satisfaction Questionnaire, VAS = Visual Analogue Scale, VB = Vaginal burning, VD = Vaginal dryness, VI = Vaginal itching, VLQ = Vaginal Laxity Questionnaire (Short form of Pelvic organ prolapse/Urinary incontinence Sexual Questionnaire), VVA and GSM = vuvlvo-vaginal atrophy/genitourinary syndrome of menopause.

*P value compared to baseline.

†Discomfort in everyday life, loss of self-esteem, problems with sexual life and couple relationship and other difficulties.

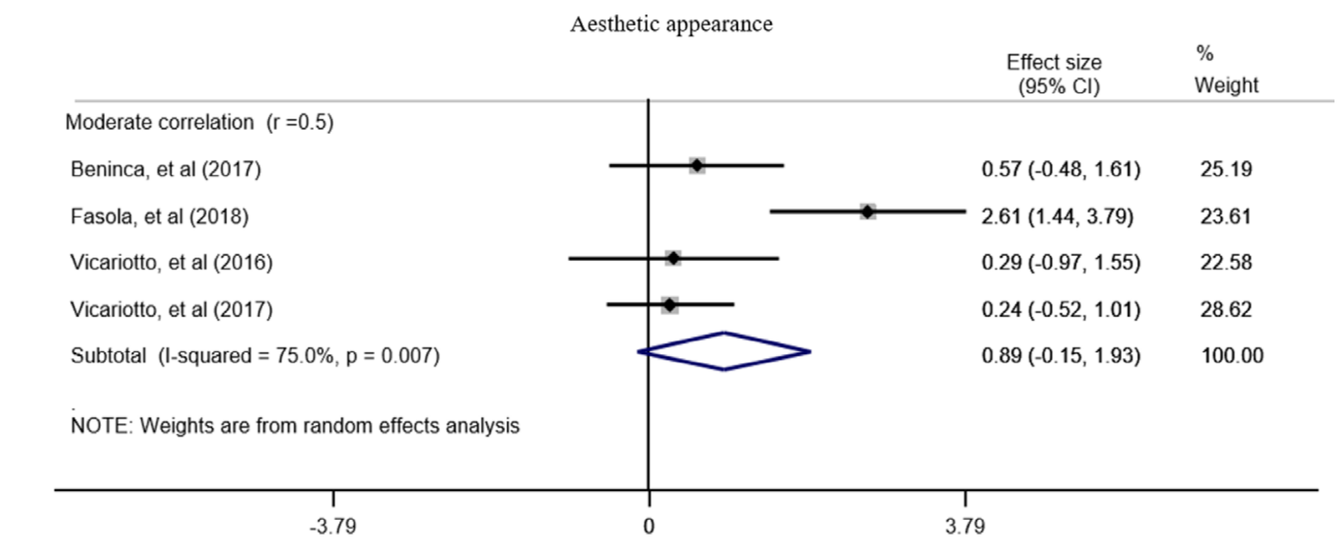

Figure 2. Effect size meta-analysis on the effect of DQRF on aesthetic appearance. DQRF = dynamic quadripolar radiofrequency.

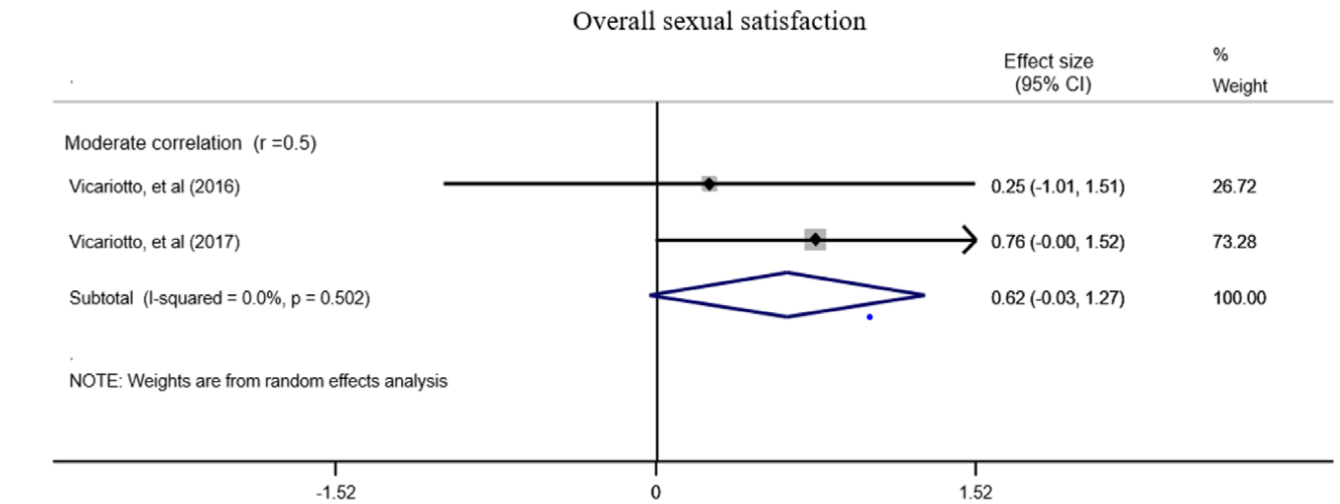

Figure 3. Effect size meta-analysis on the effect of DQRF on sexual satisfaction. DQRF = dynamic quadripolar radiofrequency.

vulvovaginal hypotrophy. Doing so limits the generalizability of the findings for a wider population which may have advanced stages of hypotrophy. There was heterogeneity in the meta-analysis of aesthetic appearance, but studies were too few to reliably explore causes of variation of findings between studies. Finally, the studies included did not contain a control group to assess confounding factors and three studies did not mention the method of selection of patients.[5,10,11] It is necessary in the future to have a control group to robustly assess the effect of DQRF treatment. In the meantime, our meta-analytic method for combining results across studies of repeated measures design, with all effect sizes transformed into a common metric and adjusted for sampling variance to reflect the precision, provides the most reliable current evidence.[8]

Recently, light and radiofrequency-based therapies have been gaining popularity due to their noninvasive nature, less down-time and easier logistics when compared to surgical procedures.[12] Patient interest in the such procedures is also increasing as it is becoming common to undergo cosmetic procedures for the improvement of vulvovaginal aesthetic appearance, as evidenced by the recent increase in labiaplasty procedures.[9,13] Patients are also overcoming social inhibitions and seeking treatment for genitourinary conditions like vaginal laxity or GSM.[14] Within radiofrequency treatments, DQRF is a novel therapy that allows the operator to convey energy with high tridimensional precision to the subepithelial layers of the vulva using four steel dynamic electrodes that electronically cycle between the receiver and transmitter states and create repelling electric fields. It also removes the necessity for the grounding pad on the upper thigh and heavy energy burdens because of Ohm's resistances in tissues.[5] Our review gives insight into outcomes of DQRF therapy based on contemporary literature.

5. Conclusion

Dynamic quaripolar radiofrequency is a potentially promising intervention for improvement in vaginal laxity, appearance, and sexual satisfaction, as observed in four monocentric case series of small patient cohorts and low level of evidence. Further studies with a control group, well-defined methods of patient selection and longer follow-up periods are necessary to reach a conclusion regarding the effect of DQRF on women's health.

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