Update in Radio-frequency Technology

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Objectives

• After the lecture the participant will be able to
  – Discuss Available Technologies for genital application including laser and radiofrequency
  – Discuss the underlying mechanism of action for radiofrequency
  – Review available published data on radiofrequency

The Technology of Laser & RF Energies in Vaginal Applications

• When determining which energy sources are optimally suited to treating the vagina it is important to identify the areas and the depth the treatment effect should reach.

  – All of the available energy sources pass through the most superficial tissue layers and may be expected to have some effect there.

• Ablative and non-ablative lasers have been shown to improve the appearance of the vulva and the integrity and function of the vaginal mucosa.

  – Importantly, they have not been shown to produce significant vaginal tightening.

• Radiofrequency systems in monopolar, bipolar or unipolar configurations can deliver energy externally to the vulva as well as to the vaginal mucosa.

Disclaimers

• Dr Michael L. Krychman MD has the following disclosures
  – Consulting Fees: Therapeutics MD, Duchesnay Palatin Technologies Applied Biology, Exelixis Viveve Medical, Materna Medical, and Valeant Pharmaceuticals
  – Speaker Fees: Valeant Pharmaceutical and Duchesnay

Comparison of Depth Penetration with Alternate Treatments

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Lasers and RF Energy on the Electromagnetic Spectrum

Laser and RF interactions with tissue can be quantified and compared, as they both reside on the electromagnetic spectrum.

Ablative lasers tend to have shallow impact
- In general, lasers have higher frequency and relatively short wavelengths.
- Their shallow penetration depths are due to the tissue’s rapid absorption and scatter of the laser’s energy.

RF systems tend to penetrate more deeply
- In general, RF generates volumetric heating in tissue due to its lower frequency and relatively longer wavelength.
- RF penetration depth is also dependent on the polar arrangement, with monopolar systems penetrating most deeply.

<table>
<thead>
<tr>
<th>Laser/RF</th>
<th>Depth of impact</th>
<th>Number of treatments required</th>
<th>Time for Results (up to # months)</th>
<th>Published Data on Laxity for sexual pleasure</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂</td>
<td>0.5mm</td>
<td>3-5</td>
<td>6</td>
<td>no</td>
</tr>
<tr>
<td>Thermi</td>
<td>1mm</td>
<td>3</td>
<td>6</td>
<td>no</td>
</tr>
<tr>
<td>Topical RF</td>
<td>1mm</td>
<td>4-6</td>
<td>6-9</td>
<td>no</td>
</tr>
</tbody>
</table>

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The Science Behind It All...

Patented CMRF treatment:
- Stimulates fibroblasts
- Subtly modifies collagen

Collagen is the main structural protein in the extracellular space in the various connective tissues in animal bodies.
- Type I collagen is the most abundant collagen of the human body which forms large, eosinophilic fibers known as collagen fibers.

The Technology Behind It All...

A fibroblast is a type of cell that synthesizes the extracellular matrix and collagen, the structural framework (stroma) for animal tissues, and plays a critical role in wound healing. Fibroblasts are the most common cells of connective tissue in animals.
Mechanism of Action

- Application of low-dose, non-ablative RF energy penetrates up to 5mm
- Activates fibroblasts within the vaginal tissue to begin production of new collagen
- Collagen remodeling process takes place over time, typically starting at 30 days and continuing up to 90 days or longer post-treatment
- Newly remodeled collagen promotes a cushioning effect and improves the integrity of the tissue in close proximity to the clitoral body, resulting in improved sexual sensation/function

CMRF delivers pulses of heat to the collagen fibers while also cooling the surface.

Etiology: The Medical Condition of Vaginal Laxity

Medical Conditions
- Diabetes (neural)
- Diabetic neuropathic
- Respiratory (COPD, chronic coughing)
- Genetic disorders of collagen metabolism

Hormonal
- Estrogen deprivation (menopause/lactation)
- Pregnancy (relaxin)

History
- History of childbirth
- History of instrumental delivery
- History of vaginal delivery
- History of significant trauma to vagina

History Cont.
- History of multiple vaginal births
- Rapid second stage
- Prolonged expulsion stage
- Insertion of large foreign objects in vagina

Behavioral
- Tobacco use
- Sexual intercourse/sexual activity
  - Risk factors
    - Early age at first intercourse
    - Sex workers etc.
    - Multiple partners
    - Athletic Activities
      - Volleyball, swim, judo, artistic gymnastics, trampoline

Symptoms of Sexual Function
- Arousal
- Orgasm
- Satisfaction
- Sexual Self Esteem
- Loss of femininity
- Loss of sensuality

Impact of Vaginal Laxity
- Symptoms of Pelvic Organ Support
  - Urinary symptoms and incontinence
  - Organ prolapse
- Vaginal Symptoms
  - Vaginal flatulence

Type of Laxity | Aesthetic Aspects | Functional Aspects
--- | --- | ---
Vulvar Laxity | Loose, unattractive vulvar anatomy | Dyspareunia, vulvar discomfort from tight clothing, sports, displacement into the introitus
Vaginal Introital Laxity | N/A | Clitoral complex affected, Altered sexual arousal, Changes in orgasmic response and sexual satisfaction
Vaginal Canal Laxity | N/A | May be associated with urinary or fecal incontinence, Cystoscale, Rectoscale

The Medical Condition of Laxity: Subtypes

The Impact of Vaginal Laxity

No Objective Measure
- Women and men experience sexuality differently
- Subjective sexual arousal vs genital sexual arousal
- Repeated failures of objective measures in FSD to predict subjective sexual experience
  - SSE, clitoral blood flow, vaginal photoplethysmography, vaginal pH, Para basal cells, vaginal dilators

- Validates scales like FSFI are widely accepted as the best indicator of female sexual function
  - 7-28 day recall period resonates with the female sexual experience

Behavioral Modification
- Safe / Low Risk
- Only regulated by FDA if device is intended for treating underlying condition

Energized Devices
- Non-invasive, office-based treatment
  - TVT or PAV
  - Publications supporting efficacy for Vmax

Surgical Intervention/Repair
- Dependent on skill of clinician
- Publications supporting efficacy
Why only the Introitus?

- Primary region for sexual pleasure for women
- Clitoral tissue wraps around this region and provides majority of sexual sensation
- Coupling and friction is key for women’s physical sensation
- Dense fibrous tissue
- Canal laser treatments are being marketed primarily for mucosal indications, post-menopausal—dryness, itchiness, painful intercourse and very mild incontinence.
  - Little supporting data available has been published
- Any tightening of the upper 2/3 of the canal achieved by surgery or energy delivery is likely diminished during intercourse due to the expansion of the canal that occurs during stimulation

Importance of Specifically Treating the Introitus

Descending movement and decreasing angle of the double vault of the clitoris under contraction.
CB = clitoral body.

Existing Peer-Reviewed Research in Vaginal Laxity

<table>
<thead>
<tr>
<th>Vaginal Laxity</th>
<th>Randomized</th>
<th>Sham-Controlled</th>
<th>Validated Sexual Function Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kolberg Tenfjord 2015</td>
<td>✓</td>
<td>✓</td>
<td>(ICIQ-VS, ICQ-TLabs)</td>
</tr>
<tr>
<td>Mittag 2015</td>
<td>✓</td>
<td>✓</td>
<td>(ICIQ-VS, ICSO-FLUTS)</td>
</tr>
<tr>
<td>Sekiguchi 2013</td>
<td>✓</td>
<td>✓</td>
<td>(m-FSFI, ICSO-FLUTS)</td>
</tr>
<tr>
<td>Lee 2014</td>
<td>✓</td>
<td>✓</td>
<td>(m-FSFI, ICSO-FLUTS)</td>
</tr>
</tbody>
</table>

When Should Laxity be Treated?

Vaginal Laxity as described by the woman herself causing personal distress

BTL Exilis Protégé Intima

- Monopolar RF, no cooling
- Vuvuz, labial and vaginal rejuvenation, remodeling, tightening
- 3 treatments – 7 to 10 days apart
- Ultrasound is not used during vaginal treatment

Publications:

BTL Ultra Femme 360

<table>
<thead>
<tr>
<th>Monopolar RF</th>
<th>No contact cooling (body and face systems do have cooling)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depth</td>
<td>Limited to around 1mm due to constant motion technique</td>
</tr>
<tr>
<td>Time on tissue</td>
<td>Limited to constant motion technique with overall treatment time of 8 minutes (way too short)</td>
</tr>
<tr>
<td>Temperature</td>
<td>Target temperature is 40°C (well below the 50-60°C necessary for collagen remodeling)</td>
</tr>
<tr>
<td>Handpieces</td>
<td>3 handpiece tips. Far right is for vulva, next is for labia and then 2 different internal applicators with varying diameters</td>
</tr>
<tr>
<td>Regimen</td>
<td>4-30 minute treatments 1-2 weeks apart. Results said to last 6 months to a year</td>
</tr>
<tr>
<td>FDA</td>
<td>To provide heating for the purpose of elevating tissue temperature for conditions such as relief of pain and increase in local circulation</td>
</tr>
</tbody>
</table>

BTL Ultra Femme 360

<table>
<thead>
<tr>
<th>Cost</th>
<th>Upgrade $33k, Stand Alone $4k-70k (3 months try and buy?)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consumables</td>
<td>Internal applicator $150</td>
</tr>
<tr>
<td>Studies</td>
<td>Internal and external $200</td>
</tr>
<tr>
<td>Claims</td>
<td>Discussion concerning vaginal laxity, atrophy, SUI and external treatments. Can be an all in one platform and treat head to toe</td>
</tr>
</tbody>
</table>

InMode Votiva

- Bipolar/Multipolar RF, no cooling
- Vaginal, labial and vaginal rejuvenation, remodeling, tightening
- Combination of two treatments, requires numbing cream
  - Forma V – internal and external
    - Requires constant motion and rotation to prevent burns
  - Fractora V – external
    - Fractionated, ablative RF with needling
    - 2-3 days downtime (icing)
    - 1 – 3 treatments, up to 2 hours each
    - No intercourse for 1 – 2 weeks post treatment

Votiva

- Multi-frequency bipolar RF handpiece that works with V-20, V-30 and Reaction IPL systems
- Integrated cooling mechanisms cools electrodes to 6°C
- External treatments only: Labial and vulvar rejuvenation, remodeling, tightening
- The V-ST handpiece for skin tightening uses Viora’s CORE technology with three individual RF channels and a fourth channel incorporating all three frequencies for greater depth penetration and control

ReVive

- Bipolar/Multipolar RF, no cooling
- Vaginal, labial and vaginal rejuvenation, remodeling, tightening
- Combination of two treatments, requires numbing cream
  - Forma V – internal and external
    - Requires constant motion and rotation to prevent burns
  - Fractora V – external
    - Fractionated, ablative RF with needling
    - 2-3 days downtime (icing)
    - 1 – 3 treatments, up to 2 hours each
    - No intercourse for 1 – 2 weeks post treatment

VIVEVE I: Randomized, Blinded, Sham-Controlled

- Subjects:
  - Pre-menopausal women, ≥ 1 full term vaginal delivery
- Study Sites:
  - 9 sites in 4 countries (Canada, Italy, Spain, Japan)
- Objective:
  - Validate safety and efficacy of Viveve system in treating vaginal tissue
- Randomization in 2:1 ratio (Active/Sham)
  - ACTIVE Group: 90 J/cm², 5 tx passes
  - SHAM Group: 1 J/cm², 3 tx passes
- Efficacy: Measured at 1, 3, and 6 months post treatment
  - Viveve Laxity Questionnaire (VLQ)
  - Validated Sexual Function Questionnaire (FSFI)
  - Female Sexual Distress Scale – Revised (FDS-R)
  - Viveve Vaginal Laxity Inventory (VLI)
- Safety: Adverse event reporting

Handpieces

- Temperature
  - Monopolar
  - Bipolar
  - Multipolar
- Time on tissue
  - Monopolar
  - Bipolar
  - Multipolar
- Depth
  - Monopolar
  - Bipolar
  - Multipolar

FDA

- Claims
  - Results said to last 6 months to a year
  - 4, 30 minute treatments 1-2 hours each
  - Fractionated, ablative RF with needling
  - Requires constant motion and rotation to prevent burns
  - Limited to around 1mm due to constant motion technique
  - Limited to 7mm and 3 moderate treatments spaced apart
  - No contact cooling
  - Requires a second handpiece for internal
  - Requires constant motion so will take 30-45 minutes to return to comfort temperature.
  - Fractora V (well below the 50°C necessary for collagen remodeling)
  - Target temperature is 40°C (well below the 50°C necessary for collagen remodeling)
  - Fractora V is ablative (hurts)

Studies

- Internal applicator $150
- Internal and external $200

Studies

- NO RCT studies.
- There are however plenty of studies on condom effectiveness...
**VIVEVE I: Questionnaires for Key Efficacy Parameters**

**VIVEVE I: Subject Disposition**

Randomized & Treated Subjects

<table>
<thead>
<tr>
<th></th>
<th>Active (n)</th>
<th>Sham (n)</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Protocol w/ Vaginal Laxity (VSQ)</td>
<td>109</td>
<td>52</td>
<td>161</td>
</tr>
</tbody>
</table>

Month 6 Follow-Up:

<table>
<thead>
<tr>
<th></th>
<th>Active</th>
<th>Sham</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Protocol w/ Vaginal Laxity (VSQ)</td>
<td>108</td>
<td>56</td>
<td>164</td>
</tr>
<tr>
<td>Per Protocol w/ Sexual Dysfunction (FSFI)</td>
<td>103</td>
<td>52</td>
<td>155</td>
</tr>
</tbody>
</table>

**Demographic & Clinical Characteristics: PP Population**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>21.2</td>
<td>4.3</td>
<td>19.3</td>
<td>12.6</td>
<td>29.3</td>
</tr>
<tr>
<td>Age</td>
<td>42.8</td>
<td>13.5</td>
<td>34.9</td>
<td>18.1</td>
<td>65.8</td>
</tr>
<tr>
<td>Female Sexual Function Index (FSFI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Areas of Focus</td>
<td>No. Questions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual Desire/Interest</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual Arousal</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lubrication</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfaction</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Maternal History: PP Population**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Areas of Focus</td>
<td>No. Questions</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sexual Desire/Interest</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual Arousal</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lubrication</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfaction</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**VIVEVE I: – Primary Endpoint VSQ**

Study achieved its primary endpoint of patients reporting NO vaginal laxity at 6 months versus a sham

Logistic Regression

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Treatment Group</th>
<th>N</th>
<th>No Laxity (%)</th>
<th>Chi-Squared p-value</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 6</td>
<td>Active</td>
<td>103</td>
<td>41 (41.7%)</td>
<td>0.005</td>
<td>3.05</td>
<td>(1.37, 6.79)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Sham</td>
<td>52</td>
<td>50 (92.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Likelihood of “no vaginal laxity” at 6 months was more than 3x greater for treated patients than sham

*80% of the active subjects showed a positive change in VSQ score at 6 months*

Adjusted Mean Improvement after a single RF treatment.

Significant and sustained improvement after a single RF treatment.

Large placebo effect diminished at 6 months.

Adjusted Mean Difference of 0.7 at 6 Months. 95% CI (0.20, 1.23) p-value = 0.007
VIVEVE I: Statistically Significant Improvement in Sexual Function (FSFI)

- Adjusted Mean Difference of 3.2 at 6 Months
- p-value = 0.009
- Placebo effect diminished at 6 months

VIVEVE I: Individual Domain Results of FSFI

<table>
<thead>
<tr>
<th>FSFI Domain</th>
<th>Positive Result (Active vs Sham)</th>
<th>p-value (Active vs Sham)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual Desire/Interest</td>
<td>Yes</td>
<td>0.081</td>
</tr>
<tr>
<td>Sexual Arousal</td>
<td>Yes</td>
<td>0.007**</td>
</tr>
<tr>
<td>Lubrication</td>
<td>Yes</td>
<td>0.005</td>
</tr>
<tr>
<td>Orgasm</td>
<td>Yes</td>
<td>0.007**</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>Yes</td>
<td>0.097</td>
</tr>
<tr>
<td>Pain</td>
<td>Yes</td>
<td>0.122</td>
</tr>
</tbody>
</table>

**Statistically Significant, p-value < 0.05
N=103, PP, Baseline FSFI≤26.5

VIVEVE I: Safety Profile

Overview of Treatment Emergent Adverse Events (TEAEs)
N=174

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Active</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with TEAE</td>
<td>38 (32.5%)</td>
<td>20 (35.1%)</td>
</tr>
<tr>
<td>Subjects with Related TEAE</td>
<td>13 (11.1%)</td>
<td>7 (12.3%)</td>
</tr>
<tr>
<td>Subjects with Serious TEAE</td>
<td>0 (0.0%)</td>
<td>1 (1.8%)</td>
</tr>
</tbody>
</table>

AE = any untoward medical occurrence, whether or not related to the device or procedure
TEAE = an AE that begins or worsened after treatment
Related = ‘Possibly Related’, ‘Related’, ‘Unknown/Undetermined’, or relationship missing
Examples of “related” TEAEs included: vaginal itching, mild uterine cramping and tenderness, feeling of heat, constipation, decrease in vaginal discharge, mild lubrication, changes in vaginal discharge, slight irritation, and mild vaginal discomfort.

• RF systems with higher power and frequencies (Viveve 50W @ 6MHz) are more easily able to reach therapeutic temperatures, than those with lower power (ThermiVa @ 20W @ 1MHz).

Is Sex Medically Necessary?

- Enhances intimacy
  - Longevity, chronic illness
  - Decreases pain; Increases oxytocin and endorphins
  - Pair bonding/cuddle hormone
  - May increase overall happiness by decreasing stress
  - Sex improves cardiovascular health and stamina
  - Sexually active men had lowered rates of stroke
  - Sex burns calories
  - 85 calories per act
  - 42 sessions of 30 minutes each is 3570 calories or a pound
  - Sex improves immunity
  - Increased IgA antibodies
  - Sex improves sexual self esteem
  - Sex reduces cancer risk
  - Prostate cancer reduced with more than 21 ejaculations per month
  - Sex strengthens pelvic floor
  - Sex improves sleep
  - Oxytocin release