Health Policy Advisory Committee on Technology

Technology Brief

Fractional CO$_2$ laser treatment of vulvovaginal atrophy

August 2016

HealthPACT
emerging health technology
Summary of findings
Fractional CO₂ laser technology consists of a non-surgical, laser-based treatment for the symptoms of vulvovaginal atrophy (VVA). This technology is rapidly disseminating into the public and private health sectors.

Current evidence on the safety and effectiveness of fractional CO₂ laser technology is limited to a few small case series. A single small comparative study was identified and no conclusions as to the effectiveness of the fractional CO₂ laser technology can be made. Conflicts of interest were noted in two of the seven studies due to authors disclosing a financial relationship with the manufacturer.

The technology is generally well tolerated by the patient, with no reports of adverse events in published literature to date. The technology may be able to provide a rapid and non-pharmacological intervention for VVA symptoms, delivered in a primary care or ambulatory setting. However, further comparative clinical evidence is required.

HealthPACT Advice
This technology is becoming widely available within the health system. There may be benefits of this technology in the treatment of VVA, particularly for patients with a history of oestrogen-dependent malignancies. However, the clinical utility of this technology is not yet supported by high-level evidence and there is potential for ‘indication creep’ without appropriate evidence. There is a need for comparative evidence and long-term follow-up data to demonstrate safety, clinical and cost effectiveness of this technology. It is of concern that this technology is marketed directly to the consumer to treat a range of gynaecological conditions without sufficient supporting evidence.

Therefore, HealthPACT does not support public investment in this technology, or its introduction into clinical practice until the publication of comparative studies that demonstrate clinical utility.
Fractional CO\textsubscript{2} laser treatment of VVA: October 2016

**Technology, Company and Licensing**

**Register ID** WP251

**Technology name** Fractional CO\textsubscript{2} laser

**Patient indication** For the treatment of vulvovaginal atrophy

**Description of the technology**

Fractional CO\textsubscript{2} laser technology consists of a non-surgical, laser-based treatment primarily for post-menopausal or post-partum vulvovaginal atrophy (VVA).\textsuperscript{1} The procedure utilises a class four CO\textsubscript{2} laser, operating at 10,600 nm. The laser pulses for approximately one millisecond, and is optically split to provide a fractionalised series of small ~200 micron dots. At the point of contact on the surrounding vaginal walls, the laser dot ablates a small area of tissue, and heats the tissue surrounding and deep to the ablation zone.\textsuperscript{1,2}

![Figure 1](https://example.com/figure1.png)

**Figure 1** (L) MonaLisa\textsuperscript{®} SmartXide\textsuperscript{2} laser system (R) 360\textdegree laser applicator (printed with permission High Tech Laser Australia Pty Ltd)

Microablative fractional CO\textsubscript{2} lasers are currently used in dermatologic and plastic surgery skin applications to stimulate tissue remodelling. The process involves interaction between certain heat shock proteins, which induce a local increase in various cytokines, including transforming growth factor-A, and basic fibroblast, epidermal, platelet-derived, and vascular endothelial growth factors. These growth factors activate fibroblasts to produce new collagen and other components of the extracellular matrix, including proteoglycans and glycosaminoglycans, and stimulates new vessel formation.\textsuperscript{3} It is claimed that similar effects are achieved when a fractionated CO\textsubscript{2} laser is applied to the vaginal epithelium, with cell proliferation and collagen formation resulting in the restoration of vaginal wall strength and blood supply.\textsuperscript{1}

The fractional CO\textsubscript{2} laser VVA procedure usually involves three treatments at approximately four to six week intervals, with one maintenance treatment annually, or as required if
symptoms reoccur. At the start of each treatment, a swab is inserted into the vagina to dry the canal. The laser probe is then inserted, and treatment is initially applied to the deeper portions of the vaginal canal. Successive applications of laser energy are applied as the probe is gradually withdrawn, according to the graduated scale on the applicator, to ensure that energy is released uniformly on the walls of the vaginal canal. The treatment itself is reported to take 15 minutes or less per session.

**Company or developer**

There are a number of manufacturers with commercially available products within Australia and New Zealand. The MonaLisa Touch® (DEKA M.E.L.A. srl, Calenzano, Italy) is distributed by High Tech Laser Australia Pty Ltd, the FemTouch™ (Lumenis®, Israel) is distributed through Lumenis (ANZ) Pty Ltd, and the FemiLift™ (Alma Lasers™, Israel) is distributed by Getz Healthcare Pty Ltd.

**Reason for assessment**

The fractional CO₂ laser technology may represent an additional treatment option for some gynaecological conditions including VVA. This technology is rapidly disseminating into the public and private health sectors of Australia and New Zealand, and therefore may be considered an established technology; however it is yet to undergo any form of health technology assessment.

**Stage of development in Australia**

- Yet to emerge
- Experimental
- Investigational
- Established
- Established but changed indication or modification of technique
- Should be taken out of use

**Licensing, reimbursement and other approval**

The FemiLift™ laser device was registered on the Australian Register of Therapeutic Goods in October 2010, the FemTouch™ laser device was registered in April 2011, and the DEKA SmartXide2 Laser System used for the MonaLisa Touch® treatment was registered in May 2012. All devices were generally registered as lasers for a range of applications, including incision, excision, vaporisation and coagulation of body soft tissue.

All of these systems have United States Food and Drug Administration (FDA) and are CE Mark approved.

Currently, only Queensland, Tasmania and Western Australia regulate class four laser operators, and users within those jurisdictions are required to complete local regulatory requirements. Training in the machine use, maintenance, and treatment protocols is usually provided by the distributors on-site with one to two days of training provided. All
distributors within Australia and New Zealand either provide laser safety training, or highly recommend or require that potential users to undertake external laser safety training (personal communication, High Tech Laser Australia Pty Ltd; Getz Healthcare Pty Ltd, Lumenis (ANZ) Pty Ltd).6

**Australian Therapeutic Goods Administration approval**

- Yes
  - Mona Lisa ARTG number: 106780
  - FemTouch ARTG number: 182239
  - Femilift ARTG number: 177041
- No
- Not applicable

**Technology type**
- Device

**Technology use**
- Therapeutic

**Patient Indication and Setting**

**Disease description and associated mortality and morbidity**

Vulvovaginal atrophy (VVA) occurs under the condition of hypoestrogenism. Accordingly, it is more common in post-menopausal women but can also occur from surgical menopause (e.g. bilateral oophorectomy), during lactation, various cancer treatments (including surgical, pelvic radiation therapy, chemotherapy, or endocrine therapy), medication usage (e.g. GnRH agonists), disordered eating, and excessive exercise causing hypothalamic amenorrhea.7,8

Vulvovaginal atrophy involves histological, morphological, and clinical changes such as alteration in collagen type ratios, flattening of collagen fibrils, decreased quantity of elastic fibres, reduced vascularisation, and thinning and flattening of the vaginal epithelium, which can superficially turn into a keratinised layer. As a consequence, the vaginal canal becomes shorter and narrower, and the vaginal epithelium becomes paler and more likely to develop petechiae. Sebaceous glands reduce the production of secretions and therefore, during sexual activity, lubrication is decreased and delayed.3

In a healthy female, as the vaginal epithelial cells exfoliate and die, they release glycogen, which is hydrolysed to glucose. The glucose is further broken down into lactic acid by the action of lactobacillus bacteria. As the vaginal epithelium thins with VVA, there is reduced exfoliation of cells into the vagina. Without the usual homeostatic sequence of events, the pH in the vagina rises (i.e. acidity decreases), resulting in a loss of lactobacilli and an overgrowth of other bacteria, including group B streptococcus, staphylococci, coliforms, and diphtheroids.7
Typically, VVA develops slowly, so symptoms may not be noticed until up to ten years following menopause. Symptoms can include vaginal dryness, irritation, soreness, infections and inflammation, itching and burning sensations, dyspareunia, and urinary frequency, urgency, and incontinence. These symptoms can have an ongoing negative effect on quality of life and sexual health, particularly if women are reluctant to discuss these issues and seek treatment from healthcare providers.

**Number of patients**

There is no located evidence on prevalence specifically within Australia or New Zealand, however international prevalence of VVA is estimated to range from about four per cent in early pre-menopausal groups to 47 per cent in the late post-menopausal group. The prevalence of VVA in post-menopausal women is likely to increase, subject to factors such as an ageing population, increased longevity, and a decline in the use of systemic hormone therapy.

In some subgroups, individual symptom prevalence can be higher than international estimates. For example, within breast cancer survivors, vaginal dryness was present in 23 per cent of pre-menopausal patients, and in 61 per cent of post-menopausal patients.

**Speciality** Gynaecology, women's sexual health

**Technology setting** Ambulatory Care, Primary Care

**Impact**

**Alternative and/or complementary technology**

The fractional CO$_2$ laser technology may represent either a complementary or substitution technology. The technology is marketed as a low-risk procedure and potential alternative to hormone replacement therapy (HRT) for the treatment of post-menopausal or post-partum VVA, vaginal laxity, mild incontinence, and dyspareunia. Additionally, it is proposed for use in conjunction with HRT, as an alternative treatment for patients not suitable for HRT, or for those patients who have found HRT to be ineffective.

**Current technology**

According to the North American Society for Menopause, first-line therapies for VVA should include non-hormonal vaginal moisturisers and low-dose vaginal oestrogen, assuming no contraindications.

Non-hormonal therapies include vaginal moisturisers and lubricants. Water-based vaginal moisturisers are available as liquids, gels, or ovules inserted every few days. Vaginal moisturisers need to be used regularly for optimal effect, and are considered safe for long-term use. Vaginal lubricants are short-acting, and are applied at the time of sexual activity to reduce dyspareunia.
Pharmacologic treatments include topical, low-dose oestrogen and systemic HRT. For symptomatic VVA that does not respond to non-hormonal interventions, low-dose vaginal oestrogen is likely to provide greater benefit, and is the preferred mode of delivery when vaginal symptoms are the only complaint. Topical oestrogen is usually administered vaginally in the form of creams, pessaries, tablets and oestradiol-releasing rings. They have several important effects on the vaginal tissue, including increased blood flow, increased secretions, increased thickness of the vaginal epithelium, and reduced pH. The reduced pH is especially important as this may help restore a healthy vaginal micro-environment and prevent infection.\textsuperscript{10} In 2006, a Cochrane Database of Systematic Reviews undertook a meta-analysis of studies relating to the use of local oestrogens for VVA symptoms, and concluded that these preparations appeared to be equally effective treatment options.\textsuperscript{11}

Although vaginal moisturizers are not as effective in resolving vaginal dryness as hormonal treatments, they can significantly decrease or even eliminate symptoms for many women.\textsuperscript{8} However, these treatments may be prone to patient rejection. In 2013, the REVIVE (REAL Women’s Views of Treatment Options for Menopausal Vaginal ChangEs) survey sought the views of 3,046 United States women with VVA symptoms. Of this cohort, 40 per cent were currently utilising one or more of these treatments, 38 per cent had lapsed on treatment, and the remainder were unaware of treatment options. For those that had lapsed on treatment, patient concerns included safety or side effects, administration methods, messiness, overall treatment efficacy, or that symptoms were not considered bothersome enough to continue treatment.\textsuperscript{12}

Systemic HRT may be indicated as a broader approach for severe vasomotor symptoms, and is administered in the form of patches, oral agents, or a higher-dose vaginal ring. When systemic HRT is used to treat other menopausal symptoms, the patient will generally derive satisfactory resolution of VVA,\textsuperscript{8} although up to 20 per cent of women may require further treatment for symptoms.\textsuperscript{7} Systemic HRT usage dropped significantly following a 2002 Women’s Health Initiative trial, which reported that systemic oestrogen plus progestin resulted in increased risk of heart attack, stroke, blood clots, and breast cancer.\textsuperscript{13} Follow-up post-intervention studies found that most risks dissipated following use cessation, although some elevation in breast cancer risk remained.\textsuperscript{14} However, a further study has reported persistent increased risk of some ovarian cancers, up to ten years after ceasing long-term use.\textsuperscript{15} Although systemic HRT is approved by the FDA for relief from VVA symptoms, recommended use is lowest dose for the shortest duration to achieve treatment goals.\textsuperscript{16} For patients with breast or other oestrogen-sensitive cancers, there are concerns that the provision of any form of oestrogen may worsen survival outcomes. As such, there are higher rates of VVA within these groups, and reduced treatment options.
**Diffusion of technology in Australia and New Zealand**

In addition to the fractional CO\textsubscript{2} laser technology, erbium-doped yttrium aluminium garnet (ER:YAG) lasers are also proposed as an effective and safe treatment for VVA.\textsuperscript{17} ER:YAG lasers use a laser of wavelength of 2,940 nm to provide a non-ablative thermal effect of approximately 45°C. It is claimed that this provides an effect similar to CO\textsubscript{2} lasers through heat shock protein activation, collagen production and anti-inflammatory actions.\textsuperscript{17, 18} Products that utilise the ER:YAG technology include the Renovalase™ (Fotona, Slovenia) and the Action II Petit Lady™ (Luctronic, Massachusetts).

Both fractional CO\textsubscript{2} and ER:YAG laser technology are currently available in multiple locations in all Australian states and territories, and New Zealand, and appears to be rapidly disseminating into the private health sector, provided through gynaecologists\textsuperscript{19}, plastic surgeons\textsuperscript{20}, women’s health and general practices\textsuperscript{21}, and skin clinics\textsuperscript{22}.

According to the Australian and New Zealand distributors, there are approximately 85 fractional CO\textsubscript{2} laser units in operation bi-nationally (personal communication, High Tech Laser Australia Pty Ltd, Getz Healthcare Pty Ltd, Lumenis (ANZ) Pty Ltd). This technology is in limited use within the public health sector, with units in use in the Royal Hospital for Women and the Royal Prince Alfred Hospital in New South Wales. The technology has also been reported in Australian and New Zealand print and electronic media.\textsuperscript{23-25}
International utilisation

<table>
<thead>
<tr>
<th>Country</th>
<th>Level of Use</th>
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<tbody>
<tr>
<td></td>
<td>Trials underway or completed</td>
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<tr>
<td>Brazil</td>
<td>✓</td>
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<tr>
<td>Canada</td>
<td>✓</td>
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<td>Central America</td>
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<td>France</td>
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<td>Hong Kong</td>
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<td>Japan</td>
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<td>United States of America</td>
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<td>Uruguay</td>
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Cost infrastructure and economic consequences

No published information on the cost-effectiveness of fractional CO$_2$ laser in comparison to other forms of treatment could be located.

The cost of a fractional CO$_2$ laser unit is approximately AU$85,000-$95,000. The base laser can also be utilised for other dermatological or surgical procedures with purchase of the correct attachments. The equipment also requires a plume extractor for operation, which may cost up to $5,000. The system also requires the use of an autoclave to sterilise the laser applicator between uses. After the capital cost, there are no ongoing costs for consumables, except with the FemiLift™ device which uses a $150 single-use applicator sleeve per treatment.

Currently, publicly available information on treatment costs within the private health sector ranges from $900$^{26}$ to $3,000$^{24}$ for a series of three treatments. Initial consultation costs with medical personnel are claimable on Medicare, however there is currently no applicable Diagnosis Related Group (DRG) or Medical Benefits Schedule (MBS) item for the treatment itself. Should the diffusion of this technology into the health sector continue, this issue may require further consideration.
Where the capital cost is the only significant expenditure, the cost per treatment should be low where high utilisation would be anticipated. Although this technology is being marketed to general practitioners, this is unlikely to be cost-effective as the usage would be low, resulting in a high cost per service.

**Ethical, cultural, access or religious considerations**

Given the intimate nature of the fractional CO2 laser treatment, there may be cultural or religious considerations. However, this only forms a potential treatment option which can be refused by the patient, and female medical practitioners offering this technology are available within most Australia and New Zealand jurisdictions if desired.

**Evidence and Policy**

**Safety and effectiveness**

A single cohort study (level III-2 interventional evidence) and six case series (level IV interventional evidence) were identified for inclusion in this technology brief. An overview of studies is presented in Table 1.

**Table 1  Included study characteristics**

<table>
<thead>
<tr>
<th>Study/location</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Number of patients, Length of follow-up, and losses to follow-up</th>
<th>Conflicts of interest</th>
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<tbody>
<tr>
<td><strong>Patient outcome studies</strong></td>
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<tr>
<td>Pieralli et al. (2016)27 Case series Italy (dual centres)</td>
<td>Oncological menopause (women with current or previous breast cancer), VVA dyspareunia, negative Pap smear</td>
<td>Prior use of moisturising agents/lubricants within 30 days, active genital infection, prolapse stage ≥II, previous reconstructive pelvic surgery or topical radiotherapy</td>
<td>n=50 Follow-up mean time: 11 months Follow-up losses: nil</td>
<td>Nil</td>
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<tr>
<td>Perino et al. (2015)28 Case series Italy (single centre)</td>
<td>Post-menopausal patients, one or more symptoms related to VVA, non-response to previous oestrogen or local therapies</td>
<td>Active genital infections, pelvic organ prolapse (POP) stage &gt;II, use of HRT (systemic or local) in last 6 months, psychotropic drugs</td>
<td>n=48 Follow-up time: 11 months Follow-up losses: nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Salvatore et al. (2014)29 Case series Italy (single centre)</td>
<td>Symptoms of VVA rated as moderate/severe, age &gt;50 years, absence of menstruation for ≥12 months and not responding/unsatisfied with previous local oestrogen therapies.</td>
<td>HRT in the 6 months, use of vaginal moisturizers or lubricants, urinary tract or active genital infections, prolapse staged &gt;II, previous reconstructive pelvic surgery, psychiatric disorders</td>
<td>n=50 Follow-up time: 3 months Follow-up losses: 1</td>
<td>None relevant</td>
</tr>
<tr>
<td>Study/location</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>Number of patients, Length of follow-up, and losses to follow-up</td>
<td>Conflicts of interest</td>
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<tr>
<td>Zerbinati et al. (2015)$^{20}$ Case series</td>
<td>Subset from Salvatore et al. (2014) trial: post-menopausal women affected by severe VVA symptoms</td>
<td>HRT in the last 12 months, use of vaginal moisturisers and active genital infections</td>
<td>n=5 Follow-up time: 2 months Follow-up losses: nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Salvatore et al. (2015)$^{3}$ Prospective cohort study</td>
<td>Post-menopausal women with VVA, symptomatic stage II or higher anterior vaginal wall prolapse surgical repair</td>
<td>Not reported</td>
<td>n=5 Follow-up time: 1 month Follow-up losses: nil</td>
<td>Three of the authors reported financial relations (expert testimonies and lectures) with DEKA Laser.</td>
</tr>
<tr>
<td>Salvatore et al. (2015)$^{31}$ Retrospective case series</td>
<td>Post-menopausal women with VVA symptoms</td>
<td>As per Salvatore et al. (2014)$^{29}$ above</td>
<td>n=77 Follow-up time: 3 months Follow-up losses: nil</td>
<td>One of the authors reported financial relationships (lectures, member of advisory boards and/or)</td>
</tr>
<tr>
<td>Salvatore et al. (2014)$^{32}$ Case series</td>
<td>Sexually active, with dyspareunia related to VVA, age &gt;50 years, absence of menstruation for ≥12 months and not responding/unsatisfied with previous local oestrogen therapies.</td>
<td>As per Salvatore et al. (2014)$^{29}$ above</td>
<td>n=15 Follow-up time: 3 months Follow-up losses: nil</td>
<td>None relevant</td>
</tr>
</tbody>
</table>

**Patient Outcome Studies**

Pieralli et al. (2016)$^{27}$ intended to evaluate the outcomes of fractional CO$_2$ laser treatment in breast cancer survivors with VVA and dyspareunia. A total of 50 patients were recruited, with a mean age of 53.3 years (range: 41-66 years), and a mean duration of menopause at enrolment of 6.6 years (level IV intervention evidence).

The study consisted of three treatments of the MonaLisa Touch$^\text{®}$ technology, spaced at 30 day intervals. Prior to treatment, and at four weeks following treatment, the first 36 patients of the study group underwent gynaecological assessment, and were scored using five parameters of the Gloria Bachmann’s Vaginal Health Index (VHI): elasticity, fluid volume, pH, epithelial integrity and moisture. Each parameter was graded from one (worst condition) to five (best condition), with VVA defined as a total score <15. Intensity of VVA dyspareunia for all patients utilised a visual analogue scale (VAS), with a score from 1 (absence of symptoms) to 5 (severe symptoms). Treatment satisfaction for all patients was evaluated post-treatment using a 5-point Likert scale (very satisfied, satisfied, uncertain, dissatisfied and very dissatisfied). Patients were also asked to inform on treatment or post-
treatment complications, such as pain, burning, itching, bleeding, leucorrhoea, or discomfort.

During the study, patient VHI score improved from a baseline mean score of 8.9 ± 1.7 to a post-treatment score of 21.6 ± 1.6, resulting in a statistically significant recovery (p<0.0001). The median of dyspareunia VAS pre-treatment was 5 (severe), while the median of VAS post-treatment was 3, a statistically significant improvement (p<0.0001). No patient required lubricants or other adjuvant therapies post-treatment during sexual activity.

Post-treatment patient satisfaction with the procedure was 18 patients (36%) were very satisfied, 20 (40%) were satisfied, 6 (12%) were uncertain, and 6 (12%) were dissatisfied. To determine long-term treatment effects, patients were further contacted at a mean time of 11 months (range of 3–25 months). At this point, 52 per cent of patients answered they were very satisfied or satisfied with the treatment results, 22 per cent were dissatisfied but decided to start a new treatment cycle, and 26 per cent were dissatisfied and did not want to repeat the treatment. The only complications reported during treatment and post-treatment were 12 patients (24%) who complained of pain at probe insertion.

Perino et al. (2015)28 examined the effects of fractional CO₂ laser on the treatment of VVA symptoms where subjects were non-responsive to previous oestrogen or local therapies. Forty-eight post-menopausal patients were evaluated using a VHI score, with VVA symptoms recorded on a one to ten VAS scale. Following treatment, patients were also asked to rate overall satisfaction using a five-point Likert scale (level IV intervention evidence). At conclusion, both VHI scores and VVA symptoms had significantly improved (p<0.0001), with approximately 92 per cent of patients either highly satisfied or satisfied with the treatment. There were no adverse events reported, and patients were tolerant of the procedure.

Salvatore et al. (2014)29 conducted an initial pilot study using fractional CO₂ laser for treatment of VVA symptoms. Fifty post-menopausal patients, unresponsive or dissatisfied with previous local oestrogen therapy, were evaluated using the VHI score, with VVA symptoms and patient pain recorded on a zero to ten VAS scale. Following the final treatment, patients were also asked to rate overall satisfaction using a five-point Likert scale (level IV intervention evidence).

Reported results included significant improvement across all WHI measures (elasticity, fluid volume, pH, epithelial integrity and moisture) and VVA symptoms (dryness, burning, itching, dyspareunia and dysuria) from baseline to follow-up (p < 0.001). Baseline pain measures on the VAS scale were 4.7 ± 1.6 for probe insertion, 2.6 ± 1.5 for probe movement, and 0.6 ± 0.8 during laser application. However, by the third treatment, reported pain had reduced to a score of one or less for all measures. No adverse events (i.e. infections, worsening of symptoms) related to the procedure were recorded throughout the study period. In relation to overall satisfaction, 16 (32.0%) patients reported being very satisfied, 26 (52.0%) were
satisfied, seven (14.0%) were uncertain, and one patient unable to tolerate the probe (2.0%) was very dissatisfied.

**Histological Studies**

Zerbinati et al (2015) reported microscopic and ultrastructural findings obtained from vaginal mucosa biopsies of five patients from the Salvatore et al. (2014) study. Biopsies were taken before treatment, and at one and two months post-treatment, with differing biopsy sites utilised for each sample. Samples were subjected to light and electron microscopy examination.

Under light microscopy examination, pre-treatment samples demonstrate an atrophic vaginal mucosa, with a thin stratified squamous epithelium, and a flat and even basal surface lacking in connective tissue indentations in the papillae. At two months post-treatment, the squamous stratified epithelium appeared thickened with multiple proliferating cell layers. The basal surface of the epithelium appeared characteristically indented, with identification of elongated blood capillaries (see Figure 2).

**Figure 2** (a) Vaginal mucosa prior to treatment (b) Two months post-treatment

Electron microscope examination of vaginal connective tissue post-treatment supported the idea of fibroblast stimulation to produce new molecular components of the extracellular matrix (i.e. collagen and ground substance components).

These reported outcomes are similar to the histological findings also reported in an earlier study by Salvatore et al. (2015). This small cohort study reported on the outcomes of five patients with VVA symptoms who required prolapse repair. Following repair, one side of the vaginal wall was treated with fractional CO$_2$ laser utilising differing power settings, with the contralateral wall remaining untreated, and as such, each patient acted as their own control. Biopsies were subjected to light and electron microscopy.

Under light microscopy, control samples showed a flattened epithelium, loss of papillae, and absence of activated fibroblasts. Following treatment, there was evidence of a thickened stratified squamous epithelium, and vessel-rich papillae. Under electron microscopy, fibroblasts demonstrated features associated with functional activation.
At time of publication, a further case study was released which examined the effect of laser treatment on the vaginal microenvironment. This study (n=53) reported significant increases in *Lactobilli* and normal flora populations ($p < 0.001$), and decrease of vaginal pH from a mean of $5.5 \pm 0.8$ to $4.7 \pm 0.5$ ($p < 0.001$). This indicates a possible explanation for the reported benefits of the treatment. Due to timing issues, a full examination of this study is not included in this brief.\(^{33}\)

**Effect on Sexual Function**

Salvatore et al (2015)\(^{31}\) investigated the effects of the MonaLisa Touch\(^{*}\) technology on sexual function and overall satisfaction with sexual life in post-menopausal women with VVA. A total of 77 patients (mean age 60.6 ± 6.2 years) underwent a series of three laser treatments at four week intervals, except for two patients who could not accept the probe. There were no reported adverse effects during treatment, or post-treatment.

Data was collected by questionnaires undertaken at pre-treatment, and four weeks following the final treatment. The questionnaires consisted of VVA symptoms on a zero to ten VAS, a version of the Female Sexual Function Index (FSFI), a zero to ten sexual satisfaction VAS, and a version of the Short Form 12 to assess physical (PCS12) and mental (MCS12) component scores of quality of life.

Following treatment, there was a reported statistically significant improvement in a range of VVA symptoms, including dryness, burning, itching, dysuria, and dyspareunia ($p < 0.001$). In relation to sexual activity, at baseline 57 women (74%) were sexually active. After one cycle of treatment, 17 of the 20 inactive patients resumed coital sexual activity. At the end of the study period, a total of 74 women (96.1%; $p < 0.001$) were sexually active. In relation to the FSFI scores, there was a reported significant increase in scores across all domains of desire, arousal, lubrication, orgasm, satisfaction and pain ($p < 0.001$), and an increase in total FSFI score from baseline of $14.8 \pm 7.7$ to $27.2 \pm 5.5$ (on a 2 to 36 point scale). At treatment conclusion, there were reported significant improvements in PCS12 (baseline score of $48.8 \pm 6.4$ to $50.7 \pm 6.5$; $p = 0.013$), and MCS12 (baseline score of $43.2 \pm 8.3$ to $46.1 \pm 7.6$; $p = 0.013$).

This study is subsequent to an initial pilot study of 15 patients undertaken in 2014 (Salvatore et al., 2014\(^{32}\)).

**Economic evaluation**

No economic studies on the cost-effectiveness of the fractional CO\(_2\) laser were identified.

**Ongoing research**

A total of three clinical trials on fractional CO\(_2\) laser treatment for VVA were identified from a search of ClinicalTrials.gov and the Australian and New Zealand Clinical Trials Registry (Table 3). Two are randomised comparative studies which compare fractional CO\(_2\) laser...
treatment to oestrogen therapy. One is a randomised controlled trial, and the other is a randomised single-blinded trial with an option to swap the treatment arm at six months. The randomised controlled trial is currently in progress, with the other trial yet to commence recruitment. The third study is a small case series study of VVA symptoms following fractional CO\(_2\) laser treatment, which is still recruiting participants.

### Table 2 Registered MonaLisa Touch\(^\circ\) clinical trial characteristics

<table>
<thead>
<tr>
<th>Study Location</th>
<th>Design</th>
<th>Number of patients</th>
<th>Intervention</th>
<th>Primary outcomes</th>
<th>Trial status (Estimated completion date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02691936 United States of America</td>
<td>Randomised single blinded clinical trial Multicentre</td>
<td>196</td>
<td>Application of 6 months of CO(_2) fractionated vaginal laser therapy or vaginal oestrogen cream therapy, option to transfer therapy at 6 months</td>
<td>Treatment effectiveness</td>
<td>Not yet recruiting (Dec 2018)</td>
</tr>
<tr>
<td>NCT02419729 Brazil</td>
<td>Randomised Controlled Trial Single centre</td>
<td>45</td>
<td>CO(_2) laser and oestrogen vs. CO(_2) laser and placebo of oestrogen vs. placebo of CO(_2) laser and oestrogen</td>
<td>Treatment effectiveness</td>
<td>Ongoing (Dec 2015)</td>
</tr>
<tr>
<td>NCT02747641 United States of America</td>
<td>Case series Single-Centre</td>
<td>15</td>
<td>Application of CO(_2) fractionated vaginal laser therapy</td>
<td>VVA symptoms utilizing Bachman Vaginal Health Index</td>
<td>Recruiting (March 2017)</td>
</tr>
</tbody>
</table>

### Other issues

This technology is widely marketed as a “vaginal rejuvenation” procedure. In addition to promoting relief of VVA symptoms, there are claims that the treatment can also produce tightening of the vaginal canal, reduction of urinary stress incontinence or bladder leakage, enhancement of sexual gratification, and improvement of female genital appearance. As such, it appears primarily aimed at post-menopausal women, however is also marketed for post-partum and other women.

In relation to evidence to date, most VVA studies consist of case-series evidence. A single comparative study used five patients as their own control\(^3\), comparing histological biopsies taken from a treated vaginal wall to the contralateral, untreated control wall. Further comparative clinical evidence is required to ascertain effectiveness and clinical utility of the MonaLisa Touch\(^\circ\) technology in relation to treatment for VVA. In relation to other claims, there is no published peer-reviewed information located that supports these assertions.

Critics have raised concerns that there is a lack of scientific data on the safety and efficacy of laser technology for gynaecological application. Criticisms include little documented literature regarding the technological mode of action, surgical indications, technique standardisation, complication rates, or definitions of successful surgical outcomes.
Additionally, it is suggested that safety aspects require further study, due to the potential for tissue damage, adhesions, scarring and resultant morbidity. Furthermore, it has also been raised that there may be unknown distal effects on proximal organs such as the rectum, urethra and bladder, or pelvic vessels and nerves.\textsuperscript{34}

Respondents agree that further high quality studies and the development of evidence-based guidelines are desirable for gynaecological applications. However, they also note that CO\textsubscript{2} lasers are utilised in many medical fields with recognised therapeutic effects, and point to published research in relation to VVA treatment.\textsuperscript{35} It should be noted that these criticisms were directed at a range of gynaecological procedures, including cosmetic gynaecological procedures, which are undertaken with surgical lasers of greater power than used during VVA treatment. Additionally, the fractional CO\textsubscript{2} lasers only penetrate to a depth of approximately 0.5mm for the VVA treatment, therefore potential adverse distal effects are unlikely.

Clinical input sought during the development of this brief found that some practitioners considered it should only be administered by specialist gynaecologists, and other concerns that this technology is being marketed directly to the consumer (personal communication). Neither the Australian Society of Plastic Surgeons (ASPS) or the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) had a specific position located regarding the gynaecological application of CO\textsubscript{2} lasers for the treatment of VVA. However, RANZCOG strongly discourages the performance of any surgical or laser procedure that lacks current peer reviewed scientific evidence, other than in the context of an appropriately constructed clinical trial.\textsuperscript{36} It would be beneficial if these peak medical bodies were to issue position statements in relation to this technology, including accepted medical indications for treatment, patient referral and selection definitions within a model of care context, agreed treatment protocols, and defined training and accreditation standards for operators.

Conflicts of interest were identified in two of the studies. In Salvatore et al. (2015)\textsuperscript{31}, the principal author disclosed a financial relationship (lectures, member of advisory boards and/or consultant) with the manufacturer. Additionally, in Salvatore et al. (2015)\textsuperscript{3}, the principal author and two other authors disclosed financial relations (expert testimonies and lectures) with the manufacturer.
Number of studies included

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

Total number of studies: 7
Total number of Level III studies: 1
Total number of Level IV studies: 6

Search criteria to be used (MeSH terms)

Atrophy
Female
Lasers, Gas/therapeutic use*
Postmenopause/physiology
Sexual Behavior/physiology*
Sexual Dysfunction, Physiological/etiology
Sexual Dysfunction, Physiological/surgery
Vagina/pathology*
Vagina/surgery*
Vulva/pathology*
Vulva/surgery*

References


14. Manson, J. E., Chlebowski, R. T. et al (2013). 'Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials'. *Jama*, 310 (13), 1353-68.


