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Endometriosis treatment with shock waves: A novel approach

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ABSTRACT

Endometriosis affects 10–15% of women. When medication is unsatisfactory, not well tolerated or unwanted, surgery remains the sole option. There is a need for a less invasive treatment. We suggest the application of shock wave therapy (SWT) to endometriotic nodules (including deep infiltrating endometriosis), endometriomas and adenomyosis. We hypothesize pain relief via an antiinflammatory effect, an antioxidant effect and neural pathways modulation, as well as a direct effect on the lesions by the energy thus delivered. Questions to be answered before a clinical application is tested include route of administration (external versus internal transducers), dose regimen, optimal duration of treatment and type of shock waves used (focalised versus radial).

Introduction

Endometriosis is defined as the ectopic localisation of endometrium. Prevalence is estimated at 10–15% of women of reproductive age and 70% of women with chronic pelvic pain [1]. Dysmenorrhea, dyspareunia, bladder and rectal pain and infertility are common, with a significant impact on quality of life of patients over decades. When pain medication and amenorrhea inducing drugs (oestroprogestative or progestin only pills, GnRH analogs, Levonorgestrel releasing intrauterine devices) are unsatisfactory, not well tolerated or unwanted, surgery remains until today the only validated solution. It should be remembered that 11–19% of women with endometriosis derive no pain relief at all from medical therapy [2]. However surgery, especially excision of deep infiltrating endometriosis (DIE, infiltration > 5 mm of peritoneum) can be challenging, and complications rates can be high. Major complications after colorectal segmental resection of bowel endometriosis occurs in 11% of women [3]. Long-term urinary and digestive side effects are common following surgery [4,5]. Surgical referral centers with the expertise to deal with DIE are not available worldwide. Adenomyosis, the benign invasion of the myometrium by ectopic endometrial tissue, is seldom eligible to conservative surgery, and remains a conundrum in women of childbearing age. Removal of endometriomas by laparoscopy, admittedly a routine procedure, can lead nevertheless to poor ovarian reserve, especially after repeat procedures [6]. We present a novel hypothetical approach to the treatment of endometriosis by shock wave therapy (SWT).

Biophysical bases of SWT

A shock wave is a form of acoustic energy resulting from a sudden and intense change in pressure, which produces waves of energy through elastic mediums like human soft tissue or bone. Shock and pressure waves are pulses, while ultrasound is a continuous oscillation [7].

In clinical settings shock waves are a sequence of single sound pulses, characterized by high point of pressure, fast reach of pressure for a short period, followed by a variable negative pressure that induce extracellular cavitation, a complex mechanism of bubble formation, expansion and collapse [8]. Acoustic shockwaves are primarily generated by three different methods, electrohydraulic, electromagnetic, and piezoelectric [9,10].

Modulation of SWT relies on shock wave intensity, frequency, number of shock waves per treatment session and total number of sessions. Shock wave intensity can be classified as low-energy ($< 0.08\ \mathrm{mJ/mm^2}$), middle-energy ($0.08–0.28\ \mathrm{mJ/mm^2}$), and high-energy ($0.28–0.60\ \mathrm{mJ/mm^2}$), with most clinical applications in the $0.001–0.40\ \mathrm{mJ/mm^2}$ range [11,12]. Shock wave frequency ranges from about 60 to about 360 shock waves per minute. The number of shock waves per treatment session ranges from about 100 to about 5000 [10].

Focused shock wave therapy (fSWT) delivers higher intensity energy, at deeper levels, whereas radial shock wave therapy (rSWT) has a wider target and may be less painful. In musculoskeletal applications higher energy levels lead to more destructive effects and lower energy levels lead to more regenerative effects on the treated tissue [7].

Rationale for SWT in endometriosis

Two broad types of biological effects can be identified in SWT: on one hand «soft» effects, obtained by low intensity fSWT or rSWT and on the other hand «disruptive» effects as used in lithotripsy. We believe both could have useful applications in endometriosis, as separate or combined techniques.

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Antiinflammatory effect

Shock waves may induce nitric oxide (NO) synthesis by way of endothelial nitric oxide synthase release [13,14]. NO is a modulator of inflammatory process and can down regulate activation of neutrophils, macrophages, mast cells, endothelial cells, and platelets [15].

Shock wave therapy has been used successfully in the treatment of inflammatory conditions such as diabetic wounds, tendinitis, plantar fasciitis, epicondylitis and chronic pelvic pain syndrome/chronic prostatitis (CPPS/CP) [7,16–19].

Endometriosis is equally a chronic inflammatory condition. Retrograde menstruation (Sampson's hypothesis) is the oldest and most widely accepted theory of endometriosis formation. Cyclic accumulation of menstrual debris in the peritoneum of women with impaired immunological response (dysfunctional macrophages, natural killer cells and cytotoxic T cells) induces a chronic inflammatory state which leads to fibrosis and adhesion formation. The peritoneal fluid of women with endometriosis has been found to contain abnormally high levels of numerous pro-inflammatory cytokines like IL-1, IL-8 and TNF-α [20]. Shock wave therapy may diminish this response and prevent evolution to more severe forms.

Antioxidant effect

NO is a potent free radical scavenger. The ability of NO to scavenge superoxide anion (O_2^-) has been documented both in vitro and in vivo [15]. Oxidative stress is part of the toxic molecular environment of endometriosis and has been linked to fertility impairment in this disease. Peritoneal iron overload (from menstrual reflux or bleeding lesions or from a deficiency in the peritoneal iron metabolism system) generates reactive oxygen species (ROS) via the Fenton reaction ($Fe^{2+}_{(aq)} + H_2O_2 \rightarrow Fe^{3+}_{(aq)} + OH^-_{(aq)} + HO^{\cdot}$). ROS impairs peritoneal lining, promoting ectopic endometrial cell adhesion. ROS also affects oocyte maturation, ovarian steroidogenesis, ovulation, implantation, formation of blastocyst, luteolysis, and luteal maintenance in pregnancy [21].

Pain threshold and gate control modulation

In chronic conditions pain threshold is progressively lowered. Smaller nociceptive stimuli are therefore transmitted by neural pathways, and then processed and amplified by the central nervous system (CNS). Shock wave induced cavitation effect may disrupt neural transmission of those stimuli and reverse the CNS amplification [18]. A gate-control effect has been also hypothesized. This is supported by the fact that local anesthesia reduces the effect of SWT for plantar fasciitis and for insertional Achilles tendinopathy [7]. Substance P liberation after SWT may mediate this gate-control mechanism [22]. Chronic refractory perineal pain after excision of a vulvar nodule has been successfully treated by SWT [23].

Pathologic tissue disruption by directed energy

Focal SWT delivers relatively high energy to the target point, and has been widely used since 1980 in lithotripsy to destroy urinary tract calculus [24]. With ultrasound or MRI guidance this energy could be used to disrupt endometriotic nodules. Although the rationale for SWT in muscluloskeletal diseases has shifted from abnormal tissue destruction to inflammation modulation and tissue regeneration [11], non invasive targeted destruction could still be useful in endometriosis if the effect is limited to the disease and do not disrupt normal neighbouring tissue. Focal width of most lithotriptors is in the 2–20 mm range, with a depth of the focal zone ranging between 28 and 50 mm. Some machines allow variation of the focal width [25,26]. A narrow focal zone is associated with greater tissue disruption and a clear-cut boundary of histological injury between targeted and neighbouring tissue. A large focal zone, on the other hand, induces less tissue destruction but more widespread small lesions [25]. Most clinically significant endometriotic nodules belong to this dimensional frame, as well as the resolution of imaging and targeting techniques [27].

Discussion

It is of the foremost importance to find non-invasive or minimally-invasive alternative treatments to surgery in endometriosis, especially challenging subtypes like deep endometriosis and adenomyosis.

Uterine artery embolisation (UAE) has been successfully used in adenomyosis. However in women of childbearing age this technique remains controversial, some investigators having reported complicated pregnancies after UAE [28–31].

There are reports of radiofrequency ablation (RFA) of abdominal wall endometriosis [32] and adenomyosis [33,34].

High energy focalised ultrasound (HIFU) has also been successfully used in abdominal wall endometriosis [35–37] and adenomyosis [38–41]. A preliminary study of HIFU in deep posterior endometriosis has reported good results [42].

However high intensity energy application to the bowel or bladder may induce necrosis and fistula formation. There is indeed a case report of recto-uterine fistula after RFA of a uterine fibroid [43], and several reports of bowel perforation after HIFU for uterine fibroids and adenomyosis [38,44,45]. SWT may present less risk of injury due to lower energy levels at the focal point. For instance, Dubernard et al. report an acoustic intensity of 413–3592 W/cm^2 with HIFU [42]. Tissue ablation temperature at target can reach 90 °C [44]. While a direct comparison is difficult due to the different physical mechanisms at play, non linear tissue attenuation, number of shock waves and other variables it is safe to assume lower intensity and temperature even with high energy SWT. A small 3 °C temperature increase has been calculated for 3000 shock wave pulses of 80 MPa peak pressure at a high experimental rate of 100 shock wave per second [46]. Values for more clinically relevant pulse rates of 1 to 2 shock waves per second barely exceed a 1 °C increase [47]. Temperature increase in kidney tissue after one shock wave reaches a maximum of 1.7×10^{-3} °C [48]. Regarding biophysical effects in other tissues, sound wave propagation in liver and muscle tissue is roughly equivalent to the one in kidney, but propagation in fat is faster and could lead to different results depending on the body fat percentage of a given patient [48]. Broad experimental data in different tissues is lacking, and the heterogeneity of endometriotic nodules renders extrapolation challenging. It should also be stressed that tissue damage remains possible without thermal injury (by cavitation or shear mechanisms). The risk of renal hematoma following shock wave lithotripsy is about 0.5% [49]. Targeting and body motion control are therefore of crucial importance. Strategies used in SWT to reduce tissue damage include slowing the pulse rate to approximately 60 shock waves per minute and «ramping up» the pulse rate (starting slow and then progressively getting faster) [26]. A new technology (dual-pulse) aims to reduce cavitation induced lesions by modulating bubble formation (bubbles collapse if subjected to another pulse early in their growth phase). Broadening the focal zone and lowering the peak positive pressure is another evolution adopted by some manufacturers [9]. The total number of shock waves should be kept low and repeat procedures avoided as scaring and fibrosis of tissue are dose-dependent [25]. Research should therefore determine the optimal dose regimen, which obtains the highest efficacy with the lowest total number of shock waves.

The rationale to use rSWT over fSWT derives form muscle and tendon studies and subsequent clinical experience, however transposition to visceral organs remains under investigation. Some promising results have been demonstrated in chronic prostatitis [18,19]. Modulation of pain, antiinflammatory and antioxidant effects may be at play.

Technical issues should be tackled, namely route of administration of SWT (external or internal transducers), guidance (ultrasound or MRI) and tolerance (in order to minimize analgesia and/or anesthesia requirements). In our opinion external SWT may be satisfactory for abdominal wall endometriosis but internal transducers (vaginal or rectal) are probably best adapted to deep endometriosis. Ultrasound guidance seems the first choice due to the widespread diffusion of the technique and lower cost. Skin tolerance is enhanced when the transducer array is large [25] but this is of limited practical importance in internal devices.

Other questions include respective indications of fSWT and rSWT in different clinical situations, combined use of SWT with medication, role of SWT before surgery and assisted reproductive techniques (ART), effect of SWT on ovarian reserve and pregnancy outcomes.

To the best of our knowledge there are no published reports of SWT use in endometriosis.

A US patent has been filed (by others) for a SWT device to be specifically used on the female genitalia [10].

Proof of concept could be demonstrated on animal models. Spontaneous endometriosis is reported in menstruating primates and endometriotic lesions have been induced experimentally in baboons, rats, mice [50] and pigs [51]. Biomedical research on primates is highly regulated, and is burdened by the scarcity of animals, high cost and ethical considerations. Induced endometriosis in rodents is often cystic and do not phenocopy human disease [50]. The small size of rodents is also a liability in SWT experimentation, as precise targeting of the lesions would be unrealistic. We therefore suggest the use of swine models which combine good availability, acceptable cost and sufficient animal size. A clear histological effect should be demonstrated, and any complication thoroughly reported. Ehtical guidelines in animal research should always be respected. The main principles are the so called 3 R's: Replacement (by other means if possible), Reduction (use of the smallest number of animals to reach scientific significance), Refinement (to avoid, alleviate or minimise the potential pain, distress or other adverse effects suffered by the animals involved). Mandatory institutional ethical reviewing of animal experimentation exists in a growing number of countries [52].

The next step would be a small-scale human test. We suggest that abdominal wall endometriosis could be addressed first, due to the lesser proximity with visceral organs and lower risk of bowel injury or intra-abdominal hemorrhage.

Conclusion

SWT is a novel approach to endometriosis treatment which may offer a valuable alternative to surgery. Technical and clinical questions should be answered before a preliminary study can be undertaken. If successful this technique could be widely used, even in low-resource settings where complex surgery remains out of reach, or when surgical risks are deemed too high by the patient or her medical team. Possible advantages over other non-invasive or minimally-invasive treatments are still to be demonstrated.

Disclosure

Dr Melki does not declare any conflict of interest.

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