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Pelvic floor dysfunction in women with deep infiltrating endometriosis: from bench to bedside

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ABSTRACT

Deep Infiltrating Endometriosis (DIE) is a severe form of endometriosis that affects the pelvic organs and often leads to pelvic floor dysfunction (PFD). This review explores the relationship between DIE and PFD, analysing diagnostic approaches, therapeutic strategies, and novel imaging tools. A narrative review was conducted using PubMed and EMBASE with no time restrictions, following SANRA guidelines. Thirteen studies were included, comprising clinical trials, observational studies, and systematic reviews. Evidence indicates that women with DIE experience pelvic floor muscle hypertonia, impaired relaxation, and heightened pain sensitivity. Pelvic floor physiotherapy (PFP) shows benefit in reducing dyspareunia and improving muscle relaxation, though its impact on urinary, bowel, and sexual functions remains inconclusive. Surgical interventions, particularly colorectal resections, are effective in alleviating dyspareunia and faecal incontinence, yet data on urinary improvement are limited. Transperineal ultrasound and elastography emerge as promising tools for diagnosing and monitoring PFD. While surgery currently represents the most effective strategy for symptom relief, integrating non-invasive options and advanced imaging may enhance outcomes. Standardized protocols and high-quality studies are needed to refine management of PFD in DIE.

INTRODUCTION

Endometriosis is a complex disease with unclear origins, affecting 10-15% of women of reproductive age, and notably, it also appears in adolescents and postmenopausal women [1-5]. Common risk factors include early menstruation, heavy menstrual cycles, ethnicity and lifestyle factors [6-9].
The disease is thought to primarily develop from retrograde menstruation, where endometrial cells

backflow into the pelvic cavity, potentially causing implantation and growth [10].

Deep Infiltrating Endometriosis (DIE) is a severe subtype of endometriosis characterized by the infiltration of pelvic structures such as the rectovaginal septum, bladder, and uterosacral ligaments. It affects a subset of women with endometriosis and is frequently associated with complex symptoms, including chronic pelvic pain, dyspareunia, urinary and intestinal dysfunction, and infertility. Despite its clinical burden, the functional complications of DIE – particularly pelvic floor dysfunction (PFD) – remain underrecognized and underexplored in both diagnosis and management.

PFD in this population may result from neuromuscular impairment and hypertonia of pelvic floor muscles, contributing to worsening of urinary symptoms, sexual dysfunction, and defecatory disorders. Diagnostic tools like transvaginal ultrasound and MRI provide structural assessment of DIE lesions, while emerging modalities such as transperineal ultrasound and elastography are increasingly used to evaluate pelvic floor function. The combination of DIE and PFD poses diagnostic and therapeutic challenges, necessitating multidisciplinary and individualized management [14-16]. Chronic pelvic pain is a hallmark symptom of endometriosis, though its severity does not consistently correlate with the disease extent [17]. This symptom is also common in other gynaecological disorders like uterine fibroids [18]. There's also an observed inverse correlation between the stage of endometriosis at diagnosis and fertility outcomes [19-23].

Diagnostic procedures for endometriosis include laparoscopy, considered the definitive test, though transvaginal ultrasound is preferred initially for less invasive diagnosis, with MRI as an additional, albeit more costly, tool [11, 12]. Currently, the classification of endometriosis for surgical purposes includes several staging systems to better inform postoperative outcomes for patients [13].

This review aims to explore the intricate relationship between DIE and PFD by summarizing current diagnostic strategies, surgical and conservative treatments, and novel approaches for optimizing care in affected women.

MATERIALS AND METHODS

In this literature review, an extensive search was conducted on PubMed and EMBASE using the original textwords and MeSH "Pelvic Floor Dysfunction AND Deep Infiltrating Endometriosis" from inception to December 2024. We included articles in the form of clinical trials, observational studies, meta-analyses, and reviews, without time restrictions; exclusion criteria were not pertinent medical content and non-use of the English language. Exclusion criteria included non-English language publications, studies not involving DIE or pelvic floor outcomes, irrelevant or duplicate articles.

Due to the narrative design of this review, a formal double-blinded screening procedure was applied. Discussion regarding inclusion or exclusion of articles was resolved by consensus after involving a third author. The analytical method was completed by reading the selected articles in their entirety, categorizing relevant issues, summarizing the findings, and conducting a comprehensive evaluation and review procedure to identify items related to the study objectives. For each included study, we extracted key information including study design, sample size, population characteristics, type of intervention, outcome measures, duration of follow-up, and principal findings. Given the substantial heterogeneity in study designs, interventions, and reported endpoints, the results were synthesized descriptively rather than subjected to quantitative pooling or meta-analysis. A total number of 50 studies was included after full text evaluation. Due to the narrative nature of the review, standardized quality appraisal tool was applied, as this review aimed primarily to provide a qualitative synthesis of the existing evidence (**Table 1**).

The selected studies were categorized based on thematic relevance. A narrative synthesis of the selected research was then finalized, adding more theoretical ideas from book chapters and articles referenced in the included studies. The review adhered to the SANRA principles for narrative reviews [24].

RESULTS

DIE and pelvic floor muscles dysfunction: prevalence and pathophysiology

In 2021, Fraga *et al*. [25] conducted a detailed cross-sectional study at a tertiary academic hospital's Endometriosis Outpatient Clinic, involving a total of 160 women. Among these, 80 were diagnosed with DIE affecting the bowel or septovaginal regions and were currently undergoing hormonal

Table 1. *Characteristics of key studies included.*

Study (Author, Year)	Population	Study Objective	Methodology	Key Results	Conclusions
Fraga *et al.*, 2021	160 women (80 with DIE, 80 control group)	Investigate pelvic floor muscle dysfunction in women with DIE	Clinical evaluation, VAS and PERFECT scales, Carnett test	DIE patients showed increased pelvic floor muscle hypertonia and pain during vaginal palpation	Need to incorporate pelvic floor muscle assessment into DIE patient care
Del Forno *et al.*, 2021	34 nulliparous women with DIE and superficial dyspareunia	Evaluate the effectiveness of pelvic floor physiotherapy (PFP) using transperineal ultrasound	3D/4D transperineal ultrasound, pain rating scale, physiotherapy	PFP improved superficial dyspareunia and muscle relaxation	PFP appears to improve dyspareunia and muscle relaxation
Mabrouk *et al.*, 2018	Symptomatic women with clinical/ sonographic diagnosis of endometriosis	Assess the association between hypertonic pelvic floor muscles and deep lesions in DIE women	3D/4D transperineal ultrasound to measure levator hiatus area (LHA)	DIE women showed a smaller LHA at rest, contraction, and during Valsalva	Transperineal ultrasound is useful for comprehensive functional assessment
Raimondo *et al.*, 2017	50 nulliparous women with DIE and 35 healthy women	Evaluate static and dynamic pelvic floor muscle morphometry using 3D/4D ultrasound	3D/4D transperineal ultrasound, measurement of LHA areas	DIE women showed less marked LHA reduction during contraction and less enlargement during Valsalva	3D/4D ultrasound can detect pelvic floor muscle dysfunction in DIE women
Meng Xie *et al.*, 2019	88 patients with DIE, endometriotic cysts, or ovarian teratoma	Assess pelvic floor muscle elasticity in DIE patients using transperineal elastography	Pre- and post-operative transperineal elastography	DIE was associated with decreased pelvic floor muscle elasticity	Transperineal elastography can monitor post-surgical changes in pelvic floor muscles
Fraga *et al.*, 2022	6 randomized controlled trials	Assess the impact of surgery on pelvic floor disorders (urinary incontinence, prolapse, bowel dysfunction, dyspareunia)	Meta-analysis, systematic review of surgical techniques	Significant improvements in dyspareunia and faecal incontinence post-surgery	Surgery improves some aspects of pelvic floor disorders, but no technique superiority was demonstrated
Ballester *et al.*, 2014	50 patients with DIE requiring surgery	Evaluate urinary dysfunction before and after DIE surgery	Urodynamic tests, electromyography, quality of life questionnaires	Pre-operative neurogenic dysfunctions correlated with DIE	Urinary dysfunction persists long-term despite surgery
Meng Xie *et al.*, 2020	34 patients undergoing surgical resection for endometriosis	Assess changes in levator ani elasticity post-surgery	Pre- and post-operative transperineal elastography	Both surgical techniques altered levator ani elasticity	Elastography can monitor post-operative pelvic floor muscle changes
Arena *et al.*, 2022	Women with OE, DIE, and healthy volunteers as controls	Evaluate pelvic floor muscle function using a quick 4-point contraction scale	3D/4D transperineal ultrasound and quick 4-point contraction scale	The quick 4-point scale can rapidly detect pelvic floor muscle dysfunction	The 4-point scale is a useful tool to detect pelvic floor muscle dysfunction
Meng Xie *et al.*, 2019	88 patients with DIE, ovarian cysts, or teratoma	Assess pelvic floor muscle elasticity using elastography	Transperineal elastography pre- and post-operation	DIE patients showed decreased pelvic floor elasticity	Elastography can monitor changes in pelvic floor muscles
Ballester *et al.*, 2014	50 patients with DIE who required surgery	Evaluate urinary dysfunction before and after DIE surgery	Urodynamic tests, electromyography, BFLUTS questionnaire	High incidence of urinary dysfunction before surgery; no significant post-surgical improvement	Urinary dysfunction persists long-term after DIE surgery
Raimondo *et al.*, 2022	Women with DIE and chronic constipation	Investigate trans-perineal ultrasound signs in women with DIE and constipation	Trans-perineal ultrasound at rest and during Valsalva manoeuvre	DIE patients with constipation had smaller LHA and higher LAM coactivation	Trans-perineal ultrasound is useful for diagnosing PFM dysfunction

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Study (Author, Year)	Population	Study Objective	Methodology	Key Results	Conclusions
Del Forno *et al.*, 2021	34 nulliparous women with DIE and dyspareunia	Evaluate the impact of PFP on pelvic floor relaxation using ultrasound	3D/4D transperineal ultrasound, pain scale, physiotherapy	PFP improved pelvic floor muscle relaxation and reduced chronic pelvic pain	PFP appears to improve pelvic floor function in DIE patients
Arena *et al.*, 2022	Women with ovarian endometriosis or DIE	Assess PFM function using a quick 4-point contraction scale	3D/4D transperineal ultrasound and quick contraction scale	Quick scale reliably detected PFM dysfunction in endometriosis patients	Quick scale is a practical tool for PFM assessment
Mabrouk *et al.*, 2018	Women with or without DIE undergoing surgery	Analyse pelvic floor muscle dysfunction in DIE patients	Clinical and sonographic assessments, laparoscopic surgery	DIE patients had smaller LHA and reduced PFM contraction	Tailored therapy is necessary for DIE-related PFM dysfunction
Fraga *et al.*, 2022	Meta-analysis of six randomized controlled trials	Evaluate the impact of surgical treatment on pelvic floor disorders	Systematic review and meta-analysis	Dyspareunia and FI improved after surgery, but no superior technique identified	Surgery can improve pelvic floor disorders, but further studies are needed

DIE: deep infiltrating endometriosis; PFM: pelvic floor muscle; PFP: pelvic floor physiotherapy; VAS: visual analogue scale; LHA: levator hiatal area; LAM: levator ani muscle; OE: ovarian endometriosis.

therapy. The other 80 women, serving as a control group, were attendees of various other outpatient services within the same hospital. Both groups were selected based on their recent history of heterosexual vaginal intercourse within the month prior to their participation in the study and underwent comprehensive physical examinations.

The study's assessments included sterile swab tests and vaginal palpation to identify conditions such as vulvodynia, vaginismus, variations in muscle tone (hyper/hypotony), trigger points, and pain along the vaginal walls. Pain intensity was quantitatively measured using the visual analogue scale (VAS), and the dynamics of pelvic floor muscle (PFM) contractions and relaxations were evaluated through the Modified Oxford scale (PERFECT). Additional diagnostic tests such as the Carnett test were employed to assess abdominal pain. Tests like the Thomas, Pace, and Ober evaluated shortening of the muscles in the lower limbs, and the Schöber test measured the mobility of the lumbosacral area.

The findings from this study revealed significant differences between the two groups. Women with DIE who were receiving hormonal therapy reported more frequent symptoms than those in the control group. Specifically, these symptoms included an increased prevalence of PFM hypertonia, trigger points, and pain during vaginal examinations. Additionally, women with DIE demonstrated weaker PFM contractions and less effective muscle relaxation compared to the control group. The assessments of pain in the abdominal area and lower limbs, particularly in aspects related to pelvic stabilization, consistently showed more pronounced issues in the group affected by DIE. The study linked the presence of pain notably to PFM hypertonia and the inability to fully relax these muscles.

The implications of these findings led the authors to advocate strongly for the inclusion of PFM assessments in the routine care protocol for patients suffering from chronic pelvic pain (CPP) associated with endometriosis. By integrating these evaluations, healthcare providers can gain better insights into the muscular dysfunctions contributing to CPP and thus tailor more effective management and treatment strategies for this patient population. This approach suggests a more nuanced understanding of the interplay between muscular and neurological factors in endometriosis-related pelvic pain, underscoring the need for a multidisciplinary approach to treatment that addresses both hormonal and musculoskeletal aspects of the disease. However, causality cannot be inferred due to the study's observational nature, and confounding by hormonal treatment or disease severity remains unaddressed. The reliance on clinical palpation and subjective measures, while clinically relevant, limits generalizability.

Pelvic floor dysfunction and surgical treatment for DIE

In 2022, Fraga *et al*. [26] carried out a comprehensive systematic review and meta-analysis, meticulously analysing six randomized controlled trials selected from the PubMed database, published up to January 5, 2021. The purpose of their study was

to evaluate the effectiveness of various surgical treatments on pelvic floor dysfunctions associated with DIE. These dysfunctions included urinary incontinence (UI), pelvic organ prolapse (POP), faecal incontinence (FI), constipation, and sexual dysfunction (dyspareunia).

The array of surgical interventions assessed was diverse, encompassing laparoscopic or open colorectal resections, more conservative approaches such as shaving or disc excision, as well as more radical procedures like segmental rectal resection. Additionally, techniques involving laparoscopy with electroablation or CO_2 laser ablation were reviewed, along with combinations of these methods, some including presacral neurectomy. This variety in surgical techniques reflects the complexity and severity of DIE, necessitating tailored surgical responses based on individual patient conditions and the extent of endometrial infiltration.

The outcomes of the meta-analysis revealed significant improvements in dyspareunia, constipation, and FI following surgical intervention. These results highlight the potential for surgical management to alleviate some of the most debilitating symptoms of DIE. However, the meta-analysis also exposed substantial variability in the results, which was attributed to the heterogeneity of the surgical methods employed across the studies. This diversity in techniques poses a challenge to conclusively determining the superiority of one method over another.

During their discussion, Fraga *et al*. recognized the difficulties inherent in synthesizing a holistic data analysis due to the varied nature of the studies involved. Although subgroup analyses did show some benefits for specific symptoms, particularly dyspareunia and FI, no single surgical technique was identified as overwhelmingly superior across all outcomes. This indicates that while surgery can be beneficial, the optimal approach may vary depending on the specifics of each case.

Moreover, Fraga *et al*. [26] pointed out a notable deficiency in the available data concerning the effects of these surgical interventions on UI and POP. This gap in data significantly impedes a thorough methodological review and understanding of how these common aspects of pelvic floor dysfunction respond to surgical treatment in the context of DIE. However, the heterogeneity in surgical techniques (shaving, disc excision, segmental resection) and outcome measures complicates interpretation. The lack of consistent reporting on urinary and prolapse outcomes weakens the review's comprehensiveness. The evidence suggests that while surgery offers symptom relief, it is unlikely to address the full spectrum of PFD and should be integrated into broader, multimodal care.

In conclusion, while the systematic review by Fraga *et al*. confirmed that surgical interventions could lead to improvements in certain symptoms of DIE, such as dyspareunia and FI, the variability in surgical practices and the lack of comprehensive data on all relevant pelvic floor dysfunctions make it challenging to definitively attribute these improvements to any specific surgical technique. The findings underscore the need for further research into standardized approaches that could potentially offer consistent results across the spectrum of DIE-related pelvic floor dysfunctions.

The impact of ultrasound imaging on pelvic floor dysfunction in DIE women

In a series of rigorous studies, researchers explored the relationship between DIE and pelvic floor muscle (PFM) dysfunction through various methodologies and patient groups, highlighting the potential of pelvic floor physiotherapy (PFP) in managing symptoms associated with DIE.

Del Forno *et al*. [27, 28] conducted two sequential randomized controlled trials involving nulliparous women diagnosed with DIE and experiencing superficial dyspareunia. The first study in 2021 involved initial assessments using 3D/4D transperineal ultrasound to examine the levator hiatal area (LHA) in different states, with subsequent PFP sessions for half the participants. Follow-up evaluations showed that the treatment group had improved PFM relaxation and reduced pain levels compared to the control group. The subsequent 2022 trial replicated the setup but expanded the follow-up assessments to include urinary, bowel, and sexual functions. Although PFP did not significantly alter these functions, it did show promise in improving constipation symptoms, suggesting a nuanced benefit of PFP in managing DIE-related complications.

Raimondo *et al*. [29], in 2017, conducted a pilot prospective study assessing PFM morphometry using the same ultrasound technology in women with DIE compared to healthy controls. Their findings indicated that women with DIE had consistently smaller LHA measurements, suggesting inherent

PFM dysfunctions that could be contributing to the symptoms of DIE.

Mabrouk *et al*. [30], in 2018 further investigated the link between PFM hypertonic dysfunction and DIE by enrolling women with ovarian endometriosis for a prospective study. Their research confirmed that women with DIE typically had smaller LHA measurements, reinforcing the theory that PFM dysfunction is a significant factor in the pathology of DIE and related pelvic organ dysfunction [31].

In a 2022 observational prospective cohort study, Raimondo *et al*. [32] examined the specific association between chronic constipation and PFM dysfunction in women with endometriosis. This study revealed distinct ultrasound characteristics in women with endometriosis and constipation, particularly noting increased signs of pelvic floor muscle hypertonia in these patients.

In 2019, Mabrouk *et al*. [33] analysed the relationship between voiding dysfunction and PFM morphometry in patients with posterior DIE. Their findings indicated a link between PFM dysfunction and voiding issues, as evidenced by LAM coactivation during the Valsalva manoeuvre being more prevalent in patients with voiding dysfunction.

Lastly, in 2022, Arena *et al*. [34] utilized a 4-point pelvic contraction scale in a study employing transperineal 3D/4D ultrasound to assess PFM function in nulliparous women scheduled for endometriosis surgery compared to healthy controls. The study demonstrated that this scale could effectively assess PFM function, offering a reliable method to detect dysfunctions and potentially guide targeted PFM rehabilitation therapies.

Collectively, these studies underscore the significant role of PFM dysfunctions in DIE and illustrate the potential of targeted pelvic floor interventions in alleviating some of the debilitating symptoms associated with this condition. However, inconsistent effects on urinary and bowel symptoms may reflect patient heterogeneity, variability in PFP delivery, or insufficient treatment duration. Raimondo and Mabrouk's morphometric findings confirm anatomical changes, but again, causality is uncertain. Together, these studies validate TPU for both diagnosis and therapeutic monitoring, though standardized protocols are still lacking.

In 2019, Meng Xie and colleagues [35] executed a prospective observational study that utilized transperineal elastography to assess the elasticity of PFM in various patient groups. This study encompassed 88 participants who were categorized based on their medical conditions: those with DIE formed Group I, those with ovarian endometrioid cysts constituted Group II, and those with ovarian teratomas were placed in Group III. The transperineal elastography conducted on these groups revealed that the PFMs in the DIE group exhibited both reduced elasticity and compromised coordination.

Building on this research, Meng Xie *et al*. [36] conducted a retrospective study in 2020 to further explore the effects of surgical treatment on PFM elasticity in DIE patients. This study involved 34 patients who had undergone laparoscopic surgery for colorectal endometriosis and were divided into two subgroups: 21 patients underwent colorectal shaving (Group I) and 13 underwent segmental colorectal resection (Group II). Transperineal elastography was utilized to measure the elasticity of the levator ani muscle before and after the surgical procedures. The findings indicated that both types of surgery – shaving and segmental resection – had a significant impact on the elasticity of the levator ani muscle in DIE patients, with the changes effectively captured by the transperineal elastography. However, small sample sizes and absence of clinical correlation with symptoms limit applicability. Larger validation studies are needed to establish its prognostic value and sensitivity to therapeutic change.

Urinary dysfunction before and after DIE surgery

In a 2014 prospective study led by Marcos Ballester and his colleagues [37], the team investigated how surgery for DIE affects urinary function and patients' quality of life. The study included 50 patients scheduled for surgical treatment due to DIE. Researchers utilized urodynamic tests and electromyography to evaluate urinary dysfunction before and after surgery. Electromyography was particularly aimed at identifying neurogenic changes associated with sacral reflexes and the pelvic floor muscles, frequently involved in cases of colorectal endometriosis.

To further understand the impact on patients' daily lives, the study incorporated the Bristol Female Lower Urinary Tract Symptoms (BFLUTS) questionnaire, a tool designed to evaluate the severity of urinary symptoms and their effect on quality of life.

The study's results indicated a high incidence of urinary symptoms and neurogenic dysfunction in patients prior to surgery. While there was a no-

table improvement in BFLUTS scores shortly after surgery, suggesting some immediate relief from symptoms, these improvements did not persist long-term. Moreover, comparisons of urodynamic tests before and after surgery showed no significant changes, pointing to a static urodynamic state despite surgical intervention.
Interestingly, the development of peripheral neuropathy post-surgery was observed solely in those patients who underwent both DIE and colorectal resection, highlighting a specific risk associated with this more invasive surgical approach [38].
Overall, the research by Ballester and his team sheds light on the complex relationship between surgical treatment for DIE, urinary dysfunction, and the broader impact on quality of life. It emphasizes the importance of cautious surgical planning and raises awareness about the potential long-term challenges and neurological risks that may accompany surgery in the treatment of DIE. However, the lack of urodynamic improvement, despite early gains in quality-of-life scores, points to a mismatch between structural and neuromuscular resolution. This disconnect likely reflects irreversible nerve injury or persistent PFM hypertonia. The findings advocate for cautious surgical planning, particularly in colorectal procedures, and emphasize the need for non-surgical adjuncts to address persistent dysfunction.

DISCUSSION

The relationship between DIE and PFD is increasingly recognized as clinically significant, yet remains inadequately understood. This review identifies recurring patterns, pelvic floor hypertonia, altered levator ani anatomy, and pain sensitization, that suggest a shared neuromuscular pathophysiology, beyond mere anatomical distortion caused by DIE lesions; especially, we found that these women suffer commonly chronic pelvic pain, urinary symptoms, gastrointestinal symptoms, and sexual dysfunction as dyspareunia.
Hormonal therapy does not seem to significantly improve chronic pelvic pain in these women [25], while the PFP seems to have a good impact on superficial dyspareunia, chronic pelvic pain and pelvic floor muscle relaxation [27]; however, PFP appears controversial [28]. It demonstrates promise, especially for dyspareunia and PFM relaxation, but results remain inconsistent across studies. The heterogeneity in treatment regimens, therapist expertise, and outcome measures likely contributes to the variable efficacy observed in analysed trials [26-31]. This variability highlights the urgent need for standardized PFP protocols and functional outcome endpoints.
Surgical treatment for DIE, particularly in cases with colorectal involvement, should improve dyspareunia and FI [26], but without solid evidence to support the superiority of a technique. Furthermore, DIE surgical treatment does not significantly improve long-term urinary measurement [37]. Instead, to treat pelvic floor dysfunction directly by, for example, the repair of the native vaginal tissue in symptomatic rectocele, is associated with a good risk profile and improvement of the disorders related to prolapse and dyspareunia [39].
At present, regarding urinary incontinence, one of the actual goals in urogynecology is the research of minimally invasive techniques for its treatment [40, 41]. Moreover, urinary dysfunction seems to be linked with sexual function: there is strong evidence that urinary incontinence negatively affects female sexual function. Treatments aimed to cure urinary incontinence (including PFMT, medications, and surgery) seem to improve quality of life by recovering, at least for sexual function [42, 43]. In this regard, pharmacotherapy with ospemifene has proven useful in treating urinary disorders in post-menopausal women with vulvovaginal atrophy [44] and a similar result was also obtained using purified bovine colostrum [45]. Both tools improved sexual function and quality of life in enrolled women. Furthermore, in women whose vulvovaginal atrophy is related to hormonal therapies for the treatment of gynaecological cancer, the use of fractional CO_2 laser seems to be a useful therapeutic tool [46]. It should be noted that recurrent post-coital urinary tract infections also have a very negative impact on the quality of sexual function. An oral combination of hyaluronic acid, chondroitin sulphate, curcumin and quercetin has shown to be effective in their prevention [47].
Moreover, it seems common evidence that ultrasound imaging, especially 3D/4D TPU, is a promising tool to use in the diagnosis of pelvic floor dysfunction and in the management and follow-up of all these women. Their ability to quantify muscle elasticity and hiatus dimensions may help stratify patients, predict symptom trajectories, and tailor interventions. However, the predictive value of these modalities remains unvalidated, and their

integration into routine practice requires further cost-effectiveness and feasibility assessment [27-29, 48].

CONCLUSIONS

PFD is a common and often unrecognized problem in women with DIE. At present, there is still a lot of uncertainty about a non-invasive useful treatment for these women, and surgery seems to remain the only solid tool to improve some aspects of this condition. However, it is not possible to prove the superiority of a technique. Promising evidence, instead, is switching the paradigm of the issue: from a purely lesion-oriented surgical model to a multidisciplinary framework incorporating functional diagnostics, physiotherapy, and individualized care, incorporating 3D/4D TPU and various treatment pathways (surgical, physical, pharmacological, or dietary supplement-based).

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution
N.I., R.M.: Conceptualization. D.V., M.R., F.M.C.: Data curation. A.C., M.F.: Formal analysis. I.M.: Investigation. C.V.: Methodology. D.D.N., G.N.: Project administration. P.F., D.D.N., N.I.: Writing – original draft. D.V., M.R., F.M.C., A.C., M.F., I.M., C.V., D.D.N., G.N.: Writing – review & editing.

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Antioxidant therapy in endometriosis treatment: systematic review

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ABSTRACT

Objective. To summarize current knowledge on the effectiveness of antioxidant therapy in endometriosis treatment.

Materials and Methods. A systematic review was conducted per PRISMA guidelines and registered in PROSPERO 2023 CRD42023454705. Studies published until November 2024 were identified through PubMed, The Cochrane Library, ClinicalTrials.gov, Google Scholar, and MEDLINE. COVIDENCE software was used for screening. Risk of bias was assessed using the Cochrane Handbook.

Results. Out of 512 studies, 11 were included in the systematic review. Endometriotic cysts weight and volume are dose-dependent parameters that are significantly lower in antioxidant treatment groups ($p < 0.05$) Neither histological cell scores nor trichrome fibrosis scores showed statistically significant differences among treatment and control groups ($p > 0.05$) in 2 out of 3 studies. Significantly lower levels of total oxidant status (TOS), nitric oxide (NO) and oxidative stress index (OSI) are evaluated in the antioxidant group compared to control. However, no significant differences were observed in malondialdehyde (MDA), superoxide dismutase (SOD) and catalase (CAT) levels. The number of follicles was significantly increased, and the atretic follicles number was significantly decreased after therapy ($p < 0.05$). The IVF, cleavage, blastocyst formation rates and blastocyst number were significantly higher in treatment group compared the control.

Conclusions. Antioxidants may be considered as a possible component of endometriosis therapy to potentially enhance fertility outcomes and slow disease progression, though current evidence is preliminary and requires further validation.

INTRODUCTION

Endometriosis is an estrogen-dependent inflammatory gynaecological disease defined by the presence of endometrial-like mucosa outside the uterine cavity. The pathogenesis of endometriosis is supported by several theories, such as immunological, implantation (Sampson's theory), dy-

sontogenetic, dissemination, metaplastic, genetic, hormonal, *etc*. [1]. Endometriosis has an impact on fertility, affecting the ovarian reserve, embryo quality, implantation and normal anatomical structure of the reproductive organs and surrounding tissues. However, the mechanisms leading to endometriosis-associated infertility are not fully understood. Currently, the role of oxidative stress (OS) leading to iron metabolism disorders in the pathogenesis of endometriosis is widely discussed. Endometriotic lesions are resistant to ferroptosis – iron-mediated programmed non-apoptotic cell death –, which allows their implantation in the peritoneal cavity [2]. There is a need for further research in this area due to its high relevance, theoretical and practical importance. A microenvironment with a high level of reactive oxygen species (ROS), free radicals and iron is created as a result of cyclic changes in ectopic endometriotic lesions, which increases their adhesion and the progression of the disease.

The presence of ROS in cells is a physiological process due to their formation in normal oxidative metabolism. They control the ovarian cycle, steroidogenesis and ovulation [3]. However, the imbalance between free radicals and the antioxidant system causes oxidative stress, leading to a reduction in oocyte quality [4].

In this systematic review, we observe the efficiency of antioxidants supplementation in endometriosis treatment.

MATERIALS AND METHODS

Study design

Our systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [5].

The present systematic review has been registered in the PROSPERO international prospective registry of systematic reviews by the National Institute of Health Research (NIHR). The registration number is PROSPERO 2023 CRD42023454705.

Search strategy

To identify relevant articles, we conducted an electronic database search using several databases: PubMed, Google Scholar, ClinicalTrials.gov, Cochrane library to identify studies using key words and MeSH terms. The date of the last screening was November 26, 2024. Using the advanced search tool on PubMed, the following combination of key words was used: ((endometriosis) OR (endometrioma)) AND (antioxidants) AND (oxidative stress) AND (treatment). No filters or limits were used. Additionally, the search was conducted using MeSH terms (endometriosis [MeSH Terms]) AND ((antioxidants [MeSH Terms]) AND (treatment [MeSH Terms]) AND (oxidative stress [MeSH Terms]).

The Cochrane Library electronic database search strategy was conducted. The combination of the search was as follows: ((endometriosis) OR (endometrioma)) AND (antioxidants) AND (oxidative stress) AND (treatment). No filters or limits were used. MeSH terms were also screened (MeSH descriptor: [Endometriosis] explode all trees and with qualifier(s): [antioxidants - MeSH]).

The search was also conducted in the ClinicalTrials.gov electronic database using an advanced search combination: endometriosis | antioxidants.

Study selection

For search conducting and further screening COVIDENCE software was used. To ensure the quality and accuracy of the search results, two investigators performed the search independently. After the initial search, all articles were reviewed based on their titles and abstracts. The full texts of the studies that appeared to be appropriate according to their titles and abstracts were reviewed. Potential trials were also identified by searching the reference lists of the eligible trials. We included randomized (RCTs) and non-randomized clinical trials. Only articles written in English were included. Abstracts from congresses and unpublished articles were not included. As this is a review of published studies, Institutional Review Board (IRB) approval was not sought.

Two investigators (E.N., I.S) independently read the full texts of the preselected articles to verify their eligibility. Any studies with duplicate records were excluded. To minimize potential bias during the review process, any disagreements about the inclusion or exclusion of preselected studies were resolved with the help of a third author (A.L).

Inclusion criteria

The inclusion criteria specified autograft endometriosis mice or rat models and women with endometriosis related infertility, receiving antioxidant therapy.

Studies that described high levels of oxidative stress markers due to non endometriosis-related

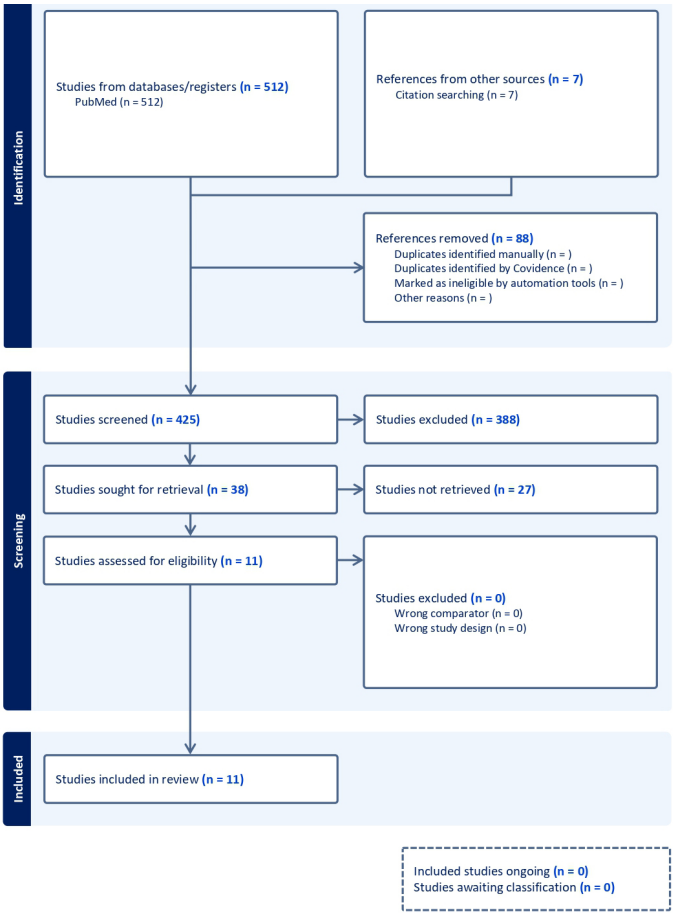

Figure 1. *PRISMA flow chart diagram.*

reasons, phytoalexins, antioxidant decoctions as a therapy were excluded.

Data extraction and quality assessment

The studies included were independently collected by two authors (E.N., I.S) using a standardized data extraction procedure. We obtained the following characteristics from our studies: study design, type of animal model, types of antioxidants and regimens used, and the number of patients in each group and the follow-up duration.

The analysis in animal models was aimed to evaluate the level of oxidative stress markers, embryo and oocyte quality, implant weight, volume and histological cell scores of endometriotic lesions after antioxidant therapy.

The analysis of human studies was aimed to establish the pregnancy outcomes in addition to previously mentioned parameters.

Risk of bias was assessed for each included study using the Cochrane Handbook for Systematic Reviews of Interventions [6]. Two reviewers (V.T., A.L) independently assessed the quality of the selected studies. A third investigator (L.P) was involved in the case of inconsistencies. In accordance with the Cochrane Handbook for Systematic Reviews of Interventions, the RoB 2 tool [7] was used to assess the risk of bias for randomized controlled trials and ROBINS-I [8] for non-randomized trials, SYRCLE's RoB tool for animal model studies [9].

RESULTS

Summary of included studies

The study selection process is illustrated by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart diagram (**Figure 1**).

A total of 512 publications were identified through an electronic database search of PubMed, Google Scholar, and ClinicalTrials.gov., Cochrane library.

Of these, 425 studies were screened for title and abstract. 388 were excluded, 38 were selected for eligibility assessment. After screening the full-text articles, 27 were excluded for failing to meet the eligibility criteria. The references of the selected studies were additionally searched for other eligible studies and 7 studies were identified. Finally, 11 trials that met the criteria were included in the systematic review. A total of 73 rats, 14 mice and 759 women from ten trials were analysed. The detailed summary of the studies analysis is shown in **Tables 1, 2**.

Antioxidants effectiveness in animal population

In 4 studies, endometriosis was induced by transplanting autologous uterine tissue onto the peritoneal wall of female Wistar albino rats [10, 11] and female NMRI mice [12, 13].

The vitamin C effectiveness in animal population

Erten *et al.* [10] and Durak *et al.* [11] evaluated the efficacy of vitamin C in the prevention and regression of endometriotic implant development in an experimentally induced autografted endometriosis rat model. Implant weight and volume, histological cell scores and trichrome fibrosis scores were measured. Both authors suggest that histological scores are independent of vitamin C dosage, in contrast to implant volume. However, the exact reason for their insensitivity is not mentioned. It could either be due to the small number of animals included or the lack of direct effects.

Hoorsan *et al.* [12] conducted a study on the efficacy of vitamin C endometriosis treatment in the NMRI mouse model. In contrast to the previous two stu-

Table 1. *Description of selected studies included in the review (rats and mice).*

First author, year of publication	Title	Population	Follow up period	Intervention	Comparison	Outcomes
Ozlem Ulas Erten *et al*., 2016 [10]	Vitamin C is effective for the prevention and regression of endometriotic implants in an experimentally induced rat model of endometriosis	Female Wistar Albino Rats (n = 33) Weight = 209g-270g A group (n = 11) B group (n = 11) C group (n = 11)	42 days	Surgical induced endometriosis (autograft model) A group: 1st operation + intravenous vitamin C 500mg/kg every 2 days B group: 1st operation; 2nd operation + intravenous vitamin C 500 mg/kg every 2 days C group:1st operation; 2nd operation	Vitamin C *vs* no vitamin C in all groups	Implant volume at the 2nd operation (mm^3) Implant volume at the 3rd operation (mm^3) Weight 1 (initial) (g) Weight 2 (final) (g) Histological cell scores Trichrome fibrosis scores
Yildirim Durak *et al*, 2013 [11]	Effect of vitamin C on the growth of experimentally induced endometriotic cysts	Female Wistar Albino Rats (n = 40) V1 group (n = 10) V2 group (n = 10) V3 group (n = 10) C group (n = 10)	6 weeks	Surgical induced endometriosis (autograft model) V1 group: 0.5 mg (2mg/kg) vit C/1 mL water for 6 weeks V2 group: 1.25 mg (5 mg/kg) vit C/1 mL water for 6 weeks V3 group: 2.5 mg (10 mg/kg) vit C/1 mL water for 6 weeks C group: distilled water 1 mL for 6 weeks Final surgical assessment	Vitamin C *vs* no vitamin C in all groups	Implant volume after operation (mm^3) Weight of cyst (mg) Histological cell scores Trichrome fibrosis scores NK cell contents
Eshrat Kalehoei *et al*, 2023 [13]	Therapeutic effects of L-arginine, L-carnitine, and mesenchymal stem cell-conditioned medium on endometriosis-induced oocyte poor quality in an experimental mouse model	Adult female NMRI mice (6–8 weeks old) n = not stated 1. Normal group 2. EMS-induced group		1. EMS induction 2. IVF LA: 250 mg/kg LC: 250 mg/kg LC BMSC-CM: 100 µL of CM/mouse	1. control 2. 250 mg/kg LA 3. 250 mg/kg LC 4. 100 µL BMSC-CM	1. *In vitro* maturation of immature oocytes: GV (%) GVBD (%) MII (%) DEG (%) 2. Blastocysts cell number N. Blast N. total cells N. TE N. ICM TE/ICM 3. The percentage of different steps of mice embryo development N. MII IVF (%) Cleavage (%) Morula (%) Blastocyst (%) Degenerated (%) 4. Blood serum antioxidant capacity TAC (nmol/mL) NO (nmol/mL) TOS (nmol/mL) OSI All these outcomes are assessed in both EMS and normal groups and according to different antioxidant therapy (CO, LA, LC, BMSC-CM)
Hayedeh Hoorsan *et al*., 2022 [12]	The effectiveness of antioxidant therapy (vitamin C) in an experimentally induced mouse model of ovarian endometriosis	Mature, virgin female NMRI mice (n = 14) A group (n = 7) B group (n = 7)	Not stated	Surgical induced endometriosis (autograft model) 2nd surgery (assessment of the endometriotic implants) A group: 50 mg/kg (0.5 mL) vit C every 2 days for 4 weeks B group: a 0.5 mL mix of water and starch Final surgical assessment	Vitamin C *vs* no vitamin C in all groups	Implant volume at the 2nd operation (mm^3) Implant volume at the 3rd operation (mm^3) Weight 1 (initial) (g) Weight 2 (final) (g) Histological cell scores Trichrome fibrosis scores Follicle number Atretic follicle number Corpus luteum number

NK: natural killer; vit C: vitamin C: EMS: endometriosis; IVF: *in vitro* fertilization; LA: L-arginine; LC: L-carnitine; BMSC-CM: bone morphogenetic stem cells; GV: Germinal vesicle; GVBD: Germinal vesicle break down; MII: metaphase II; DEG: degenerate oocytes; GVBD: Germinal vesicle break down; TOS: total oxidant status; NO: nitric oxide; TAC: total antioxidant capacity; OSI: oxidative stress index; CO: control.

Table 2. *Description of selected studies included in the review (patients - human).*

First author, year of publication	Title	Population	Follow up period	Intervention	Comparison	Outcomes
Vanessa SI *et al.*, 2015 [15]	N-Acetyl-Cysteine and L-Carnitine Prevent Meiotic Oocyte Damage Induced by Follicular Fluid From Infertile Women With Mild Endometriosis	FF samples from infertile women (n = 22) 1. EMS-associated infertility (n = 11) 2. Other infertility (n = 11)	February 2009 - February 2011	1. Laparoscopic surgery in women with EMS. 2. FF-collection 3. Bovine oocyte collection 4. *In vitro* maturation 1.NAC 1.5 mmol/L 2. LC 0.6 mg/mL 3.NAC 1.5 mmol/L + LC 0.6 mg/mL	1. (No-FF) 2. (CFF) 3. (C + NAC 1.5 mmol/L) 4. (C + LC 0.6 mg/mL) 5. (C + 2Ao); 6. (EFF) 7. (E + NAC 1.5 mmol/L) 8. (E + LC 0.6 mg/mL) 9. (E + 2Ao).	MI, n (%) TI, n (%) PA, n (%) Total no. of MII, n (%) Analyzable MII, n (%) Normal MII, n (%)
Vanessa SI *et al.*, 2021 [16]	Follicular Fluid from Infertile Women with Mild Endometriosis Impairs *In Vitro* Bovine Embryo Development: Potential Role of Oxidative Stress	FF samples from infertile women (n=22) 1. EMS-associated infertility (n = 11) 2. Other infertility (n = 11)	February 2009 - February 2011	1. Laparoscopic surgery in women with EMS. 2. FF-collection 3. Bovine oocyte collection 4. *In vitro* maturation 5. *In vitro* fertilization 6. *In vitro* embryo culture 1.NAC 1.5 mmol/L 2. LC 0.6 mg/mL 3.NAC 1.5 mmol/L + LC 0.6 mg/mL	1. (No-FF) 2. (CFF) 3. (C + NAC 1.5 mmol/L) 4. (C + LC 0.6 mg/mL) 5. (C + 2Ao) 6. (MEFF) 7. (MEFF + NAC 1.5 mmol/L) 8. (MEEF + LC 0.6 mg/mL) 9. (MEFF + 2Ao).	Presumptive zygotes (n) Cleavage rate % (n) Blastocysts formation rate % (n) Hatching rate % (n)
Xiang Lu *et al.*, 2018 [14]	Effects of vitamin C on the outcome of *in vitro* fertilization–embryo transfer in endometriosis: A randomized controlled study	Patients with EMs (n = 280) Group 1 – Vit C treatment (n = 160) Group 2 – no vit C (n = 120) Patients with no EMs (n = 150)	June 2013 -December 2016.	1. IVF-ET procedure 2. Vit. C treatment Group 1 (n = 160) received 1000 mg/day from 2 months before IVF-ET treatment until 2 weeks after ET	EMS patients *vs* no EMS patients EMS patients treated with vit C/ not treated with vit C	1. Laboratory and pregnancy outcomes in EMS patients/ no EMS patients Total Gn dosage No. of retrieved oocytes Fertilization rate (%) High-grade embryo rate (%) Implantation rate (%) Clinical pregnancy rate (%) No. of frozen embryos 2. Changes in serum levels of vit C and oxidative stress markers in EMS patients with vit C/ no vit C Serum levels of vit C (µmol/L) Serum levels of SOD (U/L) Serum levels of TAC (mmol/L) Serum levels of MDA (µM) Serum levels of ROS (CPS)
Jennifer Mier-Cabrera *et al.*, 2008 [17]	Effect of vitamins C and E supplementation on peripheral oxidative stress markers and pregnancy rate in women with endometriosis	Patients with EMs (n = 34) Group 1 – Vit C and Vit E treatment (n = 16) Group 2 – placebo (n = 18)	15 months	Group 1 - 343 mg of vitamin C and 84 mg of vitamin E	Vit C and vit E patients group *vs* placebo group	1. Oxidative stress marker levels in women with endometriosis (Baseline, at 2 months, at 4 months, at 6 months in PF, plasma) LOOH (µmol/L) MDA (µmol/L) 2. Pregnancy rate

First author, year of publication	Title	Population	Follow up period	Intervention	Comparison	Outcomes
Nalini Santanam *et al.*, 2016 [18]	Myeloperoxidase as a Potential Target in Women With Endometriosis Undergoing IV	Patients (n = 117) Complete data (n = 68) No EMs group (n = 41) Mild EMs group (n = 20) Moderate/severe EMs group (n = 7)	Not stated	1. IVF 2. Collection of FF 3. Collection of Blood Plasma Patients received 800 IU of vit E and 1000 IU of vit C for a minimum of 8 weeks No EMs group vit C+E (n = 5) Mild EMs group vit C+E (n = 5) Moderate/severe EMs group vit C+E (n = 4)	Vit C and vit E patients group *vs* placebo group	MPO level (ng/ml)
Sahar Rostami *et al.*, 2023 [20]	Astaxanthin ameliorates inflammation, oxidative stress, and reproductive outcomes in endometriosis patients undergoing assisted reproduction: A randomized, triple-blind placebo-controlled clinical trial	Infertile patients (n = 73) with EMs Complete data (n = 50) AST group (n = 25) Placebo group (n = 25)	December 2021 - September 2022.	1. IVF 2. Blood and FF collection AST group: 6 mg daily of oral AST for 12 weeks Placebo group: 6 mg daily of placebo capsules for 12 weeks	AST treatment *vs* placebo	1. OS markers and cytokine levels MDA SOD CAT TAC L-1b IL-6 TNF-a 2. ART outcomes Number of oocytes GV MI MII Oocyte maturity rate (MII %) Fertilized Fertilization rate (%) Number of frozen embryos High-quality embryos Frozen embryos Number of transferred embryos
Leila Amini *et al.*, 2021 [19]	The Effect of Combined Vitamin C and Vitamin E Supplementation on Oxidative Stress Markers in Women with Endometriosis: A Randomized, Triple-Blind Placebo-Controlled Clinical Trial	Patients with endometriosis (n = 60) A group (n = 30) B group (n = 30)	June 2017-November 2017	A group: vitamin C 1000 mg/day (2 tablets/500 mg) + vitamin E 800 IU/day (2 tablets/400 IU) for 8 weeks. B group (placebo pills (mannitol and magnesium stearate polyvinylpyrrolidone)) for 8 weeks	Vit C and vit E patients group *vs* placebo group	1. OS markers levels MDA ROS TAC 2. VAS score of dysmenorrhea, dyspareunia

CFF: control follicular fluid; OS: oxidative stress; ROS: reactive oxygen species; LC: L-carnitine; NAC: N-Acetyl-Cysteine; BMSC-CM: bone morphogenetic stem cells; TOS: total oxidant status; NO: nitric oxide; TAC: total antioxidant capacity; OSI: oxidative stress index; IVF: *In vitro* fertilization; SOD: superoxide dismutase; MDA: malondialdehyde; FF: follicular fluid; EFF: endometriosis follicular fluid; CFF: control follicular fluid; LOOH: lipid hydroperoxide; MPO: myeloperoxidase; AST: astaxanthin; ART: associated reproductive technology; CAT: catalase; TAR: Total antioxidant response; NK: Natural killer; EMS: endometriosis; TNF-a: Tumor necrosis factor; IL-1b: interleukin 1b; IL-6: interleukin 6; GV: germinal vesicle; MI: metaphase I. PA: spontaneous parthenogenetic activation; TI: telophase.

dies, the authors found a significant difference not only in the volume of endometriotic implants but also in the trichrome fibrosis scores ($p = 0.03$). Follicle, atretic follicle and corpus luteum counts were also measured. The number of follicles was significantly increased ($p = 0.0005$) and the number of atretic follicles was significantly decreased ($p = 0.006$) after vitamin C therapy.

L-arginine, L-carnitine effectiveness in animal population
The other study based on the induced endometriosis mouse model was conducted by Eshrat Kalehoei *et al*. [13]. The authors compared the effects of L-arginine (LA), L-carnitine (LC), bone morphogenetic stem cells (BMSC-CM) on endometriosis-induced oocyte quality and levels of oxidative stress markers. In the endometriosis group, mice treated with LC, LA or BMSC-CM had significantly lower levels of oxidative stress markers compared to control. In normal and endometriosis treatment groups *in vitro* fertilisation (IVF), cleavage and blastocyst formation rates were significantly improved compared to the control ($p < 0.05$).

Antioxidants effectiveness in human population
Other 7 studies were based on the follicular fluid and plasma samples collected from women with endometriosis related infertility.

The vitamin C effectiveness in human population
In human population, the efficacy of vitamin C supplementation was analysed by Lu *et al*. [14]. There was no significant difference in fertilization, implantation and pregnancy rates between all participants. The number of oocytes and frozen embryos in endometriosis groups was significantly lower than in control ($p < 0.05$). Treatment with vitamin C for 2 months improved its serum and follicular fluid concentration in patients with endometriosis, however, it did not affect oxidative stress markers rate. The results could be as follows because of several limitations: small sample size and only one time point measurement (2 months of vitamin C supplementation): comparison of different time points was not performed.

N-acetyl-cysteine, L-carnitine effectiveness in human population
Giorgi *et al*. conducted two studies [15, 16] in which the percentage of meiotically normal oocytes in metaphase II, presumptive zygotes, cleavage rate, blastocyst formation rate and hatching rate were measured. The number of meiotically abnormal and normal metaphase II oocytes was similar in all 9 groups. The authors suggest that follicular fluid (FF) from infertile women with endometriosis increases the percentage of meiotically abnormal oocytes. There was no significant difference between groups in cleavage ($p = 0.54$) and blastocyst formation ($p = 0.4349$) rates. However, the hatching rate was higher in the control follicular fluid group than in the endometriosis follicular fluid (EFF) group. The addition of antioxidants in CFF groups did not affect the hatching rate. The addition of N-acetylcysteine reduces the destructive effects of FF on the oocyte meiotic spindle and increases hatching rate. The addition of L-carnitine completely prevents this destructive effect on the meiotic spindle, but is less effective in terms of hatching rate.

The vitamin C and vitamin E combination effectiveness in human population
The effect of combined vitamin C + vitamin E treatment was evaluated by Mier-Cabrera *et al*. [17], Santanam *et al*. [18] and Amini *et al*. [19].
Mier-Cabrera *et al.* [17] analysed the lipid hydroperoxide (LOOH) and malondialdehyde (MDA) rate in plasma and peritoneal fluid. There was a statistically significant difference in plasma LOOH and MDA concentrations between control and treatment groups. Amini *et al*. [19] held randomized, triple-blind placebo-controlled clinical trial, where statistically reduced MDA ($p = 0.002$) and reactive oxygen species (ROS) ($p < 0.001$) levels in treatment group compared to placebo were evaluated.

Anti- myeloperoxidase therapy human population
Santanam *et al*. [18] suggested that the level of myeloperoxidase (MPO) – one of the oxidative stress markers – depends on the severity of endometriosis. Mean MPO levels in follicular fluid collected from women with severe endometriosis were significantly higher than in control and mild endometriosis groups. Combination antioxidant treatment did not significantly reduce MPO levels in both groups.

Astaxanthin therapy in human population
Rostami *et al*. conducted a study on the efficacy of astaxanthin (AST) on oxidative stress markers, cytokine levels and associated reproductive technology (ART) outcomes in infertile women with endo-

metriosis [20]. All parameters were reduced after antioxidant therapy except serum catalase (CAT), IL-1b, IL-6 levels. Embryo quality, number of metaphase II oocytes improved significantly after therapy. However, the number of embryos transferred, fertilisation rate and pregnancy rate were similar in both groups.

Visualisation tools were provided by the ROBVIS application [21]. According to the ROBINS-I tool, the overall risk of bias for non-randomised trials was 66.7 % low and 33.3% serious (**Figure 2**). Based on the RoB 2 tool (**Figure 3**), randomized trials had a 75% chance of low risk of bias and an 25% chance of some concern regarding the overall risk of bias. The SYRCLE's RoB tool was used to assess the quality of included animal studies (**Figure 4**). The risk of allocation concealment and random housing could not be confirmed because none of the studies offered complete information.

DISCUSSION

There is increasing evidence to suggest that specific diet patterns and nutrients may modulate the pathophysiological processes underlying endometriosis.

In this systematic review, we evaluated the efficiency of antioxidants supplementation in endometriosis treatment. We found out that antioxidants reduce the severity of endometriosis symptoms by affecting the pathogenesis of the disease.

Oxidative stress occurs when the balance between reactive oxygen species production and antioxidant capacity is disturbed, either by insufficient antioxidant protection or by increased ROS production. The relationship between ROS production and the progression of endometriosis has been studied previously [22]. Due to dysregulation of iron metabolism, these abnormal endometriotic lesions are

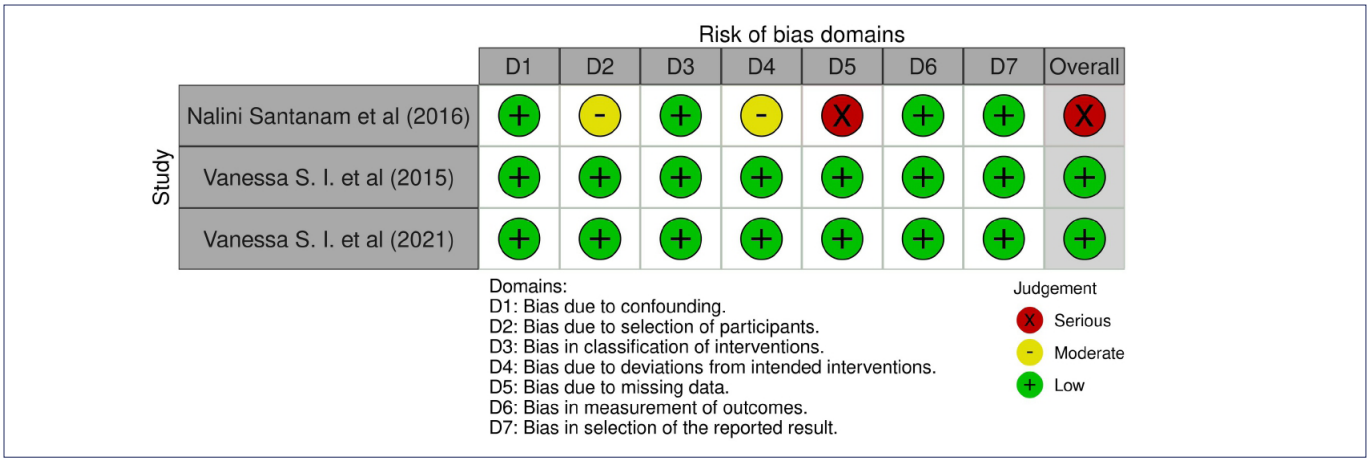

Figure 2. *ROBINS-1 tool for non-randomized trials.*
Domains: D1: Bias due to confounding. - D2: Bias due to selection of participants. - D3: Bias in classification of interventions. - D4: Bias due to deviations from intended interventions. D5: Bias due to missing data. - D6: Bias in measurement of outcomes. - D7: Bias in selection of the reported result.

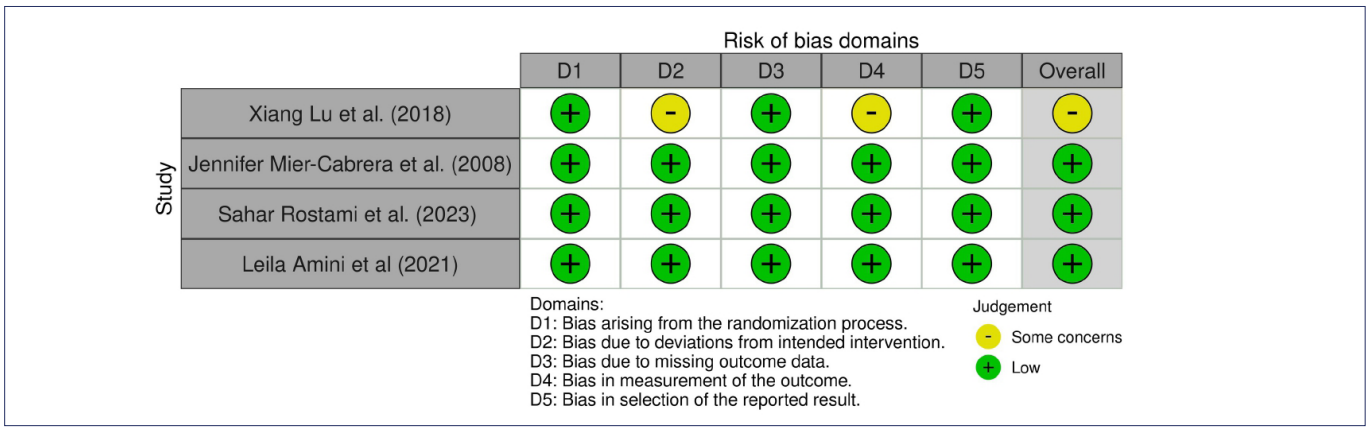

Figure 3. *RoB2 tool for randomized trials.*
Domains: D1: Bias arising from the randomization process. - D2: Bias due to deviations from intended intervention. - D3: Bias due to missing outcome data.- D4: Bias in measurement of the outcome. - D5: Bias in selection of the reported result

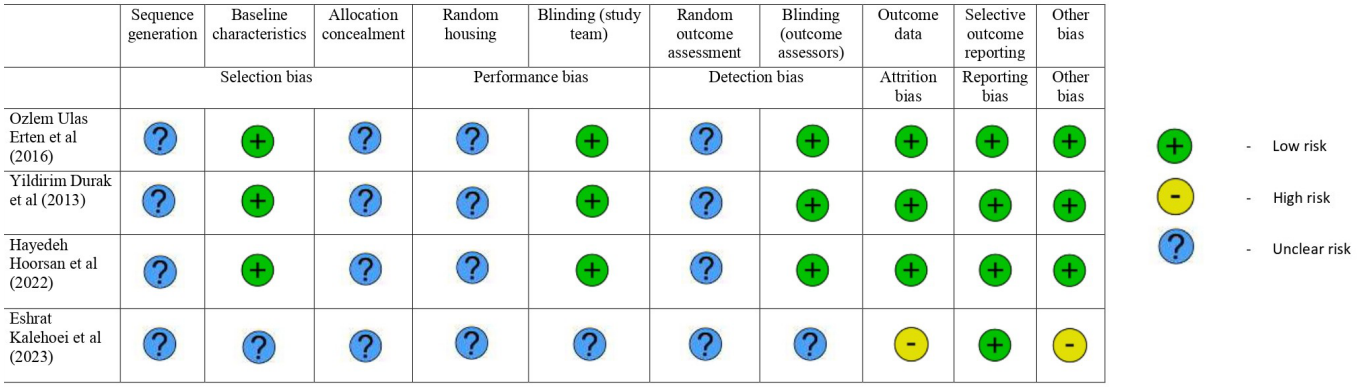

Figure 4. *SYRCLE"s risk of bias tool for each experiment al animal study.*

thought to be resistant to ferroptosis. Ferroptosis is a form of regulated, iron-catalysed cell death caused by excessive lipid peroxidation in cell membranes. This process was first described by Dixon in 2012 [23].

Li *et al*. [24] found out that there was an excess expression of ferroptosis-associated genes in the ectopic and eutopic endometrium in patients with endometriosis, showing a general trend towards inhibition of the ferroptosis pathway. Increased transferrin receptors (TFR1) and Ras gene mutations in abnormal endometriotic cells directly affect ferroptosis resistance. A local imbalance in iron homeostasis leads to oxidative stress in the intraperitoneal cavity, inflammation and ferroptosis in intact peripheral tissues. Iron-dependent ROS synthesis is based on the Fenton reaction: $Fe2+ + H2O2 \rightarrow Fe3+ + OH- + OH-$. As a result, a hydroxyl radical (-OH) is formed, leading to lipid peroxidation and accumulation of lipid LOOH, which damages the membrane. This is why ectopic endometriotic tissue has higher levels of lipid peroxidation products than normal endometrial tissue. This is also confirmed by other studies [17, 25].

In addition, we observe changes in enzyme levels: superoxide dismutase (SOD) and indicators such as TAC, total oxidant status (TOS) and oxidative stress index (OSI) in serum and FF. The decrease in TAC and SOD between patients with and without endometriosis is confirmed. It is noted that there was a significant difference in this indicator in FF as opposed to serum between both groups [14]. Total antioxidant response (TAR) is also lower in patients with endometriosis, leading to an excess of OSI [26]. Treatment with AST improved TAC and SOD levels [19]. LC and LA administration also improved the TAC, reduced TOS, nitric oxide (NO) and OSI ($p < 0.05$) [16]. However, vitamin C treatment showed no difference in oxidative stress markers and enzyme levels [14]. But there is evidence that vitamin C prevents the progression of endometriotic lesion development by reducing their weight, size and volume [10-12]. Vitamin C and vitamin E combination significantly suppressed levels of MPO (a neutrophil marker that is increased due to oxidative stress and depends on the severity of endometriosis) in FF [18]. These findings support previous data [26].

It should be mentioned that immune cells play a crucial role in ectopic endometriotic lesions detection and elimination. It is known that oxidative stress impairs the efficiency of the immune system, leading to reduced recognition of abnormal endometrial tissue, allowing its invasion, accumulation and growth in the pelvic and abdominal cavity. Antioxidants are known to stimulate the whole process of phagocytosis [27]. Durak *et al*. [11] found that NK cell (Natural killer cells) levels were significantly lower in control groups than in those on antioxidant therapy ($p < 0.01$). Similar results have been reported in other studies [28, 29]. It should be noted that the decrease in cellular immunity correlates with the severity of the disease. Whether this decrease in NK cells is a cause or a consequence of the severity of endometriosis remains unclear. The reduction in cellular immunity is related to the "endometriotic disease theory", also known as Sampson's theory, according to which the most important factor in the development of endometriosis is not the initial implantation in the peritoneal cavity, but cell mutations that cannot be eliminated due to the reduced number of immune cells. It is these ectopic endometriotic cells, ignored by regulatory factors in the peritoneal fluid, that trigger the disease [30].

All of the above factors affect fertility in women with endometriosis. The granulosa cells and the surrounding cumulus cells in the follicle are involved in the maturation of the oocyte. This process depends on the intrafollicular environment. If it is damaged, the developmental competence of the oocytes, the quality of the embryos and the clinical pregnancy rate are reduced. In the case of antioxidant therapy, IVF, cleavage and blastocyst formation rates are increased compared to no treatment. It is also important to highlight that this finding is potentially helpful for translation into clinical practice [13-16, 19]. High-level antioxidant diet can significantly influence inflammatory processes, which are directly related to the pathophysiology of endometriosis.

Strengths and limitations of the study

The limitations we encountered were mainly related to the available data sources. The patients were not similar between studies: rats and mice with induced endometriosis, human. The heterogeneity of the antioxidants should also be mentioned. A total of 6 antioxidants were included in this review, but it is difficult to compare them because of differences in regimen and dosage in each study. Studies in animal models have a lower quality of evidence than those in humans. It is important to emphasize that more research is needed in human to assess the clinical relevance and to establish the efficacy of antioxidants, as clinical trials evaluating their effects on endometriosis are still relatively limited. The main strength of this study is that we observed antioxidant supplementation as a therapy that affect oxidative stress – the main aspect of endometriosis pathogenesis. All previously published reviews were aimed to analyse the types of oxidative stress markers and their levels in patients with endometriosis, but did not observe and summarize any medications for their reduction.

Implications for future studies may include investigating the development of targeted antioxidant treatment, the possibility of delivering antioxidants directly to endometriotic lesions. This could potentially increase the efficacy of antioxidant therapy and minimize potential side effects.

CONCLUSIONS

Antioxidants may be considered as a possible component of endometriosis therapy to potentially enhance fertility outcomes and slow disease progression, though current evidence is preliminary and requires further validation. This type of treatment reduces oxidative stress markers concentration, suspend endometriotic lesions progression and improve oocyte developmental competence. However, there is still controversy about the antioxidant treatment as a monotherapy of endometriosis. That is why more clinical trials to make stronger recommendations is needed.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

L.P., E.N., S.I., V.T., A.L., V.S.: Conceptualization. E.N., I.S., A.L.: Data curation, writing – original draft. L.P., V.T., V.S.: Writing – review & editing.

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Study registration

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Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

N/A.

Informed consent

N/A.

Data sharing

N/A.

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The effect of education based on cooperative learning, problem-solving, role-playing, and video-based instruction on knowledge, attitude and practice related to breast self-examination in women

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ABSTRACT

Objective. Breast self-examination is a healthy and non-invasive way to predict breast cancer. This research investigates education based on cooperative learning, problem-solving, role-playing, and video-based instruction on knowledge, attitude, and practice related to breast self-examination in women in Iran in 2024.

Materials and Methods. This quasi-experimental study included 165 Iranian women. The intervention group consisted of 132 individuals, divided into four groups of 33. Each group attended two educational sessions, each lasting 60 minutes. Using a questionnaire, demographic, anthropometric, and knowledge, attitude, and practice. The data obtained from the survey was analysed by using group statistics, independent sample test, paired sample test, chi-square test, and ANOVA.

Results. The mean age of the women was 25.20 ± 3.00 years. The mean scores in knowledge (95%CI F = 8.46; $p < 0.001$) in all education groups improved post-intervention. The average rates of attitude and practice in all education groups did not show a significant increase in post-intervention (95%CI F = 2.30; $p > 0.05$). The mean scores on attitude and practice did not improve in the control group (95%CI; $p > 0.29$).

Conclusions. There was a general knowledge about breast cancer and breast self-examination; poor attitude to doing breast self-examination and wrong practice of breast self-examination among all the women recruited at baseline, irrespective of the group.

INTRODUCTION

Breast cancer is a widespread cancer affecting women globally. In 2020, the World Health Organization reported about 2.3 million diagnoses and 685,000 deaths from the disease [1]. In Iran, breast cancer is one of the most common cancers. According to the National Cancer Registry

System, the relative frequency among Iranian women was 25 percent in 2015 and rose to 26.4 percent in 2017, indicating a continued increase in cases [2].

To detect breast cancer early, three methods have been suggested, including mammography, clinical breast examination (CBE) and breast self-examination (BSE). Among these, BSE is a non-invasive, cost-effective, and easy-to-perform method for detecting breast cancer [3].

About one-third of breast cancers occur in women under 50, where mammography may be less effective. In these cases, self-examination can be a valuable method for early detection [4]. Proper education on breast self-examination (BSE) is fundamental as 90% of breast lumps are detected by individuals [5]. Breast self-examination (BSE) is effective when women are knowledgeable and skilled in performing it correctly [6].

Studies in Iran show that women's knowledge of breast cancer symptoms and the effectiveness of BSE as an early diagnostic tool is very low [7, 8]. Different educational methods for Breast Self-Examination (BSE) yield varying results. Various information sources enhance understanding of breast cancer and BSE. Some studies suggest that video instruction improves BSE skills, while others find face-to-face education more effective [9]. Most previous studies have compared group discussions and lectures [10, 11]. To date, no study has examined the simultaneous effects of active learning methods like role-playing and problem-solving, which have gained importance in education recently. Additionally, few studies have compared their effectiveness to inactive methods.

The purpose of this study was to investigate the effect of four educational methods, including cooperative learning, problem-solving, role-playing, and video-based instruction, on knowledge, attitude, and practice of breast self-examination in 20 to 30-year-old women in Iran in 2024.

MATERIALS AND METHODS

Participant

This quasi-experimental study, conducted in 2024 in Iran, involved 165 women using a cluster-random sampling method:

1. **Define the Population**
2. **Identify Clusters**: the population was divided into natural groups, such as health centres.
3. **List Clusters**: a register of community health centres was created.
4. **Randomly Select Clusters**: eight health centres were randomly chosen for participation
5. **Collect Data**: data was gathered from all eligible women in the selected clusters.

The educational programs delivered included cooperative learning, problem-solving, role-playing, and video-based instruction.

The inclusion criteria

Aged 20-30, married, seeking family planning services, willing to participate, not pregnant, Iranian.

Sample size

The sample size was calculated using the formula for a quasi-experimental survey [12] with a margin of error = 0.05. Considering the 10% probability of case attrition, Participants were 165 women.

$$n = \frac{\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2 (\partial_1^2 + \partial_2^2)}{(\mu_1 - \mu_2)2}$$

Participants

The intervention group comprised 132 individuals divided into four groups of 33. Each group participated in two educational sessions, with each session lasting 60 minutes. In contrast, the control group consisted of 33 individuals who attended a standard educational session at healthcare centres focused on breast self-examination (**Figure 1**). One month after the intervention, both the intervention and control groups completed the questionnaires again.

Measure tools

The data collection tools of the multiple-choice questionnaire included demographic data (16 questions), knowledge (20 questions), attitude (15 questions), and practice (6 questions). The validity and reliability of the questionnaires had been established in previous studies [14, 16]. Therefore, there was no need for re-evaluation of validity and reliability (CVI = 0.99, CVR = 0.85) [14, 15].

Knowledge

It included 20 questions about BSE. The scores of 1 and 0 were assigned to true and false responses. The items had high external consistency (Cronbach's α = 0.93) [14, 15].

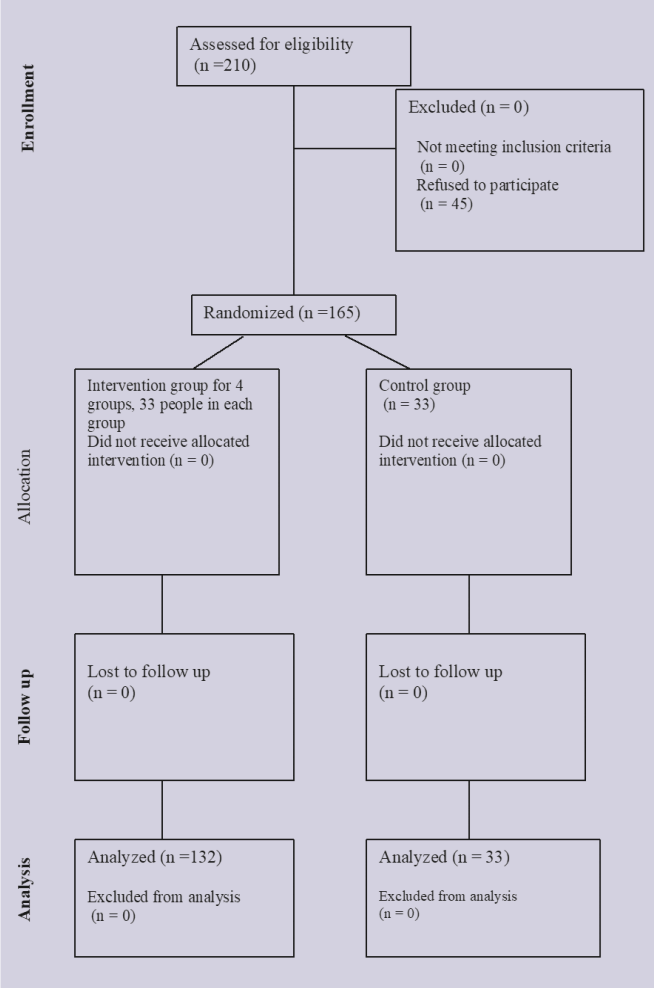

Figure 1. *The CONSORT diagram for the study.*

Attitude

This scale had 15 items; indirect attitude assessed ranging from "disagree strongly" to "agree strongly" (−2 - +2). The items had high internal consistency (Cronbach's $\alpha = 0.85$) [14, 15].

Practice

This scale had 3 items, items ranging from "disagree strongly" to "agree strongly" (−2 - +2). The items had high internal consistency (Cronbach's $\alpha = 0.80$) [14, 15].

Educational intervention

The educational content was sourced from the "Package of Basic Interventions for Non-Communicable Diseases in Iran's Primary Health Care System (IRAPEN)" by the Ministry of Health. It included an educational pamphlet and a PowerPoint based on a knowledge questionnaire, organized into two main sections [1]. Theoretical training included four parts: Breast neoplasm (prevalence, incidence, and risk factors), prevention (self-care, diagnosis), and concepts and methods of Breast Self-Examination (BSE). Topics covered include breast cancer biology, statistics, epidemiology in Iran and globally, modifiable and non-modifiable risk factors, preventive measures, and self-protection skills. The practical section demonstrated the application and steps of BSE.

In the first session, members shared their BSE experiences, guided by the educator to foster positive opinions and attitudes. This indirect approach aimed to encourage discussions among spouses and shift negative attitudes toward BSE. Post-test was administered one month after receiving the education.

Data analysis

The data was analysed using SPSS 24. The results of the Shapiro-Wilk test indicated that the significance levels obtained for the study variables, separated by the intervention and control groups, were all greater than 0.05. Therefore, the assumption holds, and it is permissible to perform parametric tests. In the next step, the prerequisite of equality of variances was examined using Levene's test, and the assumption of homogeneity of variances was confirmed (P-value > 0.05). The T-test, Paired t-test, ANOVA test, and Chi-square test were done. A significance level of $p < 0.05$ was considered for all tests.

RESULTS

The results showed that there were no significant differences in demographic information among the groups ($p = 0.869$) (**Table 1**).

The mean (standard deviation) of the knowledge scores of the participants in the problem solving, cooperative learning, role playing, educational video, and control groups showed a significant difference before and after the intervention ($p < 0.001$) (**Table 2**).

As the results of the analysis of ANOVA showed, in the variable of knowledge, the effect of the intervention on the post-test scores is significant (P-value < 0.001). In the attitude, after adjusting for the effect of pre-tests, the effect of group on the post-test scores is not significant ($p = 0.06$). In the practice, after adjusting for the effect of pre-tests, the effect of group on the post-test scores is not significant ($p = 0.54$) (**Table 3**).

Table 1. *Characteristics of the participants in the study according to the studied groups.*

	Group					
	Control n = 33	**Role playing n = 33**	**Educational video n = 33**	**Cooperative learning n = 33**	**Problem solving n = 33**	**P-value**
Age (mean and standard deviation)	24(4)	28(1)	24(3)	24(5)	26(2)	0.869*
Marital status (frequency and frequency percentage)						
Single	6(18.1)	9(27.2)	3(9.00)	13(39.3)	7(21.2)	
Married	27(81.8)	22(66.6)	29(87.8)	18(54.5)	25(75.7)	
Deceased wife	0(0)	1(3.00)	0(0)	0(0)	0(0)	0.206^
Divorced	0(0)	1(3.00)	1(3.00)	0(0)	0(0)	
Unknown	0(0)	0(0)	0(0)	2(6.00)	1(3.00)	
Literacy status (frequency and frequency percentage)						
Illiterate	0(0)	0(0)	5(15.1)	0(0)	0(0)	
Elementary to third middle school	12(36.30)	13(39.30)	14(42.40)	7(21.20)	13(39.30)	
High school to diploma	7(21.20)	9(27.20)	8(24.20)	12(36.30)	15(45.40)	0.10^
Diploma to post-diploma	2(6.00)	2(6.00)	0(0)	7(21.20)	3(9.00)	
Bachelors and Masters	11(33.30)	4(12.10)	5(15.10)	5(15.10)	2(6.00)	
Unknown	1(3.00)	5(15.10)	1(3.00)	2(6.00)	0(0)	
Income status (frequency and percentage of frequency)						
< 5 million tomans	8(24.20)	2(6.00)	3(9.00)	5(15.10)	3(9.00)	
Between 5 and 10 million tomans	11(33.30)	10(30.30)	11(33.30)	7(21.20)	14(42.20)	0.10^
> 10 million tomans	13(39.30)	19(57.50)	17(51.50)	7(21.20)	15(45.40)	
Unknown	1(3.00)	2(6.00)	2(6.00)	14(42.20)	3(9.00)	
Previous history of breast cancer in family members (frequency and frequency percentage)						
Yes	2(6.00)	2(6.00)	1(3.00)	1(3.00)	3(9.00)	
No	31(93.90)	30(90.90)	30(90.90)	31(93.90)	30(90.90)	0.747^
Unknown	0(0)	1(3.00)	2(6.00)	1(3.00)	0(0)	
Receiving education about BSE in the past (frequency and frequency percentage)						
Yes	15(45.40)	9(27.20)	8(2.00)	7(21.20)	7(17.00)	
No	18(54.50)	22(66.60)	22(75.50)	24(72.70)	26(82.90)	0.273^
Unknown	0(0)	2(6.00)	2(4.40)	2(6.00)	0(0)	

*One-way ANOVA; ^Chi square.

DISCUSSION

The mean scores in knowledge in all education groups improved post-intervention. A study by Mena *et al*. (2014) found that many women in rural and semi-urban Ghana lack awareness of Breast Cancer and its risk factors, with 67.6% of rural women lacking knowledge about its causes [16]. Molly and Mercy (2016) [17] conducted a quasi-experimental study among Mahila Mandal rural women in Mugalur, Bangalore, revealing that participants had low baseline knowledge scores on breast self-examination (BSE). They gave many incorrect responses about the frequency of BSE practice, detection methods, and stages of breast cancer. The study revealed that baseline attitudes toward breast self-examination (BSE) were generally poor, with mean scores ranging from 41.93 to 44.61. Education alone may not sufficiently address the fears and anxieties women associate with BSE, such as the fear of finding abnormalities. Emotional barriers, including fear, embarrassment, and cultural beliefs, influence attitudes and require more than just information to overcome. Misconceptions about breast health persist, highlighting the need for ongoing education. Additionally, some women may doubt the effectiveness of BSE compared to mammography, necessitating a focus on how BSE complements other screening methods. Education must be culturally sensitive and address specific

Table 2. *Comparison of the mean levels in problem solving, group learning, educational video, role playing pre- and post-intervention.*

Mean (standard deviation)					
Variable	**Control n = 33**	**Role playing n = 33**	**Educational video n = 33**	**Cooperative learning n = 33**	**Problem solving n = 33**
Marital status (frequency and frequency percentage)					
Preintervention	-2.97(4.90)	-6.12(5.61)	-6.70(3.48)	-3.39(3.43)	-5.36(4.48)
Post intervention	-5.55(4.62)	-0.85(4.39)	-1.76(4.24)	-1.09(4.93)	-1.03(5.73)
Paired t-test value	2.59	4.22	1.58	5.24	3.24
P-value	**> 0.05**	**< 0.001**	**0.012**	**< 0.001**	**< 0.05**
Preintervention	-41.93(9.37)	-44.67(10.36)	-47.48(9.27)	-45.45(7.27)	-44.61(9.9)
Postintervention	-43.55(7.19)	-46.81(4.55)	-47.18(8.83)	-46.12(3.05)	-44.01(5.91)
Paired t-test value	0.37	0.83	0.98	1.90	0.13
P-value	**0.71**	**0.40**	**0.33**	**0.06**	**0.89**
Practice					
Preintervention	2.45(2.68)	-1.39(2.67)	1.52(3.04)	1.45(2.36)	2.73(2.39)
Postintervention	2.30(2.88)	-2.36(3.13)	3.03(1.72)	2.64(1.69)	3.09(2.18)
Paired t test value	1.05	0.56	3.10	2.65	3.00
P-value	**0.29**	**0.57**	**< 0.05**	**< 0.05**	**< 0.05**

Table 3. *The analysis of ANOVA on knowledge, attitude, and practice on breast self-examination pre- and post-intervention in groups.*

		Sum of Squares	df	Mean square	F	Sig. (P-value)	Effect size
Knowledge (post-test)	Between Groups	782.764	4	195.691	8.462	0.000	0.175
	Within Groups	3,700.182	160	23.126			
	Total	4,482.945	164				
Attitude (post-test)	Between Groups	360.206	4	90.051	2.307	0.060	0.055
	Within Groups	6,206.836	159	39.037			
	Total	6,567.042	163				
Practice (post-test)	Between Groups	17.673	4	4.418	0.770	0.546	0.019
	Within Groups	917.939	160	5.737			
	Total	935.612	164				
Knowledge (pre-test)	Between Groups	360.667	4	90.167	0.760	0.550	0.017
	Within Groups	3,180.970	160	19.881			
	Total	3,541.636	164				
Attitude (pre-test)	Between Groups	524.891	4	131.223	1.516	0.200	0.037
	Within Groups	13,848.810	160	86.555			
	Total	14,373.700	164				
Practice (pre-test)	Between Groups	52.606	4	13.152	1.887	0.115	0.045
	Within Groups	11,15.030	160	6.969			
	Total	1,167.636	164				

barriers to acceptance. Even with education, some women may procrastinate on regular self-examinations, indicating a need for continuous reminders. Overall, improving attitudes toward BSE requires a multifaceted approach that considers emotional, cultural, and logistical factors, along with collaboration among healthcare providers and community organizations. Similar studies have been reported in this regard in 2024 and 2025 [18, 19].

Alinejad *et al*. (2023) [20] and Ibitoye and Thupayegale-Tshwenegae (2021) [21] found that women had a positive attitude towards adopting BSE, despite

both studies being cross-sectional. Notably, most participants were keen to educate others about BSE benefits and techniques, a finding consistent with our study, which also highlighted women's willingness to share their knowledge.

Çelik and Çalım (2020) [22] noted that training interventions, including self-demonstration, could boost motivation and attitudes toward breast self-examination (BSE). However, in present study found no initial differences between the educational and control groups. Post-intervention, the mean practice scores for BSE were not significant across all educational methods (problem solving, cooperative learning, educational video, role playing). In certain studies where poor BSE practice has been reported, it has been linked to the education level of the respondents and their partners. For example, Libretti *et al*. (2015) [23] found that there is a significant correlation between educational attainment and BSE performance. After the intervention, the average practice score of the cooperative learning, problem-solving, and video training group showed a significant increase ($p < 0.05$), while the role-playing group and control group did not show a significant change. In their study, Çelik *et al*. [22] found that women with visual impairments benefit from watching a breast self-examination training video with an audio description before performing self-examinations.

Molly and Mercy (2016) [17] attributed the lack of adoption and practice of BSE to a lack of knowledge and skills required for self-examination. After the intervention, the average practice score of the cooperative learning, problem-solving, and video training group showed a significant increase ($p < 0.05$), while the role-playing group and control group did not show a significant change. Libretti in a study in 2023 showed that the quality and reliability of hysteroscopy videos on the platform are poor. The strategic use of selected, high-quality hysteroscopy videos can enhance procedure success and alleviate patient fears [23] which is consistent with the findings of the present study.

Limitations and suggestions

The study was conducted in selected wards of Torbat Jam, which means the findings may not be representative of the entire country. Additionally, the proportion of women practicing breast self-examination (BSE) was based on self-reported responses. Other important aspects of BSE practice, such as frequency, timing, and technique, were not considered when identifying the factors associated with BSE. Therefore, we recommend that training be provided to women to improve their attitudes toward BSE. Further research should also be conducted to identify the factors that hinder the practice of BSE so that these barriers can be effectively addressed.

CONCLUSIONS

Participants showed general knowledge about breast cancer and BSE, but had a poor attitude and incorrect practices regarding BSE. The findings highlight the need to disseminate this information widely and implement state policies for educational programs on BSE within community health interventions. Non-governmental organizations should utilize these findings to develop effective breast cancer control programs at the community level. This must be done via massive exposure to the primary stakeholders and decision makers in such groups.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions

F.A.: Supervision, conceptualization, methodology, project administration. Z.J.: Conceptualization, visualization, methodology, formal analysis, investigation, writing - original draft, writing - review & editing. S.Z.S.: Methodology.

Funding

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Study registration

N/A.

Disclosure of interests

The authors declare no competing interests

Ethical approval

Ethical approval in this study was obtained, and all procedures performed on human samples were conducted following the relevant guidelines and regulations of the Helsinki Declaration. The study protocol was approved by the Research Ethics Committee (IR.TRJUMS.REC.1403.005) in Torbat Jam in Iran.

Informed consent
It is worth noting that participation in this study was completely voluntary and after full awareness of the research aims and method and other treatment options. Also, informed written consent was obtained from the legal guardians of all patients before entering the study.

Data sharing
Data are available under reasonable request to the corresponding author.

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Potential association of anti-gliadin antibodies (IgA and IgG) levels with vulvovaginal candidiasis: a case-control study

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ABSTRACT

Objective. Anti-gliadin antibodies (AGA) detection is a former diagnostic test for celiac disease (CD). This study aimed to determine whether vulvovaginal candidiasis (VVC) can induce AGA production and the significance of AGA in the diagnosis of this disease.

Materials and Methods. A case-control study was conducted to consist of 90 subjects in two groups: 50 VVC patients and 40 women without VVC. Swabs were collected from all subjects to diagnose VVC. Serum was analysed to detect AGA by ELISA assay.

Results. Levels of IgG AGA were normal in both groups. Eleven patients had elevated IgA AGA levels. Of the 11 patients, four were very positive (4%), and seven had moderate increases in antibody levels (14%). IgA AGA showed 84.76% sensitivity and 90% specificity. The diagnostic cutoff value of IgA AGA for VVC is at 20 U/ml.

Conclusions. The low number of positive IgG-AGA detected in the VVC patients suggests that using this immunomarker as a diagnostic tool for this fungal infection needs more confirmation and it's too early to establish a strong correlation between VVC and AGA levels. Confirming such correlation may help differentiate fungal infection in the vagina from the same clinical features caused by other organisms.

INTRODUCTION

Vulvovaginal candidiasis (VVC) is an infection of high prevalence and incidence in women around the world caused by the pathogenic activity of *Candida* species [1]. *C. albicans* is the most common species of *Candida* causing VVC which can affect women of all ages [2]. This type of fungi lives as a member of the normal flora of the vagina and can become pathogenic under particular circumstances [1]. Anti-gliadin antibodies (AGA) with its two classes, IgA and IgG, are mainly used in the diagnosis of celiac disease (CD) [3]. This test has become insignificant since it was found that the production of anti-gliadin antibodies is not specific to CD and can be produced in response to other diseases [4]. AGA levels may be elevated in healthy individuals or patients with diseases other than CD such as psoriasis, hepatic disorder, rheumatoid arthritis, nephritis, thyroid disorders,

sickle-cell anaemia, and other intestinal tract disorders [3, 4].

Numerous studies indicate a possible correlation between *Candida* spp. and CD [5-7]. This correlation is based on the sharing of many pathophysiological features such as the production of AGA and anti-tissue transglutaminase (anti-tTG) antibodies [5, 6]. *C. albicans* has a specific protein within its cell wall, Hwp1, which has similar amino acid sequences to the gliadin protein and has the ability to stimulate the production of AGA [7]. This study is designed based on the assumption that the ability of heavy growth of *Candida* to stimulate the production of AGA can be useful in using AGA as an indicator for the diagnosis of candidiasis. The basis for this assumption is two cases of patients with cutaneous candidiasis who did not have CD [8, 9]. These cases showed that two patients with chronic mucocutaneous candidiasis had elevated levels of AGA. Because of this, assessing the capacity of a particular type of candidiasis, VVC, to stimulate production of AGA is main goal of this study.

MATERIALS AND METHODS

Patients

A total of 90 participants, including 50 VVC-positive patients (age range: 16-57 years) and 40 women without VVC as a control group (age range: 20-30 years), were included in the case-control study. Subjects attended AL-Zahraa hospitals in AL-Najaf province of Iraq from November 2020 to February 2021. Vulvovaginal Candidiasis (VVC) was clinically diagnosed in the patient group by the gynaecological consultant of the hospital as the first step. VVC is characterized by vaginal discharge that is foamy or cheese-like, with vulvar itching, pain, and sometimes dysuria or dyspareunia [1, 2]. Patients with history of any autoimmune diseases such as CD, rheumatoid arthritis or type 1 diabetes, those under hormone treatment and with other diseases that can increase AGA levels such as psoriasis, endocrine disorders, urinary system disorders and gastrointestinal problems were excluded from this study.

Collection and processing of vaginal samples

Double swabs of the vaginal area were taken from each subject. One swab sample was microscopically examined with Gram staining to determine the morphology of *Candida* species. Another swab was cultured on Sabouraud's Dextrose agar (SDA) (Hi-Media, India). Inoculated plates were incubated at 30 °C for 24-48 hours. Identification of yeast species was performed by Vitek® 2 system (bioMérieux, France) using Vitek® 2 YST ID diagnostic cards for yeast.

Detection of anti-gliadin levels

Serum was collected from all study subjects at the same time as the swabs. Two types of antibodies against AGA were determined in the serum, including IgA and IgG by ELISA assay [10]. Levels of IgA and IgG anti-gliadin antibodies were determined using highly purified alpha-gliadin kit (AESKU. Diagnostics. Wendelsheim, Germany). The serum sample was diluted 1:101 and incubated in the ELISA microplate coated with the specific antigen. AGA levels in manufacture's manuals are: < 12 U/ml is normal, 12-18 U/ml is moderate, and > 18 U/ml is positive.

Ethical approval

The study was carried out in accordance with the Declaration of Helsinki and was endorsed by the local ethics committee of the authors College, No. 200 in June 2020. Informed written consent was obtained from all subjects before they were admitted to the study.

Statistical analysis

Data were analysed statistically with one-way analysis of variance (ANOVA) using Microsoft Excel application in Microsoft Windows 7. The level of $p < 0.05$ was considered as significant.

RESULTS

Levels of two types of AGA were evaluated in all subjects in this case-control study. All patient and control groups were negative for the IgG AGA. Antibodies against AGA IgA were determined at a concentration > 18 U/ml (positive) in only four patients (8%), with a significant difference from the control ($p = 0.003$), but not with other VVC patients ($p = 2.01$). Meanwhile, 7 patients (14%) showed moderate concentration (12-18 U/ml) of these antibodies. IgA AGA showed good specificity (84.76%) in VVC patients with 90% specificity. There was no relationship between the concentration of IgG and IgA where they were clustered on

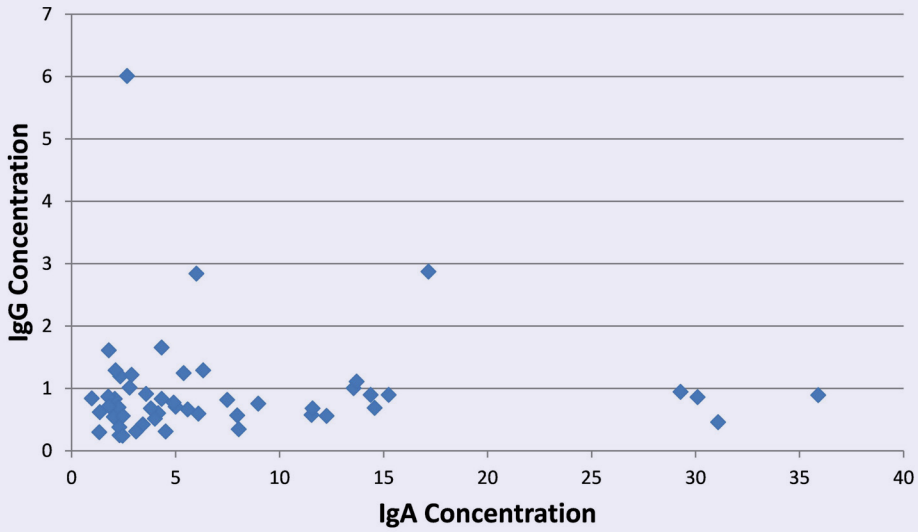

Figure 1. *Concentration of IgA AGA and IgG AGA in VVC patients.*

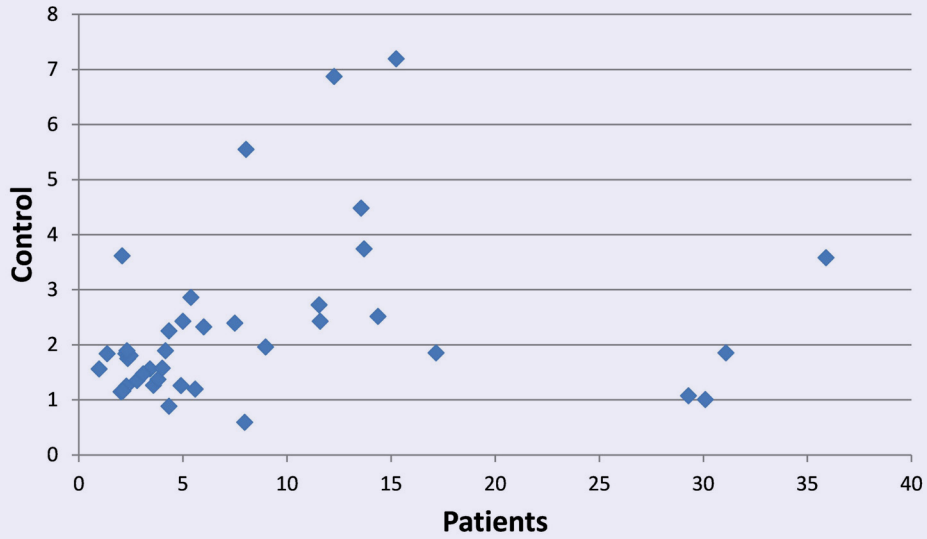

Figure 2. *Concentration of IgA AGA in VVC patients and control group.*

1-5 U/ml (**Figure 1**). There was an inconsistent positive relationship between patients and the control group in the concentration of IgA AGA. Levels of IgA AGA are higher in patients than in the control group. The IgA AGA cutoff value was set to 1-5 U/ml (**Figure 2**, **Table 1**).

Of the four patients with VVC who showed a positive result with IgA AGA, two patients were in the 24-32 age group (4%), with one patient in age group 15-23 years and another in group 33-41 years. The positive moderate results of the IgA AGA were 7 patients mostly in the 24-32 age group (10%) with a significant difference from other patients, while another one each were observed in age group 15-23 years and 42- 50 years (**Table 1**).

DISCUSSION

Vulvovaginal candidiasis (VVC) is a common genital disease which affects millions of women each year [1]. About three-quarters of all women are infected with VVC during their reproductive years [10]. A high prevalence of VVC may cost millions of dollars due to prescription drugs and physician visits [2]. The VVC can be symptomatic or asymptomatic. Several *Candida* species can cause VVC [1]. It is estimated that 75% of all women may have VVC during their lifetime and that 90% of them are infected with *C. albicans* [11].

The results of this study indicated that there were no positive IgG AGA levels in patients with VVC.

Table 1. *Anti-gliadin levels in patients with vulvovaginal candidiasis in correlation with age.*

Subject groups	Age group (year)	No. of patients (%)				Total n (%)
		AGA IgG	Anti-gliadin IgA level (U/ml)			
			Positive (> 18)	Equivocal (12 – 18)	Negative (< 12)	
Patient (n = 50)	15-23	0	1 (2)	1 (2)	16* (17.7)	18 (20)
	24-32	0	2 (4)	5* (10)	13* (14.4)	20 (22.2)
	33-41	0	1 (2)	0	5 (5.5)	6 (6.6)
	42-50	0	0	1 (2)	5 (5.5)	6 (6.6)
Control (n = 40)	20-30	0	0	0	40 (44.4)	40 (44.4)
Total n (%)		**0**	**4 (4.4)**	**7 (7.7)**	**79 (87.7)**	**90**

*Significant differences between anti-gliadin levels in the same age group.

Meanwhile, four patients had higher levels of positive AGA IgA. Detection of AGA with its two classes was the first test used for diagnosis of CD since 1950 and now has becomes a less significant test [3, 4]. The potential for candidiasis to induce AGA production was proposed based on the detection of positive AGA results in two patients with chronic mucocutaneous candidiasis [8, 9]. The first case detected a slightly elevated level of AGA in a boy with chronic mucocutaneous candidiasis that decreased later [8]. In the second case of chronic mucocutaneous candidiasis, the levels of IgG AGA were higher (365 U/L), but there was no increase in the AGA IgA level [9].

AGA IgA was detected in some patients with VVC in the current study with levels that are typically found in CD patients. IgA AGA is the most important type of AGA for diagnosis of CD [12]. The promotion of AGA by *Candida* spp. is mainly dependent upon the presence of the Hwp1 protein in its cell wall [7]. Hwp1 is a specific protein of *C. albicans* hyphae which may be used as a substrate for the enzyme human transglutaminase (TG) [7, 10]. The binding of human TG with Hwp1 produces a complex that leads to production of anti-tTG antibodies and AGA [6, 7]. Thus, the AGA level in candidiasis patients may be elevated under the activity of the Hwp1 protein of *C. albicans*. This proposed mechanism has been demonstrated by identifying higher levels of specific antibodies to anti-Hwp1, AGA and anti-tTG in the presence of *Candida* spp. in patients with CD than in healthy people [5]. The above description of the ability of the Hwp1 protein in *Candida* spp. to stimulate AGA production can explain the elevated levels of IgA AGA in some patients with VVC of the present study.

Based on the results of this study, positive IgA AGA was observed primarily in two VVC patients aged 24-32 years and one each in the 15-23 and 33-41 age groups. These findings indicate that positive IgA AGA is common in young patients with VVC, which differentiates it from CD patients. Levels of IgA AGA are often positive in children with CD more than in youth [12, 13]. Positive IgA AGA results in Pakistani CD patients were higher among youth and gradually declined with age [13]. Several studies have indicated that the level of IgA AGA is most often increased in children. Measurement of IgA AGA in 150 Iraqi children with CD revealed that younger children (1 to 5 years old) with high levels of IgA were most common compared to other ages [12].

Since AGA is specifically induced by *Candida* infections and not by other organisms, the other significant findings of the current study are to determine the type of treatment used for vulvovaginal infection. Clinical features of many vulvovaginal infections caused by various pathogenic microorganisms such as bacteria or parasites usually difficult to differentiate from that caused by fungal infection (VVC) [1, 2]. Thus, the treatment of VVC depends mainly on the identification of the causal agent and not only on clinical characteristics. In addition, significant elevated levels of AGA IgA make this type of antibody useful for both VVC diagnosis and clinically important to differentiate fungal infection from bacterial or parasite infection.

Study limitations

Many limitations are present in the current study. The smallest number of patients is the most critical one. The period of this study saw many women with suspected VVC seek treatment from gynaecological consultants at AL-Zahraa hospitals in the AL-Najaf province of Iraq. *Candida* infection in the vagina was confirmed by clinical and laboratory

tests in only 50 women. Several patients who were excluded were diagnosed with bacterial infections or trauma injuries. The selected women were required to have no suspected underlying factors for AGA, which was the second limitation of the number of participating patients in this study. Those who suffered from autoimmune diseases or other effectively diseases at the AGA level were also excluded. The AGA is a highly sensitive indicator that can be triggered by multiple disorders in the human body.

CONCLUSIONS

This primary study's findings can inspire further research into the relationship between VVC and AGA levels. It is premature to determine a strong correlation between these factors based on the current results. The final decision regarding such a type of correlation requires further studies on a large number of certified patients with VVC. Many prospective markers can be added to the diagnosis of VVC in case of confirming a strong relationship between infections with VVC and an increase or decrease in levels of AGA. The first is that AGA measurement can be useful in differentiating between VVC caused by fungi from those with the same clinical characteristics caused by bacteria or parasites [1, 12]. Thus, determining the correct causative agent will make VVC treatment more meaningful within a short time. The second is confirmed that AGA is not specific to one disease such as CD [3, 4]. The third conclusion can support the ability of *Candida* spp. to stimulate AGA production by its excretions or structural components such as the Hwp1 protein [6]. The fourth conclusion is that the measurement of AGA, especially of the IgA class, mainly provides an indicator of the potential value of this antibody for the diagnosis of VVC in some cases.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions

A.A.A.: Conceptualization, formal analysis, investigation, writing - original draft, supervision. M.J.M.: Methodology, project administration. A.A.A., M.J.M.: Resources. M.J.M. Software.

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

Ethical approval (IRB) was obtained from the ethical committee of the College of Medicine, University of Karbala with a No. 200 in June 2020.

Informed consent

All participants were volunteers and signed a consent form.

Data sharing

Data are available under reasonable request to the corresponding author.

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Aromatherapy in gynaecology and obstetrics: a systematic review of clinical applications

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ABSTRACT

Objective. Aromatherapy, a practice based on the use of essential oils, is increasingly employed in gynaecology and obstetrics as a complementary therapy to relieve pain and anxiety, especially during labour and childbirth but also in many other gynaecological conditions. The aim of this review is to provide a general overview of the clinical applications of aromatherapy, across obstetrics, gynaecology, and other medical fields in a cross-disciplinary manner.

Materials and Methods. The studies included evaluate the effectiveness of aromatherapy in reducing pain and/or anxiety during labour and childbirth or in patients affected by gynaecological cancer, in minimizing menopause symptoms or its use in other fields of medicine. Studies were excluded if they were irrelevant, methodologically weak, or based on non-representative samples. Randomized clinical trials, systematic reviews, and meta-analyses published up to 2024 were included.

Results. According to the analysed studies, aromatherapy can significantly reduce pain and anxiety during labour, improve the childbirth experience, and contribute to woman's overall psychophysical well-being. Among the 33 studies included, 84% reported significant reductions in labour pain, and 76% showed reduced anxiety levels with aromatherapy interventions, particularly with lavender and peppermint oils.

Conclusions. Aromatherapy appears to be a safe, low-cost adjunct to conventional care and may be especially valuable in settings with limited access to pharmacologic pain relief, underscoring its potential contribution to global maternal health strategies. To establish reproducibility and long-term sustainability, large-scale multicentre randomized controlled trials utilizing standardized essential oil formulations and validated outcome measures are essential.

INTRODUCTION

In recent decades, interest in complementary therapies in medicine has grown significantly [1]. Aromatherapy is defined as the science of using highly concentrated essential oils or essences distillated from plants to utilize their therapeutic properties [3]. Unlike herbal medicine, which uses whole

plants to achieve a therapeutic effect, essential oils used in aromatherapy are highly concentrated extracts derived from plant roots, leaves, bark, seeds and flowers. The concentrated chemicals in the oils give them different properties (relaxing, stimulating, pain-relieving) that can be harnessed for beneficial effect. Essential oils, which can be applied in a variety of ways, can directly reach the neocortex of the brain through connections extending to the limbic system and the hypothalamus through scent. Essential oils cross the blood-brain barrier and affect the cerebral cortex, thalamus and limbic system, the part of the brain that deals with emotions and memories. In this way, they reduce symptoms of anxiety, depression and improve sleep quality [3]. Essential oils can be divided into three types of absorption: via the skin and mucous membranes, olfactory and oral [2]. In medical and nursing contexts, absorption mostly works through the olfactory via inhalation or room scenting, or through skin and mucous membranes via percutaneous massages and embrocation [3]. A distinction can be made between psychological and pharmacological mechanisms of aromatherapy. The psychological effect, triggered by the olfactory intake of the essential oils, can be divided into three areas that control the individual scent reaction: subjective evaluation (hedonic valence), conditioning (semantic mechanism) and expectancy (placebo effect) [4]. Hence, the personality and the cultural imprint of the person smelling play a decisive role on the specific, olfactory-triggered effect. In this regard, choosing a fragrance that is personally appealing may offer individualized benefits. The pharmacological effect, however, is based on the absorption of the essential oil components via the skin and mucous membranes and the specific composition of the respective oil, and acts similar in each user. Depending on the mode of application (skin *vs* olfactory absorption), essential oils can trigger significantly different effects [5].

In gynaecology and obstetrics, aromatherapy has been adopted as a non-pharmacological method to manage pain and anxiety associated with labour and childbirth [6]. Labour pain and peripartum anxiety are among the most common concerns reported by labouring women worldwide, prompting growing interest in integrative approaches that support maternal comfort without pharmacological side effects [7]. A recent study suggests that aromatherapy can positively influence the childbirth experience by reducing pain perception and improving the emotional state of birthing women [8]. This review summarizes the available evidence on the effectiveness of aromatherapy in gynaecology and obstetrics and explores its role in other fields of medicine.

MATERIALS AND METHODS

A systematic literature review was conducted using the following databases: PubMed, Google Scholar, Scopus, Embase and Web of Science. The keywords used included: "aromatherapy", "essential oils", "labor pain", "anxiety", "gynecology", "pregnancy" and "obstetrics." Randomized clinical trials, systematic reviews, and meta-analyses published up to 2024 were included.

Included studies were those evaluating the effectiveness of aromatherapy in reducing pain and/or anxiety during labour and childbirth or in patients affected by gynaecological cancer, in minimizing menopause symptoms or its use in other fields of medicine. Studies were excluded if they were irrelevant, methodologically weak, or based on non-representative samples. **Figure 1** reports the PRISMA diagram illustrating the studies selection process.

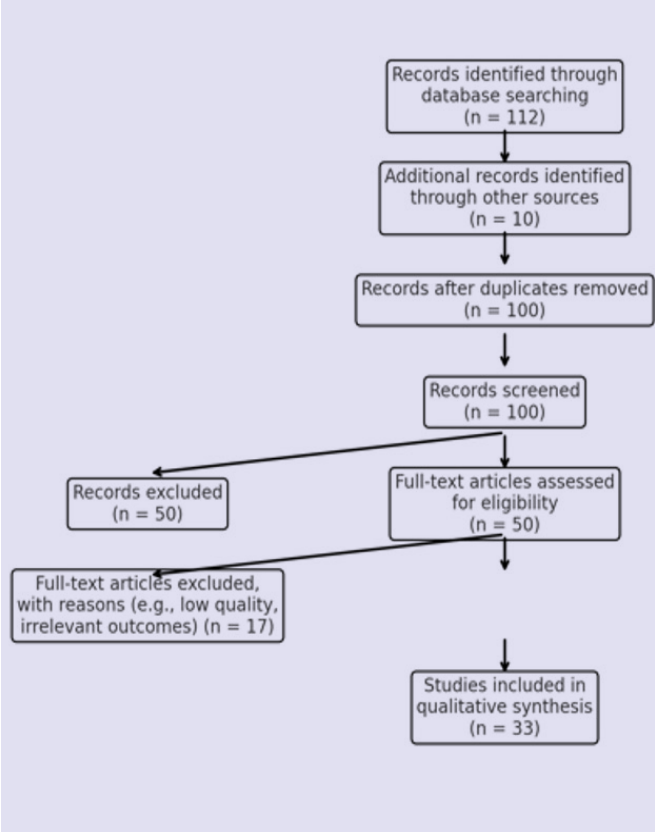

Figure 1. *PRISMA diagram.*

RESULTS

Included studies

A total of 33 studies were included, 27 of which were conducted in Iran, all assessing the effectiveness of aromatherapy in reducing pain and anxiety during labour [5]. The most used essential oils were:

- Lavender: used in 13 studies, it showed positive effects in reducing both pain and anxiety [9].
- Geranium: found to be effective in reducing labour-related anxiety [9].
- Chamomile: associated with reduced pain and anxiety [9].
- Peppermint: demonstrated both analgesic and anxiolytic properties [9].
- Sweet and bitter orange: used for their anxiety-reducing effects [9].
- Frankincense and clove: used for their calming and sedative properties [9].

Figure 2 reports the frequency of essential oil use in clinical studies.

Administration methods

Aromatherapy was primarily administered through inhalation or massage. Some studies used aromatic baths, compresses, or room diffusers [9].

Efficacy

Most of the studies reported a statistically significant reduction in pain and anxiety among women who received aromatherapy compared to control groups [9]. Lavender oil, in particular, was frequently associated with beneficial outcomes [9]. However, some studies did not report significant differences, highlighting the need for further investigation [9].

Safety

None of the studies included reported serious side effects associated with the use of aromatherapy during labour and delivery. This suggests that aromatherapy is a safe practice when used appropriately [9].

DISCUSSION

Aromatherapy in obstetrics

During pregnancy

The use of aromatherapy during pregnancy has attracted increasing attention, especially as a tool for relieving common symptoms such as nausea, anxiety, insomnia, and muscle pain [10]. Aromatherapy applied via inhalation to pregnant women improves sleep quality and reduces fatigue levels. According to these findings, lavender oil aromatherapy can be recommended to improve sleep quality and reduce fatigue levels in pregnant women during the third trimester [11]. In fact lavender is commonly used to reduce anxiety and improve sleep quality, thanks to its sedative and anxiolytic properties [10]. On the other hand, several studies

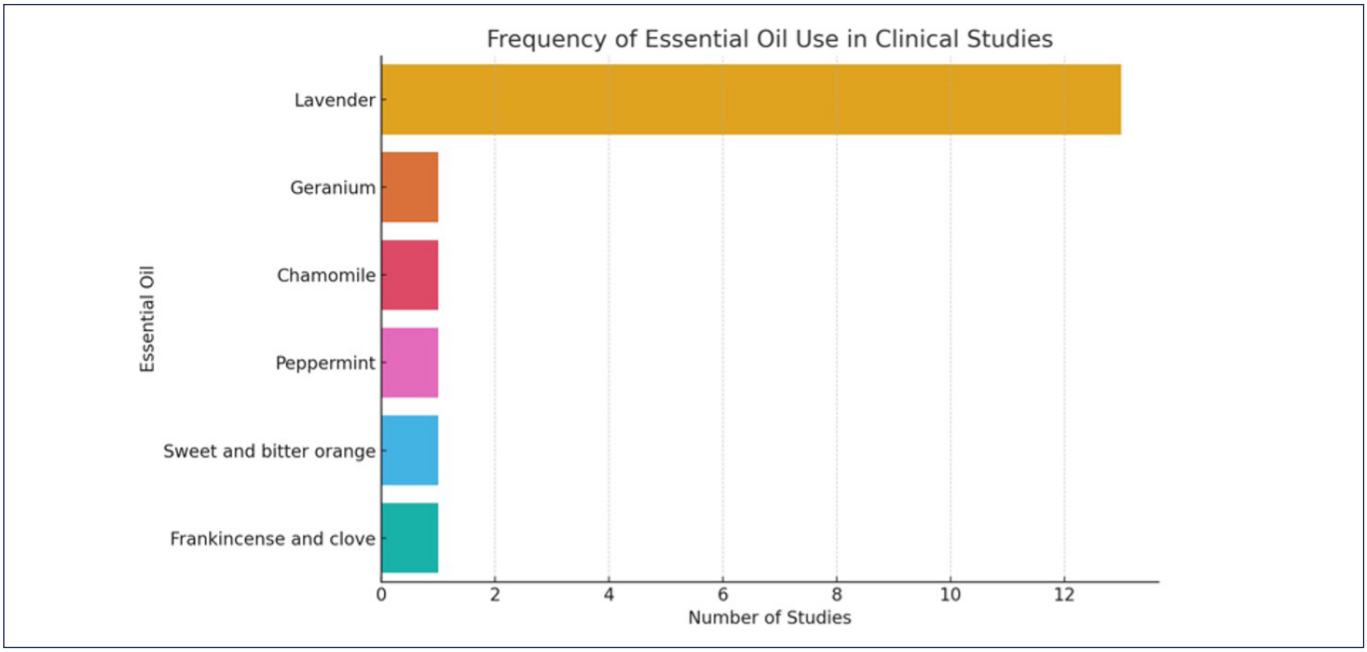

Figure 2. *Frequency of essential oil use.*

document the effectiveness of lemon and ginger essential oils in reducing morning sickness, with minimal side effects [10]. Other studies show that Rosa damascena is as effective as Metoclopramide in controlling nausea and vomiting in pregnant patients and do not negatively effects sleep quality [12]. However, the use of essential oils during pregnancy requires caution: certain oils may exhibit uterotonic effects or be contraindicated, particularly during the first trimester [10]. Rose oil should be avoided until the late third trimester due to a possible mild emmenagogic effect (herbal emmenagogues were traditionally used as abortifacients) [13]. Clary sage, also, should be avoided until term of pregnancy due to a possible effect on uterine contractions [13]. Guidelines recommend controlled use and consultation with healthcare professionals experienced in phytotherapy [10].

During labour

Aromatherapy is widely used during labour as a non-pharmacological support to manage pain and anxiety [9]. It does not have an effect on the risk of intrapartum caesarean and does not influence newborn APGAR scores, suggesting that aromatherapy can be safely administrated intrapartum [4]. Inhalation of lavender, geranium, and frankincense has demonstrated effectiveness in lowering cortisol levels and improving mood among labouring women [9]. Lavender has been associated with a significant reduction in pain perception and agitation during the early stages of labour [9], while limonene is capable of modulating neurotransmission systems associated with pain and anxiety, being effective in reducing these symptoms during labour too [14]. Also, *Camellia sinensis* essential oil reduces pain and anxiety during labour, indicating its possible applicability in good labour practice [14]. Other studies have shown how aromatherapy with narcissus flower essence can reduce the intensity of labour pain thanks to linalool compounds, making the childbirth process a more pleasant experience [15]. Aromatherapy significantly reduces pain intensity over time, especially for pregnant women in stage 1 dilatation and primiparous [14]. It also reduces the duration and pain of the latent transition and active phase of birth as well as anxiety in the active and transition phase [16]. Exposure to the aroma of sweet orange during labour also reduces mean blood pressure, heart rate, respiratory rate of pregnant women and foetal heart rate [14]. Some randomized controlled trials have shown a lower demand for analgesics among women who received aromatherapy compared to control groups [9]. Additionally, massages with essential oils contributed to a more positive birth experience and improved interactions between patients and healthcare staff [9].

Postpartum period

In the postpartum period, aromatherapy has been used to manage depressive symptoms, anxiety, insomnia, and to promote relaxation [17]. Back massage with essential oils turned out to be more effective than inhalation in improving the reduction of anxiety and pain in the postpartum period, while inhalation is also found to be more effective than no intervention [18]. So, aromatherapy can be defined as a successful non pharmacological method for reducing soreness and enhancing comfort in this phase of women's life, especially after a caesarean section [18]. Rose essential oil has been associated with a reduction in symptoms of postpartum depression in some clinical studies [17]. The use of aromatic baths and massages with essential oils has shown beneficial effects on psychological well-being and physical recovery in new mothers [17]. Preliminary evidence also suggests that aromatherapy may help strengthen the mother-infant bond and improve sleep quality, although longitudinal studies are needed to confirm these findings [17]. As well as during pregnancy and labour, the use of lavender can be useful also in the postpartum period. In fact, its regular inhalation or addition to bathwater may have beneficial effects on wound healing and pain after episiotomy [19]. Lavender oil can also be helpful to reduce dyspareunia in these women [19].

Aromatherapy in gynaecology

Premestrual syndrom (PMS)

Premenstrual syndrome, characterized by a combination of emotional and physical symptoms, affects a large portion of women of reproductive age [20] and significantly impacts their lives. Aromatherapy has demonstrated effectiveness in managing the psycho-emotional symptoms of PMS, such as irritability, mood swings, appetite changes and breast tenderness [20]. Lavender and rose essential oils are frequently used for inhalation or abdominal massages, improving mood and reducing stress [20]. Some studies also report a decrease in the intensity of breast pain and menstrual cramps [20]. Grapefruit and bergamot essential oils have

notable effects on anxiety, fatigue, bloating and sleep disturbance PMS-related, thanks to their active components like limonene, which influences the central nervous system. [21]. Coping strategies for menstrual symptoms and somatic complaints can be also reduced by the use of essential oils [21]. Therefore, aromatherapy can play an effective role in PMS as a non-invasive and safe method.

Dysmenorrhoea

Dysmenorrhoea is a gynaecologic condition that negatively affects women's social relations, daily lives, business lives, academic achievements and quality of life. For the treatment of primary and secondary dysmenorrhea, aromatherapy has often been combined with massage techniques, yielding promising results [22]. Essential oils such as lavender, clary sage, fennel, and marjoram have been used in several studies, demonstrating a significant reduction in menstrual pain [22]. The proposed mechanisms include muscle relaxation in the uterine smooth muscle and stimulation of endorphin release [22]. Several studies revealed the antimicrobial, anti-inflammatory and antioxidant properties of Rosa damascena which can be a good option for self-treatment of primary dysmenorrhea [23]. Administered by inhalation, it can be used to reduce the consumption of non-steroidal anti-inflammatory drugs, avoiding their adverse effects. Rosa damascena essential oil can be used either alone or as an additional method [23]. The calming effects of aromatherapy may also help alleviate the anxiety component often associated with chronic pain [22].

Menopause

Menopause is a natural biological process marking the end of a woman's reproductive years, characterized by the cessation of ovarian functions and the progressive decline of estrogen and progesterone levels until the stop of their production. Menopausal and postmenopausal women often experience many physical and psychological symptoms such as hot flushes, fatigue, decreased libido, headache, mood changes, anxiety, depression and sleep disturbance that can significantly impact their quality of life. Nowadays, hormone replacement therapy (HRT) is the conventional treatment of these symptoms but concerns about its safety have led many women to seek alternative approaches [24]. Essential oils can alleviate anxiety, induce relaxation and potentially alleviate stressful menopausal symptoms. Several studies shown the beneficial use of lavender oil inhalation in reducing insomnia [25] and hot flushing [26, 27]. Further research revealed that aromatherapy massage is more effective than massage alone in reducing both physical and psychological symptoms [28]. Inhalation and topical use of essential oils such as clary sage, fennel and wild orange are widespread and offer beneficial effects in alleviating menopausal symptoms and hot flushes [24]. Peppermint oil is another beneficial essential oil. In fact, aromatherapy massage with peppermint and lemon essential oil may help alleviate hot flushes and discomfort associated with menopause symptoms [29].

Osteoarthritis with associated chronic knee pain is another relevant issue experienced by women during menopausal period. Chronic pain adversely affects the quality of life impeding functionality, daily life activities, sleep quality, mental health, social relationships and the ability to fullfil occupational responsibilities [30]. Aromatherapy can be utilized as a complementary therapy in the treatment of joint diseases such as knee osteoarthritis. The components of essential oils used during aromatherapy massage are reported to reduce pain by affecting the release of neurotransmitters such as dopamine, endorphins, norepinephrine and serotonin through lymph and blood vessels in the epidermis [30]. Lavender, ginger, eucalyptus and rosemary oil is reported to be applied in the treatment of osteoarthritis with noticeable benefits [31]. Also, the use of bergamot essential oil has been widely documented for its pharmacological antinociceptive efficacy [30].

Current evidence suggests that aromatherapy alone may not be sufficient as a stand-alone treatment for managing menopausal symptoms [24]. However, incorporating aromatherapy into other intervention may offer additional relief and noticeable benefits [24].

Gynaecologic oncology

Women with gynaecological cancer, including breast cancer, often experience cancer and therapy-related side effects such as pain, fatigue, stress, sleep disturbance, cognitive impairment, neuropathy, psychological distress, changes in sexuality or clusters of several symptoms [32]. Symptomatic side effects usually do not vanish post chemotherapy but continue into aftercare and can have a strong negative impact on women's daily lives and general well-being [32]. Therefore, gynaecological

oncology patients need supportive strategies that are adapted to their individual needs and circumstances [32]. In oncology patients, aromatherapy has mainly been studied for the management of secondary symptoms such as chemotherapy-induced nausea, anxiety, insomnia, and chronic pain [33]. Although not curative, aromatherapy is recognized as a valuable palliative intervention [33]. Peppermint essential oil is frequently used for nausea control, while lavender and neroli are used to reduce anxiety and improve sleep quality [33]. In addition, it was shown that the use of aromatherapy during intracavity brachytherapy for women with cervical cancer may help reducing pain and anxiety [34]. In palliative care settings, aromatherapy has also been shown to improve quality of life and overall well-being [33]. However, in oncology, it is essential that the use of essential oils is supervised by qualified professionals, as some botanical substances may interfere with chemotherapy drugs [33] or may cause side effects themselves (lavender-based products can be associated with breast swelling or irritation of nasal mucosa) [32]. Consider patients' odour preferences and aversions is also important because they have a clear impact on motivation and perceived effects. The smell of the product alone can cause strong reactions, physical or mental responses such as nausea or vomiting and even behavioural changes. The effect of the odour alone is considered to be even more important than the effect of the chemical components [32]. Offering multiple and various fragrances and applications that cover the individual needs and patient's living circumstances represent a challenging item on which future aromatherapy researches should be focused.

Limitations and critical issue in literature

Despite the promising evidence, the literature on aromatherapy in gynaecology and obstetrics presents several limitations [9]. Many studies have small sample sizes, non-standardized methodologies, and a lack of appropriate control groups [9]. The influence of placebo effects is also not consistently accounted for [9]. Additional limitations include variability in the quality of the essential oils used and the methods of administration [9]. Moreover, the subjective perception of well-being can influence outcomes, making it challenging to objectively assess the actual effectiveness of the intervention [9].

Table 3. *Essential oils and clinical use.*

Essential oil	Primary use
Lavender	Anxiety, insomnia, labour pain
Geranium	Labor-related anxiety
Chamomile	Menstrual pain, anxiety
Peppermint	Nausea, pain relief, stimulant
Sweet Orange	Anxiety and relaxation
Rose	Postpartum depression
Ginger	Pregnancy-related nausea

Many trials combine other complementary therapies with aromatherapy, making difficult or impossible separating the effects of aromatherapy from the others. [4] In addition, the majority of trials on aromatherapy during the peripartum period were conducted in the Middle East, most notably Iran, which may limit generalizability to other populations with different perinatal practices [4]. Finally, another limitation is that very few studies have been conducted for several of the clinical indications [4] (**Table 1**).

Other clinical applications of aromatherapy

General oncology

In addition to gynaecologic oncology, aromatherapy is widely used as palliative treatment for cancer patients to alleviate symptoms related to therapies (*e.g.*, nausea, fatigue, insomnia, and anxiety) [35]. Ginger essential oil is commonly used to counter chemotherapy-induced nausea, while lavender, frankincense, and neroli are used to reduce anxiety and improve sleep quality [35]. Studies conducted in oncology centres have shown that aromatherapy, when integrated with conventional medicine, improves the patient's subjective experience and can reduce the need for anxiolytics [35].

Neurology and mental health

The use of essential oils in neurological and psychiatric contexts is well documented, particularly for the treatment of anxiety, mild depression, chronic stress, and insomnia [36]. Lavender essential oil (*Lavandula angustifolia*) in particular has demonstrated anxiolytic effects comparable to some pharmacological anxiolytics in several randomized controlled trials, with no significant side effects [36]. Lemon and Melissa (lemon balm) have also been studied for their mood-enhancing properties

and their role in cognitive stimulation in patients with mild depression or dementia [36].

Intensive care and anaesthesiology
In intensive care units, aromatherapy has been introduced as a non-invasive technique to reduce anxiety in intubated patients or those undergoing invasive procedures [37]. The use of room diffusers with lavender or chamomile oils can create a more relaxing environment and improve physiological parameters such as heart rate and blood pressure [37]. Preliminary studies suggest that aromatherapy may reduce the need for sedatives or anxiolytics in pre- and post-operative settings [37].

Rheumatology and chronic pain
In managing musculoskeletal and rheumatic pain, aromatherapy has shown anti-inflammatory and analgesic properties [38]. Eucalyptus, rosemary, and pine essential oils are often used in combination with physiotherapy massage to relieve joint pain, muscle stiffness, and inflammation [38]. Regular use in patients with fibromyalgia or rheumatoid arthritis has led to improvements in quality of life, sleep, and pain perception [38].

Dermatology
Topical use of essential oils has found applications in managing dermatitis, acne, psoriasis, and skin infections [39]. Tea tree oil has demonstrated antibacterial and antifungal activity and is used in the treatment of mild acne and fungal infections [39]. Lavender and chamomile are employed for their soothing properties on irritated or inflamed skin and promote tissue regeneration [39].

Paediatrics
Aromatherapy is also used in children, although with greater caution due to their skin and respiratory sensitivity [40]. In paediatric care, it has been used to improve sleep, calm night crying, and reduce irritability [40]. Oils such as chamomile, mandarin, and lavender are preferred for their gentle action [40]. Administration is mainly through diffusion or diluted massage [40].

Sports medicine
In sports medicine, aromatherapy has been used to accelerate muscle recovery, reduce cramps, and stimulate concentration before competitions [41]. Rosemary and peppermint are commonly used oils due to their energizing effects, while eucalyptus is known for its decongestant and anti-inflammatory properties [41, 42].

CONCLUSIONS

Aromatherapy represents a valuable complementary approach across multiple medical disciplines. Although it is not a first-line treatment, it can be integrated into clinical protocols as a holistic approach cantered on the patient's overall well-being. The documented effectiveness in various clinical settings supports the need for appropriate training of healthcare professionals, as well as the development of specific guidelines for each field of application.
Aromatherapy may be especially valuable in settings with limited access to pharmacologic pain relief, underscoring its potential contribution to global maternal health strategies.
To establish reproducibility and long-term sustainability, large-scale multicentre randomized controlled trials utilizing standardized essential oil formulations and validated outcome measures are essential.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution
A.M., A.L.: Writing – original draft. A.M., I.G., E.D., A.L.: Writing – review & editing. V.R., L.L., B.M.: Supervision.

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The authors declare that they have no conflict of interests.

Ethical approval
N/A.

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N/A.

Data sharing
Data are available along with the review.

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Different cerclage for cervical insufficiency: more of the same? A systematic review on perinatal outcomes of pre-conception laparoscopic transabdominal and elective transvaginal cervical cerclage

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ABSTRACT

Background. Cervical cerclage (CC) prevents preterm birth and mid-trimester loss (MTL) in women with cervical insufficiency. While transvaginal cerclage (TVC) is commonly used, laparoscopic abdominal cerclage (LAC) is an alternative for those with anatomical limitations. This systematic review compares pregnancy outcomes between elective TVC and pre-conceptional LAC.

Materials and Methods. Following PRISMA guidelines, we conducted a systematic search in PubMed, EMBASE, Scopus, Cochrane Library, and Science Direct in June 2024 using the terms "Elective Cervical cerclage" and "Laparoscopic cerclage". Studies were included if they involved elective TVC or LAC and reported at least one outcome of interest: delivery < 34 weeks gestation, MTL, infection, or neonatal survival. Non-original and non-English studies were excluded.

Results. 13 studies involving 1,259 patients (601 TVC, 658 LAC) were analysed. Delivery ≥ 34 weeks occurred in 71.3-87% of TVC and 71.4-100% of LAC cases. MTL was significantly higher with TVC (6.4% *vs* 3.4%; p = 0.0055). No significant differences were observed in preterm delivery < 34 weeks (9.7% *vs* 11.1%; p = 0.053) or complication rates (2.8% *vs* 1.9%; p = 0.337).

Conclusions. While TVC has traditionally been preferred, recent evidence suggests that pre-conceptional LAC may be more effective for women with a history of cervical insufficiency. Further research is necessary to confirm these findings and assess the efficacy of LAC in other high-risk populations.

INTRODUCTION

Cervical cerclage (CC) represents a successful option available for the management of women at risk for spontaneous preterm delivery and mid-trimester loss (MTL) caused by cervical insufficiency (CI) [1]. In the first trimester, transvaginal cerclage (TVC) may be performed as a preventive measure (electi-

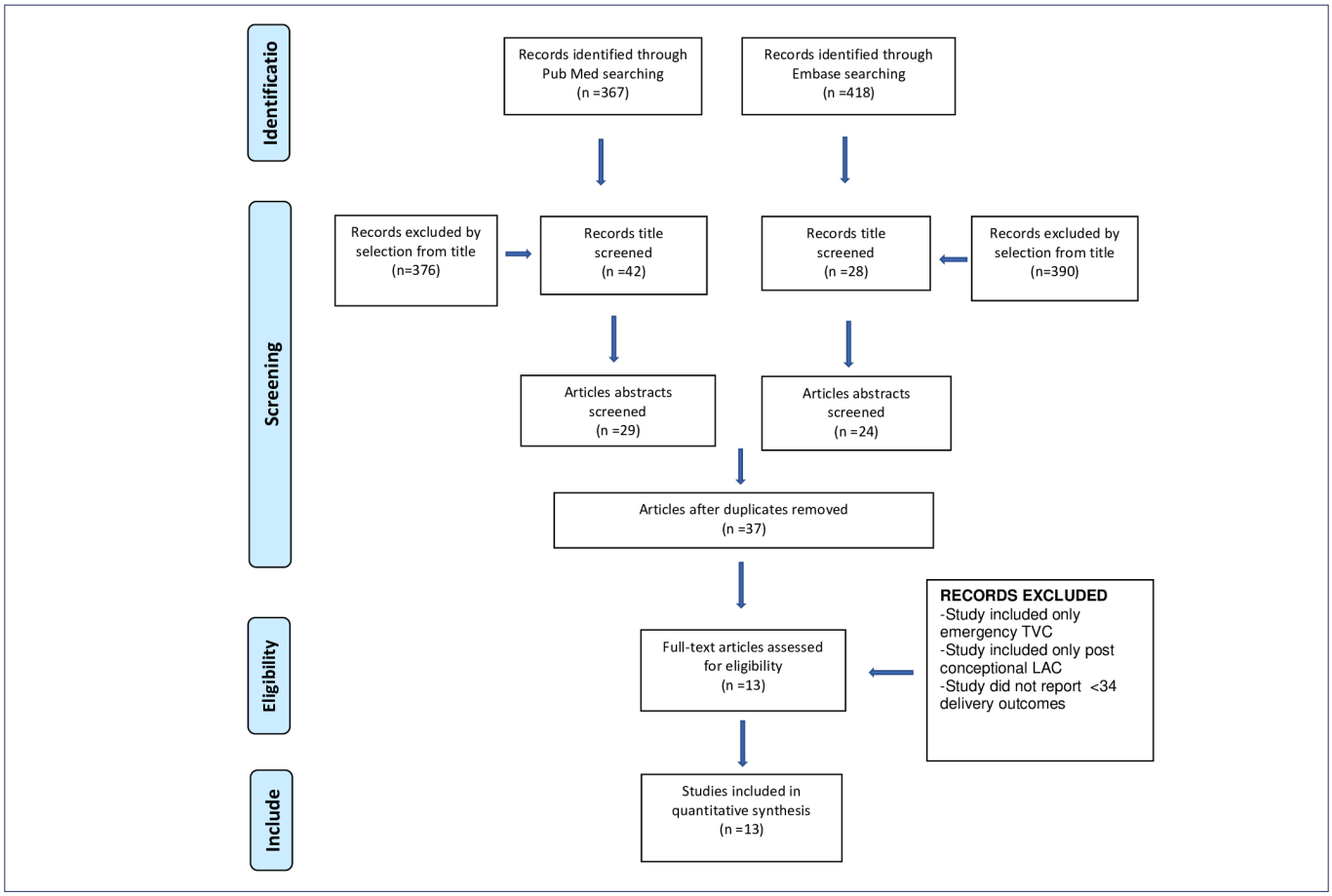

Figure 1. *PRISMA flow diagram.*

ve) if clinical history indicates a risk of mid-trimester loss or low cervical resistance, such as CI or a history of cervical cerclage placement in a previous pregnancy. This procedure may also be required for a short cervix (25mm) or cervical shortening found on ultrasound. There is also a possibility of placing an emergency cervical suture in women who already have a dilated cervix with membranes bulging without any signs of labour, infection, or heavy bleeding [2].

An alternative strategy could be represented by transabdominal cerclage. It is considered for women who had cervical insufficiency or anatomy that excluded a transvaginal cerclage [3]. Compared to the vaginal approach, the abdominal approach is considered to provide greater mechanical support to the cervix by placing the suture at or slightly above the internal ostium. In order to minimize surgical discomfort, a laparoscopic procedure can be performed [4].

Our systematic review aimed to compare the pregnancy outcomes between elective TVC and preconceptional laparoscopic abdominal cerclage (LAC) in patients with cervical insufficiency.

MATERIALS AND METHODS

The methods for this study were specified a priori based on the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [5]. The present work has been categorized on the PROSPERO International Prospective Register of Systematic Reviews as ID CRD42024558592.

Search method

In June 2024, we performed a systematic search for articles in PubMed Database, Embase, Cochrane Library, Science Direct, and Scopus Database, adopting the string "Elective Cervical cerclage" and "Laparoscopic cerclage". We provided no restriction on the country and year of publication and considered English-published articles (**Figure 1**).

Study selection

Study selection was made independently by E.B. and M.C.S. In case of discrepancy, C.R. decided on inclusion or exclusion. Inclusion criteria were: 1) studies that included patients undergoing elective

TVC or LAC; 2) articles reporting at least one outcome of interest: delivery < 34 weeks of gestation, mid-trimester loss, number of infections and chorioamnionitis and neonatal survival rate; 3) peer-reviewed articles published originally. We excluded non-original studies, preclinical trials, animal trials, abstract-only publications, and articles in languages other than English.
An email request was sent to the authors of studies that were only available as abstracts in order to obtain data from them.
We mentioned the studies selected and all reasons for exclusion in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (**Figure 1**). We assessed all included studies regarding potential conflicts of interest.

Data extraction
G.C. and M.C.D.D. extracted data for all relevant series and case reports. They extracted data on the number of pregnancies achieved, the number of deliveries beyond 34 weeks of gestation, the number of deliveries before 34 weeks of gestation, mid-trimester loss (MTL), the number of infections and chorioamnionitis, and the neonatal survival rate.
The number of pregnancies was defined as an absolute number. The number of deliveries beyond 34 weeks' gestation and before 34 weeks' gestation was defined as the ratio of live-birth deliveries to the total number of pregnant patients. The MTL rate was defined as the ratio of patients who underwent pregnancy loss between 12 and 24 weeks' gestation. The infections and chorioamnionitis rate was defined as the infections and chorioamnionitis ratio of the total number of pregnancies. The neonatal survival rate was the ratio to the total number of pregnancies.
However, the lack of information and different criteria for each paper hindered this activity.

Heterogeneity
Although our analysis applied standard methods for pooling results, potential heterogeneity across studies must be acknowledged. Differences in clinical inclusion criteria (*e.g.*, patient age ranges, disease severity, or comorbidity profiles), variations in treatment protocols, and inconsistent definitions or measurements of outcomes may have introduced heterogeneity. Furthermore, the duration of follow-up and the setting (single *vs* multicentre studies) could also contribute to between-study variability.

Quality assessment
We assessed the included studies' quality using the Newcastle–Ottawa scale (NOS) [6]. This assessment scale uses three broad factors (selection, comparability, and exposure), with the scores ranging from 0 (lowest quality) to 8 (best quality). Two authors (V.C. and C.S.) independently rated the study's quality. Any disagreement was subsequently resolved by discussion or consultation with C.R. Discrepancies were resolved through discussion and consensus among the three reviewers. If consensus could not be reached initially, the decision of the third reviewer was considered final. We reported the NOS Scale in **Appendix A**.

Statistic consideration
The nominal variables were expressed as absolute frequency and percentages and compared using Fisher's exact and Chi-square tests, according to their distribution. Continuous variables were expressed as median. No comparison between continuous variables was planned.
Patients were divided according to technique into TVC and LAC.
The null hypothesis of our study was that there was no difference in the prevalence of the MLT between patients who underwent TVC or LAC (H0: p1 = p2; H1: p1-p2 ¹ 0 two-sides). Secondary outcomes were the same evaluation for births before 34 gw and any complication related to the technique. All statistical investigations were performed using R software and R Studio vers. 2023.12.1 + 402.

Declaration of generative AI
Grammar correction tools (Grammarly, Inc.) were used to improve the quality of English and readability. The technology was used under human oversight and control.

RESULTS

Studies characteristics
After the database search, 785 articles matched the search criteria. After removing records with no full text, duplicates, and wrong study designs (*e.g.*, reviews), 37 were eligible. Of those, 13 matched the inclusion criteria and were included in the systematic review. Those data are summarized in **Table 1**.
An analysis of 5 retrospective articles examined elective TVC placed in the first trimester ba-

Table 1. *Characteristics of included studies.*

Authors, year of publication	Country	Study design	Period of enrolment	No. of participants	Cervical insufficiency treatment (LAC/elective TVC)	Inclusion criteria
To M.S. 2002	UK	Retrospective monocentric study	1995-2000	41	TVC	Singleton pregnancies who had at least one previous spontaneous delivery at 16-33 weeks of gestation
Liddell H.S. 2008	New Zealand	Retrospective monocentric study	1998-2003	11	LAC	Cervical incompetence and/or a short or absent cervix after cervical surgery MTL, cervical surgery
Burger N. B. 2012	Netherlands	Retrospective multicentre cohort study	1997-2011	56	LAC	Cervical surgery; previous failed TVC
Riiskjaer M.2012	Denmark	Prospective observational monocentric study	2004-2011	52	LAC	Cervical incompetence and/or a short or absent cervix after cervical surgery. PPROM. Preterm delivery or contractions.
Gluck O. 2016	Israel	Retrospective monocentric cohort study	2006-2014	154	TVC	MTL, preterm loss, cervical incompetence and/or a short or absent cervix after cervical surgery
Huang X. 2016	China	Prospectic observational monocentric study	2010-2015	100	LAC	Prior midtrimester loss; failed TVC
Ades A. 2018	Australia	Prospective observational study	2007-2017	225	LAC	diagnosis of cervical insufficiency based on previous obstetric history and/ or a short or absent cervix
Wei 2018	China	Retrospective monocentric study	2009-2015	276	TVC	MTL, cervical surgery
Saridogan E. 2019	England	Prospectic observational monocentric study	2004-2017	54	LAC	Cervical surgery; previous failed TVC
Yüksel Şimşek S. 2020	Turkey	Retrospective monocentric study	2012-2019	48	TVC	History of cervical insufficiency in previous pregnancy
Tian S. 2020	China	Retrospective monocentric study	2014-2018	135	LAC	History of >2 s-trimester pregnancy losses or preterm delivery or contractions <34 weeks. Singleton pregnancy. Cervical incompetence and/or a short or absent cervix
Tian S. 2020	China	Retrospective monocentric s tudy	2014-2018	82	TVC	History of >2 s-trimester pregnancy losses or preterm delivery or contractions <34 weeks. Singleton pregnancy. Cervical incompetence and/or a short or absent cervix
Abdulrahman N. 2024	Netherlands	Retrospective multicentre cohort study	1997-2007	250	LAC	Cervical incompetence and/or a short or absent cervix after cervical surgery; previous failed vaginal cerclage

TVC: transvaginal cervical cerclage; LAC: laparoscopic abdominal cerclage.

sed on the patient's obstetric history or anatomical characteristics [7-11].

A total of 8 studies evaluated pre-conceptional LAC placement based on the patient's previous obstetric history or anatomy criteria [12-18]. There were 4 retrospective studies and 4 prospective studies in this group.

Table 1 summarizes the publication year range, the studies' design, the number of participants, and the type of treatment (elective TVC or pre-conceptional LAC).

The publication years ranged from 2002 to 2024 [7-18].

In total, 1,259 patients who performed cerclages were included in this review: 601 were treated with elective TVC and 658 were treated with pre-conceptional LAC.

Outcomes

In the elective TVC studies group, 601 patients were treated. 532 pregnancies were followed up, and the percentage of delivery beyond 34 week gestation ranged from 71.3% to 87%. In the pre-conceptional LAC studies group, 658 patients were treated, and 549 pregnancies were achieved. The percentage of

Table 2. *Pregnancy outcomes of LAC and TVC.*

Authors, year of publication	Country	Pregnancies achieved	MTL (%)	Preterm delivery < 34 weeks	Delivery > 34 weeks	Infections and chorioamnionitis	Neonatal survival (%)	Cervical treatment (LAC/ elective TVC)
To M.S. 2002	UK	41	2.4%	14.6%	85.4%	NA	NA	TVC
Liddell H.S. 2008	New Zealand	10	0%	0%	100%	NA	100%	LAC
Burger N. B. 2012	Netherlands	35	8.6%	5.7%	71.4%	0%	90%	LAC
Riiskjaer M.2012	Denmark	45	11%	13%	82.5%	NA	NA	LAC
Gluck O. 2016	Israel	154	2.5%	2.59%	81.8%	1.29%	NA	TVC
Huang X. 2016	China	85	3.7%	20%	76.4%	NA	96.4%	LAC
Ades A. 2018	Australia	121	1.6%	12.4%	79.7%	1.3%	98.4%	LAC
Wei 2018	China	257	7.2%	5.1%	87%	NA	91.8%	TVC
SaridoganE. 2019	England	42	4,7%	14%	83%	NA	97%	LAC
Yüksel Şimşek S. 2020	Turkey	48	NA	20.8%	79.2%	2.1%	NA	TVC
Tian S.2020	China	74	NA	NA	94.6%	0%	97.3%	LAC
Tian S. 2020	China	80	NA	NA	71.3%	6.3%	83.8%	TVC
Abdulrahman N. 2024	Netherlands	137	18.3%	9.6%	90.4%	2.5%	96.2%	LAC

TVC: transvaginal cervical cerclage; LAC: laparoscopic abdominal cerclage; MTL: Mid trimester loss.

delivery beyond 34 weeks gestation ranged from 71.4% to 100%.

10 articles presented data on losses in the mid-trimester (between 14 and 27 weeks of pregnancy); specifically, mid-trimester loss ranged from 2.4% to 7.8% in the TVC group and from 0% to 8.6% in the LAC group.

7 articles reported the overall complication rate regarding wound infections, chorioamnionitis, and intra-operative injury; TVC group complications ranged from 1.2% to 6.3% and LAC group complications ranged from 0% to 2.5%. Only nine studies presented neonatal survival data, specifically: two studies of TVC group and seven studies of LAC group. A neonatal survival rate of 90%-100% was observed in the LAC group, compared to an average of 83.8%-91% in the TVC group. Data are summarized in **Table 2**.

Analysis of the data

Rearranging all the data reported in the literature, we compared the two techniques regarding MTL, < 34 gw deliveries, and complication rate (CR).

Concerning MTL, data were obtainable for 924 patients (456 TCV and 468 LAC). The TVC technique showed a higher rate of MTL (6.4% *vs* 3.4%; p = 0.0055). Regarding delivery previous than 34 gw, in a sample of 1123 patients (524 TVC *vs* 483 LAC), each technique failed to show itself superior to the other (9.7% in TVC *vs* 11.1% in LAC; p = 0.053). Finally, CR information was obtainable for only 614 patients (282 who underwent TVC and 332 LAC); no statistically significant difference was observed in the two groups (CR 2.8% *vs* 1.9%; p = 0.337). Those data are summarized in **Table 3**.

DISCUSSION

Data discussion

It is difficult to find one technique that is clearly superior to the other. Our study failed to show a statistically significant difference in reducing preterm deliveries. However, it did show a trend (p = 0.053), with a very slight advantage in favour of TVC (9.7% *vs* 11.1%). On the other hand, this finding can be interpreted in terms of 'non-inferiority', showing that both techniques are effective about 9 times out of 10, with an extremely low-risk profile of complications (2.8% and 1.9%). Our systematic review shows that both elective TVC and pre-conceptional LAC are effective in reducing the incidence of preterm birth before 34 weeks gestation

Table 3. *Analysis of the data reported in the literature.*

Outcome	TVC (%)	LAC (%)	P-value°
MLT+	29 (6.4)	16 (3.4)	0.0055
Preterm delivery <34 gw+	56 (9.7)	60 (11.1)	0.053
CR+	8 (2.8)	6 (1.9)	0.337

TVC: transvaginal cerclage; LAC: laparoscopic abdominal cerclage; MTL: Mid trimester loss; gw: gestational weeks; CR: Complication Rate; °chi-squared test; +Data available for a proportion of patients.

in women at risk. However, due to the inclusion criteria of the individual studies, effect sizes may have varied.
According to our research, we found no comparative studies between pre-conceptional LAC and elective TVC, except in Tian *et al*., in which patients with a history of cervical insufficiency, prophylactic LAC appears to have a better pregnancy outcome than elective TVC [11].
However, the data reported for both techniques appear superimposable even without comparative studies. This could mean that the very concept of 'cerclage' is effective against cervical incontinence, and the mode of placement and time of planning have little effect on the final outcome.

Comparison with existing literature
Several techniques can be considered for TVC. Previous research has found that pregnancy outcomes were similar in Shirodkar and McDonald cerclages [19, 20].
Conversely, with fewer complications and less damage, laparoscopic abdominal cerclage is as effective and perhaps even better than open abdominal cerclage, so it gradually replaced open abdominal cerclage as a primary surgical technique [21]. Despite this, the LAC shows a lower incidence of infections and faster patient relief [11]. Also, in our review, the lowest infection rate occurred in the LAC group, even though we were unable to report statistical significance. In addition, previous retrospective studies have shown that the two approaches have a superimposable rate of preterm deliveries while maintaining superimposable clinical outcomes of complications and hospitalizations [22].

Clinical implication
Given the overlap in neonatal outcomes in the two study groups, the 'non-inferiority' of one technique over the other should be understood as greater clinical manoeuvrability. While vaginal techniques are easier to perform, preconception treatment could lead to equal results by avoiding anxiety and worry in patients at risk of premature birth or mid-trimester loss. On the other hand, the effects of vaginal surgery are reassuring, making it possible to treat even patients who were not selected in the pre-conceptional phase as candidates for cervical cerclage. Finally, the high neonatal survival rate makes the two techniques optimal for the management of the risk of premature birth in cases of cervical-histomy insufficiency.

Strength and limitation
Our study found its strength in the systematic nature of the research, which covered everything published on the subject without date or research group limitations. The construction of a NOS scale gave due qualitative weight to the individual studies. On the other hand, a limitation was the complete absence of direct comparative studies, which made a quantitative analysis impossible. Another limitation is the absence of data on the management and timing of cerclage removal in non-pregnant patients, which was not addressed in our analysis. Dedicated studies are required to explore this specific clinical question. Further studies of a prospective nature aimed at a direct comparison will be necessary to settle the differences between the two techniques.

CONCLUSIONS

TVC has been considered the traditional approach. Studies have demonstrated that TVC is associated with fewer complications and a similar neonatal survival rate than laparoscopic approaches [3, 20]. Nevertheless, other studies have suggested that laparoscopic cerclage may be more effective than transvaginal cerclage in patients with a history of transvaginal cerclage failure. Regarding which approach should be considered first, there is still a debate. As a result of our study, LAC may be beneficial for women who have previously failed vaginal cerclages, but further research is necessary to confirm its efficacy in other high-risk groups.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions
CR: Methodology, conceptualization. EB: Data curation, writing – original draft, writing – review & editing. MCS: Data curation, writing – original draft. GA: Formal analysis. GC: Data curation. MCDD: Conceptualization. CS: Methodology. VC: Validation.

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None.

Study registration
The present work has been categorized on the PROSPERO International Prospective Register of Systematic Reviews as ID CRD42024558592.

Declaration of interests
The authors declare that they have no conflict of interests.

Ethical approval
N/A. This study is a systematic review of previously published data and did not involve the collection of new data from human participants.

Informed consent
No individual patient data were collected or reported in this study.

Data sharing
Data are available under reasonable request to the corresponding author.

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APPENDIX A. *Newcastle-Ottawa scale (NOS).*

Study	Representativeness of the exposed cohort (1)	Selection of the non-exposed cohort (1)	Item & score				Was follow up long enough for outcomes to occur (1)	Adequacy of follow up of cohorts (1)
			Ascertainment of exposure (1)	Demonstration that outcome of interest was not present at start of study (1)	Compare ability of cohorts on the basis of the design or analysis (2)	Assessment of outcome (1)		
To M.S. *et al* 2002	1	1	1	1	2	1	1	1
Liddell H.S. *et al* 2008	1	0	1	1	2	1	1	1
Burger N. B. 2012	1	1	1	1	2	1	1	1
Riiskjaer M. 2012	1	1	1	1	2	1	1	1
Gluck O. 2016	1	1	1	1	2	1	1	1
Huang X. 2016	1	1	1	1	2	1	1	1
Ades A. 2018	1	1	1	1	2	1	1	1
Wei 2018	1	1	1	1	2	1	1	1
Saridogan E.2019	1	1	1	1	2	1	1	1
Yüksel Şimşek S. 2020	1	1	1	1	2	1	1	1
Tian S. 2020	1	1	1	1	2	1	1	1
Abdulrahman N. 2024	1	1	1	1	2	1	1	1

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Translation and cross-cultural adaptation of the Get Active Questionnaire for pregnancy into Italian language

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ABSTRACT

Objective. Engaging in regular physical activity during pregnancy yields beneficial health effects for both mothers and their infants. To promote these benefits, the World Health Organization experts recommend that pregnant and postpartum women partake in at least 150 minutes of moderate-intensity aerobic exercise each week and reduce their sedentary time. The Get Active Questionnaire for Pregnancy (GAQ-P) was created in 2021 to identify pregnant women who may need further advice from their obstetric care provider regarding potential contraindications to physical activity participation. The goal of this project was to translate the GAQ-P into Italian and to culturally adapt these tools.

Materials and Methods. The GAQ-P was translated into Italian and cross-culturally adjusted using the ten recommended steps: 1. Preparation; 2. Forward Translation; 3. Reconciliation; 4. Back Translation; 5. Back Translation Review; 6. Harmonization; 7. Cognitive Debriefing; 8. Review of Cognitive Debriefing Results and Finalization; 9. Proofreading; and 10. Final Report.

Results. Utilizing the described methodology, we have developed a reliable, evidence-based screening tool. This tool aims to assist obstetric care providers in identifying pregnant patients who may not be suited for moderate to vigorous physical activity. Simultaneously, the GAQ-P can help lower the barriers for most women who should and wish to engage in physical activity during pregnancy.

Conclusions. We have developed a reliable, evidence-based screening tool. Future research should evaluate the effectiveness of this instrument and the extent of its implementation within the Italian context.

INTRODUCTION

Comprehensive research has indicated that engaging in regular physical activity during pregnancy (PAP) yields beneficial health effects for both mothers and their infants [1-3]. The World Health Organization points out several key advantages, including a reduced likelihood of preeclampsia, gestational hypertension, gestational diabetes, excessive weight gain during pregnancy, complications

during childbirth, postpartum depression, and fewer neonatal issues [4]. To promote these benefits, WHO experts recommend that pregnant and postpartum women partake in at least 150 minutes of moderate-intensity aerobic exercise each week and reduce their sedentary time. They also suggest that women who were routinely involved in vigorous sports or were physically active prior to pregnancy can maintain these activities throughout their pregnancy and postpartum, provided there are no complications. Similar recommendations have been released in various countries in recent years [5].
In 2023, the Polish Association of Gynaecologists and Obstetricians and the Polish Association of Sports Medicine created joint guidelines on following current guidance outlined above, as well as incorporating more contemporary research and practical knowledge [6]. Although the vast majority of Polish women (over 90%) are aware of the beneficial effects of PAP on the course of pregnancy [7], almost half of them are inactive while pregnant [8].
In Italy, the guidelines on physical activity during pregnancy are in line with those of the World Health Organization (WHO) and can also be found in documents produced by the Ministry of Health and other scientific societies, such as the Italian Society of Gynecology and Obstetrics (SIGO). Thanks to informative campaigns and guidelines promoted by these organizations, awareness among Italian women regarding the importance of physical activity during pregnancy is increasing. However, knowledge may vary depending on factors such as education, access to information, and personal experiences. Although many Italian women are aware of the beneficial effects of PAP on the course of pregnancy, recent studies indicate that the percentage of women who engage in physical activity during pregnancy is estimated around 20-30%. It is essential to continue promoting education and providing support so that all pregnant women can benefit from adequate and safe physical activity.
Paradoxically, one of the leading reasons for their lack of activity is the apprehension regarding the health and safety of the foetus [9]. Recent meta-analyses have shown that these concerns are entirely baseless. Prenatal exercise is not linked to miscarriage, stillbirth, neonatal mortality, preterm delivery, premature or prelabour rupture of membranes, or low birth weight [10, 11]. However, it is crucial to identify any contraindications or medical conditions that could make prenatal physical activity unwise or necessitate adjustments. Unfortunately, many women do not make their decisions about starting physical activity during pregnancy based on the latest information or credible sources. Many pregnant women in Italy receive information from healthcare professionals about the importance of physical activity during pregnancy, but the quality and quantity of this information can vary. Although there is increasing awareness among health professionals regarding the benefits of physical activity, not all women receive specific recommendations. Additionally, there is evidence indicating that women often wish to receive more information on the subject. Training for healthcare professionals on this topic is essential to ensure that all pregnant women receive adequate and evidence-based advice. Various initiatives have been launched to improve communication on this issue, but it remains an evolving area.
Thus, it is essential to develop resources that assist obstetric care providers in fulfilling their professional responsibilities. The Get Active Questionnaire for Pregnancy (GAQ-P) was created in 2021 by a team of experts led by Davenport *et al*. [12], in collaboration with the Canadian Society of Exercise Physiology (CSEP). These evidence-based instruments aim to minimize the obstacles to physical activity for most women who are eligible and eager to engage in exercise during pregnancy. The GAQ-P includes a self-administered section designed to identify pregnant women who may need further advice from their obstetric care provider regarding potential contraindications to physical activity participation (PAP). The intended users of these screening instruments are pregnant women, obstetric care providers, policymakers, and qualified exercise professionals who facilitate PAP. The goal of this project was to translate the GAQ-P into Italian and to culturally adapt these tools.

MATERIALS AND METHODS

The GAQ-P was translated into Italian and cross-culturally adjusted using the ISPOR framework as a basis [13]. We followed the ten ISPOR-recommended stages to complete the translation. The Translation and Cultural Adaptation-Principles of Good Practice framework consists in the following steps: 1. Preparation; 2. Forward Translation; 3. Reconciliation; 4. Back Translation; 5. Back Translation Review; 6. Harmonization; 7. Cognitive Debriefing; 8. Review of Cognitive Debrie-

fing Results and Finalization; 9. Proofreading; and 10. Final Report. The cognitive debriefing (refer to step 7 in the subsequent section) involved recruiting participants who voluntarily offered to participate from the outpatient population of the author. Each participant provided written informed consent.

RESULTS

Preparation

The client contacted the developer at the beginning of the process to request authorization to translate the document. The Canadian Society for Exercise Physiology (CSEP) and the author of the original instrument have both granted approval for the translation process to move forward.

First translation

The translators reside in Italy and are fluent in the Italian language. These people independently translated the original English instrument twice (V1 and V2, respectively). It takes two separate reviewers to get rid of one person's linguistic biases and make it easier to spot mistakes and different interpretations of phrases that aren't quite clear.

Reconciliation

An Italian medical authority who was not involved in the creation of V1 or V2 resolved the differences between the two versions, paving the way for the creation of a third version of the instrument (V3). The most colloquial term was selected for each statement. The reconciliation recommended a few minor word adjustments. The outcomes of each step are compiled in **Table 1**.

Back translation

The created version's quality control is known as back translation (V3). It was completed by two contracted translators who were natural English speakers and had nothing to do with V1 or V2. There were two separate back translations of V3 into English.

Revision of back translation

The original instrument has been compared with the two separate versions of the back translation by the principal researcher in Italy and the creator of the original instrument written in English. It was confirmed that one of the back translated versions most accurately reflected the original, despite literal deviations from the original. In order to preserve the original intent, minor terms in the selected document that did not match the original instrument were replaced with better alternatives (see **Table 1** for an illustration of how the procedure was established).

Harmonization

The back translations made in other nations should be compared when adapting an instrument to another language. This phase of the procedure was omitted since the authors of the Get Active Questionnaire for Pregnancy were unable to find any additional back translations.

Cognitive debriefing

Cognitive debriefing indicates the extent of comprehension, the translated version's semantic equivalency, and any incorrect or unclear terms or phrases. The primary in-country person (or another in-country consultant) should assess the newly translated measure's cognitive equivalency on a sample of five to eight respondents in the target country. Native speakers of the target language who fairly represent the target community should be the respondents. Five fitness experts with at least five years of experience in their area and five pregnant women – all fluent speakers of Italian – were given the Italian version of the GAQ-P. Every person was questioned if they understood everything and if there were any problems or recommendations for improved word or phrase construction. Every recommendation was noted.

Revision of debriefing results

Three researchers discussed and applied the participant-suggested revisions to the updated debriefing results, which were then added to the reconciled version. The original phrases' semantic significance has been preserved in the modifications.

Syntax and orthographic revision

The final version of the Italian instrument was revised for accuracy in syntax and orthography.

Final report

In order to make it easier to adapt the same instrument to different cultures in the future and to transfer the experience to other self-reported instruments, the TCA group advises creating a thorough documentation of the process [13]. For those who would like to adapt the Get Active Questionnaire

Table 1. *Activities negatively affected by symptoms.*

ITEM	Original	V1 - Olja	V2 - Alina	V3 (AI-ChatGPT)	V4 (Reconciled)	Back translation 1 - Matteo	Back translation 2 - Vittoria	V5 (ongoing revision by the team), minor changes	V6 (post Cognitive Debriefing 1) - final version GAQ-P
	GET ACTIVE QUESTIONNAIRE FOR PREGNANCY	Questionario attività fisica per la gravidanza			Questionario attività fisica per la gravidanza				QUESTIONARIO ATTIVITA' FISICA PER LA GRAVIDANZA
Part 1	Physical activity during pregnancy has many health benefits and is generally not risky for you and your baby.	L'attività fisica in gravidanza ha molti benefici per la salute e generalmente non è rischiosa per te e il tuo bambino.	L'attività fisica in gravidanza ha molti vantaggi per la salute e generalmente non è rischiosa per te e per il tuo bambino.	L'attività fisica durante la gravidanza comporta numerosi benefici per la salute e di solito non presenta rischi per te e il tuo bambino.	L'attività fisica durante la gravidanza offre numerosi benefici per la salute e di solito non comporta rischi per te e il tuo bambino	Physical activity during pregnancy has many health benefits and is usually not risky for you and your baby.	Physical activity during pregnancy has many benefits for your health and it's generally not risky for you and your baby.	L'attività fisica durante la gravidanza offre numerosi benefici per la salute e, di solito, non comporta rischi per te e il tuo bambino.	L'attività fisica durante la gravidanza offre numerosi benefici per la salute e, di solito, non comporta rischi per te e il tuo bambino.
	But for some conditions, physical activity is not recommended.	Per alcune condizioni però, l'attività fisica non è raccomandata	L'attività fisica però, non è raccomandabile per alcune condizioni.	Tuttavia, in alcune condizioni, l'attività fisica potrebbe non essere consigliata.	Per alcune condizioni però, l'attività fisica non è consigliata.	For some conditions, however, physical activity is not recommended.	However, for some conditions, physical activity is not recommended.		Per alcune condizioni però, l'attività fisica non è consigliata.
	This questionnaire is to help decide whether you should speak to your Obstetric Health Care Provider (e.g., your physician or midwife) before you begin or continue to be physically active.	Questo questionario serve per aiutarti a decidere se dovresti parlare con il medico che ti segue durante la gravidanza (es. la tua ostetrica o ginecologa/o) prima di cominciare, o continuare a essere fisicamente attiva.	Questo questionario aiuta a capire se dovresti parlarne con il tuo Obstetric Health care provider	Questo questionario serve a determinare se dovresti consultare il tuo operatore sanitario ostetrico (ad esempio, il medico o la levatrice) prima di iniziare o continuare a svolgere attività fisica.	Questo questionario serve per aiutarti a decidere se consultare il medico che ti segue durante la gravidanza (es. la tua ostetrica o ginecologa/o) prima di cominciare, o continuare a svolgere attività fisica.	This questionnaire is aimed to help you to decide whether you should speak to your Obstetric Healthcare Provider (e.g., your ob-gyn or midwife) before you start or continue to be physically active	This questionnaire is aimed to help you consider if you need to speak to your Obstetric Health Care Provider (e.g. your ob-gyn or midwife) before you start or continue to be physical active.	Questo questionario serve per aiutarti a decidere se consultare il personale sanitario che ti segue durante la gravidanza (es. la tua ostetrica o ginecologa/o) prima di cominciare o continuare a svolgere attività fisica.	Questo questionario serve per aiutarti a decidere se consultare il personale sanitario che ti segue durante la gravidanza (es. la tua ostetrica o ginecologa/o) prima di cominciare o continuare a svolgere attività fisica.
	Please answer YES or NO to each question to the best of your ability.	Per favore rispondi sì o no a ciascuna domanda, al meglio delle tue conoscenze.	Per favore rispondi sì o non ad ogni domanda il più precisamente possibile.		Per favore rispondi sì o no ad ogni domanda come meglio puoi.	Please answer yes or no to each question to the best you can.	Please answer YES or NO to each question as best as you can.	Per favore rispondi sì o no ad ogni domanda come meglio puoi	Per favore rispondi sì o no ad ogni domanda come meglio puoi
	If your health changes as your pregnancy progresses, you should fill in this questionnaire again.	Qualora la tua salute cambiasse nel corso della gravidanza, dovresti compilare nuovamente il questionario.	Se la tua salute cambia con la progressione della gravidanza dovresti ripetere il questionario.		Qualora la tua salute cambiasse nel corso della gravidanza, dovresti compilare di nuovo il questionario.	If your health changes during pregnancy you should fill in the questionnaire again.	If your health conditions change during pregnancy, you should fill in the questionnaire again.		Qualora la tua salute cambiasse nel corso della gravidanza, dovresti compilare di nuovo il questionario.

ITEM	Original	V1 - Olja	V2 - Alina	V3 (AI-ChatGPT)	V4 (Reconciled)	Back translation 1 - Matteo	Back translation 2 - Vittoria	V5 (ongoing revision by the team), minor changes	V6 (post Cognitive Debriefing 1) - final version GAQ-P
Part 2	1. In this pregnancy, do you have:	1. Nell'attuale gravidanza, hai:	1. In questa gravidanza, hai:		1. In questa gravidanza, hai:	1) In this pregnancy, do you have:	1) In this pregnancy do you have:		1. In questa gravidanza, hai:
	a. Mild, moderate or severe respiratory or cardiovascular diseases (e.g., chronic bronchitis)?	a.Leggera, moderata o importante malattia respiratoria o cardiovascolare (es. bronchite cronica)?	a.Una lieve, moderata o severa malattia respiratoria o cardiovascolare (es. bronchite cronica)?		a.Una lieve, moderata o severa malattia respiratoria o cardiovascolare (es. bronchite cronica)?	a. Mild, moderate or severe respiratory or cardiovascular diseases (e.g., chronic bronchitis)?	a. Mild, moderate or severe respiratory or cardiovascular disease (e.g. chronic bronchitis)?		a. Una lieve, moderata o severa malattia respiratoria o cardiovascolare (es. bronchite cronica)?
	b. Epilepsy that is not stable?	b.Epilessia che non è sotto controllo / stabilizzata?	b. Epilessia non stabilizzata?		b. Epilessia non stabilizzata?	b. Epilepsy that is not stable?	b. Epilepsy that is not stable?		b. Epilessia non controllata?
	c. Type 1 diabetes that is not stable or your blood sugar is outside of target ranges?	c.Diabete di tipo 1 che non è sotto controllo o glicemia fuori dai parametri normali?	c.Diabete di tipo 1 non stabilizzata o funzioni tiroidee al di fuori del range?	c. Diabete di tipo 1 non stabile o livelli di zucchero nel sangue al di fuori dei valori target?	c. Diabete di tipo 1 non stabile o livelli di zucchero nel sangue al di fuori dei parametri normali?	c. Type 1 diabetes that is not stable or your blood sugar levels outside of target ranges?	c. Type 1 diabetes that is not stable or your blood sugar levels that are outside of target ranges?		c. Diabete di tipo 1 non controllato o livelli di zucchero nel sangue al di fuori dei parametri normali?
	d. Thyroid disease that is not stable or your thyroid function is outside of target ranges?	d. Malattia della tiroide che non è sotto controllo oppure funzionalità della tiroide fuori dai parametri normali?	c.Diabete di tipo 1 non stabilizzata o funzioni tiroidee al di fuori del range?	d. Malattia tiroidea non stabile o funzione tiroidea al di fuori dei valori target?	d. Malattia della tiroide non stabile oppure funzionalità della tiroide al di fuori dei parametri normali?	d. Malattia della tiroide non controllata oppure funzionalità della tiroide al di fuori dei parametri normali?	d. Thyroid disease that is not stable or the thyroid function that is outside of target ranges?		
	e. An eating disorder(s) or malnutrition?	e. Disordine/i alimentare/i o malnutrizione?	e.Disturbo/i alimentare/i o malnutrizione?		e.Disturbo/i alimentare/i o malnutrizione?	e. An eating disorder(s) or malnutrition?	e. Eating disorder(s) or malnutrition?	e. Disordine/i alimentare/i o malnutrizione?	e. Disordine/i alimentare/i o malnutrizione?
	f. Twins (28 weeks pregnant or later)? Or are you expecting triplets or higher multiple births?	f. Gravidanza gemellare (oltre la 28a settimana)? Oppure aspetti tre bambini o un numero superiore?	f. Gemelli (alla 28 settimana o dopo)? O stai aspettando 3 gemelli o più?	f. Gemelli (dalla 28ª settimana di gravidanza in poi)? Oppure stai aspettando trillini o gravidanze multiple superiori?	f. Gravidanza gemellare (dalla 28ª settimana di gravidanza in poi)? Oppure aspetti tre gemelli o un numero superiore?	f. Twin pregnancy (28 weeks pregnant or later)? Or are you expecting triplets or higher multiple births?	f. Twin pregnancy (28 weeks pregnant or later)? Or are you expecting triplets or higher multiple births?		f. Gravidanza gemellare (dalla 28ª settimana di gravidanza in poi)? Oppure aspetti tre gemelli o un numero superiore?
	g. Low red blood cell number (anemia) with high levels of fatigue and/or light-headedness?	g. Basso numero di globuli rossi (anemia) associata ad alti livelli di affaticamento e /o giramenti di testa?	g.Basso numero di eritrociti (preeclampsia, ipertensione gestazione, ipertensione cronica non stabile)?	g. Numero basso di globuli rossi (anemia) con alti livelli di affaticamento e/o svenimenti leggeri?	g. Basso numero di globuli rossi (anemia) associata ad alti livelli di affaticamento e /o giramenti di testa?	g. Low red blood cell count (anemia) associated with high levels of fatigue and/or light-headedness?	g. Low number of red blood cells (anemia) associated with high level of fatigue and/or light-headedness?		g. Basso numero di globuli rossi (anemia) associata ad alti livelli di affaticamento e/o giramenti di testa?

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	h. High blood pressure (preeclampsia, gestational hypertension, or chronic hypertension that is not stable)?	h.Pressione alta (preeclampsia, ipertensione gestazionale, o ipertensione cronica che non è tenuta sotto controllo)?	h. Basso numero di eritrociti (preeclampsia, ipertensione gestazione, ipertensione cronica non stabile)?	h. Pressione alta (preeclampsia, ipertensione gestazionale o ipertensione cronica non stabile)?	h. Pressione alta (preeclampsia, ipertensione gestazionale o ipertensione cronica non stabile)?	h. High blood pressure (preeclampsia, gestational hypertension, or chronic hypertension that is not stable)?	h. High blood pressure (preeclampsia, gestational hypertension or chronic hypertension that is not stable)?		h. Pressione alta (preeclampsia, ipertensione gestazionale o ipertensione cronica non controllata)?
	i. A baby that is growing slowly (intrauterine growth restriction)?	i. Bambino/a che cresce lentamente (restrizione della crescita intrauterina)?	i.Un bambino che sta crescendo lentamente (restrizione della crescita intrauterina?)	i. Un bambino che sta crescendo lentamente (ritardo di crescita intrauterina)?	i.Un bambino/a che sta crescendo lentamente (restrizione della crescita intrauterina?)	i. A baby that is growing slowly (intrauterine growth restriction)?	i. A baby that is growing slowly (intrauterine growth restriction)?	i. Bambino che sta crescendo lentamente (restrizione della crescita intrauterina?)	i. Bambino che sta crescendo lentamente (restrizione della crescita intrauterina?)
	j. Unexplained bleeding, ruptured membranes or labour before 37 weeks?	j. Sanguinamento immotivato, rottura delle membrane o inizio del travaglio prima della 37a settimana?	j.Emorragia inspiegabile, rottura delle membrane o travaglio prima delle 37 settimane?	j. Sanguinamento inspiegabile, membrane rotte o parto prima delle 37 settimane?	j.Emorragia inspiegabile, rottura delle membrane o travaglio prima delle 37 settimane?	j. Unexplained bleeding, ruptured membranes or labour before 37 pregnancy weeks?	j. Unexplained bleeding, ruptured membranes or labor before 37 weeks?	j. Emorragia inspiegabile, rottura delle membrane o travaglio prima della 37a settimana?	j. Emorragia inspiegabile, rottura delle membrane o travaglio prima della 37a settimana?
	k. A placenta that is partially or completely covering the cervix (placenta previa)?	k. Placenta che parzialmente o completamente copre la cervice (placenta previa)?	k.Placenta che copre parzialmente o completamente la cervice (placenta previa)?	k. Placenta che copre parzialmente o completamente la cervice (placenta previa)?	k.Placenta che copre parzialmente o completamente la cervice (placenta previa)?	k. A placenta that is partially or completely covering the cervix (placenta previa)?	k. A placenta that is partially or completely covering the cervix (placenta previa)?		k. Placenta che copre parzialmente o completamente la cervice (placenta previa)?
	l. Weak cervical tissue (incompetent cervix)?	l. Debolezza del tessuto della cervice (incompetenza cervicale)?	l.Tessuti cervicali deboli (incompetenza cervicale)	l. Tessuto cervicale debole (cervice incompetente)?	l.Tessuti cervicali deboli (incompetenza cervicale)	l. Weak cervical tissue (incompetent cervix)?	l. Weak cervical tissue (incompetent cervix)?	l. Tessuti cervicali deboli (incontinenza cervicale)	l. Tessuti cervicali deboli (incontinenza cervicale)
	m. A stitch or tape to reinforce your cervix (cerclage)?	m.Sutura o nastro per rinforzare la cervice (cerchiaggio)?	m. Un punto o nastro per rinforzare la cervice (cerchiaggio)?		m. Un punto di sutura o nastro per rinforzare la cervice (cerchiaggio)?	m. A suture or tape to reinforce your cervix (cerclage)?	m. A suture stitch or tape to reinforce your cervix (cerclage)?	m. Punto di sutura o nastro per rinforzare la cervice (cerchiaggio)?	m. Punto di sutura o nastro per rinforzare la cervice (cerchiaggio)?
	2. In previous pregnancies, have you had:	2. Nella/e gravidanza/e precedenti hai avuto:	2. Nelle precedenti gravidanze hai avuto:	2. Nelle gravidanze precedenti, hai avuto:	2. Nelle gravidanze precedenti, hai avuto:	2) In previous pregnancies, have you had:	2) In previous pregnancy, have you had:		2. Nelle gravidanze precedenti, hai avuto:
	a. Recurrent miscarriages (loss of your baby before 20 weeks gestation two or more times)?	a.Aborti ricorrenti (perdita del bambino/a prima della 20a settimana di gestazione per due o più volte)?	a.Aborti ricorrenti (perdita del tuo bambino prima della 20esima settimana gestazione due o più volte)?	a. Aborti ricorrenti (perdita del bambino entro le 20 settimane di gestazione due o più volte)?	a.Aborti ricorrenti (perdita del tuo bambino prima della 20esima settimana gestazione due o più volte)?	a. Recurrent miscarriages (loss of your baby before 20 weeks gestation two or more times)?	a. Recurrent miscarriages (loss of your baby before 20 weeks gestation two or more times)?		a. Aborti ricorrenti (perdita del tuo bambino prima della 20a settimana di gestazione due o più volte)?

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	b. Early delivery (before 37 weeks gestation)?	b. Nascita pre termine (prima di 37 settimane di gestazione)?	b.Parto precoce (prima della 37esima settimana gestazionale)		b.Nascita prematura (prima della 37° settimane gestazionale)	b. Preterm delivery (before 37 weeks gestation)?	b. Preterm delivery (before 37 weeks)?	b. Parto prematuro (prima della 37a settimana di gestazione)	b. Parto prematuro (prima della 37a settimana di gestazione)
	3. Do you have any other medical condition that may affect your ability to be physically active during pregnancy? What is the condition? Specify:	3. Hai qualunque altra condizione medica che potrebbe influire sulla tua capacità di fare attività fisica in gravidanza? Di cosa si tratta? Specifica:	3.Hai altre condizioni mediche che potrebbero affliggere la tua abilità ad d'essere fisicamente attiva durante la gravidanza? Quale condizione? Specifica	3.Hai altre condizione mediche che potrebbero influire sulla tua abilità di fare attività fisica in gravidanza? Di cosa si tratta? Specifica:	3.Hai altre condizione mediche che potrebbero influire sulla tua abilità di fare attività fisica in gravidanza? Di cosa si tratta? Specifica:	3) Do you have any other medical condition that may affect your ability to perform physical activity during pregnancy? What is the condition? Specify:	3) Do you have any other medical condition that may be affect your ability to be physical active during pregnancy? If yes, please specify the condition:		3. Hai altre condizione mediche che potrebbero influire sulla tua abilità di fare attività fisica in gravidanza? Di cosa si tratta? Specifica:
	4. Is there any other reason you are concerned about physical activity during pregnancy?	4. Esiste un qualsiasi altro motivo che ti preoccupa riguardo all'attività fisica in gravidanza?	4.C'è qualsiasi altra ragione per la quale ti senti preoccupata per l'attività durante la gravidanza?	4.Hai qualche altra ragione per preoccuparti dell'attività fisica durante la gravidanza?	4.Hai qualche altra ragione per preoccuparti dell'attività fisica durante la gravidanza?	4) Is there any other reason to be concerned about physical activity during pregnancy?	4) Is there any other reason are you concerned about physical activity during pregnancy?	4. Hai qualche altra ragione per cui l'attività fisica in gravidanza ti preoccupa?	4. Hai qualche altra ragione per cui l'attività fisica in gravidanza ti preoccupa?
	Go to Page 2 Describe Your Physical Activity Level	Vai alla pagina 2 Descrivi il tuo livello di attività fisica		Vai alla Pagina 2 Descrivi il Tuo Livello di Attività Fisica	Vai alla pagina 2 Descrivi il tuo livello di attività fisica	Go to Page 2 Describe your physical activity level	Go to page 2 Describe Your Physical Activity Level		Vai alla pagina 2 Descrivi il tuo livello di attività fisica
Part 3	Describe Your Physical Activity Level	Descrivi il tuo livello di attività fisica:	Descrivi il livello della tua attività fisica:	Descrivi il Tuo Livello di Attività Fisica	Descrivi il tuo livello di attività fisica:	Describe your physical activity level	Describe Your Physical Activity Level		Descrivi il tuo livello di attività fisica:
	During a typical week, what types of physical activities do you take part in (e.g., swimming, walking, resistance training, yoga)?	Durante una settimana tipo, che tipo di attività fisica fai (es. nuoto, camminata, allenamento di resistenza, yoga)?	Durante la settimana tipo, quale attività fisica svolgi (ad esempio nuoto, camminare, allenamento di resistenza, yoga?)	Durante una settimana tipica, a quali tipi di attività fisica partecipi (ad esempio, nuoto, camminata, allenamento con i pesi, yoga)?	Durante la settimana tipo, quale attività fisica svolgi (es. nuoto, camminata, allenamento di resistenza, yoga)?	During a typical week, what types of physical activities do you perform (e.g., swimming, walking, resistance training, yoga)?	During a typical week, what types of physical activities do you perform (e.g. swimming, walking, resistance training, yoga)?		Durante la settimana tipo, quale attività fisica svolgi (es. nuoto, camminata, allenamento contro resistenza, yoga)?
	During the same week, please describe ON AVERAGE how often and for how long you engage in physical activity of a light, moderate or vigorous intensity.	Durante la stessa settimana, per favore descrivi quanto di frequente e per quanto tempo MEDIAMENTE fai un'attività di intensità bassa, moderata o vigorosa.	Durante la stessa settimana per favore descrivi IN MEDIA quanto spesso e per quanto tempo sei impegnata nell'attività fisica di intensità leggera, moderata o vigorosa.	Nella stessa settimana, descrivi in MEDIA con quale frequenza e per quanto tempo pratichi attività fisica a intensità leggera, moderata o vigorosa.	Per favore descrivi, IN MEDIA, quanto spesso e per quanto tempo sei impegnata nell'attività fisica di intensità leggera, moderata o vigorosa, nell'arco di una stessa settimana.	Please describe ON AVERAGE how often and for how long you engage in physical activity of a light, moderate or vigorous intensity during the week.	Please describe ON AVERAGE how often and for how long you are engaged in physical activities of light, moderate or vigorous intensity during the week.	Per favore descrivi, IN MEDIA, quanto spesso e per quanto tempo sei impegnata nell'attività fisica di intensità leggera, moderata o vigorosa, nell'arco di una settimana.	Per favore descrivi, IN MEDIA, quanto spesso e per quanto tempo sei impegnata nell'attività fisica di intensità leggera, moderata o vigorosa, nell'arco di una settimana.

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	See definitions for intensity below the box.	Trovi le definizioni di intensità sotto il riquadro.	Vedi le definizioni di intensità nel box qui sotto.	Vedi le definizioni di intensità sotto la casella.	Vedi le definizioni di intensità sotto il box.	See definitions for intensity under the box below.	You can find the definitions of intensity below the box.		Vedi le definizioni di intensità sotto il box.
Part 4	ON AVERAGE	MEDIAMENTE	In media:	In media:	In media:	ON AVERAGE	ON AVERAGE		In media:
	FREQUENCY (times per week)	FREQUENZA (n°volte a settimana)		FREQUENZA (volte a settimana)	FREQUENZA (n°volte a settimana)	FREQUENCY (times per week)	FREQUENCY (times per week)		FREQUENZA (n°volte a settimana)
	INTENSITY (see below for definitions)	INTENSITA' (vedi le definizioni sotto)		INTENSITÀ (vedi le definizioni qui sotto)	INTENSITÀ (vedi le definizioni qui sotto)	INTENSITY (see below for definitions)	INTENSITY (see below for definitions)		INTENSITÀ (vedi le definizioni qui sotto)
	DURATION (minutes per session)	DURATA (minuti per sessione)		DURATA (minuti per sessione)	DURATA (minuti per sessione)	DURATION(minutes per session)	DURATION (minutes per session)		DURATA (minuti per sessione)
	How physically active were you in the six months before pregnancy?	Quanto eri attiva fisicamente nei sei mesi prima della gravidanza?	Quanto fisicamente attiva eri durante i 6 mesi precedenti la gravidanza?	Quanto eri attivo fisicamente nei sei mesi precedenti alla gravidanza?	Quanto eri attiva fisicamente nei sei mesi precedenti la gravidanza?	How physically active were you in the six months before the pregnancy?	How physically active were you in the six month prior to pregnancy?		Quanto eri attiva fisicamente nei sei mesi precedenti la gravidanza?
	How physically active have you been during this pregnancy?	Quanto sei attiva durante questa gravidanza?	Quanto fisicamente attiva sei stata durante questa gravidanza?	Quanto sei stato attivo fisicamente durante questa gravidanza?	Quanto sei stata fisicamente attiva durante questa gravidanza?	How physically active have you been during this pregnancy?	How physically active have you been during this pregnancy?		Quanto sei stata fisicamente attiva durante questa gravidanza?
	What are your physical activity goals for the rest of your pregnancy?	Quali sono i tuoi obiettivi di attività fisica per il resto della gravidanza in corso?	Quali sono i tuoi obiettivi di attività fisica per il resto della gravidanza?	Quali sono i tuoi obiettivi di attività fisica per il resto della gravidanza?	Quali sono i tuoi obiettivi di attività fisica per il resto della gravidanza?	What are your physical activity goals for the rest of your pregnancy?	What are your physical activity goals for the rest of your pregnancy?		Quali sono i tuoi obiettivi di attività fisica per il resto della gravidanza?
	Light intensity physical activity: You are moving, but you do not sweat or breathe hard, such as walking to get the mail or light gardening.	Attività fisica di bassa intensità: Ti muovi, ma non sudi o non hai un respiro affannoso, attività come camminata attorno a casa o leggero giardinaggio.	Attività fisica di intensità leggera: ti muovi ma non sudi né respiri a fatica, come ad esempio camminare per andare a prendere la posta o fare giardinaggio leggero.	Attività fisica a intensità leggera: ti muovi, ma non sudi né respiri pesantemente, come camminare per andare a prendere la posta o fare giardinaggio leggero.	Attività fisica di intensità leggera: ti muovi ma non sudi né respiri a fatica, come ad esempio camminare per andare a prendere la posta o fare giardinaggio leggero.	Light intensity physical activity: you are moving, but you do not sweat or hardly breathe, such as walking to get the mail or doing light gardening.	Light intensity physical activity: you are moving but you don't sweat or breathe hard, such as walking to get the mail or doing light gardening.		Attività fisica di intensità leggera: ti muovi ma non sudi né respiri a fatica, come ad esempio camminare per andare a prendere la posta o fare giardinaggio leggero.
	Moderate intensity physical activity: Your heart rate goes up and you may sweat or breathe hard. You can talk, but could not sing. Examples include brisk walking.	Attività fisica di moderata intensità: I battiti cardiaci sono più elevati, e potresti sudare o respirare in modo affannoso. Puoi parlare, ma non potresti cantare. Un esempio ne sarebbe la camminata veloce.	Attività fisica di intensità moderata: la frequenza cardiaca aumenta e si può sudare o respirare a fatica. Si può parlare ma non cantare. Ad esempio una camminata veloce.	Attività fisica a intensità moderata: il battito cardiaco aumenta e potresti sudare o respirare pesantemente. Puoi parlare, ma non cantare. Esempi includono camminata veloce.	Attività fisica di intensità moderata: la frequenza cardiaca aumenta e potresti sudare o respirare a fatica. Puoi parlare, ma non cantare. Ad esempio una camminata veloce.	Moderate intensity physical activity: your heart rate rises and you may sweat or hardly breathe. You can talk, but can not sing. For instance, fast walking.	Moderate intensity physical activity: your heart rate goes up and you may sweat or breathe hard. You can talk but cannot sing. For instance, brisk walking.		Attività fisica di intensità moderata: la frequenza cardiaca aumenta e potresti sudare o respirare a fatica. Puoi parlare, ma non cantare. Ad esempio una camminata veloce.

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	Vigorous intensity physical activity: Your heart rate goes up substantially, you feel hot and sweaty, and you cannot say more than a few words without pausing to breathe. Examples include fast stationary cycling and running.	Attività fisica di intensità vigorosa: I battiti cardiaci si alzano in modo significativo, sei accaldata e sudata, e non riesci a dire più di qualche parola senza interruzioni per prendere fiato. Gli esempi includono la cyclette a passo veloce e la corsa.	Attività fisica di alta intensità: la frequenza cardiaca aumenta notevolmente, si sente caldo e si suda e non si riesce a dire più di poche parole senza doversi fermare per respirare. Alcuni esempi includono il ciclismo stazionario veloce e la corsa.	Attività fisica a intensità vigorosa: il battito cardiaco aumenta considerevolmente, ti senti caldo e sudato e non riesci a dire più di poche parole senza interromperti per respirare. Esempi includono ciclismo veloce su cyclette fisse e corsa	Attività fisica di intensità vigorosa: la frequenza cardiaca aumenta notevolmente, sei accaldata e sudata e non riesci a dire più di qualche parola senza fermarti a respirare. Ad esempio la cyclette a passo veloce e la corsa.	Vigorous intensity physical activity: your heart rate rises substantially, you feel hot and sweaty, and you cannot say more than a few words without pausing to breathe. For instance, fast stationary cycling and running	Vigorous intensity physical activity: your heart rate goes up substantially, you are hot and sweaty and you can't say more than a few words without stopping to breathe. Some examples are fast stationary cycling and running.	Attività fisica di intensità vigorosa: la frequenza cardiaca aumenta notevolmente, sei accaldata e sudata e non riesci a dire più di qualche parola senza fermarti a respirare. Ad esempio la cyclette a velocità sostenuta e la corsa.	Attività fisica di intensità vigorosa: la frequenza cardiaca aumenta notevolmente, sei accaldata e sudata e non riesci a dire più di qualche parola senza fermarti a respirare. Ad esempio la cyclette a velocità sostenuta e la corsa.
Part 5	General Advice for Being Physically Active During Pregnancy	Consigli generali per essere attivi fisicamente in gravidanza	Consigli generali per essere fisicamente attivi durante la gravidanza.	Consigli Generali per Essere Attivi Fisicamente Durante la Gravidanza	Consigli generali per essere fisicamente attivi in gravidanza	General advices for being physically active during pregnancy	General Advice for Being Physically Active During Pregnancy	Consigli generali per essere fisicamente attiva in gravidanza	Consigli generali per essere fisicamente attiva in gravidanza
	Follow the advice in the 2019 Canadian Guidelines for Physical Activity throughout Pregnancy: csepguidelines.ca/ pregnancy	Segui i consigli che trovi nelle linee guida Canadesi del 2019 sull'attività fisica in gravidanza: csepguidelines.ca/ pregnancy	Seguire i consigli delle linee guida canadesi 2019 per l'attività fisica in gravidanza: csepguidelines.ca/ pregnancy	Segui i consigli contenuti nelle Linee Guida Canadesi per l'Attività Fisica durante la Gravidanza del 2019: csepguidelines.ca/ pregnancy	Segui i consigli contenuti nelle Linee Guida Canadesi del 2019 per l'Attività Fisica in Gravidanza: csepguidelines.ca/ pregnancy	Follow the advices in the 2019 Canadian Guidelines for Physical Activity throughout Pregnancy: csepguidelines.ca/ pregnancy	Follow the advices in the 2019 Canadian Guidelines for Physical Activity throughout Pregnancy: csepguidelines.ca/ pregnancy.		Segui i consigli contenuti nelle Linee Guida Canadesi del 2019 per l'Attività Fisica in Gravidanza: csepguidelines.ca/ pregnancy
	It recommends that pregnant women get at least 150 minutes of moderate-intensity physical activity (resistance training, brisk walking, swimming, gardening), spread over three or more days of the week.	Si raccomanda alle donne in gravidanza di fare almeno 150 minuti di attività fisica di intensità moderata (allenamento di resistenza, camminata veloce, nuoto, giardinaggio), distribuiti su tre o più giorni della settimana.	Si raccomanda alle donne in gravidanza di svolgere almeno 150 minuti di attività fisica di intensità moderata (allenamento di resistenza, camminata veloce, nuoto, giardinaggio), distribuiti su tre o più giorni della settimana.	Si consiglia alle donne in gravidanza di svolgere almeno 150 minuti di attività fisica a intensità moderata (allenamento con i pesi, camminata veloce, nuoto, giardinaggio), distribuiti su tre o più giorni alla settimana.	Si raccomanda alle donne in gravidanza di svolgere almeno 150 minuti di attività fisica di intensità moderata (allenamento di resistenza, camminata veloce, nuoto, giardinaggio), distribuiti su tre o più giorni della settimana.	It recommends that pregnant women perform at least 150 minutes of moderate intensity physical activity (resistance training, fast walking, swimming, gardening), spread over three or more days of the week.	It is recommended to pregnant women to perform at least 150 minutes of moderate intensity physical activity (resistance training, brisk walking, swimming, gardening), spread over three or more days during the week.		Si raccomanda alle donne in gravidanza di svolgere almeno 150 minuti di attività fisica di intensità moderata (allenamento contro resistenza, camminata veloce, nuoto, giardinaggio), distribuiti su tre o più giorni della settimana.
	If you are planning to take part in vigorous-intensity physical activity, or be physically active at elevations above 2500 m (8200 feet), then consult with your health care provider.	Se hai intenzione di fare un'attività fisica di intensità vigorosa, oppure se hai intenzione di farlo a una quota superiore a 2.500m di altitudine, consulta il tuo medico curante.	Se stai pensando di prendere parte ad una attività fisica intensa, o essere fisicamente attiva ad altitudini maggiori 2500 metri (8200 piedi) consulta il medico curante.	Se prevedi di svolgere attività fisica a intensità vigorosa o di essere attiva fisicamente a quote superiori a 2500 m (8200 piedi), consulta il tuo operatore sanitario.	Se hai intenzione di fare un'attività fisica di intensità vigorosa, o essere fisicamente attiva ad altitudini maggiori di 2500 metri (8200 piedi) consulta il medico curante.	If you are willing to take part in vigorous-intensity physical activity, or be physically active at elevations above 2500 m (8200 feet), then consult with your healthcare provider.	If you are planning to take part in vigorous intensity physical activities or to be physically active at elevations above 2500 m (8200 feet), then speak to your healthcare provider.	Se hai intenzione di fare un'attività fisica di intensità vigorosa, o essere fisicamente attiva ad altitudini maggiori di 2500 metri (8200 piedi) consulta il tuo personale sanitario di riferimento.	Se hai intenzione di fare un'attività fisica di intensità vigorosa, o essere fisicamente attiva ad altitudini maggiori di 2500 metri (8200 piedi) consulta il tuo personale sanitario di riferimento.

ITEM	Original	V1 - Olja	V2 - Alina	V3 (AI-ChatGPT)	V4 (Reconciled)	Back translation 1 - Matteo	Back translation 2 - Vittoria	V5 (ongoing revision by the team), minor changes	V6 (post Cognitive Debriefing 1) - final version GAQ-P
	If you have any questions about physical activity during pregnancy, consult a Qualified Exercise Professional or your health care provider beforehand.	Se dovessi avere qualsiasi dubbio sull'attività fisica in gravidanza, consulta un professionista qualificato oppure il tuo medico di riferimento in anticipo.	Se hai domande sull'attività fisica in gravidanza, consulta un professionista dell'attività fisica qualificato o il tuo medico curante.	Se hai domande sull'attività fisica durante la gravidanza, consulta un Professionista dell'Esercizio Fisico Qualificato o il tuo operatore sanitario in anticipo	Se hai domande sull'attività fisica in gravidanza, consulta un Professionista dell'Esercizio Fisico Qualificato oppure il tuo medico di riferimento, in anticipo.	If you have any questions about physical activity during pregnancy, consult in advance a qualified physical activity professional or your healthcare provider.	If you have any questions about physical activity during pregnancy, please consult in advance a qualified physical exercise professional or your healthcare provider.	Se hai domande sull'attività fisica in gravidanza, consulta preventivamente un professionista dell'esercizio fisico qualificato oppure il tuo personale sanitario di riferimento.	Se hai domande sull'attività fisica in gravidanza, consulta preventivamente un professionista dell'esercizio fisico qualificato oppure il tuo personale sanitario di riferimento.
	This can help ensure that your physical activity is safe and suitable for you.	Questo può aiutare ad assicurarti che l'attività fisica che fai sia sicura e adeguata per te.	Questo può aiutare ad assicurare che la tua attività fisica sia sicura e adeguata.	Ciò può contribuire a garantire che la tua attività fisica sia sicura e adatta a te.	Ciò può contribuire a garantire che la tua attività fisica sia sicura e adatta a te.	This may help to guarantee that your physical activity is safe and suitable for you.	This can help to ensure that your physical activity is safe and suitable for you.		Ciò può contribuire a garantire che la tua attività fisica sia sicura e adatta a te.
	Declaration	Dichiarazione	Dichiarazione	Dichiarazione	Dichiarazione	Declaration	Declaration		Dichiarazione
	To the best of my knowledge, all of the information I have supplied on this questionnaire is correct.	Tutte le informazioni fornite in questo questionario sono corrette compatibilmente con la mia conoscenza.	Per quanto possibile, tutte le informazioni che ho fornito in questo questionario, sono corrette.	Nella migliore delle mie conoscenze, tutte le informazioni fornite in questo questionario sono corrette.	Per quanto ne so, tutte le informazioni che ho fornito in questo questionario sono corrette.	To the best of my knowledge, all of the information I have provided in this questionnaire is correct	To the best of my knowledge, all of the information I have provided in this questionnaire is correct	In base alla mia conoscenza, tutte le informazioni che ho fornito in questo questionario sono corrette.	In base alla mia conoscenza, tutte le informazioni che ho fornito in questo questionario sono corrette.
	If my health changes, I will complete this questionnaire again.	Qualora la mia salute dovesse cambiare, completerò nuovamente il questionario.	Se il mio stato di salute dovesse cambiare, compilerò nuovamente questo questionario	Se la mia condizione di salute cambia, completerò nuovamente questo questionario.	Se il mio stato di salute dovesse cambiare, compilerò nuovamente questo questionario.	If my health status changes, I will compile this questionnaire again.	If my health changes, I will fill out this questionnaire again.		Se il mio stato di salute dovesse cambiare, compilerò nuovamente questo questionario.
	I answered NO to all questions on Page 1.	Ho risposto NO a tutte le domande sulla Pagina 1.	Ho risposto NO a tutte le domande di pagina 1	Ho risposto NO a tutte le domande nella Pagina 1.	Ho risposto NO a tutte le domande a Pagina 1.	I answered NO to all questions on Page 1.	I answered NO to all questions on Page 1.		Ho risposto NO a tutte le domande a Pagina 1.
	Sign and date the declaration below. Physical activity is recommended.	Firma e metti la data della dichiarazione sotto. L'attività fisica è raccomandata	firmare e datare la dichiarazione sottostante. Si raccomanda l'attività fisica.	Firma e data la dichiarazione qui sotto. Si consiglia l'attività fisica.	Firma e data la dichiarazione qui sotto. Si raccomanda l'attività fisica.	Sign and date the declaration below. Physical activity is recommended.	Sing and date the declaration below. Physical activity is recommended.		Firma e data la dichiarazione qui sotto. Si raccomanda l'attività fisica.
	I answered YES to one or more questions on Page 1 and I will speak with my health care provider before beginning or continuing physical activity.	Ho risposto SÌ a una o più domande sulla Pagina 1 e mi rivolgerò al mio medico curante prima di cominciare o di continuare con l'attività fisica.	Ho risposto Si ad una o più domande a pagina 1 e ne parlerò con il mio medico curante prima di iniziare o continuare l'attività fisica.	Ho risposto SI a una o più domande nella Pagina 1 e parlerò con il mio operatore sanitario prima di iniziare o continuare l'attività fisica	Ho risposto Si ad una o più domande a pagina 1 e ne parlerò con il mio medico curante prima di iniziare o continuare l'attività fisica.	I answered YES to one or more questions on Page 1 and I will speak with my healthcare provider before starting or continuing physical activity.	I answered YES to one or more questions on Page 1 and I will speak to my health care provider before starting or continuing physical activity.	Ho risposto Sì ad una o più domande a pagina 1 e ne parlerò con il mio personale sanitario di riferimento prima di iniziare o continuare l'attività fisica.	Ho risposto Sì ad una o più domande a pagina 1 e ne parlerò con il mio personale sanitario di riferimento prima di iniziare o continuare l'attività fisica.

ITEM	Original	V1 - Olja	V2 - Alina	V3 (AI-ChatGPT)	V4 (Reconciled)	Back translation 1 - Matteo	Back translation 2 - Vittoria	V5 (ongoing revision by the team), minor changes	V6 (post Cognitive Debriefing 1) - final version GAQ-P
	The Health Care Provider Consultation Form for Prenatal Physical Activity can be used to start the conversation (www.csep.ca/getactivequestionnaire-pregnancy).	Il modulo "Health Care Provider Consultation Form for Perinatal Physical Activity" può essere usato per aiutare nella conversazione. (www.csep.ca/getactivequestionnaire-pregnancy).		Il modulo di consultazione dell'operatore sanitario sull'attività fisica prenatale può essere utilizzato per avviare la conversazione (www.csep.ca/getactivequestionnaire-pregnancy).	Il modulo "Health Care Provider Consultation Form for Perinatal Physical Activity" può essere usato per avviare la conversazione (www.csep.ca/getactivequestionnaire-pregnancy).	The "Health Care Provider Consultation Form for Prenatal Physical Activity" can be used to start the conversation (www.csep.ca/getactivequestionnaire-pregnancy).	The "Health Care Provider Consultation Form for Prenatal Physical Activity" can be used to start the conversation. (www.csep.ca/getactivequestionnaire-pregnancy).	Il "Modulo di Consultazione per Operatori Sanitari sull'Attività Fisica Prenatale" può essere usato per avviare la conversazione (www.csep.ca/getactivequestionnaire-pregnancy).	Il "Modulo di Consultazione per Operatori Sanitari sull'Attività Fisica Prenatale" può essere usato per avviare la conversazione (www.csep.ca/getactivequestionnaire-pregnancy).
	I have spoken with my health care provider who has recommended that I take part in physical activity during my pregnancy.	Ho parlato con il mio medico curante che ha consigliato l'attività fisica durante la mia gravidanza.	Ho parlato con il mio medico curante che ha raccomandato che io prenda parte all'attività fisica durante la mia gravidanza.	Ho parlato con il mio operatore sanitario che mi ha consigliato di praticare attività fisica durante la mia gravidanza.	Ho parlato con il mio medico curante che mi ha consigliato l'attività fisica durante la gravidanza.	I have spoken with my healthcare provider who has recommended to perform physical activity during the pregnancy.	I have spoken to my health care provider who has recommended me to perform physical activity during pregnancy.	Ho parlato con il mio personale sanitario di riferimento che mi ha consigliato l'attività fisica durante la gravidanza.	Ho parlato con il mio personale sanitario di riferimento che mi ha consigliato l'attività fisica durante la gravidanza.
	Sign and date the declaration below.	Firma e metti la data della dichiarazione sotto.	firmare e datare la dichiarazione sottostante	Firma e data la dichiarazione qui sotto.	Firma e data la dichiarazione qui sotto.	Sign and date the declaration below.	Sign and date the declaration below.		Firma e data la dichiarazione qui sotto.
Part 6	NAME (+ NAME OF PARENT/GUARDIAN IF APPLICABLE) [PLEASE PRINT]:	NOME (+ NOME DI UN GENITORE/ TUTORE SE APPLICABILE) [FIRMA LEGGIBILE PER FAVORE]:		NOME (+ NOME DEL GENITORE/TUTORE, SE APPLICABILE) [PER FAVORE, SCRIVI IN STAMPO]:	NOME (+ NOME DI UN GENITORE/ TUTORE SE APPLICABILE) [FIRMA LEGGIBILE PER FAVORE]:	NAME (+ NAME OF PARENT/GUARDIAN IF APPLICABLE) [PLEASE PRINT NAME]:	NAME (+ NAME OF A PARENT/ LEGAL GUARDIAN IF APPLICABLE) (PLEASE PRINT):		NOME (+ NOME DI UN GENITORE/TUTORE SE APPLICABILE) [FIRMA LEGGIBILE PER FAVORE]:
	SIGNATURE (OR SIGNATURE OF PARENT/GUARDIAN IF APPLICABLE):	FIRMA (o firma di un GENITORE/tutore se applicabile) [FIRMA LEGGIBILE PER FAVORE]:		FIRMA (O FIRMA DEL GENITORE/TUTORE, SE APPLICABILE):	FIRMA (o firma di un GENITORE/tutore se applicabile) [FIRMA LEGGIBILE PER FAVORE]:	SIGNATURE (OR SIGNATURE OF PARENT/GUARDIAN IF APPLICABLE): [PLEASE READABLE SIGN]:	SIGNATURE (OR SIGNATURE OF A PARENT/LEGAL GUARDIAN IF APPLICABLE):		FIRMA (o firma di un GENITORE/tutore se applicabile) [FIRMA LEGGIBILE PER FAVORE]:
	TODAY'S DATE (DD/MM/YYYY):	DATA ODIERNA (GG/MM/AAAA):		DATA ODIERNA (GG/MM/AAAA):	DATA ODIERNA (GG/MM/AAAA):	TODAY'S DATE (DD/MM/YYYY):	TODAY'S DATE (DD/MM/YYYY):		DATA ODIERNA (GG/MM/AAAA):
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for Pregnancy into another language, this study offers a template.

DISCUSSION

This communication explains how the GAQ-P for pregnancy was translated into Italian and adjusted for cross-cultural differences. This procedure, which was carried out in accordance with a set of guidelines [13], is the initial stage of a validation process.
After extensive consultation on this project, feedback from key target users indicated that the translations were both clear and culturally relevant. Respondents highlighted the importance of broad knowledge dissemination (*e.g.*, educational events, presentations at scientific conferences) to raise awareness of these tools and help reduce barriers to physical activity among pregnant women in Italy. Given that a significant number of Italian women remain physically inactive during pregnancy, this perspective is well-founded.
Historically, all pregnant women were encouraged to consult their obstetric care provider regarding the safety of engaging in physical activity during pregnancy. This practice posed a significant barrier to exercise participation, especially given the strong evidence now available that supports the safety and health benefits of physical activity for expectant mothers. However, it remains important to identify the small subset of women who may face contraindications to exercise during this period. The GAQ-P was created for this purpose, enabling pregnant women to complete it on their own. By responding to specific questions, they can easily evaluate their health, the progress of their pregnancy, and the amount and quality of physical activity they have engaged in, both during and prior to pregnancy. Based on their answers, they will receive guidance indicating whether they are at low risk for contraindications to prenatal physical activity, allowing them to safely start or continue exercising, or if they should seek additional screening from their obstetric care provider. Additionally, the brief, evidence-based information provided in the questionnaire may help reinforce healthy behaviours, potentially increasing the rate of physical activity participation among pregnant women in Italy.
It is important to note that engaging in daily activities and low-intensity exercises is still advised for most complications related to pregnancy [14]. Professional organizations in gynaecology and obstetrics recommend against suggesting "bed rest" or complete inactivity [15]. Such recommendations, lacking clinical support, are considered unethical due to the detrimental health effects of physical inactivity [16]. They may also contribute to unfavourable outcomes for infants [17]. Widespread misconceptions regarding the supposed dangers of physical activity during pregnancy can complicate efforts to encourage participation in physical activity.
In a study on more than 500 women in Italy, only 4.6% of the women participated in regular physical activity/exercise during the third trimester. "Lack of time" (54%) was the sole barrier negatively correlated with exercise. The facilitators of "relaxation/recreation" (18%), "prevention of health issues" (15%), "enjoyment" (10%), and "prevention of gestational weight gain" (4%) were linked to meeting exercise recommendations. This study found no correlation between meeting the recommendations and factors such as childhood exercise/social modelling or exercise networks/environments ($p = 0.294$ and $p = 0.123$). However, exercising with others was a significant predictor of consistent maternal exercise ($p < 0.001$). The majority of women did not receive any guidance on exercise during pregnancy from their doctor or midwife (60.0%). Nevertheless, those who did receive such advice were significantly more likely to exercise regularly compared to those who did not (75.0% *vs* 38.2%; $p < 0.001$) [18].
Malta *et al*. [19] demonstrated that after an educational intervention, healthcare providers were almost three times more likely to offer appropriate advice on physical activity to their pregnant patients compared to a control group lacking educational support. Resources like the GAQ-P will further enhance educational efforts and the dissemination of knowledge.
It is crucial to differentiate professional skills related to the promotion, planning, and implementation of physical activity programs [20]. Obstetric care providers should carefully assess women with medical or obstetric issues and provide them with general information about the advantages of physical activity participation (PAP) and the potential risks of inactivity. In contrast, the responsibility for designing and executing exercise programs falls to fitness professionals. The effectiveness of an exercise program relies on the proper interaction of its main components: intensity, duration, frequency, type, and progression. When working with a pregnant individual, it is vital to ensure that the exercises cater to her specific needs as an expectant

mother [20]. To achieve this, instructors, trainers, coaches, other exercise specialists, and physiotherapists must be competent and trustworthy. Their training should ideally take place in reputable institutions that uphold high educational standards, such as those consistent with European guidelines [21]. With an increasing number of women, including female athletes, wishing to maintain vigorous and high-intensity sports during pregnancy [22-24], it is essential for exercise professionals to have specialized skills in this field.

In Italy, there are qualifications for professionals working with pregnant and postpartum women. These include:

1. "Training Course for Pregnancy Sports Operators": this training program focuses on educating fitness instructors about exercise prescription for pregnant women.
2. "Master in sport and gynecology": some universities offer specialized master's programs that cover topics related to exercise and pregnancy, training professionals to support pregnant women in physical activity safely.
3. "Certifications in Physical and Sportive Education": many fitness professionals pursue certifications in pre- and postnatal fitness, which equip them with the knowledge to guide women during these stages.

These programs aim to ensure that instructors and trainers are well-prepared to support the health and well-being of pregnant and postpartum women.

The strength of this study lies in the fact that the original version of the GAQ-P was created through a multi-stage, rigorous process established by the instrument's developers [12]. As a result, the validity of both the questionnaire structure and its content has been reliably verified. The proposed methodology provided a clear and systematic approach to translation and cultural adaptation [13]. Questions may arise regarding how well these tools will be integrated into the Italian context and how widely they will be utilized by pregnant women, obstetric care providers, and fitness professionals. It is clear that comprehensive promotional and educational initiatives should be organized to support this effort.

CONCLUSIONS

Target users have given favourable feedback on the Italian version of the GAQ-P. Utilizing the ISPOR methodology, we have developed a reliable, evidence-based screening tool. This tool aims to assist obstetric care providers in identifying pregnant patients who may not be suited for moderate to vigorous physical activity. Simultaneously, the GAQ-P can help lower the barriers for most women who should and wish to engage in physical activity during pregnancy. Future research should evaluate the effectiveness of this instrument and the extent of its implementation within the Italian context.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions
The authors contributed equally to this work.

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Study registration
N/A.

Disclosure of interests
The authors declare that they have no conflict of interests.

Ethical approval
N/A.

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Microablative CO_2 laser therapy and oral adjuvants in genito-urinary syndrome, effectiveness outcomes: a pilot study

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ABSTRACT

Objective. Genitourinary syndrome is a complex of multi-organ symptoms related to hypoestrogenism. Over 50% of women in menopause are affected by severe symptoms thus the need for new therapeutic approaches. The objective of the study is to demonstrate whether oral integration of bioactive substances in CO_2 laser therapy can enhance the therapeutic effects of genitourinary syndrome.

Materials and Methods. The study conducted is a pilot study of a prospective monocentric case-control type. Sixty patients were recruited and a simple single-blind randomization was conducted to form two homogeneous groups. Half of the patients (group A) underwent CO_2 laser therapy vaginally and received placebo, while the second half (group B) underwent laser therapy and received oral supplementation with hyaluronic acid. Three treatments were administered monthly to each study group. The primary endpoint was the improvement in PISQ-12 scores from the baseline to the six-month follow-up. Secondary endpoints at six months were assessed with a symptom severity scale, PFSQ-7, I-QOL and Vaginal Health Index.

Results. Both groups showed an improvement according to the scores PISQ 12, PISQ 7, Vaginal Health Index (VHI) and Symptom score regarding itching, burning and dyspareunia. Group B achieved greater improvements with statistically significant differences ($p < 0.05$).

Conclusions. The CO_2 laser therapy represents a valid non-hormonal alternative in the treatment of genitourinary syndrome. Oral adjuvant therapies with hyaluronic acid can enhance the effectiveness of vaginal laser therapy.

INTRODUCTION

Genitourinary syndrome of menopause (GSM) is a complex of multi-organ symptoms related to hypoestrogenism that affects women with the onset of menopause. The term was coined at the Consensus Conference in Chicago in 2013 to indicate, in a broader way, the symptoms linked to hormonal depletion and not only genital atrophy [1]. Due to its aetiology, linked to the normal path of female aging, it can be defined as a paraphysiological condition. The extension of life expectancy, the desire for a

better quality of life, greater scientific knowledge and prolonged sexual activity even at an advanced age, push women to experience the symptoms of hormonal depletion for longer and with greater discomfort. Genito-urinary syndrome includes disorders of the sexual sphere such as dyspareunia and of the urinary system such as urgency, dysuria and recurrent cystitis. The female genital tract and the lower urinary tract derive embryologically from the same structure, *i.e.*, the urogenital sinus [2]. The external genitalia and lower urinary tract have common features including widespread exposure of oestrogen receptors. GSM is not just a set of symptoms but rather the reflection of precise tissue remodulations that lead to an impoverishment of collagen fibres in quantity and quality, reduction of elastic fibres and histo-architectural disruption [3].
The discomforts experienced by menopausal women in the urogenital area affect over 50% of the female population, despite the fact that the problem is still underdiagnosed and undertreated [4]. A recent survey conducted in Italy revealed, unsurprisingly, that only a small number of physicians possess the necessary competencies in the matter [5].
It is important to acknowledge the concurrent rise in both the incidence of breast cancer and the number of women who survive it. Consequently, in the forthcoming decades, a significant portion of patients will likely experience vulvo-vaginal and lower urinary tract disorders [6]. This last category of women is the most difficult to treat due to the absence of established safety profiles in the vaginal application of topical estrogens among survivors. Local hormones are the most effective therapy to date. Topical hyaluronic acid, lubricants and moisturizing creams, polynucleotides and platelet-rich plasma can be valid alternatives in the therapeutic plan.
In recent years, vulvovaginal laser therapy has received excellent feedback regarding its outcomes, improving the quality of life and sexual satisfaction of women who accepted this treatment [7]. A 2022 review analysed 312 studies on laser therapy and found only 9 to have a strong scientific basis. The results of these studies agree that fractional CO_2 laser is an effective therapy, enhancing clinical symptoms of GSM and sexual life. An improvement of VAS scale score was reported in all studies [8]. The outlook for treating stress urinary incontinence is also promising [9], although the extant literature presents greater uncertainty in this regard, leaving ample room for classic methods such as urethral slings or bulking agents [10].
According to Di Donato *et al*., women's satisfaction with laser treatment is high: 89.7% of patients would highly (value 5-7) recommend the procedure and 94.9% would be ready to repeat the procedure to maintain results [11]. Therefore, vaginal laser treatment can be considered both an effective and safe innovative therapy for the minimally invasive treatment of symptoms of GSM [10, 12]. During the treatment period, no severe complications occurred. A minority of patients reported mild complications (dysuria, dizziness, minor bleeding, mild discomfort during and after the therapy), but these resolved without the need for treatment [13]. The strong point of this therapeutic option is its safety even in women who have survived hormone-responsive tumours.
Our study stems from the desire to improve the effectiveness of laser therapy by combining various pharmacological and non-pharmacological solutions that are currently scientifically validated. The beneficial effect of hyaluronic acid on genital mucous membranes, for example, has been proven by the results obtained with its local application in gel form [14]. It is also beneficial when taken orally in the treatment of skin aging, mucous membranes and joint connective tissue [15]. The efficacy of vitamins in regulating connective tissue has likewise been demonstrated [16]. The quality and quantity of collagen fibres, in fact, are influenced by the levels of vitamin C [17], and further by those of N-Acetyl-D-Glucosamine [18, 19]. Moreover, the combination of hyaluronic acid and chondroitin sulphate reduces the inflammatory and degenerative status of the tissues [20].
It is therefore reasonable to think about enhancing the effects of vaginal laser therapy through all these adjuvants, which have been substantiated by scientific literature. Undoubtedly, hyaluronic acid (HA) is the protagonist among all bioactive molecules, due to the multiple functions it performs in the repair of tissue lesions. Regarding the possible integration of hyaluronic acid, it is widely demonstrated that the forms with low molecular weight (between 150-300 kDa) act on the differentiation mechanism of fibrocytes and on the expression of metallo-elastases by macrophages, degrading possible bacteria and promoting a protective effect. No study in the scientific literature has addressed the therapeutic possibility of combining vaginal laser treatment with oral supplementation of non-hormonal bioactive molecules. To date, hyaluronic acid is mainly used locally with newly developed equipment such as Vagy Combi and Caress Flow [21].

In the future, laser therapy will represent an increasingly valid and widespread therapeutic opportunity, especially if scientific knowledge leads to more standardised and targeted recruitment protocols. Currently, this type of therapy is regarded as third-line in cancer survivors, after non-hormonal and local hormonal therapies. The increasing scientific consensus regarding the safety and efficacy of CO_2 laser therapy [22] will certainly lead this approach to become the second viable therapeutic option, even prior to the utilisation of topical hormones. Tailored Treatment-Based Approach are the future of GSM [23].

MATERIALS AND METHODS

The study is of prospective monocentric type and has been approved by the International Review Board of the University of L'Aquila with protocol number 17/2023. The study was conducted at the San Salvatore Hospital in L'Aquila, in the urogynaecology clinic. It involved 60 menopausal patients, aged between 50 and 70 years (mean age 59.1 ± 6.2 years), suffering from mild stress urinary incontinence and vaginal atrophy. The mean BMI was 23.6 ± 3.3.
Eligible patients were randomly assigned to two study groups using a randomised procedure based on the decision of the physician in charge. The clear definition of inclusion and exclusion criteria, along with the random selection process, ensured the homogeneity of the sample cohort and the methodological validity of the comparison between groups. The study population have thus a simple single-blind randomization. All patients signed an informed consent form to participate in the research group.
The study population included women aged between 50 and 70 with vaginal atrophy following physiological or iatrogenic menopause and mild stress urinary incontinence that did not require surgical correction. All patients tested negative in pap tests performed in the last two years, vaginal and cervical swabs in the last month, and urine cultures in the last month. Furthermore, patients had to have suspended any local or systemic therapy related to the pathology for 3 or more months. Women with the following conditions were excluded from recruitment: heritable disorders of connective tissue, undiagnosed abnormal uterine bleeding, ongoing tumour pathologies, lack of sexual activity, previous pelvic radiotherapy or previous radiofrequency therapy (**Table 1**).

Table 1. *Inclusion and exclusion criteria.*

Inclusion criteria	Exclusion criteria
Vaginal atrophy following physiological and/or iatrogenic menopause and mild stress urinary incontinence that does not require surgical correction.	Genetic pathologies of the connective tissue.
Age between 50 and 70 years.	Undiagnosed AUB.
Negative PAP TEST performed in the last two years.	Current tumor pathologies.
Suspension of any local or systemic therapy relating to the pathology for 3 or more months.	Lack of sexual activity.
Negative vaginal and cervical swabs in the last month.	Previous pelvic radiotherapy.
Negative urine culture in the last month.	Previous radiofrequency therapy.

This study aims to find new ways to push laser therapy to greater efficacy profiles than those recorded to date without altering its safety profile; exploiting the beneficial properties of some bioactive molecules, in particular, low molecular weight hyaluronic acid. In the population studied, no distinction was made between women with physiological menopause and those with iatrogenic menopause.
One group then underwent the pure microablative CO_2 vaginal laser treatment, *i.e.* without local or systemic adjuvants (group A). In contrast, the second group (group B) underwent the same laser therapy and also took an oral supplement. In group A, which only underwent endovaginal laser therapy, a placebo was administered to avoid possible psychological biases. All the patients in group B declared that they had taken the Jalorest tablets continuously.
The laser therapy consisted of complete vaginal irradiation at an energy level of 90, 85 and 80 mJ/pixel, administered every 30 days for three consecutive months. During the three-month period of laser therapy, women in group B also took one tablet per day of a supplement containing 100 mg of hyaluronic acid from sodium hyaluronate, 400 mg of chondroitin sulphate, 200 mg of N-Acetyl-D-Glucosamine and 80 mg of Vitamin C. The commercial name of the supplement was Jalorest and it was identified for the right mix of components in terms of type and quantity, as compared to the extant scientific knowledge on the synthesis of collagen and the extracellular matrix. In particular, it was appreciated for the low molecular weight hyaluronic acid it contains. The pill of group A, however, did not contain pharmacological principles but only starch.

The primary endpoint was the improvement in PISQ-12 scores from the baseline to the six-month follow-up. Secondary endpoints at six months were assessed with a symptom severity scale, PFSQ-7, I-QOL and Vaginal Health Index.

Before starting any therapy (time zero, *i.e.* t_0), all patients were invited to privately complete internationally validated tests to investigate general, urinary, sexual and vaginal well-being. The following questionnaires were filled:

- I-QOL (Incontinence Quality of Life) for urinary problems.
- PISQ-12 (The Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire) for sexual problems.
- PFIQ7 (Pelvic Floor Impact Questionnaire Short form 7) for problems related to alterations of the pelvic floor.
- Vas Symptom Score scale to describe the severity of the perceived vulvo-vaginal symptoms. The VAS Symptom Score scale was designed to evaluate symptoms such as vaginal irritation/itching, sensation of dryness, local discomfort, pain of the part and dyspareunia, with a score ranging from 1 to 10.

These tests were administered once more at the follow-up conducted six months later, *i.e.* three months after the end of the final laser session (time t_1).

The last parameter taken into consideration at time 0 and time 1 was the Vaginal Health Index, which, through the analysis of five parameters (vaginal elasticity, vaginal secretions, pH, epithelial mucosa, vaginal humidity), immediately allowed to diagnose and prove the severity of vaginal atrophy. This diagnostic index ranges from a minimum score of 5 to a maximum of 25, with each parameter evaluated on a scale from 1 (none) to 5 (excellent). A total score of less than 15 is indicative of vaginal atrophy.

Statistical evaluations were conducted using both parametric and non-parametric tests for paired data. The t-student test and the Wilcoxon rank-sign test were used respectively after evaluating the normality of the distribution of the variables with the Shapiro-Wilk test. A sample of 60 patients is sufficient to identify a statistically significant difference (between pre- and post-treatment) in the endpoints for a percentage of at least 40%, with a statistical power of 0.80 and a significance level α of 0.05. The calculation of the sample size was performed with the G*Power3.1.9.7 program.

RESULTS

At the beginning of the study (t_0), all patients underwent the tests and evaluations described previously. At six months (t_1) the results were compared between the two groups examined: group A, treated with laser therapy/placebo, and group B, treated with the combination of laser therapy and the food supplement. In order to facilitate comprehension, group A will henceforth be referred to as the "laser therapy alone group". The administration of placebo pills to this group is to be implied.

An improvement was observed in the local and general status of patients in both groups. In particular, patients who consumed the supplement presented more satisfactory results. As illustrated in **Figure 1**, the group that received oral integrative therapy experienced a superior improvement in their quality of sexual life. The PISQ-12, in fact, attests to this result in **Figure 2**, where the increase in its score is significant in group B. As further evidence of this phenomenon, a greater reduction in PFIQ 7 emerged in group B compared to group A. Group B also had a significant decrease in the score of the SYMPTOM SCORE scale, in the areas of

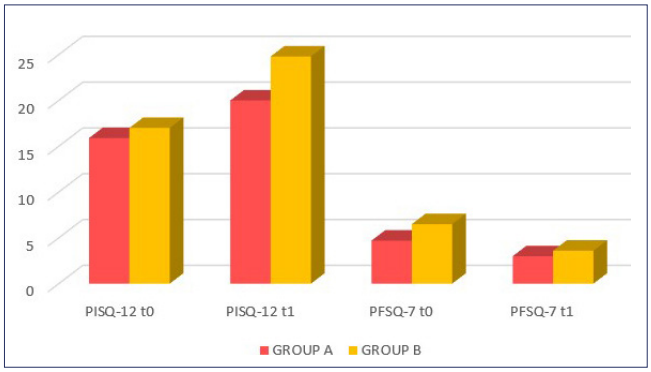

Figure 1. *The graph shows how the PISQ-12 score improves more in group B, while the PFSQ-7 score decreases more. Patients who use oral supplementation improve the most.*

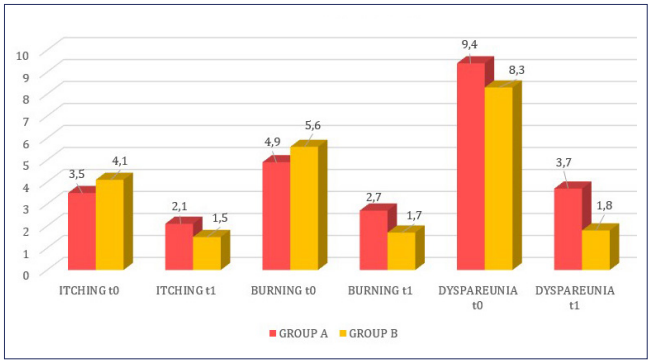

Figure 2. *All symptoms related to vaginal atrophy found improvement, especially in group B patients.*

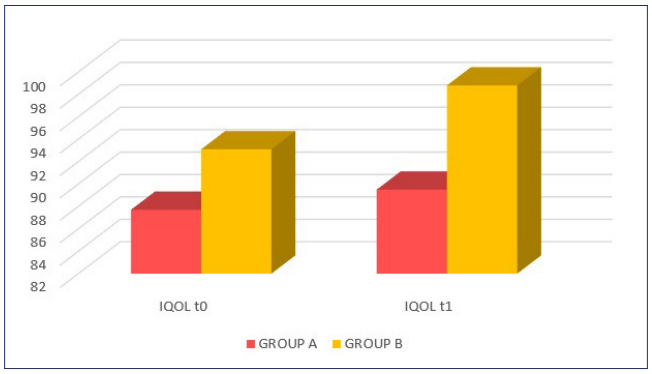

Figure 3. *Patients who took hyaluronic acid experienced a greater decrease in episodes of urinary incontinence.*

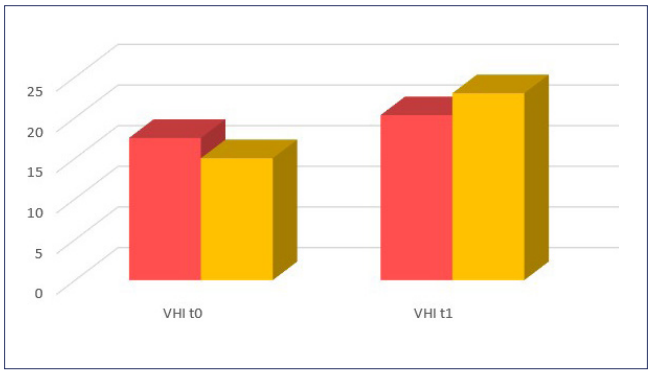

Figure 4. *Statistically significant increase in the VHI score with oral supplementation of hyaluronic acid.*

itching, burning and dyspareunia ($p < 0.05$). The difference in efficacy was also statistically significant compared to group A. As regards the pain symptom, both groups exhibited an improvement in their conditions, but the difference between the two groups was not statistically significant. It can thus be stated that microablative CO_2 laser therapy does not reduce pain more effectively when associated with hyaluronic acid. This datum is understandable considering that the integrated molecules do not have neurotrophism. The addition of supplements such as Palmitoylethanolamide (PEA) and Acetyl-L-carnitine would probably have led to a greater therapeutic surplus.

The most recent data describe an appreciable improvement in the patient's quality of life, based on their urinary and genital problems, as regards normal daily life activities and their state of mind.

As can be seen in **Figure 3**, the double treatment was associated with a significant improvement ($p < 0.05$) in I-QOL scores in the analysed menopausal women suffering from mild to moderate SUI, compared to laser treatment alone. In group A, the IQOL score increased by 2.01%, while in group B it increased by 5.77%. Although both groups experienced an improvement in symptoms, especially when hyaluronic acid was added, laser therapy generally had little impact on urinary symptoms, unlike what is reported in the scientific literature [24].

An objective and statistically significant increase in the VHI score was found with more encouraging results in group B: the average score increased from 12 pre-treatment to an average of 20 six months later ($p < 0.05$). This evidence is shown in **Figure 4**.

The laser treatment combined with the oral administration of hyaluronic acid and other bioactive compounds was well tolerated by all patients. No *de novo* side effects were found in group B compared to those typically associated with laser therapy. The most significant side effect was the perception of pain after laser therapy. None of the patients interrupted treatment due to excessive discomfort and there was no significant statistical difference between the two groups.

DISCUSSION

The study evaluates through numerical scores the difference in effectiveness in terms of quality of life, sexuality and symptoms in women suffering from genitourinary syndrome. Both groups showed an improvement after the treatment, but a better result in terms of symptom reduction and improvement in the state of vaginal mucosa was demonstrated in patients who received laser therapy combined with the food supplement. Dyspareunia presented the best resolution, which had a strong impact on women's general and marital well-being. Patients reported a reduction in pain related to sexual intercourse, a reduction in bleeding due to mechanical rubbing on the atrophic mucosa and an increase in lubrication during sexual intercourse and in everyday life. Not coincidentally, the PISQ-12 also showed improvements. Patients who reported recurrent cystitis at the start of treatment experienced an improvement in their condition after six months, with a reduction in frequency and dysuria. This was also followed by a reduction in the use of antibiotics to treat recurrent or presumed cystitis by women.

Patients with mild-moderate stress incontinence at the start of treatment, assessed with the I-QOL questionnaire, benefited from an improvement in symptoms, with a reduction in urinary losses and an enhanced quality of life. The patients' quality of life post-treatment was evaluated using the PFIQ-7

questionnaire. These scores were assessed during a medical examination in accordance with the stated results. During the gynaecological examination, it was possible to evaluate the mucosa's increased elasticity, resistance and lubrication. In patients who experienced severe pain and bleeding prior to treatment when the speculum was inserted, clinical improvement was observed after treatment. Over the months of the therapy, the vaginal pH decreased, and in some cases, it returned to the range of 3.5 to 4.5.

The results are satisfactory and demonstrate the increased effectiveness of laser therapy when used alongside adjuvants, such as oral supplements. No major adverse events have been reported in either group.

A weakness of the study is its limited sample size of 60 women, although this still allows for a good statistical analysis. While the total sample size was adequate for an initial clinical exploration, its relatively small size may have limited the statistical power of the analysis, preventing the detection of significance for differences, relevant on a clinical level nonetheless. The randomisation adopted procedure (random clinical choice by the physician) allowed for balanced assignment, but was not performed using blinded computerised randomisation to ensure blind assignment. This meant that there was a potential, albeit low, risk of selection bias. However, the homogeneity of the two groups with regard to basic characteristics (age, associated diseases, BMI, *etc*.) suggests that this risk was limited.

Scientific research has shown that hyaluronic acid with a lower molecular weight (LMW-HA) is more easily absorbed by tight junctions. It has been demonstrated that only LMW-HA with a molecular with a molecular weight of 5 kDa or lower can easily cross the intestinal barrier and reach the systemic blood circulation [25]. The hyaluronic acid used in our supplement, ExceptionHYAL (Hyaluronic acid from Sodium hyaluronate), has a molecular weight of 200-600 kDa, making it optimal for absorption. The creation of molecules with a lower molecular weight certainly represents a fertile area of research for achieving better results thanks to oral supplementation. Our study, the first to evaluate the usefulness and safety of supplementation with bioactive molecules, represents an interesting starting point. The combined effects of laser therapy and hyaluronic acid have never been studied before; on the contrary, the two therapies have been compared, demonstrating the individual effectiveness of both [26]. Only the effectiveness of combining hyaluronic acid with radiofrequency therapy has already been proven [27].

The data expressed in the study are numerical, based on scores, making the study objective and reproducible. The tests used are validated at an international level, though they can be influenced by the emotional and psychological sphere of the patient. The possible bias of the placebo effect was avoided by administering tablets without hyaluronic acid to the control group as well. Similarly, the Vaginal Health Index is an operator-dependent score. It would be interesting, therefore, to analyse the histological differences of the mucous membranes of patients in groups A and B. Ethical limits, however, make this path difficult to follow.

Menopause is a chronic condition for which the positive effects produced will naturally tend to regress. A longer period of study will allow us to understand the times of regression and the methods and frequency of reintervention. In the future, it may be possible to observe whether oral administration of hyaluronic acid alone is capable of maintaining the results obtained after treatment over the long term. It has been proven that prolonged administration of hyaluronic acid does not cause health problems [28]. Microablative CO_2 laser therapy is also considered safe and effective, although numerous research protocols are being developed to provide definitive data.

CONCLUSIONS

This study demonstrates that combining adjuvants with endovaginal laser light during treatment provides a significant advantage. Although statistical significance was not achieved in all parameters studied due to the limited sample size, the emerging patterns are consistent with recent studies and with the physiological picture of the role of hyaluronic acid (HA) in counteracting genitourinary syndrome. This shows pathophysiological and clinical consistency in favour of HA supplementation, with potential benefits in terms of response times and treatment efficacy.

These scientific data are precious for the niche of patients less responsive to laser therapy, thus being able to find a greater boost in the resolution of their urogenital problems. The use of low molecular weight hyaluronic acid orally finds, therefore, a scientific rationale confirmed in the data shown in our

research, providing an important starting point for further prospective studies on larger samples.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution
A.D.A.: Conceptualization, supervision, project administration. A.S.: Investigation, writing – original draft, writing – review & editing, resources, visualization. M.G.: Methodology, supervision. A.T.: Data curation, formal analysis, investigation, resources.

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Study registration
N/A.

Disclosure of interests
The authors declare that they have no conflict of interests.

Ethical approval
The study is conducted with approval of research protocol N 29932 of the Ethics Committee of the University of L'Aquila. The study is in line with the main ethics standard.

Informed consent
Patient consent was obtained in written format with autobiographical signature.

Data sharing
All scientific data are stored anonymously at the Pelvic Centre of the San Salvatore Hospital in L'Aquila. The data are available under reasonable request to the corresponding author.

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Placenta increta and minimally invasive surgery: our experience and narrative review of the literature

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ABSTRACT

Background. Placenta accreta spectrum disorder is a rare condition with a prevalence rate of 0.01-1.1%, increasing in incidence over the last years. It is a pathology that puts fetal life at risk, but above all maternal life. Accurate prenatal diagnosis, a multidisciplinary approach, the presence of skilled laparoscopic surgeons, appropriate equipment, resources and a tertiary hospital setting are key factors for successful management

Case presentation. We present the case of a 33-year-old woman with a complex medical history. She has undergone various surgical procedures, including a complicated myomectomy with haematoma and infection, cholecystectomy, appendectomy, and sleeve gastrectomy. Following a spontaneous delivery, she developed primary and secondary postpartum haemorrhage. The patient required uterine tamponade at the delivery hospital and subsequent uterine artery embolization at another centre, followed by total hysterectomy with bilateral salpingectomy and abdominopelvic adhesiolysis at our institution. The surgical procedure revealed a residual placenta with pathological adhesion and myometrial invasion, confirming the diagnosis of placenta accreta spectrum disorder (PASD). She was discharged in good general condition. A laparoscopic approach can be considered for delayed surgical management of this condition, even in patients with severe puerperal haemorrhage and hypovolemic shock. This strategy, with its potential to reduce morbidity, represents a compromise between postpartum hysterectomy and conservative management.

Conclusions. The use of mini-invasive laparoscopic techniques for the performance of total hysterectomy in PASD is possible, reduces the haemorrhagic risk during the intervention, improves the outcome and postoperative pain, with the final result of reducing the days of hospitalization

INTRODUCTION

Placenta accreta spectrum disorder (PASD), also known as morbidly adherent placenta, describes a range of placental pathologies, including placenta accreta, placenta increta, and placenta percreta. The most accepted hypothesis for the cause triggering the placenta accreta spectrum disorder is a defect

in the endometrial-myometrial interface, which would lead to abnormal decidualization in a uterine scar, deep placental anchoring villi and trophoblast infiltration [1]. The FIGO classification distinguishes 3 degrees of anomalies of the placental insertion based on the invasiveness in the myometrium: grade 1, 2 and 3. Grade 1 (placenta accreta) does not detach after active assistance manoeuvres at the third stage of childbirth. The macroscopic evaluation shows distension of placental "bulge", without invasion of the placental tissue through the surface of the uterus and no or minimal neovascularization. On microscopic examination, there are large areas of absence of deciduous between villi and myometrium. Grade 2 (placenta increta) presents macroscopic abnormalities such as bluish/purple coloration, distension or significant neovascularization. No placental tissue is observed to invade the surface of the uterus. The traction of the umbilical cord drags the uterus without separation of the placenta (dimple sign). Microscopic examinations show the villi to invade the muscle fibres and sometimes penetrate the lumen of the deep uterine vessels. Grade 3 (placenta percreta) is also divided into: 3A (invasion limited to the uterine serous, with a visible cleavage plane between bladder and rectum), 3B (bladder invasion) and 3C (invasion or not of the bladder, with another pelvic organ in addition) [2].

It is a rare condition with a prevalence rate of 0.01-1.1%, increasing in incidence over the last years [3]. Maybe for the increase rates of caesarean section, surgery of the uterus such as myomectomy that causing endometrial scarring [4]. This condition poses a significant risk for patient morbidity and mortality with complications such as massive haemorrhage, hysterectomy, infection, multisystem organ failure, intensive care admission and even death [5, 6].

Accurate prenatal diagnosis is crucial to improve maternal outcomes, in particular in women with high-risk factors. Ultrasound, especially with the use of Color Doppler, is most effective in the prenatal diagnosis of PASD in high-risk pregnancies. Premature detection through ultrasound allows for better clinical management, reducing maternal morbidity by enabling planned interventions [7, 8].

The ways to manage placenta accreta spectrum disorder distinguish between conservative and non-conservative uterus techniques. Conservative uterus-preserving methods, such as methotrexate administration and long-term antibiotics, were evaluated. Conservative management and approaches for fertility preservation are currently debated, as they still pose a substantial risk of complications during the postpartum period. This risk encompasses increased morbidity, mortality, infections, and the potential necessity of delayed hysterectomy [9-11]. A hysteroscopic resection was considered but was deemed to be a challenging approach due to the substantial exophytic mass obstructing the lower segment and possible complications [12]. An open caesarean hysterectomy remains the standard treatment for placenta accreta, considering its reproducibility, morbidity rate, and reduced complications compared to alternative options [5]. Although this seem to be the preferred management strategy, some studies indicate relatively high morbidity rates, including the need for transfusion, cystotomy, ureteral injuries, and infections [5, 13]. Several case reports have demonstrated the laparoscopic method efficacy in managing placenta accreta, resulting in satisfactory outcomes with minimal bleeding and bladder injuries [14, 15]. The key factors for successful management include a multidisciplinary approach, the presence of skilled laparoscopic surgeons, appropriate equipment and resources, and a tertiary hospital setting [14, 15].

CASE PRESENTATION

The patient was a nullipar 33-year-old woman with a complex medical history. Her surgical history included: laparotomy myomectomy a year earlier complicated by relaparotomy for haematoma with wall infection, cholecystectomy, appendectomy in paediatric age and sleeve gastrectomy. She reported a non-severe allergy to amoxicillin (weight 75 Kg, BMI 28.6 Kg/m^2). She was allergic to amoxicillin and iodinated contrast media (weight 75 Kg, BMI 28.6 Kg/m^2).

The woman gave birth spontaneously at another hospital a 2,850 g female newborn complicated by primary major postpartum haemorrhage (3,000 cc). She was subjected to manual secondment, RCU and Bakri balloon positioning, removed after 24 hours. In the days following delivery, a transfusion of 4 units of blood was performed and an infusion of ferric carboxymaltose was submitted, with restoration of haemoglobin values.

Almost a week later, the patient accessed an emergency to the hospital where she gave birth, reporting massive uterine bleeding. Consequently, she was given anti-haemorrhagic therapy with tranexamic acid and methylergomethrin maleate with the

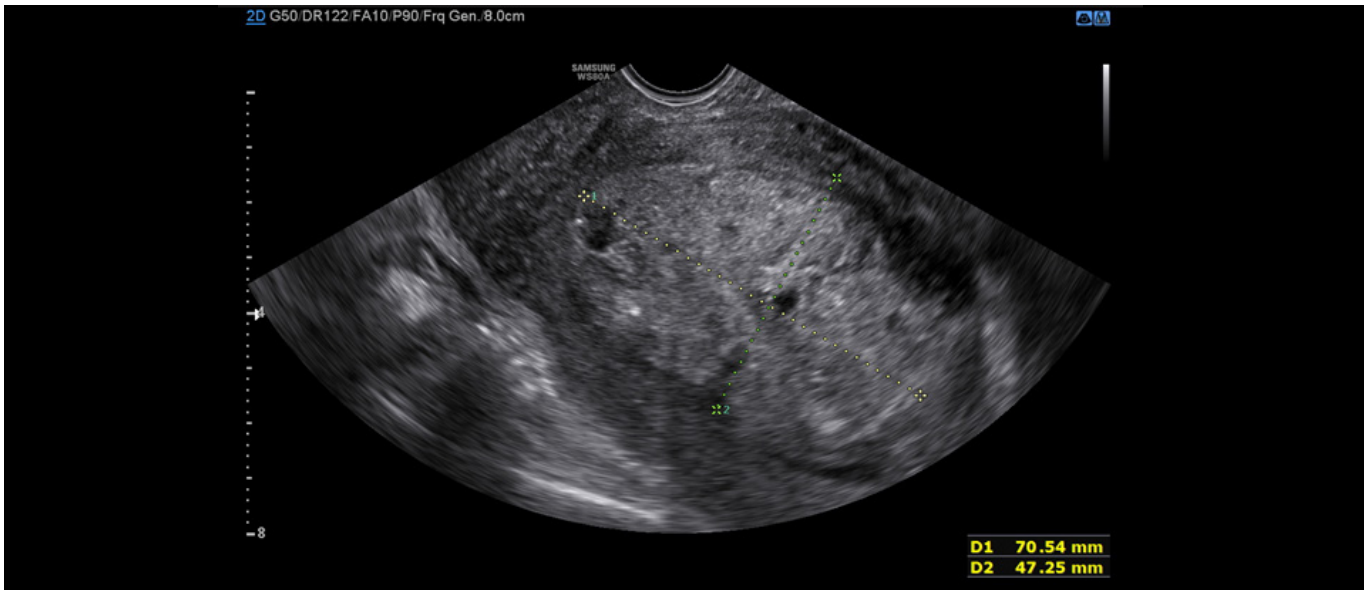

Figure 1. *Inhomogeneous area, referable to the residual placental portion.*

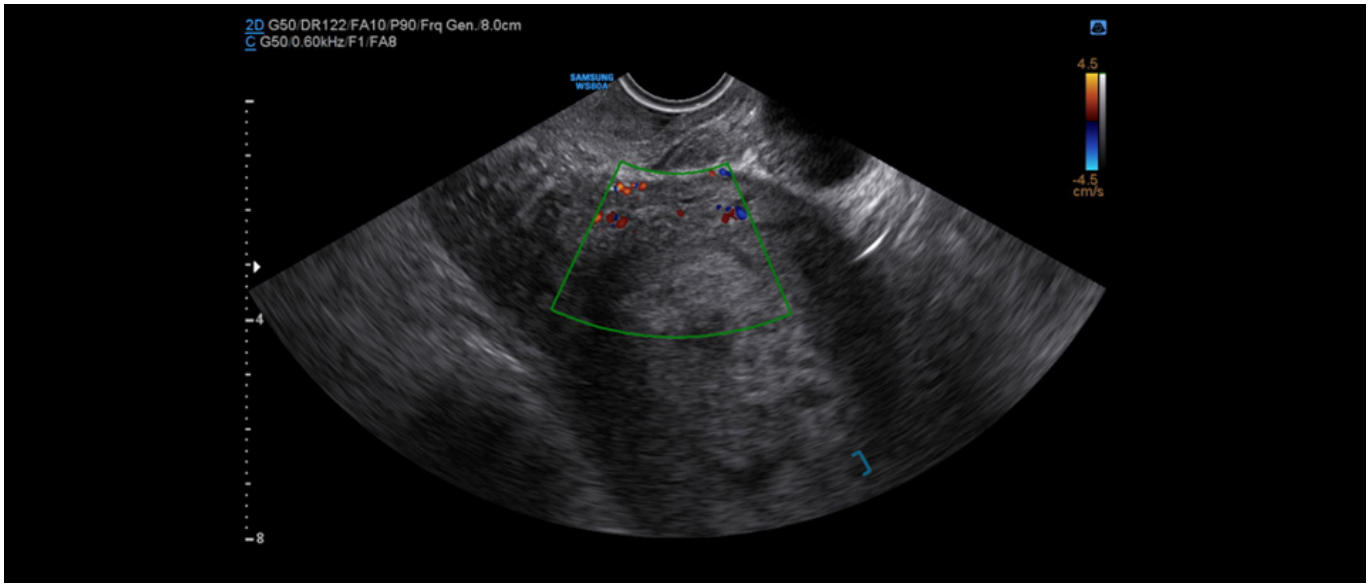

Figure 2. *Vascularization of the uterine wall and gradient margins of placental increta at the livel of the uterine fundus with residual myometrium < 1mm.*

arrest of blood loss and maintenance of stable haemoglobin values.

On the same evening following discharge from home after a new haemorrhagic loss, the patient sought medical attention at another centre. An urgent abdominal CT scan was conducted with contrast medium after premedication with prednisone and an antihistamine, revealing irregular tissue margins approximately 80 × 50 × 50 mm APxLLXCC (antero-posterior × latero-lateral × cranio-caudal) with rich vascularisation. Two ampoules of fibrinogen intravenously and 1g of tranexamic acid were administered, followed by therapy with Clindamycin 600 mg × 2/day intravenously. On the same day, an embolization procedure was performed on the uterine arteries to reduce per-vascularised placental residue. The patient was discharged in good general clinical condition.

A month later, the patient experienced new massive uterine bleeding and sought medical attention at the hospital peripheric where she had given birth. She was admitted, transfused again, and transferred immediately to our hub centre.

A USG-TV scan was conducted: the uterine cavity was occupied by an inhomogeneous formation of 70x47mm, referable to the residual placental portion, which Doppler colour score 2. The fundus uterine wall exhibited signs of accretism, with discontinuity in the area of the previous myomectomy (**Figures 1** and **2**).

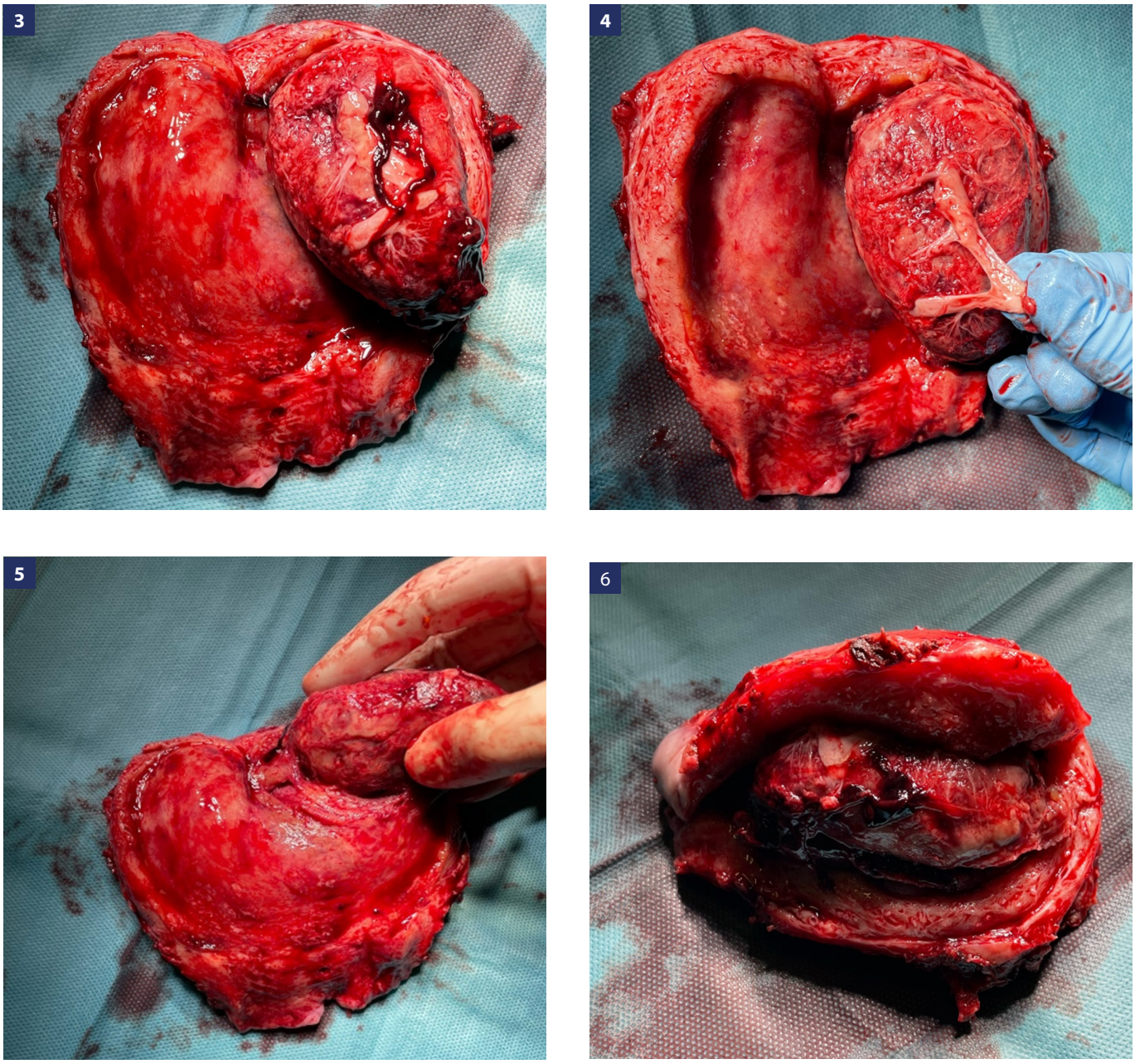

Figure 3-6. *Operative piece (uterus) with pathological myometrial invasion (incretism) of residual placenta.*

Due to severe hypovolemia (80/60 mmHg) and pre-haemorrhagic shock (Hb 6.4 g/dL), surgical intervention in emergency was undertaken.
Perioperative transfusions (4 units of blood + 600 ml of concentrated fresh plasma) were administered. The patient was subjected to a total laparoscopic 3D hysterectomy with bilateral salpingectomy. The intervention lasted three hours and 5 minutes, there were no complications and the patient was haemodynamically stable, intraoperative blood loss was 150 ml and the salient steps were: induction of pneumoperitoneum with subcostal access according to Palmer with Verres and the introduction of the optic was done through a supraumbilical access because the uterus appears like that of a 16-18 -week pregnancy, with regular surface preservation and a consistent diminution in size from the puerperal status. The Latzko space was prepared, and the uterine arteries were closed at their origin to reduce the significant vascularization of the organ. A tenacious and extensive adherential syndrome occurred between the omentum, anterior uterine wall and sigmoid and between the uterus and bladder, with a scarfold and partial uterine ventrification observed in previous surgical outcomes requiring massive adhesiolysis. The vesico-uterine fold is cautiously and progressively detached. The rest of the intervention did not present any particular

critical issues. Histological examination confirmed placental incretism at the level of the uterine wall (**Figures 3-6**, **Figure 1 supplementary**). The postoperative course was uneventful. Bowel function resumed on postoperative day 3, hemoglobin levels remained stable (9.8 g/dL on day 1 and unchanged on day 3), and vital signs were within normal limits throughout hospitalization. The patient was discharged on postoperative day 3 in good general condition.

DISCUSSION

The incidence of abnormal placentation is increasing in recent years. Among the main risk factors, surgical interventions are responsible for the creation of a scar at the level of the wall of the uterus, as in the case of myomectomy. A laparoscopic approach can be considered for delayed surgical management of this condition, even in patients with severe puerperal haemorrhage and hypovolemic shock. This strategy, with its potential to reduce morbidity, represents a compromise between postpartum hysterectomy and conservative management [16-18]. The decision between conservative management and total hysterectomy is contingent upon several factors, including the extent of placental invasion, the manifestation of infection symptoms, the woman's haemodynamic condition, the surgical proficiency of the practitioner, the availability of appropriate facilities, and the woman's aspiration to maintain fertility [16].

Uterine artery ligation, an alternative to uterine artery embolization, is used for both preventing and treating postpartum haemorrhage [19, 20]. However, placenta previa and placenta accreta are risk factors for uterine artery ligation failure [19-21]. O'Leary suggested that these failures may be due to an extensive collateral circulation in the presence of abnormal placentation. A 2007 systematic review found no evidence supporting the superiority of any specific conservative treatment for postpartum haemorrhage management [22].

A retrospective study by Bretelle *et al*. [23] found that 19% of cases managed conservatively needed hysterectomy due to treatment failure, 15% developed fever, and 12% developed disseminated intravascular coagulopathy. Timmermans *et al*. [24] reviewed 60 cases of abnormal placentation managed conservatively and found failure rates of 15%, 23%, and 25%, respectively managed without any additional interventions, with use of methotrexate or with uterine arterial embolization. Endometritis was present in 18% of cases, and fever occurred in 35%.

Post-embolization syndrome is a prevalent complication of uterine artery embolization, characterised by pelvic pain, nausea, malaise, and low-grade fevers that persist for two to seven days. It distinguishes itself from endomyometritis, which is associated with elevated fever, escalating pain, and potentially purulent vaginal discharge occurring between one week and six months post-embolization. A compliant patient who comprehends the risks and benefits and adheres to regular follow-up can be managed conservatively. Although this approach mitigates severe morbidity, haemorrhage, infection, and disseminated intravascular coagulation remain potential risks. Delayed hysterectomy subjects patients to the usual risks of surgery and anaesthesia for a second time within weeks to months of delivery, irrespective of the surgical modality employed.

This is associated with higher peri-operative complication rates compared to non-obstetric hysterectomy. This is largely attributed to the often-emergent nature of the surgery, substantial surgical blood loss, size of the gravid uterus, risk of damage to nearby organs, and to have longer hospital days [16].

For women who do not desire to preserve fertility, delayed laparoscopic hysterectomy may serve as an alternative to minimise surgical morbidity. A minimally invasive approach employing conventional laparoscopic or robotic-assisted platforms may be envisaged when hysterectomy is deemed necessary following vaginal delivery in a haemodynamically stable patient.

Appropriate patient selection is paramount, whereas many of these procedures are performed on an urgent or emergent basis amidst potentially life-threatening haemorrhage. Specific challenges associated with performing robotic-assisted hysterectomy during the peripartum period include the additional setup time required for the minimally invasive approach in a patient with the potential to become unstable, as well as the challenges encountered with port placement in patients with large uterus. Timing is also significantly operator-dependent, and it is crucial to have a surgical team with extensive experience in robotic surgery.

It is widely acknowledged that hysterectomies performed through a minimally invasive approach confer numerous advantages, including reduced postoperative pain, smaller incisions, shorter ho-

spital stays, and expedited recovery compared to open surgery. Although certain studies have indicated an association between increased body mass index (BMI) and heightened bleeding and extended operating times in laparoscopic surgery, there is evidence suggesting that in robotic-assisted laparoscopy, obese patients achieve comparable outcomes to non-obese patients [17]. Although robotics has proven to be a very effective technique, it has not demonstrated its superiority over laparoscopy in the treatment of gynecological pathologies [25, 26]. Furthermore, it is a much more expensive technique and requires the availability of a robot that is not present in all facilities. Laparoscopic technique has demonstrated its effectiveness in the treatment of gynecological pathologies even in the case of a significantly increased uterus size and in the case of a high BMI of the patient [27].

While cases of peripartum hysterectomy are frequently emergencies and performed via laparotomy, a minimally invasive approach may be considered in patients requiring hysterectomy following vaginal delivery when an experienced team is available.

Numerous case reports have highlighted the laparoscopic method of managing placenta accreta, demonstrating favourable outcomes with minimal bleeding and minimal damage to the bladder [14, 15, 28] in addition to the shorter duration compared to robotic approach.

The use of mini-invasive endoscopic techniques in performing a total hysterectomy allows the surgeons to reduce the haemorrhagic risk during the intervention and improve the outcome and postoperative pain.

The timing of delayed laparoscopic hysterectomy is controversial. Ochalski *et al.* [15] performed laparoscopic hysterectomy at 12 weeks postpartum, whereas we planned to perform the procedure at six weeks postpartum due to severe hypovolemia and pre-haemorrhagic shock.

Optimising the timing of the procedure is paramount to minimise the risk of late complications such as haemorrhage and infections.

CONCLUSIONS

Placenta accreta condition poses a significant risk for patient morbidity and mortality with complications such as massive haemorrhage, hysterectomy, infection, multisystem organ failure, intensive care admission and even death. The laparoscopic approach appears to be safe and effective both immediately after delivery and at a later stage as in our case.

Key factors for the success of this approach include a multidisciplinary approach involving for instance preoperative anaesthetic consultation, the presence of skilled laparoscopic surgeons and advanced endoscopic equipment, and the availability of blood products in case of either bleeding complications or the conversion to an open approach.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

G.S., D.D.: Conceptualization. V.G., C.P.: Methodology. D.D.: Project administration. M.C., S.C.: Validation. V.G., G.S., J.S.P.S.: Formal analysis, writing – original draft. V.G., C.P., S.C.: Investigation. V.G., G.S., D.D.: Data curation. V.G., G.S., M.C.: Writing – review & editing. D.D. Supervision.

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

This research was approved by the Institutional Review Board of the University Hospital of Alessandria (n° 0021513).

Informed consent

Informed consent was obtained from the patient involved in the study.

Data sharing

Data are available under reasonable request to the corresponding author.

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Supplement 1

Macroscopia

Perviene dall'Azienda Ospedaliero-Universitaria SS. Antonio e Biagio e Cesare Arrigo di Alessandria:

A:

-26 vetrini colorati con ematossilina-eosina e contrassegnati come 20241005216 sezioni da A1-1 a A26-1 rinominate da noi come 24 R 53 da A1 ad A26;

-2 vetrini colorati con colorazioni di IHC (ACTINA 1A4, DESMINA) contrassegnati rispettivamente come 20241005216 A5-2 e 20241005216 A5-3 da noi rinominati come 24 R 53 A5;

-2 vetrini colorati con colorazioni di IHC (ACTINA 1A4, DESMINA) contrassegnati rispettivamente come 20241005216 A7-2 e 20241005216 A7-3 da noi rinominati come 24 R 53 A7;

-1 blocchetto in paraffina contrassegnato come 2024-1-5216 A5 da noi rinominato come 24 R 53 A5;

-1 blocchetto in paraffina contrassegnato come 2024-1-5216 A7 da noi rinominato come 24 R 53 A7;

-1 blocchetto in paraffina contrassegnato come 2024-1-5216 A14 da noi rinominato come 24 R 53 A14;

-1 blocchetto in paraffina contrassegnato come 2024-1-5216 A24 da noi rinominato come 24 R 53 A24;

B:

-1 vetrino colorato con ematossilina-eosina contrassegnato come 20241005216 B1-1 da noi rinominato come 24 R 53 B1;

-1 blocchetto in paraffina contrassegnato come 2024-1-5216 B1 da noi rinominato come 24 R 53 B1;

C:

-1 vetrino colorato con ematossilina-eosina contrassegnato come 20241005216 C1-1 da noi rinominato come 24 R 53 C1;

-1 blocchetto in paraffina contrassegnato come 2024-I-5216 C1 da noi rinominato come 24 R 53 C1;

Perviene anche documentazione del centro di riferimento.

Microscopia

A) Nelle numerose sezioni esaminate si osserva un residuo placentare costituito da villi a morfologia del terzo trimestre in degenerazione con estesa emorragia intervillosa in organizzazione. | suddetti villi mostrano aspetti di penetrazione del miometrio che in alcuni punti appare ridotto a sottile rima (effettuate colorazioni immunoistochimiche per Actina Muscolo Liscio e Desmina), non documentabili chiari aspetti di superamento e di invasione dei tessuti molli circostanti che mostrano aspetti di flogosi con fibrosi.

Il quadro morfologico è indicativo di placenta increta.

Portio con metaplasia squamosa immatura in epiteli superficiali e criptici e angiectasie nel corion. Endometrio con ectasie ghiandolari ed aspetti della fase di ripristino. Adenomiosi profonda.

B-C) Tuba sinistra con congestione e flogosi granulocitaria.

Diagnosi

A) UTERO POST GRAVIDICO CON PORZIONE DI PLACENTA INCRETA

B-C) VEDI MICROSCOPIA.

Copia del referto originale verrà inviata al reparto che ha richiesto il caso.

Data Referto: 09/09/2024

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Emergency obstetric hysterectomy in the era of rising caesarean sections

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ABSTRACT

Objective. Emergency obstetric hysterectomy (EOH) is a life-saving procedure when all other measures fail to control haemorrhage in obstetric emergencies. Our hospital based retrospective study aims to evaluate the incidence, demographic profile, risk factors, clinical indications, and outcomes associated with EOH.

Materials and Methods. A retrospective analysis was conducted encompassing 34 cases of EOH out of 12,782 deliveries within a duration of 4 years and 2 months. Variables examined included maternal demographics, obstetric history, surgical indications, perioperative complications, maternal and foetal outcomes.

Results. The incidence of EOH was 0.26% (1 in 376 deliveries). The median maternal age was 31 years, with multigravida status in 85.3% of cases. A history of caesarean section was documented in 76.5%, and placenta previa in 44.1%. PAS constituted the leading indication (58.8%) for EOH, followed by atonic postpartum haemorrhage (20.6%) and uterine rupture (20.6%). Primary mode of delivery was caesarean section in our cases (82.3%). Postoperative intensive care was required in 88.2% of cases, with major complications comprising anaemia (70.6%) followed by haemorrhagic shock (29.4%). Maternal mortality was observed in 5.8% of cases and foetal mortality predominantly was attributed to prematurity, with neonatal survival in 67.6% cases.

Conclusions. EOH remains indispensable for life-threatening obstetric emergencies. The predominance of PAS underscores the necessity for judicious use of caesarean section. Enhanced antenatal risk stratification and robust tertiary support infrastructure, including rapid-access blood bank and intensive care facilities, will help to optimize maternal and neonatal outcomes.

INTRODUCTION

Emergency obstetric hysterectomy is a vital procedure to save life of a mother during obstetric emergencies although it is opted as a desperate and last resort when all other measures fail to control catastrophic haemorrhage. Severe antepartum and postpartum haemorrhage (PPH) is a major cause of maternal mortality and morbidity and is increasing in incidence worldwide [1-3]. According to recent

reports, 0.20 to 5.09 of every 1,000 postnatal women across the globe have undergone an emergency hysterectomy. Many reports have listed placenta accreta, uterine atony and uterine rupture as common indications necessitating emergency hysterectomy [4, 5]. There is enormous increase in number of caesarean deliveries in the recent times with rise in its long-term sequelae like abnormal placentation and uterine ruptures leading to increase in number of EOH. Patients who undergo EOH, require close monitoring in the post-operative period to prevent further post-operative complications such as wound infection, renal failure, disseminated intravascular coagulation (DIC), shock, septicaemia and mortality [6]. Thus, increase in incidence of EOH require utmost attention.

This study aimed to evaluate the incidence, demographic profile, risk factors, clinical indications, and outcomes associated with EOH in a tertiary care referral hospital in Delhi.

MATERIALS AND METHODS

Study setting

The present hospital-based retrospective study was conducted in the Department of Obstetrics and Gynaecology, ESI Hospital Basaidarapur, New Delhi. It is the major government referral centre as well as a teaching and training institute in North-West part of Delhi, India.

Study population

All cases of emergency obstetric hysterectomy (EOH) between Jan 2021 and March 2025 were included after fulfilling inclusion and exclusion criteria. EOH is defined as a hysterectomy done during pregnancy and within six weeks of delivery.

Inclusion criteria

- All women who delivered in the hospital during study period and underwent emergency hysterectomy for obstetric indications during pregnancy or at the time of delivery or subsequently within the defined period of puerperium (42 days).
- All women with obstetric complications of pregnancy including Molar pregnancy, ectopic pregnancies, abortions.
- The women who delivered outside the study hospital and were referred for obstetric complications fulfilling the above conditions.

Exclusion criteria

Women who underwent hysterectomy for gynaecological reasons (*e.g.*, sterilization or cancer) or outside the stipulated time of 42 days post-delivery were excluded from the study.

Data collection

Data were collected retrospectively from Jan 2021 to March 2025 from the central record section of ESI Hospital Basaidarapur, Delhi and subsequently all the data were reviewed and analysed in detail. Extracted information from medical records included:

1. Socio-demographic characteristics (age, booking status)
2. Obstetric history (parity, previous deliveries)
3. Mode of delivery (vaginal or caesarean and their indications)
4. Clinical indicators [uterine rupture, intractable PPH, Placenta accreta spectrum (PAS)]
5. Post-operative complications *e.g.* anaemia, bladder and ureter injury, shock, sepsis, disseminated intravascular coagulation (DIC), wound infection, acute kidney injury (AKI)
6. Maternal morbidity and mortality and neonatal outcome.

We found a total of 12782 deliveries in the selected time frame. Out of these, 6239 deliveries were Caesarean sections and 6543 were vaginal deliveries. Emergency obstetric hysterectomy (EOH) was performed in 34 patients.

Data analysis

The collected data of these 34 EOH deliveries was entered into the predesigned working proforma. All the information extracted was filled onto the Microsoft Excel Spreadsheet, and analysed by simple descriptive statistics performed, using IBM SPSS Version 25.0 (IBM Corp., Armonk, NY, USA) and described with the help of tables. Mean as well as standard deviation were used for categorical data and percentages were used for continuous variables. The main focus was kept on indications and surgical outcomes of EOH.

RESULTS

During the study period out of total 12,782 deliveries, 6,239 (48.8%) were caesarean deliveries and 6,543 (51.2%) were vaginal deliveries. A total of 34 emergency obstetric hysterectomies were carried

Table 1. *Socio-demographic characteristics.*

Maternal factors	Numerosity (n = 34)	Percentage
Age	Mean- 30.97; Median-31 (SD-5.408)	
Registration status		
Registered in other centres	11	32.35%
Registered in study hospital	19	55.88%
Unregistered	4	11.77%
Referral		
Referred from other hospital	15	44.1%

Table 2. *Distribution of cases by age and parity.*

Age(years)/ parity	P1	P2	P3	P4	P5 or >5	Total
< 25	0	2	1	0	0	3
25-30	2	6	2	3	0	13
31-35	0	2	9	1	0	12
> 35	3	2	0	0	1	6
Total	**5**	**12**	**12**	**4**	**1**	**34**

Table 3. *Obstetric history.*

Caesarean	n	%
Previous nil caesarean	8	23.5%
Previous 1 caesarean	16	47.1%
Previous ≥ 2 caesarean	10	29.4%

Table 4. *Mode of delivery.*

Delivery	n	%
Vaginal	2	5.9%
Caesarean	28	82.3%
Other causes	4	11.8%

Table 5. *Various indications for emergency obstetric hysterectomy*

Indication	Number	Percentage (%)
Morbidly adherent placenta/placenta accreta spectrum (PAS)	20	59%
Atonic uterine PPH	7	20.5%
Uterine rupture	7	20.5%
Placenta accreta spectrum	20	59%
Post caesarean	17	-
APH with placenta previa	15	-
APH without placenta previa with focal accreta	1	-
Rupture uterus	7	20.5%
Dehiscence of the previous scar	3	-
During evacuation of products of conception	4	
PPH	7	20.5%
Atonic	6	-
Associated with uterine Inversion	1	-
Associated with anaemia before PPH (mild/mod/severe)	5	-

PPH: post-partum haemorrhage; APH: antepartum haemorrhage.

out during this period, with the overall incidence of 1 in 376 deliveries, *i.e.* 0.26%.

Out of 34 patients, minimum age was 22 yrs and maximum was 43 yrs. Median age was 31 yrs. Only 4 (11.7%) were between 20-24 years of age, followed by 12 (35.3%) between 25-30 years and 12 (35.3%) between 31-35 years and 6 (17.6%) were more than 35 years. The majority of women (25) were in the age group of 25 to 35 years. They constituted over 73.53% of cases.

Our is a referral hospital where all complicated obstetrics case are referred from other hospitals of Delhi (**Table 1**).

Out of all, 35.3% are of parity 2 and 50% of parity ≥ 3. Only five (14.7%) primigravida women were encountered during our study period (**Table 2**).

Out of the 34 cases, 13 (38.2%) patients were full term, *i.e.* > 37 weeks of gestation and 17 patients (50%) were preterm but crossed age of viability, *i.e.* > 28 weeks till 36 weeks. Four obstetric hysterectomies (11.8%) performed during evacuation of products of conception/abortions.

Table 3 demonstrates obstetric history of the 34 cases, with only 8 cases having no history of previous caesarean section. Rest 26 with prior caesarean deliveries of which 1 had previous classical caesarean with history of previous 3 caesarean section.

Amongst the 34 patients who underwent obstetric hysterectomy, 2 had EOH performed post vaginal delivery, 28 had EOH performed post caesarean section. Four had EOH performed due to other reasons: 1 patient had molar pregnancy of less than 12 weeks and rupture during evacuation done outside hospital, 1 had ruptured uterus in a case of septic abortion while undergoing removal of products of conception, 1 was a ruptured scar ectopic and 4th was a case of ruptured cornual ectopic pregnancy with uterus damaged beyond repair (**Table 4**).

The most common indication for EOH in present study was placenta accreta spectrum (PAS) which accounted for 20 cases (placenta accreta: 17 cases (50%), placenta increta: 2 cases (5.9%), placenta percreta: 1 case (2.9%)), followed by 7 EOH done due to intractable atonic PPH and 7 hysterectomies were

Table 6. *Risk factors for major conditions necessitating emergency obstetric hysterectomy.*

Risk factor	Indication			Total number	Percentage
	PAS	PPH	Uterine rupture		
Prev 1 CS	10	2	4	16	47 %
Prev ≥ 2 CS	7	0	3	10	29.4 %
Placenta previa	12	0	3	15	44.1 %
Placental Abruption	1 (Focal)	1	0	2	5.9 %
Malpresentation/Malposition	2	2	1	4	11.8 %
History of D&C	1	0	1	2	5.9 %
Uterine inversion	0	1	0	1	2.9 %
Septic abortion	0	0	1	1	2.9 %
Hydatidiform mole with previous LSCS	0	0	1	1	2.9 %
Anaemia	2	5	0	7	20.6 %
HTN disorder of pregnancy	1	2	0	3	8.8 %
Twin pregnancies	0	3	0	3	8.8 %
No identifiable risk factor	0	1	0	1	2.9 %

CS: caesarean section; D&C: dilation and curettage; LSCS: lower segment caesarean section; HTN: hypertension.

Table 7. *Perioperative complications.*

Complications	Numerosity (n = 34)	Percentage
Pre-existing co-morbidities		
Anaemia	7	20.6%
GDM	2	5.9%
Hypertension disorders	3	8.8 %
Others	18	52.9 %
Intra-op complications		
Bladder injury	2	5.9 %
Post-op complications		
Anaemia	24	70.6%
Shock	10	29.4%
Wound infection	5	14.7%
DIC	4	11.8%
Septicaemia	2	5.8%
Others (ARF, hepatic encephalopathy, psychosis)	4	11.8%
Duration of hospital stay (days)	Mean = 9.89 ± (SD = 3.956)	

n: total number of cases; GDM: gestational diabetes mellitus; DIC: disseminated intravascular coagulation; ARF: acute renal failure.

done due to uterine rupture seen in patients with damage exceeding possibility of repair (**Table 5**).
Out of EOH in 2 normal vaginal delivery, one had PAS with excessive bleeding and other had PPH following uterine inversion post home delivery and improper reposition followed by haemorrhagic shock.
Regarding predisposing risk factors responsible for EOH, prior caesarean section was observed in 26/34 cases (76.5%) (**Table 3**).
Patients who underwent EOH, association with Placenta previa was seen in 15/34 (44.1%) cases, out of which 5/15 were placenta previa seen in previous 1 Lower segment caesarean section (LSCS), 7/15 in previous 2 LSCS and 1/15 was placenta previa in classical C section, 2/15 had no prior C sections. Out of 15 placenta previa, 10 had antepartum haemorrhage.
Previous caesarean section was significantly associated predisposing factors with PAS and uterine rupture. The other high-risk factors were multiple pregnancy, obstructed labour with multiparity, HTN/ Preeclampsia and prolonged labour and these were more associated with PPH (**Table 6**).
In two cases of PPH, obstetric hysterectomy was done 12 hrs past LSCS due to intractable PPH of unknown cause. Three cases of PPH happened in elderly primigravida and known case of hypertensive disorder in pregnancy with twin conception via *in vitro* fertilization (IVF) in study hospital.
In present study 30 patients (88.2%) required Intensive Care Unit (ICU) care, post obstetric hysterectomy for stabilization. Most patients (24, 70.6%) had excessive blood loss during surgery requiring critical care monitoring, fluid management and blood products. Anaemia was the most common post-operative complication followed by haemorrhagic shock. **Table 7** lists other complications observed in intra and post-operative period.
There were 2 maternal mortalities observed (5.8%) in the present study, both due to post-partum haemorrhage leading to haemorrhagic shock followed

Table 8. *Maternal mortality and associated factors, and foetal outcomes.*

Mother outcomes			
Cases	**Indication of EOH**	**Cause of death**	**Admission to death duration**
1	Atonic PPH with Uterine inversion	PPH with septic shock, with DIC and MODS	Within 10 days of ICU stay
2	PPH with hemoperitoneum	PPH with impending eclampsia with AKI, DIC with MODS	Within 48 hours
Foetal outcomes			
	n	**%**	
Live (single)	20	58.8%	
Live (twins)	3	8.8%	
IUD/ early neonatal death	7	20.6%	
Non-viable Pregnancy	4	11.8%	

EOH: emergency obstetric hysterectomy; PPH: postpartum haemorrhage; DIC: disseminated intravascular coagulation; MODS: multiple organ dysfunction syndrome; AKI: acute kidney injury; IUD: intrauterine death.

by DIC and Multiple Organ Dysfunction Syndrome (MODS), leading to death. Out of these 2 mortalities, one patient had vaginal delivery with uterine inversion, and other had LSCS delivery due to Footling breech and intractable PPH in post op period, of unknown aetiology (**Table 8**).

Regarding foetal outcome, most babies were born alive, 20 singleton and 3 twins (67.65%). 7 (20.6%) mortalities amongst newborns were primarily because of prematurity and related complications (**Table 8**).

DISCUSSION

Emergency obstetric hysterectomy (EOH) remains a critical intervention to manage life-threatening obstetric haemorrhage not responding to any other measures. Though EOH is rarely performed, its implications in dire obstetric conditions on maternal morbidity and mortality are substantial.

Incidence

Out of 12,782 total deliveries during the study period, 34 EOHs were performed, giving an incidence rate of 1 in 376 deliveries (0.26%). This is consistent with reported EOH incidence rates in developing countries, which vary between 0.2% to 0.8% depending on institutional protocols and referral patterns [7, 8]. In India, the studies have shown a range between 0.2 and 2.0 per 1,000 deliveries, with higher frequencies seen in high-volume institutions handling complicated referrals [9]. The increase in EOH is closely tied to the rise in caesarean delivery rates, with prior LSCS found to be a critical risk factor in nearly 70-80% of EOH cases [10-12]. Notably, 48.8% of total deliveries (12,782) in our study period were caesarean sections, reflecting the ongoing rise in caesarean rates in India, which significantly contributes to the growing burden of abnormal placentation disorders.

Demographic characteristics

The age of the study population ranged from 22 to 43 years, with a median age of 31 years. The majority (70.6%) were between 25 and 35 years of age, which aligns with the reproductive peak and is similar to other institutional reports [12, 13]. Only 11.7% of cases involved women younger than 25 years, while 17.6% were over 35, indicating that maternal age is not the sole determinant of EOH risk.

A strong association with higher parity was evident and 85.3% of patients were of parity 2 or above, with a substantial proportion being grand multiparas. This reinforces findings from previous studies linking increasing parity with uterine rupture and placenta accreta spectrum (PAS) disorders [12-15].

Antenatal registration and referral status

The study revealed that 32.35% of the EOH cases were referrals from peripheral hospitals, highlighting the tertiary hospital's role as a referral centre for complicated obstetrics cases. EOH is often a reflection of deeper issues within the healthcare system in obstetric management, particularly within referral-based tertiary care hospitals [17]. Additionally, 11.8% of the patients were unregistered antenatally. Unregistered pregnancies often lack surveillance in antenatal period and timely risk stratification, contributing to obstetric emergencies. Antenatal care offers a critical opportunity to identify high-risk conditions such as placenta previa, PAS, and hypertensive disorders [16]. Moreover, a good antenatal care and early recognition of such high-risk factors provide for timely referral and management at higher tertiary centres, thereby reducing maternal morbidity associated with it and obstetric hysterectomy.

Gestational age and timing

Most EOHs occurred beyond foetal viability: 38.2% at term (> 37 weeks) and 50% preterm (28-36 we-

eks), while 11.8% occurred while removing the products of conception. This reflects that EOH most often arises in third trimester or peripartum period, when complications such as morbidly adherent placenta or uterine rupture are more likely [16].

Obstetric history and EOH

Out of 34 patients, 76.5% patients had a history of previous caesarean section. The clear predominance of previous caesarean section prior to EOH demonstrates the shifting pattern of EOH indications from uterine rupture and atonic PPH to morbidly adherent placenta, which is known to follow caesarean-induced uterine scarring [18]. 23.5% of patients in the study had no previous history of caesarean section. Out of these, 2 patients underwent vaginal deliveries. Associated with PAS in one case and uterine inversion with PPH following home delivery in other case were the reason for EOH. These cases emphasize the importance of antenatal surveillance and institutional delivery.

Indications for obstetric hysterectomy

The leading cause of EOH in our study was Placenta Accreta Spectrum (PAS) (58.8%), including accreta (50%), increta (5.9%), and percreta (2.9%). This shift from uterine rupture and atonic PPH as historical leading causes reflects the growing burden of PAS globally. PAS was the indication in over 50-60% of hysterectomy cases in multiple regional reports [19]. Kastner *et al*. analysed 47 cases from 1991 to 1997, with placenta accreta accounting for 48.9% of the cases; 51.1% of the women in their study had a previous caesarean delivery [20]. Zelop *et al*. analysed adherent placentation accounting for 64% of the cases: 59.8% had a previous caesarean delivery [21]. An analysis of patient discharge notes in Canada revealed a consistent rise in caesarean section rates resulting in surge of complications like abnormal placentation, uterine rupture and also in the incidence of atonic postpartum haemorrhage necessitating hysterectomy [22]. In our study, 76.5% had ≥ 1 prior caesarean section history and 44.1% had placenta previa, with a strong overlap between the two. PAS was frequently associated with previous caesarean deliveries and placenta previa, two well-established risk factors. The increase in the number of caesareans sections has caused an increase in abnormal placentation, placenta previa, and uterine scarring [23, 24]. A simple prenatal ultrasound in high-risk cases of placenta previa and previous caesarean section has an excellent diagnostic accuracy in identifying PAS with sensitive ultrasound signs like disruption in bladder myometrial interface [32]. Therefore, all high-risk cases should undergo ante-natal ultrasound screening for PAS and suspected cases should timely be referred to tertiary care centres for evaluation and management.

Other indications included intractable PPH (20.6%) and uterine rupture (20.6%), the latter often following unmonitored labour or rupture of unusual sites ectopic pregnancies or injury during abortion procedures. In a study by Pawar *et al.* uterine rupture, primarily seen in multiparas and those with previous uterine surgery, accounted for 15-25% of OH cases [27]. Their incidence has decreased slightly due to better antenatal surveillance and emergency response system. Atonic PPH contributes to EOH but EOH incidence due to uterine atony is declining due to use of uterotonics and haemostatic agents and surgical techniques like brace sutures, internal artery ligation, selective arterial embolization [25, 26]. Two cases of PPH in our study were notable for delayed presentation (12 hours post-LSCS). Other cases involved elderly primigravida women with hypertensive disorders and twin pregnancies conceived through IVF. These findings highlight the complex interplay of age, ART, and comorbidities in modern obstetrics.

Maternal outcomes

Maternal outcomes after EOH are one of the indicators of maternal care. The maternal morbidity burden was significant in our study. 88.2% cases required ICU admission, primarily due to haemorrhagic shock and need for resuscitation. The most common post-operative complication was anaemia (70.6%), followed by haemorrhagic shock (29.4%) and Disseminated Intravascular Coagulation (DIC) (11.8%). Other postoperative complications included surgical site infection (14.7%), sepsis (5.8%), acute renal failure, hepatic encephalopathy, and postpartum psychosis. Our study is broadly in line with earlier observations that EOH is associated with high maternal morbidity [8, 28].

Two maternal deaths (5.8%) were recorded, one in home vaginal delivery with uterine inversion and PPH, and the other post-LSCS with unexplained PPH and rapid deterioration. Both succumbed to DIC and multi-organ dysfunction syndrome

(MODS). Chaudhary *et al*. (2021) reported maternal mortality rates of 4-6% which align with the 5.8% found in our study [17]. This mortality rate, while within the acceptable range reported globally (2-10%), reinforces the need for timely and appropriate management of high-risk pregnancies [29, 30]. Though not evident in our study, a cross-sectional trial conducted in UK revealed that life limiting foetal conditions like aneuploidy/genetic conditions may grossly increase the risk of preterm labour, post-partum haemorrhage and hypertensive disorders with subsequent rise in obstetric interventions like caesareans and hysterectomies. Such conditions in pregnancy increases maternal risk burden and highlights the importance of individualized counselling and preparedness with regards to complications, outcome and mode of delivery in continuing such pregnancy [33].

Foetal outcomes

Despite the critical nature of these obstetric emergencies, 67.6% of neonates were born alive, including three sets of twins. Foetal outcomes were influenced by gestational age and neonatal mortality (20.6%) was largely attributed to prematurity and its sequelae [10, 31].

This suggests that while maternal survival remains a priority in EOH cases, neonatal outcomes can also be improved with better antenatal planning and neonatal intensive care support (NICU).

Implications and recommendations

This study reaffirms the changing epidemiology of emergency obstetric hysterectomy, with placenta accreta spectrum emerging as the predominant indication, linked strongly to previous caesarean deliveries and placenta previa. There is an emerging trend of caesarean as mode of delivery due to patient preferences, monitoring concerns and medico-legal aspects. Additionally, anaesthesia advancements and blood bank facilities have made it a safer and painless alternative to labour. This has resulted in surge of complications like abnormal placentation, uterine rupture and atonic postpartum haemorrhage. This makes emergency obstetric hysterectomy immensely relevant in modern obstetric practice. Unregistered pregnancies, emergency referrals, and caesarean deliveries highlight systemic gaps in antenatal care, referral systems, and surgical decision-making. There are grey areas in some non-obstetrical medical conditions where there are no consensus or limited data available for the management of labour. Such conditions include controlled cardiac diseases, seizure disorders, hip and spine disorders [34], ophthalmic conditions like mild to moderate myopia, history of retinal detachment, controlled diabetic retinopathy, glaucoma, or keratoconus [35]. These conditions though not very common but add to the burden of caesarean sections. Instead promoting natural birth, painless deliveries with use of epidural anaesthesia and training budding doctors do to so should be our plan of action. Thus, refusing caesarean section for non-obstetrical conditions, not supported by scientific literature is the way forward to prevent the rise of unnecessary caesarean sections in the modern era.

Key recommendations

Reducing unnecessary primary caesarean sections, to limit cumulative scarring and future PAS. Will require implementation of protocols and labour management guidelines especially in low-risk pregnancies.

Improving antenatal registration and early risk detection, particularly for placenta previa and PAS using ultrasonography and MRI if need be.

Establishing referral protocols and preparedness plans for anticipated high risk obstetric cases between peripheral and tertiary centres.

Strengthening blood bank and ICU capabilities for managing obstetric haemorrhage, especially in high-volume obstetric centres.

Training obstetricians in conservative haemorrhage control techniques including haemostatic suturing techniques, embolization and internal artery ligation procedures to reduce unnecessary hysterectomies where possible. Also labour rooms and operation theatres should be adequately equipped with uterotonic drugs, surgical haemostatic devices and balloon tamponade kits for PPH control especially for many centres in the developing countries.

CONCLUSIONS

Emergency obstetric hysterectomy is a useful and necessary intervention in select obstetric emergencies. The shifting trend in primary indication from uterine rupture and atonic PPH to placenta accreta spectrum (PAS) accounting for nearly 59% of all cases. Association of PAS with prior caesarean section underlines the need for policy and practice changes targeting caesarean reduction. Maternal outcome

remains challenging with high rate of ICU admissions and postoperative complications and mortality rate of 5.8%. Foetal outcomes were favourable in most cases, but prematurity contributed to neonatal mortality. Incidence of EOH and associated complications can be reduced to a large extent through better antenatal surveillance, capacity building, obstetric planning and systemic improvement in maternal health services.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions
S.M.: Data curation, investigation, formal analysis, writing – original draft, writing – review & editing. D.A.R.: Conceptualization, methodology, supervision. BG: Writing – original draft, formal analysis. T.G.: Supervision, writing – review & editing. S.M.V.: Supervision.

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Study registration
N/A.

Disclosure of interests
The authors declare that they have no conflict of interests.

Ethical approval
Study was approved by Institutional Ethics Committee of ESI Hospital Basaidarapur, Delhi. (IEC No./SC-1/2023/1966). The information of all patients was coded to ensure confidentiality.

Informed consent
As it is a retrospective study from available hospital records, hence patient consent was not required, approval taken from institutional ethics committee.

Data sharing
Data are available under reasonable request to the corresponding author due to privacy/ethical restrictions.

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Evaluation of perfusion index as an indicator of postoperative pain in parturients undergoing caesarean section: an observational study

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ABSTRACT

Objective. Perfusion index (PI) is a non-invasive measure of peripheral perfusion. Previous studies have evaluated PI as an objective tool of pain assessment peri-operatively. Against this background, the present study aimed to evaluate PI as an objective indicator of pain assessment in parturients undergoing lower segment caesarean section and also to observe any correlation of PI with Visual analogue scale (VAS), heart rate (HR) and mean arterial pressure (MAP).

Materials and Methods. This prospective observational study was conducted in 40 parturients scheduled to undergo caesarean section under spinal anaesthesia. After surgery, patients were shifted to post anaesthesia care unit. Pulse co-oximeter probe was attached to the middle fingertip of the hand along with standard routine monitors. HR, MAP, VAS and PI were recorded at first request of analgesia (T1) by the patient and at 30 minutes after administration of analgesia (T2) in the form of 1 g paracetamol i.v.

Results. There was a statistically significant increase in PI from T1 to T2 (3.62 ± 2.36 to 8.51 ± 9.36; $p < 0.05$). This increase was associated with statistically significant decrease in HR (93.08 ± 12.71 *vs* 85.65 ± 10.63 beats/min), MAP (96.60 ± 11.606 *vs* 91.55 ± 10.86 mmHg) and VAS (6.23 ± 1.23 *vs* 2.53 ± 1.06) at T2 as compared to T1. A statistically significant negative correlation was observed between PI and HR/MAP/VAS from T1 to T2 ($rs = -0.433$, $p < 0.001$; $rs = 0.896$, $p < 0.001$; $rs = -0.231$, $p = 0.016$, respectively).

Conclusions. PI can be used as an additional and objective indicator of pain assessment in post anaesthesia care unit.

INTRODUCTION

Post-operative pain management is important, particularly in context of enhanced recovery after surgery as it relieves suffering, leads to earlier mobilisation, shortened hospital stay, reduced cost and increased patient satisfaction [1]. Adequate management of pain is vital in parturients undergoing lower segment caesarean section (LSCS) as it influences the capacity of the mother to take care of the new born and initiate breastfeeding [2]. Also, pain assessment should be appropriate owing to considerable physiologic changes (hormonal and emotional) in mother due to pregnancy and arrival

of baby. Visual analogue scale (VAS) is the most commonly used pain assessment tool in post-operative period in adult patients. It is easy, less time consuming and more sensitive to small changes than other descriptive ordinal scales. However, it is highly subjective and it cannot be used in patients with impaired cognitive, psychological and neurological functions and in those who are unable to express themselves verbally [3].

The perfusion index (PI), which is the ratio between the variable pulsatile alternating current (AC) and non-pulsatile direct current (DC) signals, is an indirect and non-invasive measurement of peripheral perfusion. It is calculated by means of pulse oximetry by expressing the pulsatile signal (during arterial flow) as a percentage of the non-pulsatile signal (AC/DC×100), both of which are derived from the amount of infrared (940 nm) light absorbed. The PI may decrease due to increased vasomotor tone and the contraction of peripheral blood vessels when the sympathetic nervous system is activated by pain. The PI may also increase when pain is relieved by the use of adequate analgesics [4-9]. There are a few previous studies which have evaluated PI as an objective tool of pain assessment peri-operatively and in critically ill patients [5-7, 9]. It eliminates psychological factors such as personality, age, gender, fear, anxiety, depression, anger etc for pain assessment. However, the literature is scarce regarding the same when it comes to obstetric patients who are going through emotional turmoil and levels of fear and anxiety are running high. Therefore, the present study was planned to evaluate PI as an indicator for post-operative pain in patients undergoing lower segment caesarean section. The null hypothesis was that there will be no change in PI with pain. Primary objective was to observe the change in PI with pain and administration of analgesia. Secondary objectives were to observe any correlation of PI with Visual analogue scale (VAS), heart rate (HR) and mean arterial pressure (MAP).

MATERIALS AND METHODS

The present prospective, observational study was carried out in the Department of Anaesthesiology and Critical Care at Pt. B.D. Sharma PGIMS, Rohtak following approval from Institutional Ethics Committee (IEC) vide letter no. BREC/Th/20/Anesth16 dated 02/04/2021 with CTRI no. CTRI/2022/03/041169 from March to September, 2022. Forty pregnant females belonging to American Society of Anaesthesiologist's (ASA) class II, scheduled to undergo lower segment caesarean section under regional anaesthesia were enrolled. Patients with age <18 years, history of neurological, psychological, or any chronic pain disorder, drug allergy, any contraindication to regional anaesthesia and conversion to general anaesthesia were excluded from the study.

Sample size

Mohammad *et al.* reported the mean change in PI value 30 minutes after rescue analgesia compared to baseline as 0.86 ± 0.96 [5]. Assuming these as references values, the minimum required sample size at power of 80% and type 1 error of 5%, number of participants required in the study were 40.

Hence by using following formula:

$$N = 2 \times \frac{(Z_{\alpha/2} + Z_{\beta})^2}{(\delta_0)^2} \times SD^2$$

N = size per group

SD = Standard Deviation = 0.6

δ = mean difference = 0.96

$Z_{\alpha/2} = Z_{0.05/2} = Z_{0.025} = 1.96$ — From Z table at type I error of 5

$Z_{\beta} = Z_{0.20} = 0.842$ — at 80% power

$$N = 2 \times \frac{(Z_{\alpha/2} + Z_{\beta})^2}{(\delta_0)^2} \times SD^2$$

$= 2\ (1.96+0.84)^2\ (0.96)^2\ /\ (0.6)^2$

$= 15.68 * 0.92\ /\ 0.36$

$=14.59/\ 0.36$

$=40.52$

$=40$

Statistical analysis

The data was compiled and entered into Microsoft Excel spread sheet. The quantitative variables such as HR, MAP, PI, VAS, temperature, duration of surgery, height and weight of patients were expressed as mean ± SD and were assessed for normality using Kolnogorov Smirnov non parametric test. The qualitative variables such as age type of surgery level of block) were expressed as frequencies/percentages and compared using chi square test. The paired t-test was used to compare normally distributed paired data. A P-value < 0.05 was con-

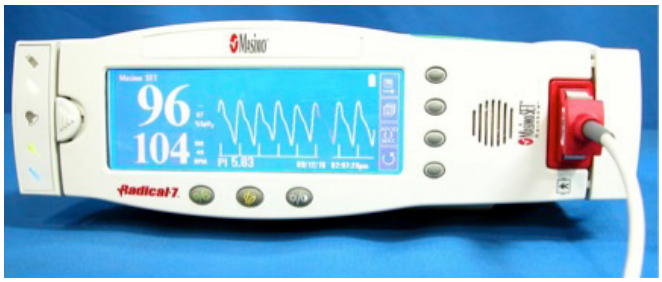

Figure 1. *PI measurement using Masimo Radical 7; Masimo corp, Irvine, CA, USA.*

sidered statistically significant. Test data Analysis was done using SPSS version 20 (IBM SPSS Statistics inc, Chicago llinois, USA) Windows software program. Descriptive statistics included computation of percentages, means and standard deviation.

Patient and public involvement

Informed witnessed consent for participation in the study was obtained from the patients. Preoperative fasting of 6 hours prior to surgery was ensured. Patients were trained to express their level of pain using VAS to increase the familiarity with the scale. We showed them a 10 cm line with "no pain" at one end and "worst pain imaginable" at the other, and asked them to mark a spot that best represents their current pain level that can range from 0 to 10. A standardised routine protocol was used for anaesthesia in all patients. After shifting the patient to operation theatre, ASA standard monitors including lead II electrocardiography, pulse oximetry, and NIBP measurement was instituted. HR and MAP were recorded on the operation theatre table prior to any intervention. An intravenous access was established and co-loading with 15 ml/kg Ringers' lactate infusion was initiated. Under all aseptic precautions, subarachnoid block was performed at L3-L4 or L4-L5 interspace with patient in sitting position, using 12.5 mg of hyperbaric bupivacaine (0.5%). After spinal block, patients were placed in supine position with a wedge underneath left buttock and oxygen was provided via a facemask.

After completion of surgery, patients were shifted to PACU where following monitors were attached to the patient: ECG, NIBP, temperature probe. To monitor the PI, pulse co-oximeter probe (Masimo Radical 7; Masimo corp, Irvine, CA,USA) as shown in **Figure 1** was attached to the middle fingertip of the hand contralateral to the site of blood pressure monitoring and was wrapped in a sheet to decrease heat loss and interference by ambient light [4, 5]. Baseline values of HR, MAP, PI, peripheral oxygen

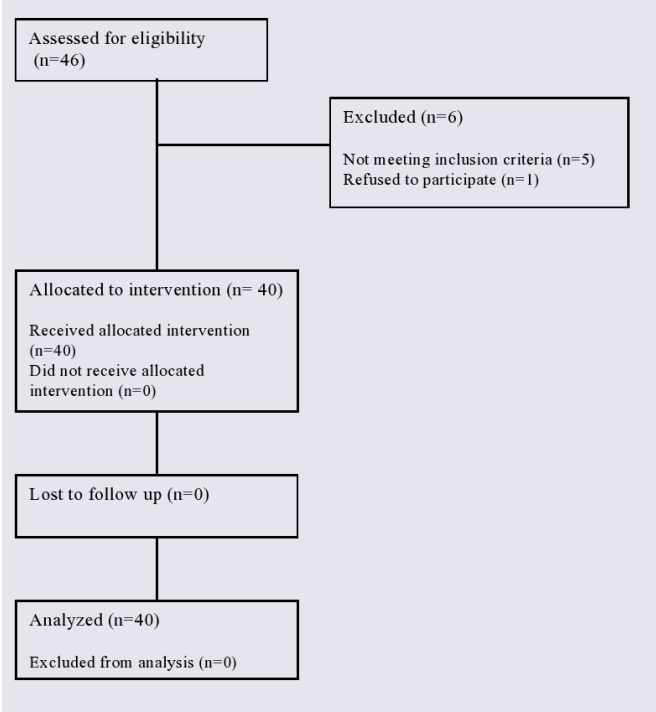

Figure 2. *Consort diagram.*

saturation (SpO_2) and level of block were recorded as soon as the patient was shifted to recovery room (T0). An oxygen mask was applied if $SpO_2 < 95\%$. The patients were kept warm with woollen blankets, warm i.v. fluids, and a warm environment. All patients were observed till the end of study period in PACU. The person recording the parameters was blinded to the timings of analgesia requirement and administration.

Time of the first request for analgesia (T1): When patients complained of pain in PACU and requested for analgesia, VAS, PI, HR, MAP, SpO_2 and temperature were noted. For all patients, analgesia was given with injection paracetamol 1g i.v.

Thirty minutes after analgesic administration (T2): after 30 minutes of first administration of rescue analgesia, second measurements of the above-mentioned parameters were noted in all the patients: VAS for pain intensity, PI, HR, MAP, SpO_2 and temperature.

RESULTS

Total 40 patients were analysed who were in age group of 18 to 39 years (**Figure 2**). Mean age of the patients was 25 ± 3.78 years. Mean height of the patients was 155.48 ± 5.14 cm and mean weight was 49.15 kg. Mean duration of surgery was 1.71 ± 0.37 hours. Mean temperature was 36.52 ± 0.06 °C,

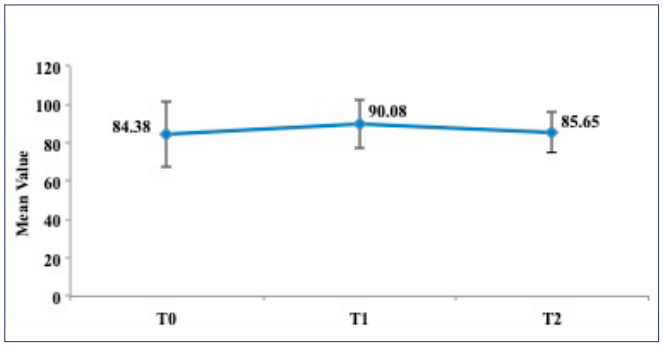

Figure 3. *Mean HR at various time points.*

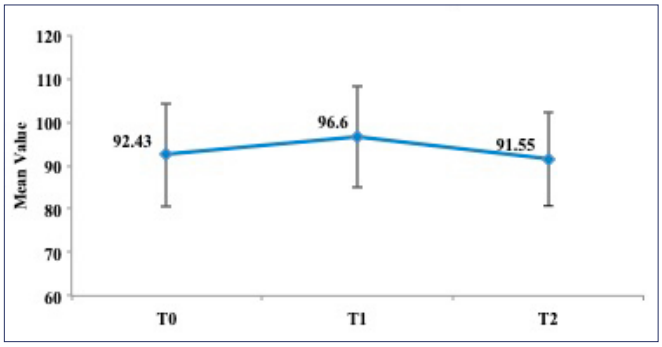

Figure 4. *Mean MAP in mmHg at observed time points.*

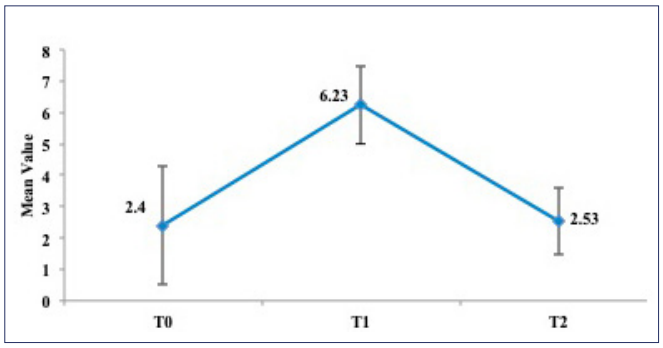

Figure 5. *Mean VAS at various time points.*

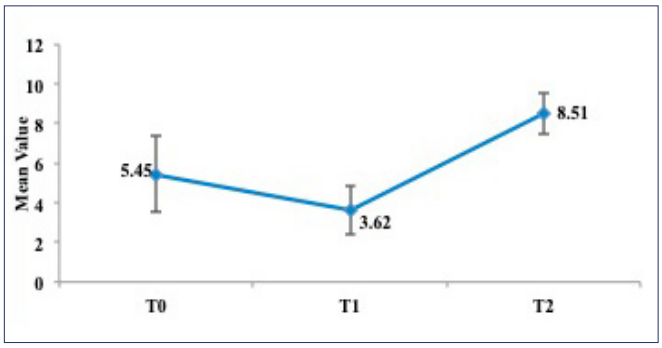

Figure 6. *Comparison of mean PI at observed time points.*

36.505 ± 0.07 °C and 36.51 ± 0.06 °C at T0, T1 and T2 respectively (p = 0.640). The average length of PACU stay was 2.5 hours in our study. All patients made analgesia request during the course of their PACU stay. Mean T0 to T1 interval was 60 ± 10.5 minutes. Mean values of HR, MAP, VAS and PI at T0, T1 and T2 is shown in **Figures 3, 4, 5** and **6** respectively. HR increased significantly from T0 to T1 with a mean difference of 6.225 (p = 0.001), while it decreased significantly from T1 to T2 with mean difference of 7.425 (p = 0.001) (**Figure 3**). It was observed that MAP increased from T0 to T1 with mean difference of 4.175 which was statistically significant (p < 0.001); it decreased from T1 to T2 with mean difference of 7.325 which was statistically significant (p = 0.006) (**Figure 4**). VAS increased from T0 to T1 with a mean difference of 3.825 which was statistically significant (p = 0.001), while it decreased significantly from T1 to T2 with a mean difference of 3.700 (p = 0.001) (**Figure 5**). This signifies that there was a significant increase in HR, MAP and VAS values with pain while a significant decrease was observed after analgesic administration. PI decreased from T0 to T1 with mean difference of 1.828, this finding was found to be statistically non-significant (p = 0.489). PI increased from T1 to T2 with a mean difference of 4.888 which was statistically significant (p = 0.001) (**Figure 6**). PI values decreased with pain and increased after analgesic administration.

Table 1. *Correlation of percentage change among study variables from T0 to T1.*

		MAP % increase	VAS % increase	PI % decrease
% change in HR (beats/min)	Spearman Correlation	0.539	0.649	0.474
	P-value	< 0.001**	< 0.001**	< 0.001**
% change in MAP (mmHg)	Spearman Correlation	1	0.548	0.756
	P-value		< 0.001**	< 0.001**
% change in VAS	Spearman Correlation		1	0.258
	P-value			0.009*

HR: heart rate; MAP: mean arterial pressure; VAS: visual analogue scale; PI: perfusion index.

The increase in HR from T0 to T1 showed a negative correlation with decrease in PI from T0 to T1, with a spearman correlation coefficient value of 0.474, which was statistically significant (p < 0.001). The increase in MAP from T0 to T1 showed a significant negative correlation with decrease in PI From T0 to T1 (spearman correlation coefficient = 0.756; p < 0.001). The increase in VAS score showed a significant negative correlation with mean decrease in PI from T0 to T1 (spearman correlation coefficient = 0.258; p = 0.009) (**Table 1**). This indicates that the

Table 2. *Correlation of percentage change among study variables from T1 to T2.*

		MAP % decrease	VAS % decrease	PI % increase
% change in HR (beats/min)	Spearman Correlation	0.423	0.537	0.433
	P-value	< 0.001**	< 0.001**	< 0.001**
% change in MAP (mmHg)	Spearman Correlation	1	0.678	0.896
	P-value		< 0.001**	< 0.001**
% change in VAS	Spearman Correlation		1	0.231
	P-value			0.016*

HR: heart rate; MAP: mean arterial pressure; VAS: visual analogue scale; PI: perfusion index.

increase in HR, MAP and VAS observed with pain was significantly correlated with decrease in PI values at that time.

The decrease in HR from T1 to T2 showed a significant negative correlation with increase in PI from T1 to T2, with spearman correlation coefficient of 0.433 which was statistically significant ($p < 0.001$). The mean decrease in MAP from T1 to T2 was negatively correlated with increase in PI from T1 to T2, with a correlation coefficient of 0.896 ($p < 0.001$). The decrease in VAS was negatively correlated with increase in PI from T1 to T2 (spearman correlation coefficient = 0.231; $p = 0.016$) (**Table 2**). This indicates that the decrease in HR, MAP and VAS observed after analgesia was significantly correlated with increase in PI values at that time.

DISCUSSION

Pain is difficult to measure due to its multifaceted and subjective nature. Obstetric patients are anxious and emotional and therefore an objective indicator of pain is required. Currently, there exists no valid and reliable method of objectively quantifying pain. PI has been reported to decrease with a noxious stimulus that causes vasoconstriction and it has also been reported to increase with vasodilation caused by pain relief [5-7,10,12]. In our study, we have evaluated perfusion index as an indicator of post-operative pain in parturients undergoing caesarean section, and its potential use as an objective indicator for quantification of pain. We observed that there was a decrease in PI values with pain which increased after pain relief. The increase in HR, MAP and VAS observed with pain was negatively correlated with decrease in PI values at that time. The decrease in HR, MAP and VAS observed after analgesia was significantly correlated with increase in PI values at that time.

We included 40 pregnant females belonging to age group 18 to 39 years scheduled to undergo LSCS under regional anaesthesia. Age associated difference of changes in PI were evaluated in a previous study and it was observed that changes are more significant and detectable in younger age groups rather than elderly (> 60 years) [13, 14]. However, in our study we included patients of similar age group (18 to 39 years). Thus, no age-related bias was present in our study.

There were few limitations. It was a single centre study with lack of control group and potential Hawthorne effect, thus impacting the internal and external validity of the study. Our study had a small sample size limited to a subgroup of patients *i.e.* ASA II parturients, which limits its applicability to broader patient populations, including high-risk obstetric cases or non-obstetric surgical patients. Future research involving more diverse populations groups is warranted. Another limitation of our study is that multivariate analysis was not done to adjust for potential confounders such as temperature, anxiety, or baseline hemodynamic variability.

We observed a statistically significant increase in HR at T1 as compared to baseline with mean difference of 6.225. There was a statistically significant decrease at T2 as compared to T1 with mean difference of 7.425 beats/min. Our results are similar to the previous studies [5-7, 12]. We observed a statistically significant increase in MAP at T1 as compared to baseline with a mean difference of 4.175 mmHg ($p = 0.004$). There was a statistically significant decrease in MAP at T2 as compared to T1 with mean difference of 7.325 mmHg. Nociception driven sympathetic drive causes an increase in HR and MAP, thus explaining the increase in values at T1, *i.e.* at first request of analgesia by patients, and the decrease with pain relief at T2 [15, 16]. Similar changes in MAP were observed in previous studies [4, 5, 12].

PI decreased from T0 to T1 in our study as pain causes an increased vasomotor tone due to sympathetic nervous system stimulation [17]. This leads to decreased peripheral perfusion and hence a decreased value of perfusion index. PI increased from T1 to T2 with pain relief, due to vasodilation caused by decreased sympathetic vasomotor tone caused

after analgesia administration. Similarly, Mohamed *et al*. evaluated PI as an objective indicator of pain in adult patients undergoing lumbar spine discectomy and observed a statistically significant increase in PI, 30 minutes after administration of rescue analgesic in the recovery room (1.89 ± 1.73) as compared to the PI value at first request of analgesia (1.03 ± 1.01) ($p < 0.001$) [5]. Salah *et al*. conducted an observational study in 40 postoperative patients and observed mean PI was 1.45 before analgesic administration (at request of analgesia), while it was 1.15 after analgesic administration 5 mg nalbuphine increments on patient's request ($p = 0.004$) [12]. Tapar *et al*. studied patients undergoing elective surgeries under general anaesthesia and observed statistically significant increase in PI value after the administration of rescue analgesic in post-operative area as compared to pre-analgesic values. The mean PI value increased from 2.80 ± 0.77 (pre analgesic) to 3.97 ± 0.94 (post analgesic) ($p < 0.001$) [7]. Chu *et al*. studied the utility of PI as a discharge criteria for post-operative pain assessment in PACU and recorded a statistically significant increase in PI value after analgesic administration ($p = 0.0001$) [4]. Kupeli *et al*. evaluated PI as an objective tool for assessment of pain in labour analgesia and recorded a statistically significant increase in mean PI value 5 minutes after administration of epidural analgesia as compared to the pre-epidural values (2.6 ± 1.4 *vs* 1.8 ± 1.1 respectively; $p < 0.05$) [9]. Lee *et al*. analysed data of 100 patients in retrospective study to evaluate correlation between perfusion index and analgesic efficacy in transforaminal block for lumbosacral radicular pain. The authors observed that in patients with > 50% reduction in pain after a successful transforaminal block (responders), the change in perfusion index > 0.27 was observed at 5 min after block when compared to non-responders (< 50 % reduction in pain after transforaminal block) ($p < 0.05$) [8].

In our study, the percentage increase in HR shows a negative correlation with percentage decrease in PI from T0 to T1 ($r_{s=}$-0.474; $p < 0.001$). Similarly, Hasanin *et al*. evaluated PI as a tool for assessment of pain in sedated critically ill patients after the application of painful stimulus, *i.e.* changing the patient's position, which resulted in a significant increase in HR and significant decrease in PI. A weak negative correlation was observed between PI and HR values after the positioning of patient ($r_s = -0.24$; $p = 0.02$) [6].

The percentage decrease in HR of patients in our study from T1 to T2 shows a statistically significant negative correlation with percentage increase in PI from T1 to T2 ($r_s = -0.433$; $p < 0.001$). Mohamed *et al*. also observed a statistically significant negative correlation between percentage decrease in HR and percentage increase in PI after administration of rescue analgesic ($p < 0.05$) [5]. Kupeli *et al*. evaluated PI as an objective tool for assessment of pain in labour analgesia and recorded a negative and statistically significant correlation between PI and HR values 5 minutes after administration of epidural analgesia (r_s: 0.58; $p = 0.001$) [9]. Salah *et al*. observed no significant correlation between PI and HR values before or after analgesic administration. The results of this study are different from our study as the authors included post-operative patients admitted in ICU who were receiving continuous analgesic cover in the form of 1 g paracetamol i.v. 6 hourly. The change in variables was probably not significant enough to detect correlation between variables [12].

We observed significant negative correlation between percentage decrease in MAP and percentage increase in PI from T1 to T2. ($r_s = -0.896$; $p < 0.001$). Mohamed *et al*. evaluated PI as an objective indicator of pain in adult patients undergoing lumbar spine discectomy. The authors observed that the correlation between decrease in MAP and increase in PI was not statistically significant ($p > 0.05$) [5].

We observed that percentage decrease in VAS significantly correlated with percentage increase in PI from T1 to T2. The correlation was found to be statistically significant ($r_s = -0.231$; $p = 0.016$). Our findings are similar to Kupeli *et al*. and Tapar *et al*. Kupeli *et al*. evaluated PI as an objective tool for assessment of pain in labour analgesia and recorded a statistically significant negative corelation between PI and VAS at the 10, 30, 60 minutes and at 2 hours after drug administration from epidural catheter. The authors suggested that the increase in PI was associated with adequate pain relief and decrease in VAS scores [9]. Tapar *et al*. studied PI in patients undergoing elective surgeries under general anaesthesia and reported a weak negative correlation between change in VAS and PI values before and after administration of analgesia ($r_s = -0.255$; $p = 0.016$) [7].

CONCLUSIONS

We observed a statistically significant decrease in PI and increase in HR, MAP and VAS at first re-

quest of analgesia. There was a statistically significant increase in PI and decrease in HR, MAP and VAS after 30 minutes of analgesic administration. PI decreases with pain while it increases with pain relief. Also, we observed that a statistically significant negative correlation exists between change in PI with change in HR/MAP/VAS before and after analgesia.

Thus, PI is an objective complementary indicator of post-operative pain and can be used as an adjunct to standard tools like VAS in parturients undergoing lower segment caesarean section. However, we conclude that larger randomised control trials are required to establish its use in routine clinical practice.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions

V.A.: Conceptualization, methodology, writing - original draft, data curation, writing - review & editing. P.S.: Data collection, data curation, writing - original draft. S.K.: Conceptualization, methodology, validation, supervision. R.R., A.A.: Data collection, visualization.

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Study registration

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Disclosure of interests

All authors have no financial relationships (such as employment, consultancies, stock ownership or options, honoraria, patents, and paid expert testimony), personal, political, intellectual (organizing education) or religious interests, according to the ICMJE recommendations.

The authors declare that no AI tool was used in the during the preparation of this manuscript.

Ethical approval

The present prospective, observational study was carried out in the Department of Anaesthesiology and Critical Care at Pt. B.D. Sharma PGIMS, Rohtak following approval from Institutional Ethics Committee (IEC) vide letter no. BREC/Th/20/Anesth16 dated 02/04/2021.

Informed consent

Informed witnessed consent for participation in the study was obtained from the patients after explaining the details of the study.

Data sharing

Data are available under reasonable request to the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Menopausal vaginal syndrome (MVS): a new-nonhormonal topical therapy

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ABSTRACT

Objective. The aim of this clinic retrospective study was to assess the regression of Menopausal Vaginal Syndrome following topical therapy with 2 g vaginal device *in ovuli* based on "DuoLact-EvoGold", whose active ingredients are: "A. Lactoferrin, *Lactobacillus casei* and *acidophilus*, FOS, and GOS and B. Natural vitamin E and Extravirgin Olive Oil".

Materials and Methods. The treatment consisted of one ovule 2 g "Duolact-Evogold" administered each evening for 10 consecutive days, followed by a 15day treatment suspension, and then a maintenance phase of 5 days. Symptom severity was evaluated using the Verbal Numerical Scale, while vaginoscopic findings and vaginal pH were assessed using the Visual Analogue Scale and Visual Colorimetric Scale. The "Grading classification" uses a score from 0 to 3. Sexual satisfaction was measured by the "Female Sexual Function Index".

Results. At baseline (T0), the most severe symptoms in patients with Menopausal Vaginal Syndrome were vaginal dryness and dyspareunia (each present in 47 patients; 78.3 %) and postcoital spotting (27 patients; 45%). Complete regression at T3 was observed for vaginal dryness and dyspareunia in 47 (78.3%) and 45 (75%) patients, respectively; complete absence of postcoital spotting was noted in 40 patients (66.7%). Spontaneous vaginal pain regressed completely.

Conclusions. Local therapy with "DuoLac-EvoGold" appears promising for the treatment of MVS, given its high rate of complete symptom regression.

INTRODUCTION

With menopause, the vagina undergoes both anatomical and physicochemical changes affecting the mucosa, muscle tissue, and connective tissue. In menopause, estrogenic deficiency leads to mucosal thinning, leaving only basal and parabasal cells. In the stroma, collagen and lipofuscin deposition

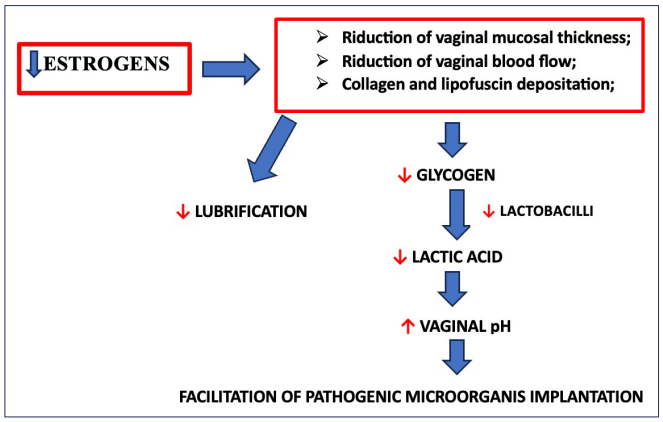

Figure 1. *Vaginal physiopathology in menopause.*

Table 1. *Clinical examination of the menopausal vagina.*

Atrophic, smooth vaginal mucosa with hyperkeratotic areas
Vaginal and/or urethral meatal stenosis
Ecchymotic and telangiectatic areas of the vaginal mucosa

Table 2. *Menopausal vagino urinary symptoms.*

Vaginal dryness Dyspareunia Vaginal burning Vaginal pain Itching Post-coital spotting Urinary symptoms	Urgency Dysuria Frequency Burning

Table 3. *Genitourinary complications in menopause.*

Vaginitis
Cystitis
Haematuria
Colporrhagia

occur, and the stroma becomes infiltrated by lymphocytes and plasma cells. The connective tissue appears dense and fibrotic, the subepithelial elastic network is fragmented, and blood flow is reduced (**Figure 1**).

Clinically, the menopausal vagina presents an atrophic, smooth mucosa with hyperkeratotic areas, vaginal and/or urethral meatal stenosis, and often ecchymotictelangiectatic areas (**Table 1**). Initially, symptoms may be confined to the vagina (Menopausal Vaginal Syndrome: MVS), whereas in advanced menopause, the urinary tract may also be involved, potentially leading to severe complications and the Genitourinary Syndrome of Menopause (GSM) (**Tables 2** and **3**). Physiologically, in reproductive age, vaginal pH is 4-4.5: lactobacilli metabolize glucose to lactic acid, lowering vaginal pH and forming a primary barrier against pathogens [1-3]; in menopause, alkalinization often raises pH to ≥ 6.8 causing the onset of vaginal infections [1]. Estrogenic deficiency reduces cellular maturity, decreases glycogen production, lowers lactic acid formation, and thus alkalinizes the vaginal environment [1].

Acid pH (≤ 4-4.5) is important in the prevention of the infections [4, 5]. An important bioactive factor in the cervical-vaginal mucosa is lactoferrin with adjuvant function to lactobacilli [6].

In menopause, CST IV predominates (pH > 5), characterized by *Candidatus Lachnocurva vaginae*, *Gardnerella vaginalis*, *Atopobium vaginae*, Prevotella, *Streptococcus*, *Enterococcus*, *Bifidobacterium*, and *Staphylococcus*. A pH > 5 increases bacterial adhesion to the vaginal mucosa [1]. This predisposition leads to recurrent vaginal and genitourinary infections, affecting 28-40 % of women in advanced menopause (**Tables 2** and **3**) [7].

Topical estrogenic therapy (suppositories or creams) has yielded the best results in menopause. Absorption depends on the degree of vaginal atrophy, receptor integrity, and vehicle used, being greatest at treatment onset and with severe atrophy [8]. Topical estrogen is contraindicated in a history of endometrial or breast carcinoma and atypical endometrial hyperplasia.

Recently, restoration of vaginal trophism with good patient compliance has been achieved using oral ospemifene tablets and intravaginal prasterone suppositories. Ospemifene, a selective estrogen receptor modulator (SERM), stimulates vaginal estrogen receptors, combating atrophic symptoms [9, 10]. Prasterone (dehydroepiandrosterone) is an inactive steroid precursor converted locally into estrogens and androgens with selective action on the vaginal mucosa [11, 12]. Literature remains cautious regarding both agents in patients with gynaecological oncologic history [10, 12].

Among nonhormonal topical therapies, polycarbophil vaginal (PCV) gel, a highly adhesive polymer with strong buffering action, acidifies vaginal pH and rapidly alleviates symptoms of vaginal atrophy (dryness, pain, mucosal irritation) [13, 14].

Innovative physical therapies include fractional CO_2 laser and dynamic quadripolar radiofrequency, which alleviate GSM symptoms by promoting regeneration of epithelial and subepithelial vaginal tissues, improving vaginal trophism and MVS symptomatology [15].

Objective of the study

The purpose of the study is to evaluate the regression of MVS, after topical therapy with 2 g vaginal

suppositories based on "DuoLact-Evogold" whose active ingredients are: A. Lactoferrin, *Lactobacillus casei* and *acidophilus*, FOS (βFructoOligoSaccharides) and GOS (αGlucoOligoSaccharides); and B. Natural vitamin E and Extravirgin Olive Oil. The following parameters were considered:

- Attenuation or disappearance of symptomatology.
- Improvement of the clinical/structural vaginal picture.
- Satisfactory sexual life.
- Limitation of complications.

MATERIALS AND METHODS

The retrospective study took into consideration sixtythree patients with MVS attending the Lower Female Genital Tract Pathology Service at the Obstetrics and Gynaecology Unit of Città di Castello (PG) USL1 Umbria from January 1 to December 12, 2024.
Inclusion criteria were patients affected by MVS with the following symptoms: vaginal itching, vaginal burning, vaginal pain, dyspareunia, vaginal dryness, post-coital spotting.
Patients with the following pathologies were excluded from the study: urinary tract and cervical-vaginal infections, neoplastic lesions, positive PAP smear and/or HPV Test, genito-urinary prolapse.
Three patients were excluded from treatment: one with CIN 3, one with a urinary tract infection and genitourinary prolapse and one with Pap Test ASCH and positive HPV test.
The remaining 60 patients were treated with DuoLac-EvoGold 2 g suppositories.
The indications for topical treatment with 2 g "DuoLac-EvoGold" suppositories were as follows:

1. Vaginal menopausal symptomatology (vaginal dryness, dyspareunia, vaginal burning, vaginal itching, vaginal pain, postcoital spotting) (**Table 2**);
2. Severe dyspareunia and post-coital spotting: lubricating effect and adjuvant in the repair processes of the vaginal mucosa.
3. Restoration of vaginal trophism.
4. Vaginal atrophy in oncological patients undergoing chemotherapy and/or radiotherapy and/or oophorectomy with contraindications to the use of hormonal therapies.
5. Vaginal atrophy with contraindications to Hormone Replacement Therapy (HRT).

Patient age ranged from 50 to 80 years (mean 68.6 years). Obstetric history was as follows: 42 multiparous, 10 nulliparous, 8 with previous caesarean section. Gynaecological history included: three total laparohysterectomies with bilateral adnexectomy for uterine fibromatosis; three radical laparohysterectomies with bilateral adnexectomy plus chemo and radiotherapy (two for invasive endometrial carcinoma, one for invasive cervical carcinoma); one radical mastectomy with axillary lymphadenectomy plus chemo and radiotherapy for infiltrating mammary adenocarcinoma.
In the 53 patients without hysterectomy, colposcopy showed nonvisible SCJ T3, cervical mucosal atrophy, and normal transformation zone. All 60 underwent vaginoscopy to assess mucosal atrophy and ecchymotictelangiectatic areas. For colposcopy and vaginoscopy, performed at three time points with physiological solution, 3% acetic acid, and Lugol's iodine, was used a Zeiss 150 FC colposcope. Vulvology exam was normal in all. No patient had received HRT.
The mechanism of action for topical vaginal therapy with 2 g **"**DuoLac-EvoGold**"** suppositories in MVS is shown in **Table 4**.

Table 4. *The mechanism of action for topical vaginal therapy with 2 g "DuoLac-EvoGold" suppositories.*

DuoLact
Lactoferrin
Bacteriostatic and bactericidal effects
Interactions with lipoteichoic acid, LPS, and bacterial membranes
Inhibition of bacterial adhesion to host tissue
Promotion of biofilm formation
Suppression of TNF α and IL 6 expression
Lactobacillus casei
Produces lactic acid, fostering beneficial vaginal bacteria
Promotes growth of Lactobacillus acidophilus via amylase-media carbohydrate metabolism
Lactobacillus acidophilus
Adheres to vaginal epithelial cells, obstructing pathogen interaction
Bactericidal activity against *G. vaginalis, E. coli, A. vaginae, S. aureus*
Immunostimulatory effects
FOS (β fructooligosaccharides) & GOS (α gluco oligosaccharides)
Prebiotics that promote growth of lactobacilli and bifidobacteria, enhancing lactic acid synthesis in the vaginal microbiome
EvoGold
Vitamin E
Antioxidant properties; protects cell membranes from oxidative damage and supports cellular renewal
Extra virgin olive oil
Protective effect on vaginal mucosa via phenolic derivatives (reducing oxidative mechanisms, enhancing cell vitality, decreasing histological alterations)
Antitumoral and antibacterial effects
Upregulates genes involved in cellular differentiation

Table 5. *Clinical, vaginoscopic, and vaginal pH grading.*

Score	Clinical grading VNS (Verbal Numerical Scale)					
	Dryness	**Dyspareunia**	**Vaginal burning**	**Spontaneous pain**	**Itching**	**Postcoital spotting**
	Absent	Absent	Absent	Absent	Absent	Absent
0	< 3	< 3	< 3	< 3	< 3	< 3
1	3 – 7	3 – 7	3 – 7	3 – 7	3 – 7	3 – 7
2	> 7	> 7	> 7	> 7	> 7	> 7
3						
Score	**Vaginoscopic grading VAS (Visual Analogue Scale)**					
	Mucosal atrophy	**Vaginal and/or urethral stenosis**	**Ecchymotic teleangectatic areas**			
	Normal	Absent	Absent			
0	↓ 1/3	↓ 1/3	1/3			
1	↓ 2/3	↓ 2/3	1/3			
2	↓>2/3	↓ >2/3	>2/3			
3						
Score	**Vaginal pH grading VCS (Visual Colorimetric Scale)**					
0	4-4.5 (Normal)					
1	4.6 – 5.6 (Mild Abnormality)					
2	5.7 – 6.7 (Moderate Abnormality)					
3	> 6.8 (Severe Abnormality)					

Therapy

In the period from 1st January to 12th December 2024 the therapy involved the administration of one 2 g "DuoLact-EvoGold" suppository every evening to the 60 patients for 10 consecutive days; then a 15day suspension; then maintenance with one suppository every evening for 5 days. Evaluations at baseline (T0), after 10 days (T1°), and after 5 days of maintenance (T3°) included symptom assessment, vaginoscopy, vaginal pH, and sexual grading test (FSFI).

- Time 0 (T0): after vaginal symptom assessment, vaginoscopy, vaginal pH, FSFI begin with one suppository nightly for 10 nights.
- Time 1 (T1°): after 10 days, reevaluate vaginal pH, symptoms, vaginoscopy, FSFI.
- Time 2 (T2°): after 15 days off therapy, patient applied one suppository nightly for 5 nights.
- Time 3 (T3°): after 5 days of treatment, reevaluate vaginal pH, symptoms, vaginoscopy, FSFI.

The clinical records of patients with MVS included a detailed recent and past obstetric and gynaecological history, menstrual history, vaginoscopic, vulvological and colposcopic examinations and any previous use of hormonal therapies, vaginal symptoms, vaginoscopy with assessment of vaginal mucosal atrophy, vaginal and/or urethral stenosis and ecchymotic and teleangiectatic areas, vaginal pH and quality of sexual life were also notated.

The following tests were performed before the therapy: HPV test, Pap test, cervicalvaginal and urethral swabs, urine exam. The symptoms are "Graded" by Verbal Numerical Scale (VNS), vaginoscopic and pH findings by Visual Analogue Scale (VAS) and Visual Colorimetric Scale (VCS). Grading is associated with a specific score (0-1-2-3) (**Table 5**).

Clinical grading was evaluated according to the intensity of the symptom (0; < 3; 3-7; > 7) (VNS: Verbal Numerical Scale) to which the respective score was given (0-1-2-3); the symptoms considered were the following: vaginal dryness, dyspareunia, vaginal burning, vaginal pain, postcoital spotting.

For vaginoscopic grading the following parameters have been taken into consideration by means of VAS:

1. degree of vaginal mucosal atrophy by histological evaluation: absent; reduction of 1/3; reduction of 2/3; reduction > 2/3;

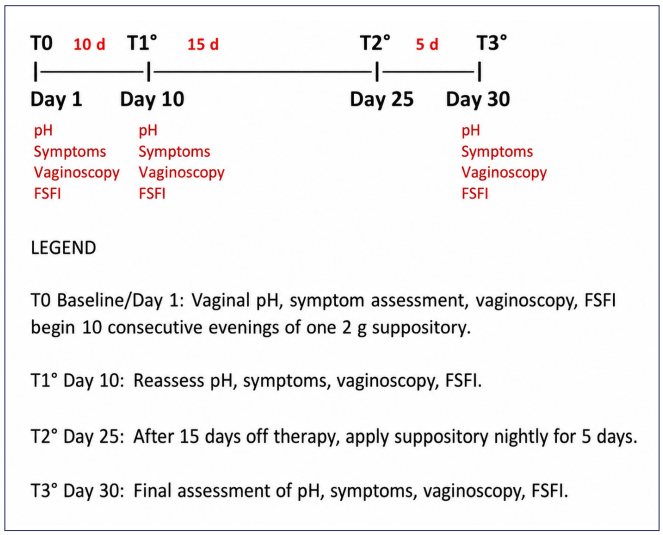

Figure 2. *Protocol.*

2. Vaginal and/or urethral meatus stenosis: absent; reduction of 1/3; reduction of 2/3; reduction > 2/3; vaginal stenosis: clinical evaluation; urethral stenosis: evaluation by cautious use of Hegar dilators - Ø 1-2-3 mm - for approximately 5 mm;
3. ecchymotic telangiectatic areas whose extension has been assessed (absent; 1/3, 2/3 and >2/3); visual assessment of the extension of the vaginal areas affected by menopausal ecchymosis/telangiectasia. Patients with uterus: examination of the ant-post-right/left side wall; Patients without uterus: examination of the ant-post-right/left side wall-vaginal dome divided into 4 quadrants.

For the vaginoscopic grading, the individual numerical evaluations were given a score of 0-1-2-3 in relation to the thickness of mucosal atrophy, diameter of vaginal stenosis and/or urethral meatus and the extent of ecchymotic-telangiectatic areas.
For the vaginal pH grading, the following parameters were considered in range using VCS: pH 4-4.5 (normal); pH 4.6-5.6 (mild abnormality); pH 5.7-6.7 (moderate abnormality); pH ≥ 6.8 (severe abnormality). For the Vaginal pH grading, the individual numerical evaluations were given a score (0-1-2-3).
The degree of sexual satisfaction was expressed with the Female Sexual Function Index (FSFI). The score has been obtained from 19 questions that investigate multiple aspects of sexual life: desire, excitement, lubrication, reaching orgasm, the degree of satisfaction and pain during sexual intercourse. Each answer to each single question expressed a score, the sum of these scores provided a result that went from 2 to 36: severe sexual disorder < 10; moderate sexual disorder from 11 to 17; mild sexual disorder from 18 to 26; normality > 26.
Follow-ups have been performed after 10 days of therapy (T1°) (symptomatology, vaginoscopy, vaginal pH, quality of sexual life) and at 30 days (T3°) (symptomatology, vaginoscopy, vaginal pH and quality of sexual life) after 5 days of therapy; 15 days of therapeutic suspension were planned from the 10th to the 25th day (**Figure 2**). At the end of the treatment, to evaluate the efficacy index of topical medical therapy, four parameters were considered (symptomatology, vaginoscopic examination, vaginal pH and quality of sexual life).
The retrospective study has also evaluated the complications that could arise during treatment.
The therapeutic efficacy index allowed to classify the VMS after therapy as "regressed", "improved" or "persistent".

RESULTS

The clinical, vaginoscopic, vaginal pH and FSFI parameters were evaluated at the 1st visit and start of therapy (T0), at 10 days of therapy (T1) and at 30 days (end of therapy) (T3) (**Tables 2** and **6**).
Table 6 summarizes in T0 (start of therapy – day 1) and T3° (end of therapy) the clinical grading expressed by VNS, the vaginoscopic grading by VAS and the vaginal pH grading by VCS.
For the evaluation of the "clinical grading", the VNS was used with the corresponding score. The following symptomatic parameters were considered: vaginal dryness, dyspareunia, vaginal burning, spontaneous vaginal pain, vaginal itching and postcoital spotting (**Tables 2** and **6**; **Figure 3**).
The "vaginal dryness" at T0 (1st visit) was present in 47 patients (78.3%) with a score of 3 (severe symptomatology) and in 13 (21.7%) with a score of 2 (moderate symptomatology); at T3 (end of therapy) in 47 patients (78%) there was a complete absence of the symptom (score 0).
The "dyspareunia" at T0 (1st visit) was present in 47 patients (78.3%) with a score of 3 (severe symptomatology) and in 13 (21.7%) with a score of 2 (moderate symptomatology); at T3 (end of therapy) in 45 patients (75.0%) there was a complete regression of the symptom (score 0).
The "vaginal burning" at T0 (1st visit) was present in 34 patients (56.6%) with a score of 2 (moderate symptomatology), in 13 (21.7%) a scores of 1 (mild symptomatology) and in 13 (21.7%) a score of 0 (absence of symptom) while at T3 47 patients (78.3%) had a score of 0 (complete absence of the symptom).
The "spontaneous vaginal pain" at T0 (1st visit) was present in 20 patients (33.3%) with a score of 2 (moderate symptomatology), in 7 (11.7%) a score of 1 (mild symptomatology), in 33 (55.0%) a score of 0 (absence of symptoms), while at T3 (end of therapy) 60 patients (100%) presented a score of 0 (complete absence of the symptom).
The "vaginal itching" at T0 (1st visit) was present in 27 patients (45.0%) with a score of 2 (moderate symptomatology), in 6 (10%) with a score of 1 (mild symptomatology), in 27 (45%) with a score of 0 (complete absence of the symptom) while at T3 (end of therapy), 40 patients (66.7%) had a score of 0 (complete absence of the symptom).
For "postcoital spotting" at T0 (1st visit) 27 patients (45%) presented a score of 3 (severe symptomatology), 13 (21.7%) a scores of 1 (mild symptomatology), 20 (33.3%) a scores of 0 (absence of symptoms)

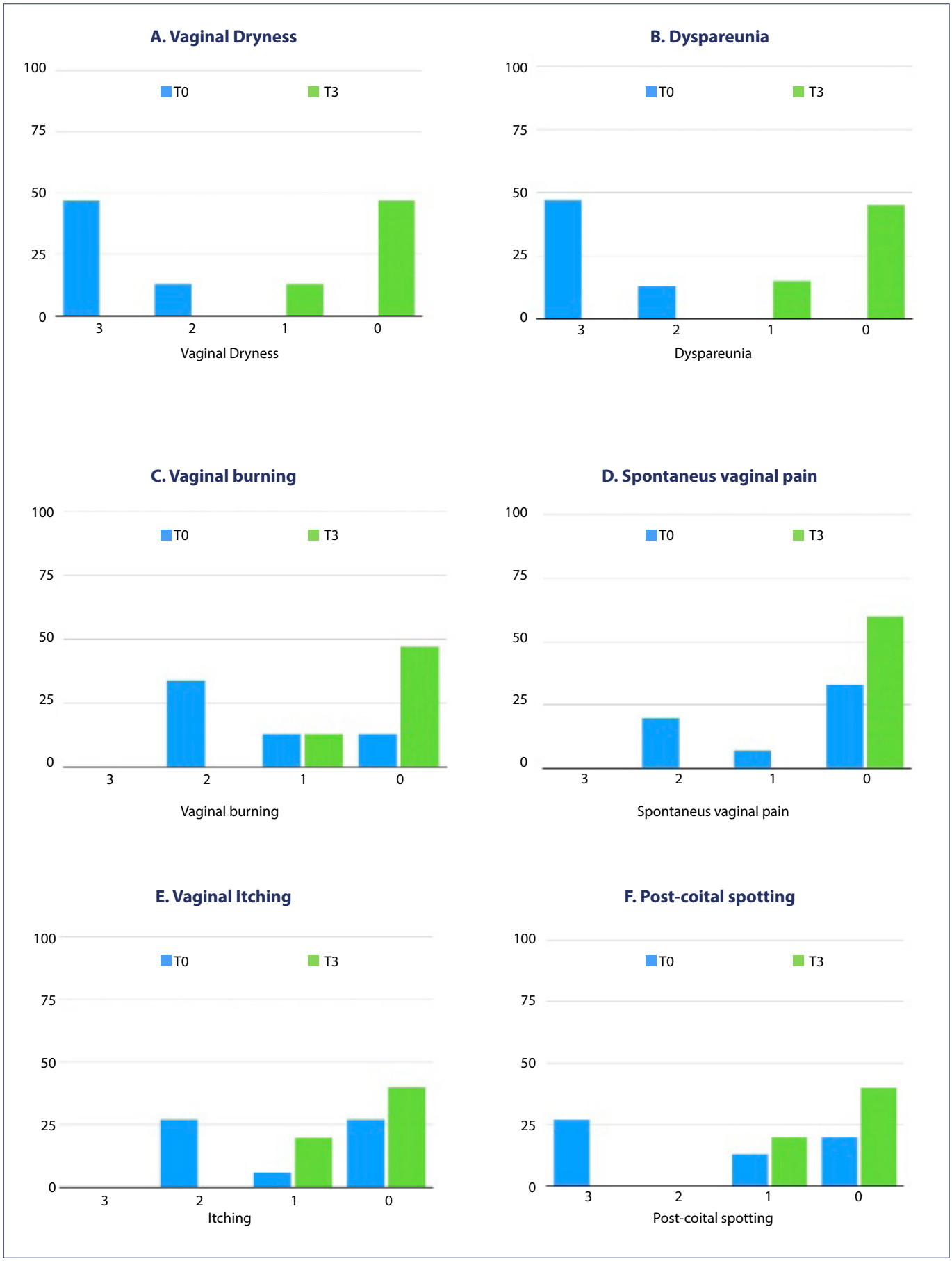

Figure 3. *Clinical grading (T0-T3).*

T0: Baseline; T3: end of the therapy

Table 6. *Clinical, vaginoscopic and vaginal pH grading, (T0 - T3°).*

Score	Clinical grading VNS (Verbal Numerical Scale)					
	Vaginal dryness		Dyspareunia		Vaginal burning	
	T0	T3°	T0	T3°	T0	T3°
0	--	47 (78%)	--	45 (75.0%)	13 (21.7%)	47 (78.3%)
1	--	13 (21.7%)	--	15 (25.0%)	13 (21.7%)	13 (21.7%)
2	13 (21.7%)	--	13 (21.7%)	--	34 (56.6%)	--
3	47 (78.3%)	--	47 (78.3%)	--	--	--
Score	**Clinical grading VNS (Verbal Numerical Scale)**					
	Spontaneous vaginal pain		Vaginal itching		Post-coital spotting	
	T0	T3°	T0	T3°	T0	T3°
0	33 (55.0%)	60 (100%)	27 (45.0%)	40(66.7%)	20 (33.3%)	40 (66.7%)
1	7 (11.7%)	--	6 (10.0%)	--	13 (21.7%)	20 (33.3%)
2	20 (33.3%)	--	27 (45.0%)	--	--	--
3	--	--	--		27 (45%)	--
Score	**Vaginoscopic grading VAS (Visual Analogue Scale)**					
	Mucosal atrophy		Vaginal and/or urethral stenosis		Ecchymotic telangiectatic areas	
	T0	T3°	T0	T3°	T0	T3°
0	--	--	7 (11.7%)	7 (11.7%)	3 (5.0%)	20 (33.3%)
1	13 (21.7%)	40 (66.7%)	20 (33.3%)	40 (66.7%)	7 (11.7%)	33 (55.0%)
2	27 (45.0%)	20 (33.3%)	20 (33.3%)	13 (21.6%)	7 (11.7%)	7 (11.7%)
3	20 (33.3%)	--	13 (21.7%)	--	43 (71.6%)	--
Score	**Vaginal pH grading VCS (Visual Colorimetric Scale)**					
	pH		T0		T3°	
0	4 - 4.5 (Normal)				53 (88.3%)	
1	4.6 – 5.6 (Mild)		7 (11.7%)		7 (11.7%)	
2	5.7 – 6.7 (Moderate)		6 (10.0%)		--	
3	≥ 6.8 (Severe)		47 (78.3%)		--	

T0: Baseline (Start of therapy - Day 1); T3°: Day 30 (End of the therapy) – See **Figure 2.**

while at T3 (end of therapy) 40 patients (66.7%) presented a score of 0 (complete absence of the symptom).

For the evaluation of the "vaginoscopic grading" the VAS was used with the corresponding score. The following parameters were considered: thickness of vaginal mucosal atrophy; diameter of vaginal and/or urethral stenosis; ecchymotic and/or telangiectatic areas whose extension was evaluated (**Table 6**, **Figure 4**).

The "vaginal mucosal atrophy" at T0 (first visit) was present in 20 patients (33.3%) with mucosal reduction > 2/3 (score 3) (severe atrophy), in 27 (45.0%) with mucosal reduction of 2/3 (score 2) (moderate atrophy), in 13 (21.7%) with mucosal reduction of 1/3 (score 1) (mild atrophy); no patients had normal mucosal trophism (score 0); at the end of therapy at T3 no complete absence of atrophy (score 0) nor persistence of severe atrophy (score 3) was observed at T3.

The "vaginal and/or urethral stenosis" at T0 (first visit) was present in 13 patients (21.7%) with score 3 (severe stenosis), in 20 (33.3%) with score 2 (moderate stenosis), in 20 (33.3%) with score 1 (mild stenosis) and in 7 (11.7%) with score 0 (absent stenosis); at T3 only in 7 patients (11.7%) the stenosis was regressed (score 0).

The "ecchymotic and/or telangiectatic areas" at T0 were present in 43 patients (71.6%) (area > 2/3) with score 3 (severe vaginoscopy), in 7 (11.7%) (area ≈ 2/3) with score 2 (moderate vaginoscopy), in 7 (11.7%) (area ≈ 1/3) with score 1 (mild vaginoscopy), in 3 (5%) (absence of ecchymotic and/or telangiectatic areas) with score 0; at T3 20 patients (33.3%) had score 0 (complete absence of ecchymotic and/or telangiectatic areas).

The "vaginal pH grading" was evaluated with VCS. At T0 (1st visit) 47 patients (78.3%) presented score 3 (severe pH abnormality), 6 (10%) score 2 (moderate pH abnormality), 7 (11.7%) score 1 (mild

Figure 4. *Vaginoscopic grading – vaginal pH grading – FSFI (T0-T3)*

T0: Baseline; T3: end of the therapy.

pH abnormality); no patients had normal pH; at T3 (end of therapy) 53 patients (88.3%) presented normal pH (score 0) (**Table 6**, **Figure 4**).
In **Table 7**, all clinical, vaginoscopic and vaginal pH parameters were evaluated at T0 (baseline visit), T1 (after 10 days of treatment) and T3 (day 30, after 5 days of retreatment).
The parameters related to sexual function were evaluated with the FSFI. From the graph, on the abscissa all patients treated with "DuoLact-Evo-Gold" are indicated while on the ordinate at T0 is shown the FSFI score obtained before therapy and at T3 the score at the end of therapy. A substantial improvement in the score is demonstrated in all patients. In some patients the "sexual satisfaction" index exceeds 26. A general increase in FSFI values from T0 (1st visit) to T3 (end of therapy) is observed, indicating an overall improvement in sexual function in the patients included in the study (**Figure 4**).

DISCUSSION

In menopause, with the progressive cessation of hormone production, the vaginal mucosa becomes atrophic, glycogenproducing epithelial cells disappear, lactobacilli are markedly reduced, and the vaginal environment presents a pH > 6.8. The vaginal microbiota is thus composed predominantly of a mixed bacterial flora of faecal origin that is potentially pathogenic, which increases the risk of genitourinary disorders [7].
The therapy for MVS includes a wide range of therapeutic options (**Table 8**).

Table 7. *Clinical, vaginoscopic and vaginal pH grading (T0 - T1° - T3°).*

Score	Clinical grading VNS (Verbal Numerical Scale)								
	Vaginal dryness			Dyspareunia			Vaginal burning		
	T0	T1°	T3°	T0	T1°	T3°	T0	T1°	T3°
0	--	--	47(78%)	--	--	45(75.0%)	13(21.7%)	20(33.3%)	47(78.3%)
1	--	13(21.7%)	13(21.7%)	--	13(21.7%)	15(25.0%)	13(21.7%)	20(33.3%)	13(21.7%)
2	13(21.7%)	47(78.3%)	--	13(21.7%)	47(78.3%)	-	34(56.6%)	20(33.3%)	--
3	47(78.3%)	--	--	47(78.3%)	--	--	--	--	--
Score	**Clinical grading VNS (Verbal Numerical Scale)**								
	Spontaneous pain			**Itching**			**Post-coital spotting**		
	T0	**T1°**	**T3°**	**T0**	**T1°**	**T3°**	**T0**	**T1°**	**T3°**
0	33(55.0%)	40(66.7%)	60(100%)	27(45.0%)	27(45.0.%)	40(66.7%)	20(33.3%)	20(33.3%) 27(45.0%)	40(66.7%)
1	7(11.7%)	13(21.7%)	--	6(10.0%) 27(45.0%)	20(33.3%) 13(21.7%)	--	13(21.7%)	13(21.7%)	20(33.3%)
2	20(33.3%)	7(11.6%)	--	--	--	--	--	--	--
3	--	--	--				27 (45%)		--
Score	**Vaginoscopic grading VAS (Visual Analogue Scale)**								
	Mucosal atrophy			**Vaginal and/or urethral stenosis**			**Ecchymotic telangiectatic areas**		
	T0	**T1°**	**T3°**	**T0**	**T1°**	**T3°**	**T0**	**T1°**	**T3°**
0	--	--	--	7(11.7%) 20(33.3%) 20(33.3%)	7(11.7%) 40(66.7%)	7(11.7%) 40(66.7%)	3(5.0%) 7(11.7%)	6 (10.0%) 27 45.0%)	20(33.3%) 33(55.0%)
1	13(21.7%)	40(66.7%)	40(66.7%)	13(21.7%)	13(21.6%)	13(21.6%)	7(11.7%)	27(45.0%)	7(11.7%)
2	27(45.0%)	20 (33.3%)	20(33.3%)		--	--	43(71.6%)	--	--
3	20(33.3%)	--	--						
Score	**Vaginal pH grading VCS (Visual Colorimetric Scale)**								
	pH			**T0**		**T1°**		**T3°**	
0	4 - 4.5 (Normal)					20(33.3%)		53(88,3%)	
1	4.6 – 5.6 (Mild)			7 (11.7%)		33 (55.0%)		7(11.7%)	
2	5.7 – 6.7 (Moderate)			6(10.0%)		7(11.7%)		--	
3	≥ 6.8 (Severe)			47(78.3%)		--		--	

T0: baseline (Day 1); T1°: Day 10; T2°: Day 25; T3°: Day 30 (End of the therapy) – See **Figure 2.**

Table 8. *Treatment options for menopausal vaginal syndrome (MVS).*

Hormonal therapy
Systemic hormone replacement (if indicated for other reasons): estrogens, estrogen–progestin, tibolone, TSEC
Vaginal estrogen therapy
Vaginal progesterone
SERMs
Ospemifene
Non-hormonal therapy
Non-hormonal lubricants, moisturizers, and emollients (*e.g.*, hyaluronic acid with lactic acid, calendula)
Topical hyaluronic acid
Hyaluronic acid with autologous platelet-rich plasma
Hyaluronic acid with high-concentration norm baric oxygen
Local bovine colostrum
Colostrum with visnadine and prenyl-flavonoids
Isoflavones
Polycarbophil vaginal gel (PCV)
Phisical therapies
Radiofrequency
Fractional CO_2 laser

It has been repeatedly demonstrated that topical hormonal treatments (estradiol, estriol, prasterone) are significantly superior to placebo for the improvement of GSM (genitourinary syndrome of menopause) and are nevertheless considered the "Gold Standard" for this syndrome [16, 17]. However, Scientific Society Guidelines indicate that nonhormonal, hydrating and lubricating products should be regarded as firstline treatment for GSM.

From a literature review of 136 studies meeting the search criteria, several medical and physical therapies were considered (vaginal dehydroepiandrosterone, ospemifene, policarbophilbased moisturizing cream, tibolone, vaginal hyaluronic acid, testosterone, and CO_2 laser therapy). All therapies improved the subjective and objective signs of atrophy. Except for hyaluronic acid, all therapies improved sexual function. The authors concluded that most nonestrogenic therapies are effective treatments for the various symptoms of menopausal vaginal syndrome (MVS) [18]. Estrogenic topical vaginal therapies achieve results in MVS comparable to nonhormonal ones (hyaluronic acid, policarbophil gel, CO_2 laser, etc.); hormonal therapies are contraindicated in patients with a positive oncological history of breast or endometrial cancer [19].

Vaginal hormonal therapies (estrogens – dehydroepiandrosterone) are safe and effective and improve the symptoms of MVS. Systemic hormonal therapy is less effective on vaginal atrophy symptomatology [8, 20].

Twentyfive primary studies on the treatment of MVS with ospemifene demonstrated a high clinical response to symptoms (vaginal dryness and dyspareunia), with a favourable safety profile and very few adverse events [10, 21-23].

Over the years, many nonhormonal treatments have been used in cases of menopausal vaginal syndrome associated with mucosal atrophy. The most frequently used "lubricating/emollient substances" consist of a combination of several active ingredients (hyaluronic acid for hydrating action, lactic acid to restore physiological vaginal pH, calendula for hydrating and emollient properties, a complex of naturalorigin functional substances with soothing and antiinflammatory properties such as Betula alba, Scrophularia nodosa, Aloe barbadensis).

In recent years, alternative physical and nonhormonal topical vaginal therapies have been proposed. Among the "physical therapies", fractional CO_2 laser [24-26], radiofrequency, and lipofilling have seen predominant use, with initially encouraging results. However, the pain associated with these physical procedures, their high costs, and the need for repeat interventions for recurrences are their major drawbacks. Recently, warnings from some American Scientific Societies regarding the risk of facilitating the progression of preneoplastic lesions have led to reduced use of CO_2 laser in cases of vaginal atrophy [27].

The use of "nonhormonal topical vaginal therapies" refers to the following substances: local hyaluronic acid; hyaluronic acid combined with autologous plateletrich plasma; hyaluronic acid combined with highconcentration norm baric oxygen; local colostrum; colostrum combined with visnadine and prenylflavonoids; isoflavones and PCV.

Hyaluronic acid is a natural polysaccharide present in large quantities in the extracellular matrix of the skin, cartilage, and submucosal connective structures. At the vaginal level it draws water by osmosis, ensuring adequate mucosal hydration.

In vitro studies on platelet cultures (PRP: Platelet Rich Plasma) or platelets with hyaluronic acid (PRPHA: Platelet Rich Plasma – Hyaluronic Acid) in autologous plasma on vaginal mucosa taken from surgical interventions for genital prolapse in postmenopausal women have shown an increase in the S and G2M phases of the cell cycle, confirming im-

proved cell proliferation, increased fibroblasts and collagen, and prevention of cellular senescence [28]. The use of hyaluronic acid combined with highconcentration norm baric oxygen in MVS has shown significant improvement in both patientreported subjective symptoms and the clinical picture of the vagina (elasticity and mucosal trophism). The greatest benefit concerns the reduction of vaginal dryness and the disappearance of dyspareunia. Oxygenation of the vaginal mucosa promotes mucosal regenerative activity [29, 30].

Numerous studies have been conducted on the topical vaginal use of bovine colostrum, considering various indices related to the clinical and morphological aspects of the vaginal mucosa: total and single Verbal Rating Scale (VRS), Maturation Index (MI), FSFI and Vaginal Health Index (VHI). Improvement was noted in all indices. However, in the presence of mucosal atrophy, colostrum predominantly reduces vaginal dryness, promotes trophism, and reduces dyspareunia. This effect persists for about one month and is supported by improvement of the vaginal environment [31, 32].

The efficacy of colostrum cream combined with visnadine and prenylflavonoids was also evaluated, showing significant improvements in various MVS parameters. Visnadine has a vasodilatory effect, ensuring improved vaginal blood flow and thus better hydration and lubrication. Prenylation of flavonoids may increase their bioactivity but decrease their bioavailability [33].

Retrospective literature surveys on the use and efficacy of isoflavones in MVS over three time periods (1996-2013 Medline, 1990-2013 Scopus, 2013-Cochrane Central Register) selected 7 studies on cellular maturation and 2 on vaginal dryness. Soy isoflavones appeared to improve vaginal symptoms *versus* control but were more effective in quantitative analysis, albeit not statistically significant. While soy isoflavones can improve menopausal vaginal symptoms, studies remain inconclusive due to vast heterogeneity [34].

The effects of phytoestrogens on urogenital menopausal symptoms were evaluated by a systematic review from 2000 to 2020 (PubMed, Embase, Web of Science, Cochrane Library, Scopus, ProQuest), selecting 33 articles. Various phytoestrogens were used: *Pueraria mirifica*, fennel, hops (*Humulus lupulus* L.), *Glycine max* (L.) *Merr*, soy, red clover, *Cimicifuga racemosa*, genistein, daidzein, glycitein, and isoflavones in various forms (oral capsules and tablets, dietary supplements, creams, gels, and vaginal suppositories). A nonsignificant symptomatic urogenital improvement was demonstrated, greater with vaginal use. The study's limitation is heterogeneity of active ingredients and modes of use [35].

A significant increase in blood vessels in the vaginal mucosa of postmenopausal women was observed after topical treatment with 4% *Glycine max* (L.) *Merr* isoflavone gel, ensuring good vaginal lubrication and improved dyspareunia [36].

Use of PCV gel in perimenopausal and postmenopausal women, administered twice weekly for 30 and 180 days, resulted in a reduction of VAS scores for vaginal dryness, irritation, and dyspareunia, improvement in VHI and reduction in GSS (Global Symptom Score). No side effects were reported. PCV administration for 30 days rapidly improves atrophy symptoms, and extending to 6 months further increases efficacy. No contraindications were reported [13]. A randomized prospective study in MVS compared moisturizing polycarbophil gel *versus* hyaluronic acid with overlapping results for vaginal dryness [37].

From the retrospective survey on the use of "Duo-Lac-EvoGold" suppositories, the most severe symptoms (score 3) at the first examination (T0) in women with MVS were vaginal dryness and dyspareunia in 47/60 (78.3%) and postcoital spotting in 27/60 (45%) (**Table 7**); at T3 complete absence of the symptom (score 0) was observed in 47/60 (78.3%), 45/60 (75,0%), and 40/60 (66.7%) respectively.

Vaginal burning, spontaneous pain, and itching were not severe at T0 but mild to moderate; at T3 absence of these symptoms was seen in 47/60 (78.3%), 60/60 (100%), and 40/60 (66.7%) respectively.

Vaginal mucosal atrophy, vaginal/urethral stenosis, and ecchymotictelangiectatic areas were severe (score 3) at T0 in 20/60 (33.3%), 13/60 (21.7%), and 43/60 (71.6%) respectively. At T3 no patient had severe ecchymotictelangiectatic areas and 20/60 (33.3%) had no altered vaginal areas (score 0); vaginal atrophy at T3 was moderate in 20/60 (33.3%) and mild in 40/60 (66.7%), with no severe or absent atrophy. Vaginal/urethral stenosis at T3 was mild-moderate in 53/60 (88.3%), unchanged without atrophy (score 0) and no patients with severe stenosis.

Vaginal pH at T0 was severely abnormal (pH > 6.8, score 3) in 47/60 (78.3%) and regressed to normal (4.0-4.5, score 0) in 53/60 (88.3%) at T3.

In the FSFI, the wide variability of individual scores visible in the graph may reflect different individual responses. Most T3 scores are higher than T0, suggesting the therapeutic path contributed positively

to multiple aspects of sexual function (desire, arousal, lubrication, orgasm, etc.). This improvement is attributable to reduction of menopausal physical discomforts (vaginal dryness, dyspareunia, vaginal burning) (**Figure 4**).

Of the 60 patients treated with "DuoLac-EvoGold", 36 (59.8%) showed complete clinical resolution of MVS, while 24 (40.2%) had mild–moderate persistence (improved MVS). No patients had severe persistence.

Normalization of vaginal pH is determined by *Lactobacillus casei* and *Lactobacillus acidophilus* reducing vaginal dryness and dyspareunia [38]. *L. casei* promotes growth of *L. acidophilus*, whose adhesion to vaginal epithelial cells hinders pathogen interaction with the mucosa. Lactoferrin also inhibits bacterial adhesion and has bactericidal effect [39]. Besides regression of MVS with reduction of its two main symptoms – vaginal dryness and dyspareunia – lactoferrin and lactobacilli casei and acidophilus reduce the risk of vaginal infections [1, 40]. In the Omicron Factor are Vitamin E and extravirgin olive oil. Vitamin E, besides antioxidant properties, protects cell membranes from oxidative damage and promotes renewal of vaginal mucosal cells. Extravirgin olive oil exerts a protective effect on vaginal mucosa via phenolic derivatives, reducing oxidative mechanisms and increasing cell vitality, thereby reducing histological alterations [41, 42]. Both Vitamin E and olive oil help reduce vaginal lesions responsible for postcoital spotting and partially reverse vaginal mucosal atrophy.

Preliminary findings may serve as justification for prospective, randomized comparative studies, including a control group, aimed at confirming efficacy, safety and long-term outcomes in a more standardized setting.

CONCLUSIONS

Although topical hormone therapy is considered the "Gold Standard" for improvement of MVS according to the most recent literature data, also nonhormonal therapies are effective treatments free from side effects and contraindication [9-11, 13, 15, 16, 18, 39, 43]; in particular local vaginal hydrating and lubricating therapies should be considered the "firstline treatment".

Topical treatment of MVS with "DuoLac-EvoGold" resulted in complete regression in approximately 60% and partial regression in 40% of cases. The symptomatology most frequently regressed, expressed by VNS score, was vaginal dryness (78.3%), dyspareunia (75%), vaginal burning (78.3%), and spontaneous pain (100%). Vaginal pH returned to normal (4-4.5) in approximately 90% of cases, reducing the risk of vaginal infections. The study of 60 MVS cases treated with "DuoLac-EvoGold" demonstrated improvement of postcoital spotting (66.7%) due to the reepithelializing effect of Vitamin E and the phenols of olive oil in improving mucosal atrophy. The mean trend of "sexual function" after therapy shows a growth trend which, in the context of this retrospective survey, indicates the efficacy of the adopted approach in improving sexual function. Unlike hormonal treatments, there are no contraindications to the use of "DuoLac-EvoGold" in patients with a positive history of endometrial or breast carcinoma.

Therefore, "DuoLac-EvoGold" is promising for the treatment of MVS both for symptom regression and for restoration of normal vaginal pH. It is a "nonhormonal topical vaginal therapy" free of side effects with good patient compliance in MVS. Furthermore, its use in MVS may represent an excellent prevention of GSM by reducing the risks of urethritis and cystitis in menopause.

Treatment showed symptomatic improvement in this limited cohort, but further prospective controlled studies are needed to confirm efficacy and safety.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions

A.B., M.T., L.A., D.R., G.C.DR.: Conceptualization, investigation, methodology, resources, software, visualization. A.B., M.T., L.A., D.R.: Data curation. A.B., G.C.DR.: Formal analysis. A.B., G.CD.R.: Project administration, supervision, validation, writing-original draft, writing – review & editing.

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None.

Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

The study was conducted retrospectively using data extracted from a full anonymized database. No identifiable patient-level data were accessed for the purposes of the analysis, and no additional intervention or patient contact was performed. The requirement for Ethics Committee review was assessed according to applicable local regulations and institutional policies. Patient's anonymity has been preserved in accordance with the Declaration of Helsinki.

Informed consent

All patients signed written informed consent, all are reported under explicit consent of the patients: patient's anonymity have been preserved in accordance with the Declaration of Helsinki.

Data sharing

Data are available under reasonable request to the corresponding author.

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