September 2026 - Vol. 38 - N. 3 - Quarterly - ISSN 2385 – 0868

Italian Journal of

Gynæcology & Obstetrics

The Official Journal of the Società Italiana di Ginecologia e Ostetricia (SIGO)

Quarterly

edra

Italian Journal
of

Gynæcology & Obstetrics

The Official Journal of the
Società Italiana di Ginecologia e Ostetricia
(SIGO)

Quarterly

edra

Table of contents

Italian Journal of
Gynæcology & Obstetrics
September 2026 - Vol. 38 - N. 3 - Quarterly - ISSN 2385 – 0868

Sentinel lymph node mapping in endometrial cancer: new insights into an essential tool

Francesco **Sgalambro** [1], Stefano **Di Michele** [2,*], Santo **Di Stefano** [1], Giulia **Trupia** [1], Giuseppe **Sarpietro** [1], Saverio **Tateo** [3], Basilio **Pecorino** [4], Benito **Chiofalo** [4], Giuseppe **Scibilia** [5]

[1] Department of General Surgery and Medical-Surgical Specialty, Gynecology and Obstetrics Unit, Rodolico University Hospital, University of Catania, Catania, Italy.
[2] Division of Gynecology and Obstetrics, Department of Surgical Sciences, University of Cagliari, Cagliari, Italy.
[3] Department of Obstetrics and Gynecology, Centre Hospitalier de Troyes, Troyes, France.
[4] Department of Medicine and Surgery, Kore University of Enna, Enna, Italy.
[5] Department of Gynecology and Obstetrics, Giovanni Paolo II Hospital, ASP 7, Ragusa, Italy.

ARTICLE INFO

History
Received: 29 April 2025
Received in revised form: 12 June 2025
Accepted: 24 July 2025
Available online: 10 September 2026

DOI: 10.36129/jog.2025.241

Key words
Sentinel lymph node; endometrial cancer; minimally invasive surgical procedures.

***Corresponding author:** Stefano **Di Michele**, M.D. Department of Surgical Sciences, University of Cagliari, via Università 40, 09124 Cagliari, Italy.
Email: dr.dimichelestefano@gmail.com.
ORCID: 0009-0005-9644-7919.

ABSTRACT

Objective. This narrative review summarizes current evidence on sentinel lymph-node (SLN) mapping in endometrial cancer (EC), focusing on tracer performance, injection techniques, detection rates (DR), surgical approaches, and ultrastaging. A comprehensive search of PubMed, Embase, and the Cochrane Library was performed (inception – 15 April 2025) using the terms "sentinel lymph node" AND "endometrial cancer", without year limits. Studies, guidelines, and technical reports addressing SLN mapping in EC were screened, and data were extracted narratively according to SANRA recommendations.

Results. Three tracer classes are routinely used: indocyanine green (ICG), technetium-99m colloid, and methylene blue. Cervical ICG injection, performed superficially and deeply at 3 and 9 o'clock or in four quadrants, provides the highest bilateral detection rate (DR; approximately 93-98%), with intraoperative re-injection increasing DR by about 5%. Hysteroscopic and trans-myometrial routes improve para-aortic mapping but are technically more demanding and achieve lower pelvic DRs. Combining ICG with technetium or methylene blue offers no consistent benefit over ICG alone. Minimally invasive surgery maintains high DRs (91-95%) while reducing postoperative morbidity compared with laparotomy. Serial-section ultrastaging with cytokeratin immunohistochemistry detects an additional 3-4% of micrometastases or isolated tumour cells compared with routine haematoxylin-eosin assessment.

Conclusions. SLN biopsy provides an accurate nodal assessment while sparing patients the morbidity associated with systematic lymphadenectomy. Cervical ICG injection, coupled with minimally invasive surgery and meticulous ultrastaging, currently represents the most effective and reproducible strategy for SLN mapping in EC.

INTRODUCTION

Endometrial cancer (EC) is the most common gynaecologic malignancy in high-income countries, and its incidence continues to rise worldwide [1].
Most women present early with abnormal uterine bleeding; a small proportion remain asymptomatic, and some rare gynaecologic tumours that mimic EC may instead present late with non-specific signs and an elevated thrombo-embolic risk [2-5]. If neglected, it may lead to severe anaemia requiring blood transfusion or iron supplementation [6].
Beyond classical risk factors, dysbiosis of the gut microbiome is emerging as a potentially modifiable contributor to EC pathogenesis [7].
The primary treatment for EC involves surgical intervention, typically comprising a total hysterectomy and bilateral salpingo-oophorectomy, accompanied by minimal lymphadenectomy [8].
Minimally invasive surgery, including conventional laparoscopy, single-site access, and robotics, achieves oncologic equivalence with less morbidity in early-stage disease [9-11], allowing for successful lymph node sampling [12, 13].
In advanced EC, multivisceral cytoreduction may require bowel resection [14] or ureteral reimplantation [15], similar to the surgical approach used in other advanced multiorgan involvement gynaecological diseases, such as endometriosis [16-21].
Because nodal metastasis is detected in only ~4% of apparent stage-I cases, current guidelines permit omission of systematic lymphadenectomy in low-risk disease [22, 23].
Nonetheless, nodal status remains critical for adjuvant-therapy decisions, and sentinel lymph-node (SLN) mapping has replaced complete lymphadenectomy in many centres, lowering rates of lower-limb lymphoedema [24, 25]. The most widely used SLN mapping algorithm is the Memorial Sloan Katterin algorithm [26].
Attention is now shifting to survivorship: fatigue, insomnia, and overall quality-of-life decrements are common after EC surgery [27, 28]. In other gynaecological cancers, such as advanced cervical carcinoma, neoadjuvant chemotherapy after surgery has been applied, although with poor results [29]. In EC, the gold standard, when possible, is radical surgery followed by adjuvant therapy, which can be chemotherapy, radiotherapy, or a combination of these [22].
Similarly, the accurate identification of hysteroscopic criteria underscores the importance of precise diagnostic techniques in managing gynaecological pathologies [30]. This precision in the diagnostic approach mirrors sentinel lymph node mapping for endometrial carcinoma, where correctly identifying lymph nodes is crucial. Such meticulous nodal mapping can significantly influence therapeutic decisions and surgical staging strategies, demonstrating the vital role of accuracy in improving patient outcomes across gynaecological oncology.
Recently, TCGA-based molecular subgroups (POLE-mutated, MMR-deficient, p53-abnormal, NSMP) are likely to individualize the need for nodal assessment in EC. This is because these subgroups have distinct clinical and prognostic implications that can guide treatment decisions, including the necessity for lymph node dissection [31].
This narrative review critically appraises contemporary evidence on SLN mapping in EC, with emphasis on tracer choice, injection technique, detection rate (DR), surgical performance, and ultrastaging.

MATERIALS AND METHODS

This article is a narrative review of the existing literature on the types of tracers used for SLN biopsy in EC. It specifically examines the effectiveness of different tracers, analysing their impact on DR, including the method of injection, surgical techniques, and subsequent outcomes when employing ultra-staging protocols.
An extensive literature search was conducted on PubMed, Embase, and the Cochrane Library from inception to April 15, 2025. Articles were searched using the keywords “sentinel lymph node and endometrial cancer”. No filter on the year of publication was applied.
For this review, we considered any human investigation that examined SLN mapping in EC. To be eligible, a study had to focus on one or more elements of the SLN pathway, such as the tracer employed, the site or technique of injection, the diagnostic or bilateral detection rate, the histopathological ultrastaging protocol, or subsequent surgical and oncological outcomes (recurrence-free or overall survival). We accepted a wide range of study designs, including randomised or non-randomised clinical trials, prospective or retrospective cohort studies, case-control series, larger case series, systematic reviews or meta-analyses, and guidelines or consensus papers from relevant societies.
Conversely, we excluded articles that dealt exclusively with systematic lymphadenectomy and offe-

red no SLN component, or that combined EC with other tumour sites without providing separable results, were also omitted. The selected articles were thoroughly reviewed and evaluated to identify studies that aligned with the goals of this review. The narrative review was assessed according to SANRA guidelines [32].

TRACERS AND INJECTION TECHNIQUE: METHOD OF INJECTION FOR A SINGLE TRACER

In EC, tracers used for SLN biopsy can be categorized into three types: colorimetric, radio-nuclear, and near-infrared dyes. Indocyanine green (ICG) is used as a near-infrared tracer; Technetium colloid 99 (99mTc) serves as the radio-nuclear tracer; and methylene blue (MB) is employed as the colorimetric tracer [33] that enables the visualization of the lymphatic vessel path [34].

Types of tracers and method of injection for SNL biopsy: advantages and disadvantages

- ICG is a tricarbocyanine dye that emits a fluorescent signal within the near-infrared (NIR) light range. It is FDA-approved for vascular and hepatobiliary imaging, although it is commonly used off-label for lymphatic mapping [35]. The pharmacokinetics of ICG show a consistent volume of distribution closely matching that of plasma, with minimal tissue binding and a negligible fraction of unbound molecules in the blood [36]. However, ICG binds significantly to plasma proteins, particularly alpha-lipoproteins, which restricts its extravascular distribution but does not impede its clearance. The elimination of ICG involves active hepatic uptake and subsequent biliary excretion, leading to its appearance in the feces, which turn green. The dye's half-life ranges from 2.2 to 3 minutes in healthy adults [37]. The primary advantages of ICG include its capacity for real-time lymphatic mapping, non-radioactivity, reduced risk of allergic reactions, and the feasibility of completing the procedure in a single surgical stage. The main limitation is the necessity for specialized NIR imaging equipment [38]. Despite its low risk of anaphylaxis (1/42,000), ICG should be avoided in patients with severe iodine allergies or liver failure [37]. Several ICG tracer studies for SNL biopsy in EC describe the cervical injection route [12]. The injection is made in the cervix indifferently at 3 o'clock and 9 o'clock deep and superficial or in the four quadrants of the uterine cervix [37, 39]. Different dilutions of ICG with sterile injectable solutions are proposed. Usually, 25 mg of ICG is diluted in 20 mL of sterile injectable solution or 25 mg of ICG in 10 mL [37]. A substantial portion of the literature describes the use of ICG via the hysteroscopic injection route, targeting both the subendoemetrial area around the tumour and the four quadrants of the uterus, tailored according to the lesion's extent [40]. Moreover, while cervical ICG injection yields a higher SLN DR than hysteroscopic endometrial injection in EC patients [41], reinjecting ICG during the surgical procedure can significantly enhance the DR. This strategy aims to improve SLN mapping accuracy and outcomes during surgery [42].
- Technetium colloid 99 (99mTc) is a metastable nuclear isomer used in SLN detection via nuclear imaging and intraoperative gamma counters. Its property to emit gamma rays with suitable photon energy and a short biological half-life minimizes radiation exposure while allowing timely scanning [43]. These properties make the isotope appropriate only for diagnostic applications, not for therapeutic interventions. A gamma-detecting probe identifies areas with "hot" tracer signals during surgery. Once the general region of elevated uptake is localized, the surgeon employs dissection techniques to visually locate the blue (or green) dyes within the area showing increased gamma signal activity [44]. The gamma-detecting probe is then used to quantify the signal strength of the resected SLN. It is one of the original techniques of SLN mapping utilized in managing other cancers, such as breast and vulvar cancer. The advantage of radiolabeled isotopes is their ability to penetrate deeply into tissue, which can benefit patients with EC, where lymphatic drainage can be unpredictable and nodal basins may contain fat [45]. Disadvantages include the need for a separate injection procedure in nuclear medicine, which means the intervention must be performed with a different medical team and at a different time [46]. Radiocolloid injections for EC SLN biopsy are administered hysteroscopically or via the cervical route [47]. Typically, the hysteroscopic method is performed a day before the surgical intervention, targeting the subendometrial layer both around the tumour and across the four quadrants of

the uterus. Conversely, cervical injections occur at the classical landmarks of 3 and 9 o'clock or throughout the four quadrants of the uterine cervix [43]. While literature extensively documents hysteroscopy and cervical injections of technetium-99m (Tc99m), only a few studies discuss the use of TUMIR, applying Tc99m via ultrasound to inject both the anterior and posterior parts of the myometrium for EC SLN biopsy [48].

- Methylene blue (MB), an aromatic heterocyclic organic compound, is a cost-effective alternative for SNL biopsy. Though not FDA-approved, it is often used off-label, showing equivalence to isosulfan blue in other cancers [33]. MB reaches lymph nodes within five minutes post-injection and stains them within twenty-one minutes. While economical and straightforward to administer, MB carries risks of paradoxical methemoglobinemia and serotonin syndrome, especially in patients on serotonergic medications, and is contraindicated in individuals with favism [49,50]. The MB colorimetric dye injections use various routes, including cervical, hysteroscopic, and uterine subserosal and combinations of trans-cervical and trans-uterine methods [49]. Typically, MB cervical injections are administered into the four quadrants of the cervix [51]. Hysteroscopically, MB is injected into the four walls of the uterus and/or around any isolated tumours or skip lesions [34]. While MB injections via hysteroscopy and the cervical route are generally performed pre-operatively, uterine subserosal MB injections are conducted intraoperatively. Specifically, MB is injected into eight subserosal sites during abdominal surgery: the most superior parts of the anterior and posterior midlines of the fundus, the anterior and posterior midparts of the uterus, the anterior and posterior lower parts of the uterus, and at both cornual ends. Additionally, injections are made into the cervicosubserosal myometrium at the 12, 3, 6, and 9 o'clock positions, often combining subserosal and cervicosubserosal approaches [52].

The diverse applications and combinations of these tracers, ICG, 99mTc, and MB, illustrate their varied utility in clinical studies, offering distinct benefits and challenges in sentinel lymph node mapping for EC.

Tracer injection site in EC

Injection sites for sentinel lymph node (SLN) biopsy in EC are typically cervical or uterine [27]. The tracer is directly inoculated into the cervix using a needle [28]. Options for uterine injections include hysteroscopic-guided administration, transvaginal ultrasound-guided myometrial injection of the radiotracer (TUMIR), or through trans-subserosal abdominal surgery [5, 48, 52-57]. Obesity, a well-established risk factor for EC, has been shown to disrupt lymphatic architecture, thereby potentially affecting lymphatic drainage and the accuracy of sentinel lymph node mapping [58]. Moreover, conditions such as polycystic ovary syndrome (PCOS), which are characterized by hormonal imbalances and metabolic dysregulation, may further compound these alterations in lymphatic function [59]. These metabolic and endocrine factors not only increase the incidence of EC but might also influence the pattern of lymphatic spread, underscoring the need for early, tailored diagnostic and staging strategies [60] in affected patients [61-63] (**Table 1**).

Tracer injection methods: pros and cons

Cervical injection has become the most favoured technique, as it is simple and yields the highest rates of SLN detection. It is good practice to inject the tracer slowly into the submucosa or superficial cervical stroma to maximize lymphatic absorption and minimize staining of deep pelvic tissues [56]. Mounting evidence suggests that cervical injection preserves the accuracy of detection of pelvic metastatic disease that may result from the confluence of lymphatic pathways from different regions of the uterus exiting the cervix through the lateral parameters [57]. The uterus has three lymphatic drainage pathways: the upper paracervical pathway, which is the classical pelvic pathway; the lower paracervical pathway; and the pelvic-infundibulum pathway. Some para-aortic lymph nodes are likely reached only through lymphatics with deep injections via this latter route. However, the accuracy of para-aortic mapping has not been thoroughly studied or documented [55].

Differently, the hysteroscopy method of injection for SNL biopsy in EC has been investigated in several studies [64]; particularly, the subserosal uterine fundus [65], myometrium [66], and subendometrial layer have been explored with injection both around the tumour if the lesion is localized and in the four walls of the uterus. Hysteroscopic injection offers superior lymphatic mapping at the lumbar aortic level, although the technique can be challenging, particularly in EC patients where normal anatomy may be altered [55]. Numerous retro-

Table 1. *Summary overview of tracer and injection site.*

Tracer	Injection Site	Method of Injection	Advantages	Disadvantages
ICG	Cervix	Slow injection into the submucosa or superficial cervical stroma in the four quadrants of the cervix or at 3 and 9 o'clock.	Easy procedure; accurate detection of pelvic lymph nodes; possibility of re-injection during surgery.	Less detection of lymphatic drainage from the uterine parameters.
ICG	Uterus (hysteroscopy-guided)	Subendometrial injection around the tumour and in the four quadrants of the uterus.	Enhanced lymphatic mapping at the lumbar aortic level.	Technique complexity, especially in patients with altered anatomy due to endometrial cancer.
99mTc	Cervix	Injection at classic landmarks at 3 and 9 o'clock or in the four quadrants of the uterine cervix.	High detection rate of SNL biopsy as a single tracer without reinjection.	Procedure must be performed a day before the surgical intervention.
99mTc	Uterus (hysteroscopy-guided)	Injection around the tumour and the four quadrants of the uterus.	Improved lymphatic mapping at the lumbar aortic level.	Procedure must be performed a day before the surgical intervention.
99mTc	TUMIR	Ultrasound-guided injection into the anterior and posterior parts of the myometrium.	Enhances the ability to perform para-aortic SNL biopsy.	Multidisciplinary approach required; anaesthesia necessary; potential for complications such as transabdominal lesions.
MB	Cervix	Injection into the four quadrants of the uterine cervix.	Inexpensive and readily available.	Risks of paradoxical methemoglobinemia and serotonin syndrome, particularly in patients on serotonergic psychiatric medications; contraindicated in patients with G6PD deficiency.
MB	Uterus (hysteroscopy-guided)	Injection around the tumour and the four quadrants of the uterus before surgery.	Higher detection rate than cervical injection.	Injection performed pre-operatively.
MB	Uterine subserosal	Injection at eight uterine subserosal sites or at the cervicosubserosal myometrium at four sites (12, 3, 6, and 9 o'clock positions).	Injection performed during surgery.	Lacks a specific injection site; technique variability.

ICG: Indocyanine Green; MB: Methylene Blue; 99mTc: Technetium-99m; DR: Detection Rate.

spective studies and reviews have also established hysteroscopy as the gold standard for examining the endometrium [67]. This surgical approach has a wide range of applications. It is especially effective for treating benign conditions like intrauterine adhesions [47], submucosal uterine fibroids [53], or genitourinary syndrome [68], which can significantly impact a patient's quality of life and sexual function. The importance of addressing these conditions extends beyond immediate symptom relief, as they often affect intimate aspects of life, underscoring the need for innovative treatments that consider overall well-being, fertility, and sexual health [69, 70]. Hysteroscopy also serves as a valuable surveillance tool for patient groups such as breast cancer survivors, offering a potentially helpful predictive model based on hysteroscopic findings [5].

Additionally, another method for uterine injection is the TUMIR [48]. This procedure is conducted by a gynaecologist ultrasound specialist in collaboration with a nuclear medicine physician and involves the transabdominal injection of the radiotracer into the anterior myometrium [48]. Leading scientific societies recognize TUMIR injection for intermediate/high-risk EC due to its enhanced ability for SNL biopsy in para-aortic dissection [71]. While TUMIR injection offers significant advantages, it also presents drawbacks, such as the need for anaesthesia, the involvement of multiple specialists, and potential complications like transabdominal lesions during the injection process [48].

Moreover, in preventive care for EC, particularly among postmenopausal women, hysteroscopic sampling is often the preferred method for endometrial biopsy [54] even in the presence of severe adhesiolysis that hardens the endoscopic procedures [72, 73]. This offers new insights into interventions on social media platforms, which reflect contemporary practices and patient engagement trends addressing the importance of increasing prevention [74, 75]. Ultimately, office hysteroscopy enables prompt diagnosis and, in selected cases, treatment of intrauterine pathology before further surgical procedures, generally without the need for anaesthesia. Its feasibility relies on standardized minimally invasive techniques, although procedural pain remains an important determinant of

patient tolerance and successful completion, and the optimal pain-management strategy has yet to be established [76-79].

DR OF SNL BIOPSY

The SNL biopsy targets the uterine lymphatic drainage system's initial lymph node or nodes [80]. The DR evaluates the success of the SNL biopsy, measuring the procedure's ability to unilaterally or bilaterally identify lymph nodes positive for metastases [51]. Current research on SLN mapping in EC is highly encouraging [47]. If the SLN is not detected, the surgeon must perform a systematic lymphadenectomy. Additionally, even if the SLN is identified, any visibly enlarged lymph nodes must be excised [26]. On one hand, the DR is influenced by the surgeon's expertise and meticulous attention to technical details. On the other hand, the DR of an SLN biopsy can be affected by various factors, including the type of tracer used, the injection site, surgical techniques, and the anatomopathological analysis protocol [26] (**Table 2**).

DR related to the type of tracers and the method of injection

In many studies of SNL biopsy in EC, MB is used either as a single dye or in combination with radiocolloid [47]. Studies comparing hysteroscopic to cervical injection of MB alone have shown a higher unilateral DR for hysteroscopic MB injections [49]. Conversely, when MB is combined with radiocolloids, cervical injections are more prevalent than hysteroscopic injections [55]. While several studies report no significant difference in DR sensitivity between radiocolloid MB99m cervical injections and hysteroscopic or TUMIR injections [40, 48], it is crucial to note that TUMIR injections have shown high DRs in patients with high-risk EC but significantly lower DRs in early-risk EC patients [48]. Furthermore, ICG, whether used alone or in combination and injected into the cervix, has demonstrated the most effective pelvic SNL biopsy success [81]. Re-injection of ICG during surgery has been shown to increase DR, achieving a peak of 98% significantly [82]. The simplicity of performing cervical ICG injections, their reproducibility, low cost, minimal adverse reactions, and the feasibility of re-injection during surgery have led to a consensus in the literature that cervical injection of ICG is the most successful method for detecting SNL in EC [83].

DR related to surgical technique

Among the key factors in SLN mapping is the execution technique. SLN biopsy in EC can utilize invasive methods like laparotomy and minimally invasive techniques such as laparoscopy, robotic surgery, single-port, or multi-site approaches [84, 85]. The benefits of minimally invasive techniques over laparotomy include reduced postoperative pain, better cosmetic outcomes, quicker recovery, and decreased risk of surgical dehiscence [9]. Ad-

Table 2. *Overview of DR related to SLN biopsy technique.*

Tracer	Injection Method	Detection Rate (DR)	Advantages	Disadvantages
MB	Cervical	High	Cost-effective, simple to administer.	Risk of methemoglobinemia, serotonin syndrome in some cases.
MB	Hysteroscopic	Lower than cervical	Allows targeted injection close to tumour.	Higher complexity, risk of methemoglobinemia.
MB+99mTc	Cervical	Unspecified	Enhanced tissue penetration due to radiocolloid combination.	Requires nuclear medicine facilities, potential radiation exposure.
ICG	Cervical	Up to 98%	High detection rate, real-time mapping, minimal side effects.	Requires specialized NIR imaging equipment.
ICG	Hysteroscopic	Lower than cervical	Detailed mapping close to tumour.	Requires specialized equipment, more complex procedure.
99mTc	Hysteroscopic	High DR	Deep tissue penetration, precise localization.	Requires separate nuclear medicine procedure, radiation exposure.
99mTc	Cervical	Unspecified	Allows for timely scanning and localization.	Requires nuclear medicine capabilities, radiation exposure.
99mTc	TUMIR	Lower in early-risk EC	Enhanced ability for para-aortic dissection in high-risk EC.	Involves anaesthesia, higher complexity, requires multiple specialists.

ICG: Indocyanine Green; MB: Methylene Blue; 99mTc: Technetium-99m; TUMIR: Transvaginal Ultrasound-guided Myometrial Injection of Radiotracer.

ditionally, these techniques mitigate complications associated with auxiliary ports and shorten surgical times, particularly in single-site laparoscopy, which is considered the gold standard for adnexal pathologies and requires further evaluation for its feasibility in lymphadenectomy or SLN biopsy [83, 86-88]. However, non-invasive surgical techniques are related to a greater surgical complexity and learning curve [89] except for the hysterectomy via vaginal natural orifice transluminal endoscopic surgery (vNOTES) which has shown to have a less learning curve [87, 90]. Laparotomy remains a method for SLN biopsy in EC, especially when using 99mTc for myometrium and/or subserosal injections, with DR ranging from 61% to 93% [91]. Adding MB dye to laparotomy does not significantly alter the DR, which remains between 63% and 89% [55, 92]. Literature indicates that non-invasive surgical techniques are widely employed for SLN biopsy in early-stage EC, whether using single tracers, dyes, or radiocolloids. These techniques are preferred because laparoscopic and robotic optics incorporate infrared systems tailored for ICG, providing significant advantages with a simple switch [93]. The DR for SLN biopsy using ICG and 99mTc through non-invasive methods like laparoscopy or robotic surgery has been investigated both with the infrared tracer alone and in combination with 99mTc, showing no significant differences in DR, which typically remains between 91% and 95% [94]. Non-invasive techniques using ICG alone achieve a nearly unilateral DR ranging from 91% to 98%, whether in laparoscopy or robotic surgeries [95]. It is crucial to emphasize that higher DRs are obtained through non-invasive surgical performance and ICG reinjection during the surgical procedure [96].

DR related to ultrastaging

Ultra-staging enhances the detection of malignant cells in lymph nodes removed during surgeries for EC. This process involves advanced techniques such as deeper serial sectioning and immunohistochemical (IHC) staining to uncover tumour cells that are not visible with routine Hematoxylin and Eosin (H&E) staining [97]. The protocol for the pathological processing of SLNs varies among institutions, including the number of sections examined, the depth of sectioning within the tissue block, the distance in μm between sections, and the incorporation of IHC. Typically, a non-sentinel lymph node examination involves a single H&E section along the node's long axis, with deeper levels or IHC applied at the pathologist's discretion [98]. A typical histological examination of a non-sentinel lymph node involves a single H&E section along the long axis of the lymph node (intact or bisected), with deeper levels or IHC performed at the pathologist's discretion [98]. The ultrasound examination for SLNs typically entails slicing along the long axis at 2 mm intervals, inspecting all slices under a microscope, and conducting at least one representative H&E level; additional H&E levels or IHC studies may be incorporated [88].

No universal guideline for the SLN ultra-staging protocol in EC exists, but several methods were proposed between 2011 and 2016:

- The Memorial Sloan Kettering (MSK) group suggests an initial routine H&E evaluation, followed by two adjacent 5 μm sections (one H&E and one AE1/AE3 cytokeratin) cut from each paraffin block at intervals of 50 μm [51, 88].
- The Touhami *et al.* group employs six serial sections cut at 40 μm intervals examined by H&E, with an additional section stained with IHC (AE1/AE3 cytokeratin) between the third and fourth levels [99].
- Desai *et al.* analysed SLNs by sectioning the block at 50 μm intervals, staining levels 1, 3, and 5 with H&E and levels 2 and 4 with AE1/AE3 [100].
- Raimond *et al.* prepared a cytological smear, sectioned it at 3 mm intervals, and further sectioned it at 200 μm intervals, with H&E-negative nodes undergoing AE1/AE3 staining [101].

The key benefit of immunohistochemical ultra-staging is its ability to detect an additional 3-4% of SLN micrometastases and isolated tumour cells (ITCs), the latter being less than 0.2 mm in diameter, which would be missed by routine H&E staining. The clinical relevance of ITCs is debated, but their identification highlights ultra-staging sensitivity [102].

Consequently, the DR is significantly improved in studies utilizing ultra-staging protocols, regardless of the tracer type or surgical technique employed [103].

DISCUSSION

There is now broad agreement that cervical ICG injection provides the most reliable and reprodu-

cible SLN mapping in apparent stage-I EC. Bilateral DR consistently exceed 90%, false-negative rates are < 5%, and the procedure virtually eliminates lower-limb lymphoedema when compared with systematic lymphadenectomy. Minimally invasive approaches, including laparoscopy, robotics, and single-site surgery, do not compromise oncologic safety, provided that the SLN algorithm and ultrastaging are applied rigorously [104].

Survival evidence: what do the data really show?

Early prospective cohorts were underpowered for survival end-points, but recent multicentre series provide substantive long-term data.

The most extensive propensity-matched analysis to date utilized the Surveillance, Epidemiology, and End Results database (6019 SLN *vs* 6019 lymph node dissection group). Nahshon *et al.* found higher 1-year overall survival in the SLN group, an advantage limited to grade 1-2 endometrioid cancers, while survival was equivalent in high-grade tumours, indicating that SLN sampling does not compromise early survival across disease grades [105].

In a contemporary, multicentre Italian cohort restricted to high-intermediate/high-risk histotypes (n = 242; 60-month follow-up), sentinel mapping alone yielded disease-free and overall survival curves that were superimposable to those of complete nodal dissection, while halving the rates of lower-limb lymphoedema [106].

Taken together, these studies strongly suggest that, when performed correctly, SLN mapping does not compromise oncologic outcomes, even in patients with intermediate- and high-risk EC.

Persisting controversies

Regarding paraaortic mapping, hysteroscopic or TUMIR technetium injections improve lumbar-aortic detection, but they add logistical complexity and radiation exposure. Whether knowledge of para-aortic status alters adjuvant-therapy decisions or survival remains unproven [46, 48].

Retroperitoneal staging in EC has evolved from systematic para-aortic dissection to selective techniques such as TUMIR tracer injection, yet emphasises that robust survival data are still lacking [107].

Ultrastaging detects an additional 3-4% of micrometastases and isolated tumour cells; however, the prognostic significance of these findings and the need for intensified adjuvant therapy remain a topic of debate. Although both modern series included such patients, randomised evidence is lacking; ongoing trials should clarify whether SLN mapping alone suffices in serous, clear-cell, and carcinosarcoma subtypes (non-endometrioid, grade 3) [102, 103].

Quality of life and enhanced recovery

Patient-reported outcomes consistently favour SLN mapping owing to shorter hospital stay, quicker mobilisation and dramatically lower rates of chronic lymphoedema. Integration of Enhanced Recovery After Surgery (ERAS) programmes has further reduced fatigue and sleep disturbance during survivorship. These gains underscore the importance of balancing oncologic efficacy with functional outcomes [108].

Italian data on minimally invasive surgery in gynaecologic oncology confirm that laparoscopy combined with ERAS shortens median length of stay from 4 to 2 days in early-stage EC, without increasing readmissions [109].

Future directions

Emerging genomic data, exemplified by the four TCGA classes reviewed by Besharat *et al.* [110], are set to reshape nodal surgery in EC. POLE-ultramutated tumours, which carry an excellent prognosis, may safely forgo any nodal assessment, whereas p53-abnormal (copy-number-high) cancers could still justify systematic para-aortic dissection and intensified adjuvant therapy. Machine-learning models that combine radiomic features with these molecular fingerprints are being explored to pre-operatively assign patients to either sentinel-node mapping or complete lymphadenectomy. Definitive proof will come from the prospective randomised trials now comparing cervical ICG-guided SLN biopsy with conventional lymphadenectomy in high-risk cohorts. These trials are crucial for validating a genomically tailored surgical strategy.

CONCLUSIONS

Recent revisions of the FIGO system illustrate how EC staging has shifted from a purely anatomical, uterus-confined framework [111] to an integrated model that now weighs extra-uterine spread, molecular subtype, host immunocompetence, and nodal status (FIGO 2023). This broader perspective has re-framed surgical staging: rather than removing every pelvic and para-aortic node, the current goal is to obtain the correct nodal information with the least morbidity [112].

Evidence remains mixed. Some series still report a survival benefit for systematic lymphadenectomy in biologically aggressive tumours. In contrast, others demonstrate that, in low-risk disease, where nodal positivity is as low as 0-4% and seldom exceeds 10% even in intermediate-risk cases, the additional risks of comprehensive dissection outweigh any oncologic gain [113]. Against this backdrop, sentinel-node biopsy offers a logical compromise: it targets the first echelon nodes that truly determine stage, maintains the false-negative rate within accepted limits, and simultaneously curtails lymphoedema, operative time, hospital stay, and antibiotic use [114]. Technical refinements have made the approach increasingly robust. Superficial and deep cervical injections of ICG remain the most reproducible route, achieving near-universal pelvic mapping [37]. When combined with robotic or laparoscopic optics capable of near-infrared imaging, and, when required, a second intra-operative ICG injection, detection rates routinely exceed 95s% [115].

Finally, meticulous ultra-staging with serial sectioning and immunohistochemistry uncovers a further 3-4% of micrometastases or isolated tumour cells, safeguarding diagnostic accuracy without resorting to blanket lymphadenectomy [51].

In summary, contemporary data support a paradigm in which sentinel-node mapping, performed with cervical ICG and comprehensive ultra-staging, should be the default strategy for nodal evaluation across most risk groups. Systematic lymphadenectomy is increasingly reserved for selected p53-abnormal or grossly node-positive cases, a shift that aligns surgical ambition with molecular risk and patient-centred outcomes.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

F.S.: Conceptualization, project administration, writing – original draft. S.D.M.: Writing – review & editing, supervision. S.D.S, G.T.: Visualization. G.S.: Investigation, methodology. S.T.: Conceptualization. B.P.: Data curation. B.C., G.S.: Supervision.

Funding

None.

Study registration

N/A.

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.

REFERENCES

1. Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. Lancet. 2022;399(10333):1412-1428. doi:10.1016/S0140-6736(22)00323-3.
2. Mereu L, Tateo S, Klersy C, Martinotti Gabellotti E, Polatti F. Stratification of venous thromboembolism risk in ovarian cancer patients during chemotherapy. Int J Gynecol Cancer. 2009;19(1):79-83. doi:10.1111/IGJ.0b013e318199035e.
3. Tateo S, Mereu L, Salamano S, et al. Ovarian cancer and venous thromboembolic risk. Gynecol Oncol. 2005;99(1):119-125. doi:10.1016/j.ygyno.2005.05.009.
4. Ferrara M, Pecorino B, D'Agate MG, Angelico G, Capoluongo ED, Malapelle U, et al. Uterine Tumours Resembling Ovarian Sex-Cord Tumors: A Case Report and Review of the Literature. J Clin Med. 2023;12:7131. doi:10.3390/jcm12227131.
5. Vitale SG, Angioni S, D'Alterio MN, et al. Risk of endometrial malignancy in women treated for breast cancer: the BLUSH prediction model - evidence from a comprehensive multicentric retrospective cohort study. Climacteric. 2024;27(5):482-488. doi:10.1080/13697137.2024.2376189.
6. Vitale SG, Fiore M, La Rosa VL, Rapisarda AMC, Mazza G, Paratore M, et al. Liposomal ferric pyrophosphate and ascorbic acid supplementation in pregnant women with iron deficiency anaemia: haematochemical, obstetric, neonatal and psychological outcomes in a prospective observational study. Int J Food Sci Nutr. 2022;73:221-9. doi:10.1080/09637486.2021.1950129.
7. D'Alterio MN, Giuliani C, Scicchitano F, Laganà AS, Oltolina NM, Sorrentino F, et al. Possible role of microbiome in the pathogenesis of endo-

metriosis. Minerva Obstet Gynecol 2021;73:193-214. doi:10.23736/S2724-606X.21.04788-2.
8. Tinelli R, Cicinelli E, Tinelli A, Bettocchi S, Angioni S, Litta P. Laparoscopic treatment of early-stage endometrial cancer with and without uterine manipulator: Our experience and review of literature. Surg Oncol. 2016;25:98-103. doi:10.1016/j.suronc.2016.03.005.
9. Mereu L, Dalprà F, Tateo S. Laparoendoscopic Single Site Hysterectomy: Literature Review and Procedure Description. J Clin Med. 2021;10(10):2073. doi:10.3390/jcm10102073.
10. Liliana M, Alessandro P, Giada C, Luca M. Single-port access laparoscopic hysterectomy: a new dimension of minimally invasive surgery. J Gynecol Endosc Surg. 2011;2:11-7. doi:10.4103/0974-1216.85273.
11. Mereu L, Angioni S, Melis GB, Mencaglia L. Single access laparoscopy for adnexal pathologies using a novel reusable port and curved instruments. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet. 2010;109:78-80. doi:10.1016/j.ijgo.2009.11.012.
12. Mereu L, Berlanda V, Surico D, et al. Evaluation of quality of life, body image and surgical outcomes of robotic total laparoscopic hysterectomy and sentinel lymph node mapping in low-risk endometrial cancer patients - A Robotic Gyne Club study. Acta Obstet Gynecol Scand. 2020;99(9):1238-1245. doi:10.1111/aogs.13844.
13. Tateo S, Nozza A, Del Pezzo C, Mereu L. Robotic single-site pelvic lymphadenectomy. Gynecol Oncol. 2014;134:631. doi:10.1016/j.ygyno.2014.06.027.
14. Mereu L, Ruffo G, Landi S, Barbieri F, Zaccoletti R, Fiaccavento A, et al. Laparoscopic treatment of deep endometriosis with segmental colorectal resection: short-term morbidity. J Minim Invasive Gynecol. 2007;14:463-9. doi:10.1016/j.jmig.2007.02.008.
15. Mereu L, Gagliardi ML, Clarizia R, Mainardi P, Landi S, Minelli L. Laparoscopic management of ureteral endometriosis in case of moderate-severe hydroureteronephrosis. Fertil Steril. 2010;93:46-51. doi:10.1016/j.fertnstert.2008.09.076.
16. Landi S, Pontrelli G, Surico D, et al. Laparoscopic disk resection for bowel endometriosis using a circular stapler and a new endoscopic method to control postoperative bleeding from the stapler line. J Am Coll Surg. 2008;207(2):205-209. doi:10.1016/j.jamcollsurg.2008.02.037.
17. Mereu L, Ruffo G, Landi S, et al. Laparoscopic treatment of deep endometriosis with segmental colorectal resection: short-term morbidity. J Minim Invasive Gynecol. 2007;14(4):463-469. doi:10.1016/j.jmig.2007.02.008.
18. Di Michele S, Bramante S, Angioni S, Bernassola M, De Vita T, Iaccarino DA, et al. Superficial Peritoneal Endometriosis Vaporization Using a CO2 Laser: A Long-Term Single-Center Experience. J Clin Med. 2024;13:1722. doi:10.3390/jcm13061722.
19. Di Michele S, Bramante S, Rosati M. A Systematic Review of Ureteral Reimplantation Techniques in Endometriosis: Laparoscopic Versus Robotic-Assisted Approach. J Clin Med. 2024;13:5677. doi:10.3390/jcm13195677.
20. Mereu L, Florio P, Carri G, Pontis A, Petraglia F, Mencaglia L. Clinical outcomes associated with surgical treatment of endometrioma coupled with resection of the posterior broad ligament. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet. 2012;116:57-60. doi:10.1016/j.ijgo.2011.08.017.
21. Daniilidis A, Angioni S, Di Michele S, Dinas K, Gkrozou F, D'Alterio MN. Deep Endometriosis and Infertility: What Is the Impact of Surgery? J Clin Med. 2022;11:6727. doi:10.3390/jcm11226727.
22. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up. Radiother Oncol. 2015;117(3):559-581. doi:10.1016/j.radonc.2015.11.013.
23. Barlin JN, Zhou Q, St Clair CM, et al. Classification and regression tree (CART) analysis of endometrial carcinoma: Seeing the forest for the trees. Gynecol Oncol. 2013;130(3):452-456. doi:10.1016/j.ygyno.2013.06.009.
24. Rovira R, Mereu L, Planchamp F, Falconer H, El-Balat A, Barahona M, et al. ESGE/ESGO/SERGS consensus statement on surgical steps in minimally invasive surgery in gynecologic oncology: transperitoneal and extraperitoneal approach for paraaortic lymphadenectomy. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc. 2024;34:1673-6. doi:10.1136/ijgc-2024-005796.
25. Della Corte L, Giampaolino P, Mercorio A, et al. Sentinel lymph node biopsy in endometrial cancer: state of the art. Transl Cancer Res. 2020;9(12):7725-7733. doi:10.21037/tcr.2020.04.21.
26. Abu-Rustum N, Yashar C, Arend R, et al. Uterine Neoplasms, Version 1.2023, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr

Canc Netw. 2023;21(2):181-209. doi:10.6004/jnccn.2023.0006.
27. Alexithymia in Women with Deep Endometriosis? A Pilot Study - Irene Melis, Mirian Agus, Nicola Pluchino, Attilio Di Spiezio Sardo, Pietro Litta, Gian Benedetto Melis, Stefano Angioni, 2014. Available at: https://journals.sagepub.com/doi/abs/10.5301/je.5000172. Accessed on March 19, 2025.
28. Nock NL, Dimitropoulos A, Zanotti KM, Waggoner S, Nagel C, Golubic M, et al. Sleep, quality of life, and depression in endometrial cancer survivors with obesity seeking weight loss. Support Care Cancer. 2020;28(5):2311-2319. doi:10.1007/s00520-019-05051-1.
29. Mereu L, Pecorino B, Ferrara M, Tomaselli V, Scibilia G, Scollo P. Neoadjuvant Chemotherapy plus Radical Surgery in Locally Advanced Cervical Cancer: Retrospective Single-Center Study. Cancers. 2023;15:5207. doi:10.3390/cancers15215207.
30. Riemma G, Parry JP, De Franciscis P, Carugno J, Lettieri D, Cobellis L, et al. Hysteroscopic Criteria for the Diagnosis of Chronic Endometritis: a Systematic Review and Diagnostic Test Accuracy Meta-analysis. Am J Obstet Gynecol. 2025:S0002-9378(25)00148-6. doi:10.1016/j.ajog.2025.03.005.
31. Yang Y, Wu SF, Bao W. Molecular subtypes of endometrial cancer: Implications for adjuvant treatment strategies. Int J Gynecol Obstet. 2024;164:436-59. doi:10.1002/ijgo.14969.
32. Baethge C, Goldbeck-Wood S, Mertens S. SANRA-a scale for the quality assessment of narrative review articles. Res Integr Peer Rev. 2019;4:5. doi:10.1186/s41073-019-0064-8.
33. Blessing WD, Stolier AJ, Teng SC, Bolton JS, Fuhrman GM. A comparison of methylene blue and lymphazurin in breast cancer sentinel node mapping. Am J Surg. 2002;184(4):341-345. doi:10.1016/s0002-9610(02)00948-0.
34. Holloway RW, Ahmad S, Kendrick JE, et al. A Prospective Cohort Study Comparing Colorimetric and Fluorescent Imaging for Sentinel Lymph Node Mapping in Endometrial Cancer. Ann Surg Oncol. 2017;24(7):1972-1979. doi:10.1245/s10434-017-5825-3.
35. Schaafsma BE, Mieog JS, Hutteman M, et al. The clinical use of indocyanine green as a near-infrared fluorescent contrast agent for image-guided oncologic surgery. J Surg Oncol. 2011;104(3):323-332. doi:10.1002/jso.21943.
36. Gioux S, Choi HS, Frangioni JV. Image-guided surgery using invisible near-infrared light: fundamentals of clinical translation. Mol Imaging. 2010;9(5):237-255..
37. Jewell EL, Huang JJ, Abu-Rustum NR, et al. Detection of sentinel lymph nodes in minimally invasive surgery using indocyanine green and near-infrared fluorescence imaging for uterine and cervical malignancies. Gynecol Oncol. 2014;133(2):274-277. doi:10.1016/j.ygyno.2014.02.028.
38. Imboden S, Mereu L, Siegenthaler F, et al. Oncological safety and perioperative morbidity in low-risk endometrial cancer with sentinel lymph-node dissection. Eur J Surg Oncol. 2019;45(9):1638-1643. doi:10.1016/j.ejso.2019.05.026.
39. Holloway RW, Bravo RA, Rakowski JA, et al. Detection of sentinel lymph nodes in patients with endometrial cancer undergoing robotic-assisted staging: a comparison of colorimetric and fluorescence imaging. Gynecol Oncol. 2012;126(1):25-29. doi:10.1016/j.ygyno.2012.04.009.
40. Perrone AM, Casadio P, Formelli G, et al. Cervical and hysteroscopic injection for identification of sentinel lymph node in endometrial cancer. Gynecol Oncol. 2008;111(1):62-67. doi:10.1016/j.ygyno.2008.05.032.
41. Rossi EC, Jackson A, Ivanova A, Boggess JF. Detection of sentinel nodes for endometrial cancer with robotic assisted fluorescence imaging: cervical versus hysteroscopic injection. Int J Gynecol Cancer. 2013;23(9):1704-1711. doi:10.1097/IGC.0b013e3182a616f6.
42. Papadia A, Buda A, Gasparri ML, et al. Correction to: The impact of different doses of indocyanine green on the sentinel lymph-node mapping in early stage endometrial cancer. J Cancer Res Clin Oncol. 2018;144(11):2193. doi:10.1007/s00432-018-2741-2.
43. Perissinotti A, Paredes P, Vidal-Sicart S, et al. Use of SPECT/CT for improved sentinel lymph node localization in endometrial cancer. Gynecol Oncol. 2013;129(1):42-48. doi:10.1016/j.ygyno.2013.01.022.
44. Pandit-Taskar N, Gemignani ML, Lyall A, Larson SM, Barakat RR, Abu Rustum NR. Single photon emission computed tomography SPECT-CT improves sentinel node detection and localization in cervical and uterine malignancy. Gynecol Oncol. 2010;117(1):59-64. doi:10.1016/j.ygyno.2009.12.021.

45. Levenback CF, Ali S, Coleman RL, et al. Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: a gynecologic oncology group study. J Clin Oncol. 2012;30(31):3786-3791. doi:10.1200/JCO.2011.41.2528.
46. Holloway RW, Abu-Rustum NR, Backes FJ, et al. Sentinel lymph node mapping and staging in endometrial cancer: A Society of Gynecologic Oncology literature review with consensus recommendations. Gynecol Oncol. 2017;146(2):405-415. doi:10.1016/j.ygyno.2017.05.027.
47. Ballester M, Dubernard G, Lécuru F, et al. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). Lancet Oncol. 2011;12(5):469-476. doi:10.1016/S1470-2045(11)70070-5.
48. Angeles MA, Migliorelli F, Vidal-Sicart S, et al. Paraaortic sentinel lymph node detection in intermediate and high-risk endometrial cancer by transvaginal ultrasound-guided myometrial injection of radiotracer (TUMIR). J Gynecol Oncol. 2021;32(4):e52. doi:10.3802/jgo.2021.32.e52.
49. El-Agwany AS, Meleis MH. Value and best way for detection of Sentinel lymph node in early stage endometrial cancer: Selective lymphadenectomy algorithm. Eur J Obstet Gynecol Reprod Biol. 2018;225:35-39. doi:10.1016/j.ejogrb.2018.03.042.
50. Albo D, Wayne JD, Hunt KK, et al. Anaphylactic reactions to isosulfan blue dye during sentinel lymph node biopsy for breast cancer. Am J Surg. 2001;182(4):393-398. doi:10.1016/s0002-9610(01)00734-6.
51. Barlin JN, Khoury-Collado F, Kim CH, et al. The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: beyond removal of blue nodes. Gynecol Oncol. 2012;125(3):531-535. doi:10.1016/j.ygyno.2012.02.021.
52. Meleis Mahmoud E, El-Agwany Ahmed S. Sentinel lymph node detection in clinical stage I endometrial cancer by cervical and subserosal myometrial blue dye labeling. Evidence Based Women's Health J. 2015;5(4):202-206. doi:10.1097/01.EBX.0000471724.19386.84.
53. Vitale SG, Moore O, Riemma G, Carugno J, Yarto ML, Haimovich S. Hysteroscopic laser ablation of symptomatic uterine fibroids: insights from a prospective study. Climacteric. 2023;26(5):497-502. doi:10.1080/13697137.2023.2205581.
54. Vitale SG, Laganà AS, Caruso S, et al. Comparison of three biopsy forceps for hysteroscopic endometrial biopsy in postmenopausal patients (HYGREB-1): A multicenter, single-blind randomized clinical trial. Int J Gynaecol Obstet. 2021;155(3):425-432. doi:10.1002/ijgo.13669.
55. Niikura H, Kaiho-Sakuma M, Tokunaga H, et al. Tracer injection sites and combinations for sentinel lymph node detection in patients with endometrial cancer. Gynecol Oncol. 2013;131(2):299-303. doi:10.1016/j.ygyno.2013.08.018.
56. Abu-Rustum NR, Khoury-Collado F, Pandit-Taskar N, et al. Sentinel lymph node mapping for grade 1 endometrial cancer: is it the answer to the surgical staging dilemma?. Gynecol Oncol. 2009;113(2):163-169. doi:10.1016/j.ygyno.2009.01.003.
57. Rossi EC, Kowalski LD, Scalici J, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 2017;18(3):384-392. doi:10.1016/S1470-2045(17)30068-2.
58. Nitti MD, Hespe GE, Kataru RP, García Nores GD, Savetsky IL, Torrisi JS, et al. Obesity-induced lymphatic dysfunction is reversible with weight loss. J Physiol. 2016;594:7073-87. doi:10.1113/JP273061.
59. Di Michele S, Fulghesu AM, Pittui E, Cordella M, Sicilia G, Mandurino G, et al. Ultrasound Assessment in Polycystic Ovary Syndrome Diagnosis: From Origins to Future Perspectives—A Comprehensive Review. Biomedicines. 2025;13:453. doi:10.3390/biomedicines13020453.
60. Ali D-E-S, Shah M, Ali A, Malik MO, Rehman F, Badshah H, et al. Treatment with Metformin and Combination of Metformin Plus Pioglitazone on Serum Levels of IL-6 and IL-8 in Polycystic Ovary Syndrome: A Randomized Clinical Trial. Horm Metab Res Horm Stoffwechselforschung Horm Metab. 2019;51:714-22. doi:10.1055/a-1018-9606.
61. Fulghesu AM, Di Michele S, Zangaris I, Cordella M, Pittui E, Scalise G, et al. Clinical and Ultrasound Features of Normocyclic Non-Hyperandrogenic Adolescents in Early Gynecological Life. Gynecol Obstet Invest. 2024:1-13. doi:10.1159/000542393.
62. Kataru RP, Park HJ, Baik JE, Li C, Shin J, Mehrara BJ. Regulation of Lymphatic Function in Obesity. Front Physiol. 2020;11:459. doi:10.3389/fphys.2020.00459.

63. Vitale SG, Di Michele S, Tassi A, Succu C, Angioni S, Fulghesu AM. Sustained Metabolic Improvements with Low-Dose Metformin Combined with Oral Contraceptives in Female Adolescents with PCOS: A Single-Center Retrospective Cohort Study. Adv Ther. 2025. doi:10.1007/s12325-025-03251-2.
64. Mücke J, Klapdor R, Schneider M, et al. Isthmocervical labelling and SPECT/CT for optimized sentinel detection in endometrial cancer: technique, experience and results. Gynecol Oncol. 2014;134(2):287-292. doi:10.1016/j.ygyno.2014.05.001.
65. Burke TW, Levenback C, Tornos C, Morris M, Wharton JT, Gershenson DM. Intraabdominal lymphatic mapping to direct selective pelvic and paraaortic lymphadenectomy in women with high-risk endometrial cancer: results of a pilot study. Gynecol Oncol. 1996;62(2):169-173. doi:10.1006/gyno.1996.0211.
66. Holub Z, Jabor A, Kliment L. Comparison of two procedures for sentinel lymph node detection in patients with endometrial cancer: a pilot study. Eur J Gynaecol Oncol. 2002;23(1):53-57.
67. Luerti M, Vitagliano A, Di Spiezio Sardo A, Angioni S, Garuti G, De Angelis C, et al. Effectiveness of Hysteroscopic Techniques for Endometrial Polyp Removal: The Italian Multicenter Trial. J Minim Invasive Gynecol. 2019;26:1169-76. doi:10.1016/j.jmig.2018.12.002.
68. Vitale SG, Saponara S, Succu AG, Sicilia G, Martsidis K, D'Alterio MN, et al. Efficacy and Safety of Non-Ablative Dual Wavelength Diode Laser Therapy for Genitourinary Syndrome of Menopause: A Single-Center Prospective Study. Adv Ther. 2024;41:4617-27. doi:10.1007/s12325-024-03004-7.
69. Vitale SG, Caruso S, Rapisarda AMC, Valenti G, Rossetti D, Cianci S, et al. Biocompatible porcine dermis graft to treat severe cystocele: impact on quality of life and sexuality. Arch Gynecol Obstet. 2016;293:125-31. doi:10.1007/s00404-015-3820-0.
70. Vitale SG, Parry JP, Carugno J, Cholkeri-Singh A, Della Corte L, Cianci S, et al. Surgical and Reproductive Outcomes after Hysteroscopic Removal of Retained Products of Conception: A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 2021;28:204-17. doi:10.1016/j.jmig.2020.10.028.
71. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. Int J Gynecol Cancer. 2016;26(1):2-30. doi:10.1097/IGC.0000000000000609.
72. Urman B, Yakin K, Ertas S, Alper E, Aksakal E, Riemma G, et al. Fertility and anatomical outcomes following hysteroscopic adhesiolysis: An 11-year retrospective cohort study to validate a new classification system for intrauterine adhesions (Urman-Vitale Classification System). Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet. 2024;165:644-54. doi:10.1002/ijgo.15262.
73. Vitale SG, Riemma G, Carugno J, Perez-Medina T, Alonso Pacheco L, Haimovich S, et al. Postsurgical barrier strategies to avoid the recurrence of intrauterine adhesion formation after hysteroscopic adhesiolysis: a network meta-analysis of randomized controlled trials. Am J Obstet Gynecol. 2022;226:487-498.e8. doi:10.1016/j.ajog.2021.09.015.
74. Vitale SG, Angioni S, Saponara S, Sicilia G, Mignacca A, Caiazzo A, et al. Hysteroscopic metroplasty and its reproductive impact among the social networks: A cross-sectional analysis on video quality, reliability and creators' opinions on YouTube, TikTok and Instagram. Int J Med Inf. 2024;195:105776. doi:10.1016/j.ijmedinf.2024.105776.
75. Vitale SG, Angioni S, Saponara S, Sicilia G, Etrusco A, D'Alterio MN, et al. TikTok as a platform for hysteroscopy information: An analytical video-based cross-sectional study to assess quality, reliability, and accuracy. Int J Gynecol Obstet.;n/a. doi:10.1002/ijgo.15846.
76. Chiofalo B, Palmara V, Vilos GA, Pacheco LA, Lasmar RB, Shawki O, et al. Reproductive outcomes of infertile women undergoing "see and treat" office hysteroscopy: a retrospective observational study. Minim Invasive Ther Allied Technol MITAT Off J Soc Minim Invasive Ther. 2021;30:147-53. doi:10.1080/13645706.2019.1705352.
77. Vitale SG, Di Spiezio Sardo A, Riemma G, De Franciscis P, Alonso Pacheco L, Carugno J. In-office hysteroscopic removal of retained or fragmented intrauterine device without anesthesia: a cross-sectional analysis of an international survey. Updat Surg. 2022;74:1079-85. doi:10.1007/s13304-022-01246-0.
78. Vitale SG, Laganà AS, Török P, Lasmar RB, Carugno J, Palumbo M, et al. Virtual sonographic hysteroscopy in assisted reproduction: A retrospective cost-effectiveness analysis. Int J Gyna-

ecol Obstet Off Organ Int Fed Gynaecol Obstet. 2022;156:112-8. doi:10.1002/ijgo.13651.
79. Loddo A, Di Michele S, D'Ancona G, Angioni S. Music and oral premedication for pain management during outpatient hysteroscopy: results from a randomised controlled trial. Facts Views Vis Obgyn. 2026 Jun 22;18(2):113-121. doi: 10.52054/FVVO.2026.343.
80. Delaloye JF, Pampallona S, Chardonnens E, et al. Intraoperative lymphatic mapping and sentinel node biopsy using hysteroscopy in patients with endometrial cancer. Gynecol Oncol. 2007;106(1):89-93. doi:10.1016/j.ygyno.2007.03.003.
81. Tanner EJ, Sinno AK, Stone RL, Levinson KL, Long KC, Fader AN. Factors associated with successful bilateral sentinel lymph node mapping in endometrial cancer. Gynecol Oncol. 2015;138(3):542-547. doi:10.1016/j.ygyno.2015.06.024.
82. Maramai M, Achilarre MT, Aloisi A, et al. Cervical re-injection of indocyanine green to improve sentinel lymph node detection in endometrial cancer. Gynecol Oncol. 2021;162(1):38-42. doi:10.1016/j.ygyno.2021.04.026.
83. Kang S, Yoo HJ, Hwang JH, Lim MC, Seo SS, Park SY. Sentinel lymph node biopsy in endometrial cancer: meta-analysis of 26 studies. Gynecol Oncol. 2011;123(3):522-527. doi:10.1016/j.ygyno.2011.08.034.
84. Gedgaudaite M, Sukovas A, Paskauskas S, et al. The Feasibility of Sentinel Lymph-Node, Mapped with Indocyanine Green, Biopsy in Endometrial Cancer Patients: A Prospective Study. Medicina (Kaunas). 2022;58(6):712. doi:10.3390/medicina58060712.
85. Maccauro M, Lucignani G, Aliberti G, et al. Sentinel lymph node detection following the hysteroscopic peritumoural injection of 99mTc-labelled albumin nanocolloid in endometrial cancer. Eur J Nucl Med Mol Imaging. 2005;32(5):569-574. doi:10.1007/s00259-004-1709-4.
86. Mereu L, Dalprà F, Berlanda V, et al. Anastomotic Leakage after Colorectal Surgery in Ovarian Cancer: Drainage, Stoma Utility and Risk Factors. Cancers (Basel). 2022;14(24):6243. doi:10.3390/cancers14246243.
87. Mereu L, Pecorino B, Ferrara M, et al. Cumulative Sum Analysis of Learning Curve Process for Vaginal Natural Orifice Transluminal Endoscopic Surgery Hysterectomy. J Minim Invasive Gynecol. 2023;30(7):582-586. doi:10.1016/j.jmig.2023.03.013.
88. Holloway RW, Gupta S, Stavitzski NM, et al. Sentinel lymph node mapping with staging lymphadenectomy for patients with endometrial cancer increases the detection of metastasis. Gynecol Oncol. 2016;141(2):206-210. doi:10.1016/j.ygyno.2016.02.018.
89. Barlin JN, Khoury-Collado F, Kim CH, et al. The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: beyond removal of blue nodes. Gynecol Oncol. 2012;125(3):531-535. doi:10.1016/j.ygyno.2012.02.021.
90. Scollo P, Pecorino B, Ferrara M, Mereu L. Uterosacral Ligament Suspension Sec Shull by Vaginal Natural Transluminal Endoscopic Surgery (vNOTES). J Obstet Gynaecol Can. 2022;44(6):703. doi:10.1016/j.jogc.2022.02.126.
91. El-Agwany AS, Meleis MH. Value and best way for detection of Sentinel lymph node in early stage endometrial cancer: Selective lymphadenectomy algorithm. Eur J Obstet Gynecol Reprod Biol. 2018;225:35-39. doi:10.1016/j.ejogrb.2018.03.042.
92. Frumovitz M, Bodurka DC, Broaddus RR, et al. Lymphatic mapping and sentinel node biopsy in women with high-risk endometrial cancer. Gynecol Oncol. 2007;104(1):100-103. doi:10.1016/j.ygyno.2006.07.033.
93. Imboden S, Mereu L, Siegenthaler F, et al. Oncological safety and perioperative morbidity in low-risk endometrial cancer with sentinel lymph-node dissection. Eur J Surg Oncol. 2019;45(9):1638-1643. doi:10.1016/j.ejso.2019.05.026.
94. Cabrera S, Bebia V, Franco-Camps S, et al. Technetium-99m-indocyanine green versus technetium-99m-methylene blue for sentinel lymph node biopsy in early-stage endometrial cancer. Int J Gynecol Cancer. 2020;30(3):311-317. doi:10.1136/ijgc-2019-000923.
95. Casarin J, Multinu F, Pasupathy K, et al. Frozen Section for Detection of Lymph Nodes After Cervical Injection with Indocyanine Green (ICG) for Sentinel Lymph Node Technique in Endometrial Cancer Staging. Ann Surg Oncol. 2018;25(12):3692-3698. doi:10.1245/s10434-018-6698-9.
96. Imboden S, Mereu L, Siegenthaler F, et al. Oncological safety and perioperative morbidity in low-risk endometrial cancer with sentinel lymph-node dissection. Eur J Surg Oncol. 2019;45(9):1638-1643. doi:10.1016/j.ejso.2019.05.026.
97. Cochran AJ. Prediction of outcome for patients with cutaneous melanoma. Pigment Cell Res.

1997;10(3):162-167. doi:10.1111/j.1600-0749.1997.tb00479.x.
98. Lester SC, Bose S, Chen YY, et al. Protocol for the examination of specimens from patients with invasive carcinoma of the breast. Arch Pathol Lab Med. 2009;133(10):1515-1538. doi:10.5858/133.10.1515.
99. Touhami O, Trinh XB, Gregoire J, et al. Predictors of non-sentinel lymph node (non-SLN) metastasis in patients with sentinel lymph node (SLN) metastasis in endometrial cancer. Gynecol Oncol. 2015;138(1):41-45. doi:10.1016/j.ygyno.2015.04.008.
100. Desai PH, Hughes P, Tobias DH, et al. Accuracy of robotic sentinel lymph node detection (RSLND) for patients with endometrial cancer (EC). Gynecol Oncol. 2014;135(2):196-200. doi:10.1016/j.ygyno.2014.08.032.
101. Raimond E, Ballester M, Hudry D, et al. Impact of sentinel lymph node biopsy on the therapeutic management of early-stage endometrial cancer: Results of a retrospective multicenter study. Gynecol Oncol. 2014;133(3):506-511. doi:10.1016/j.ygyno.2014.03.019.
102. Plante M, Stanleigh J, Renaud MC, Sebastianelli A, Grondin K, Grégoire J. Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: Does adjuvant treatment matter?. Gynecol Oncol. 2017;146(2):240-246. doi:10.1016/j.ygyno.2017.05.024.
103. Kim CH, Soslow RA, Park KJ, et al. Pathologic ultrastaging improves micrometastasis detection in sentinel lymph nodes during endometrial cancer staging. Int J Gynecol Cancer. 2013;23(5):964-970. doi:10.1097/IGC.0b013e3182954da8.
104. Bogani G, Giannini A, Vizza E, Di Donato V, Raspagliesi F. Sentinel node mapping in endometrial cancer. J Gynecol Oncol. 2024;35:e29. doi:10.3802/jgo.2024.35.e29.
105. Nahshon C, Kadan Y, Lavie O, Ostrovsky L, Segev Y. Sentinel lymph node sampling versus full lymphadenectomy in endometrial cancer: a SEER database analysis. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc. 2023;33:1557-63. doi:10.1136/ijgc-2023-004474.
106. Cuccu I, Raspagliesi F, Malzoni M, Vizza E, Papadia A, Donato VD, et al. Sentinel node mapping in high-intermediate and high-risk endometrial cancer: Analysis of 5-year oncologic outcomes. Eur J Surg Oncol. 2024;50. doi:10.1016/j.ejso.2024.108018.
107. Cuccu I, Sgamba L, Cannicchio A, De Angelis E, D'Augè TG, Di Bartolomeo G, et al. Evolution of retroperitoneal staging in endometrial cancer: narrative review and overview of literature. Ital J Gynaecol Obstet. 2023;35(2)168-175. doi:10.36129/jog.2023.105.
108. Ferrari F, Bizzarri N, Fagotti A, Scambia G, Gozzini E, Soleymani Majd H, et al. Early non-compliance to ERAS in gynecological open surgery for malignancies, and post-operative complications: a multicenter, prospective, observational, cohort study. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc. 2025:ijgc-2024-005648. doi:10.1136/ijgc-2024-005648.
109. Golia D'Auge T, De Angelis E, Cuccu I, Lagana AS, Etrusco A, Di Donato V, et al. Precision and progress: minimally invasive surgery in gynaecologic cancer treatment. Ital J Gynaecol Obstet. 2025;37(1):43-54. doi:10.36129/jog.2025.199.
110. Besharat AR, Giannini A, Caserta D. Pathogenesis and Treatments of Endometrial Carcinoma. Clin Exp Obstet Gynecol. 2023;50:229. doi:10.31083/j.ceog5011229.
111. Mikuta JJ. International federation of gynecology and obstetrics staging of endometrial cancer 1988. Cancer. 1993;71:1460-3. doi:10.1002/cncr.2820710409.
112. Berek JS, Matias-Guiu X, Creutzberg C, Fotopoulou C, Gaffney D, Kehoe S, et al. FIGO staging of endometrial cancer: 2023. Int J Gynaecol Obstet. 2023;162(2):383-394. doi: 10.1002/ijgo.14923.
113. Mary T, Kaylee U, Anze U, Katina R, Richard G M. Patient, disease and surgeon predictors of successful bilateral sentinel lymph node mapping for endometrial cancer: A retrospective, multicenter analysis. Clin J Obstet Gynecol. 2022;5:072-9. doi:10.29328/journal.cjog.1001111.
114. Cai T, Nesi G, Mazzoli S, et al. Asymptomatic bacteriuria treatment is associated with a higher prevalence of antibiotic resistant strains in women with urinary tract infections. Clin Infect Dis. 2015;61(11):1655-1661. doi:10.1093/cid/civ696.
115. Paley PJ, Veljovich DS, Press JZ, Isacson C, Pizer E, Shah C. A prospective investigation of fluorescence imaging to detect sentinel lymph nodes at robotic-assisted endometrial cancer staging. Am J Obstet Gynecol. 2016;215(1):117.e1-117.e1177. doi:10.1016/j.ajog.2015.12.046.

Italian Journal of
Gynæcology & Obstetrics
September 2026 - Vol. 38 - N. 3 - Quarterly - ISSN 2385 – 0868

Ultrasound assessment of foetal pancreatic circumference and gestational diabetes: a state-of-the-art of current evidence

Maria Cristina **Sangiovanni** *, Carlo **De Cicco Nardone**, Roberto **Montera**, Daniela **Luvero**, Federica **Guzzo**, Roberto **Angioli**, Corrado **Terranova**, Francesco **Plotti**

Gynaecology and Obstetrics, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy.

ARTICLE INFO

History
Received: 14 July 2025
Received in revised form: 07 October 2025
Accepted: 09 December 2025
Available online: 10 September 2026

DOI: 10.36129/jog.2026.255

Key words
Foetal pancreas; ultrasonography; glucose tolerance test; prenatal screening; gestational diabetes.

***Corresponding author:** Maria Cristina **Sangiovanni**, M.D. Gynaecology and Obstetrics, Fondazione Policlinico Universitario Campus Bio-Medico, via Alvaro del Portillo 20, 00128 Rome, Italy.
Email: mc.sangiovanni@libero.it.
ORCID: 0009-0003-9653-7821.

ABSTRACT

Objective. This state-of-the-art review aims to evaluate the current evidence on the association between foetal pancreatic circumference (PC) and Gestational Diabetes Mellitus (GDM), analysing the feasibility, diagnostic performance, and methodological consistency of this novel sonographic parameter.

Materials and Methods. A comprehensive literature search was conducted to March 2025. Studies were included if they evaluated foetal PC via ultrasound in the second trimester and assessed its association with GDM. Quality was assessed using the MINORS tool. Due to the limited number and heterogeneity of studies, data were synthesized narratively.

Results. Twenty studies were screened. Three observational studies met the inclusion criteria. Two studies reported a significant association between increased foetal PC and GDM, suggesting PC ≥ 80th percentile as a potential predictive threshold. Conversely, one study found no significant correlation. All studies confirmed the technical feasibility and reproducibility of PC measurement during mid-gestation. Quality assessment revealed moderate-to-high methodological rigour.

Conclusions. Despite preliminary results suggesting foetal PC as a promising and accessible marker for early GDM risk stratification, current evidence remains inconclusive. The novelty of this approach highlights the urgent need for standardised protocols and large-scale multicentre studies. If validated, foetal PC could offer a reliable alternative to the oral glucose tolerance test (OGTT), especially in settings where OGTT adherence is low or infeasible.

INTRODUCTION

Gestational Diabetes Mellitus (GDM) is the leading health disease in pregnant women [1], affecting approximately 16.5% of pregnant women worldwide [2]. GDM is associated with multiple risk factors [3], including low pre-pregnancy physical activity, advanced maternal age, and a family history of diabetes, with pre-pregnancy overweight and obesity representing a particularly significant determinant [4].

GDM pose significant foetal complications, such as adverse perinatal outcomes and a longer-term risk of obesity and glucose intolerance in offspring [5]. Moreover, mothers with GDM have a high risk of developing hypertensive disorders during pregnancy and a high risk of diabetes mellitus thereafter [5]. Early identification of women at risk for GDM is crucial for implementing timely interventions and improving perinatal outcomes [6].

According to the 2021 Recommendation Statement by the US Preventive Services Task Force (USPSTF) [7], there is moderate certainty of benefit in screening for GDM at 24 weeks of gestation or later, as it may improve maternal and foetal outcomes [8].

Actually, an Oral Glucose Tolerance Test (OGGT) remains the gold standard for the screening and diagnosis of GDM [9, 10].

The OGTT is the only test recommended by the World Health Organization (WHO) [11], the National Institute for Health and Care Excellence (NICE) [12], the American Diabetes Association (ADA) [13] and the International Federation of Obstetrics and Gynaecology (FIGO) [14].

From a clinical point of view, ultrasound remains central in follow-up: it allows not only monitoring growth (preventing macrosomia and guiding possible therapies such as insulin) [15], but also identifying signs of foetal distress (via Doppler such as Umbilical Artery Pulsatility Index or Cerebro-placental ratio) [16] to optimise the timing of delivery [17].

Beyond growth surveillance, ultrasound Doppler provides a haemodynamic context in GDM, with diabetic pregnancies exhibiting higher umbilical artery resistance and thicker placentae; such evidence supports the novel parallel exploration of foetal ultrasound markers, such as pancreatic circumference (PC), for risk stratification [18].

In recent years, there has been growing interest in utilizing ultrasound measurements of PC as a potential predictive marker for GDM [19]. This approach is relatively novel, with initial studies emerging only in the past few years, suggesting a possible link between foetal pancreatic growth and maternal glycaemic status.

However, the clinical application of foetal pancreatic measurements remains under investigation, indicating the need for further research to validate these findings and establish standardized measurement protocols.

Given the novelty of this topic in the literature and the importance of early detection of GDM, this state-of-the-art review aims to critically evaluate the current evidence on the association between foetal pancreatic size and the risk of GDM, assessing the validity and reliability of this measurement as a predictive tool.

MATERIALS AND METHODS

Study design

This state-of-the-art review was conducted in accordance with the principles of systematic exploration and synthesis, adapted to reflect the early and limited body of literature on this emerging topic. Given the small number of eligible studies, no meta-analysis was performed at this stage, and the emphasis was placed on a comprehensive qualitative appraisal of the available evidence.

Eligibility criteria

Studies were included if they met the following criteria: 1) pregnant women with singleton gestations undergoing second-trimester foetal ultrasound; 2) measurement of foetal PC; 3) diagnosis of GDM as an outcome; 4) observational study design; 5) English language; 6) full-text availability. Case reports, reviews, editorials, and studies without data on GDM were excluded.

Information sources and search strategy

A comprehensive literature search was conducted in March 2025 using PubMed, Scopus, Web of Science, and Embase, spanning from inception to March 2025 (with the last research update on 28 March 2025).

The search strategy included the terms: ("foetal pancreas" OR "foetal pancreatic circumference" OR "foetal pancreas size") AND ("gestational diabetes" OR "GDM").

Study selection

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [20] guidelines were used to improve the reporting of the reviewers. All retrieved records were imported into a reference manager, and duplicates were removed. Two reviewers (MCS, FP) independently screened titles and abstracts. Full texts were then assessed for eligibility. Discrepancies were resolved by consensus.

No ethical approval or patient consent is required, as all analyses were based on previously published studies. The analysis is not a registered study. Re-

viewers used the search protocol previously described to identify the literature. The reviewers initially screened titles, then abstracts, and later full papers. When a paper was considered potentially relevant, its full text was reviewed. If a study could not be unequivocally excluded due to its title and abstract, a discussion ensued between the two independent reviewers. The full text of all papers not excluded was evaluated. The number of articles excluded or included was registered and reported in a PRISMA flowchart [21, 22] (**Figure 1**).

Data collection process and data items

Data were extracted using a standardized Excel sheet. Variables included: author, year, study design, population characteristics, gestational age at measurement, ultrasound method, PC values, diagnostic criteria for GDM, effect estimates, confounding factors, and conclusions.

Quality assessment of studies and risk of bias

The reviewers (M.C.S. and F.P.) performed a qualitative analysis of the studies. The Methodological Index for Non-Randomized Studies (MINORS) [23] was used for quality assessment of non-randomized studies. The reliability of this score has already been demonstrated. The simplicity of MINORS, comprising only 12 items, makes this item readily usable by both readers and researchers. Given that all included studies employed non-randomised observational designs, and none were structured as classical cohort or case-control comparisons, the MINORS tool was deemed the most suitable instrument for quality assessment.

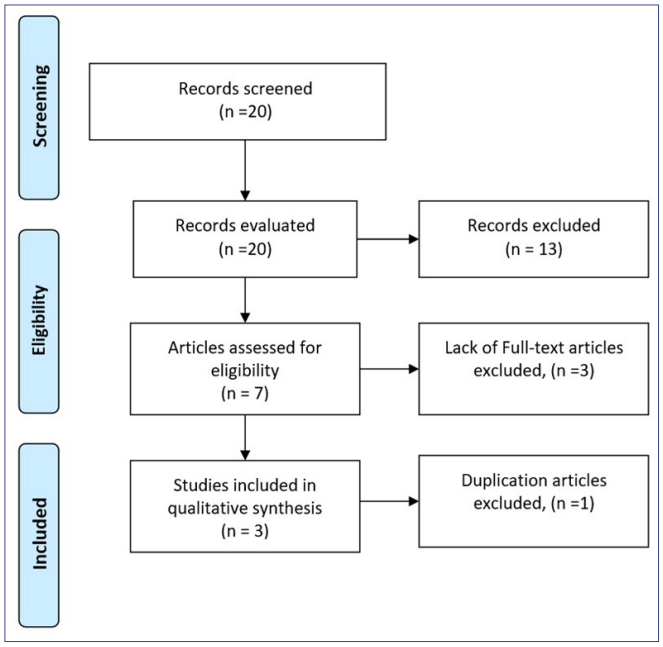

Figure 1. *Prisma 2020 flow diagram illustrating the selection process of studies included in the state-of-the-art review.*

Statistical analysis

Given the limited number of included studies and the heterogeneity of their designs and outcomes, no formal meta-analysis was conducted. Instead, the findings were synthesized narratively, highlighting key similarities, differences, and methodological considerations.

Study flow and justification for inclusion numbers

The initial search identified 20 studies. After abstract screening, 13 studies were excluded. Three studies were excluded due to a lack of full-text access. One study was excluded as a duplication. Thus, only three studies met the eligibility criteria and were included in the present state-of-the-art review, as shown in **Figure 1**. Due to the novelty of the topic, the number of eligible studies is limited. This reflects the emerging interest in using foetal pancreas measurements to predict GDM.

RESULTS

Three observational studies investigating the relationship between PC and the risk of GDM were included in this article.

The first study, conducted by Gilboa *et al.* [24], was a prospective cross-sectional observational study involving 91 pregnancies complicated by GDM and 34 with pregestational diabetes mellitus (PGDM). The authors measured foetal PC using high-resolution ultrasound machines (Voluson 730, E8, and E10; GE Medical Systems) between the 19th and 38th weeks of gestation. Their findings showed that foetal PC was significantly larger in pregnancies complicated by GDM compared to normoglycemic pregnancies. Additionally, the foetal PC significantly correlated with estimated foetal weight (EFW), abdominal circumference (AC), and gestational age (Pearson correlation coefficient = 0.802, 0.762, 0.764, $p < 0.001$) [24].

In the study conducted by Gilboa *et al.* [24], Thirty-four women with pregestational diabetes Mellitus (PGDM) were also included; all were treated with insulin, and 82.3% received therapy via an insulin pump. In this subgroup, foetal PC correlated significantly with abdominal circumfe-

rence (AC), estimated foetal weight (EFW), and gestational age (Pearson's r = 0.817, 0.681, and 0.710, respectively; all $p < 0.001$). When plotted against the normal 5th-95th centile reference range, PGDM PC values clustered around the median with wide dispersion ($r^2 = 0.508$, $p < 0.001$); the weekly mean Z-score decreased across gestation, positive until ~25 weeks and negative toward term. Notably, PC did not correlate with the EFW centile (r = 0.156, p = 0.446; cubic $r^2 = 0.026$, p = 0.741).

Findings reported in the article [24] suggest that all included patients (GMD and PGDM) achieved effective glycaemic control under multidisciplinary follow-up in the endocrinology/maternal-foetal medicine clinic. In fact, authors discuss that the observed findings may reflect optimal pre-conception glycaemic control in the population. Study reports that within the GDM cohort, glycaemic control was achieved with lifestyle measures in 14/91 (15.4%) women, while the remaining required insulin or oral hypoglycaemic agents; all PGDM patients were on insulin therapy (most on pumps). Overall, the authors concluded that foetal PC could serve as a potential early ultrasound marker for the detection of GDM. By contrast, in women with PGDM, foetal PC was comparable to non-diabetic controls, and the EFW centile remained around the median, possibly reflecting effective pre-conception glycaemic control [24].

The second study, a retrospective cohort by Gilboa *et al.* [25], examined 195 pregnancies (24 with GDM and 171 normoglycemic) assessed between the 20th and 25th weeks of gestation using the same ultrasound equipment. This study introduced percentile-based cut-offs and identified that a foetal PC ≥ 80th percentile was significantly associated with the later diagnosis of GDM (82.4 ± 14.6 in the GDM group *vs* 62.8 ± 7.6 in the non-GDM group; $p < 0.001$ [22]).

The article reported that the foetal PC centile was correlated positively with the EFW centile (Pearson's coefficient, 0.243; p = 0.001) [25]. Specifically, the odds ratio for developing GDM in foetuses with a PC ≥ 80th percentile was approximately 5.0, and the area under the receiver operating characteristic curve (AUC) for GDM prediction was 0.71, indicating moderate diagnostic accuracy. The authors suggested that foetal PC could be integrated into second-trimester screening as an early, non-invasive tool to identify pregnancies at high risk of GDM [25].

The third study, by Guleroglu *et al.* [26], was a prospective observational study involving 109 pregnant women (19 with GDM and 90 normoglycemic), in which foetal PC was measured at two time points: between the 20th and 22nd weeks, and between the 24th and 28th weeks of gestation. Unlike the previous two studies, this study did not find a statistically significant difference ($p > 0.05$) in the median values of foetal PC between women who developed GDM and those who did not, reporting that the increase in pancreatic size observed between 20-22 and 24-28 weeks in both groups was interpreted as a physiological consequence of overall foetal growth, remaining comparable between GDM and normoglycemic pregnancies at each time point, and concluding that foetal pancreatic size does not provide potential for early prediction of GDM at 20-22 weeks of gestation.

The authors [26] also investigated other maternal serum biomarkers, such as glycated albumin, suggesting that while biochemical markers might offer predictive value, foetal PC alone did not demonstrate a clear correlation with GDM in their cohort.

A qualitative assessment of the methodological quality of the included studies was conducted using the Methodological Index for Non-Randomized Studies (MINORS) [23]. Total scores ranged from 11 to 13 out of 16, indicating moderate to high quality, as shown in **Table 1**.

Gilboa *et al.* [24] obtained the highest score (13/16), reflecting a clearly stated aim, prospective design,

Table 1. *Methodological quality assessment of the studies included in the review according to the Methodological Index for Non-Randomized Studies (MINORS).*

Study	1. Clearly stated aim	2. Inclusion of consecutive patients	3. Prospective data collection	4. Endpoints appropriate to the aim of the study	5. Unbiased assessment of the study endpoint	6. Follow-up period appropriate to the aim	7. Loss to follow-up less than 5%	8. Prospective calculation of the study size	Total Score
Gilboa *et al.* (2022)	2	2	2	2	1	2	1	1	13
Gilboa *et al.* (2024)	2	2	0	2	1	2	2	0	11
Guleroglu *et al.* (2022)	2	1	2	2	1	2	1	0	11

appropriate endpoints, and adequate follow-up. Both Gilboa *et al*. [25] and Guleroglu *et al*. [26] received a total score of 11/16, with limitations primarily due to retrospective data collection in one case, and the lack of prospective sample size calculation and fully unbiased endpoint assessment in both. Overall, the quality of the evidence was acceptable but underlined the need for larger, standardised prospective studies in this field. Due to the limited number and heterogeneity of studies, no meta-analysis was performed.

DISCUSSION

The measurement of PC has emerged as a novel ultrasonographic marker with potential application in the early identification of pregnancies at risk for GDM.

Regarding the diagnostic criteria for GDM, studies adopted different thresholds, thereby reducing comparability among studies.

Gilboa *et al.* [24] adopted the Israeli Society of Obstetrics and Gynecology two-step approach [27]: GDM was diagnosed by 1-h 50 g GCT ≥ 200 mg/Dl followed by 100 g OGTT (3 h) using Carpenter-Coustan cut-offs [28] (95/180/155/140 mg/dL at 0/60/120/180 min); PGDM was defined by a pre-pregnancy diabetes diagnosis.

Likewise, in the study by Gilboa *et al.* [25], a two-step strategy was used at 25-28 weeks (screening 50 g GCT with a 140 mg/dL threshold, followed, if positive, by 100 g OGTT (3 h) with Carpenter-Coustan cut-offs). In contrast, Guleroglu *et al.* [26] applied a one-step 75 g OGTT (2 h) at 24-28 weeks (International Association of Diabetes and Pregnancy Study Group -IADPSG- criteria [29]). This heterogeneity in testing strategy (one- *vs* two-step), timing (24-28 *vs* 25-28 weeks), and diagnostic cut-offs is a potential source of clinical and methodological variability when comparing associations between foetal PC and GDM across studies.

In all three studies included in the present article [24-26], detailed protocols were provided regarding the ultrasound technique used to assess PC, ensuring the comparability of data across cohorts. The foetal pancreas is visualized as a hyperechoic structure bordered by the stomach and spine, enabling consistent identification.

All three studies employed 2D ultrasound to assess foetal PC using a transverse abdominal view, with the pancreas identified between the stomach and the aorta. In both 2021 and 2024 studies by Gilboa *et al.* [24, 25] The foetal spine was positioned to optimise visualisation, and a consistent sonographic technique was applied. The 2021 study focused on biometric correlations, while the 2024 study evaluated diagnostic cut-offs, particularly the 75th and 80th percentiles, for predicting GDM.

Guleroglu *et al*. [26] used a similar imaging approach but with slight caudal angulation and specific spine positioning (between 3-5 or 7-9 o'clock) to enhance visibility. Unlike the others, this study performed measurements at two time points (20-22 and 24-28 weeks) and reported high intra-observer agreement (Kappa 0.83-0.89), underscoring the method's reproducibility.

Despite slight variations in technique and timing, all studies confirmed that foetal PC can be reliably measured in the second trimester using standard ultrasound.

The feasibility of foetal pancreatic measurement via ultrasound was previously demonstrated by Hata *et al.*, who reported that the pancreas can be consistently visualised (up to 80% of cases) from 20 weeks of gestation onward as an echogenic, S-shaped structure [30]. Building on this, more recent work by Yang Li *et al.* [36] confirmed that the optimal visualisation of the PC is reached between 22 and 27 weeks, highlighting the need for standardised protocols for measurement.

A valuable technical reference on foetal pancreatic imaging has been recently provided by Singh [31], who described a reproducible sonographic approach using splenic vessels as anatomical landmarks. According to the author, by positioning the foetal spine between 3-5 or 7-9 o'clock and applying a slight caudal angulation, the pancreas can be clearly visualized from as early as 18 weeks [31]. The use of high-definition power Doppler further enhances identification, highlighting the importance of standardized imaging protocols to improve reproducibility and diagnostic consistency [31].

From a clinical perspective, the measurement of foetal PC may serve as an indirect marker of foetal exposure to maternal glycemia. In line with Pedersen's hypothesis in 1920, maternal hyperglycaemia induces foetal hyperinsulinemia, which may lead to β-cell hyperplasia and pancreatic enlargement as an adaptive foetal response [32].

A key advantage of incorporating foetal PC as a potential screening tool for GDM lies in its non-invasive nature and its compatibility with routine mid-trimester ultrasound evaluations. Currently,

the OGTT remains the gold standard for GDM screening, despite being considered imperfect. However, it is increasingly being challenged for its clinical practicality, reliability, and patient acceptability [33].

A recent study by Lachmann *et al.* [34], conducted in a large UK tertiary obstetric centre, found that 12.7% of women invited for OGTT did not complete testing, with 32.2% never completing the protocol at all. The most frequently cited barriers were the inability to tolerate the test protocol (*e.g.*, nausea, vomiting, prolonged fasting), social or mental health issues, and difficulty managing multiple antenatal appointments. Notably, younger age, lower socio-economic status, higher parity, and minority ethnic background were all significantly associated with non-completion. The authors [34] emphasise the need for alternative methods of GDM testing that are easier to schedule and tolerate, especially for vulnerable populations.

In this context, foetal PC measurement offers several practical advantages. It is non-invasive, quick, and requires no additional maternal preparation, unlike the OGTT, which necessitates fasting and multiple venous blood draws over two hours. Additionally, it can be integrated seamlessly into the standard second-trimester anomaly scan, minimizing the need for separate clinical visits and improving adherence to screening protocols, particularly in under-resourced settings.

A detailed critical analysis of the included studies highlights both the potential and limitations of foetal PC as a marker related to GDM.

Gilboa *et al.* [24] conducted a prospective cross-sectional study that provided clear sonographic imaging protocols and distinct analyses for GDM and PGDM subgroups. The study's prospective nature and detailed foetal pancreatic measurements represent its principal strengths. However, its cross-sectional design precludes temporal inference, thereby limiting the ability to draw causal conclusions. Moreover, the absence of a prespecified sample size calculation and the lack of multivariable adjustment for confounding variables, such as AC, EFW, maternal body mass index (BMI), and gestational age at scanning, reduce the robustness. The single-centre setting and lack of external validation limit the generalizability of the findings.

Gilboa *et al.* [25] conducted a retrospective cohort design involving a low-risk population assessed during routine second-trimester anatomy scans. A key innovation of this retrospective cohort was the introduction of centile-based thresholds for foetal PC. In their analyses, the 80th centile cut-off yielded the highest sensitivity and positive predictive value (PPV) for subsequent maternal GDM, with corresponding increases in odds ratios for higher PC centiles. This approach is clinically relevant due to alignment with standard prenatal screening. However, limitations include the retrospective design, a relatively small GDM subgroup (n = 24), and a lack of external validation. Notably, despite observing correlations between PC and EFW centiles, the study did not conduct analyses to isolate the independent predictive value of PC beyond standard foetal biometric parameters.

The prospective study by Guleroglu *et al.* [26] focused on assessing the reproducibility of PC measurement at two clinically pertinent gestational periods (20-22 and 24-28 weeks). This study demonstrated high intra-observer reliability for PC measurement, thereby reinforcing the feasibility of the measurement. However, no significant differences in PC were found between the GDM and control groups (normal glucose tolerance group, NGT) at either time point. The study's limited sample size (90 women with NGT and 19 women with GDM), single-centre design, and minimal adjustment for maternal and foetal covariates restrict statistical power and external validity.

A central clinical question is whether an increased foetal PC reflects a pancreas-specific enlargement related to GDM, or instead mirrors overall foetal macrosomia, a well-known consequence of GDM [35].

Across all three studies, PC showed strong positive correlations with standard growth measures. In the study by Gilboa *et al.* [24], even if PC was higher in GDM, the strong correlations with AC, EFW and gestational age (Pearson's $r > 0.7$) indicate that larger PC may partly capture overall foetal size. Notably, in the PGDM subgroup with glycaemic control, PC and EFW centiles hovered around the median, suggesting that pancreatic enlargement is not evident when overgrowth is mitigated. Gilboa *et al.* [25], likewise, higher PC centiles were linked to subsequent GDM; however, correlations with EFW centiles and the absence of adjustment analyses leave it uncertain whether PC has predictive value independent of overall size. Consistently, Guleroglu *et al.* [26] found no between-group differences in PC at mid-gestation, aligning with the lack of an overgrowth signal.

Taken together, these findings support a biologically plausible pathway whereby maternal hyperglycaemia in GDM induces foetal hyperinsulinemia, which can drive both pancreatic enlargement and macrosomia. Thus, the observed association between foetal PC and GDM may be partly confounded or mediated by foetal size. Disentangling these mechanisms requires analyses that 1) adjust for AC/EFW and key maternal covariates, 2) test the incremental predictive value of PC beyond standard biometry, and 3) explore mediation to quantify the indirect effect through macrosomia.
Future studies should therefore aim to determine whether foetal PC offers incremental predictive value beyond conventional biometric parameters, through multivariable and mediation analyses that could clarify its role as an independent sonographic marker of GDM.
This article presents several strengths, including its systematic methodology, the inclusion of detailed ultrasound protocols, and its focus on a novel, non-invasive parameter for early assessment of GDM risk. The most significant limitation of this study is the small number of studies included, which reflects the overall scarcity of literature on this emerging topic. In fact, three potentially relevant studies were excluded due to the unavailability of full-text access, which may have limited the completeness of the evidence synthesis. Moreover, two out of the three studies were authored by the same research group. They employed similar methodologies, further limiting the heterogeneity of the available evidence and potentially affecting the generalizability of the findings, as results from a single research team may reflect centre-specific practices or population characteristics.
Methodologically, the three studies included in the present article share a broadly similar sonographic approach, confirming the technical feasibility and reproducibility of PC measurement. However, differences in study design, cohorts, sample sizes, OGTT criteria and analytical framework may affect interpretability and generalizability.
If future prospective studies confirm the diagnostic validity and reproducibility of foetal PC as a predictive biomarker for GDM, it could represent a paradigm shift in prenatal care, allowing earlier and more acceptable risk stratification. This could be especially relevant in populations where compliance with OGTT is low or in settings lacking resources for universal biochemical screening. Nevertheless, further research is needed to determine optimal cut-off values, standardize measurement protocols, and assess the added value of foetal PC compared to traditional risk factors or combined predictive models.

CONCLUSIONS

Building upon the findings of a limited number of studies, considering the novelty of the topic, we explored the technical methodology and clinical implications of foetal PC measurement. The ultrasound assessment of foetal PC represents a promising, non-invasive indicator for early risk stratification of GDM.
While two studies supported the predictive value of foetal PC for GDM, one failed to demonstrate a significant association, reflecting variability in current findings.
Overall, the results of currently available evidence, although suggesting a possible association between this ultrasound parameter and GDM, are still preliminary and do not allow definitive conclusions due to the limited number of included studies, methodological heterogeneity, and the lack of large-scale studies.
The study suggests the technical feasibility and reproducibility of the measurement in the second trimester, but highlights the need for further investigations to validate this marker and to establish standardized measurement protocols.
It is also necessary to clarify whether PC serves as an independent predictor with respect to standard foetal biometric measurements, such as estimated foetal weight and abdominal circumference.
If validated, foetal PC could serve as a practical and patient-friendly alternative to the OGTT, particularly in settings with low screening adherence. Its integration into routine second-trimester ultrasound could improve early risk stratification and enhance prenatal care.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions

M.C.S.: Conceptualization, methodology, writing – original draft, supervision. C.D.C.N.: Formal analysis, data curation, writing – review & editing. R.M.: Investigation, visualization, writing – review & editing. D.L.: Resources, validation. F.G.: Project administration, writing – review & editing. R.A.:

Supervision, validation. C.T.: Data curation, writing – review & editing. F.P.: Supervision.

Funding
None.

Study registration
N/A.

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

Ethical approval
N/A.

Informed consent
N/A.

Data sharing
The data used in this review are publicly available and derived from previously published articles. No new datasets were generated or analysed in this study.

ACKNOWLEDGEMENTS

The authors would like to thank all the professionals involved in the development of this work.

REFERENCES

1. Choudhury AA, Devi Rajeswari V. Gestational diabetes mellitus - A metabolic and reproductive disorder. Biomed Pharmacother. 2021;143:112183. doi: 10.1016/j.biopha.2021.112183.
2. Pletneva S, Enkova E, Khoperskaya O, Shamarin S, Enkova V. Gestational diabetes mellitus: state of art. Meditsinskiy Sov Med Counc. 2023:136-141. doi: 10.21518/ms2023-112.
3. Amiri FN, Faramarzi M, Bakhtiari A, Omidvar S. Risk Factors for Gestational Diabetes Mellitus: A Case-Control Study. Am J Lifestyle Med. 2018;15(2):184-190. doi: 10.1177/1559827618791980
4. Faraidoon R, Ali SM. Birth weight in high risk and normal pregnancy: a comparative study. Ital J Gynaecol Obstet. 2024;36(4):455-465. doi: 10.36129/jog.2024.164.
5. Buchanan TA, Xiang AH, Page KA. Gestational Diabetes Mellitus: Risks and Management during and after Pregnancy. Nat Rev Endocrinol. 2012;8(11):639-649. doi: 10.1038/nrendo.2012.96.
6. Lamain-de Ruiter M, Kwee A, Naaktgeboren CA, Franx A, Moons KGM, Koster MPH. Prediction models for the risk of gestational diabetes: a systematic review. Diagn Progn Res. 2017;1:3. doi: 10.1186/s41512-016-0005-7.
7. US Preventive Services Task Force, Davidson KW, Barry MJ, Mangione CM, Cabana M, Caughey AB, et al. Screening for Gestational Diabetes: US Preventive Services Task Force Recommendation Statement. JAMA. 2021;326(6):531-538. doi: 10.1001/jama.2021.11922.
8. Zhang C, Catalano P. Screening for Gestational Diabetes. JAMA. 2021;326(6):487-489. doi: 10.1001/jama.2021.12190.
9. Torlone E, Festa C, Formoso G, Scavini M, Sculli, MA, Succurro, E, et al. Italian recommendations for the diagnosis of gestational diabetes during COVID-19 pandemic: Position statement of the Italian Association of Clinical Diabetologists (AMD) and the Italian Diabetes Society (SID), diabetes, and pregnancy study group. Nutr Metab Cardiovasc Dis. 2020;30(9):1418-1422. doi: 10.1016/j.numecd.2020.05.023.
10. Eyth E, Basit H, Swift CJ. Glucose Tolerance Test. StatPearls. 2025. Aavailable at: http://www.ncbi.nlm.nih.gov/books/NBK532915/. Accessed on April 10, 2025.
11. Adam JMF, Tarigan NP. Comparison of The World Health Organization (WHO) two-step strategy and OGTT for diabetes mellitus screening. Acta Medica Indones. 2004;36(1):3-7.
12. Diabetes in pregnancy: management from preconception to the postnatal period. 2020. Available at: http://www.ncbi.nlm.nih.gov/books/NBK555331/. Accessed on July13, 2025.
13. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2024. Diabetes Care. American Diabetes Association. Available at: https://diabetesjournals.org/care/article/47/Supplement_1/S20/153954/2-Diagnosis-and-Classification-of-Diabetes. Accessed on April 10, 2025.
14. Dahiya K. New FIGO Guidelines on Gestational Diabetes [24P]. Obstet Gynecol. 2017;129(5):S170. doi: 10.1097/01.AOG.0000514097.03289.82.
15. Impact of Gestational Diabetes Mellitus on Fetal Growth and Nutritional Status in Newborns.

Available at: https://www.mdpi.com/2072-6643/16/23/4093. Accessed on March 28, 2025.
16. Rane BM, Malau-Aduli BS, Alele F, O'Brien C. Prognostic Accuracy of Antenatal Doppler Ultrasound Measures in Predicting Adverse Perinatal Outcomes for Pregnancies Complicated by Diabetes: A Systematic Review. AJOG Glob Rep. 2023;3(3):100241. doi: 10.1016/j.xagr.2023.100241.
17. Li X, Li TT, Tian RX, Fei JJ, Wang XX, Yu HH, et al. Gestational diabetes mellitus: The optimal time of delivery. World J Diabetes. 2023;14(3):179-187. doi: 10.4239/wjd.v14.i3.179.
18. Rauf F, Ahmed SMY, Mehreen M, Gilani SA, Jelany S, Gilani HSA, et al. Doppler comparison of fetoplacental blood flow characteristics between pre-gestational diabetic and non-diabetic pregnant women during second and third trimester of pregnancy. Ital J Gynaecol Obstet. 2025;37(2):233-241. doi: 10.36129/jog.2025.202.
19. Liao R, Zhang Z, Zhang Y, Lin Y, Chen R, Wang L, et al. New measurement indicator of ultrasound assessment of the fetal pancreas based on anatomical landmarks and its application to fetuses with gestational diabetes mellitus. J Perinat Med. 2024;52(9):1002-1009. doi: 10.1515/jpm-2024-0260.
20. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100. doi: 10.1371/journal.pmed.1000100.
21. PRISMA statement. Available at: https://www.prisma-statement.org. Accessed on April 10, 2025.
22. PRISMA 2020 flow diagram. PRISMA Statement. Available at: https://www.prisma-statement.org/prisma-2020-flow-diagram]. Accessed on April 10, 2025.
23. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg. 2003;73(9):712-6. doi: 10.1046/j.1445-2197.2003.02748.x.
24. Gilboa Y, Krekora M, Perlman S, Bardin R, Kassif E, Achiron R, et al. Sonographic measurement of the fetal pancreas in women with gestational diabetes. Arch Med Sci. 2021;18(2):382-387. doi: 10.5114/aoms/140578.
25. Gilboa Y, Geron Y, Perlman S, Drukker L, Ofir K, Ellert A, et al. Predictive capacity of fetal pancreatic circumference for gestational diabetes mellitus. Ultrasound Obstet Gynecol. 2024;64(3):348-353. doi: 10.1002/uog.27719.
26. Guleroglu FY, Ozmen AB, Bakirci IT, Dogu SY, Yılmaz I, Cetin A. Fetal pancreas size and maternal serum biomarkers glycated albumin and insulin-regulated aminopeptidase provide no potential for early prediction of gestational diabetes mellitus. Arch Gynecol Obstet. 2023;308(5):1505-1514. doi: 10.1007/s00404-022-06860-2.
27. Lieberman N, Kalter-Leibovici O, Hod M. Global adaptation of IADPSG recommendations: a national approach. Int J Gynaecol Obstet. 2011;115 Suppl 1:S45-7. doi: 10.1016/S0020-7292(11)60013-1.
28. Harper LM, Mele L, Landon MB, Carpenter MW, Ramin SM, Reddy UM, et al. Carpenter-Coustan Compared With National Diabetes Data Group Criteria for Diagnosing Gestational Diabetes. Obstet Gynecol. 2016;127(5):893-898. doi: 10.1097/AOG.0000000000001383.
29. Basri NI, Mahdy ZA, Ahmad S, Abdul Karim AK, Shan LP, Abdul Manaf MR, et al. The World Health Organization (WHO) versus The International Association of Diabetes and Pregnancy Study Group (IADPSG) diagnostic criteria of gestational diabetes mellitus (GDM) and their associated maternal and neonatal outcomes. Horm Mol Biol Clin Investig. 2018;34(1). doi: 10.1515/hmbci-2017-0077.
30. Hata K, Hata T, Kitao M. Ultrasonographic identification and measurement of the human fetal pancreas in utero. Int J Gynaecol Obstet. 1988;26(1):61-4. doi: 10.1016/0020-7292(88)90197-x.
31. Singh D. Splenic vessels: putting a spotlight on the fetal pancreas. Ultrasound Obstet Gynecol. 2022;60(2):294-295. doi: 10.1002/uog.24897.
32. Hufnagel A, Dearden L, Fernandez-Twinn DS, Ozanne SE. Programming of cardiometabolic health: the role of maternal and fetal hyperinsulinaemia. J Endocrinol. 2022;253(2):R47-R63. doi: 10.1530/JOE-21-0332.
33. Kirke AB, Spry E, Atkinson D, Sinclair C, Marley JV. Oral glucose tolerance test-The imperfect gold standard for gestational diabetes screening: A qualitative study involving clinicians in regional, rural and remote areas of Western Australia. Health Promot J Austr. 2025;36(1):e899. doi: 10.1002/hpja.899.

34. Lachmann EH, Fox RA, Dennison RA, Usher-Smith JA, Meek CL, Aiken CE. Barriers to completing oral glucose tolerance testing in women at risk of gestational diabetes. Diabet Med. 2020;37(9):1482-1489. doi: 10.1111/dme.14292.
35. Bernea EG, Uyy E, Mihai DA, Ceausu I, Ionescu-Tirgoviste C, Suica VI, Ivan L, Antohe F. New born macrosomia in gestational diabetes mellitus. Exp Ther Med. 2022;24(6):710. doi: 10.3892/etm.2022.11646.
36 Li Y, Lu J, Cheng H, Sun T, Leng J, Ma T, et al. High-frequency ultrasound imaging to assess fetal pancreas: a promising application. J Matern Fetal Neonatal Med. 2023;36:2291994. doi: 10.1080/14767058.2023.2291994.

Italian Journal of
Gynæcology & Obstetrics
September 2026 - Vol. 38 - N. 3 - Quarterly - ISSN 2385 – 0868

Exploring robot-assisted vesicovaginal fistula repair: two case reports and a narrative literature review

Michele **Di Dio** [1], Giuseppe **Azzarone** [2], Claudio **Bisegna** [1], Vincenzo **Zaccone** [1], Anna **Perri** [3], Paola **Quaresima** [4,*], Riccardo **Bertolo** [5], Fabrizio **Di Maida** [6], Giuseppina **Amendola** [7], Alberto **Piana** [8], Maurizio **Guido** [2], Michele **Morelli** [2]

[1] Department of Urology, Azienda Ospedaliera SS Annunziata, Cosenza, Italy.
[2] Department of Obstetrics and Gynaecology University of Calabria (UNICAL), Cosenza, Italy.
[3] Department of Education, Culture and Society, University of Calabria (UNICAL), Cosenza, Italy.
[4] Department of Obstetrics and Gynaecology, Azienda Sanitaria Provinciale di Cosenza, Cosenza, Italy.
[5] AOUI Verona, University of Verona, Verona, Italy.
[6] Department of Experimental and Clinical Medicine, Unit of Oncologic Minimally Invasive Urology and Andrology, University of Florence, Careggi Hospital, Florence, Italy.
[7] Department of Obstetrics and Gynaecology, Lamezia Terme Hospital, Lamezia Terme, Italy.
[8] Department of Oncology, Division of Urology, University of Turin, San Luigi Gonzaga Hospital, Orbassano, Turin, Italy.

ARTICLE INFO

History
Received: 27 October 2025
Received in revised form: N/A
Accepted: 09 December 2025
Available online: 10 September 2026

DOI: 10.36129/jog.2026.257

Key words
Vesicovaginal fistula; robotic surgery; minimally invasive surgery.

***Corresponding author:** Paola **Quaresima**, M.D.
Department of Obstetrics and Gynaecology,
Azienda Sanitaria Provinciale di Cosenza,
viale degli Alimena 8, Cosenza, Italy.
Email: dr.paolaquaresima@gmail.com.
ORCID: 0000-0002-5081-5430.

ABSTRACT

Background. Vesicovaginal fistula (VVF) is a rare occurrence in Western countries, primarily resulting from iatrogenic injuries. Surgical repair becomes necessary when conservative management fails, However, timing and surgical approaches (vaginal, laparotomic, laparoscopic, robot-assisted) are still under debate.

Case presentation. We aim to present two case reports with a step-by-step description of the adopted robot-assisted surgical approach for the VVFs repair, highlighting its feasibility in primary and recurrent cases, along with a narrative literature review of previously described robot-assisted managed VVF cases.

Conclusions. Robot-assisted VVFs surgical repair represents a state-of-the-art treatment, combining advanced technology with surgical expertise to achieve optimal postoperative out-comes. In our experience, it is feasible, safe, effective, and represents a viable approach, especially in complex cases.

INTRODUCTION

Vesicovaginal fistula (VVF) is an anomalous communication between bladder and vagina, resulting in a continuous urine leakage through the vagina, accounting for approximately 1%-4% of the genitourinary fistulas (**Figure 1**) [1]. The global incidence of the urogenital fistula is hard to define

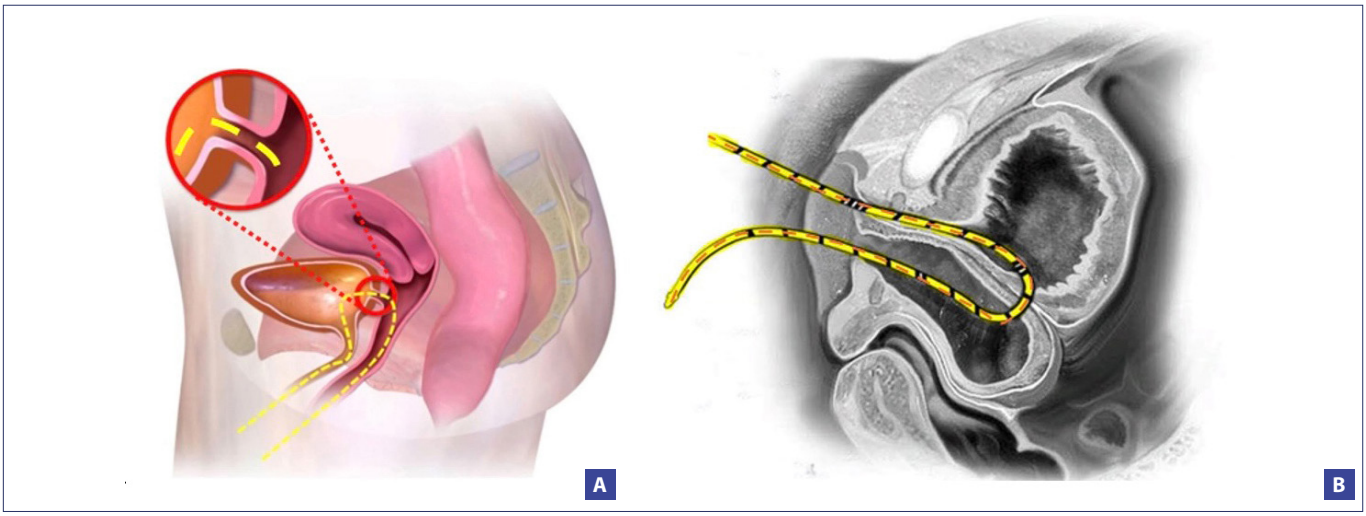

Figure 1. *Anatomical description of a VVF.*

(A) Detailed view of the fistulous tract. **(B)** Ureteral catheter (yellow), serving as a reference point for accurate identification and surgical planning.

accurately. The World Health Organization (WHO) estimates that around 50.000-100.000 women are diagnosed worldwide with urogenital fistulae annually [2]. Causes include obstetric injury, postsurgical sequelae, radiation therapy, inflammation/infection, or trauma. In low-income countries, where perinatal obstetric care is often lacking, the most common VVF aetiology is prolonged labour. In high-income countries, VVF is primarily due to iatrogenic lesions after surgical procedures such as hysterectomy or mesh placement for urinary incontinence, with an overall incidence ranging from 0.3% to 2% [3]. VVFs can be classified as simple or complex; the former are isolated and small (≤ 0.5 cm), whereas the latter include previously failed fistula repairs or large-sized (≥ 2.5 cm) fistulas. These last are often a result of chronic diseases or radiotherapy [4]. VVFs related to surgical procedures mostly occur within 7 to 10 days after surgery. However, some reports describe symptoms onset up to 6 weeks postoperatively [4]. Complementary to an accurate clinical investigation, cystoscopy and voiding cystourethrography are crucial to determine the size, number, and location of VVFs [5]. The oldest reference about VVF comes from the Kahun papyrus, ancient Egypt (2000 before Christ) [6]. VVF modern surgery dates to 1675, when Johann Fatio reported the first therapeutic success. In 1852, James Marion Sims first described a transvaginal surgical approach, whereas in 1888, Trendelenburg introduced the transabdominal approach [7]. In 1928, Martius introduced the concept of the "interposition flap" a flap of adipose tissue obtained from the labia major interposed between the bladder and vaginal sutures [8]. In 1942, Latzko described his transvaginal technique for VVF repair, which remains a gold standard today. This last approach involves a partial colpoclesis, where the fistulous tract is excised, and the vaginal wall is closed in layers without direct bladder repair. It is particularly effective for supra-trigonal fistulas, ensuring high success rates while preserving bladder capacity [9]. A transabdominal technique, characterized by a wide cystotomy with dissection and excision of the fistulous tract, was described by O'Conor in 1950 [10]. Nezhat *et al.* were the first to publish a case report about a laparoscopic repair of VVF in 1994 [11]. The newest strategy to treat such conditions is combining a robot-assisted laparoscopic approach. The first report was published in 2005 by Melamud *et al*. [12]. The above-mentioned technique has demonstrated high healing rates (over 95%) with excellent aesthetic results [13]. However, limited evidence about long-term prognosis is yet available. Therefore, we present two successful laparoscopic robot-assisted VVF repair cases, one in a primary and one in a recurrent case, with a long-term available outcome. Moreover, we conducted a narrative literature review on laparoscopic robot-assisted VVFs managed cases to assess the advantages and limits of such a technique.

CASE PRESENTATION

Case A

A 69-year-old Caucasian, nulliparous, obese woman was referred to the urological unit of the "SS.

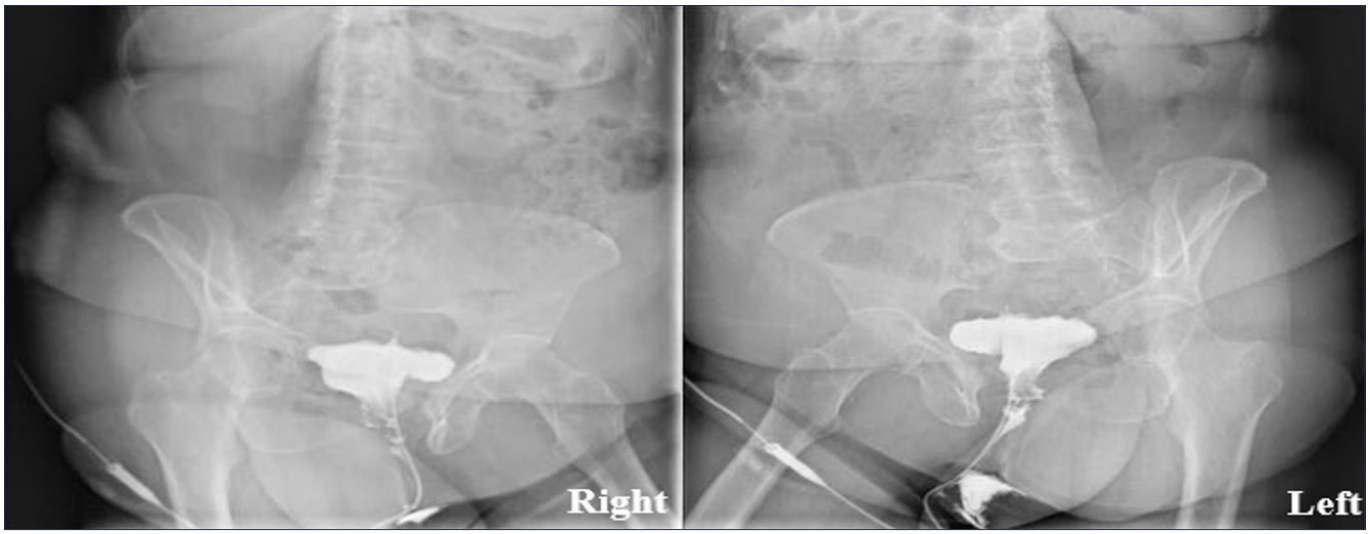

Figure 2. *Retrograde cystourethrography image.*

Demonstration of a Fistulous communication between the posterior wall of urinary bladder and anterior wall of vagina. Evident appearance of contrast fluid in the vaginal cavity.

Annunziata" hospital in Cosenza (Italy) reporting abnormal, involuntary urinary loss on the second postoperative day after a total laparoscopic hysterectomy. Retrograde urethrocystography and voiding cystourethrography demonstrated contrast extravasation from the bladder into the vaginal cavity, consistent with a VVF (**Figure 2**). This last was of about 1 cm in size connecting the posterior wall of the bladder with the anterior wall of the vagina, notably situated away from the bladder trigone. Three months after surgery, the patient underwent a robot-assisted laparoscopic repair of the VVF conducted by two highly experienced robotic surgeons (M.D.D. and M.M.) using the robotic platform da Vinci Xi Surgical System (Intuitive Surgical, Sunnyvale, CA, USA). Based on the appearance of vesicovaginal tissues, an extravesical approach has been chosen to repair the VVF. The first step consisted into the realization of well-defined surgical planes to effectively separate the bladder from the vagina, allowing their separate closure (**Figure 3 A,B**). The favourable tissue quality obviated the need for an intravesical

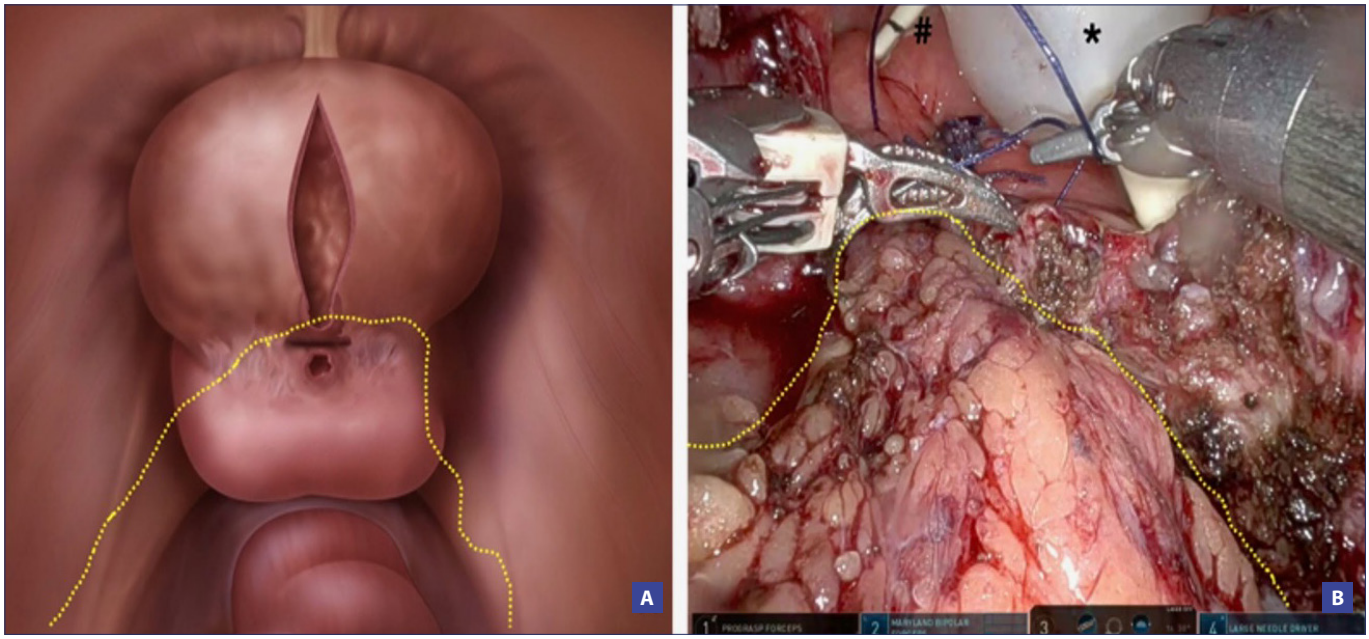

Figure 3. *Schematic representation of omental flap interposition technique.*

(A) Schematic representation of omental flap interposition (highlighted with a dashed yellow line) during robotic transvesical vesicovaginal fistula repair. **(B)** The exposed bladder mucosa after cystotomy, the re-paired fistulous tract, the Foley catheter balloon (*), and a mono-J catheter (#) emerging from a ureteral orifice can be observed.

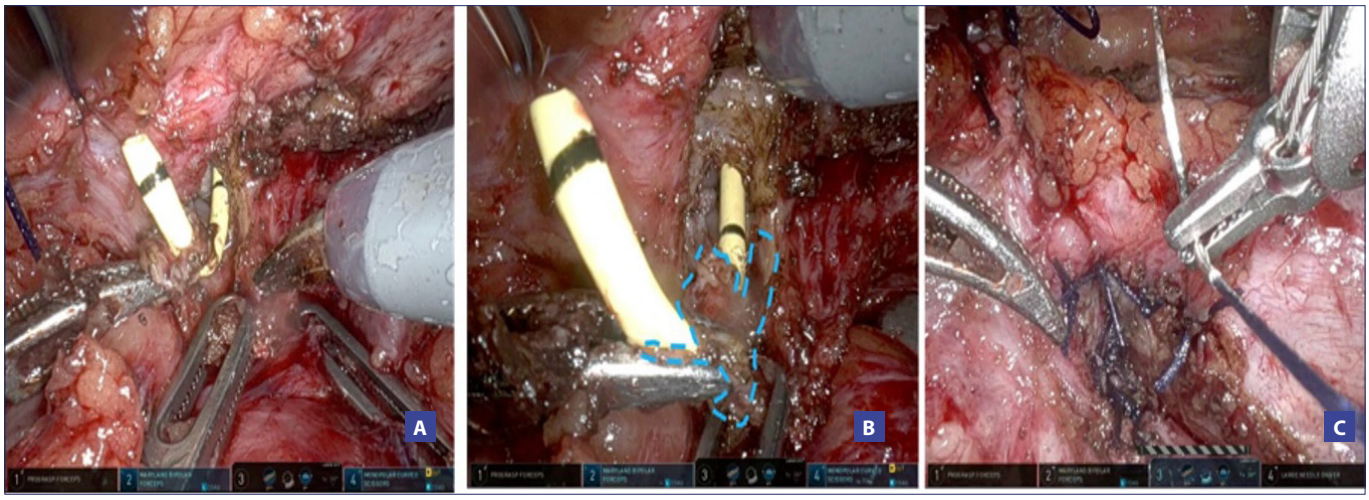

Figure 4. *Schematic description of Robot-assisted extravesical vesicovaginal fistula repair.*

(A) The fistulous tract is easily identified using a pre-positioned catheter from the preliminary endo-scopic phase. **(B)** Once localized, the fistula is excised externally without a longitudinal cystotomy, ensuring precise removal of the tract and adjacent scar tissue with adequate margins of healthy tissue. **(C)** Finally, the vaginal layer and bladder wall are sutured in opposing perpendicular orientation.

approach, enabling operators to repair the fistula without opening the bladder. This strategy is less invasive, preserves bladder integrity, and facilitates a more efficient postoperative recovery. To minimize the risk of recurrence, the vaginal and bladder walls were sutured in a perpendicular, opposing fashion. Following adhesiolysis from prior surgeries, the Omentum was mobilized and interposed between the bladder and the vagina (**Figure 4 A-C**). The procedure was completed with a hydrodistension bladder leak test, pelvic drain placement, and a Foley bladder catheter insertion, secured in conjunction with the ureteral stents. Console time was 115 min. The estimated blood loss was 60 cc, and no surgical-related complications were reported. The ureteral catheters were removed on the first postoperative day (POD), while abdominal drainage was removed after 48 hours. Perioperative antibiotic prophylaxis was administered for 5 days. The patient was discharged home on the 4th POD with an indwelling urethral catheter, which was removed after 15 days following a normal result at the voiding cystourethrography. At the 6-month and one-year follow-up assessment, the patient maintained unobstructed urinary voiding patterns, without any VVF recurrence.

Case B

A 47-year-old Caucasian, multiparous woman, who had already received a laparoscopic treatment to solve a VVF occurring after total laparotomic hysterectomy with bilateral adnexectomy, was referred nine months after the repairing surgery to the Urologic Unit of the "SS. Annunziata" hospital in Cosenza (Italy), reporting recurrent abnormal, involuntary urinary loss. Retrograde urethrocystography and voiding cystourethrography demonstrated contrast extravasation into the vaginal cavity, consistent with a VVF connecting the posterior bladder wall to the anterior vaginal wall. The fistulous tract, measuring approximately 1.5 cm in size, was located very close to the ureteral orifices, an area corresponding to the intertrigonal bar. Two weeks later, the patient underwent a robot-assisted laparoscopic repair of the recurrent VVF. In this challenging case, surgeons (M.D.D. and M.M.) considered taking advantage of the robotic approach, aiming to overcome the technical limitations of traditional laparoscopy, namely the significant technical challenges posed by VVF dissection and intracorporeal suturing. The robotic system, with its advanced Endo-Wrist instruments, combined with a three-dimensional visualization, improved depth perception, motion scaling, tremor filtration, higher magnification, and an ergonomically favourable setup, enables procedures even in most unfavourable scenarios. Due to the proximity to the ureteral orifices, the considerable size of the fistula, and the presence of retracted tissues with dense fibrous adhesions, surgeons opted for a trans vesical approach. This strategy allowed a complete circumferential excision of the fibrous and scar tissue around the fistula while preserving both ureteral orifices. In this second case, the Omentum was short, rigid, and firmly attached

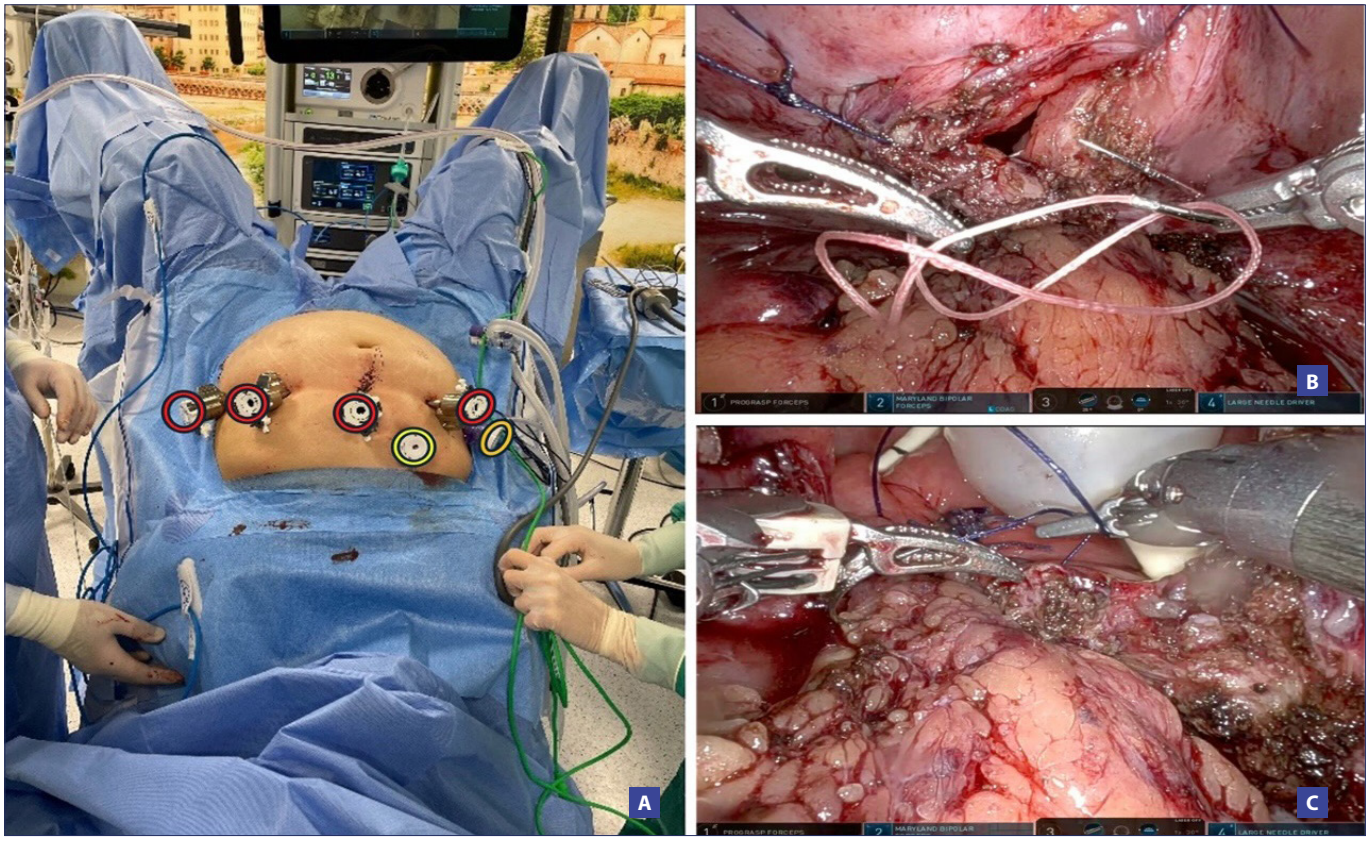

Figure 5. *Schematic representation of urachal flap interposition technique.*

(A) Robot assisted surgical setting. **(B,C)** Intraoperative findings showing the interposition of an urachal flap, supplemented by a peritoneal leaflet, between the bladder and vaginal walls to ensure suture line separation and minimize the risk of fistula recurrence.

to the abdominal wall. Consequently, a urachal flap, supplemented by a peritoneal leaflet, was mobilized and interposed between the bladder and vagina to effectively separate the suture lines and reduce the risk of fistula recurrence (**Figure 5**). Also in this case, the procedure was concluded with a hydrodistension bladder leak test to confirm bladder integrity, followed by the placement of a pelvic drain and the insertion of a Foley catheter secured in conjunction with the ureteral stents. Console time was 145 min. The estimated blood loss was 80 cc, and no surgical-related complications were reported. The ureteral catheters were removed on the 1st POD, while the abdominal drainage was removed after 48 hours. Perioperative antibiotic prophylaxis was administered for 5 days. The patient was discharged home on the 4th POD with an indwelling urethral catheter, which was removed after 15 days following a normal result at the voiding cystourethrography. At the 6-month and one year follow-up assessment, the patient maintained unobstructed urinary voiding patterns, without any instances of VVF recurrence detected.

DISCUSSION

VVFs as abnormal communications between the bladder and the vagina. They carry significant morbidity burden, including urinary incontinence, recurrent urinary tract infections, vaginal discharge, and psychological distress [7]. VVFs have a rare occurrence in Western countries, primarily resulting from iatrogenic injuries. Surgical repair becomes necessary when conservative management fails, However, timing and surgical approaches (vaginal, laparotomic, laparoscopic, robot-assisted) are still under debate. The newest strategy to treat such conditions is combining a robot-assisted to a laparoscopic approach, whom main surgical phases and key points are listed in **Table 1**.

The first report was published in 2005 by Melamud *et al.* [12], where, the above-mentioned technique, has demonstrated high healing rates (over 95%) with excellent aesthetic results [13-17], however, limited evidence about long-term prognosis is yet available. Aiming to describe the advantages and limits of such a technique, we've realised a narrative literature review using PubMed, Scopus, Google Scholar,

Table 1. *Main phases of Robot-assisted VVF repair.*

Endoscopic phase
- Cysto-vaginoscopy; safety JJ ureteral catheter placement
- VVF tract identification via guidewire/5 Fr ureteral catheter
Robotic phase
- Port Placement and pneumoperitoneum induction: 8-mm robotic camera port 2 cm above the umbilicus using, two 8-mm robotic ports along the pararectal lines on both sides, an 8 mm port above the left iliac crest dedicated to the Da Vinci Xi fourth arm for bladder retraction, and supplementary 5 mm and 12 mm ports for the assistant, one near the right iliac crest and another between the optic port and the right 8 mm port
- Intestinal adhesiolysis and Douglas pouch exposure
- Isolation of the vesicovaginal space, exposing the fistula tract
- Excision of the fibrotic tract tissue. One of two approaches is selected based on the degree of tissue scarring, adhesions, and the characteristics of the fistula. For patients with complex VVF , those with altered pelvic anatomy due to previous surgeries or radiotherapy, or fistulas located in the trigonal zone a trans vesical approach is used. This involves a monopolar longitudinal cystotomy of the posterior bladder wall for direct visualization of the fistula tract, followed by a circumferential "tennis racket-shaped" incision around the fistula margins with monopolar robotic scissors to excise the scarred and necrotic tissue. Alternatively, when feasible, the fistula is identified and excised using an external approach without a longitudinal cystotomy, ensuring precise removal of the fistulous tract with adequate margins of healthy tissue. In both methods, the excised tissue is sent for histopathological analysis
- Closure of the vaginal and bladder breach with tension free techniques. The vaginal incision is then closed transversely using a continuous 3-0 monofilament synthetic absorbable suture whereas the bladder is closed longitudinally in two layers with a continuous 4-0 monofilament absorbable suture
- Bladder water-tightness test
- Interposition of Omentum or other tissue if technically feasible
- Abdominal drainage and urinary catheter

JJ: double J; VVF: Vulvo vaginal fistula; Fr: French.

and Web of Science databases from their inception through January 2024. The following search strings were "robotic surgery AND vesicovaginal fistula", "robot-assisted surgery AND vesicovaginal fistula", "robotic surgery AND vesicovaginal fistula repair", "robot-assisted surgery AND vesicovaginal fistula repair". English restriction was applied. Studies that were not focused on robot-assisted VVF management were excluded. The selection included original research articles, clinical guidelines, retrospective and prospective cohort studies, case-control studies, case reports, and expert consensus statements. Three independent reviewers (G.C., M.M., and M.D.D.) screened titles and abstracts for inclusion. As a narrative review, no formal guidelines were followed. A total of 315 results were found. After the selection process, 15 studies were included [12, 17-30], results available on **Table 2**. Most of the study population was in their forties, with a mean age of 47. The most common cause of VVF was iatrogenic injury following surgical procedures, such as hysterectomy or mesh placement for urinary incontinence. Most patients underwent primary robotic VVF repair more than 12 weeks after the initial surgery. A total of 80 cases were reported. The mean fistula size, described in 8 out of 15 studies (53.3%), was 1.49 cm. The mean blood loss, reported and quantified in 11 out of 15 studies (73.3%), was minimal and clinically insignificant, averaging 73.08 ml. The median operative time, specified in 11 out of 15 studies (73.3%), was 197.27 minutes. Console time was separately reported in only 2 out of 15 studies (13.3%), with a mean duration of 133.75 minutes. In 13 out of 15 studies (86.7%), an interposition flaps enhanced fistula closure and healing. The most utilized flaps included omental flaps (6/13), sigmoid epiploicae (1/13), colonic epiploicae (1/13), peritoneal flaps (2/13), and amniotic allograft interposition tissue flaps (2/13). In one study, fibrin glue was employed as an alternative. Regarding urinary diversion devices, five studies did not specify their use, one reported the absence of any device, one utilized a ureteral catheter, and eight employed a Double J stent. No major postoperative complications were recorded. Only one study reported a minor event, classified as Clavien-Dindo grade I. The median follow-up duration across the included studies was relatively short (8.68 months) and did not exceed 12 months in 12 out of 15 studies (80%). However, long-term follow-up data from 2 out of 15 studies (13.3%) are promising, with durations of 14.25 and 28.3 months without recurrence. The success rate was 100% in 14 out of 15 studies (93.3%); only one study reported two cases of failure involving complex fistulas necessitating reintervention.

Since Melamund *et al*. first documented a robot-assisted VVF repair in 2005, the field has seen

a growing body of evidence over the past decade [12]. Successful VVF repair relies on several key principles, including optimal visualization, careful dissection, precise tissue alignment, a tension-free and watertight closure, the use of well vascularized tissue flaps, and adequate postoperative urinary drainage [29, 30]. While these fundamentals remain constant across different surgical approaches, minor variations exist. One of the most notable changes is the preference for a limited posterior cystotomy rather than a complete bladder bisection, which helps in reducing surgical trauma and shortening the suture line. Different strategies have been proposed to facilitate intraoperative fistula localization. One method involves cystoscopy illumination, where the robotic camera light is temporarily turned off to enhance visualization. Alternatively, a Foley or Fogarty catheter can be inserted through the fistula to aid identification [31]. A cost-effective approach, described by Bora *et al*., involves positioning a ureteric catheter through the fistula tract, allowing the scrub assistant to apply gentle traction to pinpoint the exact site, enabling a precise incision over the posterior bladder wall [22, 29].

Historically, VVF management involved urinary diversion through feeding tubes, suprapubic catheters, and urethral catheters, primarily to ensure continuous drainage, prevent excessive bladder distension, and reduce the risk of suture dehiscence. In modern practice, DJ stents have become more common for ureteral drainage, while urethral catheters remain standard for bladder decompression. According to our literature review out of 15 studies 8/15 preferred DJ stents to secure ureteral drainage. The described cases secured an empty bladder using a urethral Foley catheter.

Multilayer closure and interposition flaps are widely recognized as key elements in the surgical management of VVFs. While some approaches advocate for a double-layer bladder closure, others report similar success rates with a single layer technique. A review by Miklos *et al*. found no significant difference in outcomes between laparoscopic and robotic VVF repairs, regardless of whether a single layer or double layer closure was realized [32]. However, in an experimental study on mongrel dogs, Sokol *et al*. demonstrated improved outcomes with a double-layer bladder closure compared to a single-layer approach [33]. In this scenario, our institution has consistently adopted the double layer bladder closure to ensure a watertight, reinforced repair. This approach has yielded encouraging results that align with the existing evidence. Tissue interposition has been considered an effective practice in repairing VVFs. Different techniques have been described in the available literature. The most adopted tissues are omental/peritoneal flaps, sigmoid epiploic, and/or amniotic allografts. These flaps serve a dual purpose: from one side they allow creating a physical barrier between the bladder and vagina; at the same time, from the other, they will enhance vascularity and promote tissue healing. However, the necessity of interposition flaps remains debatable, particularly in non-radiated patients. A study by Miklos *et al*. found no significant impact on cure rates with or without flaps, concluding that the quality of the fistula closure itself is the most critical factor for successful outcomes. This observation holds particularly true for simple VVFs. On the other hand, for recurrent VVF cases, evidence is conflicting. If Miklos *et al*. reported that in such instances interposition grafts did not provide a clear advantage [32], Bora *et al*. reported the effectiveness of sigmoid epiploicae flaps, emphasizing their accessibility and proximity to the fistula site, which can be beneficial in specific clinical scenarios [29].

Surgical duration for robot-assisted VVF repair varies significantly in published studies, ranging from 95 to 305 minutes (**Table 2**). These differences stem from factors such as surgeon expertise and differences in how operative time is measured, with some studies reporting only console time. Blood loss during surgery is typically minimal, generally falling between negligible levels. Postoperative hospitalization is usually brief, reflecting the well-established benefits of minimally invasive surgery, which promotes faster recovery and reduced morbidity. Reported follow-up periods are inconsistent across studies, spanning from 3 to 28.3 months after surgery.

Complications following robotic VVF repair have been reported to be low. Gellhaus *et al*. reported a single immediate postoperative event, classified as Clavien grade 3, where the patient developed colonic dilation requiring colonoscopic decompression [26]. Additionally, two cases of recurrence were identified in the same cohort [29].

Complex VVFs are defined as those larger than 3 cm, those that have failed previous repairs or require reoperations, those with a distal margin within 1.5 cm of the bladder neck, post radiation fistulas, fistulas near the ureteric orifice, those with extensive fibrosis, or those associated with a rec-

Table 2. *Literature review about robot-assisted VVF repair cases.*

Reference	n. of patients	Age (yrs)	Fistula Dimensions (cm)	Blood loss (mL)	Surgical duration time (min)	Interposed tissue	Urethral drainage method	Postoperative complications	Mean follow-up (months)	Success outcome (%)
Melamund *et al.* [12], 2005	1	44	N/A	50	280	Fibrin glue	Double-J stent	-	4	100% (1/1)
Sundaram *et al.* [17], 2006	5	26–68	3.1	70	233	Omental flap	Double-J stent (2/5)	-	6	100% (5/5)
Schimpf *et al.* [18], 2007	1	41	1	Minimal	240	Perisigmoid fat	Double-J stent	-	3	100% (1/1)
Sears *et al.* [19], 2007	1	47	N/A	Not measured	N/A	Omental flap	Not specified	-	NR	100% (1/1)
Hemal *et al.* [20], 2009	3	32	1–1.5	100	127.5 (console)	Pedicled peritoneal flap	Not specified	-	3	100% (3/3)
Gupta *et al.* [21], 2010	12	27	2.8	88	140 (console)	Amniofix; omentum; colonic epiploicae; peritoneum	Double-J stent	-	6	100% (12/12)
Kurz *et al.* [22], 2012	3	40–64	N/A	N/A	N/A	Peritoneal flap	Double-J stent	-	10	100% (3/3)
Rogers *et al.* [23], 2014	2	42–51	N/A	N/A	N/A	Omental flap	Not specified	-	12	100% (2/2)
Dutto and O'Rielly [24], 2013	1	56	0.8	N/A	N/A	Pedicled colonic epiploicae	Double-J stent	-	6	100% (1/1)
Bragayrac *et al.* [25], 2014	4	46	1.5	100	117.5	Omental flap	Double-J stent	-	14.25	100% (4/4)
Gellhaus *et al.* [26], 2015	10	52	N/A	52.8	249	Omental flap	Not specified	1	28.3	100% (10/10)
Martini *et al.* [27], 2016	1	43	N/A	50	95	/	Ureteric catheter	-	6	100% (1/1)
Price *et al.* [28], 2016	1	66	1	50	305	Amniofix	Not specified	-	5	100% (1/1)
Bora *et al.* [29], 2016	30	43	–	50	133	Omental flap; sigmoid epiploicae; peritoneum	None	-	6	93% (28/30)
Matei *et al.* [12, 30], 2017	5	62	0.5	120	250	/	Double-J stent	-	12	100% (5/5)

tovaginal fistula. Although trans-vaginal repair is minimally invasive, it poses technical challenges for supra-trigonal VVFs, in patients with radiation induced vaginal narrowing, or when simultaneous ureteric reimplantation is needed. While the prone transvaginal approach may alleviate some of these issues, its complex positioning can complicate aesthetic management. In contrast, the abdominal approach offers a more expansive operative field, enabling the repair of complex fistulas that may require ureteric reimplantation or augmentation cystoplasty, and allowing the use of interpositional tissues such as the Omentum without compromising vaginal length. Moreover, the advent of robot-assisted surgery has significantly reduced the morbidity associated with open transabdominal repairs, providing improved ergonomics, enhanced suturing in the confined pelvic space, and magnified visualization for precise reconstruction of complex fistulas [33, 34].

A key measure of success in VVF repair is the restoration of urinary continence. While the application of robot-assisted techniques in VVF surgery is expanding, current reports remain limited due to small patient cohorts and short follow-up durations. Most studies indicate high success rates, with

nearly all published series except one showing a 100% closure rate. However, larger studies are still lacking, making it difficult to draw definitive conclusions. One of the most comprehensive analyses, conducted by Bora *et al*., reported a 93% success rate, with two cases of recurrence out of 30 patients, both involving complex fistulas [29]. These outcomes are comparable to those observed in laparoscopic and open approaches, as documented by Miklos *et al*., suggesting that robotic techniques may offer similar effectiveness with the potential benefits of minimally invasive surgery [35]. Despite successful anatomical closure, a subset of patients up to 20% may continue to experience urinary incontinence due to factors unrelated to the fistula itself. Miklos *et al*. developed a predictive risk model to address this, analysing 401 VVF cases to identify patients at higher risk for persistent incontinence after surgery. This underscores the importance of preoperative counselling, ensuring patients understand the potential for residual incontinence even after a technically successful repair [35].

Robotic surgery combines the benefits of laparoscopy with stereoscopic vision and the ability to employ wrist movements commonly used in open surgery. Enhanced and highly magnified three-dimensional (3-D) high-definition (HD) vision, improved dexterity, accurate depth perception with an immersive surgical experience and enhanced ergonomics offer surgeons advanced capabilities and patients improved outcomes [17, 35-42]. Furthermore, these technical benefits are highlighted by its low morbidity, namely reduced blood loss, shorter hospital stays, faster recovery times, and superior functional and cosmetic outcomes [15]. However, based on a consensus review of existing literature by the European Association of Urology Robotic Urology Section (ERUS) Scientific Working Group for Reconstructive Urology, there is no consensus recommendation for robotic VVF repair. The selection of the surgical approach (*i.e*. vaginal or abdominal, laparoscopic, or with robotic assistance), the decision to use flaps, and whether to opt for a trans or extra-vesical approach, should be tailored to the characteristics of the patient and the fistula itself [34].

The results from our research encourage the adoption of robot assisted VVFs repair in primary and recurrent cases, considering its successful rate associated with short- and long-term good outcome. Limitation from our study is the little number of available cases, bigger sample are needed to increase the accuracy of our results.

CONCLUSIONS

Robot-assisted VVFs surgical repair represents a state-of-the-art treatment, combining advanced technology with surgical expertise to achieve optimal postoperative outcomes. In our experience, it is feasible, safe, effective, and represents a viable approach, especially in complex cases. With its intrinsic technique advantages, the robotic approach allowed access to narrow spaces otherwise difficult to reach, improving the procedure success rate and even management of re-do VVF repair cases. Ongoing advancements in robotic instrumentation, imaging modalities, and surgical techniques hold promise for further enhancing the safety, efficacy, and accessibility of this approach in the management of urogynaecology disorders.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

M.M., G.Az., M.G., M.D.D.: Conceptualization. G.Az., G.A.: Data curation. G.Az.: Formal analysis, software. M.M., G.Az.: Investigation. G.Az., A.Pe., R.B., F.D.M., A.Pi.: Methodology. M.M.: Project administration, resources, visualization. M.M., M.D.D.: Supervision. M.M., M.D.D.: Validation. G.Az., C.B., V.Z., M.M., P.Q., M.G., M.D.D.: Writing – original draft, writing – review & editing.

Funding

None.

Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

For this case report, formal IRB approval is exempted, although all procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent
Written informed consent was obtained from all subjects involved in the study.

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

REFERENCES

1. Malik MA, Sohail M, Malik MT, Khalid N, Akram A. Changing trends in the etiology and management of vesicovaginal fistula. Int J Urol. 2018;25(1):25-29. doi: 10.1111/iju.13419.
2. Obstetric Fistula Availablefrom: https://www.who.int/news-room/facts-in-pictures/detail/10-facts-on-obstetric-fistula. Accessed on February 16, 2025.
3. Hilton P. Vesico-vaginal fistula: new perspectives. Curr Opin Obstet Gynecol. 2001;13(5):513-20. doi: 10.1097/00001703-200110000-00011.
4. Stamatakos M, Sargedi C, Stasinou T, Kontzoglou K. Vesicovaginal fistula: diagnosis and management. Indian J Surg. 2014;76(2):131-6. doi: 10.1007/s12262-012-0787-y..
5. Chinthakanan O, Sirisreetreerux P, Saraluck A. Vesicovaginal Fistulas: Prevalence, Impact, and Management Challenges. Medicina (Kaunas). 2023;59(11):1947. doi: 10.3390/medicina59111947.
6. Zacharin RF. A history of obstetric vesicovaginal fistula. Aust N Z J Surg. 2000;70(12):851-4. doi: 10.1046/j.1440-1622.2000.01990.x.
7. Sims JM. On the treatment of vesico-vaginal fistula. 1852. Int Urogynecol J Pelvic Floor Dysfunct. 1998;9(4):236-48. doi: 10.1007/BF01901610.
8. Ghotb Sajjadi S. Hortváth Ö.P. Kalmár, K. Martius Flap: Historical and Anatomical Considerations. Eur J Plast Surg. 2012;35:711-716. doi:10.1007/s00238-012-0742-y.
9. Latzko, W. Postoperative Vesicovaginal Fistulas: Genesis and Therapy. Am J Sur. 1942;58:211-228. doi:10.1016/S0002-9610(42)90009-6.
10. O'conor VJ, Sokol JK. Vesicovaginal fistula from the standpoint of the urologist. J Urol. 1951;66(4):579-85. doi: 10.1016/S0022-5347(17)74381-9.
11. Nezhat CH, Nezhat F, Nezhat C, Rottenberg H. Laparoscopic repair of a vesicovaginal fistula: a case report. Obstet Gynecol. 1994;83(5 Pt 2):899-901.
12. Melamud O, Eichel L, Turbow B, Shanberg A. Laparoscopic vesicovaginal fistula repair with robotic reconstruction. Urology. 2005;65(1):163-6. doi: 10.1016/j.urology.2004.09.052.
13. Bodner-Adler B, Hanzal E, Pablik E, Koelbl H, Bodner K. Management of vesicovaginal fistulas (VVFs) in women following benign gynaecologic surgery: A systematic review and meta-analysis. PLoS One. 2017;12(2):e0171554. doi: 10.1371/journal.pone.0171554.
14. Patel VR, Thaly R, Shah K. Robotic radical prostatectomy: outcomes of 500 cases. BJU Int. 2007;99(5):1109-12. doi: 10.1111/j.1464-410X.2007.06762.x.
15. Pick DL, Lee DI, Skarecky DW, Ahlering TE. Anatomic guide for port placement for daVinci robotic radical prostatectomy. J Endourol. 2004;18(6):572-5. doi: 10.1089/end.2004.18.572.
16. Hemal AK, Eun D, Tewari A, Menon M. Nuances in the optimum placement of ports in pelvic and upper urinary tract surgery using the da Vinci robot. Urol Clin North Am. 2004;31(4):683-92, viii. doi: 10.1016/j.ucl.2004.06.010.
17. Sundaram BM, Kalidasan G, Hemal AK. Robotic repair of vesicovaginal fistula: case series of five patients. Urology. 2006;67(5):970-3. doi: 10.1016/j.urology.2005.11.014.
18. Schimpf MO, Morgenstern JH, Tulikangas PK, Wagner JR. Vesicovaginal fistula repair without intentional cystotomy using the laparoscopic robotic approach: a case report. JSLS. 2007;11(3):378-80.
19. Sears CL, Schenkman N, Lockrow EG. Use of end-to-end anastomotic sizer with occlusion balloon to prevent loss of pneumoperitoneum in robotic vesicovaginal fistula repair. Urology. 2007;70(3):581-2. doi: 10.1016/j.urology.2007.05.026.
20. Hemal AK, Sharma N, Mukherjee S. Robotic repair of complex vesicouterine fistula with and without hysterectomy. Urol Int. 2009;82(4):411-5. doi: 10.1159/000218529.
21. Gupta NP, Mishra S, Hemal AK, Mishra A, Seth A, Dogra PN. Comparative analysis of outcome between open and robotic surgical repair of recurrent supra-trigonal vesico-vaginal fistula. J Endourol. 2010;24(11):1779-82. doi: 10.1089/end.2010.0049.
22. Kurz M, Horstmann M, John H. Robot-assisted laparoscopic repair of high vesicovaginal fistulae with peritoneal flap inlay. Eur Urol. 2012;61(1):229-30. doi: 10.1016/j.eururo.2011.09.022.
23. Rogers AE, Thiel DD, Brisson TE, Petrou SP. Robotic assisted laparoscopic repair of vesico-vagi-

nal fistula: the extravesical approach. Can J Urol. 2012;19(5):6474-6.
24. Dutto L, O'Reilly B. Robotic repair of vesico-vaginal fistula with perisigmoid fat flap interposition: state of the art for a challenging case? Int Urogynecol J. 2013;24(12):2029-30. doi: 10.1007/s00192-013-2081-3.
25. Bragayrac LA, Azhar RA, Fernandez G, Cabrera M, Saenz E, Machuca V, et al. Robotic repair of vesicovaginal fistulae with the transperitoneal-transvaginal approach: a case series. Int Braz J Urol. 2014;40(6):810-5. doi: 10.1590/S1677-5538.IBJU.2014.06.12.
26. Gellhaus PT, Bhandari A, Monn MF, Gardner TA, Kanagarajah P, Reilly CE, et al. Robotic management of genitourinary injuries from obstetric and gynaecological operations: a multi-institutional report of outcomes. BJU Int. 2015;115(3):430-6. doi: 10.1111/bju.12785.
27. Martini A, Dattolo E, Frizzi J, Villari D, Paoletti MC. Robotic vesico-vaginal fistula repair with no omental flap interposition. Int Urogynecol J. 2016;27(8):1277-8. doi: 10.1007/s00192-016-2989-5.
28. Price DT, Price TC. Robotic repair of a vesicovaginal fistula in an irradiated field using a dehydrated amniotic allograft as an interposition patch. J Robot Surg. 2016;10(1):77-80. doi: 10.1007/s11701-015-0546-8.
29. Bora GS, Singh S, Mavuduru RS, Devana SK, Kumar S, Mete UK, et al. Robot-assisted vesicovaginal fistula repair: a safe and feasible technique. Int Urogynecol J. 2017;28(6):957-962. doi: 10.1007/s00192-016-3194-2.
30. Matei DV, Zanagnolo V, Vartolomei MD, Crisan N, Ferro M, Bocciolone L, et al. Robot-Assisted Vesico-Vaginal Fistula Repair: Our Technique and Review of the Literature. Urol Int. 2017;99(2):137-142. doi: 10.1159/000475887.
31. Sotelo R, Mariano MB, García-Segui A, Dubois R, Spaliviero M, Keklikian W, et al. Laparoscopic repair of vesicovaginal fistula. J Urol. 2005;173(5):1615-8. doi: 10.1097/01.ju.0000154701.97539.ef.
32. Miklos JR, Moore RD. Failed omental flap vesicovaginal fistula repair subsequently repaired laparoscopically without an omental flap. Female Pelvic Med Reconstr Surg. 2012;18(6):372-3. doi: 10.1097/SPV.0b013e3182751139.
33. Sokol AI, Paraiso MF, Cogan SL, Bedaiwy MA, Escobar PF, Barber MD. Prevention of vesicovaginal fistulas after laparoscopic hysterectomy with electrosurgical cystotomy in female mongrel dogs. Am J Obstet Gynecol. 2004;190(3):628-33. doi: 10.1016/j.ajog.2003.09.062.
34. Randazzo M, Lengauer L, Rochat CH, Ploumidis A, Kröpfl D, Rassweiler J, et al. Best Practices in Robotic-assisted Repair of Vesicovaginal Fistula: A Consensus Report from the European Association of Urology Robotic Urology Section Scientific Working Group for Reconstructive Urology. Eur Urol. 2020;78(3):432-442. doi: 10.1016/j.eururo.2020.06.029.
35. Miklos JR, Moore RD, Chinthakanan O. Laparoscopic and Robotic-assisted Vesicovaginal Fistula Repair: A Systematic Review of the Literature. J Minim Invasive Gynecol. 2015;22(5):727-36. doi: 10.1016/j.jmig.2015.03.001.
36. Angioli R, Penalver M, Muzii L, Mendez L, Mirhashemi R, Bellati F, Crocè C, Panici PB. Guidelines of how to manage vesicovaginal fistula. Crit Rev Oncol Hematol. 2003;48(3):295-304. doi: 10.1016/s1040-8428(03)00123-9.
37. Leng WW, Amundsen CL, McGuire EJ. Management of female genitourinary fistulas: transvesical or transvaginal approach? J Urol. 1998;160(6 Pt 1):1995-9. doi: 10.1097/00005392-199812010-00013.
38. Porpiglia F, Fiori C, Morra I, Ragni F, Vaccino D, Scarpa RM. Laparoscopic vesico-vaginal fistula repair: our experience and review of the literature. Surg Laparosc Endosc Percutan Tech. 2009;19(5):410-4. doi: 10.1097/SLE.0b013e3181b7315c.
39. Meneses AD, Oliveira AQ, de Araujo DA, Santos DT, de Carvalho LY, Eulalio WMN Filho, et al. Transabdominal and transvesical laparoscopic correction of vesico-vaginal fistula: 42 cases experience. Int Braz J Urol. 2020;46(2):296-297. doi: 10.1590/S1677-5538.IBJU.2018.0743.
40. Manharlal Tilala Y, Panda S, Shankar Paul A, Kumar Mohanty P, Choudhur S, Swain S. Comparative Analysis Between Laparoscopic Extravesical Repair and Laparoscopic O'Connor Repair for Supratrigonal Vesicovaginal Fistula. Urol Res Pract. 2024;50(1):58-65. doi: 10.5152/tud.2024.23147.
41. Jairath A, B SS, Mishra S, Ganpule A, Sabnis R, Desai M. Robotic repair of vesicovaginal fistula - initial experience. Int Braz J Urol. 2016;42(1):168-9. doi: 10.1590/S1677-5538.IBJU.2014.0629.
42. Lecoanet P, Madanelo M, Tricard T, Mauger de Varennes A, Haudebert C, Richard C, et al. Robot-assisted vesicovaginal fistula repair: comparison of the extravesical and transvesical techniques. Int Urogynecol J. 2023;34(10):2479-2485. doi: 10.1007/s00192-023-05565-7.

Italian Journal of
Gynæcology & Obstetrics
September 2026 - Vol. 38 - N. 3 - Quarterly - ISSN 2385 – 0868

Clinical outcomes among pregnancy complicated by cancer: analysis of 41 cases

Madhva **Prasad** *, Anahita **Chauhan**, Priyanka **Deshpande,** Shreshta **Mahanti**

Department of OBGYN, Seth GS Medical College and KEM Hospital, Mumbai, India.

ARTICLE INFO

History
Received: 01 October 2025
Received in revised form: 30 November 2025
Accepted: 22 December 2025
Available online: 10 September 2026

DOI: 10.36129/jog.2026.259

Key words
Cancer-survivor; indirect maternal mortality; high-risk pregnancy; critical care obstetrics.

***Corresponding author:** Madhva **Prasad**, MS, DNB, FICOG. Department of OBGYN, St Johns Medical College Hospital, Bangalore 560097, India.
Email: madhva@gmail.com.
ORCID: 0000-0001-5507-7812

ABSTRACT

Objective. With a rising incidence of cancer in the reproductive age group and a rising contribution of indirect causes towards maternal mortality, the entity of cancer in pregnancy deserves more attention. Data from India is largely limited to individual case reports. To describe the demographic details, details regarding cancer, obstetric and neonatal outcomes among patients with cancer in pregnancy.

Materials and Methods. A retrospective observational study was conducted by screening delivery and MTP records for the terms "cancer", "malignancy" in the "risks" column to identify patients. Three years data (January 2016-December 2018) was collected. Relevant obstetric history, pregnancy course, cancer treatment details and obstetric/neonatal outcomes were noted. Results were tabulated. No comparison group was taken.

Results. Over a 3-year period, 41 pregnancies with cancer with an average age of 28.7 years, majority second gravida were identified. Malignancies of the reproductive tract (n = 11) and breast (n = 7) were the most common, followed by other organs. Nineteen patients (46.34%) had cancer prior to pregnancy. 28 patients underwent MTP and nine were preterm deliveries. Only four patients delivered at term. Six mothers needed ICU care and there were three mortalities.

Conclusions. Cancer in pregnancy, though rare, can pose several challenges to the obstetrician and the oncologist. Further prospective data is needed on the topic of cancer and pregnancy.

INTRODUCTION

While the vast majority of pregnancies are uneventful and uncomplicated, obstetricians are well-versed in dealing with medical conditions complicating pregnancy such as hypertension, diabetes, *etc*. However, as a rarity, some medical conditions with grave prognosis may occur first or be noticed first in the course of pregnancy. An example of one such grave condition is cancer. What happens when these two conditions – pregnancy and cancer occur simultaneously – is the focus of this article.
Most recent cancer registries estimate that the incidence of cancer has been rising over the last few decades (global estimate of 14.9 million incident cancer cases and 8.2 million deaths in 2013) [1]. Mathur *et al*. [2] have confirmed such a trend (an estimated 13 lakh patients with cancer in India). Based on an

observation in Tunisia, Dimassi *et al*. [3] suggest that cancer appears to be the most common cause of death in women belonging to the reproductive age group, with a recommendation that cancer in the reproductive age group should receive more attention.

In general, gynaecologists are looking for many ways to prevent cancer too [4]. The contribution of cancer of maternal mortality is quite low (only 1% in a large analysis of indirect maternal mortality) [5]. However, with the reducing prevalence of direct causes of maternal mortality [6], due to the robust improvement in maternal healthcare, the proportion attributed to rare causes like cancer may become more prominent.

Cancer with pregnancy is in itself very rare. A study in Nepal showed a prevalence of around 1 in 1,000 deliveries [7]. In the western literature, cancer attributable maternal mortality is also very less (around 3.16 per 100,000 live births) [8]. Most literature pertaining to cancer and pregnancy are in the form of case reports or very small case series [9-13]. In this context, the objectives of the study were to describe the demographic details, details regarding cancer, obstetric and neonatal outcomes among patients with cancer in pregnancy.

MATERIALS AND METHODS

This was a retrospective observational study involving review of records in a tertiary care centre located in Western urban India. The labour ward register and the medical termination of pregnancy register were screened by the investigators of the study for the terms "cancer", "malignancy" or any other similar were identified and noted. The admission papers were retrieved from the medical records department were reviewed and patient details were noted by two investigators. All MTPs which had been conducted in patients with malignancy, for any reason, were identified and the indoor papers of these patients were also scrutinized. Data was collected for a duration of 3 years (January 2016-December 2018). All patients with pregnancy and cancer (immaterial of the trimester of presentation, registration status and all types of cancers) were included. Those who had delivered elsewhere, those who had inadequate data or missing records were excluded.

Demographic details, obstetric history, details course of the pregnancy (terminated or continued, need for hospitalization, antenatal complications), details of the cancer treatment (nature of malignancy, site, histological type, time of diagnosis, treatment details, chemotherapy, radiotherapy, *etc*., relationship between cancer diagnosis and pregnancy), and the outcomes of the present pregnancy were noted in detail. Gestational age at the time of delivery, the type of delivery, need for intensive care unit admission and any attendant complications were noted. Neonatal outcomes in terms of need for NICU admission were noted. If there was a mortality, the relevant details were noted with more detail.

Statistical analysis

The results were tabulated and represented using appropriate statistical methods of representation using Microsoft excel. No comparison groups were taken, and advanced statistical analysis was not required.

RESULTS

Over a 3-year period, 41 pregnancies with cancer were identified.

Demographic details

The average age was 28.7 ± 4.05 years, the youngest being 21 years and the oldest being 40 years. Being a tertiary care referral institute, most of the patients were referred from a geographical location away far from the treating institute.

Obstetric details

The gravidity distribution is shown in **Table 1**. Majority of the patients were second gravida. Among the multigravida patients (n = 35), there were 5 patients who did not have any living issues.

Tissue of origin of the cancer

There were 11 malignancies of the reproductive tract and remaining 30 were of other organs. The

Table 1. *Distribution of parity.*

Gravida status	Number (%) (n = 41)
Primigravida	6 (14.63%)
Gravida 2	16 (39.02%)
Gravida 3	10 (24.39%)
Gravida 4 and above	9 (21.95%)

Table 2. *Tissue of origin of the cancer (n = 41).*

System involved	Type of malignancy	Number
Reproductive organs (n = 11)	Squamous cell carcinoma cervix	4
	Adenocarcinoma cervix	2
	Ovarian epithelial	2
	Adenocarcinoma endometrium Uterus	3
Breast (n = 7)	Adenocarcinoma Breast	7
Gastrointestinal (n = 6)	Oesophagus (adenocarcinoma)	1
	Krukenberg tumour	1
	Rectum (all adenocarcinoma)	4
Endocrine (n = 5)	Pancreas (adenocarcinoma)	1
	Adrenal Carcinoma	1
	Malignant Pheochromocytoma	1
	Thyroid (Papillary)	1
	Thyroid (Medullary)	1
Brain (n = 4)	Oligodendroglioma	1
	Glioblastoma multiforme	2
	Hemangiopericytoma	1
Haematological (n = 3)	Acute myeloid leukaemia	1
	Chronic myeloid leukaemia	2
Soft tissue / bone (n = 3)	Ewing sarcoma	2
	Giant Cell Tumour	1
Lung (n = 1)	Squamous cell carcinoma	1
Tongue (n = 1)	Squamous cell carcinoma	1

details of these types of malignancies are presented in **Table 2**. As a single entity, cancer of the breast was the most common

Time of diagnosis malignancy in relation to pregnancy

Out of the 44 patients, 19 (46.34%) were known to have cancer prior to occurrence of pregnancy. 5 (12.1%) were detected during the first trimester of pregnancy. 17 patients (41.4%) were detected in 2nd trimester. None of the patients were detected in 3rd trimester or postpartum period (**Table 3**).

Treatment details of patients who had cancer prior to pregnancy (n = 19).

Out of 19 patients who had cancer prior to pregnancy, 14 had received chemotherapy, 10 had received radiotherapy and 11 had undergone an operative procedure.

Table 3. *Time of diagnosis malignancy in relation to pregnancy.*

Time of diagnosis	Number (%) (n = 41)
Before pregnancy	19 (46.34%)
During pregnancy 1st trimester	5 (12.19%)
During pregnancy 2nd trimester	17 (41.46%)
During pregnancy 3rd trimester peripartum	0
Postpartum period	0

Operative details

The operative procedures that the patients (n = 11) had undergone were unilateral adnexectomy omentectomy (n = 1), adrenalectomy (n = 2), radical esophagectomy (n = 1), radical mastectomy (n = 3), radical resection of colon (n = 1), total thyroidectomy (n = 2) and unilateral salphingoophorectomy (n = 1). Out of these 11 patients who had undergone an operative procedure, 4 patients had undergone operative procedure less than 1 year before detection of the index pregnancy.

Contraception history of the patients who had cancer detected prior to index pregnancy.

Among the 19 patients who were known to have cancer prior to pregnancy, 18 were not on any contraceptive method. In one patient's records, there was no mention of contraception history at all.

Treatment details of patients who were diagnosed during pregnancy (n = 22).

Eleven patients were initiated on chemo-radiotherapy as appropriate soon after termination of pregnancy (4 first trimester MTPs and 7 second trimester MTPs). Seven patients needed chemo-radiotherapy but had to wait till the completion of pregnancy (MTP could not be performed). Eleven patients underwent operative procedures peri-delivery / peri-abortion, the distribution of which is shown in **Table 4**.

Table 4. *Operative procedures performed among patients detected to have malignancy during pregnancy (n = 11).*

Operative procedures performed with foetus-in-situ	Number
Craniotomy with excision of lesion	2
Diversion Sigmoidostomy	1
Procedures done in the immediate postpartum period	**Number**
Breast Conservation surgery	2
Sigmoidectomy	3
Bilateral salpingoophorectomy	1
Hemi-tongue resection	1
Thyroidectomy	1

Table 5. *Pregnancy outcomes (n = 41).*

Gestational age	Details	Number
Up to 12 weeks (n = 15)	MTP	14
	Spontaneous abortion	1
12 – 20 weeks (n = 13)	MTPs	13
	Spontaneous abortions	0
Preterm (n = 9)	Preterm caesarean	6
<28 weeks: 3	Preterm vaginal	3
28-34 weeks: 4	Delivery	
34-37 weeks: 2		
Term (n = 4)	Caesarean	1
	Vaginal delivery	3

Pregnancy outcomes (n = 41)

Pregnancy outcomes are presented in a composite format in **Table 5**. Twenty-eight patients underwent termination of pregnancy. With respect to trimester, 15 were in the first trimester and 13 were in the second trimester. With respect to time of detection, 11 MTPs were in patients who had been diagnosed in the index pregnancy and 17 were in patients who had been diagnosed prior.

Thirteen patients delivered beyond period of foetal viability. Of these, four patients delivered at term and nine were preterm deliveries. All these deliveries yielded live births. There were 13 deliveries, out of which one was twins. Of 14 neonates, 8 were male and 6 were females. Though 10 neonates needed NICU admission, there were no neonatal deaths.

Pregnancy morbidity and mortality

Number of admissions needed in antenatal period.

The number of admissions (excluding the one needed for completion of pregnancy, MTP or delivery) were noted. Majority of the patients 31/41 (75.6%) required only no admissions. Among the remaining 10 patients, 5 required one admission, and the remaining five needed more than one admission. The average duration of stay was calculated to be 8.87 days.

ICU care.

Six patients needed ICU care for decompensation in the general condition. Out of these six patients, three were in the post-delivery period.

Mortality

In this study, there were three mortalities. A brief description of the three cases is presented below.

25-year-old G3P1L0A1 who was detected to have Acute Myeloid Leukemia in the late 3rd trimester of pregnancy. She underwent induction of labour at 38 weeks of gestation and delivered live female child (no PPH). Post-delivery, she was started on chemotherapy. Succumbed on day 14 of postnatal life despite multiple blood and blood product transfusions including G-CSF injections, due to severe bleeding diathesis.

24-year-old G2P1L1 with Ewing's Sarcoma Femur. Deep Venous thrombosis (paraneoplastic syndrome) occurred in antenatal period needing anticoagulation. She went into spontaneous preterm labour and delivered a fresh stillbirth. Due to persisted DIC despite therapy, operative procedure could not be performed, and she succumbed on day 34 of delivery.

34-year-old primigravida with sudden seizures and unconsciousness diagnosed with large oligodendroglioma. Due to raised ICP unresponsive to medical therapy, emergency craniotomy was needed in antenatal period, wherein there was brief recovery in GCS. Three days post-procedure she went into spontaneous labour and delivered a live birth. She succumbed on day 9 of delivery due to neurological complications.

DISCUSSION

Main findings

This was a retrospective analysis of 3 years of cancer cases in pregnancy, and an entire range of malignancies was noted, breast cancer being the most common one. It was surprising to note that there were no cases of gestational trophoblastic neoplasia.

Cancer and pregnancy: a rare interplay of two otherwise common conditions

Boussios *et al.* have reported nine cases of lung cancer in pregnancy, in an international collaborative study [14]. Girault *et al.* identified only 20 cases of brain tumours over 8 years in a single centre study [15]. Yu *et al.* have reviewed the available evidence of thyroid cancer in pregnancy, have suggested that more patient data needs to be generated [16]. Blake *et al*. reviewed epithelial ovarian cancers in pregnancy and found only 105 cases over 50 years eligible for review [17]. Rare cancers like vulval cancers have also been reported in pregnancy [18]. The one type of cancer with a high incidence and probably adequate literature is breast cancer [19]. Azim *et al*. in their article titled "Managing cancer during pregnancy: what evidence do we have?" have emphasized the fact that adequate data is not available in this matter, and with further data,

complex management issues can be looked into with better light [20]. None of these analyses have attempted in giving any incidence/prevalence statistics because of the inherent risk of hospital bias. The same principle is followed in the study also, and only the numbers (and no proportions) have been presented.

Strengths and limitations of the present study

It is hoped that this data presented here adds to the existing pool of knowledge regarding this otherwise rare topic. The authors acknowledge that, being a retrospective observational study, despite meticulous attempts at analysis, there may be some cases which may have been missed, and this is a drawback of this study.

Management of each case is individualized

Usually, patients are sent to high volume tertiary care centres for obstetric care, be it delivery or for medical abortion. In the analysis, a detailed description of each individual case and the course is not possible due to need for brevity. In most situations, management is highly individualized and decided on a case-to-case basis, involving a multi-disciplinary approach, following the risk-benefit ratio principles, taking care of both maternal and foetal well-being.

The diagnostic techniques, chemotherapy protocols compatible with pregnancy, and decision-making processes regarding timing of delivery and cancer treatment, definitely need further refinement.

Cancer cervix – impact of HPV and pregnancy

In this study, there were 6 patients with cancer cervix but none of them had undergone a Pap smear during early antenatal period. The utilization of pregnancy as a time for early diagnosis of cervical cancer needs better clarity and consensus. The concept that performing Pap smear during pregnancy may lead to "over-diagnosis" is counteracted by the advancing average of pregnancy world over, as noted by Nygård *et al.* [21]. A recent meta-analysis [22] focussed on the natural history of High-grade CIN lesions detected during pregnancy. The results of 10 studies were reviewed and the authors concluded that "it is worth noting that a small percentage of high-grade CIN would progress to cervical cancer during pregnancy".

Fertility issues among cancer survivors

A recent review analysing the bidirectional effects of HPV on male and female reproductive health highlights its influence on pregnancy outcomes and fertility-sparing management advances. All these sensitize us towards the importance of integrating vaccination and fertility-preserving strategies in preventive care. These findings should positively impact our policy towards integrating HPV screening during pregnancy and the peripartum period [23]. In the recently reported ETERNITY project, 36 patients with early-stage cervical cancer (stages IB2, IB3) were treated with neoadjuvant therapy and conization, and followed up for around 36 months. Among 6 participants seeking fertility, 5 had successful conception, highlighting that specific interventions for cancer can preserve fertility, without increasing morbidity or mortality [24].

Similar encouraging results are observed in a systematic review of 443 early-stage cancer cervix patients with 443 patients [25].

Contraception usage among cancer survivors

In our study, out of the 19 patients who had been diagnosed to have cancer prior to detection of pregnancy and on regular follow-up, none were on any contraception. Out of these 19 patients, barring three patients (one was primigravidae and two multigravidas did not have a living issue), 16 already had a living issue. This phenomenon of non-usage of contraception among this set of cancer survivors, draws parallel to the non-usage of contraception among women with high-risk medical conditions [26].

Poor implementation of contraceptive advice and lack of regular practise of referral to contraception counselling is a trend noted among many specialist physicians [27], and this study shows that oncologists also fall in the same bracket.

"Methods of fertility preservation after cancer treatment" is a well-researched topic [28, 29]. However, not much is known about whether fertility is preserved without any intervention after cancer treatment. Balachandren *et al.* [29] have reviewed the topic of fertility and ovarian reserve after cancer diagnosis, and have highlighted the dearth of knowledge about the topic.

Hypothetical patient's thought processes such as "*I have cancer, hence, I won't conceive*" and "*I have cancer, let me enjoy my life as long as I live*" can paradoxically lead to increased coital frequency, though has not been substantiated in contemporary literature [30]. The study here, though small in size, shows that a sizeable number of women can remain fertile after cancer diagnosis/ treatment.

Occurrence of pregnancy prevents optimal cancer management

Cancer mortality is high, and there are many reasons for the same, which is common medical knowledge, and rapid strides are being made in the management of cancer [31-33]. Cancer needs surgical, chemotherapy or radiotherapy. Diagnosis of pregnancy may prevent or delay the prompt administration of appropriate cancer therapy. Even among patients in remission, side-effects of anti-neoplastic agents and pregnancy-related changes can push patients towards life-threatening emergencies [9]. In such scenarios, the valiant efforts by the oncologist team are set aside by the occurrence of pregnancy. Through this article, the authors would like to highlight that pregnancy occurrence should not be a deterrent to receiving optimal oncological care. To prevent such a catastrophe, introduction of the term "onco-contraception", on similar lines to "onco-fertility" can be considered.

CONCLUSIONS

Pregnancy with cancer presents unique challenges to the obstetrician and the oncologist, which must be handled with a multidisciplinary effort, vigilance and care. Policy upgrades regarding utilization of pregnancy as a time for cervical cancer and HPV screening is needed. Follow-up among cancer-survivors merits consideration regarding fertility concerns (both fertility preservation and contraception). Further prospective studies on the topic of cancer and pregnancy overlap are to be encouraged.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

M.P.: Conceptualization, methodology, formal analysis, supervision, writing - original draft, writing - review & editing. A.C.: Conceptualization, project administration, supervision, validation, writing - review & editing. P.D., S.M.: Data curation, resources, software, formal analysis, methodology.

Funding

None.

Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

This study was performed after Institutional Ethics Committee clearance (EC/OA-130/2018).

Informed consent

Not needed in retrospective studies

Data sharing

Data are available under reasonable request to the corresponding author.

REFERENCES

1. Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, et al. The Global Burden of Cancer 2013. JAMA Oncol. 2015;1(4):505. 10.1001/jamaoncol.2015.0735.
2. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, et al. ICMR-NCDIR-NCRP Investigator Group. Cancer Statistics, 2020: Report From National Cancer Registry Programme, India. JCO Glob Oncol. 2020;6:1063-1075. doi:10.1200/GO.20.00122.
3. Dimassi K, Saibi A, Saidi O, Ben Romdhane H. Cancer mortality among reproductive age women in Tunisia. Tunis Med. 2016; 94(1):16-22.
4. Ghizzoni V, Fagotti A, Marchetti C et al. Ovarian cancer surgery and BRCA test: a nationwide Italian survey. Ital J Gynaecol Obst. 2020;32(3):56-61. doi: 10.36129/jog.32.01.06.
5. Lumbiganon P, Laopaiboon M, Intarut N, Vogel J, Souza J, Gülmezoglu A, et al. Indirect causes of severe adverse maternal outcomes: a secondary analysis of the WHO Multicountry Survey on Maternal and Newborn Health. BJOG. 2014;121:32-9. doi: 10.1111/1471-0528.12647.
6. National Family Health Survey 5. Available from http://rchiips.org/nfhs/factsheet_NFHS-5.shtml. Accessed on May 07, 2021.
7. Pariyar J, Shrestha B, Rauniyar BP, Regmi SC, Shrestha J, Jha AK, et al. Cancer with pregnancy in a cancer hospital. J Nepal Health Res Counc. 2012;10(22):224-8.
8. Sachs BP, Penzias AS, Brown DA, Driscoll SG, Jewett JF. Cancer-related maternal mortality in Massachusetts, 1954-1985. Gynecol Oncol. 1990;36(3):395-400. doi: 10.1016/0090-8258(90)90150-j.

9. Prasad M, Chamariya S, Khadkikar R, Chauhan AR. Pregnancy in breast cancer survivor with anthracycline induced cardiomyopathy. Int J Res Med Sci. 2015;3(6):1559-61. doi: 10.18203/2320-6012.ijrms20150192.
10. Shukla A, G S J, Palakode S. Ewing's sarcoma in pregnancy. BMJ Case Rep. 2025;18(5):e263727. doi: 10.1136/bcr-2024-263727.
11. Garg A, Aggarwal M, Kashyap R. Pregnancy and Its Successful Outcome in a Patient with Multiple Myeloma. J Obstet Gynaecol India. 2021;71(1):78-81. doi: 10.1007/s13224-019-01296-2.
12. Vishnu N, Kulkarni AV, Vidhyalakshmi S, Sambandam S, Garg P, LeelaKrishnan V, et al. Fibrolamellar variant of hepatocellular carcinoma presenting during pregnancy: management dilemmas. Ann Hepatobiliary Pancreat Surg. 2017;21(1):48-51. doi: 10.14701/ahbps.2017.21.1.48.
13. Ramesh P, Srikumar S, Mahendran V, Nair SS, Radhamany K. Pregnancy-Associated Breast Cancer: A Realistic Approach. J Obstet Gynaecol India. 2019;69(6):514-519. doi: 10.1007/s13224-019-01249-9.
14. Boussios S, Han SN, Fruscio R, Halaska MJ, Ottevanger PB, Peccatori FA, et al. Lung cancer in pregnancy: report of nine cases from an international collaborative study. Lung Cancer. 2013;82(3):499-505. doi: 10.1016/j.lungcan.2013.09.002.
15. Girault A, Dommergues M, Nizard J. Impact of maternal brain tumours on perinatal and maternal management and outcome: a single referral centre retrospective study. Eur J Obstet Gynecol Reprod Biol. 2014;183:132-6. doi: 10.1016/j.ejogrb.2014.10.027.
16. Yu S, Bischoff L. Thyroid Cancer in Pregnancy. Semin Reprod Med. 2016;34(06):351-5. doi: 10.1055/s-0036-1593484.
17. Blake EA, Kodama M, Yunokawa M, Ross MS, Ueda Y, Grubbs BH, et al. Feto-maternal outcomes of pregnancy complicated by epithelial ovarian cancer: a systematic review of literature. Eur J Obstet Gynecol Reprod Biol. 2015;186:97-105. doi: 10.1016/j.ejogrb.2015.01.010.
18. Bruce KH, Tran AM. Treatment of invasive Paget's disease of the vulva in pregnancy: A case report. Gynecol Oncol Rep. 2020;33:100602. doi: 10.1016/j.gore.2020.100602.
19. Sanderson M, Daling JR, Doody DR, Malone KE. Perinatal Factors and Mortality Ifrom Breast Cancer. Cancer Epidemiol Biomarkers Prev. 2006;15(10):1984-7. doi: 10.1158/1055-9965.EPI-06-0350
20. Azim HA, Peccatori FA. Managing cancer during pregnancy: what evidence do we have? Pol Arch Med Wewn. Pol Arch Med Wewn. 2011;121(1-2):29-34. doi: 10.20452/pamw.1015.
21. Nygård M, Daltveit AK, Thoresen SO, Nygård JF. Effect of an antepartum Pap smear on the coverage of a cervical cancer screening programme: a population-based prospective study. BMC Health Serv Res. 2007;7:10. doi: 10.1186/1472-6963-7-10.
22. Chen C, Xu Y, Huang W, Du Y, Hu C. Natural history of histologically confirmed high-grade cervical intraepithelial neoplasia during pregnancy: meta-analysis. BMJ Open. 2021;11(8):e048055. doi: 10.1136/bmjopen-2020-048055.
23. Terrinoni M, Golia D'Augè T, Mascellino G, Adinolfi F, Palisciano M, Rossetti D, et al. Human Papillomavirus Across the Reproductive Lifespan: An Integrative Review of Fertility, Pregnancy Outcomes, and Fertility-Sparing Management. Medicina (Kaunas). 2025;61(8):1499. doi: 10.3390/medicina61081499
24. Bogani G, Scambia G, Malzoni M, et al. Investigators of the ETERNITY Project. Chemo-conization in Early-sTage cERvical caNcer >2 cm scheduled for fertilItY-sparing approach: an analysis of the ETERNITY project. Int J Gynecol Cancer. 2025;35(4):101643. doi: 10.1016/j.ijgc.2025.101643.
25. Bonassi Machado R, Gandolpho AC, Santana N, Bocardo RC, Palandri N, Morassutti Machado R. Contraception for women with heart disease: an update. Minerva Ginecol. 2017;69(3):259-268. doi: 10.23736/S0026-4784.17.04041-2.
26. Prasad M, More PP, Chaudhari KM. Knowledge, Attitudes and Practices Regarding Contraception Among Physicians in a Tertiary Care Centre in Urban India. J Obstet Gynaecol India. 2020;70(6):533-534. doi: 10.1007/s13224-020-01337-1.
27. Del-Pozo-Lérida S, Salvador C, Martínez-Soler F, Tortosa A, Perucho M, Giménez-Bonafé P. Preservation of fertility in patients with cancer (Review). Oncol Rep. 2019;41(5):2607-2614. doi: 10.3892/or.2019.7063.
28. Carneiro MM, Cota AM, Amaral MC, Pedrosa ML, Martins BO, Furtado MH, et al. Motherhood after breast cancer: can we balance fertility preservation and cancer treatment? A nar-

rative review of the literature. JBRA Assist Reprod. 2018;22(3):244-252. doi: 10.5935/1518-0557.20180032.
29. Balachandren N, Davies M. Fertility, ovarian reserve and cancer. Maturitas. 2017;105:64-68. doi: 10.1016/j.maturitas.2017.07.013.
30. Sharma J, Kataki A, Barman D, Sharma A, Kalita M. Cancer statistics in Kamrup urban district: Incidence and mortality in 2007-2011. Indian J Cancer. 2016;53(4):600. doi:10.4103/0019-509X.204764.
31. Cuccu I, Sgamba L, Cannicchio A, De Angelis E, Golia D'Augè T, Di Bartolomeo G, et al. Evolution of retroperitoneal staging in endometrial cancer: narrative review and overview of literature. Ital J Gynaecol Obstet. 2023;35(2):168-175. doi: 10.36129/jog.2023.105.
32. Golia D'Augè T, De Angelis E, Cuccu I, Laganà AS, Etrusco A, Di Donato V, et al. Precision and progress: minimally invasive surgery in gynaecologic cancer treatment. Ital J Gynaecol Obstet. 2025;37(1):43-54. doi: 10.36129/jog.2025.199.
33. D'Amato A, Riemma G, Agrifoglio V et al. Reproductive Outcomes in Young Women with Early-Stage Cervical Cancer Greater than 2 cm Undergoing Fertility-Sparing Treatment: A Systematic Review. Medicina (Kaunas). 2024;60(4):608. doi: 10.3390/medicina60040608.

Italian Journal of
Gynæcology & Obstetrics
September 2026 - Vol. 38 - N. 3 - Quarterly - ISSN 2385 – 0868

Metabolomic analysis of gynaecological cancer: identification of novel biomarkers using gas chromatography-mass spectrometry

Hiroaki **Takagi** [1,*], Chunhua **Zhang** [2], Sumire **Shimada** [1], Emi **Takata** [1], Masahiro **Takakura** [1], Toshiyuki **Sasagawa** [1]

[1] Department of Obstetrics and Gynaecology, Kanazawa Medical University, School of Medicine, Ishikawa, Japan.
[2] MILS International, Yokohama, Japan.

ARTICLE INFO

History
Received: 18 September 2025
Received in revised form: 22 November 2025
Accepted: 18 December 2025
Available online: 10 September 2026

DOI: 10.36129/jog.2026.260

Key words
Biomarker; cervical neoplasm; endometrial neoplasm; gas chromatography-mass spectrometry; ovarian neoplasm.

***Corresponding author:** Hiroaki **Takagi**, M.D., Ph.D. Department of Obstetrics and Gynaecology, Kanazawa Medical University, School of Medicine, Daigaku 1-1, Uchinada, Ishikawa, 920-0293, Japan.
Email: terry-1@kanazawa-med.ac.jp.
ORCID: 0000-0002-3511-1849.

ABSTRACT

Objective. This study aimed to identify novel biomarkers for gynaecological cancers – including ovarian, cervical, and endometrial cancers – using gas chromatography-mass spectrometry.

Materials and Methods. A case-control study was conducted with 16 Japanese women as controls and 73 women diagnosed with gynaecological cancers. Urine and serum samples were analysed for 90 metabolites, including amino acids, organic acids, sugars, fatty acids, and tricarboxylic acid cycle components.

Results. Significant variations were observed in numerous metabolites between the control group and patients with ovarian, cervical, and endometrial cancers. Notably, levels of glutamine, 1,5-anhydroglucitol (1,5-AG), and lactate differed significantly according to the Kruskal-Wallis test. Receiver operating characteristic (ROC) analysis showed that the area under the curve (AUC) values for urine and serum glutamine ranged from 0.764 to 0.895 across the three cancer types. For 1,5-AG, the AUC values were 0.852-0.896 for urine samples and 1.000 for serum samples. Lactate yielded AUC values ranging from 0.727 to 0.924 in urine and serum samples.

Conclusions. This study demonstrated clear differences in metabolites between controls and gynaecological cancer patients. Glutamine, 1,5-AG, and lactate may serve as useful biomarkers for ovarian, cervical, and endometrial cancers.

INTRODUCTION

Primary gynaecological cancers – including ovarian, cervical, and endometrial cancers – remain a significant global health concern for women. These malignancies often present with nonspecific symptoms in their early stages, making timely and accurate diagnosis critical for improving clinical outcomes. Although conventional tumour markers are widely used for screening and monitoring, their limited sensitivity and specificity have prompted the search for more reliable diagnostic strategies.

Cancer cells exhibit distinct metabolic behaviour, favouring glycolysis over oxidative phosphorylation even in oxygen-rich environments – a phenomenon known as the Warburg effect [1, 2]. This metabolic reprogramming supports rapid proliferation and survival by altering sugar, amino acid, and lipid metabolic pathways [3-5]. Metabolomics has emerged as a powerful tool to investigate these changes, offering insights into cancer biology and potential biomarkers.

Gas chromatography-mass spectrometry (GC/MS) is a widely adopted analytical technique in metabolomics, capable of detecting low-molecular-weight volatile metabolites with high sensitivity and specificity [6, 7]. Although GC/MS has been applied to explore cancer-related metabolites [8-10], comprehensive metabolic profiling in gynaecological cancers remains limited.

Several studies have identified metabolites as promising biomarkers for various malignancies [11]. In addition, molecular markers such as L1CAM have demonstrated prognostic relevance in endometrial cancer [12]. Recent investigations have highlighted diagnostic challenges in cervical adenocarcinoma [13] and evaluated clinical outcomes in ovarian cancer [14], collectively reinforcing the paradigm shift toward individualized care in gynaecologic oncology.

Building on these insights, the present study aimed to identify novel metabolic biomarkers for the early detection of ovarian, cervical, and endometrial cancers using GC/MS-based profiling of urine and serum specimens.

MATERIALS AND METHODS

Patients

This case-control study was approved by the Institutional Review Board of Kanazawa Medical University and conducted between 2017 and 2023. During this period, 38 Japanese women who underwent routine health examinations were screened. Of these, 22 were excluded according to predefined criteria, and 16 women without gynaecological abnormalities were ultimately selected as controls. In addition, 73 Japanese women with histologically confirmed gynaecological cancers who subsequently underwent surgical treatment were enrolled after providing written informed consent. The cancer cohort included patients with ovarian cancer (n = 23; high-grade serous, clear cell, mucinous, and endometrioid carcinomas), cervical cancer (n = 23; squamous cell carcinoma and adenocarcinoma), and endometrial cancer (n = 27; FIGO grades 1-3).

Matching criteria

Controls (healthy women) and cases (ovarian, cervical, and endometrial cancers) were matched based on some parameters. The mean age of the control group was 48.1 years (SD = 6.4), which overlapped with the case groups. No significant differences in BMI were observed between groups, minimizing the influence of obesity-related metabolic variations. The proportions of nulliparous and parous women were balanced, and the prevalence of smoking was comparable between groups.

Exclusion criteria

Controls: individuals with metabolic disorders, recent infections, or medication use that could affect metabolite profiles were excluded. Cases: patients undergoing active treatment, with prior chemotherapy or radiotherapy, or with compromised sample integrity (*e.g.*, haemolysis or contamination) were excluded.

Specimen collection and handling

Fasting morning urine (15 mL) and venous blood (5 mL) samples were collected from each participant. Blood samples were centrifuged at 1,800 rpm for 3 minutes at 4 °C, and both serum and urine samples were aliquoted and stored at -80 °C within 2 hours of collection. Sample integrity was assessed by evaluating haemolysis and measuring total protein concentrations.

Quality control measures

Histopathological diagnoses were independently confirmed by two board-certified pathologists. Sample processing protocols were standardized to minimize batch effects. Clinical data – including age, BMI, tumour histology, disease stage, and laboratory parameters – were systematically extracted from electronic medical records. All analytical procedures were conducted in a blinded fashion to ensure objectivity.

Gas chromatography-mass spectrometry

GC/MS analysis was performed using a JMS-K9 instrument (JEOL, Tokyo, Japan), which enables sensitive and precise detection of trace components in complex biological samples. Urine and serum

metabolites – including amino acids, organic acids, sugars, fatty acids, and tricarboxylic acid (TCA) cycle-related compounds – were separated by gas chromatography and identified by mass spectrometry. Urine metabolites were normalized to creatinine levels, and serum metabolites were corrected using internal standards.

Statistical analysis

A total of 90 metabolites were examined: 28 amino acids, 24 organic acids, 15 sugars, 15 fatty acids, and 8 TCA cycle-related compounds (**Table 1**). Comparisons between controls and cancer patients were performed using the Mann-Whitney U test and the Kruskal-Wallis test. Receiver operating characteristic (ROC) curve analyses were conducted with EZR (version 1.68; Saitama Medical Center, Jichi Medical University, Japan) to assess the diagnostic performance of selected metabolites. For each metabolite, the area under the curve (AUC) was calculated, and optimal cutoff values were determined using the Youden Index. The statistical significance of AUCs was evaluated with DeLong's method, and P-values were adjusted for multiple testing using the Benjamini–Hochberg procedure to control the false discovery rate. All other statistical analyses were performed with GraphPad Prism 9 (version 9.2.0; GraphPad Software, San Diego, CA, USA). A P-value < 0.05 was considered statistically significant.

RESULTS

The clinical characteristics of the participants' urine and serum samples are summarized in **Table 2** and **Table 3**, respectively. Cervical cancer was more prevalent among multiparous women, whereas endometrial cancer was more common among nulliparous individuals. Additionally, diabetes was more frequently observed in patients with endometrial cancer.

Due to missing urine samples, the final analysis included 16 controls, 11 ovarian cancer patients, 6 cervical cancer patients, and 19 endometrial cancer patients. Serum sample loss was minimal, with samples available from 16 controls, 23 ovarian cancer patients, 23 cervical cancer patients, and 27 endometrial cancer patients.

A total of 90 metabolites were analysed in urine and serum samples from both control and cancer groups. Significant differences in metabolite levels

Table 1. *List of analysed metabolites.*

Amino acids					
1	Alanine	**11**	Homoserine	**21**	Lysine 1
2	Glycine 1	**12**	Aspartate	**22**	Glutamine
3	Sarcosine	**13**	Methionine	**23**	Tyrosine 1
4	Valine	**14**	Pyroglutamate	**24**	Histidine
5	Leucine	**15**	4-Hydroxyproline	**25**	Lysine 2
6	Proline	**16**	Phenylalanine 1	**26**	Tyrosine 2
7	Isoleucine	**17**	Ornithine	**27**	β-Alanine
8	Glycine 2	**18**	Glutamate	**28**	Dimethylglycine
9	Serine	**19**	Phenylalanine 2		
10	Threonine	**20**	Asparagine		
Organic acids					
1	Glycolate	**11**	Phenyllactic acid	**21**	Hypoxanthine
2	3HP	**12**	Glycerol 3-phosphate	**22**	Urate
3	Cresol	**13**	Vitamin C	**23**	Pseudouridine
4	3HIB	**14**	Phthalic acid	**24**	Xanthine
5	2HIV	**15**	2-ketoisocaproate		
6	3HIV	**16**	2-hydroxyisobutyrate		
7	Urea	**17**	3AIB		
8	Phosphate	**18**	4-Deoxytetronic acid		
9	Glutarate	**19**	3-Deoxytetronic acid		
10	Erythronate	**20**	2-Deoxytetronic acid		
Sugars					
1	Erythritol	**11**	Arabinose		
2	Arabitol	**12**	Fucose		
3	Fructose	**13**	Sucrose		
4	Glucose1	**14**	Lactose		
5	Mannitol	**15**	1,5-Anhydroglucitol		
6	Chiro-inositol				
7	Glucose2				
8	Epi-inositol				
9	Myo-inositol				
10	Ribose				
Fatty acids					
1	Glycerol	**11**	C16:0		
2	Adipate	**12**	C16:1		
3	Suberate	**13**	C18:0		
4	Sebacate	**14**	C18:1		
5	C12DC:1	**15**	C18:2		
6	C6:0				
7	C8:0				
8	C10:0				
9	C12:0				
10	C14:0				
TCA cycle					
1	Lactate				
2	2HB				
3	Pyruvate				
4	3HB				
5	Succinate				
6	Fumarate				
7	Malate				
8	Citrate				

3HP: 3-hydroxypropionic acid; 3HIB: 3-hydroxyisobutyric acid; 2HIV: 2-hydroxyisovaleric acid; 3HIV: 3-hydroxy 3-methylbutyrate; 3AIB: 3-aminoisobutyric acid; 2HB: 2-hydroxybutyric acid; 3HB: 3-hydroxybutyric acid; C6:0: Caproic acid; C8:0: Octanoic acid; C10:0: Decanoic acid; C12:0: Lauric acid; C14:0: Myristic acid; C16:0: Palmitic acid; C16:1: Palmitoleic acid; C18:0: Stearic acid; C18:1: Oleic acid; C18:2: Linoleic acid.

Table 2. *Participant characteristics (urine cohort).*

Variables (urine)	Control (n = 16)	Ovarian cancer (n = 11)	Cervical cancer (n = 8)	Endometrial cancer (n = 19)
Age, mean (SD)	48.1 (6.4)	53.8 (17.6)	54.9 (17.6)	56.3 (13.7)
Age, range	38 - 59	31 - 84	36 - 82	29 - 74
BMI, median	21.3	20.3	20.4	24.8
Parity				
Nulliparous, 0	0	5	0	8
Multiparous, 1 - 4	16	6	7	11
Smoking status				
Non-smoker	12	10	7	19
Smoker	4	1	1	0
Diabetes mellitus				
No	16	10	7	13
Yes	0	1	1	6
Diagnostic pathology				
Ovarian cancer		High grade serous ca (n = 6) Clear cell ca (n = 3) Mucinous ca (n = 2)		
Cervical cancer			Squamous cell ca (n = 2) Cervical adenoca (n = 6)	
Endometrial cancer				Endometrioid ca G1 (n = 10) Endometrioid ca G2 (n = 7) Endometrioid ca G3 (n = 29)

SD: standard deviation; BMI: Body mass index; Ca: carcinoma.

Table 3. *Participant characteristics (serum cohort).*

Variables (serum)	Control (n = 16)	Ovarian cancer (n = 23)	Cervical cancer (n = 23)	Endometrial cancer (n = 27)
Age, mean (SD)	48.1 (6.4)	57.1 (16.4)	53.5 (15.8)	55.9 (14.1)
Age, range	38 - 59	31 - 84	31 - 82	29 - 75
BMI, median	21.3	20.9	21.0	24.2
Parity				
Nulliparous, 0	0	9	2	10
Multiparous, 1 - 4	16	14	21	17
Smoking status				
Non-smoker	12	22	19	25
Smoker	4	1	4	2
Diabetes mellitus				
No	16	18	20	20
Yes	0	5	3	7
Diagnostic pathology		High grade serous ca (n = 12)		
Ovarian cancer		Clear cell ca (n = 6) Mucinous ca (n = 3) Endometrial ca (n = 2)		
Cervical cancer			Squamous cell ca (n = 13) Cervical adenoca (n = 10)	
Endometrial cancer				Endometrioid ca G1 (n = 15) Endometrioid ca G2 (n = 10) Endometrioid ca G3 (n = 2)

SD: standard deviation; BMI: Body mass index; Ca: carcinoma.

Table 4. *Metabolite levels in controls and patients with gynaecological cancer.*

Metabolites	Control *vs* Ovarian cancer	Control vs Cervical cancer	Control vs Endometrial cancer
Amino acids			
Urine-Glutamine	0.0003***	0.0001***	< 0.0001****
Serum-Glutamine	< 0.0001****	0.0023**	0.0035**
Organic acids			
Urine-PLA	0.0004***	0.0066**	0.0009***
Serum-PLA	0.0001***	0.0695	0.0327*
Sugars			
Urine-1,5-AG	0.0007***	0.0005***	< 0.0001****
Serum-1,5-AG	< 0.0001****	< 0.0001****	< 0.0001****
Fatty acids			
Urine-C14:0	< 0.0001****	0.0002***	< 0.0001****
Serum-C14:0	0.0094**	0.0086**	0.0076**
Urine-C18:2	0.0002***	0.0002***	0.0005***
Serum-C18:2	< 0.0001****	0.0134*	0.0003***
TCA related			
Urine-Lactate	0.0501	0.0028**	< 0.0001****
Serum-Lactate	< 0.0001****	< 0.0001****	< 0.0001****

PLA: phenyllactic acid; 1,5-AG: 1,5-anhydroglucitol; C14:0: myristic acid; C18:2: linoleic acid. Statistical significance was assessed using the Mann–Whitney U test. Asterisks indicate significance levels: $p < 0.05$ *, $p < 0.01$**, $p < 0.001$***, $p < 0.0001$ ****.

were observed between cancer patients and controls. Glutamine was consistently elevated in both urine and serum across all cancer types. As shown in **Table 4**, phenyllactic acid (PLA), 1,5-anhydroglucitol (1,5-AG), myristic acid (C14:0), and linoleic acid (C18:2) also exhibited notable changes. Lactate was elevated in serum for all cancers, while urine lactate was increased in cervical and endometrial cancers, with only a borderline trend in ovarian cancer. These results suggest that these metabolites may serve as useful biomarkers for gynaecological cancers.
Among the metabolites examined, glutamine, 1,5-AG, and lactate showed statistically significant differences according to the Kruskal-Wallis test (**Figure 1**).
Urine glutamine levels were significantly higher in patients with ovarian ($p = 0.0080$), cervical ($p = 0.0142$), and endometrial cancer ($p = 0.0015$) compared with controls. Serum glutamine levels were elevated in ovarian cancer ($p < 0.0001$) and cervical cancer ($p = 0.0322$). In endometrial cancer, levels showed a slight increase, but this was not statistically significant ($p = 0.0504$). ROC analysis revealed AUC values for urine and serum glutamine of 0.838 and 0.891 (ovarian), 0.895 and 0.783 (cervical), and 0.841 and 0.764 (endometrial), respectively.
For 1,5-AG, urine levels were significantly higher in patients with cervical ($p = 0.0020$) and endometrial cancer ($p = 0.0001$), but no significant difference was observed in ovarian cancer patients ($p = 0.1233$). Serum 1,5-AG levels showed significant differences across all cancer types ($p < 0.0001$). The corresponding AUC values for urine and serum 1,5-AG were 0.852 and 1.000 (ovarian), 0.879 and 1.000 (cervical), and 0.896 and 1.000 (endometrial), respectively.
Similarly, urine lactate levels were significantly elevated in patients with cervical ($p = 0.0300$) and endometrial cancer ($p = 0.0004$), but not in those with ovarian cancer ($p = 0.2407$). Serum lactate levels differed significantly among all cancer types, with P-values of < 0.0001, 0.0002, and 0.0001, respectively. AUC values for urine and serum lactate were 0.727 and 0.902 (ovarian), 0.867 and 0.859 (cervical), and 0.891 and 0.924 (endometrial), respectively.
Collectively, these findings (**Table 5**) underscore the diagnostic potential of glutamine, 1,5-AG, and lactate as promising biomarkers for the early detection of ovarian, cervical, and endometrial cancers.

DISCUSSION

Metabolic reprogramming has emerged as a hallmark of gynaecological cancers, reflecting the

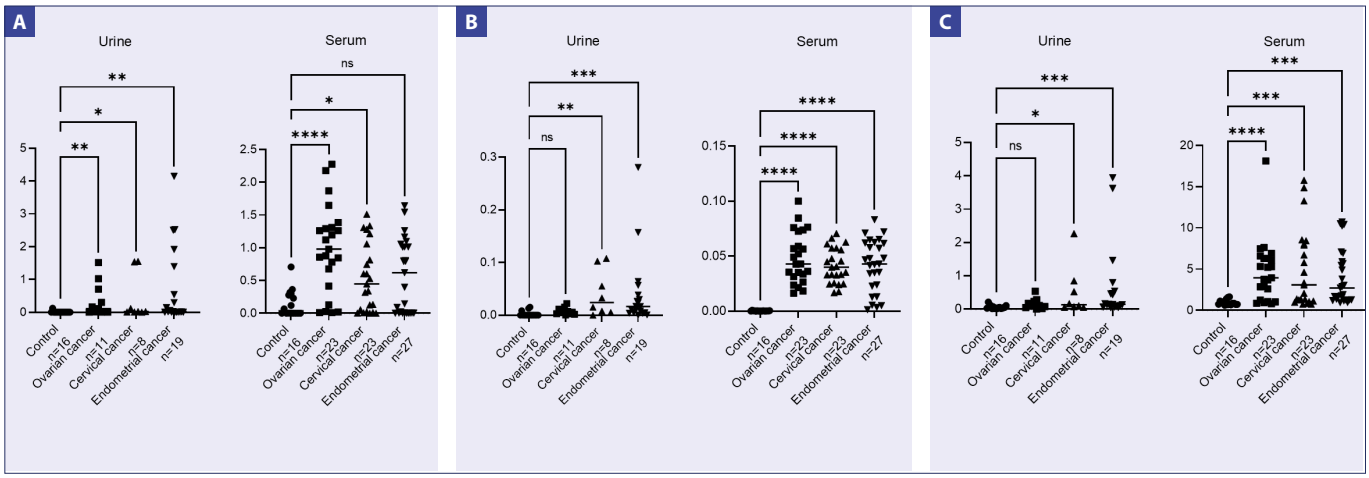

Figure 1. *Comparative analysis of urine and serum metabolites in patients with gynaecological cancer.*

(A) Glutamine: comparison of urine glutamine levels between the control (n = 16) and ovarian cancer (n = 11) groups; p = 0.0080. Comparison of urine glutamine levels between the control (n = 16) and cervical cancer (n = 8) groups; p = 0.0142. Comparison of urine glutamine levels between the control (n = 16) and endometrial cancer (n = 19) groups; p = 0.0015. Comparison of serum glutamine levels between the control (n = 16) and ovarian cancer (n = 23) groups; p < 0.0001. Comparison of serum glutamine levels between the control (n = 16) and cervical cancer (n = 23) groups; p = 0.0322. Comparison of serum glutamine levels between the control (n = 16) and endometrial cancer (n = 27) groups; p = 0.0504. **(B)** 1,5-Anhydroglucitol: comparison of urine 1,5-anhydroglucitol levels between the control (n = 16) and ovarian cancer (n = 11) groups; p = 0.1233. Comparison of urine 1,5-anhydroglucitol levels between the control (n = 16) and cervical cancer (n = 8) groups; p = 0.0020. Comparison of urine 1,5-anhydroglucitol levels between the control (n = 16) and endometrial cancer (n = 19) groups; p = 0.0001. Comparison of serum 1,5-anhydroglucitol levels between the control (n = 16) and ovarian cancer (n = 23) groups; p < 0.0001. Comparison of serum 1,5-anhydroglucitol levels between the control (n = 16) and cervical cancer (n = 23) groups; p < 0.0001. Comparison of serum 1,5-anhydroglucitol levels between the control (n = 16) and endometrial cancer (n = 27) groups; p < 0.0001. **(C)** Lactate: comparison of urine lactate levels between the control (n = 16) and ovarian cancer (n = 11) groups; p = 0.2407. Comparison of urine lactate levels between the control (n = 16) and cervical cancer (n = 8) groups; p = 0.0300. Comparison of urine lactate levels between the control (n = 16) and endometrial cancer (n = 19) groups; p = 0.0004. Comparison of serum lactate levels between the control (n = 16) and ovarian cancer (n = 23) groups; p < 0.0001. Comparison of serum lactate levels between the control (n = 16) and cervical cancer (n = 23) groups; p = 0.0002. Comparison of serum lactate levels between the control (n = 16) and endometrial cancer (n = 27) groups; p = 0.0001.

Table 5. *Diagnostic performance of urine and serum metabolites in gynaecological cancers based on roc analysis.*

Cancer type	Sample	AUC	95%CI	Cut-off point	Sensitivity (%)	Specificity (%)
Glutamine						
Ovarian Cancer	Urine	0.838	0.688 – 0.988	> 0.014	72.73	93.75
	Serum	0.891	0.792 – 0.991	> 0.415	78.26	93.75
Cervical Cancer	Urine	0.895	0.747 – 1.000	> 0.010	87.50	93.75
	Serum	0.783	0.637 – 0.928	> 0.449	52.17	93.75
Endometrial Cancer	Urine	0.841	0.723 – 0.957	> 0.0002	73.68	93.75
	Serum	0.764	0.617 – 0.911	> 0.397	55.56	93.75
1,5-Anhydroglucitol						
Ovarian Cancer	Urine	0.852	0.690 – 1.000	> 0.0003	100.0	81.25
	Serum	1.000	1.000 – 1.000	> 0.016	100.0	100.0
Cervical Cancer	Urine	0.879	0.722 – 1.000	> 0.005	87.50	81.25
	Serum	1.000	1.000 – 1.000	> 0.017	100.0	100.0
Endometrial Cancer	Urine	0.896	0.791 – 1.000	> 0.001	94.74	81.25
	Serum	1.000	1.000 – 1.000	> 0.001	100.0	100.0
Lactate						
Ovarian Cancer	Urine	0.727	0.501 – 0.954	> 0.083	72.73	81.25
	Serum	0.902	0.811 – 0.993	> 2.602	73.91	100.0
Cervical Cancer	Urine	0.867	0.724 – 1.000	> 0.059	100.0	68.75
	Serum	0.859	0.745 – 0.973	> 1.128	78.26	81.25
Endometrial Cancer	Urine	0.891	0.787 – 0.996	> 0.063	89.47	75.00
	Serum	0.924	0.847 – 1.000	> 1.141	92.59	81.25

AUC: Area Under the Curve; CI: Confidence Interval.

unique bioenergetic and biosynthetic demands of tumour cells. In this study, we performed comprehensive metabolomic profiling of urine and serum samples to explore their diagnostic potential. Among the 90 metabolites analysed, glutamine, 1,5-AG, and lactate exhibited significant alterations between healthy controls and cancer patients, implicating their involvement in tumour-associated metabolic pathways.

Glutamine, a conditionally essential amino acid, plays a central role in maintaining redox balance and supporting anabolic processes in cancer cells [15-22]. In our cohort, both urine and serum glutamine levels were significantly altered in cancer patients compared with controls, with the most pronounced differences observed in ovarian cancer, where glutamine dependence is well established [19-21]. Elevated expression of SNAT1, a glutamine transporter, has been linked to poor prognosis in cervical cancer. In endometrial cancer, glutamine-driven metabolism promotes tumour growth and inhibits autophagy. These findings underscore glutamine's pivotal role in tumour progression and its potential as a therapeutic target in gynaecological cancers.

1,5-AG, a glucose-like polyol that reflects short-term glycaemic control, competes with glucose for renal reabsorption. In this study, both urinary and serum levels of 1,5-AG were significantly altered in cancer patients, although urinary levels in ovarian cancer did not differ significantly from controls. Previous studies have reported inconsistent associations between 1,5-AG and cancer risk, including its predictive value for cancer mortality and an inverse relationship with pancreatic cancer [23-25]. Our findings suggest a positive association with gynaecological cancers, even after excluding patients with diabetes. These discrepancies may reflect tumour-specific metabolic adaptations and warrant further investigation in larger, more diverse cohorts.

Lactate, a key byproduct of aerobic glycolysis, contributes to tumour progression by modulating immune responses, promoting angiogenesis, and facilitating metastasis [26-29]. In our study, elevated lactate levels were observed in both urine and serum samples from patients with cervical and endometrial cancers, consistent with previous reports of increased lactate production in ovarian cancer cells [30-32]. High plasma lactate has also been associated with cervical lesion severity, poor survival in head and neck cancers [33], and enhanced proliferation in endometrial cancer as revealed by NMR-based metabolomics [34]. Metabolic studies in cervical cancer further support the roles of lactate and glutamine in tumour progression [35]. These findings suggest that elevated lactate levels may reflect enhanced glycolytic activity and mitochondrial reprogramming in gynaecological cancers.

Beyond metabolic profiling, clinical parameters also influence prognosis. Vizza *et al*. [36] demonstrated that vaginal cuff length in low-risk endometrial cancer surgery correlates with survival and recurrence. Perrone *et al*. [37] emphasized the therapeutic relevance of targeting the BRAF pathway in low-grade serous ovarian cancer. D'Oria *et al*. [38] provided an updated overview of systemic pharmacotherapy for recurrent cervical cancer. These studies highlight the importance of integrating metabolic, molecular, and surgical factors to improve prognostic accuracy and support personalized management in gynaecological cancers.

ROC analysis revealed high AUC values for glutamine, 1,5-AG, and lactate, indicating strong discriminatory power between cancer patients and healthy individuals. These results support their potential utility as non-invasive biomarkers for early detection.

This study has several limitations. First, the relatively small sample size limits the generalizability of our findings. Second, sample subdivision and repeated GC/MS analyses may have introduced minor variability. Third, the study population consisted exclusively of Japanese women, which may limit applicability to other ethnic groups. Finally, the cross-sectional design precludes assessment of longitudinal metabolic changes during disease progression or treatment. Larger, multicentre prospective studies are needed to validate these findings and enhance diagnostic robustness.

CONCLUSIONS

In conclusion, the metabolites glutamine, 1,5-AG, and lactate exhibited significant alterations in both urine and serum samples from patients with gynaecological cancers. Supported by ROC analysis with high AUC values, these metabolites reflect key aspects of cancer metabolism and hold promise as robust non-invasive biomarkers for early detection and prognostic assessment in gynaecological cancers.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution
H.T.: Conceptualization, formal analysis, writing – original draft, writing – review & editing. S.S., E.T.: Data curation. C.Z.: Formal analysis, writing – review & editing. M.T., T.S.: Formal analysis.

Funding
None.

Study registration
N/A.

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

Ethical approval
This study was approved by the Institutional Review Board of Kanazawa Medical University [approval number: I282].

Informed consent
All participants signed an informed consent statement before participating in the study.

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

REFERENCES

1. Warburg, O. On the origin of cancer cells. Science. 1956;123:309-314. doi:10.1126/science.123.3191.309.
2. Kozal K, Jóźwiak P, Krześlak A. Contemporary Perspectives on the Warburg Effect Inhibition in Cancer Therapy. Cancer Control. 2021;28:10732748211041243. doi:10.1177/10732748211041243.
3. Hay N. Reprogramming glucose metabolism in cancer: can it be exploited for cancer therapy? Nat Rev Cancer. 2016;16(10):635-49. doi:10.1038/nrc.2016.77.
4. Lieu EL, Nguyen T, Rhyne S, Kim J. Amino acids in cancer. Exp Mol Med. 2020;52(1):15-30. doi:10.1038/s12276-020-0375-3.
5. Snaebjornsson MT, Janaki-Raman S, Schulze A. Greasing the Wheels of the Cancer Machine: The Role of Lipid Metabolism in Cancer. Cell Metab. 2020;31(1):62-76. doi:10.1016/j.cmet.2019.11.010.
6. Fiehn O. Metabolomics by Gas Chromatography-Mass Spectrometry: Combined Targeted and Untargeted Profiling. Curr Protoc Mol Biol. 2016;114:30.4.1-30.4.32. doi:10.1002/0471142727.mb3004s114.
7. Medeiros PM, Simoneit BR. Gas chromatography coupled to mass spectrometry for analyses of organic compounds and biomarkers as tracers for geological, environmental, and forensic research. J Sep Sci. 2007;30(10):1516-1536. doi:10.1002/jssc.200600399.
8. He J, Han Z, Luo W, Shen J, Xie F, Liao L, et al. Serum organic acid metabolites can be used as potential biomarkers to identify prostatitis, benign prostatic hyperplasia, and prostate cancer. Front Immunol. 2023;13:998447. doi:10.3389/fimmu.2022.998447.
9. Jajin MG, Abooshahab R, Hooshmand K, Moradi A, Siadat SD, Mirzazadeh R, et al. Gas chromatography-mass spectrometry-based untargeted metabolomics reveals metabolic perturbations in medullary thyroid carcinoma. Sci Rep. 2022;12(1):8397. doi:10.1038/s41598-022-12590-x.
10. Barberini L, Restivo A, Noto A, Deidda S, Fattuoni C, Fanos V, et al. A gas chromatography-mass spectrometry (GC-MS) metabolomic approach in human colorectal cancer (CRC): the emerging role of monosaccharides and amino acids. Ann Transl Med. 2019;7(23):727. doi:10.21037/atm.2019.12.34.
11. Wang W, Rong Z, Wang G, Hou Y, Yang F, Qiu M. Cancer metabolites: promising biomarkers for cancer liquid biopsy. Biomark Res. 2023;11(1):66. doi:10.1186/s40364-023-00507-3.
12. Giannini A, D'Oria O, Corrado G, Bruno V, Sperduti I, Bogani G, et al. The role of L1CAM as predictor of poor prognosis in stage I endometrial cancer: a systematic review and meta-analysis. Arch Gynecol Obstet. 2024;309(3):789-799. doi:10.1007/s00404-023-07149-8.
13. T errinoni M, Rossetti D, Di Renzo GC. Adenocarcinoma in situ of the cervix in a young patient: a diagnostic problem. Ital J Gynaecol Obstet. 2025;37(3):253-256. doi:10.36129/jog.2025.198.
14. Abdelhameed M, Zawam HH. Survival and reproductive outcomes after fertility-sparing surgery and postoperative adjuvant chemotherapy in malignant ovarian germ cell tumors. Ital J Gynaecol Obstet. 2025;37(2):140-146. doi:10.36129/jog.2025.203.

15. Albrecht J, Sidoryk-Węgrzynowicz M, Zielińska M, Aschner M. Roles of glutamine in neurotransmission. Neuron Glia Biol. 2010;6(4):263-276. doi:10.1017/S1740925X11000093.
16. Li T, Copeland C, Le A. Glutamine Metabolism in Cancer. Adv Exp Med Biol. 2021;1311:17-38. doi:10.1007/978-3-030-65768-0_2.
17. Gong T, Zheng C, Ou X, Zheng J, Yu J, Chen S, et al. Glutamine metabolism in cancers: Targeting the oxidative homeostasis. Front Oncol. 2022;12:994672. doi:10.3389/fonc.2022.994672.
18. Jin J, Byun JK, Choi YK, Park KG. Targeting glutamine metabolism as a therapeutic strategy for cancer. Exp Mol Med. 2023;55(4):706-715. doi:10.1038/s12276-023-00971-9.
19. Yang L, Moss T, Mangala LS, Marini J, Zhao H, Wahlig S, et al. Metabolic shifts toward glutamine regulate tumor growth, invasion and bioenergetics in ovarian cancer. Mol Syst Biol. 2014;10(5):728. doi:10.1002/msb.20134892.
20. Yuan L, Sheng X, Willson AK, Roque DR, Stine JE, Guo H, et al. Glutamine promotes ovarian cancer cell proliferation through the mTOR/S6 pathway. Endocr Relat Cancer. 2015;22(4):577-591. doi:10.1530/ERC-15-0192.
21. Yang X, Li Z, Ren H, Peng X, Fu J. New progress of glutamine metabolism in the occurrence, development, and treatment of ovarian cancer from mechanism to clinic. Front Oncol. 2022;12:1018642. doi:10.3389/fonc.2022.1018642.
22. Xu F, Shi J, Qin X, Zheng Z, Chen M, Lin Z, et al. Hormone-Glutamine Metabolism: A Critical Regulatory Axis in Endocrine-Related Cancers. Int J Mol Sci. 2022;23(17):10086. doi:10.3390/ijms231710086.
23. Pramodkumar TA, Jayashri R, Gokulakrishnan K, Velmurugan K, Pradeepa R, Anjana RM, et al. Relationship of glycemic control markers - 1,5 anhydroglucitol, fructosamine, and glycated hemoglobin among Asian Indians with different degrees of glucose intolerance. Indian J Endocrinol Metab. 2016; 20(5):690-695. doi:10.4103/2230-8210.190559.
24. Kira S, Ito C, Fujikawa R, Misumi M. Association between a biomarker of glucose spikes, 1,5-anhydroglucitol, and cancer mortality. BMJ Open Diabetes Res Care. 2020;8(1):e001607. doi:10.1136/bmjdrc-2020-001607.
25. Nakagawa T, Kobayashi T, Nishiumi S, Hidaka A, Yamaji T, Sawada N, et al. Metabolome analysis for pancreatic cancer risk in nested case-control study: Japan Public Health Center-based prospective Study. Cancer Sci. 2018;109(5):1672-1681. doi:10.1111/cas.13573.
26. Lee TY. Lactate: a multifunctional signaling molecule. Yeungnam Univ J Med. 2021;38(3):183-193. doi:10.12701/yujm.2020.00892.
27. de la Cruz-López KG, Castro-Muñoz LJ, Reyes-Hernández DO, García-Carrancá A, Manzo-Merino J. Lactate in the Regulation of Tumor Microenvironment and Therapeutic Approaches. Front Oncol. 2019;9:1143. doi:10.3389/fonc.2019.01143.
28. Hirschhaeuser F, Sattler UG, Mueller-Klieser W. Lactate: A Metabolic Key Player in Cancer. Cancer Res. 2011;71(22):6921-6925. doi:10.1158/0008-5472.
29. Doherty JR, Cleveland JL. Targeting lactate metabolism for cancer therapeutics. J Clin Invest. 2013;123(9):3685-3692. doi:10.1172/JCI69741.
30. Gu J, Zhou J, Chen Q, Xu X, Gao J, Li X, et al. Tumor metabolite lactate promotes tumorigenesis by modulating MOESIN lactylation and enhancing TGF-b signaling in regulatory T cells. Cell Rep. 2022;39(12):110986. doi:10.1016/j.celrep.2022.110986.
31. Ha JH, Jayaraman M, Nadhan R, Kashyap S, Mukherjee P, Isidoro C, et al. Unraveling Autocrine Signaling Pathways through Metabolic Fingerprinting in Serous Ovarian Cancer Cells. Biomedicines. 2021;9(12):1927. doi:10.3390/biomedicines9121927.
32. Zhong X, Ran R, Gao S, Shi M, Shi X, Long F, et al. Complex metabolic interactions between ovary, plasma, urine, and hair in ovarian cancer. Front Oncol. 2022;12:916375. doi:10.3389/fonc.2022.916375.
33. Blatt S, Voelxen N, Sagheb K, Pabst AM, Walenta S, Schroeder T, et al. Lactate as a predictive marker for tumor recurrence in patients with head and neck squamous cell carcinoma (HNSCC) post radiation: a prospective study over 15 years. Clin Oral Investig. 2016;20(8):2097-2104. doi:10.1007/s00784-015-1699-6.
34. Skorupa A, Poński M, Ciszek M, Cichoń B, Klimek M, Witek A, et al. Grading of endometrial cancer using 1H HRMAS NMR based metabolomics. Sci Rep. 2021;11(1):18160. doi:10.1038/s41598-021-97505-y.
35. Li B, Sui L. Metabolic reprogramming in cervical cancer and metabolomics perspectives. Nutr Metab (Lond). 2021;18(1):93. doi:10.1186/s12986-021-00615-7.

36. Vizza E, Bruno V, Cutillo G, Mancini E, Sperduti I, Patrizi L, et al. Prognostic Role of the Removed Vaginal Cuff and Its Correlation with L1CAM in Low-Risk Endometrial Adenocarcinoma. Cancers. 2021;14(1):34. doi:10.3390/cancers14010034.
37. Perrone C, Angioli R, Luvero D, Giannini A, Di Donato V, Cuccu I, et al. Targeting BRAF pathway in low-grade serous ovarian cancer. J Gynecol Oncol. 2024;35(4):e104. doi:10.3802/jgo.2024.35.e104.
38. D'Oria O, Bogani G, Cuccu I, D'Auge TG, Di Donato V, Caserta D, et al. Pharmacotherapy for the treatment of recurrent cervical cancer: an update of the literature. Expert Opin Pharmacother. 2024;25(1):55-65. doi:10.1080/14656566.2023.2298329.

Italian Journal of
Gynæcology & Obstetrics
September 2026 - Vol. 38 - N. 3 - Quarterly - ISSN 2385 – 0868

Comparative efficacy of letrozole *versus* letrozole-metformin in the ovulation and clinical pregnancy rate in polycystic ovary syndrome: a prospective randomized controlled study

Sakshi **Chopra** *, Ruchi **Hooda**, M. Gouri **Devi**

Department of Reproductive Medicine, Ridge IVF Centre, New Delhi, India.

ARTICLE INFO

History
Received: 02 August 2025
Received in revised form: 22 November 2025
Accepted: 22 January 2026
Available online: 10 September 2026

DOI: 10.36129/jog.2026.261

Key words
PCOS; letrozole; metformin; ovulation.

***Corresponding author:** Sakshi **Chopra**, MBBS DGO DNB FRM. Department of Reproductive Medicine, Ridge IVF Centre, 109, United India Appts, Mayur Vihar, Phase 1, extension, Delhi 110091, India.
Email: 385saki@gmail.com.
ORCID: 0000-0002-4905-2237.

ABSTRACT

Objective. The study provides an insight on the effect of letrozole and letrozole-metformin combination on the formation of mature follicle, ovulation, endometrial thickness and pregnancy rates in anovulatory polycystic ovary syndrome (PCOS) infertile women.

Materials and Methods. A prospective randomised controlled study conducted at Ridge IVF Centre, Delhi from May 2024-April 2025. 120 women of ages 21-40 years affected by PCOS and trying naturally for conception were included. Patients were randomly selected into 2 groups: Group A (letrozole and metformin) and Group B (letrozole only).

Metformin 500 mg twice daily was added from day 1 of cycle. Letrozole 2.5 mg BD was started from day 2/3 of menstrual cycle. Follicular monitoring was done from day 10 by transvaginal sonography and once a mature follicle of size > 18 mm is seen on TVS, injection. hCG 10,000 IU was given. Once ovulation was documented, couple was advised for alternate day intercourse and luteal phase support was given for 14 days. Pregnancy confirmation was done by S.ßhCG after 14 days.

Results. The study showed that the formation of mature follicle was more in letrozole-metformin group and ovulation rate was higher in letrozole only group. The endometrial thickness on the day of the trigger was comparable in both groups. The clinical pregnancy was slightly higher in combination group, but not statistically significant.

Conclusions. Adding metformin to letrozole does insignificant improvement in ovulation patterns in PCOS anovulatory women.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinological disorder affecting 4-12% of women [1-2]. It has been the most controversial medical condition affecting women of reproductive age group. It is one of the causes for anovulatory female infertility. PCOS is a heterogeneous disorder with a combination of genetic, reproductive and metabolic characteristics. These women are at risk

of Type 2 diabetes mellitus (DM) and cardiovascular disease.

According to 2003 Rotterdam Consensus revised diagnostic criteria, at least two of the following is required for the diagnosis of PCOS:

1. oligo or anovulation, or both, that is, menstrual disturbance;
2. clinical or biochemical signs, or both, of hyperandrogenism;
3. PCO on ultrasound and exclusion of other aetiologies of menstrual disturbance and hyperandrogenism (such as congenital adrenal hyperplasia, androgen-secreting tumours, Cushing's syndrome) [3].

A recent update to guidelines in view of advancement in ultrasound technology and resolution, state that the diagnostic criteria for ultrasound PCO morphology is either 20 or more follicles per ovary or increased ovarian volume, over 10 mL, when using a transvaginal ultrasound scan [4].

Insulin resistance is a very common feature of PCOS, owing to either genetic propensity or obesity [5]. It is not a diagnostic feature of this disorder. In PCOS, hyperinsulinemia can induce androgen production and decrease the levels of sex hormone binding globulin. A high level of androgen levels affects the oocytes growth and causes atresia of follicles. PCOS is responsible for about 80% of anovulatory infertility [6]. Women with insulin resistance have increased prevalence of hirsutism than women with non-insulin-resistant PCOS [7]. These women are more likely to develop resistance to ovulation induction treatment.

Lifestyle modification including weight loss and exercise reduces central fat, improves insulin sensitivity, reduces testosterone levels and restoring ovulation in overweight, infertile women with PCOS [7].

Metformin is the member of the biguanide family that has been used for the treatment of T2DM. Metformin works by improving the insulin sensitivity of peripheral tissues [8], which results in a reduction of circulating insulin levels. The main side effects associated with metformin treatment are the gastrointestinal symptoms of nausea, diarrhoea, flatulence, bloating, anorexia, metallic taste and abdominal pain, causing reluctance in its use over a prolong period [9].

Within the ovary, metformin has a direct impact on cells to reduce excessive steroidogenesis and folliculogenesis [9]. It reduces theca cell proliferation, decreases androgen production, reduces pituitary luteinizing hormone and increase sex hormone binding globulin by the liver and promotes ovulation.

Letrozole is a nonsteroidal reversible and competitive aromatase inhibitor. Letrozole has a half-life of about 45 hours [10]. It has a central effect on the pituitary-hypothalamic axis by releasing it from estrogen negative feedback and a local ovarian effect by blocking androgen conversion to estrogen, with the concomitant accumulation of androgens inside the ovary, augmenting the follicular FSH receptor expression, and promoting folliculogenesis [11].

This study provides an insight on the effect of letrozole and letrozole-metformin combination on anovulatory PCOS infertile women in ovulation and pregnancy.

MATERIALS AND METHODS

Study site

The study was a prospective randomised controlled study conducted in Department of Assisted Reproduction at Ridge IVF centre, New Delhi from May 2024-April 2025. The approval was taken from the ethics committee on board for the study.

Inclusion criteria

Women of all ages (21-40 years) who were affected by PCOS according to Rotterdam criteria with normal hysterosalpingogram and were trying naturally for conception were included.

Exclusion criteria

Patients with hormonal disorder like hyperprolactinemia, hypo or hyperthyroidism or diabetes, endometriosis, uterine fibroid, male factor infertility were excluded from study.

All patients were admitted through OPD after complete evaluation with history, examination, investigation and verbal informed consent for inclusion in the study. Blood for Insulin Postprandial is sent 1 ½ hours after meals on first visit along with other investigations.

Patients were selected randomly into 2 groups: Group A (letrozole and metformin) and Group B (letrozole only). Letrozole and metformin was administered as oral preparations.

In Group A, tablet metformin 500 mg twice daily with meals starting from day 1 of cycle was added and continued for three months and continued even after conception till first 3 months of pregnancy. Patients were followed for 3 months to evaluate

for pregnancy in both the groups. Oral ovulogen letrozole 2.5 mg BD was started from day 2/3 of menstrual cycle after spontaneous or withdrawal bleeding in both groups. Follicular monitoring was done from day 10 and follicle growth was monitored by transvaginal sonography (TVS). Once a mature follicle of size > 18 mm was seen, injection hCG 10,000 IU was given as a trigger. Once follicular rupture was documented, couple was advised for alternate day intercourse and luteal phase support was given with dydrogesterone 10 mg BD for 14 days. Pregnancy confirmation was done by estimating the S.ßhCG concentration in the blood after 14 days and doubling of the S.ßhCG after 48 hours. The clinical pregnancy was established by the presence of gestational sac by ultrasonography performed at 6-7 weeks of pregnancy.

Treatment was repeated for 3 months if the patient fails to ovulate or achieve pregnancy.

The primary outcomes were assessed as documentation of mature follicle (> 18mm) and documentation of ovulation (ovulation rate).

The secondary outcomes were assessed as measurement of ovarian volume, hormonal profile on day 2 (S.FSH, S.LH, S.E2), endometrial thickness on day of hCG trigger and clinical pregnancy rate.

Statistical analysis

The collected data was entered in Microsoft Excel and then analysed and statistically evaluated using SPSS-25 version. Normality of each variable was assessed by using the Kolmogorov-Smirnov test. Quantitative data was expressed by mean, standard deviation and difference between means of two group were tested by Unpaired t test or Mann-Whitney U test. Qualitative data were expressed in percentage and difference between percentage of two group were tested by chi square test or Fisher exact test. P-value less than 0.05 was considered statistically significant.

RESULTS

The baseline characteristics of participants in both groups were largely comparable (**Table 1**). The mean age was similar in Group A (30.13 ± 3.21 years) and Group B (30.22 ± 3.25 years). The mean BMI was slightly higher in Group A (27.68 ± 4.78 kg/m^2) compared to Group B (26.22 ± 4.12 kg/m^2), though this difference was not statistically significant (p = 0.07). In terms of type of infertility, primary infertility was predominant in both groups: 76.7% in Group A and 80.0% in Group B.

However, a significant difference was observed in menstrual cycle regularity. 56.7% of Group A had irregular cycles compared to only 18.3% in Group B, and regular cycles were more common in Group B with statistical difference < 0.001 (**Table 1**).

In **Table 2**, comparison of hormonal and ultrasonographic parameters were done. Right ovarian volume was significantly higher in Group A (9.83 ± 1.48 ml) compared to Group B (6.76 ± 1.94 ml), and similarly, the left ovarian volume was also greater in Group A (9.24 ± 1.07 ml *vs* 6.86 ± 2.01 ml) with statistically significant (p < 0.001) (**Figure 1**).

Serum AMH levels were high in Group A (8.12 ± 3.42 ng/ml) as compared to Group B (6.13 ± 2.44 ng/ml). Baseline Serum FSH was marginally higher in Group A (6.50 ± 1.29) than in Group B (6.02 ± 1.61), with borderline significance (p = 0.05). Serum LH levels were significantly hi-

Table 1. *Data comparing the baseline characteristics between Group A and Group B.*

	Group A (letrozole-metformin) (n = 60)	Group B (letrozole) (n = 60)	P-value
Mean age in years	30.13 ± 3.21	30.22 ± 3.25	0.88
Mean BMI (kg/m^2)	27.68 ± 4.78	26.22 ± 4.12	0.07
Type of infertility			
Primary	46(76.7%)	48(80.0%)	0.65
Secondary	14(23.3%)	12(20.0%)	
Cycle			
Irregular	34 (56.7%)	11 (18.3%)	**<0.001**
Regular	26 (43.3%)	49 (81.7%)	**<0.001**

BMI: body mass index; n: number of participants. Data are presented as mean ± standard deviation (SD) or n %.

Table 2. *Data comparing the other parameters between Group A and Group*

	Group A (letrozole-metformin) (n = 60)	Group B (letrozole) (n = 60)	P-value
RT ovary VOL (ml)	9.83 ± 1.48	6.76 ± 1.94	**<0.001**
LT ovary VOL (ml)	9.24 ± 1.07	6.86 ± 2.01	**<0.001**
S.AMH (ng/ml)	8.12 ± 3.42	6.13 ± 2.44	**0.001**
S.FSH	6.50 ± 1.29	6.02 ± 1.61	0.05
S.LH	7.40 ± 3.19	6.31 ± 4.17	**0.01**
S.E2	43.27 ± 17.42	36.65 ± 13.07	**0.02**
Insulin PP (µU/ml)	67.98 ± 27.23	26.92 ± 15.62	**<0.001**
Endometrial thickness (mm)	8.83 ± 1.65	8.80 ± 1.21	0.92

RT: right; LT: left; VOL: volume; AMH: anti mullerian hormone; LH: luteinizing hormone; E2: estradiol; PP: postprandial; n: number of participants. Data are presented as mean ± standard deviation (SD).

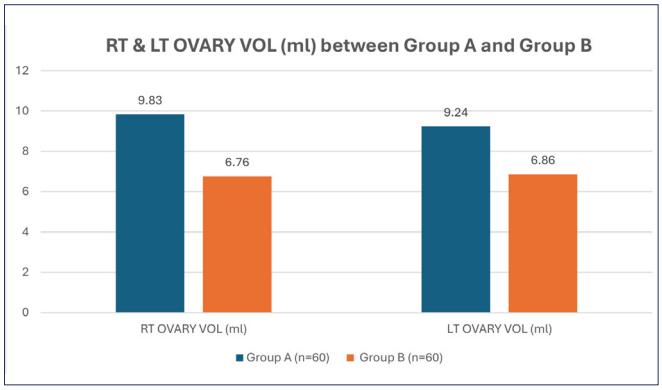

Figure 1. *Ovarian volume of right and left ovary.*

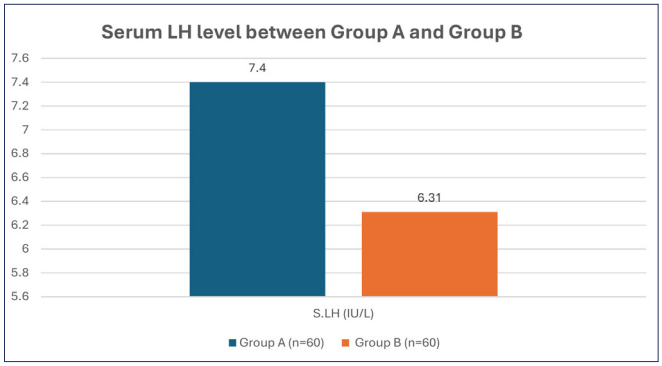

Figure 2. *Serum LH on day 2 of cycle*

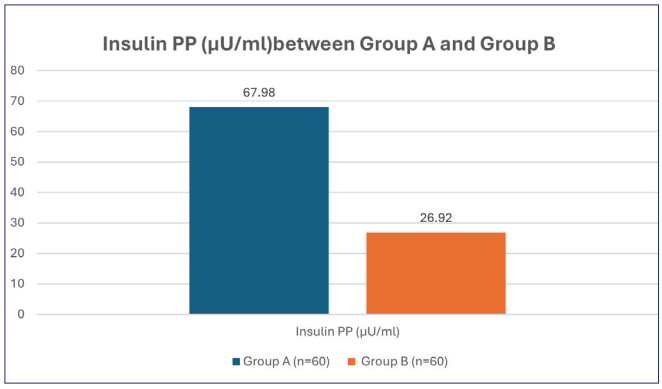

Figure 3. *Insulin post prandial.*

Table 3. *Data comparing clinical hirsutism between Group A and Group B.*

Clinical hirsutism	Group A (letrozole-metformin) (n = 60)	Group B (letrozole) (n = 60)	P-value
Absent	35 (58.3%)	50 (83.3%)	**<0.01**
Present	25 (41.7%)	10 (16.7%)	

Table 4. *Data comparing different outcome between Group A and Group B.*

	Group A (letrozole-metformin) (n = 60)	Group B (letrozole) (n = 60)	P-value
Mature follicle			**0.01**
No	7(11.7%)	0	
Yes	53(88.3%)	60	
Ovulation			**0.002**
No	18(30.0%)	4(6.7%)	
Yes	42(70.0%)	56(93.3%)	
S.βhCG			0.07
Negative	36(60.0%)	45(75.0%)	
Positive	24(40.0%)	15(25.0%)	
Clinical pregnancy			0.07
No	36(60.0%)	46(76.7%)	
Yes	24(40.0%)	14(23.3%)	

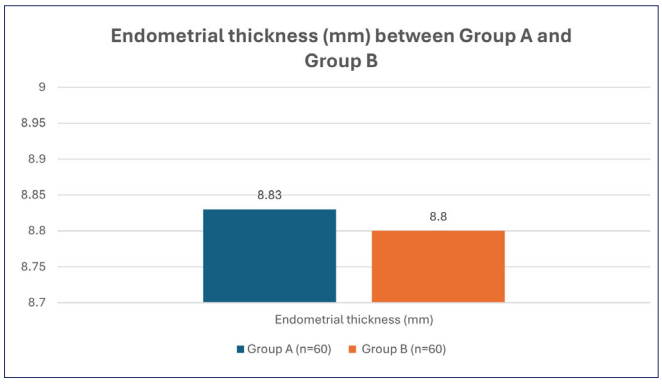

Figure 4. *Endometrial thickness on the trigger day.*

gher in Group A (7.40 ± 3.19) compared to Group B (6.31 ± 4.17) (p = 0.01) (**Figure 2**) and serum estradiol (E2) levels were also higher in Group A (43.27 ± 17.42 *vs* 36.65 ± 13.07).

A striking difference was observed in postprandial insulin levels, which were markedly elevated in Group A (67.98 ± 27.23 µU/ml) compared to Group B (26.92 ± 15.62 µU/ml), showing a highly significant difference (p < 0.001) (**Figure 3**).

Endometrial thickness on the trigger day was comparable between both groups (8.83 ± 1.65 mm in Group A *vs* 8.80 ± 1.21 mm in Group B (**Figure 4**).

The comparison of clinical hirsutism between Group A and Group B (**Table 3**) showed a higher proportion of individuals experienced clinical hirsutism in Group A (41.7%), compared to just 16.7% in Group B.

In **Table 4**, clinical outcomes to ovulation induction was compared. A higher proportion of individuals in Group B (100%) had mature follicles compared to Group A (88.3%). Still, it was found that Group B (93.3%) achieved higher ovulation compared to Group A (70%), with a P-value of 0.002. In terms of pregnancy, Group A had a higher percentage of po-

sitive S.βhCG results (40.0%), compared to Group B (25.0%), and higher clinical pregnancy rate (40% *vs* 23.3%) but not statistically significant.

DISCUSSION

PCOS is the most prevalent endocrine disorder in the reproductive age of women. In these patients, medications such as clomiphene citrate, letrozole and metformin are used to induce ovulation and overcome infertility [12].

Clomiphene citrate binds to estrogen receptors for prolonged periods *i.e*. weeks (2 weeks) rather than hours as with natural estrogen. This extended binding ultimately depletes estrogen receptors' concentrations by interfering with the normal process estrogen receptors' replenishment and may be responsible for the peripheral antiestrogenic effect of clomiphene citrate on the endometrium and cervix [13].

Compared to CC, letrozole is cleared from circulation more rapidly due to shorter half-life; associated with monofollicular growth and thicker endometrium. Letrozole is devoid of any antiestrogenic peripheral actions and has no impact on the endometrial receptivity and cervical mucous quality [14].

Metformin, an insulin sensitizer may be used alone or in concert with other medications such as clomiphene citrate, letrozole it has been shown to increase the ovulatory response to clomiphene citrate in patients who were previously clomiphene resistant [15].

In our study, demographic parameters *i.e*. age, BMI, type of infertility was comparable in both groups. The only significant demographic character was menstrual cycle regularity. As women were selected randomly in the study, cycles were more irregular in letrozole-metformin group, but cycle regularity is not the sole criterion for metformin use [4]. A study also has reported similar age, BMI and duration of infertility distribution in both groups [16].

In Group A, patients had higher insulin PP, day 2 S.FSH, S. LH, S.E2 and S.AMH levels. The clinical hirsutism was also higher in metformin-letrozole group.

When ovulation parameters were compared, it was found that group B participants had higher achievement of formation of mature follicle than Group A, and ovulation rate was higher. In a different study no significant differences between the letrozole and the metformin-letrozole groups regarding ovulation rate, number of patients with growing follicle, number of follicles ≥ 18 at day 12, number of ruptured follicles after 48 hours of injection of hCG, serum E2, parity, clinical presentation, period of infertility, FSH, LH were found [16].

In our study, clinical pregnancy rate was slightly higher in Group A, but not statistically significant. A retrospective study on 268 women undergoing ovulation induction/IUI in 2012-2016 has found that the addition of metformin to Letrozole does not improve follicular recruitment or pregnancy rates in OI/IUI cycles in infertile PCOS women [17]. Liu *et al*. revealed a pregnancy rate of 57.9% in letrozole in addition to metformin gathering and just 46.8% in patients who got letrozole alone [18].

In our study the endometrial thickness was comparable in both groups (8.83 *vs* 8.80). A study by Morad *et al*. found superior endometrial thickness with letrozole than clomiphene citrate showing CC antiestrogenic effects [19]. A significant improvement in endometrial thickness in metformin-letrozole group was found in other work [16]. On other hand, EL-Gharib *et al*. found non-significant change between endometrial thickness in both letrozole and letrozole metformin groups, like our study results [20].

The risk of gestational diabetes in pregnancy is high in PCOS especially androgenic PCOS. The hormonal and metabolic profile of hyperandrogenic PCOS patients includes insulin resistance, and an elevated androgen levels both of which are risk factors for the development of GDM. Women with PCOS are at further risk of obstetric complications including hypertensive disorders, preterm birth, induction of labour and caesarean delivery [21]. Similarly in IVF conceived pregnancies risk of GDM is high as many females have significant risk factors for GDM, such as advanced maternal age, obesity, multiple pregnancies and PCOS, suggesting a potential relationship between GDM and ART [22].

Limitations

The study involved a smaller number of participants. In clinical situations, individual treatment dosages varied, and it was not fully considered in our study. The study's limited duration prevented a thorough examination of longer-term outcomes.

CONCLUSIONS

PCOS is a complex disorder that requires a comprehensive approach to management, addressing

both reproductive and metabolic concerns. While multiple treatment options are available for PCOS, a combination of lifestyle changes, medication, and, in some cases, surgical interventions, may be necessary to address the diverse manifestations of the disorder. Only letrozole 2.5 mg BD given from day 2 for ovulation induction and performing follicular monitoring is the standard protocol in PCOS from our research, as adding metformin to letrozole does insignificant improvement in ovulation patterns in PCOS anovulatory women. The ovulation rate was slightly higher in letrozole group. Similarly, pregnancy rates were also insignificant in both groups.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution
S.C.: Conceptualization, writing – original draft, Writing – review & editing, data curation. R.H.: writing – review & editing. M.G.D.: Supervision.

Funding
None.

Study registration
This study was not prospectively registered and institutional ethics committee approval was obtained before participants recruitment.

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

Ethical approval
This study was approved by the Ethics Committee of Ridge IVF, Gouri Hospital (No. RIDGE/HEC/001/2025 date: 29/4/2024).

Informed consent
Informed consent was obtained from all participants.

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

ACKNOWLEDGEMENTS

We would like to thank Dr. Piyush for the valuable assistance with the formal analysis.

REFERENCES

1. Diamanti-Kandarakis E, Kouli CR, Bergiele AT, Filandra FA, Tsianateli TC, Spina GG, et al. A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. J Clin Endocrinol Metab. 1999;84(11):4006-11. doi: 10.1210/jcem.84.11.6148.
2. Tehrani FR, Simbar M, Tohidi M, Hosseinpanah F, Azizi F. The prevalence of polycystic ovary syndrome in a community sample of Iranian population: Iranian PCOS prevalence study. Reprod Biol Endocrinol. 2011;9:39. doi: 10.1186/1477-7827-9-39. P
3. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81(1):19-25. doi: 10.1016/j.fertnstert.2003.10.004.
4. Teede HJ, Tay CT, Laven JJE, Dokras A, Moran LJ, Piltonen TT, et al. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Eur J Endocrinol. 2023;189(2):G43-G64. doi: 10.1093/ejendo/lvad096.
5. Baptiste CG, Battista MC, Trottier A, Baillargeon JP. Insulin and hyperandrogenism in women with polycystic ovary syndrome. J Steroid Biochem Mol Biol. 2010;122(1-3):42-52. doi: 10.1016/j.jsbmb.2009.12.010.
6. Liu X, Zhang J, Wang S. Global, regional, and national burden of infertility attributable to PCOS, 1990-2019. Hum Reprod. 2024;39(1):108-118. doi: 10.1093/humrep/dead241.
7. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab. 2006;91(11):4237-45. doi: 10.1210/jc.2006-0178.
8. Bailey CJ, Turner RC. Metformin. N Engl J Med. 1996;334(9):574-9. doi: 10.1056/NEJM199602293340906.
9. Diamanti-Kandarakis E, Christakou CD, Kandaraki E, Economou FN. Metformin: an old medication of new fashion: evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. Eur J Endocrinol. 2010;162(2):193-212. doi: 10.1530/EJE-09-0733.

10. Buzdar AU, Robertson JF, Eiermann W, Nabholtz JM. An overview of the pharmacology and pharmacokinetics of the newer generation aromatase inhibitors anastrozole, letrozole, and exemestane. Cancer. 2002;95(9):2006-16. doi: 10.1002/cncr.10908.
11. El Omda F, Abd El Fattah A, Hashish M, Khalil M. A Randomized Trial of Combined Letrozole with Metformin Versus Clomiphene Citrate with Metformin in Polycystic Ovary (PCOS) patients. Egypt J Hospital Med. 2018;72(4):4382-4388. doi: 10.21608/ejhm.2018.9294.
12. Farshchian N, Teimuri Nezhad S, Bahrami Kamangar P. The combination of letrozole and metformin has a better therapeutic effect on uterine and ovarian arteries in PCOS patients than the combination of clomiphene citrate and metformin. AMJ. 2018;11(6):326-330. doi: 10.21767/AMJ.2018.3252.
13. Greenblatt RB, Barfield WE, Jungck EC, Ray AW. Induction of ovulation with MRL/41. Preliminary report. JAMA. 1961;178:101-4. doi: 10.1001/jama.1961.03040410001001.
14. Pritts EA. Letrozole for ovulation induction and controlled ovarian hyperstimulation. Curr Opin Obstet Gynecol. 2010;22(4):289-94. doi: 10.1097/GCO.0b013e32833beebf.
15. Sohrabvand F, Ansari Sh, Bagheri M. Efficacy of combined metformin-letrozole in comparison with metformin-clomiphene citrate in clomiphene-resistant infertile women with polycystic ovarian disease. Hum Reprod. 2006;21(6):1432-5. doi: 10.1093/humrep/del020.
16. Hamada S, Abdallah K, Samir K. Comparative Study Between the Effect of Letrozole Versus Letrozole with Metformin in Treatment of Anovulation in Overweight Women. AIMJ. 2022;3(7):89-95
17. Hurley EG, Adams, SR, Kalakota N, Rios J, Thomas M. The addition of metformin during ovulation induction with letrozole does not affect pregnancy outcome in infertile women with polycystic ovary syndrome. Fertil Steril. 2017;108. e246. doi: 10.1016/j.fertnstert.2017.07.740.
18. Liu C, Feng G, Huang W, Wang Q, Yang S, Tan J, et al. Comparison of clomiphene citrate and letrozole for ovulation induction in women with polycystic ovary syndrome: a prospective randomized trial. Gynecol Endocrinol. 2017;33(11):872-876. doi: 10.1080/09513590.2017.1332174.
19. Morad AWA, Elhadi Farag MA. Impact of letrozole on ultrasonographic markers of endometrial receptivity in polycystic ovarysyndrome women with poor endometrial response to clomiphene citrate despite adequate ovulation. Middle East Fertil Soc J. 2015;20(3):182-187. doi: 10.1016/j.mefs.2014.08.004
20. EL-Gharib MN, EL-Ebiary MT, Raoof Farahat MA (2020) The Negligible Effect of Metformin Addition to Letrozole in Treating Overweight Women with PCOS. J Obst Gynecol Surg. 2020;1(2):1-6.
21. Quaresima P, Myers SH, Pintaudi B, D'Anna R, Morelli M, Unfer V. Gestational diabetes mellitus and polycystic ovary syndrome, a position statement from EGOI-PCOS. Front Endocrinol (Lausanne). 2025;16:1501110. doi: 10.3389/fendo.2025.1501110.
22. Ghanem YM, El Kassar Y, Magdy MM, Amara M, Amin NG. Potential risk of gestational diabetes mellitus in females undergoing in vitro fertilization: a pilot study. Clin Diabetes Endocrinol. 2024;10(1):7. doi: 10.1186/s40842-024-00164-x.

Italian Journal of
Gynæcology & Obstetrics
September 2026 - Vol. 38 - N. 3 - Quarterly - ISSN 2385 – 0868

The association between previous abortion and risk of placenta accreta spectrum: a meta-analysis

Sara **Abdoli** [1], Farideh **Kazemi** [2], Salman **Khazaei** [3], Ensiyeh **Jenabi** [2,*]

[1] Student Research Committee, Hamadan University of Medical Sciences, Hamadan, Iran.
[2] Mother and Child Care Research Center, Institute of Health Sciences and Technology, Hamadan University of Medical Sciences, Hamadan, Iran.
[3] Research Center for Health Sciences, Hamadan University of Medical Sciences, Hamadan, Iran.

ARTICLE INFO

History
Received: 22 November 2025
Received in revised form: 17 December 2025
Accepted: 23 January 2026
Available online: 10 September 2026

DOI: 10.36129/jog.2026.263

Key words
Placenta accreta spectrum; abortion; meta-analysis; pregnancy.

***Corresponding author:** Ensiyeh **Jenabi**, Associate Professor.
Mother and Child Care Research Center, Institute of Health Sciences and Technology, Hamadan University of Medical Sciences, Shahid Fahmideh Street, Hamadan, Iran.
Email: en.jenabi@yahoo.com.
ORCID: 0000-0002-4536-0814.

ABSTRACT

Background. Several studies have yielded conflicting results regarding the potential link between previous abortion and placenta accreta spectrum (PAS), contributing to ongoing controversy on the matter. To address this discrepancy, we conducted a meta-analysis to elucidate the association between previous abortion and the risk of PAS.

Methods. To examine the association between prior abortion and PAS, we systematically searched major databases, including PubMed (Medline), Web of Science, and Scopus. A random-effects model was used for the meta-analysis, and study quality was evaluated using the Newcastle-Ottawa Scale (NOS).

Results. The final analysis included five cohort studies and six case-control studies with a total population of 115,422 participants. We examined the association between previous abortion and the risk of PAS based on crude and adjusted studies. The association between previous abortion and the risk of PAS in crude studies was 1.62 (95%CI 1.46-1.77; I^2 = 17.8%). In adjusted studies, the association was 2.37 (95%CI 1.62-3.12; I^2 = 79.5%). Substantial heterogeneity was observed in studies using adjusted analyses, while minimal heterogeneity was found in studies reporting crude estimates.

Conclusions. This meta-analysis reported that prior abortion is a risk factor for PAS. Given these significant implications, healthcare providers should incorporate PAS risk assessment into pre-abortion evaluations and carefully consider the choice of termination method.

INTRODUCTION

Placenta accreta spectrum (PAS) is characterized by pathological placental implantation, classified into three progressive stages: Placenta accreta (abnormal adherence of villi to the myometrium without invasion), Placenta increta (penetration of trophoblastic tissue into the uterine muscle), Placenta percreta (transmural invasion extending beyond the uterus to adjacent organs) [1]. The underlying pathophysiology of PAS is primarily related to defective decidualization of the basal decidua, whi-

ch allows excessive and uncontrolled trophoblastic invasion into the myometrium. Prior endometrial injury or uterine scarring can disrupt the normal placental-uterine interface, predisposing affected women to abnormal placental adherence. A meta-analysis reported the prevalence of PAS between 0.01% to 0.1% of deliveries [2]. This disorder is rapidly increasing worldwide due to the rising trend of caesarean deliveries [3]. Epidemiologic data indicate a strong association between prior caesarean delivery and PAS risk. In a systematic review, the incidence of PAS increased from approximately 0.3% in women with one previous caesarean to 6.74% in women with five or more caesareans [4]. Other cohort data suggest PAS rates rising from around 0.03% to 2.8% with increasing caesarean number, highlighting the dose-response relationship between surgical scarring and abnormal placentation [5]. PAS disorder represents a critical obstetric complication with potentially life-threatening maternal consequences, including severe haemorrhage and organ damage [6]. Its significance lies in the increase in maternal and foetal mortality [7]. PAS is a leading cause of severe postpartum haemorrhage, frequently resulting in life-threatening maternal haemorrhage that often requires massive blood transfusion and emergency peripartum hysterectomy. This condition significantly contributes to both severe maternal morbidity and mortality [8]. Some risk factors that increase the risk of PAS include multiple pregnancies, obesity, *in vitro* fertilization (IVF), maternal age, smoking and previous caesarean sections [9, 10]. Previous abortion has also been suggested as a potential risk factor for PAS, as it may cause varying degrees of endometrial damage depending on the type and frequency of abortion. Induced abortion, particularly when associated with surgical curettage, may directly injure the endometrium and impair subsequent decidual regeneration. In contrast, spontaneous abortion may exert different effects depending on gestational age and the need for uterine intervention, while recurrent abortions may result in cumulative endometrial injury and uterine scarring [9]. Several epidemiological studies have reported that women with a history of prior pregnancy loss or abortion, especially when associated with endometrial injury from uterine procedures such as dilatation and curettage, are at increased risk of abnormal placentation including PAS in subsequent pregnancies. For example, a recent systematic review and metaanalysis found a significant association between prior abortion and PAS (OR 1.65; 95%CI 1.43-1.92) [11], and a large case-control study in Iran demonstrated a positive link between previous abortion and PAS outcomes [12]. Identifying responsible factors is crucial as it allows for early interventions to improve perinatal outcomes and reduce associated morbidity and mortality [13]. Several observational studies have reported a significant association between previous abortion and the risk of PAS [14, 15], whereas other studies have failed to demonstrate such a relationship. These inconsistent findings across the literature have contributed to ongoing controversy regarding the role of prior abortion in the development of PAS. Epidemiologic studies have also suggested that women with a history of foetal loss may be at increased risk of abnormal placentation, including placenta previa and PAS, in subsequent pregnancies, further supporting the biological plausibility of this association [16, 17].

To date, only one meta-analysis has examined the association between prior abortion and the risk of PAS. This meta-analysis, which included six studies published up to February 2017, found no significant increase in the risk of abnormally invasive placenta associated with previous abortion [18]. However, this study had several important limitations, including the small number of included studies, heterogeneity in the definition and classification of abortion, and insufficient differentiation between induced and spontaneous abortions. Furthermore, in recent years, additional epidemiological studies with larger sample sizes and improved study designs have been published, which were not incorporated into the previous meta-analysis. These developments may substantially influence the pooled risk estimates.

Therefore, given the rising incidence of PAS and the need for up-to-date and robust evidence to inform clinical practice, an updated meta-analysis incorporating newly published studies, addressing heterogeneity, and more carefully evaluating abortion types is warranted. The present study was conducted to fulfil this need.

MATERIALS AND METHODS

This meta-analysis was conducted in strict accordance with the 2020 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, ensuring comprehensive reporting of all methodological processes and results. We followed

PECO framework for performing this study: Population – pregnant women; Exposure – Women with previous abortion; Comparison – women without previous abortion; Outcome – risk of PAS.

Inclusion and exclusion criteria

We included primary studies that assessed the association between previous spontaneous abortion and the risk of PAS, encompassing observational studies such as cohort, case-control, and cross-sectional studies. Studies with inadequate data for outcome measurement were excluded. Additionally, we excluded letters to the editor, case reports, case series, systematic reviews, as well as *in vitro* and animal studies.

Information sources and search

PubMed (Medline), Web of Science, and Scopus were systematically searched up to March 30, 2024, using combinations of keywords: (morbidly adherent placenta OR placenta accreta OR placenta increta OR placenta percreta OR abnormally invasive placenta) AND (previous abortion OR previous miscarriage OR history of miscarriage OR history of abortion OR prior miscarriage OR prior abortion) (**Supplement 1**). Additionally, reference lists were examined to identify additional sources.

Study selection

We employed the Population, Exposure, Comparison, and Outcome (PECO) model to select eligible studies. The Population consisted of pregnant women, the Exposure was previous abortion, and the Comparison was made with non-previous abortion. The Outcome of interest was PAS. Two investigators (E.J. and S.A.) independently screened all titles and abstracts, and subsequently reviewed the full texts that were deemed definitely or possibly eligible. Any disagreements between the two authors were resolved through discussion.

Data extraction

Data extraction was performed using Stata software (version 13.0), capturing the following variables from each included study: first author, publication year, study design, diagnostic criteria, study population characteristics, maternal age distribution, and adjusted confounding variables.

Methodological quality

Study quality was assessed using the modified Newcastle-Ottawa Scale (NOS) for observational studies [19]. This instrument evaluates three domains: 1) participant selection criteria, 2) comparability between PAS and non-PAS groups, and 3) outcome assessment methodology. Based on the standard NOS scoring system (range 0-9), we classified studies scoring 7-9 as high quality and those scoring ≤ 6 as low quality.

Heterogeneity and reporting biases

To evaluate heterogeneity among studies, we utilized the chi-square test [20] and the I^2 statistic. An I^2 statistic greater than 50% was considered indicative of high heterogeneity [21]. Additionally, regression tests, including Egger's and Begg's [22] were employed to examine publication bias.

Summary measures

Primary outcomes were analysed as dichotomous variables (PAS *vs* non-PAS groups), with effects estimated as odds ratios (ORs) and corresponding 95% confidence intervals. All analyses employed a DerSimonian-Laird random-effects model to account for between-study heterogeneity [23]. Statistical significance was defined as $p < 0.05$ using two-tailed tests, with all computations performed in Stata/Version 13.0 (StataCorp LP, Texas, USA).

RESULTS

Description of studies

Our systematic search identified 439 potentially relevant records through initial screening. After title/abstract review and evaluation of 17 full-text articles until March 30, 2024 (**Figure 1**), 11 studies

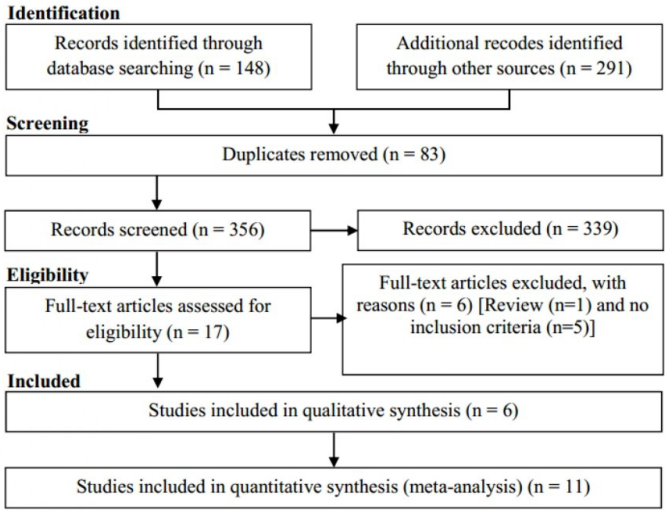

Figure 1. *Flowchart of the process selection of the studies.*

Table 1. *Characteristics of the included studies in the present meta-analysis.*

1st author, year	Design	Sample	Mean of maternal age (Year)	Diagnosis criteria	Abortion type	Estimate	Adjustment	Quality
Eshkoli, 2013 [14]	Cohort	34,869	Not reported	Clinical and histopathological reports	Recurrent abortions	OR	Crude/ Adjusted	High
Sun, 2023 [15]	Cohort	75,773	Not reported	Not reported	Previous abortion	OR	Crude/ Adjusted	High
Tadayon, 2022 [28]	Case-control	739	Case: 32.8, Control: 28.7	Surgeon's confirmation during delivery and histopathological findings	Previous abortion	OR	Crude	High
Moeini, 2021 [30]	Case-control	513	Case: 32.6, Control: 31.6	By second- or third-month ultrasonography and confirmed by a perinatologist	Previous abortion	OR	Crude	High
Ogawa, 2022 [26]	Cohort	2,253	Not reported	Obstetricians, such as difficult piecemeal manual removal of the placenta	History of miscarriage	RR	Crude/ Adjusted	High
Parra-Herran, 2016 [29]	Case-control	61	Case: 35.0, Control: 34.4	Histopathologic diagnosis	History of miscarriage	OR	Crude	High
Alchalabi, 2014 [25]	Cohort	81	Case: 34.7, Control: 31.1	Ultrasonography	History of miscarriage	OR	Crude	High
Klar, 2013 [27]	Case-control	483	Case: 32.47, Control: 31.39	Histopathologic confirmation	Previous abortion	OR	Crude/ Adjusted	High
Wu, 2005 [17]	Case-control	450	Not reported	Histopathologic confirmation	Previous abortion	OR	Crude	High
Elbery, 2020 [24]	Cohort	33	31.33	Ultrasonography and histological diagnosis	Previous abortion	OR	Crude	Low
Kamara, 2013 [16]	Case-control	167	Not reported	Clinical and histological diagnosis	Previous miscarriage	OR	Crude	High

Variables controlled: study [14] – year of birth, maternal age, recurrent abortions, second-trimester vaginal bleeding, previous CD, placenta previa; study [15] – pre-pregnancy BMI, maternal age, mode of delivery, parity; study [22]: year of birth, maternal age, parity, history of miscarriage, conception method, previous caesarean, smoking; study [27] – previous abortions, previous curettages, previous caesarean sections, maternal age, parity, gravity, smoking.

met our inclusion criteria. The excluded studies (n = 6) comprised one systematic review and five articles failing eligibility requirements. The final analysis included five cohort studies [14, 15, 24-26] and six case-control studies [16, 17, 27-30], all published in English, encompassing a total population of 115,422 participants (**Table 1**). The total number of included cases was 3,381 participants.

Effects of exposure

Figure 2 presents the meta-analysis results evaluating the association between prior abortion and PAS risk, stratified by crude and adjusted analyses. Crude analyses demonstrated a statistically significant increased risk of PAS (OR = 1.62; 95%CI 1.46-1.77), with low heterogeneity (I^2 = 17.8%). Adjusted analyses revealed a stronger association (OR = 2.37; 95%CI 1.62-3.12), though with substantial heterogeneity (I^2 = 79.5%). Heterogeneity was markedly higher in adjusted studies compared to crude analyses (**Figure 2**). Notably, Ogawa *et al*. provided stratified results, reporting both crude and adjusted estimates for women with 1-2 prior abortions and ≥ 3 prior abortions [26].

Subgroup analysis

We stratified crude analyses by study design to evaluate the association between prior abortion

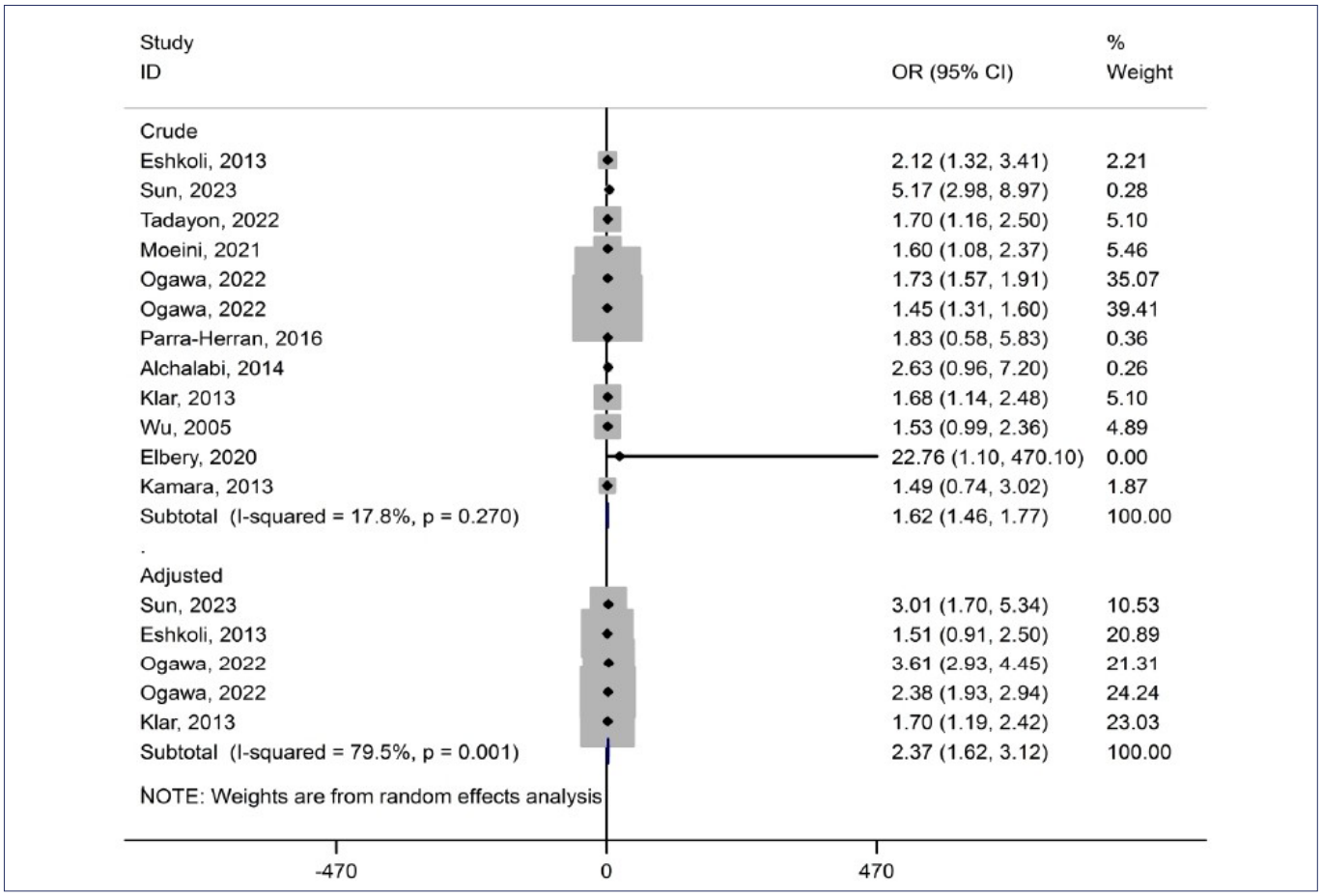

Figure 2. *The association between previous abortion and risk of placenta accreta spectrum (PAS).*

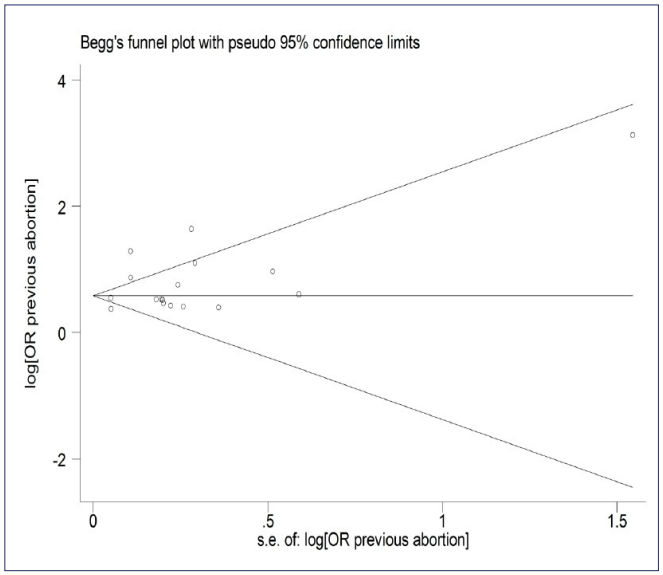

Figure 3. *Funnel plot of previous abortion and risk of placenta accreta spectrum (PAS).accreta spectrum (PAS).*

and PAS risk. The association between previous abortion and the risk of PAS in cohort studies was significant [2.15 (95%CI 1.74, 2.57; $I^2 = 82.2\%$)]. In case-control studies, the association was significant [1.64 (95%CI 1.35, 1.92; $I^2 = 0.0\%$)]. The heterogeneity was substantially higher in cohort studies compared to case-control designs.

Publication bias

Publication bias was evaluated using Begg's rank correlation test (p = 0.323) and Egger's linear regression test (p = 0.143). Both tests indicated no statistically significant evidence of publication bias among the included studies (**Figure 3**).

Quality of the studies

Quality assessment using the NOS demonstrated that all included studies except one met our pre-defined threshold for high methodological quality (scores ≥ 7), with detailed scoring presented in **Table 2**.

DISCUSSION

The meta-analysis demonstrates a consistent association between prior abortion and increased PAS risk. While substantial heterogeneity was detected

Table 2. *Score of quality of studies based on the Newcastle Ottawa Scale (NOS).*

First author, year	Selection	Comparability	Exposure	Total quality score
Eshkoli, 2013	4	2	2	8
Sun, 2023	3	2	3	8
Tadayon, 2022	3	1	3	7
Moeini, 2021	4	1	2	7
Ogawa, 2022	4	2	3	9
Parra-Herran, 2016	3	1	3	7
Alchalabi, 2014	3	1	3	7
Klar, 2013	3	2	3	8
Wu, 2005	3	1	3	7
Elbery, 2020	2	1	2	5
Kamara, 2013	3	1	3	7

Low quality (< 7 points); High quality (> 7 points).

in adjusted analyses, crude estimates demonstrated remarkable consistency across studies, suggesting that variability in covariate adjustment approaches may contribute to between-study differences.

Only a meta-analysis has been conducted regarding the association between prior abortion and the risk of PAS, and the authors included six studies in PubMed and Scopus published through February 2017. The findings indicate that previous abortion did not significantly increase the risk of abnormally invasive placenta (OR 1.36; 95%CI 0.84-2.20) [18]. While comprehensive searches were performed in PubMed and Scopus, the exclusion of Web of Science may have introduced selection bias. These methodological constraints should be considered when interpreting the findings. In the present meta-analysis, PubMed (Medline), Web of Science, and Scopus were systematically searched with 11 studies.

Studies have shown that women with a history of foetal loss are at a higher risk of abnormal placentation. An *et al*., based on a multivariable logistic regression model, reported an association between increased occurrence of placenta percreta and a higher number of previous miscarriages [31]. While our meta-analysis identified a significant association, these findings contrast with a Japanese cohort study [32]. PAS disorders may develop following any iatrogenic or spontaneous endometrial injury that disrupts the decidua basalis [33]. Uterine curettage, as a fundamental technique for induced abortion, can lead to endometrial damage [34]. It should be noted, however, that combining medical and surgical abortions may dilute the observed effect if the mechanism is primarily one of mechanical trauma.

Multiple theories have been proposed to explain the mechanism of PAS. It's possible that mechanical factors such as primary defects in the decidua due to trauma from surgery or biological factors such as abnormal uterine decidual response to trophoblast infiltration, or a combination of both, may be involved [35]. In PAS, invading trophoblast cells penetrate deep into the uterine wall, becoming hypertrophic and increasing in number, while large trophoblast cells with multiple nuclei decrease [34]. Previously, it was thought that a fundamental defect in trophoblast biological function led to excessive invasion beyond the physiological attachment zone of the endometrium to the myometrium. The current hypothesis suggests that a defect at the junction of the endometrium-myometrium, possibly due to previous surgeries, prevents proper decidualization of the endometrium, allowing for abnormal trophoblast invasion [8].

The heterogeneity between the results could be due to the fact that the studies included in this meta-analysis did not specify the type of abortion (medical *versus* surgical).

This meta-analysis had several limitations: 1) Heterogeneity concerns. Considerable heterogeneity was observed among adjusted studies ($I^2 = 79.5\%$). However, interpretation requires caution, as the Q-test has limited power with few studies; 2) Unadjusted confounding. Some included studies did not fully account for potential confounders (*e.g.*,

prior caesarean delivery, maternal age), which may introduce residual information bias. However, there is a risk that the association found is driven by the correlation between abortion history and multiparty/prior caesareans rather than abortion itself; 3) Lack of abortion-type stratification: subgroup analysis by abortion method (surgical *vs* medical) was not possible due to insufficient reporting in primary studies; 4) We did not use other electronic databases such as Cochrane Library and Embase in this study, which is a limitation of the present study. Despite these limitations, our findings, based on 115,422 participants across 11 studies, consistently demonstrate that previous abortion is associated with an increased risk of PAS.

CONCLUSIONS

This meta-analysis reported that prior abortion is a risk factor for PAS. These findings suggest clinicians should incorporate PAS risk assessment into abortion counselling, particularly for patients with additional risk factors (*e.g.*, multiparity, advanced maternal age). Procedure selection may benefit from considering potential differential effects on endometrial integrity. Although endometrial injury may influence PAS risk, the current evidence does not allow definitive recommendations regarding the abortion procedure. Further research is required to clarify whether the method of abortion affects endometrial integrity and subsequent PAS risk.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

E.J., S.A.: Conceptualization, data curation, writing – original draft. E.J., S.A. F.K: Investigation, methodology. S.K: Formal analysis. All authors: writing – review & editing.

Funding

This study was financially supported by Hamadan University of Medical Sciences with Code: 140304193205.

Study registration

An attempt was made to register the review protocol in PROSPERO. However, the application was submitted after the start of data extraction and was therefore not eligible for registration, as PROSPERO only accepts prospectively registered systematic reviews submitted before data extraction begins. Consequently, the review was not registered in PROSPERO.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

This study received ethical approval from the Institutional Review Board of Hamadan University of Medical Sciences (IR.UMSHA.REC.1403.226; July 13, 2024). All procedures were conducted in strict compliance with the ethical principles outlined in the Declaration of Helsinki (2013 revision).

Informed consent

N/A.

Data sharing

Data are available under reasonable request to the corresponding author.

REFERENCES

1. Yang X, Zheng W, Yan J, Yang H. High Risk Factors for Placenta Accreta Other than Pregnancy and Their Impact on Patient Prognosis. Matern Fetal Med. 2023;5(3):137-143. doi: 10.1097/FM9.0000000000000183.
2. Jauniaux E, Bunce C, Grønbeck L, Langhoff-Roos J. Prevalence and main outcomes of placenta accreta spectrum: a systematic review and meta-analysis. Am J Obstet Gynecol. 2019;221(3):208-218. doi: 10.1016/j.ajog.2019.01.233.
3. Morlando M, Collins S. Placenta accreta spectrum disorders: challenges, risks, and management strategies. Int J Women's Health. 2020;1033-1045. doi: 10.2147/IJWH.S224191.
4. American College of Obstetricians and Gynecologists; Society for Maternal-Fetal Medicine. Placenta accreta spectrum. Obstetric Care Consensus No. 7. Obst Gyn. 2018;132(6):e259-e275.
5. White A, Malik M, Pruszynski JE, Do QN, Spong CY, Herrera CL. Contemporary Placenta Accreta Spectrum Disorder Incidence and Risk Factors. Obstet Gynecol. 2025;145(6):665-673. doi: 10.1097/AOG.0000000000005919.
6. Wekere FCC, Inimgba NM, Kua PL, Okagua KE, Asikimabo-Ofori S, Ocheche US, et al. Placenta

Accreta Spectrum: Prevalence, Trend and Association with Sociodemographic / Obstetric Factors in a Tertiary Health Facility in Niger Delta, Nigeria. Niger Med J. 2023;63(6):467-473.
7. Faralli I, Del Negro V, Chinè A, Aleksa N, Ciminello E, Piccioni MG. Placenta accreta spectrum (PAS) disorder: ultrasound versus magnetic resonance imaging. Diagnostics. 2022;12(11):2769. doi: 10.3390/diagnostics12112769.
8. Bartels HC, Postle JD, Downey P, Brennan DJ. Placenta Accreta Spectrum: A Review of Pathology, Molecular Biology, and Biomarkers. Dis Markers. 2018;2018:1507674. doi: 10.1155/2018/1507674.
9. Jenabi E, Salimi Z, Salehi AM, Khazaei S.The environmental risk factors prior to conception associated with placenta accreta spectrum: An umbrella review. J Gynecol Obstet Hum Reprod. 2022;51(7):102406. doi: 10.1016/j.jogoh.2022.102406.
10. Jenabi E, Salehi AM, Masoumi SZ, Maleki A. Maternal Smoking and the Risk of Placenta Accreta Spectrum: A Systematic Review and Meta-Analysis. Biomed Res Int. 2022;2022:2399888. doi: 10.1155/2022/2399888
11. Yang R, Zhang L, Sun L, Wu J, Bi S, Hu M, et al. Risk of Placenta Accreta Spectrum Disorder After Prior Non-Cesarean Delivery Uterine Surgery: A Systematic Review and Meta-analysis. Obstet Gynecol. 2025;145(6):628-638. doi: 10.1097/AOG.0000000000005824.
12. Sharami SH, Milani F, Fallah Arzpeyma S, Fakour F, Jafarzadeh Z, Haghparast Z, et al. Placenta accreta outcomes and risk factors in a referral hospital in north of Iran: A case control study. Health Sci Rep. 2024;7(4):e2006. doi: 10.1002/hsr2.2006.
13. Liu X, Wang Y, Wu Y, Zeng J, Yuan X, Tong C, et al. What we know about placenta accreta spectrum (PAS). Eur J Obstet Gynecol Reprod Biol. 2021;259:81-89. doi: 10.1016/j.ejogrb.2021.02.001.
14. Eshkoli T, Weintraub AY, Sergienko R, Sheiner E. Placenta accreta: risk factors, perinatal outcomes, and consequences for subsequent births. Am J Obstet Gynecol. 2013;208(3):219.e1-7. doi: 10.1016/j.ajog.2012.12.037.
15. Sun H, Mao J, Su X, Du Q. Impact of spontaneous abortion history and induced abortion history on perinatal outcomes of singleton pregnancies. BMC Public Health. 2023;23(1):2360. doi: 10.1186/s12889-023-17264-5.
16. Kamara M, Henderson J, Doherty D, Dickinson J, Pennell C. The risk of placenta accreta following primary elective caesarean delivery: a case–control study. BJOG. 2013;120(7):879-886. doi: 10.1111/1471-0528.12148.
17. Wu S, Kocherginsky M, Hibbard JU. Abnormal placentation: twenty-year analysis. Am J Obstet Gynecol. 2005;192(5):1458-61. doi: 10.1016/j.ajog.2004.12.074.
18. Iacovelli A, Liberati M, Khalil A, Timor-Trisch I, Leombroni M, Buca D, et al. Risk factors for abnormally invasive placenta: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2020;33(3):471-481. doi: 10.1080/14767058.2018.1493453.
19. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
20. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions Version 5.0.0. The Cochrane Collaboration. 2008. doi:10.1002/9780470712184.
21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557.
22. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-634. doi: 10.1136/bmj.315.7109.629.
23. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88. doi: 10.1016/0197-2456(86)90046-2.
24. Elbery S, Mahmoud M, Mansour A, Rashed M, Salem H. Incidence and Risk Factors of Morbidely Adherent Placenta in Cases with Previous Caesarean Section in Benha University Hospital. Benha J Appl Sci. 2020;5(4 part (2)):341-346. doi: 10.21608/bjas.2020.136386.
25. Alchalabi Ha, Lataifeh I, Obeidat B, Zayed F, Khader YS, Obeidat N. Morbidly adherent placenta previa in current practice: prediction and maternal morbidity in a series of 23 women who underwent hysterectomy. J Matern Fetal Neonatal Med .2014;27(17):1734-1737. doi: 10.3109/14767058.2013.879700.
26. Ogawa K, Jwa SC, Morisaki N, Sago H. Risk factors and clinical outcomes for placenta accreta spectrum with or without placenta previa. Arch Gynecol Obstet. 2022;305(3):607-615. doi: 10.1007/s00404-021-06189-2.

27. Klar M, Laub M, Schulte-Moenting J, Proempeler H, Kunze M. Clinical risk factors for complete and partial placental retention–a case-control study. J Perinat Med. 2013;41(5):529-534. doi: 10.1515/jpm-2012-0260.
28. Tadayon M, Javadifar N, Dastoorpoor M, Shahbazian N. Frequency, Risk Factors, and Pregnancy Outcomes in Cases with Placenta Accreta Spectrum Disorder: A Case-Control Study. J Reprod Infertil. 2022;23(4):279. doi: 10.18502/jri.v23i4.10814.
29. Parra-Herran C, Djordjevic B.Histopathology of placenta creta: chorionic villi intrusion into myometrial vascular spaces and extravillous trophoblast proliferation are frequent and specific findings with implications for diagnosis and pathogenesis. Int J Gynecol Pathol. 2016;35(6):497-508. doi: 10.1097/PGP.0000000000000250.
30. Moeini R, Dalili H, Kavyani Z, Shariat M, Charousaei H, Akhondzadeh A, et al. Maternal and neonatal outcomes of abnormal placentation: a case–control study. J Matern Fetal Neonatal Med. 2021;34(19):3097-3103. doi: 10.1080/14767058.2019.1678128.
31. An P, Zhang J, Yang F, Wang Z, Hu Y, Li X. USMRI Features and Clinical Data-Based Model for Predicting the Degree of Placenta Accreta Spectrum Disorders and Developing Prediction Models. Int J Clin Pract. 2022;2022:9527412. doi: 10.1155/2022/9527412.
32. Kyozuka H, Yamaguchi A, Suzuki D, Fujimori K, Hosoya M, Yasumura S, et al. Risk factors for placenta accreta spectrum: findings from the Japan environment and Children's study. BMC. 2019;19(1):447. doi: 10.1186/s12884-019-2608-9.
33. Silver RM, Branch DW. Placenta accreta spectrum. N Engl J Med. 2018;378(16):1529-1536. doi: 10.1056/NEJMcp1709324.
34. Li R, Tang X, Qiu X, Wang W, Wang Q. Associations of characteristics of previous induced abortion with different grades of current placenta accreta spectrum disorders. J Matern Fetal Neonatal Med. 2023;36(2):2253349. doi: 10.1080/14767058.2023.2253349.
35. Jauniaux E, Collins S, Burton GJ. Placenta accreta spectrum: pathophysiology and evidence-based anatomy for prenatal ultrasound imaging. Am J Obstet Gynecol. 2018;218(1):75-87. doi: 10.1016/j.ajog.2017.05.067.

Supplement 1. *Strategy search.*

1) Prior abortion
2) Previous abortion
3) Previous miscarriage
4) Prior miscarriage
5) History of abortion
6) History of miscarriage
7) Morbidly adherent placenta
8) Placenta accreta
9) Placenta increta
10) Placenta percreta
11) Abnormally invasive placenta
12) #1 OR #2 OR #3 OR #4 OR #5 OR #6
13) #7 OR #8 OR #9 OR #10 Or #11
14) #12 AND #13

Italian Journal of
Gynæcology & Obstetrics
September 2026 - Vol. 38 - N. 3 - Quarterly - ISSN 2385 – 0868

Ultrasound-guided hysteroscopy (UGHys) for the management of high-risk retained products of conception: a retrospective case series

Milo **Giani** *, Elisa **Wu**, Ernesto **Gallucci**, Massimiliano **Fambrini**, Felice **Petraglia**, Maria Elisabetta **Coccia**

Department of Obstetrics and Gynecology, "Careggi" University Hospital, University of Florence, Florence, Italy.

ARTICLE INFO

History
Received: 02 October 2025
Received in revised form: 08 December 2025
Accepted: 26 January 2026
Available online: 10 September 2026

DOI: 10.36129/jog.2026.264

Key words
Retained products of conception; residual trophoblastic tissue; operative hysteroscopy; enhanced myometrial vascularity; doppler ultrasound.

***Corresponding author:** Milo **Giani**, M.D. Department of Obstetrics and Gynecology, "Careggi" University Hospital, largo Brambilla 3, 50134 Florence, Italy.
Email: milo.giani@gmail.com; milo.giani@unifi.it.
ORCID: 0000-0003-1063-3410.

ABSTRACT

Objective. Retained Products of Conception (RPOC) can be highly vascularized, increasing the risk of severe or life-threatening haemorrhage during surgery. Identification of high-risk cases is crucial to minimize complications. The aim of this study was to assess single-step Ultrasound-Guided Hysteroscopy (UGHys), a minimally invasive technique combining ultrasound and hysteroscopic guidance for highly vascularized RPOC.

Materials and Methods. We conducted a retrospective study at Careggi Hospital in 2024 on the obstetric population hospitalized for delivery or miscarriage to identify cases of RPOC. Transvaginal ultrasound (TVUS) with Doppler, performed according to International Endometrial Tumor Analysis (IETA) criteria, was used to stratify patients by bleeding risk. Low-risk cases were managed conservatively with TVUS follow-up, whereas high-risk cases underwent UGHys removal. The primary outcome was procedural success, defined as complete removal without bleeding.

Results. Among 3,944 screened patients, 62 surgical RPOC were included (1.57%), of whom 6 (9.67%) were classified as high-risk. Mean gestational age at termination was higher in the high-risk group (9.67 ± 2.84 *vs* 6.94 ± 1.79 weeks; p = 0.034), a difference that was also clinically relevant. All high-risk cases were successfully treated with UGHys. No intra- or post-operative complications occurred, all patients were discharged the same day, and no repeat hysteroscopy was required.

Conclusions. UGHys appears to be a safe and effective single-step technique for managing highly vascularized RPOC, achieving complete removal avoiding complications and preserving fertility. RPOC following pregnancies beyond nine weeks or with prolonged persistence are more likely to show high vascularity and therefore warrant careful assessment.

INTRODUCTION

Retained products of conception (RPOC) is defined as placental or trophoblastic tissue retained in the uterine cavity after a pregnancy. RPOC can be highly vascularized, resembling an arteriovenous malformation (AVM) [1-3]. Accurate identification of a highly vascularized RPOC is crucial, as an improper surgical approach could result in life-threatening haemorrhage. RPOC can complicate

pregnancies, regardless of gestational age, type of delivery, spontaneous or induced abortion [4-7].
Currently, there are no established diagnostic criteria or standardized therapeutic protocols for the management of highly vascularized RPOC. Transvaginal ultrasound (TVUS) plays a key role in diagnosis and the presence of an endometrial tissue, thickened endometrium, irregular myometrial-endometrial interface, complex endometrial fluid or an echogenic focus without apparent mass are sonographic findings that may indicate RPOC [8-11]. Recently, an ultrasonographic endometrial thickness of > 15 mm, measured two weeks after primary treatment, has been proposed as a diagnostic criterion for RPOC after abortion [12]. Additionally, the use of colour Doppler imaging is crucial for diagnosis. An echogenic, well-vascularized intracavitary lesion detected after a miscarriage or delivery, is suggestive of retained tissue [13]. Furthermore, Kamaya *et al.*, classified RPOC using colour Doppler into three types, ranging from type 0 (no vascularization) to type 3, where the endometrial vascularity is greater than that in the myometrium [1]. Other authors have also referred to these vascularized areas as "marked vascularity" (MV) or "enhanced myometrial vascularity" (EMV) [14-16].
In the last two decades, hysteroscopy has proven to be an effective treatment for RPOC and to be superior to dilation and curettage (D&C) for its removal due to the achievement of a higher rate of complete treatment, reduction of the incidence of intrauterine adhesions (IUAs) and improving pregnancy rates [4, 17-20]. Office hysteroscopy is feasible for patients with RPOCs < 30mm and absent or minimal vascularization on Doppler TVUS [21].
The main unresolved issue concerns determining the most effective approach to treating women at high-risk of bleeding, particularly in cases where Doppler TVUS reveals highly vascularized RPOC resembling an AVM, a condition variably described in the literature as "type 3 vascularization", "EMV" or "MV". A two-step hysteroscopy procedure has been proposed for the management of complex RPOCs (*i.e.* highly vascularized). In those studies, operative hysteroscopies were performed on patients who had preoperative TVUS done by external providers, with or without the use of colour Doppler flow. As a result, proper selection of women truly at high-risk of bleeding was not guaranteed [4, 22]. Recently, Dewilde *et al*. proposed an algorithm for the management of cases with enhanced myometrial vascularity [23].
In these patients, the goal is not only to achieve complete removal of RPOC while minimizing the risk of excessive bleeding, and preserve the structural and functional integrity of the uterine cavity and endometrium, so optimizing future pregnancy outcomes. To achieve this, we propose a single-step hysteroscopy combined with ultrasound for the management of highly vascularized RPOC.

MATERIALS AND METHODS

The present retrospective, single-centre study, recruited patients diagnosed with RPOC from January 1st to December 31st, 2024, at the Department of Obstetrics and Gynecology of Careggi Hospital in Florence. 3,103 vaginal or caesarean deliveries, 325 medical and 69 surgical abortions, 307 medical and 140 surgical terminations of pregnancy were recorded, resulting in a total of 3,944 patients. All data were obtained from existing patient files and electronic medical records, consistent with the retrospective study design. In our routine clinical practice, a gynaecological examination with TVUS is performed one month after caesarean or vaginal delivery and two weeks after spontaneous or induced abortion.
In case of RPOC diagnosis, patients were managed according to the protocol outlined in the flowchart shown in **Figure 1**.
Patients diagnosed with RPOC underwent TVUS examination using a Voluson S10 Expert (GE Healthcare, Milwaukee, WI) equipped with a 2.9 to 9.7

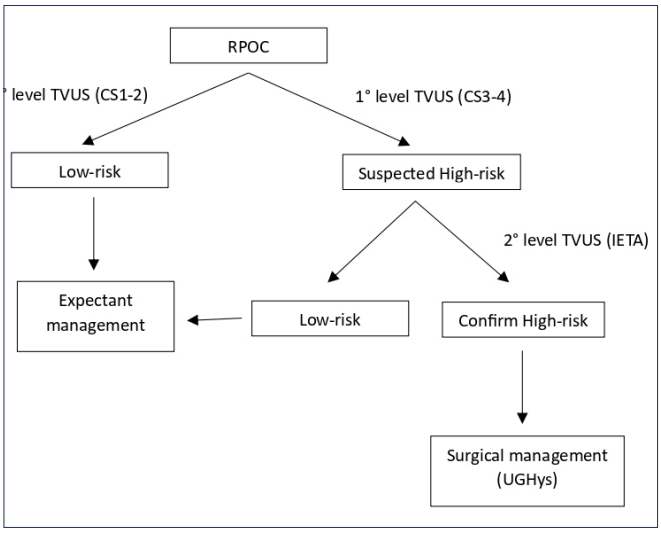

Figure 1. *Protocol for the Management of Retained Products of Conception (RPOC).*

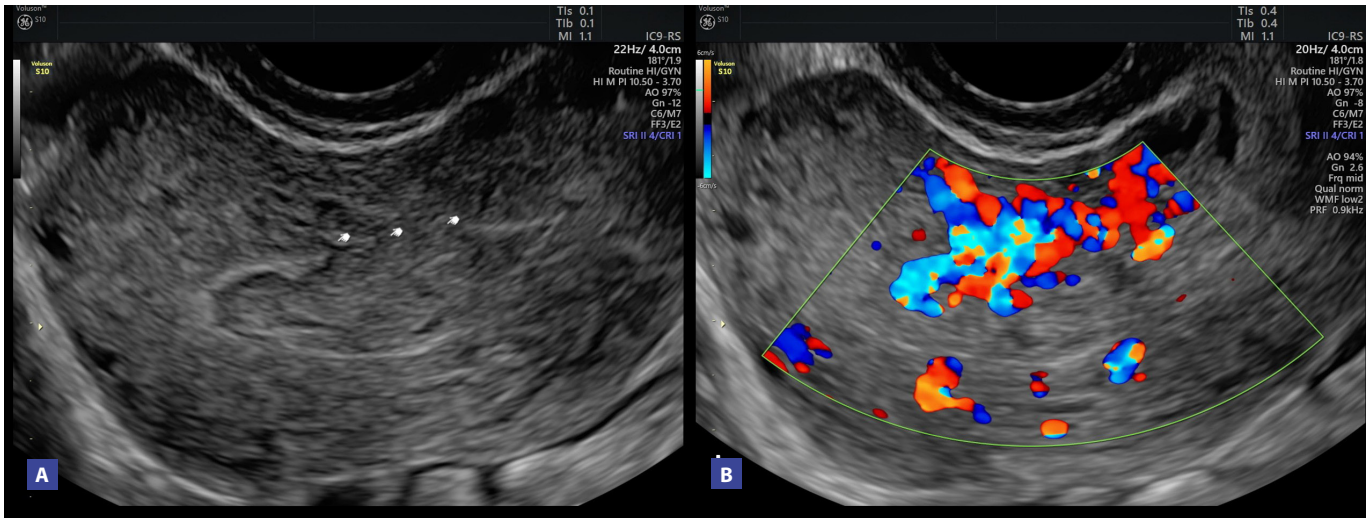

Figure 2. *High-risk RPOC case.* ***(a)*** *RPOC with evident interruption of the endometrial-myometrial junction.* ***(b)*** *RPOC on colour Doppler imaging showing vascularization with a dominant vessel crossing the disrupted endometrial-myometrial junction.*

MHz endocavitary probe. All sonographic and colour Doppler second-look examinations were conducted by two investigators (M.E.C. and M.G.). The examination began with the assessment of uterine position and measurements. Following the visualization of the ovaries, the uterine cavity was evaluated using the terms and definitions established by the International Endometrial Tumor Analysis (IETA) group [24]. RPOC vascularity was assessed using the colour Doppler box, which included the endometrium and the surrounding myometrium, with frequencies at least 5.0 MHz and pulse repetition frequency between 0.3 and 0.9 kHz. Amount of blood was scored (CS1-CS4) using the International Ovarian Tumor Analyses (IOTA), as applied to ovarian masses [25]. No specific peak systolic velocity cut-off was applied to identify highly vascularized RPOC, although velocities exceeding 60 cm/s were considered highly suspicious. The typical TVUS appearance of RPOC was described according to the recommendations of the IETA group. Therefore, a characteristic RPOC was considered as an endometrial lesion arising from the endometrium, with non-uniform echogenicity (mixed echogenicity, with greater hyperechogenic component), irregular edges and interrupted endometrial-myometrial junction. Colour Doppler assessment, using a pulse repetition frequency 0.6-0.9 kHz, had to include the endometrium and the underlying myometrium. The presence of a dominant vessel crossing the interrupted endometrial-myometrial junction was a typical finding (**Figure 2**). No specific endometrial thickness cut-off has been shown to reliably distinguish the presence or absence of RPOC.

Patients with minimal or no vascularization (colour score 1 or 2) were classified as low risk for bleeding. RPOCs measuring < 30 mm, with CS 1 or 2 on Doppler TVUS and without bleeding, were primarily managed conservatively with TVUS follow-up until complete resolution. Cases of increased vascularization (CS3-4) had a second-look TVUS performed by a senior sonographer to confirm the suspicion of highly-risk RPOC, quantifying the size and displaying anastomotic vessels using colour Doppler score.

High-risk RPOC was defined according to IETA criteria as follows:

1. persistence of trophoblastic tissue on follow-up scans, regardless of quantity;
2. presence of still "active" tissue, characterized by marked vascularity on colour Doppler;
3. identification of one or more dominant invasive vessels crossing the endo-myometrial junction and penetrating into the myometrium.

Study registration and ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Regional Ethical Committee (CEAVC 10189, amendment 16 May 2018, 2018-017, CINECA 10189). Written informed consent was obtained from all participants.

Statistical analysis

Patient characteristics were analysed using Fisher's exact test or Chi-squared test, as appropriate (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The difference between groups was assessed using an independent samples t-test with unequal variances (Welch's t-test). A P-value < 0.05 was considered statistically significant. Because this was a retrospective study, all eligible cases within the study period were included to maximize statistical power; therefore, no a priori power calculation was performed.

Ultrasound-guided hysteroscopy (UGHys) for high-risk retained products of conception

High-risk RPOC cases were managed with operative hysteroscopy under ultrasound guidance (UGHys), a minimally invasive approach that is recommended and routinely implemented in our institution as part of standard clinical practice, in operation room under general anaesthesia.

A TVUS was repeated before starting hysteroscopy, with an empty bladder to confirm the presence of high-risk RPOC and the exact site of the dominant vessel (point of adhesion of the retained tissue). The ultrasound machine was positioned to the right of the patient. Subsequently, the bladder was filled with 120 mL of saline solution to facilitate transabdominal ultrasound window during hysteroscopic procedure. The hysteroscopy procedure was conducted under ultrasound guidance with strictly communication between the hysteroscopist and the sonographer. During cervical dilatation with Hegar instruments, ultrasound guidance helped avoiding high-risk RPOC to prevent bleeding.

A 26Fr resectoscope with an angled loop is introduced and used in a "cold" (non-activated) mode to grasp and remove the retained tissue from the opposite side of the trophoblastic adhesion zone, functioning similarly to a curette (**Figure 3**). In the area of adhesions and high-risk of bleeding, ultrasound identified endometrial-myometrial junction interruption with vascular invasion. The surgeon carefully removed the tissue to minimize the risk of haemorrhage. In cases of bulky RPOC or mild bleeding, where the hysteroscopic visualization was compromised, ultrasound guidance was essential for accurately directing the resectoscope loop toward the retained tissue. Bleeding naturally resolved after complete removal of RPOC. In presence of vessel haemorrhage, ultrasound guided hysteroscopist to identify the source of bleeding for selected coagulation (**Figure 4**).

The complete removal of RPOC was confirmed by hysteroscopic visualization of empty uterine cavity and absence of retained tissue by TVUS.

The operative room was equipped for major bleeding including intrauterine balloon catheters. RPOC tissue was sent for pathological examination. TVUS at 15 days postoperatively, confirmed the absence of intrauterine remnants and assessed the improvement of sonographic findings, particularly the partial restoration of the endometrial-myometrial junction.

RESULTS

A total of 62 (1.57% of cases) RPOC surgical procedures were performed, 42 hysteroscopies and 20

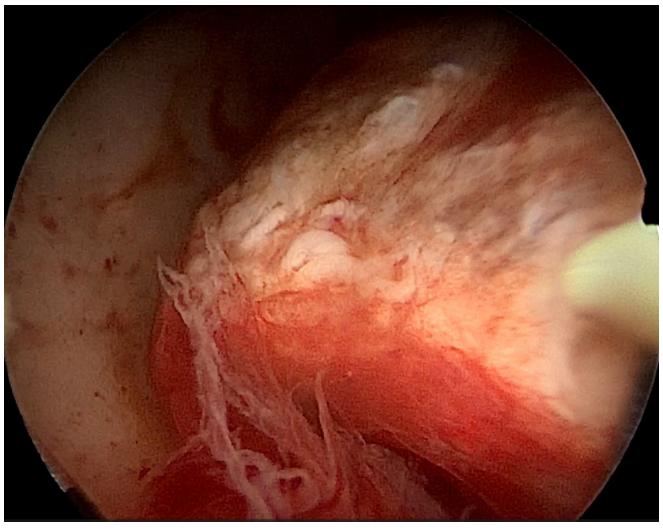

Figure 3. *Hysteroscopic vision of a retained products of conception.*

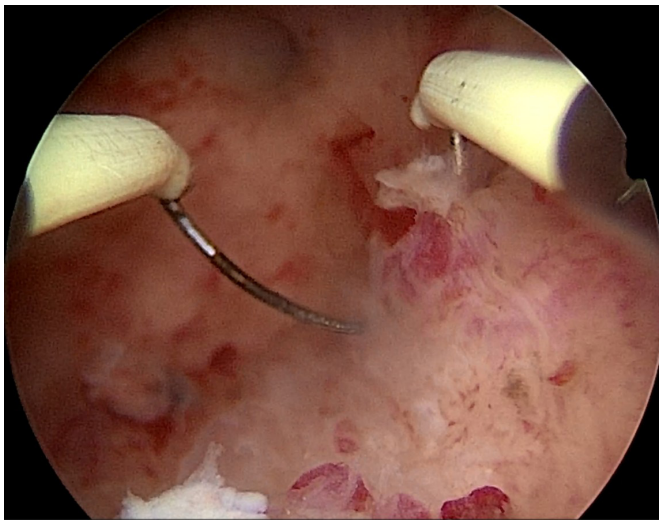

Figure 4. *Vessel previously attached to the RPOC, bleeding if touched.*

D&C. The 62 patients were stratified into two risk groups: low-bleeding-risk (56 patients, 90.33%) and high-bleeding-risk (6 patients, 9.67%).

The main demographic and ultrasonographic characteristics of the patients are reported in **Table 1**.

The majority of RPOC cases occurred after medical termination of pregnancy (39 cases, 62.9%), followed by vaginal delivery (17 cases, 27.4%), caesarean section (5 cases, 8.1%) and surgical termination of pregnancy (1 case, 1.6%) (**Table 2**). No cases of high-bleeding-risk RPOC were observed following caesarean delivery or surgical termination of pregnancy. The interval between the delivery and the surgical intervention was 9.78 weeks (SD ± 11.1) in the low-risk group and 8.14 weeks (SD ± 1.6) in the high-risk group. Conversely, the interval between early pregnancy loss and surgery was 4.27 weeks (SD ± 3.0) in the low-risk group and 11.57 weeks (SD ± 7.9) in the high-risk group. The high-risk group showed a significantly higher mean gestational age at the time of first-trimester pregnancy termination compared to the low-risk group (9.67 weeks *vs* 6.94 weeks; p = 0.034).

Regarding symptoms, vaginal bleeding was the most frequently reported, occurring in 3 of the 6 patients in the high-bleeding-risk group (50%) and in 18 of the 56 patients in the low-bleeding-risk group (32.1%, p = 0.034). Notably, two of the six high-risk patients presented to the emergency department due to bleeding.

The six high-bleeding-risk RPOCs were managed using UGHys procedure. One patient had the uterine cavity completely filled and obscured by the retained placental tissue. Two patients were bleeding at the time of hysteroscopy, so the visualization of the uterine cavity and the retained tissue was limited. After the complete removal of the retained tissue, no major bleeding was observed, and the Foley catheter was never required. Intraoperative blood loss was measured in all cases and ranged from 20 to 120 mL, as recorded in the graduated collection bag. The fluid deficit during the procedure was also monitored and never exceeded 400 mL.

All patients classified as high-risk of bleeding, had histological analysis response of chorionic villi associated with a decidual flap, along with necrotic-ischemic or inflammatory-haemorrhagic changes. The mean size of placental remnants was 33.3 mm (range: 19-55 mm). Notably, none of the patients classified in the high-risk group had documented coagulation disorders.

All patients were admitted and discharged on the same day. None required a second hysteroscopic procedure

Table 1. *Demographic and sonographic data of patients with RPOC.*

	RPOC low-risk (n = 56)	RPOC high-risk (n = 6)	P-value
Age (yrs, mean)	35.4 (range 27-47)	33.3 (range 22-40)	0.33
BMI (mean)	23.1 (range 18-32)	23.5 (range 21-27)	0.55
Smoke (n of patients)	7 (12.5%)	3 (50%)	0.045
n of previous pregnancies	2.78 (SD ± 1.44)	2.33 (SD ± 1.75)	0.54
n of previous deliveries	1.28 (SD ± 0.97)	0.83 (SD ± 0.75)	0.23
Conception by ART (n of patients)	5 (8.9%)	1 (16.66%)	>0.9
Previous caesarean section (n of patients)	17 (30.3%)	0 (%)	0.18
Previous intrauterine curettage (n of patients)	23 (41%)	2 (33.33%)	>0.9
Previous myomectomy (n of patients)	2 (3.5%)	0 (%)	>0.9
Interval between term pregnancy to surgery (weeks)	9.78 (SD ± 11.1)	8.14 (SD ± 1.6)	0.57
Interval between early pregnancy to surgery (weeks)	4.27 (SD ± 3)	11.57 (SD ± 7.9)	0.162
RPOC thickness on TVUS (mm)	19.03 (9-47)	24.6 (11-46)	
Colour Doppler score (n of patients)	CS1 = 36 CS2 = 18 CS3 = 2 CS4 = /	CS1 = / CS2 = / CS3 = 2 CS4 = 4	<0.001
RPOC size histopathology (mm)	24.7 (5-60)	33.33 (19-55)	

n: number; BMI: body mass index; ART: assisted reproductive technology.

Table 2. *Early and term pregnancy with low and high-risk RPOC.*

	RPOC low-risk (n = 56)	RPOC high-risk (n = 6)	Total n (%)	P-value
Gestational age after term pregnancy (weeks)	38.5 (SD ± 2.6)	39.9 (SD ± 0.4)		0.055
Vaginal delivery	15	2	17 (27.4)	0.7
Caesarean section	5	0	5 (8.1)	0.4
Gestational age after early pregnancy termination (weeks)	6.94 (SD ± 1.79)	9.67 (SD ± 2.84)		0.034
Medical pregnancy termination	35	4	39 (62.9)	0.8
Surgical pregnancy termination	1	0	1 (1.6)	0.7

for complete removal of retained tissue. The ultrasound control at fifteen days after the procedure confirm complete removal of the retained tissue in all cases and a partial restore endo-myometrial junction.

DISCUSSION

Main findings

A key challenge in the diagnosis and management of RPOC patients concerns the accurate interpretation of ultrasound findings, particularly the assessment of colour Doppler. As an intrauterine lesion, RPOC should be describe with the terms and definitions of the International Endometrial Tumor Analysis (IETA) terminology [24]. Therefore, a characteristic retained products of conception should be described as an endometrial lesion arising from the endometrium, with non-uniform echogenicity (mixed echogenicity, with greater hyperechogenic component), irregular edges and interrupted underlying endometrial-myometrial junction. Colour Doppler assessment, using a pulse repetition frequency 0.6-0.9 kHz, should include both the endometrium and the underlying myometrium. The most critical clinical indicator and sonographic pattern is bleeding and/or persistence of an endometrial lesion over time, that remains attached to and infiltrates the underlying myometrium. Accurate use of TVUS and Doppler requires specific skills, therefore, all cases of suspected or highly vascularized RPOCs should be referred for a second-level evaluation by an experienced sonographer.

Our analysis identified a statistically significant higher risk of developing highly vascularized RPOC in later gestational ages compared to earlier gestational ages (mean gestational age: 9.67 weeks *vs* 6.94 weeks; P-value 0.034), an association that has not been previously reported in the scientific literature. This increased risk may be linked to the physiologic remodelling of maternal spiral arteries, which regulate uteroplacental blood inflow into the intervillous space. Prior to 8 weeks of gestation, these arteries remain largely occluded by trophoblast plugs and from tortuous, non-perfused networks, resulting in limited placental perfusion. Beginning around 9 weeks, recanalization of the spiral arteries initiates from the placental periphery – a process typically completed by 12 weeks – leading to progressive increases in vascularization and blood flow within the placental bed [26, 27]. Therefore, caution is recommended when managing RPOC after first-trimester termination beyond 9 weeks' gestation.

Another notable observation concerns the interval between early pregnancy termination and subsequent surgery. The interval between the end of early pregnancy and surgery differed between the low- and high-risk groups, suggesting that prolonged persistence of the lesion may represent a significant risk factor for the development of increased vascularization. The presence of retained tissue beyond 9 weeks' gestation – thus following the onset of spiral artery remodelling – is associated with inevitable villous necrosis over time. As hypothesized by Borell, this necrosis may contribute to the formation of a fistulous circuit, resulting in arterial-to-venous shunting and ultimately to the development of a highly vascularized RPOC [28].

Expectant management is not recommended in high-risk RPOC patients, particularly in patients experiencing vaginal bleeding (observed in 50% of our cohort). A prolonged follow-up – extended over several months – increase patient anxiety, the risk of infection, delay of conception and follow-up drop-out; in fact, expectant management of patients with highly vascularized RPOCs remains questionable due to its high failure rate [29, 30].

In high-bleeding-risk RPOC, the integrated approach offered by Ultrasound-Guided Hysteroscopy (UGHys) enhances procedural safety. Compared with conventional blind dilation and curettage (D&C), UGHys provides direct visualization of the uterine cavity and real-time ultrasound monitoring, reducing the risk of uterine perforation, particularly relevant in postpartum uteri, which are structurally softened and more vulnerable to injury. Ultrasound guidance also improves the accuracy of resectoscope navigation, allows identification of the bleeding vessel with colour Doppler, and facilitates the complete removal of placental remnants, even in bulky or actively bleeding RPOC with limited endoscopic visibility. Manual vacuum aspiration (MVA) is also considered a method for managing RPOC; however, as a blind technique, it may be less suitable in highly vascularized or bleeding cases. These aspects make UGHys a safer and more controlled option than both blind D&C and MVA in high-risk cases. An additional strength of our study is the educational value of ultrasound guidance during operative hysteroscopy. Real-time imaging can support trainees, including residents in obstetrics and gynaecology, by improving their

understanding of uterine anatomy, vascular patterns, and procedural steps. This aligns with the growing role of digital visual resources in gynaecologic training and may enhance learning effectiveness and procedural safety [31]. UGHys is a safe procedure that avoids emergency procedures such as D&C, embolization or hysterectomy. It preserves the morphological and functional integrity of the uterus, thereby its potential to support future pregnancies.

Strengths and limitations

The main strength of our study lies in the systematic application of International Endometrial Tumor Analysis (IETA), terminology to describe RPOC ultrasound features, together with standardized Doppler assessment. Moreover, we provide new evidence linking later gestational age and prolonged persistence of retained tissue with a higher risk of developing highly vascularized RPOC. Long-term follow-up was not part of the study design, as per the hospital-approved protocol; however, at the 15-30-day ultrasound control, an intact uterine cavity and cessation of bleeding were documented in all cases. The main limitations are its retrospective, single-centre design and the limited number of high-risk cases, which reduces the statistical strength of subgroup analyses.

CONCLUSIONS

To our knowledge, this is the first study recommending the use of International Endometrial Tumor Analysis (IETA) terminology to describe RPOC on TVUS and suggesting that later gestational age and prolonged lesion persistence are significant risk factors for developing highly vascularized RPOC. UGHys appears to be a safe and effective treatment option in these patients, with the potential to preserve reproductive outcomes.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

M.G.: Conceptualization, visualization, writing – original draft, writing – review & editing. E.W.: Investigation, data curation. E.G.: Formal analysis, data curation. M.F.: Methodology, validation. F.P.: Supervision. M.E.C.: Conceptualization, project administration, writing – review & editing.

Funding

None.

Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

This study was approved by the Regional Ethical Committee (CEAVC 10189, amendment 16 May 2018, 2018-017, CINECA 10189).

Informed consent

Written informed consent was obtained from all participants.

Data sharing

Data are available under reasonable request to the corresponding author. Due to confidentiality and their extraction from the ArchiMed management system, only encrypted datasets can be shared.

ACKNOWLEDGEMENTS

We thank the entire staff of the Maternal and Child Department of the Azienda Ospedaliero-Universitaria Careggi, whose dedicated work ensures high-quality care for women. We also extend our gratitude to all the residents working within the department for their constant commitment and support in daily clinical practice.

REFERENCES

1. Kamaya A, Petrovitch I, Chen B, Frederick CE, Brooke Jeffrey R. Retained Products of Conception: Spectrum of Color Doppler Findings. J Ultrasound Med. 2009;28(8):1031-41. doi: 10.7863/jum.2009.28.8.1031.
2. Jain K, Fogata M. Retained products of conception mimicking a large endometrial AVM: Complete resolution following spontaneous abortion. J Clin Ultrasound. 2007;35(1):42-47. doi: 10.1002/jcu.20250.
3. Kido A, Togashi K, Koyama T, Ito K, Tatsumi K, Fujii S, et al. Retained Products of Conception Masquerading as Acquired Arteriovenous Malfor-

mation. J Comput Assist Tomogr. 2003;27(1):88-92. doi: 10.1097/00004728-200301000-00016.
4. Foreste V, Gallo A, Manzi A, Riccardi C, Carugno J, Di Spiezio Sardo A. Hysteroscopy and retained products of conception: An update. Gynecol Minim Invasive Ther. 2021;10(4):203-209. doi: 10.4103/GMIT.GMIT_125_20.
5. Smorgick N, Barel O, Fuchs N, Ben-Ami I, Pansky M, Vaknin Z. Hysteroscopic management of retained products of conception: Meta-analysis and literature review. Eur J Obstet Gynecol Reprod Biol. 2014;173(1):19-22. doi: 10.1016/j.ejogrb.2013.11.020.
6. Sellmyer MA, Desser TS, Maturen KE, Brooke Jeffrey R, Kamaya A. Physiologic, histologic, and imaging features of retained products of conception. Radiographics. 2013;33(3):781-796. doi: 10.1148/rg.333125177.
7. Chawla S. Sharma R. Retained Products of Conception (RPOC): Diagnosis, Complication & Management. J Obstet Gynaecol India. 2023;73(5):374-380. doi: 10.1007/s13224-023-01873-6.
8. Ustunyurt E, Kaymak O, Iskender C, Ustunyurt OB, Celik C, Danisman N. Role of transvaginal sonography in the diagnosis of retained products of conception. Arch Gynecol Obstet. 2008;277(2):151-4. doi: 10.1007/s00404-007-0436-z.
9. Vardar Z, Dupuis CS, Goldstein AJ, Siddiqui E, Vardar BU, Kim YH. Pelvic ultrasonography of the postpartum uterus in patients presenting to the emergency room with vaginal bleeding and pelvic pain. Ultrasonography. 2022;41(4):782-795. doi: 10.14366/usg.22004.
10. Durfee SM, Frates MC, Luong A, Benson CB. The Sonographic and Color Doppler Features of Retained Products of Conception. J Ultrasound Med. 2005;24(9):1188-9. doi: 10.7863/jum.2005.24.9.1181.
11. Lin YH, Cheng YY, Ding DC. Hysteroscopic management of retained products of conception. Gynecol Minim Invasive Ther. 2018;7(3):133-135. doi: 10.4103/GMIT.GMIT_27_18.
12. Hamel CC, van Wessel S, Carnegy A, Coppus SFPJ, Snijders MPMl, Clark J et al. Diagnostic criteria for retained products of conception—A scoping review. Acta Obstet Gynecol Scand. 2021;100(12):2135-2143. doi: 10.1111/aogs.14229.
13. Van Den Bosch T, Daemen A, Van Schoubroeck D, Pochet N, De Moor B, Timmerman D. Occurrence and Outcome of Residual Trophoblastic Tissue A Prospective Study. J Ultrasound Med. 2008;27(3):357-61. doi: 10.7863/jum.2008.27.3.357.
14. Grewal K, Al-Memar M, Fourie H, Stalder C, Timmerman D, Bourne T. Natural history of pregnancy-related enhanced myometrial vascularity following miscarriage. Ultrasound Obstet Gynecol. 2020;55(5):676-682. doi: 10.1002/uog.21872.
15. Van Schoubroeck D, Van Den Bosch T, Scharpe K, Lu C, Van Huffel S, Timmerman D. Prospective evaluation of blood flow in the myometrium and uterine arteries in the puerperium. Ultrasound Obstet Gynecol. 2004;23(4):378-381. doi: 10.1002/uog.963.
16. Bazeries P, Paisant-Thouveny F, Yahya S, Bouvier A, Nedelcu C, Boussion F, et al. Uterine Artery Embolization for Retained Products of Conception with Marked Vascularity: A Safe and Efficient First-Line Treatment. Cardiovasc Intervent Radiol. 2017;40(4):520-529. doi: 10.1007/s00270-016-1543-7.
17. Rein D. T, Schmidt T, Hess A. P, Volkmer A, Schöndorf T, Breidenbach M. Hysteroscopic Management of Residual Trophoblastic Tissue Is Superior to Ultrasound-Guided Curettage. J Minim Invasive Gynecol. 2011;18(6):774-778. doi: 10.1016/j.jmig.2011.08.003.
18. Hooker AB, Aydin H, Brölmann HAM, Huirne JAF. Long-term complications and reproductive outcome after the management of retained products of conception: A systematic review. Fertil Steril. 2016;105(1):156-164. doi: 10.1016/j.fertnstert.2015.09.021.
19. Faivre E, Deffieux X, Mrazguia C, Gervaise A, Chauveaud-Lambling A, Frydman R, et al. Hysteroscopic Management of Residual Trophoblastic Tissue and Reproductive Outcome: A Pilot Study. J Minim Invasive Gynecol. 2009;16(4):487-490. doi: 10.1016/j.jmig.2009.04.011.
20. Golan A, Dishi M, Shalev A, Keidar R, Ginath S, Sagiv R. Operative Hysteroscopy to Remove Retained Products of Conception: Novel Treatment of an Old Problem. J Minim Invasive Gynecol. 2011;18(1):100-103. doi: 10.1016/j.jmig.2010.09.001.
21. Jakopič Maček K, Blaganje M, Kenda Šuster N, Drusany StaričK, Kobal B. Office hysteroscopy in removing retained products of conception–a highly successful approach with minimal complications. J Obstet Gynaecol. 2020;40(8):1122-1126. doi: 10.1080/01443615.2019.1679736.

22. Smorgick N, Rabinovitch I, Levinsohn-Tavor O, Maymon R, Vaknin Z, Pansky M. Two-step hysteroscopy for management of morbidly adherent retained products of conception. Arch Gynecol Obstet. 2019;300(3):669-674. doi: 10.1007/s00404-019-05246-1.
23. Dewilde K, Groszmann Y, Van Schoubroeck, Grewal K, Huirne J, de Leeuw, R et al. Enhanced myometrial vascularity secondary to retained pregnancy tissue: time to stop misusing the term arteriovenous malformation. Ultrasound Obstet Gynecol. 2024;63(1):5-8. doi: 10.1002/uog.27476.
24. Leone FPG, Timmerman D, Bourne T, Valentin L, Epstein E, Goldstein SR, et al. Terms, definitions and measurements to describe the sonographic features of the endometrium and intrauterine lesions: A consensus opinion from the International Endometrial Tumor Analysis (IETA) group. Ultrasound Obstet Gynaecol. 2010;35(1):103-12. doi: 10.1002/uog.7487.
25. Timmerman D, Valentin L, Bourne TH, Collins WP, Verrelst H, Vergote I. Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) group. Ultrasound Obstet Gynecol. 2000;16(5):500-5. doi: 10.1046/j.1469-0705.2000.00287.x.
26. Jauniaux E, Gulbis B, Burton GJ. The human first trimester gestational sac limits rather than facilitates oxygen transfer to the foetus--a review. Placenta. 2003;24 Suppl A:S86-93. doi: 10.1053/plac.2002.0932.
27. Redman CW, Sargent IL. Latest Advances in Understanding Preeclampsia. Science. 2005;308(5728):1592-4. doi: doi:10.1126/science.1111726.
28. Borell U, Fernstrom I. Arteriovenous fistulae of the uterus and adnexa; an arteriographic study. Acta radiol. 1958;49(1):1-16. doi: 10.3109/00016925809170973.
29. Akiba N, Iriyama T, Nakayama T, Semaya T, Sayama S, Kumasawa K et al. Ultrasonographic vascularity assessment for predicting future severe hemorrhage in retained products of conception after second-trimester abortion. J Mater Fetal Neonatal Med. 2021;34(4):562-568. doi: 10.1080/14767058.2019.1610739.
30. Wada Y, Takahashi H, Suzuki H, Ohashi M, Ogoyama M, Nagayama S, et al. Expectant management of retained products of conception following abortion: A retrospective cohort study. Eur J Obstet Gynecol Reprod Biol. 2021;260:1-5. doi: 10.1016/j.ejogrb.2021.02.028.
31. Libretti A, Vitale SG, Saponara S, Corsini C, Aquino CI, Savasta F, et al. Hysteroscopy in the new media: quality and reliability analysis of hysteroscopy procedures on YouTube™. Arch Gynecol Obstet. 2023;308(5):1515-1524. doi: 10.1007/s00404-023-07172-9.

Italian Journal of
Gynæcology & Obstetrics
September 2026 - Vol. 38 - N. 3 - Quarterly - ISSN 2385 – 0868

Effect of neoadjuvant chemotherapy on primary and metastatic tumour burden in epithelial ovarian cancer: a retrospective analysis of oncologic surgeries at a university hospital

Hasan Hüseyin **Uçkan** [1,*], Mehmet Coşkun **Salman** [2], Kunter **Yüce** [2]

[1] Department of Obstetrics and Gynecology, Aydın City Hospital, Aydın, Türkiye.
[2] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Hacettepe University, Ankara, Türkiye.

ARTICLE INFO

History
Received: 29 September 2025
Received in revised form: 19 December 2025
Accepted: 26 January 2026
Available online: 10 September 2026

DOI: 10.36129/jog.2026.265

Key words
Epithelial ovarian cancer; neoadjuvant chemotherapy; cytoreductive surgery.

***Corresponding author:** Hasan Hüseyin **Uçkan**, Dr. Department of Obstetrics and Gynecology, Aydın City Hospital, Merkez Atatürk caddesi No:96, 09020, Efeler Aydin, Turkey.
Email: hsnuckan@gmail.com.
ORCID: 0000-0001-5129-3227.

ABSTRACT

Objective. To assess the effect of neoadjuvant chemotherapy (NACT) on pathological tumour burden in the primary tumour site and metastatic regions in patients with advanced epithelial ovarian cancer (EOC).

Materials and Methods. This retrospective study included FIGO stage III-IV EOC patients who underwent either primary debulking surgery (PDS) or NACT followed by interval debulking surgery (IDS). Tumour involvement in the ovaries (primary site) and other anatomical locations (metastatic sites) was recorded separately. Pre-treatment CA-125 levels and postoperative pathological findings were compared between groups.

Results. Seventy-six patients were evaluated (36 NACT+IDS, 40 PDS). Pre-treatment CA-125 levels were significantly higher in the NACT group. Although direct quantitative measurement of tumour burden was not performed, NACT-treated patients showed a marked decrease in CA-125 levels and a clinically evident reduction in tumour volume at IDS. Pathological assessment revealed lower tumour involvement in the ovaries after NACT, whereas metastatic site involvement remained comparable between the groups.

Conclusions. NACT may reduce primary tumour burden and facilitate cytoreductive surgery; however, its effect on metastatic regions appears limited. These findings support the possibility that biological heterogeneity may contribute to regional differences in chemotherapy response. Given the retrospective design, limited sample size, and absence of standardized histopathologic response scoring or molecular profiling, prospective multicentre studies incorporating detailed molecular characterization are required to better elucidate NACT response patterns in EOC.

INTRODUCTION

Ovarian cancer (OC) is the fifth leading cause of cancer-related death among women [1]. Despite advances in treatment, five-year survival rates for advanced-stage OC have shown limited improvement over the past decade.

For FIGO stage III-IV patients, primary debulking surgery (PDS) is the standard initial treatment. Since the 2012 NCCN guideline recommended

neoadjuvant chemotherapy (NACT) with interval debulking surgery (IDS) for high-risk surgical candidates, the use of NACT has increased [2-5]. NACT reduces surgical morbidity and improves optimal cytoreduction rates; however, randomized trials have not shown a clear advantage of NACT over PDS in progression-free or overall survival [2, 6-8].

Only a limited number of studies have evaluated the pathological response to NACT in epithelial ovarian cancer (EOC). These studies have employed various histopathologic assessment tools, such as pathological complete response (pCR) and chemotherapy response scoring (CRS), and have shown improved outcomes in patients achieving pCR. Nevertheless, pCR rates in EOC remain low, generally ranging from 0% to 4-14% [6, 8-11]. Accurate pCR assessment is difficult because IDS often requires extensive tissue removal. Moreover, no comprehensive study has compared NACT response between the primary tumour and different metastatic sites.

EOC exhibits biological and genetic heterogeneity, supported by its ability to spread through hematogenous, lymphatic, and direct invasion pathways. This heterogeneity may contribute to regional variations in chemotherapy response. Recent studies highlighting promising results with inhibitors targeting the BRAF and MEK pathways [12] and the established roles of BRCA1/2 mutations and homologous recombination deficiency (HRD) in mediating chemotherapy sensitivity [13], underscore the growing importance of tumour biology in guiding therapeutic decision-making.

Given that diverse metastatic pathways may reflect underlying molecular heterogeneity, which could influence regional chemotherapy response, this study aimed to evaluate the pathological effects of NACT separately in the primary tumor and in distinct metastatic sites.

PATIENTS AND METHODS

This retrospective study included patients with advanced-stage EOC who were treated at the Department of Obstetrics and Gynecology, Hacettepe University, between 01/01/2009 and 01/05/2017. Patients with a diagnosis of FIGO stage III-IV EOC were included in the study. The diagnosis was confirmed by biopsy, cytological evaluation, or histopathological examination of surgical specimens. Patients with non-epithelial ovarian tumours, incomplete clinical data, unavailable pathology specimens, or those whose initial surgery or pathological evaluation had been performed at another institution were excluded.

Patients were divided into two groups: those who underwent interval debulking surgery (IDS) after neoadjuvant chemotherapy (NACT), and those who underwent primary debulking surgery (PDS). NACT consisted of paclitaxel plus carboplatin administered every three weeks according to standard protocols. Most patients received three cycles; however, four or more cycles were given when clinically indicated.

All surgical specimens were evaluated by gynaecologic pathologists. The ovaries and fallopian tubes were considered the primary tumour site. Metastatic sites included the omentum, peritoneal surfaces, pelvic and paraaortic lymph nodes, peritoneal implants, and solid organ metastases. For each anatomical region, tumour involvement was recorded as present or absent. No quantitative scoring system was used; assessment was based on tumour positivity in the primary site and in metastatic regions. Clinical, laboratory, surgical, and pathological data were retrieved retrospectively from the hospital's electronic medical record system. The study was approved by the Hacettepe University Faculty of Medicine Clinical Research Ethics Committee (Date: 16/05/2017, Approval No:GO 17/456-44). Owing to the retrospective design, additional informed consent was not required; all data were anonymized and evaluated in accordance with the principles of the Declaration of Helsinki. Demographic characteristics, CA-125 levels at diagnosis, surgical findings, and pathological outcomes were compared between groups. Tumour involvement in the primary and metastatic sites was analysed separately for both groups.

Statistical analysis

Statistical analyses were performed using SPSS software (IBM SPSS Statistics for Windows, Version 23.0; IBM Corp., Armonk, NY, USA). The normality of distribution was assessed with the Kolmogorov-Smirnov test. Numerical variables with normal distribution were presented as mean ± standard deviation, whereas non-normally distributed variables were presented as median (min-max). Categorical variables were expressed as frequencies and percentages.

The Mann–Whitney U test was used for comparisons of non-normally distributed numerical va-

Table 1. *Demographic characteristics of patients in the NACT-IDS and PDS groups.*

Characteristic	Study Group	Control Group
Age (median)	60	55.5
Menopausal status		
Perimenopausal	9	9
Postmenopausal	27	31
CA-125 at diagnosis (median)	1,387	301.5
CA-125 at diagnosis (mean)	2,881.21	783.69
Number of NACT cycles		
3 cycles	28	0
4 or more cycles	8	0

Table 2. *Histological subtypes in patients undergoing NACT-IDS versus PDS.*

Histological Type	NACT Group	PDS Group	Pearson Chi-Square
Serous carcinoma	32 (88.9%)	25 (62.5%)	0.008
Other histologies	4 (11.1%)	15 (37.5%)	0.008

Table 3. *CA-125 levels at diagnosis in NACT-IDS and PDS groups.*

CA-125	NACT-IDS	PDS	P-value
Minimum	152	7	
Maximum	19,716	4,575	
Median	1,387	301.50	<0.001

Table 4. *Pre- and post-NACT CA-125 levels in the NACT-IDS group.*

CA-125	At diagnosis	Post-NACT	P-value
Minimum	152	4	
Maximum	19,716	2,464	
Median	1,387	33.5	<0.001

Table 5. *CA-125 levels before debulking surgery in NACT-IDS versus PDS groups.*

CA-125	Post-NACT	PDS	P-value
Minimum	4	7	
Maximum	2,464	4,575	
Median	33.5	301.50	<0.001

riables. The Wilcoxon signed-rank test was applied for paired non-normally distributed variables. Pearson's chi-square test or Fisher's exact chi-square test was used for comparisons of categorical variables, as appropriate.

RESULTS

Between 01/01/2009 and 01/05/2017, data from 383 patients who underwent surgery for OC at our institution were identified through the pathology database. Of the 52 patients who had received neoadjuvant chemotherapy (NACT), 16 were excluded because IDS could not be completed or relevant data were unavailable. The study group (NACT-IDS) consisted of 36 patients, and the control group included 40 patients who underwent primary debulking surgery (PDS).

The demographic characteristics of the patients are presented in **Table 1**. The median CA-125 level at diagnosis was 1,387 in the NACT-IDS group and 301.5 in the PDS group. CA-125 levels were significantly higher in the NACT group ($p < 0.001$). Among the patients receiving NACT, 8 received four or more cycles, while 28 received three cycles; no patient received fewer than three cycles. All patients were treated with a paclitaxel-carboplatin regimen.

Based on the final pathological evaluation, histologic diagnoses were categorized as serous epithelial carcinoma or other histologic subtypes. In the NACT-IDS group, 32 patients (88.9%) had serous histology, and 4 patients (11.1%) had non-serous tumours. In the PDS group, 25 patients (62.5%) had serous histology, and 15 patients (37.5%) had other histologic subtypes. Serous tumors were more frequent in the NACT group, and this difference was statistically significant ($p = 0.008$) (**Table 2**).

CA-125 values for the NACT–IDS and PDS groups are presented in **Tables 3**, **4**, and **5**. At diagnosis, CA-125 levels were significantly higher in the NACT-IDS group compared with the PDS group ($p < 0.001$). In the NACT group, CA-125 levels measured after completion of chemotherapy were significantly lower than the baseline diagnostic values ($p < 0.001$). When preoperative CA-125 levels were compared, the NACT-IDS group had significantly lower values than the PDS group ($p < 0.001$).

Tumour involvement in the ovaries, omentum, peritoneum, and retroperitoneal lymph nodes was assessed in both groups (**Table 6**). Among the 36 patients in the NACT–IDS group, ovarian involvement was present in 20 patients (55.6%) and absent in 16 patients (44.4%). In the PDS group, ovarian involvement was observed in 37 of 40 patients (92.5%), while 3 patients (7.5%) had no ovarian disease. Ovarian involvement was significantly lower in the NACT–IDS group ($p < 0.001$). There were no statistically significant differences between the two groups regarding tumour invol-

Table 6. *Histological subtypes in patients undergoing NACT-IDS versus PDS.*

Histological Type	Anatomical Site	NACT Group	PDS Group	P-value
Ovarian mass	Positive	20 (55.6%)	37 (92.5%)	<0.001
	Negative	16 (44.4%)	3 (7.5%)	<0.001
Omental mass	Positive	23 (63.9%)	17 (42.5%)	0.062
	Negative	13 (36.1%)	23 (57.5%)	0.062
Peritoneal mass	Positive	28 (77.8%)	23 (57.5%)	0.06
	Negative	8 (22.2%)	17 (42.5%)	0.06
Pelvic lymph node	Positive	9 (25%)	11 (27.5%)	0.805
	Negative	27 (75%)	29 (72.5%)	0.805
Paraaortic lymph node	Positive	12 (33.3%)	12 (30%)	0.755
	Negative	24 (66.7%)	28 (70%)	0.755

vement of the peritoneum, omentum, pelvic lymph nodes, or paraaortic lymph nodes (**Table 6**).

DISCUSSION

In this study, we evaluated the effect of neoadjuvant chemotherapy (NACT) on the primary tumour and metastatic sites in EOC. Although NACT substantially reduced overall tumour burden, our findings indicate that it did not achieve complete pathological response in most metastatic regions.

Previous studies have shown that NACT reduces postoperative morbidity without compromising survival and offers surgical advantages such as reduced blood loss, shorter operative time and hospitalization, and higher rates of optimal cytoreduction [14-16]. These benefits have largely been attributed to a decrease in tumour burden. Although we did not directly quantify tumour burden in our cohort, intraoperative assessments during interval debulking surgery revealed a notable reduction in tumour volume compared with initial surgical biopsies. In addition, CA-125 levels demonstrated a significant decline after NACT, further supporting its effect on tumour burden reduction.

The number of studies evaluating the pathological response to NACT in EOC is limited. Existing reports have used various scoring systems, including pathological complete response (pCR) and chemotherapy response scoring (CRS), to assess treatment response [2-5, 7, 9, 14]. Although pCR has been associated with improved prognosis, pCR rates in OC remain low, typically ranging between 0% and 4-14% [2-8, 10, 17]. Consistent with prior literature, no cases of pCR were observed in our study. This finding may be attributable to chemotherapy resistance arising from underlying biological heterogeneity.

To date, no comprehensive study has directly compared the response to NACT at the primary tumour site *versus* different metastatic regions. In our analysis, ovarian involvement was significantly lower in the NACT group, suggesting a more pronounced response in the primary tumour site. Although biological or vascular differences in the primary tumour region may contribute to this finding, further molecular and histopathological investigations are needed to clarify the underlying mechanisms.

In 2015, Böhm *et al*. introduced a chemotherapy response score (CRS) to evaluate treatment response in omental implants, demonstrating that higher CRS scores were associated with improved progression-free and overall survival. They also suggested that chemotherapy sensitivity may be more prognostically relevant than the extent of cytoreduction [17]. However, that study did not extensively evaluate response patterns across the primary tumour and all metastatic sites. In our study, while the primary tumour demonstrated a more favourable response to NACT, persistent tumour positivity in metastatic regions indicates that assessing pathological response in each site separately may have clinical relevance. Given the capacity of EOC to metastasize through multiple pathways, different genetic variants may emerge in distinct metastatic locations, potentially contributing to varied levels of chemotherapy resistance. Indeed, recent studies highlight the roles of BRCA1/2 mutations and homologous recombination deficiency (HRD) in shaping chemotherapy sensitivity and may help explain regional differences in treatment response [13]. Similarly, molecular investigations of the BRAF and MEK pathways offer additional insight into resistance mechanisms observed in certain metastatic areas [12].

Sokolenko *et al*. examined tumour tissue before and after NACT in BRCA1-mutated patients and reported that, in 11 of 17 cases, post-treatment residual tumour consisted predominantly of cells retaining BRCA function [18]. The authors suggested that this pattern reflects clonal selection of BRCA-proficient, chemotherapy-resistant cells rather than acquisition of new mutations [18]. This finding implies that continuing platinum-based therapy in tumours that have developed resistance may yield limited benefit. As cancer treatment is a dynamic process, adapting therapeutic strategies according to biological response may improve long-term outcomes.

While NACT in our study did not achieve complete response in all tumour regions, this should not be viewed solely as treatment failure. Instead, early identification of chemotherapy resistance may offer an opportunity to modify treatment regimens and guide the development of more effective personalized therapies.

CONCLUSIONS

Our study demonstrates that although neoadjuvant chemotherapy (NACT) leads to a marked reduction in overall tumour burden, its effect on metastatic sites appears limited. Given its retrospective design, small sample size, and the absence of long-term follow-up and survival data, these findings should be interpreted with caution. Furthermore, the lack of detailed histopathologic response scoring and molecular profiling restricts a more comprehensive evaluation of the biological response to NACT.
To better understand the clinical relevance of the differing response patterns observed in primary and metastatic tumour sites, prospective multicentre studies incorporating molecular biomarkers (including BRCA/HRD status and other genetic alterations) and standardized histopathologic response scoring are needed. Such studies may help identify mechanisms of chemotherapy resistance at an earlier stage and contribute to the development of personalized treatment strategies, facilitating timely integration of emerging targeted therapies.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions
H.H.U.: Conceptualization, data curation, writing – original draft. M.C.S.: Methodology, formal analysis, supervision, writing – review & editing. K.Y.: Investigation, validation, writing – review & editing.

Funding
None.

Study registration
N/A.

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

Ethical approval
This retrospective study was approved by the Institutional Review Board of Hacettepe University (Date: 16/05/2017, Approval No:GO 17/456-44). All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent
This study was based on retrospective analysis of anonymized patient data. Informed consent was waived by the Institutional Review Board.

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

REFERENCES

1. American Cancer Society. Key Statistics for Ovarian Cancer. Available at: https://www.cancer.org/cancer/ovarian-cancer/about/key-statistics.html. Accessed on December 20, 2021.
2. Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010;363(10):943-953. doi:10.1056/NEJMoa0908806.
3. Kehoe S, Hook J, Nankivell M, Jayson GC, Kaye S, Lopes T, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet. 2015;386(9990):249-257. doi:10.1016/S0140-6736(14)62223-6.
4. Melamed A, Hinchcliff EM, Clemmer JT, Bregar AJ, Uppal S, Bostock I, et al. Trends in the use of neoadjuvant chemotherapy for advanced ovarian cancer in the United States. Gynecol Oncol. 2016;143(2):236-240. doi:10.1016/j.ygyno.2016.09.002.
5. Knisely AT, St Clair CM, Hou JY, Khoury Collado F, Hershman DL, Wright JD, et al. Trends in primary treatment and median survival among women with advanced-stage epithelial ovarian cancer in the US from 2004 to 2016. JAMA Netw Open. 2020;3(9):e2017517. doi:10.1001/jamanetworkopen.2020.17517.

6. Sassen S, Schmalfeldt B, Avril N, Kuhn W, Busch R, Höfler H, et al. Histopathologic assessment of tumor regression after neoadjuvant chemotherapy in advanced-stage ovarian cancer. Hum Pathol. 2007;38(6):926-934. doi:10.1016/j.humpath.2006.12.008.
7. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: AGO-OVAR and GINECO. Cancer. 2009;115(6):1234-1244. doi:10.1002/cncr.24149.
8. Gorodnova TV, Kotiv KB, Ivantsov AO, Mikheyeva ON, Mikhailiuk GI, Lisyanskaya AS, et al. Efficacy of neoadjuvant therapy with cisplatin plus mitomycin C in BRCA1-mutated ovarian cancer. Int J Gynecol Cancer. 2018;28(8):1498-1506. doi:10.1097/IGC.0000000000001352.
9. Petrillo M, Zannoni GF, Tortorella L, Pedone Anchora L, Salutari V, Ercoli A, et al. Prognostic role and predictors of complete pathologic response to neoadjuvant chemotherapy in primary unresectable ovarian cancer. Am J Obstet Gynecol. 2014;211(6):632.e1-632.e8. doi:10.1016/j.ajog.2014.06.034.
10. Ferron JG, Uzan C, Rey A, Gouy S, Pautier P, Lhommé C, et al. Histological response is not a prognostic factor after neoadjuvant chemotherapy in advanced-stage ovarian cancer with no residual disease. Eur J Obstet Gynecol Reprod Biol. 2009;147(1):101-105. doi:10.1016/j.ejogrb.2009.07.016.
11. Miller K, Price JH, Dobbs SP, McClelland RH, Kennedy K, McCluggage WG. An immunohistochemical and morphological analysis of post-chemotherapy ovarian carcinoma. J Clin Pathol. 2008;61(5):652-657. doi:10.1136/jcp.2007.053793.
12. Perrone C, Angioli R, Luvero D, Giannini A, Di Donato V, Cuccu I, et al. Targeting BRAF pathway in low-grade serous ovarian cancer. J Gynecol Oncol. 2024;35(4):e104. doi:10.3802/jgo.2024.35.e104.
13. Tonti N, Golia D'Augè T, Cuccu I, De Angelis E, D'Oria O, Perniola G, et al. The role of tumor biomarkers in tailoring the approach to advanced ovarian cancer. Int J Mol Sci. 2024;25(20):11239. doi:10.3390/ijms252011239.
14. Hou JY, Kelly MG, Yu H, McAlpine JN, Azodi M, Rutherford TJ, et al. Neoadjuvant chemotherapy lessens surgical morbidity in advanced ovarian cancer and leads to improved survival in stage IV disease. Gynecol Oncol. 2007;105(1):211-217. doi:10.1016/j.ygyno.2006.11.025.
15. Kang S, Nam BH. Does neoadjuvant chemotherapy increase optimal cytoreduction rate in advanced ovarian cancer? Meta-analysis of 21 studies. Ann Surg Oncol. 2009;16(8):2315-2320. doi:10.1245/s10434-009-0558-6.
16. Morice P, Camatte S, El-Khoury C, Haddad B, Benifla JL, Castaigne D, et al. Results of interval debulking surgery compared with primary debulking surgery in advanced stage ovarian cancer. J Am Coll Surg. 2003;197(6):955-963. doi:10.1016/j.jamcollsurg.2003.06.004.
17. Böhm S, Faruqi A, Said I, Lockley M, Brockbank E, Jeyarajah A, et al. Chemotherapy Response Score: Development and Validation of a System to Quantify Histopathologic Response to Neoadjuvant Chemotherapy in Tubo-Ovarian High-Grade Serous Carcinoma. J Clin Oncol. 2015;33(22):2457-2463. doi:10.1200/JCO.2014.60.5212.
18. Sokolenko AP, Savonevich EL, Ivantsov AO, Raskin GA, Kuligina ES, Gorodnova TV, et al. Rapid selection of BRCA1-proficient tumor cells during neoadjuvant therapy for ovarian cancer in BRCA1 mutation carriers. Cancer Lett. 2017;397:127-132. doi:10.1016/j.canlet.2017.03.036.

Italian Journal of
Gynæcology & Obstetrics
September 2026 - Vol. 38 - N. 3 - Quarterly - ISSN 2385 – 0868

Mental health outcomes in infertility and fertility treatment: a systematic review of prevalence, correlates, and psychosocial interventions

Saima **Bilal** [1], Syed Muhammad Yousaf **Farooq** [1,2,*], Muhammad Farrukh **Asif** [1], Syed Amir **Gilani** [3], Muhammad **Moazzam** [1], Yasmeen **Niazi** [1]

[1] Office of Research, Innovation and Commercialization, Green International University, Lahore, Pakistan.
[2] Department of Radiography and Imaging Technology, Green International University, Lahore, Pakistan.
[3] Department of Medical Diagnostic Imaging, College of Health Sciences, University of Sharjah, United Arab Emirates.

ARTICLE INFO

History
Received: 02 October 2025
Received in revised form: 17 December 2025
Accepted: 22 January 2026
Available online: 10 September 2026

DOI: 10.36129/jog.2026.262

Key words
Infertility; mental health; depression; anxiety; fertility treatment.

***Corresponding author:** Syed Muhammad Yousaf **Farooq**, Dr., MPhil., Ph.D. Department of Radiography and Imaging Technology, Green International University, Bhobtian Avenue, 9 Km Raiwind Road (near Bhubtain Chowk), Lahore, 55150, Pakistan.
Email: Yousafgelani@gmail.com.
ORICD: 0000-0001-5768-224X.

ABSTRACT

Objective. Infertility and fertility treatments are associated with substantial mental health burdens, yet systematic evidence on prevalence, correlates, and interventions across global contexts remains fragmented. The objective is to systematically review mental health outcomes, including prevalence of depression, anxiety, stress, and quality of life impairments, alongside correlates and effects of psychosocial interventions in individuals undergoing infertility evaluation and fertility treatments.

Methods. Systematic extraction from 38 diverse studies (cross-sectional n = 17, prospective cohorts n = 6, RCTs n = 4, others), spanning low/middle-income (*e.g.*, Iran n = 6, India n = 3) and high-income countries, assessing standardized outcomes via DASS, FertiQoL, GHQ-28, MINI, and others in clinic-based samples (n = total > 30,000).

Results. Clinically significant depression (40-60%) and anxiety (40-75%) prevailed, with infertility-specific stress in 80-92%; women exceeded men (39% *vs* 15% MDD). Emotional/relational QoL domains scored lowest. Correlates included female gender, childlessness, low SES, stigma, and poor sleep (OR = 9-16). RCTs showed hope therapy reduced depression (AMD = -3.1, $p < 0.001$) and ACT improved FertiQoL (AMD = 14.8, $p < 0.001$). Pre-treatment depression lowered treatment initiation (OR = 0.55) and live birth odds (aOR = 0.83); emotional QoL predicted pregnancy (+2.4%/unit).

Conclusions. High mental health morbidity underscores need for routine screening and scalable interventions like ACT/hope therapy to enhance both psychological well-being and reproductive success, particularly in high-burden LMIC settings.

INTRODUCTION

Infertility is a major global public health concern with profound psychological and social consequences. Epidemiological estimates suggest that around 10-15% of reproductive-age couples worldwide experience infertility, with rates often higher in low- and middle-income countries

where infectious, environmental, and health-system factors compound reproductive risk [1, 2]. Beyond biomedical implications, infertility threatens core social roles related to parenthood, marriage, and family continuity, particularly in pronatalist cultures where childbearing is strongly linked to social status, marital stability, and economic security. A literature review synthesizes data from 32 low-bias studies involving 124,556 women, reporting a pooled prevalence of infertility at 46.25% (95%CI 37.73-54.77) and primary infertility at 51.5% (95%CI 32.74-70.26), though these figures reflect clinic-based samples rather than population-level lifetime rates [1]. The cited WHO foundation aligns with broader global assessments, such as lifetime prevalence near 17.5% (1 in 6 people), with comparable rates across income levels but elevated burdens in low-resource settings due to untreated STIs and poor care access [3].

Infertility and its treatment are closely associated with elevated rates of common mental disorders, especially depression, anxiety, and stress-related conditions. Clinic-based studies consistently report that approximately 40-60% of women undergoing infertility evaluation or assisted reproductive technologies (ART) meet criteria for clinically significant depressive or anxiety symptoms, substantially exceeding rates in the general population or fertile controls [4]. Infertility-specific stress, encompassing personal, marital, and social domains, is even more pervasive, affecting 80–90% of patients in several cohorts, with personal and marital distress typically exceeding social stress [5]. Men are also affected, though prevalence estimates are generally lower; in mixed-gender samples, major depressive disorder is observed in roughly 15-30% of male partners during treatment episodes [6].

Multiple, interacting mechanisms contribute to this heightened mental health burden. At the individual level, the chronic uncertainty of not conceiving, repeated treatment failures, and invasive procedures contribute to sustained emotional strain, fear, and hopelessness. Biological and iatrogenic factors such as hormonal stimulation, physical side effects of treatment, and sleep disruption may further exacerbate vulnerability to mood and anxiety disorders. Relationally, infertility can strain couple dynamics, diminishing partner support and increasing conflict over finances, sexual intimacy, and treatment decisions; in some settings, women report neglect, emotional abuse, or violence from partners and in-laws in the context of childlessness [7]. Socially, stigma, blame (often directed at women even when male factor infertility is present), and community scrutiny intensify shame and isolation, particularly in societies where motherhood is central to female identity and social value [8].

Socioeconomic and structural determinants play a critical role in shaping mental health outcomes in this population. Low income, unemployment, rural residence, and lower educational attainment are repeatedly associated with higher levels of depression, anxiety, and poorer quality of life among infertile individuals. In many countries, high out-of-pocket costs for fertility treatment create additional financial stress, with couples sometimes incurring substantial debt or sacrificing other basic needs to pursue ART [9]. Conversely, some studies indicate that higher education and better economic resources are not uniformly protective, as more educated women in resource-intense ART settings may experience heightened performance pressure, perfectionism, and awareness of prognostic uncertainty, which can drive anxiety. For instance, a study analysed 1,420 Spanish university students and found that academic perfectionism positively correlates with better grades but negatively affects well-being dimensions (*e.g.*, personal growth, life satisfaction), with women showing compromised well-being across all areas. In resource-intense, high-demand settings like medicine ($\beta = -0.461$ for degree demand mediating perfectionism-well-being link), perfectionism exacerbates mental health risks, including higher suicidal thoughts in women ($M = 29.99$ *vs* non-suicidal, $t = -7.66$, $p < 0.001$) [10].

Importantly, mental health is not only a consequence but may also influence treatment engagement and reproductive outcomes. Depressive symptoms have been associated with lower likelihood of initiating or continuing recommended fertility treatment, potentially due to reduced motivation, pessimistic expectations, or difficulties in navigating complex care pathways [11]. Pre-existing depression and anxiety, as well as the use of certain psychotropic medications, have been linked in some studies to modestly reduced odds of pregnancy and live birth and to higher miscarriage risk, although findings differ by drug class and clinical context [12]. At the same time, better emotional quality of life prior to embryo transfer and higher resilience appear to predict more favourable pregnancy outcomes, suggesting bidirectional relationships between psychological well-being and fertility treatment success.

In response to this substantial burden, a range of psychosocial interventions has been developed and evaluated for people with infertility. Group-based hope-oriented counselling, mindfulness-based cognitive approaches, and acceptance and commitment therapy have shown clinically meaningful reductions in depression and stress and improvements in fertility-related quality of life among women and couples undergoing or recovering from fertility treatment. However, despite high levels of distress, mental health service utilization remains low; only a minority of highly distressed patients report receiving information about, or engaging with, specialized psychological support in fertility settings. This gap underscores the need for integrated models of care that incorporate routine psychological assessment, early identification of high-risk individuals, and accessible, evidence-based psychosocial interventions alongside medical treatment for infertility.

MATERIALS AND METHODS

Study design and reporting standards

This study was designed as a systematic review of observational and interventional studies examining mental health outcomes among individuals and couples who experienced infertility and/or underwent fertility treatment. The review followed the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines and was conducted according to a protocol defined a priority [13, 14]. The protocol specified the review question, eligibility criteria, search strategy, methods for study selection, data extraction, risk of bias assessment, and data synthesis. **Figure 1** represents the PRISMA diagram for the selected studies.

Eligibility Criteria

Eligibility criteria were structured using the PICOS framework [15, 16]. The population included women, men, or couples with primary or secondary infertility, or those who underwent any fertility treatment, including medical management, ovulation induction, intrauterine insemination, IVF, or ICSI, as well as relevant comparison groups such as fertile controls or general population samples where available. The exposures and interventions of interest encompassed Infertility or fertility treatment as exposures in observational studies and psychosocial or psychological interventions (*e.g.* cognitivebehavioural therapy, mindfulnessbased interventions, acceptance and commitment therapy, hopeoriented or group counselling, infertilityfocused psychoeducation) in interventional studies.

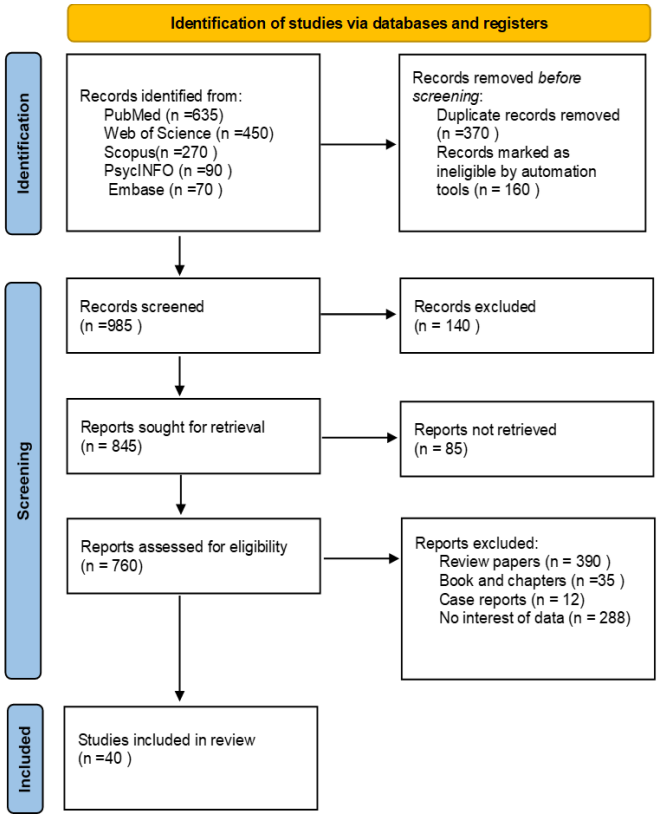

Figure 1. *PRISMA diagram for selection of inclusion studies (n = 40).*

Information sources and search strategy

A comprehensive search strategy was implemented across major electronic databases, including PubMed, Google Scholar, Web of Science, Scopus, and Cochrane, from database inception from 2015 to 2025. The search used a combination of controlled vocabulary (*e.g.* MeSH, Emtree) and freetext terms related to infertility and mental health.

Core concepts included "infertility", "subfertility", "assisted reproductive technology", "IVF", and "IUI", combined with terms such as "mental health", "depression", "anxiety", "stress", "psychiatric", "common mental disorders", "distress", "quality of life", "FertiQoL", and "psychological intervention" using Boolean operators ("AND" / "OR") as appropriate. Search strategies were tailored to each database's indexing system and were refined iteratively. Reference lists of all included articles and relevant systematic reviews were handsearched to identify additional studies. Where applicable, grey literature sources (*e.g.* trial registries)

were also explored, and all search dates and strategies were documented in detail.

Study selection

The study selection process was conducted in two stages by two independent reviewers to reduce selection bias. First, titles and abstracts retrieved from the searches were screened against the predefined eligibility criteria to identify potentially relevant records. Second, fulltext articles of all potentially eligible studies were obtained and assessed independently by the same reviewers for final inclusion. Reasons for exclusion at the fulltext stage (*e.g.* ineligible population, design, or outcomes) were systematically recorded. The overall selection process was summarized in a PRISMA flow diagram, showing the number of records identified, screened, excluded, and included.

Data extraction and management

Data extraction was carried out independently by two reviewers using a standardized, piloted data extraction form. Extracted variables included study identifiers (authors, year, country), study design, setting, sample size, sampling method, participant characteristics (*e.g.* age, sex, type and duration of infertility, treatment type, socioeconomic indicators), details of comparison groups where relevant, mental health and qualityoflife instruments.

Quality assessment

Methodological quality of the included studies was evaluated independently by two reviewers. The Joanna Briggs Institute (JBI) Critical Appraisal Checklist examine the quality assessment [16]. Representativeness, sampling methods, measurement validity, response rates, and data analysis were used in evaluating the studies. The studies were classified into these three levels of risk: low, moderate and high bias using these criteria. A score was assigned on the low risk of bias, moderate risk of bias, and high risk of bias and the papers were scored and categorised into these levels: low risk of bias when the score was 7 or higher, moderate risk of bias when the score was 4 to 6, and high risk of bias when the score was lower than 4. Some studies when they pointed out to the existence of bias, the meta-analysis did not incorporate them.

Data synthesis

Given the anticipated heterogeneity in study design, populations, and measurement instruments, a narrative synthesis approach was applied. Findings were organized according to mental health outcomes (*e.g.*, depression, anxiety, stress, quality of life). Correlates were synthesized across studies to highlight consistent associations and gaps. Where available, effect sizes, prevalence estimates, and mean scores were summarized. Subgroup analyses (*e.g.*, fertility treatment type, cultural context, sociodemographic factors) were highlighted to provide contextual interpretation.

RESULTS

Study characteristics

Studies spanned diverse global regions, with heavy representation from low- and middle-income countries including Pakistan (n = 3), India (n = 3), Iran (n = 6), Bangladesh (n = 2), and Ethiopia (n = 2), alongside higher-income settings in Canada (n = 2), USA (n=4), Sweden (n = 2), and others. Most employed cross-sectional designs (n = 17), capturing point-in-time mental health snapshots in infertility clinics, while prospective cohorts (n = 6) tracked changes over treatment periods up to 18 months, and register-based cohorts (n = 2) leveraged national data for long-term outcomes spanning 10 years. Randomized controlled trials (n = 4) evaluated interventions like hope therapy and mindfulness-based cognitive therapy, with sample sizes ranging from 54 to 60 participants. **Table 1** shows the characteristics of populations included in this study.

Population demographics

Participants were predominantly women (85-95% in most studies), with mean ages typically 29-35 years across clinic samples; older cohorts (mean 35-41 years) appeared in IVF-specific studies. Infertility durations averaged 4-7 years, with primary infertility more common (60-80%); many were nulliparous or childless (50-78%), married (85-95%), and from urban settings, though rural participants featured prominently in South Asian and African studies. Socioeconomic profiles varied: high unemployment among women (55-96%), low household incomes (< $5,000/year equivalents), and lower education (high school or less in 40-70%), particularly in LMIC contexts: higher-income, college-educated samples prevailed in US/European studies. **Table 1** provided the detailed of these populations.

Table 1. *Basic characteristics of included studies (n = 40).*

Reference	Author(s)/Year	Country	Study Design	Sample Size	Population Characteristics	Aims/Objectives
[17]	Raguz *et al.*, 2014	Canada	Prospective cohort	1296	Mothers postpartum, primiparous and multiparous, diverse backgrounds	To assess mental health outcomes of mothers who conceived using fertility treatment
[18]	Saleem S *et al.*/2019	Pakistan	Cross-Sectional	169	Women with primary infertility, aged 19-45, married ≥1 year	To examine attachment styles, social support, and mental health in infertile women
[19]	Prasad *et al.* (2017)	India	Cross-sectional	186	Infertile women undergoing first IVF cycle; Mean age: 31.35 yrs; Mean infertility duration: 7.38 yrs; Majority had family income <Rs. 500,000/year.	To assess psychological distress, quality of life, and mental health in women undergoing ART.
[20]	Yusuf L. (2016)	Pakistan	Case-Control Study	200	Females with female-factor infertility (cases) vs fertile females accompanying patients (controls). Mean age ~20-30 years. Excluded those with pre-existing mental health issues and male-factor infertility.	To find the prevalence of depression, anxiety, and stress among females suffering from infertility.
[21]	Rahimi *et al.* (2021)	Iran	Randomized Controlled Trial	60	Women with failed IVF cycles, minimum education of junior high school, living in Tabriz. Excluded those with psychiatric problems, chronic physical diseases, or recent severe psychological crises.	To determine the effects of hope-oriented group counseling on mental health (primary) and quality of life (secondary) in infertile women with failed IVF cycles.
[22]	Holley *et al.* (2015)	United States	Prospective cohort study	174	Heterosexual couples; Mean age W=36.4, M=37.8; 70% White; 67% college graduates; Mean infertility=2.4 years	Examine prevalence and predictors of MDD during fertility treatment
[23]	Cesta *et al.* (2016)	Sweden	Nationwide register-based cohort study	23,557	Nulliparous women undergoing first fresh IVF cycle; mean age ~33; Swedish national sample	Investigate associations between depression, anxiety, antidepressants before IVF and cycle outcomes (pregnancy, live birth, miscarriage)
[24]	Patel A. *et al.* (2016)	India	Cross-sectional Study	300	Women diagnosed with primary infertility. Age range 20-49 yrs (median 29). 62% rural, 55% joint families, 64% unemployed. Excluded secondary infertility.	To estimate the prevalence of infertility-specific stress and identify its predictors in women with primary infertility.
[25]	Bakhtiyar K. *et al.* (2019)	Iran	Matched Case-Control Study	720	Infertile women and fertile controls matched for age, education, and duration of marriage. Excluded those with psychological problems, recent stressful events, or substance use.	To investigate the impact of infertility on women's quality of life.
[26]	Pasch *et al.* (2016)	USA	Prospective longitudinal cohort study	352	Heterosexual couples; first fertility clinic visit; no previous IVF; average age mid-30s; predominantly white, highly educated, high income.	To Determine extent of clinical distress. 2. Mental health service (MHS) use and clinic information provision. 3. Assess if MHS was targeted to the most distressed.
[27]	Wu *et al.* (2020)	Taiwan	Prospective longitudinal cohort study	686	Infertile women undergoing IVF; mean age 35.7; excluded those with mental disorders or recent major trauma.	To investigate the association between QoL (measured before embryo transfer) and IVF pregnancy outcomes.
[28]	Alam *et al.* (2018)	Bangladesh	Cross-sectional study	112 married infertile women	Women attending infertility outpatient clinic; mean age 28.5 years; mean infertility duration 4.46 years.	To investigate the psychological impacts (depression, anxiety) of infertility among married women.
[29]	Alosaimi *et al.* (2015)	Saudi Arabia	Cross-sectional observational study	406	Infertile men and women attending clinics; mean age women 31.5, men 35.4; high unemployment in women (68%).	To measure the rate of psychiatric disorders in infertile men and women seeking treatment.
[30]	Crawford *et al.* (2017)	USA	Prospective observational study	416	New female infertility patients; mean age 35.1; predominantly Caucasian (80%), highly educated (86% college degree+).	To determine if screening positive for depression is correlated with pursuing infertility treatment.

→

Reference	Author(s)/Year	Country	Study Design	Sample Size	Population Characteristics	Aims/Objectives
[31]	Pedro *et al.* (2019)	Denmark	10-year longitudinal register-based cohort study	1009 women	Women initiating ART treatment; mean age 31.8; mean infertility duration 3.45 years.	To explore if infertility-related stress predicts a first redeemed prescription of antidepressants after ART.
[32]	Gordon & Balsom (2020)	Canada & USA	Cross-sectional online survey	92	Women (20-45 yrs) whose fertility treatments were suspended due to COVID-19; mean age 34.2; mean TTC 36 months	To examine the psychological impact of treatment suspensions and identify psychosocial predictors
[33]	Patel *et al.* (2018)	India	Cross-sectional dyadic study	81	Distressed infertile couples undergoing IUI; mean infertility duration 4 years	To compare illness cognitions (helplessness, acceptance, benefits), anxiety, and depression between men and women in infertile couples
[34]	Khan *et al.* (2019)	Pakistan	Case-control study	60	Married women (20-40 yrs); infertile group from hospital gynae departments, fertile group from community	To compare levels of depression, anxiety, and stress between infertile and fertile women
[35]	Catalao *et al.* (2020)	Ethiopia	Population-based cohort study	1026	Rural women in 3rd trimester; followed for 6.5 years; high fertility, low contraceptive use setting	To examine impact of poor mental health on unmet need for contraception and fertility rate
[36]	Shargh *et al.* (2016)	Iran	Randomized controlled trial	60 women (30 intervention, 30 control)	Infertile women (20-45 yrs); mean infertility duration 4-7 years; low education level (53.33% elementary)	To determine effectiveness of Mindfulness-Based Cognitive Therapy (MBCT) on marital satisfaction and general health
[37]	Jiang & Yang (2022)	China	Cross-sectional survey (CLDS 2018)	4,245	Women of childbearing age (15-49 yrs, mean 41.1); 94.4% married; 79.3% rural Hukou; mean births: 1.79	To examine the impact of fertility (number of births) on the physical and mental health of Chinese women of childbearing age and confirm the "motherhood health penalty".
[38]	Keenan & Grundy (2019)	10 European Countries (e.g., Sweden, France, Italy)	Longitudinal (SHARE waves 1-2)	19,928	Adults aged 50-79 years; 11% childless; 11% men & 15% women had early first birth (<23/<20 yrs)	To investigate associations between fertility history (timing, parity) and changes in a range of physical and mental health indicators in older adults.
[39]	Namdar *et al.* (2017)	Iran	Cross-sectional	146	Mean age: 29.4 ± 5.2 yrs; Mean marriage duration: 6.6 ± 0.5 yrs; 39.7% with academic education; 15.8% from rural areas	To determine the general health and QOL of infertile women and identify affecting socio-demographic conditions.
[40]	Sezgin *et al.* (2016)	Turkey	Cross-sectional	100	Urban; Mean age ~30 yrs; 74% employed; Mean marriage duration infertile: 9.3 yrs, fertile: 6.4 yrs	To compare psychiatric symptoms, disability, and QOL between infertile and fertile urban women in Turkey.
[41]	Zivaridelavar *et al.* (2016)	Iran	Prospective Cohort	63	Fertile women undergoing ART due to male factor infertility; Mean age: 29.17 yrs; Mean infertility duration: 5.84 yrs	To evaluate the effect of the ART process on the mental health of fertile women (with male factor infertility) before and after ovarian stimulation/oocyte retrieval.
[42]	Hosseinpanahi *et al.* (2020)	Iran	Randomized Controlled Trial	54	Infertile couples; Mean age (women): 30.9 yrs; Mean infertility duration: 2.7 yrs	To determine the effect of ACT-based counseling on mental health and quality of life in infertile couples.
[43]	Roberts *et al.* (2020)	India	Mixed-Method Cross-Sectional	74	Low-income women from Mumbai slums with infertility; Mean age: 26.7 yrs; Mean marriage duration: 7.7 yrs	To assess mental health and stigma among low-income women with infertility in a pronatalist culture.
[44]	Vikström *et al.* (2015)	Sweden	Cross-Sectional	470	Women 20–23 years post-IVF treatment; Mean age at follow-up: >45 yrs for majority	To assess long-term mental health in women post-IVF and compare outcomes based on parenthood status.
[45]	Hasan *et al.* (2023)	Bangladesh	Cross-Sectional	300	Infertile women receiving treatment in Dhaka; Mean age: >30 yrs for majority; 69.3% primary infertility	To assess mental health and quality of life among infertile women in Bangladesh and identify influencing factors.

Reference	Author(s)/Year	Country	Study Design	Sample Size	Population Characteristics	Aims/Objectives
[46]	Sohbati *et al.* (2021)	Iran	Cross-sectional	300	Infertile women (female factor); Mean age: 29.16 ± 5.81 yrs; Majority had high school education (52%); 65% had relatively favorable economic status	To determine psychological well-being (PWB) and its relationship with demographic factors and fertility history in infertile women.
[47]	Teklemicheal *et al.* (2022)	Ethiopia	Cross-sectional	96	Infertile women (non-IVF treatment); Mean age: 31.5 ± 5.9 yrs; 78.1% childless; 68.8% housewives; 53.1% secondary infertility	To determine the prevalence of infertility-related psychological stress and its demographic-clinical correlates in Ethiopian women.
[48]	Wang *et al.* (2023)	China	Cross-sectional	1712	Infertile women undergoing ART; Mean age: 32.1 ± 4.59 yrs; 65.3% with junior college degree or above; 48.8% aged 30–35 yrs	To investigate the incidence and risk factors of anxiety and depression in infertile women undergoing fertility treatment.
[49]	Li *et al.* (2019)	China	Cross-sectional	498	Infertile women undergoing IVF-ET; Mean age: 32.19 yrs; All from Northeast China	To evaluate fertility quality of life (QoL) and examine whether resilience moderates the relationship between infertility-related stress and fertility QoL.
[50]	Setswe & Roomaney (2025)	South Africa	Cross-sectional	210	Patients seeking fertility treatment in Cape Town; Predominantly female (79.5%), married/cohabiting (96.2%), higher-income, well-educated; Mean age not reported.	To investigate the predictors (demographic, clinical, psychosocial) of psychosocial well-being among fertility patients.
[51]	Moutzouroulia *et al.* (2025)	Greece	Cross-sectional	128	Women undergoing first IVF/ICSI/IUI treatment; Mean age: 41.5 yrs; Majority married (88.3%), employed (81.3%), university-educated (53.9%).	To explore the impact of infertility and IVF on women's mental health and quality of life.
[52]	Kamışlı *et al.* (2021)	Turkey	Cross-sectional	70	Women diagnosed with infertility applying for IVF; Mean age: ~31-33 yrs; Mean infertility duration: 6.1 yrs; 60% unemployed; 41.4% high school graduates	To determine the levels of hopelessness, anxiety, and depression and their relationship with socio-demographic characteristics in women applying for infertility treatment.
[53]	Evans-Hoeker *et al.* (2018)	USA	Prospective Cohort (Secondary Analysis of RCTs)	1,65	Infertile couples (female partners with PCOS or unexplained infertility); Mean female age: ~30.7 yrs; Mean male age: ~33.0 yrs; 5.96% of women and 2.28% of men had active major depression (MD); 5.72% of women used antidepressants.	To determine if maternal major depression (MD), antidepressant use, or paternal MD are associated with pregnancy outcomes after non-IVF fertility treatments.
[54]	Huang *et al.* (2019)	Taiwan	Cross-sectional	97 women	Women with primary infertility undergoing IVF; Mean age: 35.7 yrs; Mean infertility duration: 51.5 mos; 63.5% had received repeated IVF treatment.	To investigate the status of emotional distress (anxiety, depression) and sleep quality, and examine factors predicting sleep disturbances in women during the hormonal stimulation phase of IVF.
[55]	Haham *et al.* (2021)	Canada	Cross-sectional	181	Women whose fertility treatments (IVF, FET, IUI, ovulation induction) were suspended due to COVID-19; Mean age: 37.7 yrs; 70% had no children; 93% had a partner; 61% reported above-average income.	To investigate patients' views and emotional reactions to the suspension of fertility treatments during the COVID-19 pandemic and identify factors affecting psychological distress.
[56]	Yokota *et al.* (2022)	Japan	Cross-sectional	254	Japanese women undergoing infertility treatment; mean age 35.9 yrs; married; no children; primary infertility only	To examine the association between infertility stigma and anxiety, depression, and psychological distress using a validated scale.

Fertility treatment types

Treatments encompassed a spectrum from non-IVF options like ovulation induction (OI), timed intercourse, and intrauterine insemination (IUI) to advanced ART including IVF, ICSI, and frozen embryo transfer (FET). IVF/ICSI dominated ART-focused studies (n = 12), often first-cycle or with prior failures; non-IVF treatments appeared in ovulation drug/surgery cohorts and general clinic attendees. Some studies compared infertile groups to fertile controls without specifying treatments, while others examined pre-ART histories or post-treatment follow-up (*e.g.*, 20-23 years post-IVF).

Mental health outcomes assessed

Core outcomes included depression (n = 29 studies), anxiety (n = 26), and stress (general, n = 14; infertility-specific, n = 8), with prevalence rates often 40-60% for depression/anxiety and 70-90% for stress. Quality of life measures (n = 15) targeted fertility-specific (FertiQoL), general (SF-12/36, WHOQOL-BREF), or multidimensional domains (emotional, relational, physical); broader psychiatric screening (n = 5) covered 18+ disorders via MINI or SCL-90. Less common variables were parenting morale, hopelessness, suicidality, sleep quality, resilience, stigma, coping styles, marital satisfaction, and antidepressant prescriptions as proxies for incident mental health needs. **Table 2** represents the main finding of studies included in this work.

Measurement Instruments

Validated scales dominated: Depression via EPDS, CES-D, PHQ-9, BDI, HAM-D; anxiety via STAI, HAM-A, BAI, GAD-7; stress via DASS-21/42, PSS, COMPI-FPSS. QoL used FertiQoL (core/treatment subscales), SF-12/36 (MCS/PCS), WHOQOL-BREF; general health via GHQ-28 (somatic, anxiety/depression subscales), MINI, SRQ-20. Fertility-specific tools included FPI (stress), Fertility-QoL, ICQ (illness cognitions); others like Ryff PWB, PHQ-15 (somatic), PSQI (sleep), and study-specific stigma/support measures supplemented core assessments.

Key findings on prevalence and patterns

High prevalence characterized findings: 30-60% met psychiatric disorder criteria; infertility-specific stress affected 80-92%, with personal > marital/social domains; QoL lowest in emotional/relational areas. Infertile groups showed 2-5x higher mean depression/anxiety/stress scores *vs* controls; women > men in distress; childless/unsuccessful outcomes linked to persistent elevations even decades post-treatment. Paradoxes emerged: some fertile comparisons showed higher social QoL; high parity/childbirth in non-infertile cohorts worsened later-life mental health.

Correlates and predictors

Demographic: Female gender, older age (>35), childlessness, primary infertility, longer infertility/marriage duration (4-7+ years), low SES (income, education, rural), unemployment/homemaking. Clinical: Female/mixed infertility factors, prior failures/abortions, somatic symptoms, poor sleep, non-SSRI antidepressants, PCOS/unexplained diagnoses. Psychosocial: Insecure attachment, low support/stigma/violence, maladaptive coping (avoidance, wishful thinking), high personal/marital stress, low resilience/acceptance, hopelessness. Protective: Higher education/income (mixed), employment (contextual), secure attachment, partner support, interventions.

Intervention effects

RCTs (n = 4) reported significant post-intervention reductions: hope therapy lowered depression (AMD = -3.1, $p < 0.001$), stress (-1.7, $p = 0.018$); MBCT improved GHQ mental health ($p = 0.002$), marital satisfaction ($p = 0.043$); ACT counselling boosted FertiQoL (AMD = 14.8, $p < 0.001$), GHQ (-8.4, $p < 0.001$). Effects held for couples, with baseline distress predicting greater gains; anxiety changes were smaller/non-significant in some trials. Service utilization remained low (11-21%), with untargeted info provision despite 40-75% clinical distress rates.

Reproductive outcome links

Pre-treatment depression/anxiety slightly reduced pregnancy/live birth odds (AOR = 0.83-0.86); non-SSRI use raised miscarriage risk (RR = 1.87). Higher emotional QoL pre-transfer boosted ongoing pregnancy/live birth probabilities (2.4-2.6% per unit); depression screens halved treatment initiation odds (OR = 0.55). Male partner depression lowered conception (RR = 0.44); infertility stress predicted later antidepressants (OR = 1.80-2.85).

Risk of bias

The risk of bias across the included studies was generally low to moderate, with several studies employing validated assessment tools and standardized protocols enhancing internal validity. Howe-

Table 2. *Main findings of included studies (n = 40).*

Reference	Author(s)/ Year	Fertility Treatment Type	Mental Health Outcomes Assessed	Measurement Instruments	Main Findings / Results	Correlates / Predictors
[17]	Raguz *et al.*, 2014	Assisted reproductive techniques (ART), general fertility treatment	Postpartum depression, anxiety, perceived stress, parenting morale	Edinburgh Postnatal Depression Scale, Spielberger State Anxiety Inventory, Perceived Stress Scale, Parenting Morale Index	No significant difference in depression, anxiety, or stress; lower parenting morale in spontaneous conception group; fertility treatment group had higher parenting morale	Age, parity, mental health history, mode of conception, postpartum mental health, parenting morale
[18]	Saleem S *et al.*/2019	Medical treatment for primary infertility	Depression, Anxiety, Stress (DASS)	Adult Attachment Questionnaire, MSPSS, DASS	Women with secure attachment perceive more social support and have fewer mental health problems. Insecure attachment correlates with higher stress and depression. Education and social support are strong predictors.	Attachment style, social support, education, age, duration of marriage
[19]	Prasad *et al.* (2017)	IVF/ICSI	Depression, Anxiety, General Life Stress, Quality of Life (QoL)	HAM-D, ADI, HAM-A, SCAT, PSLES, FertiQoL, CMI	Depression: 60.11–64.86% had clinically significant depression. Anxiety: 27–37% had moderate to severe anxiety. Stress: 80% reported high general life stress. QoL: Lowest scores in relational (mean=46.4) and emotional (mean=49.07) domains. Core FertiQoL scores were significantly lower than treatment scores.	Education: Positively correlated with better QoL and treatment tolerability. Age: Negatively correlated with treatment tolerability. Key Stressors: Marital conflict, in-law conflicts, financial problems, sexual problems.
[20]	Yusuf L. (2016)	Not specified (patients attending an infertility clinic)	Depression, Anxiety, Stress	Validated Urdu version of the 42-item Depression, Anxiety, Stress Scale (DASS)	Significantly higher mean scores for depression (16.14 vs 3.90), anxiety (14.63 vs 3.69), and stress (19.72 vs 5.87) in the infertile group compared to controls (p=0.00). 79% of infertile women had some depression, 70% had anxiety, and 69% had stress.	Infertility status was a major predictor of poor mental health outcomes. Level of education and occupation did not significantly affect the scores (i.e., they were not found to be protective factors in this population).
[21]	Rahimi *et al.* (2021)	Hope-Oriented Group Counseling (six 45-60 min weekly sessions) vs routine care	Depression, Anxiety, Stress, Quality of Life	Depression Anxiety Stress Scale-21 (DASS-21), SF-12 Quality of Life Scale	Hope-oriented counseling significantly reduced stress (AMD=-1.7, p=0.018) and depression (AMD=-3.1, p<0.001) scores, and improved QoL (AMD=6.9, p<0.001) compared to the control group one-month post-intervention. The reduction in anxiety was not statistically significant (AMD=-1.1, p=0.153).	The intervention (hope therapy) was the primary predictor of improved outcomes. Higher baseline scores likely predicted greater improvement. Other potential predictors (e.g., duration of infertility) were not reported as significant moderators in this analysis.
[22]	Holley *et al.* (2015)	IVF, IUI, medication (unsuccessful outcomes only)	MDD, depressive symptoms, anxiety symptoms	CIDI (diagnosis), CES-D (symptoms), STAI (anxiety)	39.1% of women and 15.3% of men met MDD criteria during 18-month treatment period	Past MDD history (strongest predictor), baseline depression, baseline anxiety, low partner support (women only)
[23]	Cesta *et al.* (2016)	IVF (first fresh cycle with embryo transfer)	Depression/ Anxiety diagnoses, Antidepressant use	National Patient Register (diagnoses), Prescribed Drug Register (medications)	4.4% had depression/anxiety/antidepressant use. Associated with slightly decreased odds of pregnancy (AOR=0.86) and live birth (AOR=0.83). No significant association for SSRIs alone. Non-SSRI antidepressants and diagnosis-only showed reduced odds.	Diagnosis of depression/anxiety (without antidepressants), use of non-SSRI antidepressants. SSRIs alone were not a significant predictor of negative outcomes.

Reference	Author(s)/ Year	Fertility Treatment Type	Mental Health Outcomes Assessed	Measurement Instruments	Main Findings / Results	Correlates / Predictors
[24]	Patel A. *et al.* (2016)	Various (OI with timed intercourse, IUI, IVF; 97% were advised but had not taken IVF due to financial constraints)	Infertility-specific stress, Psychiatric morbidity	Semi-structured questionnaire, ICD-10 Clinical Descriptions and Diagnostic Guidelines, Psychological Evaluation Test for Infertility (clinician-rated)	The prevalence of infertility-specific stress was 80%.	Predictors from Multivariate Analysis: Female factor infertility (vs male factor), Significant coping difficulties. Other associated factors from Univariate Analysis: >5 years marital life, >5 years infertility duration, history of gynecological surgery, cycles of OI/IUI, present/past psychiatric morbidity, gynecological diagnosis (uterine/ovarian factors), premenstrual dysphoria.
[25]	Bakhtiyar K. *et al.* (2019)	N/A (Comparison of infertile vs fertile women, not an intervention)	Quality of Life (Physical, Mental, Social, Environmental Health)	WHOQOL-BREF questionnaire	Infertile women had significantly lower scores in physical health (AMD=-3.6, p<0.001) and mental health (AMD=-16.0, p<0.001) dimensions. They had a significantly higher score in social health (AMD=+20.0, p<0.001). The total QoL score was higher in infertile women (AMD=+21.6, p<0.001), driven by the large increase in the social domain.	Main Predictor/Correlate: Infertility status. Other Correlates: Lower physical/mental QoL was associated with lower education, unemployment, not owning a home, and having underlying diseases. Higher social QoL was associated with longer marriage duration, lower education, being a housewife, and undergoing costly treatments like IVF.
[26]	Pasch *et al.* (2016)	Any fertility treatment (58% female factor, 7% male, 31% mixed)	Depression, Anxiety, MHS information provision and use	CES-D (depression), STAI-State (anxiety), Study-specific questions on MHS	1. 56.5% of women and 32.1% of men had clinical depression at ≥1 point; 16.5% of women and 5.8% of men had prolonged depression. 2. 75.9% of women and 60.6% of men had clinical anxiety at ≥1 point. 3. 21% of women and 11.3% of men used MHS. 4. 26.7% of women and 24.1% of men received MHS information from their clinic. 5. MHS use was higher in distressed patients, but information provision was not targeted to them.	Predictors of Higher Distress: Unsuccessful treatment outcome (remaining childless). Predictors of MHS Use: Being in the "at-risk" or "high-risk" distress group. Not a Predictor of MHS Info: Distress level did not predict receiving information from the clinic.
[27]	Wu *et al.* (2020)	IVF	Quality of Life (QoL) specific to infertility	FertiQoL (Taiwanese version)	1. Lowest QoL scores were in the emotional (62.0) and treatment tolerability (59.4) domains. 2. A one-unit increase in the emotional QoL score significantly increased the probabilities of ongoing pregnancy by 2.4% and live birth by 2.6% (p<0.05). 3. Other QoL domains were not significantly associated with outcomes.	Predictors of Positive Pregnancy Outcome: Higher emotional QoL score before transfer. Other Predictors (from univariate analysis): Younger maternal age, higher AMH, shorter infertility duration, higher number of oocytes retrieved, higher number of embryos transferred, blastocyst-stage (Day 4-5) transfer, use of frozen-thawed embryos.
[28]	Alam *et al.* (2018)	Not specified (patients seeking treatment)	Depression, Anxiety	Goldberg Depression Questionnaire (GDQ), Beck Anxiety Inventory (BAI)	1. 62.5% of women showed depression (10.7% minor-moderate, 32.1% moderate-severe). 2. 37.5% had anxiety disorders (12.5% moderate, 25% potentially concerning levels). 3. Prevalence of disorders increased with age and duration of infertility.	Predictors of Depression: Older age, not having a living child, negligence by husband. Predictors of Anxiety: Lower monthly income, negligence by husband, violence by in-laws. Not Predictors: Type of family, education level, employment status.
[29]	Alosaimi *et al.* (2015)	Not specified (patients at infertility clinics)	18 common psychiatric illnesses (e.g., depression, anxiety, bipolar, substance-related)	Mini International Neuropsychiatric Interview (MINI) - Arabic version	1. Self-reported psychiatric disorders were low (4.5% men, 10.2% women), but MINI identified 30% of men and 36.9% of women had a disorder. 2. Most common disorders were depression (21.7%) and anxiety (21.2%). 3. Women had significantly higher rates of suicidality and depression. Men had higher rates of bipolar and substance-related disorders.	Predictors of Psychiatric Disorders: Lower monthly income (for both genders), polygamy (for women). Gender Differences: Female gender predicted higher depression/suicidality; male gender predicted bipolar/substance disorders.

Reference	Author(s)/ Year	Fertility Treatment Type	Mental Health Outcomes Assessed	Measurement Instruments	Main Findings / Results	Correlates / Predictors
[30]	Crawford *et al.* (2017)	Any recommended treatment (oral meds, IUI, IVF, surgery)	Depression	NIH PROMIS Depression 4-item short form	1. 41% of women screened positive for depression. 2. Women with a positive screen had 0.55 times the odds of initiating any treatment (95% CI: 0.31–0.95) and were less likely to pursue oral medications or IVF. 3. Only 62% of all women initiated recommended treatment.	Predictors of Not Initiating Treatment: Positive depression screen, older age, non-Caucasian race, unmarried, higher BMI, nulliparity, diagnosis of DOR. Not Associated: Income (though education was used as a proxy).
[31]	Pedro *et al.* (2019)	ART (IVF, ICSI)	First-time redeemed prescription of antidepressants	COMPI Fertility Problem Stress Scales (COMPI-FPSS), Stress Profile Questionnaire	1. 13.7% of women redeemed a first-time antidepressant prescription during the 10-year follow-up. 2. High personal stress (adj OR=2.14) and high marital stress (adj OR=1.80) significantly predicted antidepressant prescription. 3. High general physical stress was the strongest predictor (adj OR=2.85). Social stress was not a significant predictor.	Predictors of Antidepressant Use: High personal infertility-related stress, high marital infertility-related stress, high general physical stress. Stratified by Outcome: The risk was significantly higher for women who did not achieve childbirth during follow-up.
[32]	Gordon & Balsom (2020)	IVF (54%), IUI (35%), FET (5%), Other (6%)	Depressive symptoms, perceived mental health impact, change in quality of life	PHQ-9, study-specific QoL and mental health impact measures, IUS-12, LOT-R, DPQ-R, ICQ, Infertility Coping Questionnaire	1. 52% had clinical depressive symptoms (PHQ-9 ≥10). 2. Significant decline in QoL (M=-1.3/7, p<.0001) and mental health (M=-2.1/±5, p<.001). 3. 86% reported negative mental health impact from suspensions.	Lower defensive pessimism, greater infertility acceptance, better quality social support, more social support seeking, less avoidance. Longer time TTC predicted worse outcomes.
[33]	Patel *et al.* (2018)	IUI	Infertility-specific stress, anxiety, depression, helplessness, acceptance, perceived benefits	FPI, MINI, HAM-A, HAM-D, Illness Cognition Questionnaire (ICQ)	Women reported significantly higher infertility-specific stress (p=0.002), anxiety (p<0.001), depression (p<0.001), and helplessness (p=0.01) than men. Women had lower acceptance (p=0.01). No gender difference in perceived benefits; neither partner found infertility beneficial.	Higher distress in women, higher helplessness and lower acceptance in women, no perceived benefits from infertility for either gender.
[34]	Khan *et al.* (2019)	Not specified (comparison based on fertility status)	Depression, Anxiety, Stress	Depression Anxiety and Stress Scale (DASS)	Infertile women had significantly higher depression (10.83 vs 4.17, p=0.000), anxiety (11.60 vs 5.50, p=0.001), and stress (19.67 vs 12.10, p=0.000) scores than fertile women.	Infertility status (primary correlate). Majority of infertile women were housewives (96.7%) and had low income (46.7%).
[35]	Catalao *et al.* (2020)	Not a treatment study; observational of family planning behaviors	Common Mental Disorders (CMD: depression, anxiety)	Self-Reporting Questionnaire-20 (SRQ-20)	Higher CMD symptoms at 1 year postnatal were associated with unmet need for contraception at 2.5 years (aOR 1.06; 95% CI 1.01–1.12). No association found between CMD and number of pregnancies. Unmet need was high (50.4%-64.0%).	Lower socioeconomic status (SES) was also a significant predictor of unmet need (aOR 1.79). CMD symptoms were higher at 1 year postnatal.
[36]	Shargh *et al.* (2016)	Not specified (psychological intervention study)	Marital satisfaction, General mental health (somatic, anxiety, depression, social function)	Enrich Marital Satisfaction Questionnaire, General Health Questionnaire (GHQ-28)	MBCT group showed significant improvement in marital satisfaction (Mean=115.4 vs 107.0, p=0.043) and general mental health (Mean=55.09 vs 45.31, p=0.002) compared to control group post-intervention.	MBCT intervention was the primary factor. Majority had low education and long infertility duration (70% for 4-7 years).

Reference	Author(s)/ Year	Fertility Treatment Type	Mental Health Outcomes Assessed	Measurement Instruments	Main Findings / Results	Correlates / Predictors
[37]	Jiang & Yang (2022)	N/A (Observational study of fertility history)	Self-rated physical health, Depression (Mental health)	Self-rated health (5-point Likert), Center for Epidemiological Studies Depression (CES-D) Scale	A higher number of births had significant adverse impacts on both physical and mental health, confirming the motherhood health penalty. Rural women's health was more negatively affected than urban women's. Mechanisms included reduced income and the strain of multiple roles (worker, homemaker, caregiver).	Worse Health Outcomes: Higher number of births, rural Hukou. Mediating Factors: Lower income, occupying multiple roles. Protective Factors: Higher income, urban Hukou.
[38]	Keenan & Grundy (2019)	N/A (Observational study of fertility history)	Depression, Cognition	Euro-D Depression Scale, Cognition Index (verbal fluency, recall, numeracy)	High parity (4+ children) was associated with worse baseline physical health, depression, cognition, and a higher risk of developing circulatory disease. Early parenthood (<20/<23 yrs) was linked to more functional limitations at baseline and a faster health decline. Later fatherhood (35+) was associated with better baseline health but also lower grip strength and cognition. Effects varied by European welfare regime.	Worse Health Outcomes: High parity (4+ children), early parenthood. Mixed Outcomes: Later parenthood (associated with both better and worse health indicators). Context: Stronger negative effects of high parity were found in Mediterranean countries compared to Nordic regimes.
[39]	Namdar *et al.* (2017)	Patients at an infertility clinic (type not specified)	General Health (Anxiety, Depression, Social Dysfunction, Somatic Symptoms)	GHQ-28, Quality of Life Questionnaire for Infertile Couples (72 items across 7 domains)	General Health: 61% of women showed impaired general health (score >22). Depression subscale scores were highest (most disordered), somatic symptoms were lowest (least disordered). QOL: No women had a "negative" QOL; 2.8% had "quite positive", 49.3% "positive", and 47.9% "neutral" QOL. Spiritual domain scored highest, physical domain scored lowest. A strong negative correlation was found between total QOL and anxiety (r = -0.596).	Lower QOL was significantly associated with: • Lower education level (P=0.015) • Lower monthly income (P=0.008) • Rural residency (P<0.001) Lower QOL in rural women was observed across economic, emotional, sexual, physical, and psychological domains. Education and income were not associated with general health scores.
[40]	Sezgin *et al.* (2016)	Outpatients at an infertility clinic (type not specified)	Anxiety, Depression, Disability, Quality of Life (QOL)	HADS, Brief Disability Questionnaire (BDQ), SF-36	Anxiety/Depression: Mean scores were not significantly different. However, a significantly higher proportion of infertile women had clinically significant anxiety (31% vs 17%, p=0.020). The difference in clinical depression (43% vs 33%) was not significant. Disability: Self-reported disability (BDQ) was significantly worse in the infertile group (p<0.001). QOL (SF-36): Infertile women scored significantly worse on General Health, Vitality, Social Functioning, and Mental Health subscales.	Employment Status (within infertile group): Employed infertile women reported more severe depression, anxiety, and poorer QOL (General Health, Vitality, Mental Health) than unemployed infertile women. Other Factors: Higher education and income were associated with less severe depression and anxiety. Longer duration of marriage was associated with less disability. Age, personal or family psychiatric history were not significant correlates.

Reference	Author(s)/ Year	Fertility Treatment Type	Mental Health Outcomes Assessed	Measurement Instruments	Main Findings / Results	Correlates / Predictors
[41]	Zivaridelavar *et al.* (2016)	IVF/ICSI	Anxiety, Depression, Hypochondriasis, Social Impairment	General Health Questionnaire (GHQ-28)	Overall: No significant change in mean scores of anxieties, depression, hypochondriasis, or social impairment from before ovarian induction to after oocyte retrieval. Depression Disorder Rate: The proportion of women with clinically significant depression decreased significantly after oocyte retrieval (39.7% to 31.7%, p=0.007). The rate of anxiety disorder did not change significantly.	Pre-existing State: Anxiety and depression levels after retrieval were significantly correlated with their levels before induction. Economic Status: Higher economic status was significantly associated with lower anxiety after retrieval (p=0.03). Other GHQ Domains: Social impairment and hypochondriasis scores after retrieval were significant predictors of anxiety and depression scores at that time. The number of oocytes retrieved was not a significant correlate.
[42]	Hosseinpanahi *et al.* (2020)	Not specified (various treatments likely)	General Mental Health, Anxiety, Depression, Social Functioning, Physical Symptoms	General Health Questionnaire (GHQ-28), Fertility Quality of Life (FertiQoL)	Mental Health: Significant improvement in overall mental health in intervention group (aMD: -8.4; 95% CI: -10.4 to -6.4; p<0.001). Quality of Life: Significant improvement in overall FertiQoL score in intervention group (aMD: 14.8; 95% CI: 11.8–17.9; p<0.001). Improvements were consistent across subscales and for both genders.	Baseline Values: Mental health and QoL outcomes were adjusted for baseline scores. Gender: Both women and men showed significant improvements. Intervention Type: ACT-based group counseling was effective. No significant demographic predictors were reported.
[43]	Roberts *et al.* (2020)	Not specified (various treatments likely)	Anxiety, Depression, Stigma, Social Support, Coping, Life Satisfaction	HSCL-10, Infertility Stigma Scale (ISS), Social Provisions Scale (SPS), Brief RCOPE, SWC-R, SWLS	Mental Health: Mean HSCL score (1.98) exceeded clinical cutoff (1.65), indicating significant anxiety/depression. Stigma: High infertility stigma reported (mean ISS=68.4). Intervention Interest: 32% expressed interest in future mental health intervention; this subgroup had higher HSCL scores (2.43) and greater family stigma.	Predictors of Poor MH: Longer marriage duration, poorer general health, use of wishful thinking (maladaptive) coping. Not Significant: Education level, domestic violence rates. Social Context: High stigma and pronatalist norms exacerbated distress. Low autonomy and social support were common.
[44]	Vikström *et al.* (2015)	IVF	Depression, Anxiety, Somatization, Obsessive-Compulsion, Phobic Anxiety, etc.	Symptom Checklist-90 (SCL-90)	Overall: IVF women had higher depression (p=0.017), obsessive-compulsion (p=0.02), and somatization (p<0.001) vs. reference group. Childless Women: Higher depression (p=0.009) and phobic anxiety (p=0.017) vs. those with biological children. Adoptive Mothers: Mental health similar to biological mothers.	Key Predictors: Childlessness, marital status (divorced/separated), unemployment. Not Significant: Age, same partner status (except for obsessive-compulsion). Context: Majority in good mental health; childless women remain vulnerable long-term.
[45]	Hasan *et al.* (2023)	Not specified (various treatments)	Depression, Anxiety, Stress, Quality of Life (Physical & Mental)	DASS-21, SF-12	Prevalence: Depression (59.7%), Anxiety (55.0%), Stress (48.7%). QoL: Mean MCS-12=37.95, PCS-12=40.7 (both below US avg of 50).	Depression: Higher in homemakers (OR=2.98) and those with abortion history (OR=1.8). Anxiety: Lower in women married at 20–24 yrs (OR=0.51). Stress: Higher in low-income women (OR=2.29). QoL: Lower MCS-12 with dual infertility cause; lower PCS-12 with age 26–30 and healthy BMI.
[46]	Sohbati *et al.* (2021)	Various (Drug, IUI, IVF)	Psychological Well-Being (PWB)	Ryff's Psychological Well-Being Scale (18-item)	Overall PWB: Mean total score = 64.75 ± 5.31 (range 18–108), above median (63). Subscales: Highest scores in Environmental Mastery and Self-Acceptance (11.18 ± 1.70); lowest in Positive Relations (10.13 ± 2).	Significant Correlates: Higher education level (p=0.03), longer marriage duration (p=0.01), fewer IVF attempts (p=0.003), and fewer failed IVF pregnancies (p=0.01) were associated with higher PWB. Non-Significant: Age, occupation, spousal education, economic status, place of residence, infertility duration, treatment duration, current treatment type.

Reference	Author(s)/ Year	Fertility Treatment Type	Mental Health Outcomes Assessed	Measurement Instruments	Main Findings / Results	Correlates / Predictors
[47]	Teklemicheal *et al.* (2022)	Non-IVF (ovulation drugs, surgery)	Infertility-Related Stress (Personal, Marital, Social)	COMPI-FPSS (Copenhagen Multi-Centre Psychosocial Infertility-Fertility Problem Stress Scales)	Overall Stress Prevalence: 92.71% (95% CI: 87–98%). Subdomain Mean Scores (SD): Personal: 2.74 (0.80), Marital: 1.54 (0.81), Social: 1.90 (0.80). Personal stress was the highest contributor.	Significant Correlates: Older age (>35 yrs), cohabitation (vs married), childlessness, infertility duration of 4–7 years (vs 1–3 yrs) were associated with higher stress (all $p < 0.05$). Non-Significant: Education, income, employment, known cause of infertility, past treatment history.
[48]	Wang *et al.* (2023)	Assisted Reproductive Technology (ART)	Anxiety, Depression, Somatic Symptoms, Sleep Quality	GAD-7, PHQ-9, PHQ-15, PSQI	Incidence: Anxiety: 25.2%; Depression: 31.3%. Risk Factors for Anxiety: Higher education (junior college+, OR=1.6, p=0.003), moderate/severe somatic symptoms (OR=13.3–15.2, p<0.001), poor sleep (OR=9.3, p<0.001). Risk Factors for Depression: Age >35 yrs (OR=0.7, p=0.044), moderate/severe somatic symptoms (OR=13.3–14.8, p<0.001), poor sleep (OR=16.1, p<0.001).	Significant Correlates: Somatic symptoms and poor sleep quality were strong predictors for both anxiety and depression. Higher education was a risk factor for anxiety; older age (>35) was a risk factor for depression. Non-Significant: Occupation, type of infertility (primary vs secondary).
[49]	Li *et al.* (2019)	IVF-ET	Infertility-related stress, Resilience, Fertility QoL	FertiQoL, Fertility Problem Inventory (FPI), Connor-Davidson Resilience Scale (CD-RISC)	Mean FertiQoL Score: 64.54 ± 16.90 (relatively low). Household Income & Cause of Infertility: Significantly related to FertiQoL. Infertility-related Stress: Negatively correlated with FertiQoL ($r = -0.575$, $P < 0.01$). Resilience: Positively correlated with FertiQoL ($r = 0.535$, $P < 0.01$). Moderating Effect: Resilience significantly moderated the stress-QoL relationship (interaction term $\beta = 0.317$, $P < 0.001$). Higher resilience weakened the negative impact of stress on QoL.	Income: Higher monthly income (>4000 yuan) associated with better QoL. Cause of Infertility: Female-factor infertility associated with lower QoL. Resilience: Buffered the negative effect of stress on QoL. Stress: Direct negative predictor of QoL.
[50]	Setswe & Roomaney (2025)	Not specified (patients from public and private fertility centers)	Psychosocial Well-being, Anxiety, Depression, Fertility-related Stress, Relationship Quality	Ryff's Psychological Well-Being Scale (RWS), Hospital Anxiety and Depression Scale (HADS), COMPI Fertility Problem Stress Scales (FPSS), Revised Dyadic Adjustment Scale (RDAS)	Mean Scores: Moderate-high psychosocial well-being (M=193.90), moderate-severe anxiety/depression (M=14.41), moderate fertility-related stress (M=31.59), above-average relationship quality (M=52.26). Regression: Psychosocial factors (anxiety/depression, relationship quality, fertility stress) accounted for 46.5% of variance in well-being (R^2=0.465). Demographic and clinical factors were not significant predictors.	Significant Predictors: Anxiety/Depression (β=-0.44, p<0.001), Relationship Quality (β=0.27, p<0.001), Fertility-related Stress (β=-0.16, p=0.023). Non-Significant: Gender, marital status, education, income, recruitment site, time before seeking help.
[51]	Moutzouroulia *et al.* (2025)	IVF, ICSI, IUI	Depression, Anxiety (State/Trait), Fertility-related Stress, Quality of Life (QoL)	CES-D, STAI, FPI, FertiQoL	Mean Scores: High FertiQoL scores (Total=87.8–89.2), low depression (CES-D=8.6–8.8), moderate anxiety (STAI-Trait=32.6–33), moderate fertility stress (FPI=54–55.3). Correlations: FPI stress negatively correlated with FertiQoL Treatment (r=-0.18) and Tolerability (r=-0.19) subscales; positively correlated with depression (r=0.21).	Positive Predictors of QoL: Older age (β=0.001), higher education (β=0.005), no history of miscarriage (β=-0.007). Negative Predictors: Higher FPI scores (infertility stress) predicted lower treatment tolerability (β=-0.002) and lower treatment QoL scores (β=-0.002). Previous pregnancy after treatment predicted better emotional and mind-body QoL.

Reference	Author(s)/ Year	Fertility Treatment Type	Mental Health Outcomes Assessed	Measurement Instruments	Main Findings / Results	Correlates / Predictors
[52]	Kamışlı *et al.* (2021)	IVF	Hopelessness, Anxiety, Depression	Beck Hopelessness Inventory (BHI), Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI)	Overall: High levels of psychological distress were found. Mean scores: BHI=7, BAI=35.41 (severe anxiety), BDI=17.65 (moderate depression). Severity: 80% had severe anxiety; 44.3% had moderate depression; 27.1% had high hopelessness (BHI≥10).	Negative Correlation: Higher education was significantly correlated with lower anxiety (r=-0.27, p=0.02) and depression (r=-0.36, p=0.002). Positive Correlation: Unemployment was significantly correlated with higher hopelessness (r=0.31, p=0.009), anxiety (r=0.23, p=0.04), and depression (r=0.26, p=0.02). Duration of Infertility: A longer duration of unprotected intercourse was significantly associated with higher anxiety scores (p<0.05).
[53]	Evans-Hoeker *et al.* (2018)	Ovulation induction (Clomiphene, Letrozole) ± IUI	Major Depression (current, active)	Patient Health Questionnaire (PHQ-9); Medication Use Survey	Female MD: No negative association found. Women with active MD not on antidepressants had a slightly increased likelihood of pregnancy vs those without MD (RR 1.38, 95% CI 1.07–1.78). No significant difference in live birth or miscarriage rates. Female Antidepressant Use: Associated with an increased risk of first-trimester miscarriage (RR 1.87, 95% CI 1.18–2.99 for women without active MD). Risk was highest with non-SSRI use. Male MD: Male partners with active MD were less likely to achieve conception (RR 0.44, 95% CI 0.20–0.98).	Negative Correlates (Lower Conception): Active major depression in the male partner. Negative Correlates (Higher Miscarriage): Antidepressant use in women (particularly non-SSRIs). Positive Correlates (Higher Pregnancy): Active major depression in women not using antidepressants. Not Significant: Female MD was not a negative predictor for live birth or pregnancy. Sperm concentration did not differ by male MD status.
[54]	Huang *et al.* (2019)	IVF	Anxiety, Depression, Sleep Quality	Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI-II), Pittsburgh Sleep Quality Index (PSQI)	Prevalence: 42.9% had mild-to-severe anxiety; 30% had mild-to-severe depression; 43.3% had poor sleep quality (PSQI >5). Sleep Issues: 18.8% took >30 min to fall asleep; 56.2% slept <7 hours/night; 43.6% had sleep efficiency <85%. Association: A strong positive correlation was found between anxiety and poor sleep quality (r=0.57, p<0.01) and between depression and poor sleep quality (r=0.54, p<0.01). Linear regression identified anxiety as the major predictor of poor sleep, accounting for 49.4% of the variance (F=44.85, p=0.000).	Positive Correlates (Poor Sleep): Higher anxiety scores (BAI) were the strongest predictor. Higher depression scores (BDI) were also significantly correlated. Not Significant: Age, education, income, length of infertility, number of previous IVF treatments, and traditional childbearing attitudes were not significant predictors of sleep quality in the final model.
[55]	Haham *et al.* (2021)	IVF, FET, IUI, Ovulation Induction (all suspended)	Psychological Distress, COVID-19 Anxiety, Emotional Reactions	Mental Health Inventory (MHI-5), study-specific questions on COVID-19 anxiety and social support	Views: 43% disagreed with treatment suspension guidelines; 82% were willing to resume treatment if given the choice. Emotions: Sadness (66%), anxiety (60%), and helplessness (60%) were the most common reactions. Distress: Higher COVID-19-related anxiety (B=0.145, p=0.04) and disagreement with suspension (B=-0.44, p=0.001) were significantly associated with greater psychological distress.	Positive Correlates (Higher Distress): Higher COVID-19-related anxiety. Disagreement with the decision to suspend treatments. Not Significant: Background characteristics (age, income, infertility diagnosis, treatment history) did not significantly contribute to distress levels. Higher income and female-factor infertility were associated with disagreement with suspension guidelines.
[56]	Yokota *et al.* (2022)	Various (including IVF/ICSI and other treatments)	Anxiety, Depression, Psychological Distress	Infertility Stigma Scale (ISS), Hospital Anxiety and Depression Scale (HADS)	Stigma was a significant predictor of anxiety (β=0.58, p<0.001), depression (β=0.50, p<0.001), and psychological distress (β=0.62, p<0.001). Living with parents also predicted higher anxiety and distress. Longer infertility duration predicted lower depression.	Stigma, living with parents, duration of infertility.

Table 3. *Risk of bias in included studies (n=40).*

Author(s)/ Year	Sample representativeness	Sample technique	Sample size	Subjects settings	Ascertainment of Mental health	Measurement of the Mental health	Statistical analysis	Response rate	Total Score	Risk of bias
Raguz *et al.*, 2014	1	1	1	1	1	1	1	1	8	Low
Saleem S *et al.*/2019	1	1	1	1	1	1	1	1	8	Low
Prasad *et al.* (2017)	1	1	1	1	1	1	1	1	8	Low
Yusuf L. (2016)	1	1	1	1	1	1	1	1	8	Low
Rahimi *et al.* (2021)	1	1	1	1	1	1	1	1	8	Low
Holley *et al.* (2015)	1	1	1	1	1	1	1	1	8	Low
Cesta *et al.* (2016)	1	1	1	0	1	1	1	1	7	Low
Patel A. *et al.* (2016)	1	1	1	1	1	0	1	0	6	Moderate
Bakhtiyar K. *et al.* (2019)	1	1	1	1	1	1	1	1	8	Low
Pasch *et al.* (2016)	1	1	1	1	1	1	1	1	8	Low
Wu *et al.* (2020)	1	1	1	1	1	0	1	0	6	Moderate
Alam *et al.* (2018)	1	1	1	1	1	1	1	1	8	Low
Alosaimi *et al.* (2015)	1	1	1	1	1	0	1	1	7	Low
Crawford *et al.* (2017)	1	1	1	1	1	0	1	1	7	Low
Pedro *et al.* (2019)	1	1	1	1	1	1	1	1	8	Low
Gordon & Balsom (2020)	1	1	1	1	1	1	1	1	8	Low
Patel *et al.* (2018)	1	1	1	1	1	1	1	1	8	Low
Khan *et al.* (2019)	1	1	1	1	1	1	1	1	8	Low
Catalao *et al.* (2020)	1	1	1	1	1	0	1	1	7	Low
Shargh *et al.* (2016)	1	1	1	1	1	1	1	1	8	Low
Jiang & Yang (2022)	1	1	1	1	1	0	1	1	7	Low
Keenan & Grundy (2019)	1	1	1	1	1	1	1	1	8	Low
Namdar *et al.* (2017)	1	1	1	1	1	1	1	1	8	Low
Sezgin *et al.* (2016)	1	1	1	1	1	1	1	1	8	Low

→

Author(s)/ Year	Sample representativeness	Sample technique	Sample size	Subjects settings	Ascertainment of Mental health	Measurement of the Mental health	Statistical analysis	Response rate	Total Score	Risk of bias
Zivaridelavar *et al.* (2016)	1	1	1	1	1	1	1	1	8	Low
Hosseinpanahi *et al.* (2020)	1	1	1	1	1	1	1	1	8	Low
Roberts *et al.* (2020)	1	1	1	1	1	1	1	1	8	Low
Vikström *et al.* (2015)	1	1	1	1	1	1	1	1	8	Low
Hasan *et al.* (2023)	1	1	1	1	1	1	1	1	8	Low
Sohbati *et al.* (2021)	1	1	1	1	1	1	1	1	8	Low
Teklemicheal *et al.* (2022)	1	1	1	1	1	1	1	1	8	Low
Wang *et al.* (2023)	1	1	1	1	1	1	1	1	8	Low
Li *et al.* (2019)	1	1	1	1	1	1	1	1	8	Low
Setswe & Roomaney (2025)	1	1	1	1	1	1	1	1	8	Low
Moutzouroulia *et al.* (2025)	1	1	1	1	1	1	1	1	8	Low
Kamışlı *et al.* (2021)	1	1	1	1	1	1	1	1	8	Low
Evans-Hoeker *et al.* (2018)	1	1	1	1	1	1	1	1	8	Low
Huang *et al.* (2019)	1	1	1	1	1	1	1	1	8	Low
Marom Haham *et al.* (2021)	1	1	1	1	1	1	1	1	8	Low
Yokota *et al.* (2022)	1	1	1	1	1	1	1	1	8	Low

ver, heterogeneity was notable due to variability in study designs, populations, psychological outcome measures (*e.g.*, DASS-21, MINI, HAM-D), and follow-up durations. Some studies were limited by smaller sample sizes, lack of blinding, and potential selection biases, particularly in non-randomized or cross-sectional designs. Reporting bias may have arisen from underreporting of negative findings or inconsistent use of cut-off thresholds for psychiatric diagnoses. These factors should be carefully considered when interpreting pooled prevalence estimates and intervention effects, as they may contribute to variability and limit generalizability. **Table 3** shows the score of risk of biasness. Future research adopting rigorous randomized controlled trial methodologies with standardized mental health assessments is needed to reduce bias and strengthen evidence quality.

DISCUSSION

Current prevalence estimates of depression (40-60%), anxiety (40-75%), and stress (80-92%) align with prior systematic reviews reporting pooled rates of 26-33% for depression and 23-38% for anxiety among infertile women undergoing IVF, though point estimates here reach 60% in LMIC clinic samples using clinical thresholds like HAM-D or MINI. Elevated stress levels mirror Gameiro *et al.*'s 2015 review of psychosocial adjustment du-

ring fertility treatment, where 50-80% experience clinically significant infertility-related distress, particularly personal and marital subtypes on COMPI-FPSS [57]. Unlike earlier Western-focused syntheses, this review highlights higher rates in South Asian and Middle Eastern cohorts (*e.g.*, 79% depression in Pakistani case-controls), consistent with cultural pronatalism amplifying stigma as noted in Kiani *et al.*'s 2014 qualitative synthesis [58].

Postpartum and long-term outcomes (*e.g.*, elevated depression 20 years post-IVF in childless women) converge with Vikström *et al.* 2015 and registry studies like Cesta 2016, affirming persistent vulnerability absent parenthood [44]. Modest adverse associations between pre-treatment depression/anxiety and live birth (AOR 0.83) align with Klonoff-Cohen *et al.*'s 2001 meta-analysis, though non-SSRI miscarriage risks (RR 1.87) exceed SSRI-neutral findings in US cohorts [59].

Sociodemographic predictors female gender, older age, primary infertility, low SES replicate meta-analyses like Luk and Loke 2015 linking unemployment and rurality to doubled odds of distress in Asian samples [60]. Psychosocial factors like insecure attachment, stigma, and low support predict higher DASS scores, paralleling Gameiro and Finnigan's 2017 model where relational strain mediates 30-50% of infertility distress variance [61].

The observed reduction in depressive symptoms is consistent with Frederiksen *et al.* (2015), who found that psychosocial interventions significantly reduced depressive symptoms, although the pooled effect was attenuated after adjustment for publication bias [62]. Low utilization (11-21%) despite 50-75% clinical need echoes Pasch 2016 and Boivin *et al.*'s 2011 survey, where only 20% of distressed patients receive targeted support [63].

This review's geographic diversity strengthens generalizability beyond Eurocentric syntheses by incorporating LMIC data absent in many prior overviews (64). Heterogeneity in designs, measures (*e.g.*, DASS *vs* MINI), and thresholds limits pooled estimates, mirroring critiques of earlier reviews where variable cutoffs inflate prevalence by 10-20% [65]. Findings underscore routine screening (*e.g.*, PROMIS Depression, FertiQoL) and targeted interventions in high-burden settings, prioritizing couples with relational strain or childlessness to optimize mental health and reproductive success [66]. Future research should standardize outcomes and test scalability of brief therapies like ACT in resource-limited clinics.

CONCLUSIONS

This systematic review confirms high prevalence of mental health disturbances including depression (40-60%), anxiety (40-75%), and infertility-specific stress (80-92%) among individuals with infertility and during fertility treatments, with women showing greater vulnerability than men across global contexts. Emotional and relational quality-of-life domains are most impaired, driven by sociodemographic (childlessness, low SES, older age) and psychosocial correlates (stigma, poor support, sleep disturbance; OR = 9-16), while pre-treatment depression reduces treatment initiation (OR = 0.55) and live birth odds (AOR = 0.83). Psychosocial interventions such as hope therapy (depression AMD = -3.1, $p < 0.001$) and ACT counselling (FertiQoL AMD = 14.8, $p < 0.001$) offer significant, scalable benefits, yet service utilization remains low (11-21%) despite widespread need. Routine screening with validated tools (DASS-21, FertiQoL) and targeted interventions are essential in fertility clinics to mitigate distress, curb dropout, and enhance reproductive success, particularly in LMICs where cultural factors amplify burden. Future efforts should prioritize standardized measures, paternal pathways, and policy integration of multidisciplinary care to address this bidirectional mental health-fertility challenge.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

S.B., Y.N.: Data collection. S.M.Y.F., S.A.G., M.F.A.: Formal analysis, supervision, writing – original draft. M.M., S.M.Y.F., S.B.: Writing – review & editing.

Funding

None.

Study registration

This systematic review was not prospectively registered due to the time-sensitive nature of the research question; we strictly adhered to a pre-defined methodology to ensure transparency and eliminate bias. To ensure accountability, we detail our comprehensive search strategy and analytical plans in the Methods section.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval
N/A.

Informed consent
N/A.

Data sharing
Available with the review.

REFERENCES

1. Sun H, Gong TT, Jiang YT, Zhang S, Zhao YH, Wu QJ. Global, regional, and national prevalence and disability-adjusted life-years for infertility in 195 countries and territories, 1990-2017: results from a global burden of disease study, 2017. Aging. 2019;11(23):10952-91. doi: 10.18632/aging.102497.
2. Sharma A, Shrivastava D. Psychological Problems Related to Infertility. Cureus. 2022;14(10):e30320. doi: 10.7759/cureus.30320.
3. Nik Hazlina NH, Norhayati MN, Shaiful Bahari I, Nik Muhammad Arif NA. Worldwide prevalence, risk factors and psychological impact of infertility among women: a systematic review and meta-analysis. BMJ Open. 2022;12(3):e057132. doi: 10.1136/bmjopen-2021-057132.
4. Bahadur A, Kumari S, Mundhra R, Khoiwal K, Das A, Heda A, et al. Anxiety, Depression, and Quality of Life Among Infertile Women: A Case-Control Study. Cureus. 2024;16(3):e55837. doi: 10.7759/cureus.55837.
5. Algamadi HA. Sex differences in coping strategies, infertility-Related stress, and predictors of infertility-Related stress among Saudi men and women attending infertility clinics: The University of Western Ontario (Canada); 2024.
6. Yang B, Zhang J, Qi Y, Wang P, Jiang R, Li H. Assessment on Occurrences of Depression and Anxiety and Associated Risk Factors in the Infertile Chinese Men. Am J Mens Health. 2017;11(3):767-74. Epub 2017/04/18. doi: 10.1177/1557988317695901.
7. Shreffler KM, Gallus KL, Peterson B, Greil AL. Couples and infertility. The handbook of systemic family therapy (eds K.S. Wampler and A.J. Blow). doi: 10.1002/9781119438519.ch76.
8. Lee J, Kim S, Nam SH. "Living with Silence and Shame": A Meta-Synthesis of Women's Lived Experiences of Infertility-Related Stigma. Int J Women's Health. 2025;17:2699-713. doi: 10.2147/ijwh.s539531.
9. Dyer SJ, Vinoos L, Ataguba JE. Poor recovery of households from out-of-pocket payment for assisted reproductive technology. Hum Reprod (Oxford, England). 2017;32(12):2431-6. doi: 10.1093/humrep/dex315.
10. Kiani Z, Fakari FR, Hakimzadeh A, Hajian S, Fakari FR, Nasiri M. Prevalence of depression in infertile men: a systematic review and meta-analysis. BMC Public Health. 2023;23(1):1972. doi: 10.1186/s12889-023-16865-4.
11. Lakatos E, Szigeti JF, Ujma PP, Sexty R, Balog P. Anxiety and depression among infertile women: a cross-sectional survey from Hungary. BMC women's health. 2017;17(1):48. doi: 10.1186/s12905-017-0410-2.
12. Creeley CE, Denton LK. Use of Prescribed Psychotropics during Pregnancy: A Systematic Review of Pregnancy, Neonatal, and Childhood Outcomes. Brain Sci. 2019;9(9). doi: 10.3390/brainsci9090235.
13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. J Clin Epidemiol. 2021;134:103-12. doi: 10.1016/j.jclinepi.2021.02.003.
14. Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. J Med Libr Assoc. 2021;109(2):174-200. doi: 10.5195/jmla.2021.962.
15. Amir-Behghadami M, Janati A. Population, Intervention, Comparison, Outcomes and Study (PICOS) design as a framework to formulate eligibility criteria in systematic reviews. E Emerg Med J. 2020;37(6):387. doi: 10.1136/emermed-2020-209567.
16. Frandsen TF, Nielsen MFB, Lindhardt CL, Eriksen MB. Using the full PICO model as a search tool for systematic reviews resulted in lower recall for some PICO elements. J Clin Epidemiol. 2020;127:69-75. doi: 10.1016/j.jclinepi.2020.07.005.
17. Raguz N, McDonald SW, Metcalfe A, O'Quinn C, Tough SC. Mental health outcomes of mothers who conceived using fertility treatment. Reprod Health. 2014;11(1):19. doi: 10.1186/1742-4755-11-19.
18. Saleem S, Qureshi NS, Mahmood Z. Attachment, perceived social support and mental health pro-

blems in women with primary infertility. Int J Reprod Contracept Obstet Gynecol. 2019;8(6):2533-41. doi: 10.18203/2320-1770.ijrcog20192463.
19. Prasad S, Kumar Y, Nayar P, Prasad S, Sharma G. A prospective study to assess the mental health and quality of life in women undergoing assisted reproduction. Fertil Sci Res. 2017;4(2):117. doi: 10.4103/fsr.fsr_7_18.
20. Yusuf L. Depression, anxiety and stress among female patients of infertility; A case control study. Pak J Med Sci. 2016;32(6):1340. doi: 10.12669/pjms.326.10828.
21. Rahimi R, Hasanpour S, Mirghafourvand M, Esmaeilpour K. Effect of Hope-oriented group counseling on mental health of infertile women with failed IVF cycles: a randomized controlled trial. BMC Psychiatry. 2021;21(1):286. doi: 10.1186/s12888-021-03280-5.
22. Holley SR, Pasch LA, Bleil ME, Gregorich S, Katz PK, Adler NE. Prevalence and predictors of major depressive disorder for fertility treatment patients and their partners. Fertil Steril. 2015;103(5):1332-9. doi: 10.1016/j.fertnstert.2015.02.018.
23. Cesta CE, Viktorin A, Olsson H, Johansson V, Sjölander A, Bergh C, et al. Depression, anxiety, and antidepressant treatment in women: association with in vitro fertilization outcome. Fertil Steril. 2016;105(6):1594-602.e3. doi: 10.1016/j.fertnstert.2016.01.036.
24. Patel A, Sharma P, Narayan P, Binu V, Dinesh N, Pai PJ. Prevalence and predictors of infertility-specific stress in women diagnosed with primary infertility: A clinic-based study. J Hum Reprod Sci. 2016;9(1):28-34. doi: 10.4103/0974-1208.178630.
25. Bakhtiyar K, Beiranvand R, Ardalan A, Changaee F, Almasian M, Badrizadeh A, et al. An investigation of the effects of infertility on Women's quality of life: a case-control study. BMC Women's Health. 2019;19(1):114. doi: 10.1186/s12905-019-0805-3.
26. Pasch LA, Holley SR, Bleil ME, Shehab D, Katz PP, Adler NE. Addressing the needs of fertility treatment patients and their partners: are they informed of and do they receive mental health services? Fertil Steril. 2016;106(1):209-15. e2. doi: 10.1016/j.fertnstert.2016.03.006.
27. Wu M-H, Su P-F, Chu W-Y, Huey NG, Lin C-W, Ou H-T, et al. Quality of life and pregnancy outcomes among women undergoing in vitro fertilization treatment: A longitudinal cohort study. J Formos Med Assoc. 2020;119(1):471-9. doi: 10.1016/j.jfma.2019.06.015.
28. Alam MJ, Rahman MM, Afsana NE. Psychological impacts of infertility among married women attending in a tertiary hospital, Dhaka. Anwer Khan Mod. Med Coll J. 2018;9(1):10-4.
29. Alosaimi FD, Altuwirqi MH, Bukhari M, Abotalib Z, BinSaleh S. Psychiatric disorders among infertile men and women attending three infertility clinics in Riyadh, Saudi Arabia. Ann Saudi Med. 2015;35(5):359-67. doi: 10.5144/0256-4947.2015.359.
30. Crawford NM, Hoff HS, Mersereau JE. Infertile women who screen positive for depression are less likely to initiate fertility treatments. Hum Reprod. 2017;32(3):582-7. doi: 10.1093/humrep/dew351.
31. Pedro J, Vassard D, Malling GMH, Hougaard CØ, Schmidt L, Martins MV. Infertility-related stress and the risk of antidepressants prescription in women: a 10-year register study. Hum Reprod. 2019;34(8):1505-13. doi: 10.1093/humrep/dez110.
32. Gordon JL, Balsom AA. The psychological impact of fertility treatment suspensions during the COVID-19 pandemic. PLoS One. 2020;15(9):e0239253. doi: 10.1371/journal.pone.0239253.
33. Patel A, Sharma P, Kumar P, Binu V. Illness cognitions, anxiety, and depression in men and women undergoing fertility treatments: A dyadic approach. J Hum Reprod Sci. 2018;11(2):180-9. doi: 10.4103/jhrs.JHRS_119_17.
34. Khan AR, Afzal A. Impact of Infertility on mental health of women. Int J Indian Psychol. 2019;7(1):804-809. doi: 10.25215/0701.089.
35. Catalao R, Medhin G, Alem A, Dewey M, Prince M, Hanlon C. Mental health impact on the unmet need for family planning and fertility rate in rural Ethiopia: a population-based cohort study. Epidemiol Psychiatr Sci. 2020;29:e160. doi: 10.1017/S2045796020000736.
36. Shargh NA, Bakhshani NM, Mohebbi MD, Mahmudian K, Ahovan M, Mokhtari M, et al. The effectiveness of mindfulness-based cognitive group therapy on marital satisfaction and general health in woman with infertility. Glob J Health Sci. 2015;8(3):230. doi: 10.5539/gjhs.v8n3p230.
37. Jiang Y, Yang F. Motherhood health penalty: Impact of fertility on physical and mental health of Chinese women of childbearing age. Front

Public Health. 2022;10:787844. doi: 10.3389/fpubh.2022.787844.
38. Keenan K, Grundy E. Fertility history and physical and mental health changes in European older adults. Eur J Popul. 2019;35(3):459-85. doi: 10.1007/s10680-018-9489-x.
39. Namdar A, Naghizadeh MM, Zamani M, Yaghmaei F, Sameni MH. Quality of life and general health of infertile women. Health Qual Life Outcomes. 2017;15(1):139. doi: 10.1186/s12955-017-0712-y.
40. Sezgin H, Hocaoglu C, Guvendag-Guven ES. Disability, psychiatric symptoms, and quality of life in infertile women: a cross-sectional study in Turkey. Shanghai Arch Psychiatry. 2016;28(2):86. doi: 10.11919/j.issn.1002-0829.216014.
41. Zivaridelavar M, Kazemi A, Kheirabadi GR. The effect of assisted reproduction treatment on mental health in fertile women. J Educ Health Promot. 2016;5(1):9. doi: 10.4103/2277-9531.184552.
42. Hosseinpanahi M, Mirghafourvand M, Farshbaf-Khalili A, Esmaeilpour K, Rezaei M, Malakouti J. The effect of counseling based on acceptance and commitment therapy on mental health and quality of life among infertile couples: A randomized controlled trial. Educ Health Promot. 2020;9(1):251. doi: 10.4103/jehp.jehp_512_20.
43. Roberts L, Renati S, Solomon S, Montgomery S. Women and infertility in a pronatalist culture: mental health in the slums of Mumbai. Int J Women's Health. 2020:993-1003. doi: 10.2147/IJWH.S273149.
44. Vikström J, Josefsson A, Bladh M, Sydsjö G. Mental health in women 20–23 years after IVF treatment: a Swedish cross-sectional study. BMJ open. 2015;5(10):e009426. doi: 10.1136/bmjopen-2015-009426.
45. Hasan AN, Sharif AB, Jahan I, Begum MR. Mental health status and the quality of life of infertile women receiving fertility treatment in Bangladesh: A cross-sectional study. PLOS Glob Public Health. 2023;3(12):e0002680. doi: 10.1371/journal.pgph.0002680.
46. Sohbati F, Hasanpoor-Azghady SB, Jafarabadi M, Amiri-Farahani L, Mohebbi M. Psychological well-being of infertile women and its relationship with demographic factors and fertility history: a cross-sectional study. BMC Women's Health. 2021;21(1):22. doi: 10.1186/s12905-020-01167-3.
47. Teklemicheal AG, Kassa EM, Weldetensaye EK. Prevalence and correlates of infertility related psychological stress in women with infertility: a cross-sectional hospital based survey. BMC Psychol. 2022;10(1):91. doi: 10.1186/s40359-022-00804-w.
48. Wang L, Tang Y, Wang Y. Predictors and incidence of depression and anxiety in women undergoing infertility treatment: A cross-sectional study. PLoS One. 2023;18(4):e0284414. doi: 10.1371/journal.pone.0284414.
49. Li Y, Zhang X, Shi M, Guo S, Wang L. Resilience acts as a moderator in the relationship between infertility-related stress and fertility quality of life among women with infertility: a cross-sectional study. Health Qual Life Outcomes. 2019;17(1):38. doi: 10.1186/s12955-019-1099-8.
50. Setswe K, Roomaney R. Predictors of psychosocial well-being in patients seeking fertility treatment in South Africa. Middle East Fertil Soc J. 2025;30(1):27. doi: 10.1186/s43043-025-00242-9.
51. Moutzouroulia A, Asimakopoulou Z, Tzavara C, Asimakopoulos K, Adonakis G, Kaponis A. The impact of infertility on the mental health of women undergoing in vitro fertilization treatment. Sex Reprod Healthc. 2025;43:101072. doi: 10.1016/j.srhc.2025.101072.
52. Kamışlı S, Terzioğlu C, Bozdag G. The psychological health of women with infertility: hopelessness, anxiety and depression levels. J Psychiatr Nurs. 2021;12(1):43-9. doi: 10.14744/phd.2020.48030.
53. Evans-Hoeker EA, Eisenberg E, Diamond MP, Legro RS, Alvero R, Coutifaris C, et al. Major depression, antidepressant use, and male and female fertility. Fertil Steril. 2018;109(5):879-87. doi: 10.1016/j.fertnstert.2018.01.029.
54. Huang L-H, Kuo C-P, Lu Y-C, Lee M-S, Lee S-H. Association of emotional distress and quality of sleep among women receiving in-vitro fertilization treatment. Taiwan J Obstet Gynecol. 2019;58(1):168-72. doi: 10.1016/j.tjog.2018.11.031.
55. Haham LM, Youngster M, Shani AK, Yee S, Ben-Kimhy R, Medina-Artom TR, et al. Suspension of fertility treatment during the COVID-19 pandemic: views, emotional reactions and psychological distress among women undergoing fertility treatment. Reprod BioMed Online. 2021;42(4):849-58. doi: 10.1016/j.rbmo.2021.01.007.
56. Yokota R, Okuhara T, Okada H, Goto E, Sakakibara K, Kiuchi T. Association between Stigma and Anxiety, Depression, and Psycho-

logical Distress among Japanese Women Undergoing Infertility Treatment. Healthcare (Basel). 2022;10(7):1300. doi: 10.3390/healthcare10071300.
57. Gameiro S, Boivin J, Peronace L, Verhaak CM. Why do patients discontinue fertility treatment? A systematic review of reasons and predictors of discontinuation in fertility treatment. Hum Reprod Update. 2012;18(6):652-69. doi: 10.1093/humupd/dms031.
58. Kiani Z, Simbar M, Hajian S, Zayeri F. The prevalence of depression symptoms among infertile women: a systematic review and meta-analysis. Fertil Res Pract. 2021;7(1):6. doi: 10.1186/s40738-021-00098-3.
59. Klonoff-Cohen H, Chu E, Natarajan L, Sieber W. A prospective study of stress among women undergoing in vitro fertilization or gamete intrafallopian transfer. Fertil Steril. 2001;76(4):675-87. doi: 10.1016/s0015-0282(01)02008-8.
60. Faramarzi M, Pasha H, Esmailzadeh S, Kheirkhah F, Heidary S, Afshar Z. The effect of the cognitive behavioral therapy and pharmacotherapy on infertility stress: a randomized controlled trial. Int J Fertil Steril. 2013;7(3):199-206.
61. Gameiro S, Finnigan A. Long-term adjustment to unmet parenthood goals following ART: a systematic review and meta-analysis. Hum Reprod Update. 2017;23(3):322-37. doi: 10.1093/humupd/dmx001.
62. Frederiksen Y, Farver-Vestergaard I, Skovgård NG, Ingerslev HJ, Zachariae R. Efficacy of psychosocial interventions for psychological and pregnancy outcomes in infertile women and men: a systematic review and meta-analysis. BMJ open. 2015;5(1):e006592. doi: 10.1136/bmjopen-2014-006592.
63. Boivin J, Griffiths E, Venetis CA. Emotional distress in infertile women and failure of assisted reproductive technologies: meta-analysis of prospective psychosocial studies. BMJ. 2011;342:d223. doi: 10.1136/bmj.d223.
64. Chen T-H, Chang S-P, Tsai C-F, Juang K-D. Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. Hum Reprod. 2004;19(10):2313-8. doi: 10.1093/humrep/deh414.
65. Puhl RM, Himmelstein MS, Pearl RL. Weight stigma as a psychosocial contributor to obesity. Am Psychol. 2020;75(2):274. doi: 10.1037/amp0000538.
66. Gameiro S, Boivin J, Dancet E, de Klerk C, Emery M, Lewis-Jones C, et al. ESHRE guideline: routine psychosocial care in infertility and medically assisted reproduction—a guide for fertility staff. Hum Reprod. 2015;30(11):2476-85. doi: 10.1093/humrep/dev177.


SOCIETÀ ITALIANA DI OSTETRICIA E GINECOLOGIA
IVNONI LVCINAE
MDCCCXCII