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# Infertility, Endometriosis and the Treatment Link to Cancer

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**Abstract:** Infertility, endometriosis, and ovarian cancer share several reproductive, hormonal, inflammatory, metabolic, and genetic pathways. However, the extent to which ovarian cancer is associated with the underlying causes of infertility rather than fertility treatment remains uncertain. Objective: To evaluate the clinical, reproductive, metabolic, treatment-related, and molecular characteristics associated with infertility among women diagnosed with ovarian cancer, with particular emphasis on endometriosis and fertility treatment exposure. Materials and Methods: A 10-year prospective comparative observational study was conducted between March 2016 and March 2026 at the Medical Health and Research Institute, Telangana, India, in collaboration with MNJ Institute of Oncology and Regional Cancer Centre. The study included 1,000 women with histopathologically confirmed ovarian cancer, comprising 150 women with a documented history of infertility and 850 without infertility. Demographic, metabolic, reproductive, infertility-related, fertility treatment, and selected molecular characteristics were compared. Statistical analyses included chi-square or Fisher's exact tests, with $p < 0.05$ considered statistically significant. Results: Women with infertility showed a distinct clinical and reproductive profile compared with those without infertility. Obesity, physical inactivity, diabetes, dyslipidemia, thyroid disorders, nulliparity, delayed first pregnancy, irregular menstrual cycles, and miscarriage history were more frequently observed in the infertility group. Among 150 infertile women, 16 ovarian cancer cases were identified, with unexplained infertility representing the largest etiological subgroup (43.8%), followed by diminished ovarian reserve (18.8%) and endometriosis (12.5%). Ovarian cancer cases were observed following ovulation induction, IUI, and IVF/ICSI, with no statistically significant evidence of disproportionate occurrence in women receiving advanced assisted reproductive techniques. Molecular analysis of the 16 infertility-associated ovarian cancer cases identified BRCA pathogenic variants in 50%, predominantly involving BRCA1. Proteomic findings in infertility-associated endometriosis demonstrated increased expression of extracellular matrix-related proteins, particularly Tenascin-X (TNXB), which showed an approximately seven-fold increase. Conclusion: The findings suggest that infertility-associated ovarian cancer is multifactorial and may be more strongly influenced by underlying reproductive, endocrine, inflammatory, metabolic, and genetic abnormalities than by fertility treatment alone. Endometriosis, persistent infertility, nulliparity, and molecular alterations involving extracellular matrix remodeling may contribute to ovarian carcinogenesis. Larger prospective multicentric studies with long-term follow-up are needed to clarify causal relationships and identify women who may benefit from targeted risk assessment and surveillance.

**Keywords:** Endometriosis, Infertility, Ovarian Cancer, Unexplained Infertility, IVF/ICSI, Tenascin-X (TNXB)

## INTRODUCTION

Infertility is among the most common heterogeneous reproductive disorders, affecting 10-15% couples globally (1). It is associated with long-term metabolic, endocrine and gynecological consequences. It is estimated that one in seven couples trying to conceive are diagnosed with infertility. Female infertility contributes to approximately 35–40% of infertile cases, which encompasses a spectrum of disorders, including ovulatory dysfunction (such as polyendocrine metabolic syndrome [PMOS]), tubal pathology, endometriosis, diminished ovarian reserve, and unexplained infertility (2). These conditions are frequently associated with hormonal imbalance, chronic inflammation, oxidative stress, altered cellular proliferation and metabolic disturbances, which may contribute to carcinogenesis.

Ovarian cancer is the eighth most common malignancy among women, remains the most lethal gynecological cancer worldwide largely due to its asymptomatic progression and late-stage diagnosis (3). Reproductive factors such as nulliparity, delayed childbearing, and uninterrupted ovulatory cycles have been implicated in ovarian carcinogenesis through the "incessant ovulation" hypothesis, where repeated ovulation-induced epithelial injury may increase the likelihood of malignant transformation (4). Infertility and ovarian cancer share a complex relationship influenced by reproductive, hormonal, metabolic, and treatment-related factors (5).

Unexplained infertility has increasingly been associated with a higher susceptibility to ovarian cancer, particularly among women with prolonged infertility duration and persistent nulliparity (6). Although classified as idiopathic, it may reflect subtle endocrine dysregulation, immunological, inflammatory, or genetic abnormalities that are not detectable through routine investigations, may contribute to ovarian epithelial injury and malignant transformation. In addition, women with unexplained infertility often undergo multiple fertility treatment cycles, making it difficult to clearly distinguish the independent effects of infertility from treatment exposure (7). However, current evidence suggests that the underlying reproductive and endocrine abnormalities associated with infertility may contribute more significantly to ovarian cancer risk than fertility treatment alone. Unexplained infertility is one of the most frequently observed infertility etiologies among ovarian cancer patients with a history of infertility. Unidentified intrinsic ovarian, endocrine, immunological, or genetic abnormalities may contribute to ovarian epithelial injury and malignant transformation (8).

Endometriosis is a chronic estrogen-dependent inflammatory disorder characterized by the presence of ectopic endometrial tissue outside the uterine cavity. It is a well-established cause of infertility and has consistently been associated with an increased proportion of ovarian cancer, particularly endometrioid and clear-cell ovarian carcinoma (9). Similarly, ovulatory disorders such as polycystic ovary syndrome (PCOS), which involve hormonal imbalance, insulin resistance, and chronic anovulation, may contribute to carcinogenesis through endocrine and metabolic dysregulation (10).

The biological mechanisms linking endometriosis and ovarian cancer include chronic inflammation, oxidative stress, repeated tissue injury and repair, altered immune response, and increased local estrogen production (11). Persistent inflammatory cytokine exposure within the peritoneal environment may induce DNA damage and promote neoplastic transformation of endometriotic lesions.

Women with endometriosis-associated infertility often demonstrate prolonged infertility duration, repeated ovulatory cycles, and exposure to fertility treatments, all of which may further influence ovarian cancer risk (12). In the present study, endometriosis was frequently observed among infertile ovarian cancer patients, supporting previous evidence that chronic inflammatory reproductive disorders may contribute to ovarian carcinogenesis.

The relationship between infertility and ovarian cancer is also influenced by several molecular and genetic factors involved in inflammation, tissue remodeling, angiogenesis, and tumor progression (13). Among these Tenascin-X (TNXB), an extracellular matrix glycoprotein, has emerged as an important molecule in infertility associated ovarian carcinogenesis. Increased expression of Tenascin has been reported in endometriosis, unexplained infertility, and ovarian malignancies, suggesting a possible mechanistic link between chronic inflammatory reproductive disorders and carcinogenesis (14).

Assisted reproductive techniques such as in vitro fertilization (IVF) commonly involve controlled ovarian stimulation to induce multiple follicular development and improve pregnancy outcomes (15). However, the supraphysiologic hormonal stimulation associated with fertility treatments has raised concerns regarding a possible long-term increase in ovarian cancer risk(16). Despite advances in surgical and chemotherapeutic management, ovarian cancer continues to have poor survival outcomes, emphasizing the importance of identifying contributing risk factors and underlying mechanisms.

The role of fertility treatments remains controversial. Ovulation induction agents and assisted reproductive technologies may increase ovarian stimulation, the observed cancer risk may be more closely linked to the underlying infertility condition rather than treatment exposure itself (17). Confounding factors including age, parity, obesity, diabetes, and lifestyle characteristics further complicate interpretation.

Given these complexities, the present 10-year ropspective cohort study aims to evaluate the association between infertility and ovarian cancer by examining demographic, metabolic, reproductive, and treatment-related factors. The study specifically compares baseline characteristics between infertile and non-infertile women, analyzes infertility types and etiologies in relation to ovarian cancer occurrence, and assesses the impact of fertility treatments and drug exposure on cancer risk.

## MATERIALS AND METHODS

This study was designed as a prospective hospital-based comparative observational study conducted over a 10-year period (March 2016 to March 2026) at the Medical Health and Research Institute, Telangana, India, in collaboration with MNJ Institute of Oncology and Regional Cancer Centre. A total of 1,000 women with histopathologically confirmed ovarian cancer and complete reproductive, infertility, and treatment records were included in the study. Among these, 150 women had a documented history of infertility and prior fertility treatment exposure, whereas 850 women had no history of infertility and served as the comparison group. Reproductive, metabolic, infertility-related, treatment-related, and molecular characteristics were prospectively evaluated and compared according to infertility status.

Women aged ≥18 years with complete clinical, reproductive, infertility, IVF, and treatment-related records were eligible for inclusion. Patients with incomplete medical documentation, previous malignancies, or Patients with previously diagnosed hereditary cancer syndromes other than those identified during study-related molecular evaluation were excluded. Data were prospectively retrieved from hospital medical records, oncology register, infertility clinic databases, and assisted reproductive technology (ART) records using a standardized data abstraction protocol with cross-verification to ensure data accuracy and consistency.

Comprehensive demographic, metabolic, reproductive, infertility-related, treatment-related, and molecular parameters were evaluated. Demographic variables included age, residence, educational status, marital duration, and socioeconomic background. Lifestyle and metabolic parameters assessed comprised smoking status, alcohol consumption, physical activity, body mass index (BMI), diabetes mellitus, hypertension, dyslipidemia, and thyroid disorders. Reproductive variables included parity, age at first pregnancy, menstrual regularity, miscarriage history, hormonal contraceptive use, and duration of infertility.

Detailed infertility profiling was performed, including classification into primary and secondary infertility, duration of infertility, and etiological subtypes such as polycystic ovary syndrome (PCOS), endometriosis, tubal factor infertility, diminished ovarian reserve, unexplained infertility, and male factor infertility. Among women with infertility, prior exposure to fertility treatment modalities before ovarian cancer diagnosis was evaluated, including ovulation induction, intrauterine insemination (IUI), and in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI). IVF outcomes were further categorized into women who successfully conceived following ART procedures and those who failed to conceive despite IVF treatment. Additional treatment-related parameters included number of treatment cycles, repeated ovarian stimulation exposure, and fertility drug utilization, including clomiphene citrate, human menopausal gonadotropins (HMG), and GnRH agonists.

To explore the molecular basis underlying infertility-associated ovarian carcinogenesis, Molecular and proteomic analyses were performed in a selected subset of infertility-associated ovarian cancer cases for which archived tissue samples and molecular data were available. BRCA mutation profiling was undertaken to assess hereditary susceptibility, including evaluation of BRCA1 and BRCA2 mutation status among women with prior infertility treatment exposure. Furthermore, extracellular matrix-associated molecular alterations were investigated with particular emphasis on Tenascin family proteins, especially Tenascin-X (TNXB), along with related proteins including Laminin-β1, MLLT4, and ZC3H13. These biomarkers were analyzed for their potential involvement in chronic inflammation, extracellular matrix remodeling, angiogenesis, cellular adhesion, and infertility-associated endometriosis-related ovarian tumorigenesis.

The primary study outcome was the distribution of infertility related characteristics among women diagnosed with ovarian cancer in relation to infertility status, infertility etiology, IVF outcomes, fertility treatment exposure, and molecular abnormalities including BRCA mutations and Tenascin expression profiles. To reduce potential bias, standardized diagnostic criteria and operational definitions were uniformly applied throughout the study.

Major confounding variables including age, parity, BMI, metabolic disorders, and associated comorbidities were incorporated into the statistical analysis.

Statistical analysis was performed using SPSS software (version XX; IBM Corp., Armonk, NY, USA), with continuous variables expressed as mean ± standard deviation and categorical variables as frequencies and percentages. Group comparisons were conducted using the chi-square test or Fisher's exact test, and a two-tailed p-value < 0.05 was considered statistically significant. Comparative proportions were evaluated using Chi-square or Fisher's exact test. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were calculated where appropriate to estimate the association between infertility-related variables and ovarian cancer occurrence. The study protocol was approved by the Institutional Ethics Committee of Medical Health and Research Institute and collaborating centers, and due to the prospective nature of the study, a waiver of informed consent was granted. All data were anonymized, and patient confidentiality was maintained in accordance with institutional policies and international ethical guidelines.

## RESULTS

Among women diagnosed with ovarian cancer, those with a history of infertility demonstrated significantly different demographic, metabolic, and reproductive characteristics compared with women without infertility. A higher proportion of infertile women were aged 30–39 years ($p = 0.02$) and had longer marital duration ≥10 years ($p = 0.008$), suggesting delayed childbearing. Higher educational attainment was also more frequent ($p = 0.01$).

Metabolic factors such as obesity (BMI ≥30 kg/m², $p < 0.001$) and physical inactivity ($p = 0.02$) were more prevalent, along with comorbidities including diabetes ($p = 0.03$), dyslipidemia ($p = 0.02$), and thyroid disorders ($p = 0.04$).

Reproductive characteristics such as nulliparity ($p = 0.003$), delayed age at first pregnancy ($p = 0.006$), irregular menstrual cycles ($p < 0.001$), and miscarriage history ($p = 0.02$) were also significantly more common.

Collectively, these findings demonstrate that ovarian cancer patients with a history of infertility exhibit a distinct metabolic, endocrine, and reproductive profile compared with ovarian cancer patients without infertility as shown in Table 1, Figure 1 and Figure 2.

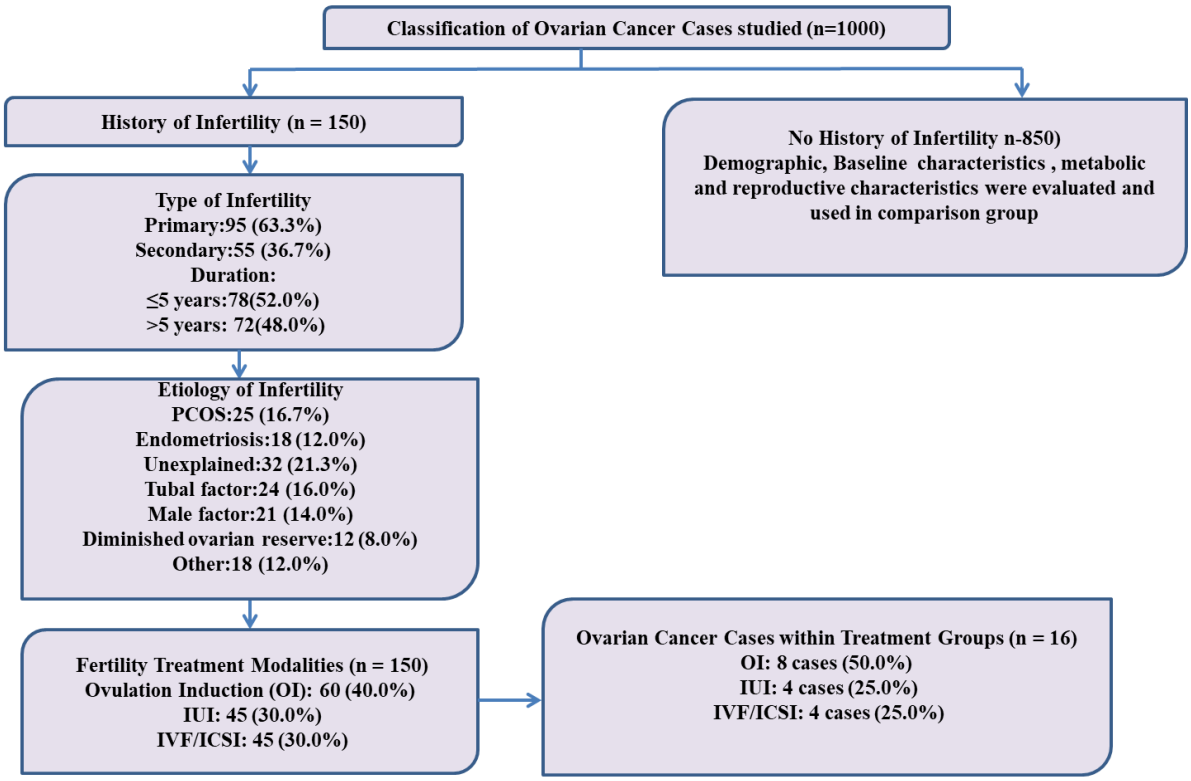


**Figure 1: Overview of workflow**

**Table 1: Baseline Characteristics and Predisposing Factors among Patients with Ovarian Cancer (10-year prospective Study, n = 1000)**

| Variable | History of Infertility (n=150) | No Infertility (n=850) | p-value |
|---|---|---|---|
| Age (years) | | | 0.02 |
| 20–29 | 42 (28.0%) | 330 (38.8%) | |
| 30–39 | 78 (52.0%) | 370 (43.5%) | |
| ≥40 | 30 (20.0%) | 150 (17.7%) | |
| Residence | | | 0.11 |
| Urban | 95 (63.3%) | 480 (56.5%) | |
| Rural | 55 (36.7%) | 370 (43.5%) | |
| Education | | | 0.01 |
| Secondary | 80 (53.3%) | 560 (65.9%) | |
| Higher | 70 (46.7%) | 290 (34.1%) | |
| Marital duration ≥10 yrs | 90 (60.0%) | 410 (48.2%) | 0.008 |
| Lifestyle Factors | | | |
| Smoking | 18 (12.0%) | 70 (8.2%) | 0.12 |
| Alcohol | 12 (8.0%) | 55 (6.5%) | 0.48 |
| Physical inactivity | 60 (40.0%) | 260 (30.6%) | 0.02 |
| BMI ≥30 kg/m² | 38 (25.3%) | 125 (14.7%) | <0.001 |
| Comorbidities | | | |
| Diabetes | 20 (13.3%) | 65 (7.6%) | 0.03 |
| Hypertension | 22 (14.7%) | 85 (10.0%) | 0.09 |
| Dyslipidemia | 24 (16.0%) | 80 (9.4%) | 0.02 |
| Thyroid disorders | 18 (12.0%) | 60 (7.1%) | 0.04 |
| Reproductive History | | | |
| Nulliparity | 65 (43.3%) | 260 (30.6%) | 0.003 |
| Parity ≥2 | 44 (29.3%) | 330 (38.8%) | 0.03 |

| | | | |
|---|---|---|---|
| Age ≥30 at first pregnancy | 63 (42.0%) | 255 (30.0%) | 0.006 |
| Irregular cycles | 52 (34.7%) | 95 (11.2%) | <0.001 |
| Miscarriage history | 28 (18.7%) | 95 (11.2%) | 0.02 |
| Hormonal contraceptive use | 40 (26.7%) | 300 (35.3%) | 0.04 |

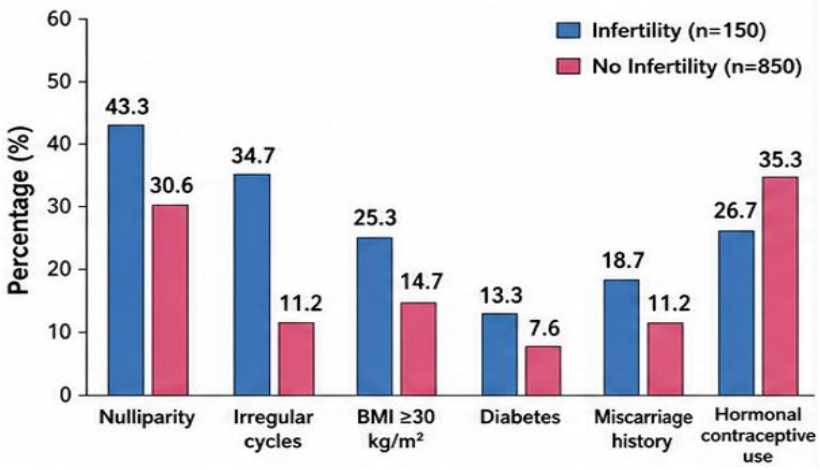


**Figure 2: Baseline and Reproductive Characteristics among Women with and Without History of Infertility**

Among ovarian cancer patients with a history of infertility (n = 150), 150 women had documented fertility treatment exposure histories, of whom 60 had undergone ovulation induction, 45 intrauterine insemination, and 45 IVF/ICSI. A higher proportion of these cases occurred among women with primary infertility and those with longer duration (>5 years).

With respect to etiology, a greater number of cases were observed among women with unexplained infertility and diminished ovarian reserve, while no cases were identified in male factor infertility.

Among the 16 ovarian cancer cases identified in women with infertility, unexplained infertility represented the largest etiological subgroup (43.8%), followed by diminished ovarian reserve (18.8%), endometriosis (12.5%), and tubal factor infertility (12.5%). These findings describe the distribution of infertility etiologies among ovarian cancer cases and do not establish causality or relative risk as shown in Table 2, Figure 3 and Figure 4.

**Table 2: Distribution of Infertility Etiologies among Ovarian Cancer Cases with History of Infertility (n = 16)**

| Infertility Etiology | Ovarian Cancer Cases (n) | Percentage (%) |
|---|---|---|
| Unexplained infertility | 7 | 43.8 |
| Diminished ovarian reserve | 3 | 18.8 |
| Endometriosis | 2 | 12.5 |
| Tubal factor infertility | 2 | 12.5 |
| PCOS | 1 | 6.3 |
| Other causes | 1 | 6.3 |
| Male factor infertility | 0 | 0 |
| Total | 16 | 100 |

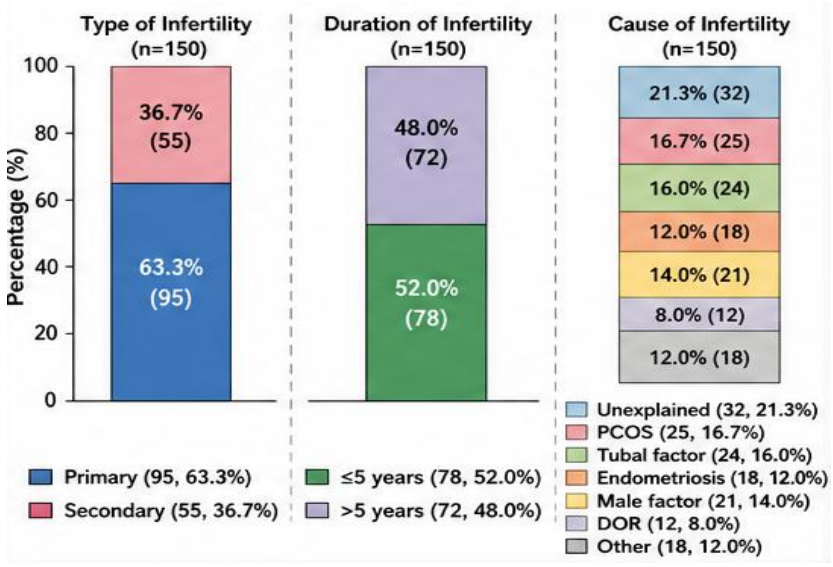


**Figure 3: Distribution of Infertility Characteristics among Infertile Women (n = 150)**

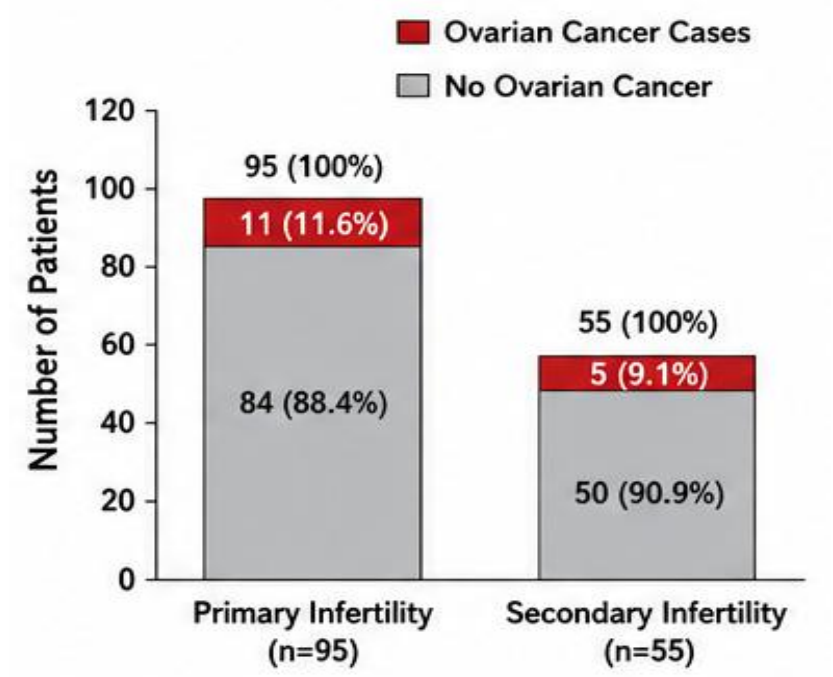


**Figure 4: Occurrence of Ovarian Cancer within Infertility Subgroups (n = 150)**

The classification of ovarian cancer cases according to infertility history and fertility treatment exposure in this 10-year prospective cohort study (March 2016–March 2026). Among the 1,000 women included in the study, 150 had a history of infertility and 850 had no documented history of infertility. Demographic, baseline, metabolic, and reproductive characteristics were evaluated in both groups.

Among women with a history of infertility, 95 (63.3%) had primary infertility and 55 (36.7%) had secondary infertility. The duration of infertility was ≤5 years in 78 women (52.0%) and >5 years in 72 women (48.0%). The etiological factors identified included unexplained infertility (21.3%), PCOS (16.7%), tubal factor infertility (16.0%), male factor

infertility (14.0%), endometriosis (12.0%), other causes (12.0%), and diminished ovarian reserve (8.0%).

Regarding fertility treatment exposure, 60 women (40.0%) underwent ovulation induction (OI), 45 (30.0%) underwent intrauterine insemination (IUI), and 45 (30.0%) underwent in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI). Conception occurred in 25 women receiving OI, 20 women receiving IUI, and 18 women receiving IVF/ICSI, while 35, 25, and 27 women, respectively, did not conceive following treatment.

Among the 150 women with infertility, 16 ovarian cancer cases were identified during the study period. These cases were distributed across fertility treatment categories according to prior treatment exposure. Ovarian cancer occurred in 8 of 60 women who underwent ovulation induction (13.3%), 4 of 45 women who underwent IUI (8.9%), and 4 of 45 women who underwent IVF/ICSI (8.9%).

Among infertile women with ovarian cancer, ovarian cancer cases were identified in 8 women exposed to OI, 4 exposed to IUI, and 4 exposed to IVF/ICSI, corresponding to proportions of 13.3%, 8.9%, and 8.9% within each treatment group, respectively. Women were classified according to the most advanced fertility treatment modality received before ovarian cancer diagnosis. These findings summarize the infertility characteristics, fertility treatment modalities, conception outcomes, and treatment-specific distribution of ovarian cancer cases within the study population as shown in Figure 5.

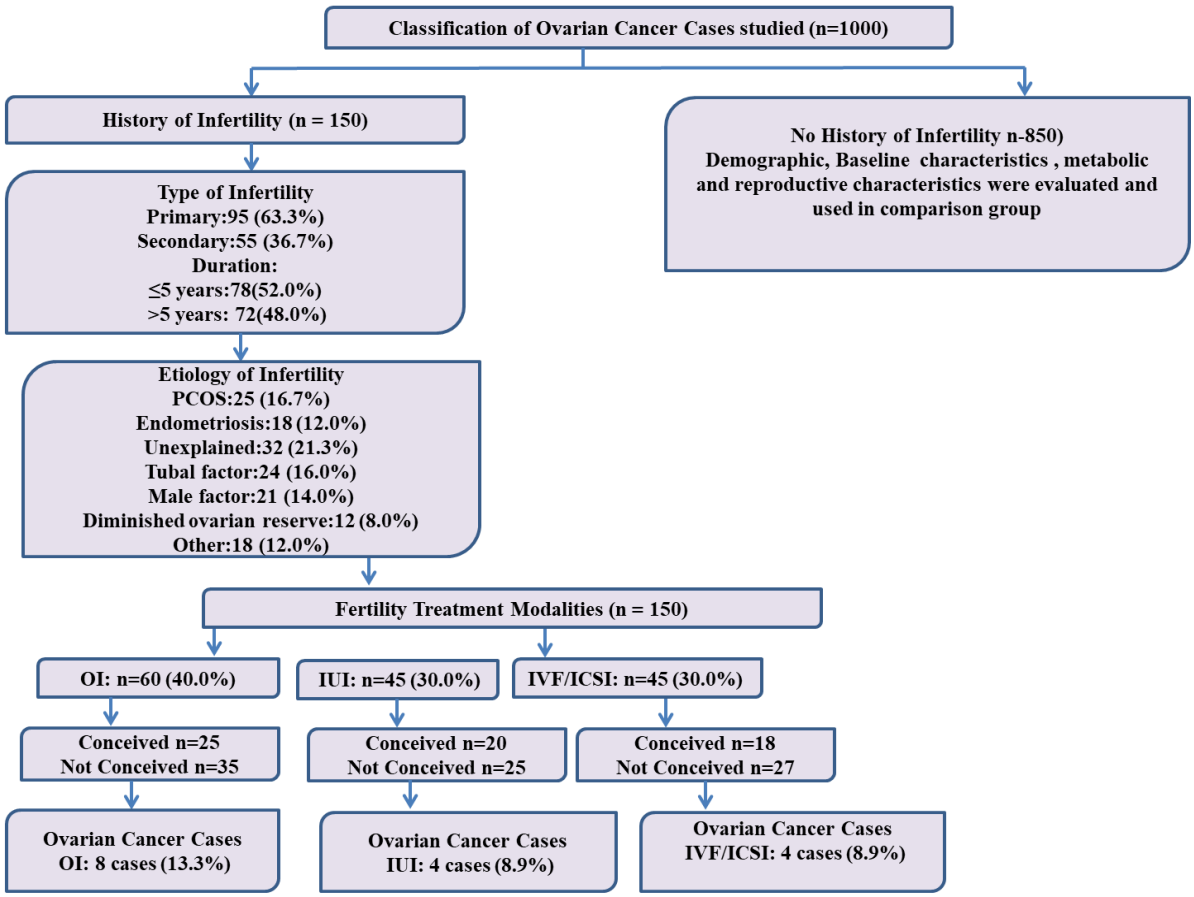


**Figure 5: Classification of ovarian cancer patients according to infertility history, infertility characteristics, fertility treatment exposure, and ovarian cancer distribution**

Among the 150 women with infertility, ovulation induction was the most commonly utilized treatment modality (40.0%), followed by intrauterine insemination (IUI) (30.0%) and in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) (30%).

A total of 16 ovarian cancer cases were identified, distributed in the treatment history: 8 cases (13.3%) occurred among women who underwent ovulation induction, while 4 cases each (8.9%) were observed in the IUI and IVF/ICSI groups. Among the 16 ovarian cancer cases identified in infertile women, 8 had prior exposure to ovulation induction, 4 to IUI, and 4 to IVF/ICSI. Of these cases, 4 women had achieved conception following treatment, whereas 12 had failed to conceive. The majority of ovarian cancer cases occurred among women who remained nulliparous despite fertility treatment**.** Although the highest number of ovarian cancer cases was noted in the ovulation induction group, this likely reflects the higher utilization of this modality rather than indicating a causal association. Importantly, no disproportionate clustering of cases was observed among women undergoing advanced assisted reproductive techniques such as IVF/ICSI.

The distribution of ovarian cancer cases across fertility treatment modalities did not demonstrate a marked concentration within any specific treatment group; however, statistical comparisons were not significant and subgroup numbers were small, and the observed distribution is more consistent with underlying treatment patterns rather than treatment-specific risk as shown in **Table 3 and Figure 6.**

**Table 3: Fertility Treatment Outcomes among Infertile Women who subsequently Developed Ovarian Cancer (n=16)**

| Treatment Modality | Conceived (n) | Failed to Conceive (n) | Total Ovarian Cancer Cases |
|---|---|---|---|
| Ovulation Induction | 2 | 6 | 8 |
| IUI | 1 | 3 | 4 |
| IVF/ICSI | 1 | 3 | 4 |
| Total | 4 | 12 | 16 |

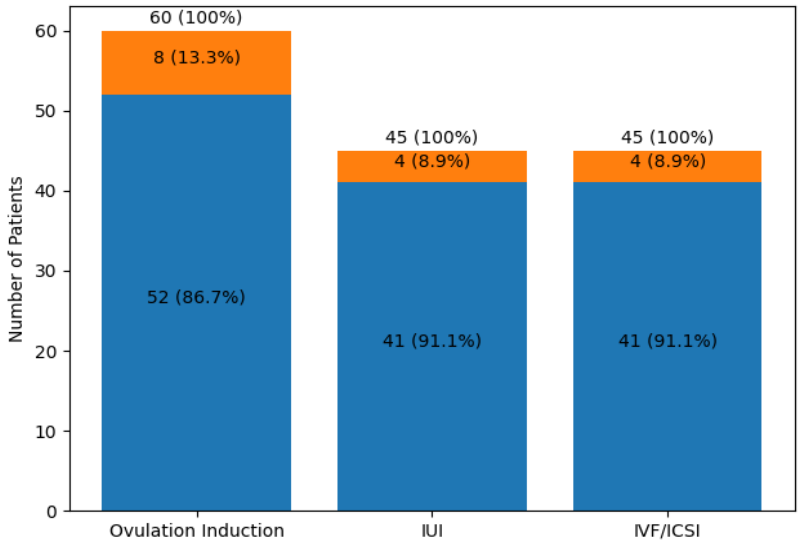


**Figure 6: Fertility treatment modalities and Ovarian cancer occurrence (n = 150)**

**Table 4: Distribution of Ovarian Cancer Cases by Type of Fertility Drug Exposure (n = 150)**

| Fertility Drug Exposure | Number of Women | Ovarian Cancer Cases (n) | Proportion of Ovarian Cancer Cases (%) |
|---|---|---|---|
| Clomiphene citrate | 40 | 3 | 7.5% |
| Clomiphene + HMG | 25 | 2 | 8.0% |
| HMG alone | 15 | 3 | 20.0% |
| HMG + GnRH agonist | 25 | 4 | 16.0% |
| ≥6 treatment cycles (any drug) regimen | 45 | 4 | 8.89% |

Variation in the proportion of ovarian cancer cases was observed across different fertility drug regimens. Numerically higher proportions of ovarian cancer cases were observed among women receiving gonadotropin-based regimens; however, these findings should be interpreted cautiously because of small subgroup sizes and potential confounding by infertility severity, particularly HMG alone and in combination with GnRH agonists, compared to clomiphene-based regimens.

However, these findings should be interpreted cautiously due to small subgroup sizes and the possibility that treatment choice reflects underlying infertility severity rather than a direct pharmacological effect.

However, given the relatively small sample sizes within subgroups, these findings should be interpreted with caution as shown in Table 4.

**Table 5: Occurrence of ovarian cancer cases according to Fertility Treatment Modality (n = 150)**

| Treatment | Total (n) | Ovarian Cancer Cases (n) | Proportion of Ovarian Cancer Cases (%) |
|---|---|---|---|
| Ovulation Induction | 60 | 8 | 13.33% |
| IUI (Reference) | 45 | 4 | 8.9% |
| IVF/ICSI | 45 | 4 | 8.9% |

The proportion of ovarian cancer cases was numerically higher among women who underwent ovulation induction (13.3%) compared with IUI (8.9%) and IVF/ICSI (8.9%). However, these findings should be interpreted cautiously because of the small subgroup sizes and the absence of statistically significant differences

These findings are consistent with previous evidence suggesting that underlying infertility-related factors may play a more significant role than treatment exposure alone as shown in Table 5 and Figure 7.

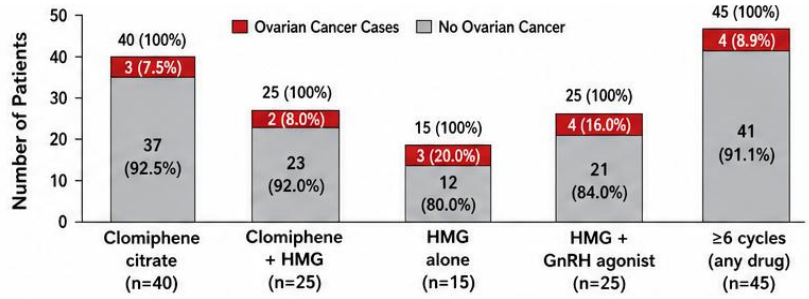


**Figure 7: Fertility Drug Exposure and Occurrence of Ovarian Cancer among Infertile Women (n = 150)**

**Table 6: Distribution of BRCA Mutations among Ovarian Cancer Patients with History of Infertility Treatment (n = 16)**

| BRCA Status | Number (n) | Percentage (%) |
|---|---|---|
| BRCA1 Positive | 5 | 31.25 |
| BRCA2 Positive | 2 | 12.50 |
| BRCA1 + BRCA2 Positive | 1 | 6.25 |
| BRCA Negative | 8 | 50.00 |
| Total Tested | 16 | 100.00 |

Among the 16 ovarian cancer patients with a history of infertility treatment who underwent molecular evaluation, BRCA pathogenic variants were identified in 8 patients (50.0%). BRCA1 mutations were the most frequently detected abnormality, occurring in 5 patients (31.25%), followed by BRCA2 mutations in 2 patients (12.5%). Concurrent BRCA1 and BRCA2 mutations were observed in 1 patient (6.25%). The remaining 8 patients (50.0%) were negative for BRCA mutations. These findings suggest a predominance of BRCA1-associated hereditary susceptibility among infertility-associated ovarian cancer cases evaluated in the present study as shown in Table 6

**Table 7: Differential Proteomic Expression of Extracellular Matrix-Associated Proteins in Infertility-Associated Endometriosis**

| Accession Number | Protein Description | Gene Symbol | Subcellular Localization | Protein Score | Fold Change | Possible Biological Significance |
|---|---|---|---|---|---|---|
| A0A087WWA5 | Tenascin-X | TNXB | Extracellular matrix protein | 26.79 | 7.27 | Associated with extracellular matrix remodeling, chronic inflammation, angiogenesis, cellular adhesion, tissue invasion, and possible ovarian epithelial transformation |

| | | | | | | |
|---|---|---|---|---|---|---|
| Q96C95 | MLLT4 protein (Fragment) | MLLT4 | Cytoplasmic/Cell adhesion related | 46.29 | 2.23 | May contribute to abnormal cellular migration, adhesion, and invasive mechanisms |
| A0PJJ2 | ZC3H13 protein (Fragment) | ZC3H13 | Nucleus | 165.38 | 2.02 | Involved in cellular signaling and regulation of inflammatory pathways |
| A0A7I2V4J9 | Laminin subunit beta-1 | LAMB1 | Extracellular membrane, extracellular matrix, basement membrane | 8.54 | 2.42 | Associated with extracellular matrix integrity, tissue remodeling, and tumor microenvironment alterations |

The observed distribution of ovarian cancer cases among women with unexplained infertility and endometriosis may be biologically supported by molecular evidence demonstrating dysregulated extracellular matrix remodeling and inflammatory pathway activation. Complementary proteomic analysis conducted at the collaborating Medical Health and Research Institute demonstrated significant overexpression of extracellular matrix-associated proteins in infertile women with severe endometriosis, particularly Tenascin-X (TNXB), which showed an approximately seven-fold increase in expression levels compared with controls. Additional proteins identified with increased expression included MLLT4, ZC3H13, and Laminin subunit-β1, all of which are involved in cellular adhesion, tissue remodeling, migration, inflammatory signaling, and angiogenesis as shown in Table 7.

## DISCUSSION

The present 10-year prospective study demonstrated distinct differences in reproductive and metabolic characteristics between women with ovarian cancer who had a history of infertility and compared with those without infertility among those evaluated during the study period. Women with infertility had distinct endocrine, metabolic, and reproductive characteristics including prolonged marital duration, nulliparity, obesity, irregular menstrual cycles, thyroid dysfunction, diabetes, and dyslipidemia. Similar observations were reported by Hanson et al.[6] described female infertility as a heterogeneous condition associated with several reproductive disorders and comorbidities, supporting the multifactorial pattern observed in our study.

In our study, Women aged 30–39 years constituted the largest subgroup among infertile women with ovarian cancer, suggesting a potential link between delayed parity, prolonged infertility duration, and malignancy. Smolarz et al. explained that repeated ovulatory cycles and uninterrupted ovarian epithelial repair may increase susceptibility to malignant transformation through the “incessant ovulation” mechanism (Smolarz et al.,

2025) [18]. The significantly higher prevalence of nulliparity and delayed first pregnancy observed in the present cohort further supports this hypothesis.

Among the 150 women with infertility, 16 ovarian cancer cases were identified. Unexplained infertility was the largest etiological subgroup, accounting for 43.8% of cases, followed by diminished ovarian reserve (18.8%). Endometriosis and tubal factor infertility each accounted for 12.5% of cases. Rizzuto et al.[20], in their systematic review, emphasized the difficulty in distinguishing the effects of underlying infertility from the effects of ovarian-stimulating treatment when evaluating ovarian cancer outcomes. Our findings similarly suggest that unexplained infertility may represent an important clinical characteristic among women with infertility-associated ovarian cancer, although the present results do not establish a causal relationship.

Endometriosis was identified in 12.5% of infertility-associated ovarian cancer cases in our study. Barnard et al.[3] recently reported that endometriosis is associated with an increased risk of ovarian cancer, with particularly strong associations observed in specific forms of endometriosis, including deep infiltrating disease and ovarian endometriomas. Similarly, Steinbuch et al.[11] highlighted the roles of chronic inflammation, oxidative stress, hormonal alterations, and molecular changes in the development of endometriosis-associated ovarian cancer. These observations provide biological support for the presence of endometriosis among ovarian cancer cases in our cohort, although the small number of cases prevents conclusions regarding its independent contribution to cancer risk.

The molecular findings of our study provide additional insight into the potential biological mechanisms underlying infertility-associated endometriosis. Proteomic analysis demonstrated increased expression of extracellular matrix-associated proteins, with TNXB showing the greatest increase at approximately 7.27-fold. Increased expression of MLLT4, ZC3H13, and Laminin-ß1 was also observed. These proteins are involved in extracellular matrix remodeling, cellular adhesion, migration, inflammatory signaling, and angiogenesis. Steinbuch et al.[11] described alterations in inflammatory pathways and the tumor microenvironment as important mechanisms in endometriosis-associated ovarian carcinogenesis. Therefore, the increased expression of TNXB and related proteins observed in our study may represent a potential molecular link between chronic inflammation, tissue remodeling, and ovarian epithelial transformation. Nevertheless, these findings should be considered exploratory and require validation in larger molecular studies.

The association between fertility treatment and ovarian cancer remains an important area of investigation. In our study, ovarian cancer occurred in 8 of 60 women who underwent ovulation induction (13.3%), compared with 4 of 45 women who underwent IUI (8.9%) and 4 of 45 women who underwent IVF/ICSI (8.9%). Although the proportion was numerically higher in the ovulation induction group, the difference was not statistically significant. Importantly, no disproportionate concentration of ovarian cancer cases was observed among women undergoing IVF/ICSI.

Li et al.[17] reported in a recent meta-analysis that the relationship between ovarian-stimulating drugs and ovarian tumor development remains complex and may be influenced by factors related to infertility and reproductive history. Likewise, the Practice Committee of the American Society for Reproductive Medicine et al.[6] emphasized that the effects of fertility treatment are difficult to separate from underlying infertility, endometriosis, and nulliparity. These observations are consistent with our findings, in which

ovarian cancer occurrence was not disproportionately concentrated among women receiving IVF/ICSI. Therefore, our results do not support a direct causal association between advanced fertility treatment and ovarian cancer.

When fertility drug exposure was examined, numerically higher proportions of ovarian cancer cases were observed among women receiving HMG alone or HMG combined with a GnRH agonist. However, these findings should be interpreted cautiously because of the small number of women and ovarian cancer cases within each subgroup. Women receiving more intensive ovarian stimulation may have more severe or persistent infertility, which makes it difficult to separate the possible effect of treatment from the underlying reproductive condition. This limitation was also emphasized by Li et al.[17], whose analysis highlighted the importance of confounding factors when interpreting associations between ovarian-stimulating drugs and ovarian tumor occurrence.

Another notable finding was that 12 of the 16 infertile women who developed ovarian cancer failed to conceive following fertility treatment, whereas only 4 achieved conception. Thus, the majority of ovarian cancer cases occurred among women with persistent infertility despite treatment. Rizzuto et al.[20] similarly emphasized the importance of underlying infertility when evaluating cancer outcomes following fertility treatment. In our cohort, persistent infertility and continued nulliparity appeared to be important characteristics of women who subsequently developed ovarian cancer. However, because of the limited number of cases, no causal conclusion can be drawn.

Molecular analysis identified BRCA pathogenic variants in 8 of the 16 infertility-associated ovarian cancer cases evaluated. BRCA1 mutations were identified in 5 women, BRCA2 mutations in 2 women, and concurrent BRCA1 and BRCA2 mutations in 1 woman. The predominance of BRCA1 among mutation-positive cases suggests that hereditary susceptibility may contribute to ovarian cancer development in a subset of women with infertility and previous fertility treatment exposure. Molecular profiling showed increased prevalence of BRCA pathogenic variants among ovarian cancer patients with infertility treatment exposure with BRCA1 predominating over BRCA2, consistent with hereditary risk patterns [18] However, molecular analysis was limited to a small number of cases, and these findings should therefore be considered exploratory.

Proteomic evaluation identified significant upregulation of extracellular matrix-related proteins, notably Tenascin-X (TNXB), in endometriosis-associated infertility. Additional overexpressed proteins included Laminin-β1, MLLT4, and ZC3H13, which are implicated in dysregulated extracellular matrix remodeling, angiogenesis, inflammatory signaling, tissue invasion, and cellular adhesion. Wendel JR et al. highlighted that extracellular matrix dysregulation and altered tumor microenvironment signaling are critical molecular mechanisms linking endometriosis and ovarian cancer development [19]. The nearly seven-fold increase in TNXB expression observed in the present study suggests that extracellular matrix remodeling may represent an important molecular bridge connecting chronic infertility-associated inflammation with ovarian epithelial transformation.

Overall, the present study supports a multifactorial interpretation of infertility-associated ovarian cancer. Persistent infertility, nulliparity, delayed reproductive events, metabolic abnormalities, endometriosis, and genetic susceptibility were important characteristics identified in our study population. Barnard et al.[12] and Steinbuch et al.[11] provide recent evidence supporting the biological relationship between endometriosis and

ovarian cancer, while Li et al.[17] and the Practice Committee of the American Society for Reproductive Medicine et al.[21] highlight the difficulty of separating fertility treatment effects from underlying infertility and reproductive factors. Taken together, our findings suggest that the underlying biological and reproductive characteristics of infertile women may be more relevant to ovarian cancer occurrence than fertility treatment exposure alone. Larger prospective multicentric studies with detailed characterization of infertility etiology, treatment exposure, genetic susceptibility, and long-term follow-up are required to clarify these relationships.

The present study has several strengths including its large sample size, long observational duration, comprehensive infertility characterization, inclusion of fertility treatment variables, and integration of molecular and proteomic analyses. Nevertheless, certain limitations should be acknowledged. The prospective study design limits causal interpretation and may introduce selection bias. Some treatment and molecular subgroups contained relatively small sample sizes, reducing statistical power. Residual confounding related to environmental exposures, genetic susceptibility, and lifestyle factors may also exist. Additionally, the tertiary referral setting may limit generalizability of findings to the broader population.

Overall, the present findings suggest that infertility-associated ovarian cancer risk is multifactorial and appears to be driven predominantly by underlying endocrine, inflammatory, reproductive, and genetic abnormalities rather than fertility treatment exposure alone. Chronic inflammatory conditions such as endometriosis, unexplained infertility, metabolic dysfunction, oxidative stress, and extracellular matrix remodeling may collectively contribute to ovarian carcinogenesis. Further prospective multicentric studies integrating genomic, proteomic, and long-term clinical follow-up are warranted to better elucidate the biological mechanisms linking infertility and ovarian cancer.

## Data Availability Statement

The datasets analyzed in this study are not publicly available but are available from the corresponding author upon reasonable request. Requests to access the datasets should be directed to Dr.Roya Rozati, drroyarozati@gmail.com

## Ethics Statement

Medical Ethics Committee of Medical Health and Research Institute. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin due to the prospective nature of this study. All patient data were fully anonymized prior to analysis.

## Author Contributions

RR: Validation, Visualization, Writing – original draft, Formal analysis, Software, Writing – review & editing. YL: Data curation, Methodology, Writing – original draft. WT,TNA: Conceptualization, Data curation, Writing – review & editing. AGM: Data curation,

Supervision, Writing – review & editing. VAA: Formal analysis, Investigation, Writing – original draft. RR: Conceptualization, Funding acquisition, Project administration, Writing – review & editing.

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**Abbreviations**

BRCA, breast cancer gene 1/2; BMI, body mass index; GnRH, gonadotropin-releasing hormone; HMG, human menopausal gonadotropin; IUI, intrauterine insemination; IVF/ICSI, in vitro fertilization/intracytoplasmic sperm injection; PCOS, polycystic ovary syndrome; TNXB, Tenascin-X.

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**Conflict of Interest**

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Generative AI Statement**

The author(s) declared that generative AI was not used in the creation of this manuscript. Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

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