Research Article ISSN 2639-9342

Gynecology & Reproductive Health

Infertility, Treatment and The Link to Cancer

Roya Rozati[1]*, Wajeeda Tabasum[2], Vikram Aiman Ayapati MD[2], Gautam Mehdi Ayapati[2], Mahnasee Banu[3], Rasheeda Khatoon[3], Kajjam Vani[3], Mohammed Sarosh Ahmed[4], Rajesh Neeluri[5], Anga Venkata Suresh[6], Abid Ali[7] and Muhammad Siddique Ahmed Khan[8]

[1]*Dept of Obst & Gynec, Shadan Institute of Medical Sciences, Medical and Research Director, Medical Health and Research Institute (MHRI), Hyderabad.*

[2]*Research Scholar, Medical Health and Research Institute (MHRI), Hyderabad.*

[3]*MS-OBGY, Shadan Institute of Medical Sciences.*

[4]*Associate Professor, Deccan College of Medical Sciences, Hyderabad.*

[5]*Professor, Malla Reddy Medical College for Women, Hyderabad.*

[6]*Associate Professor, Gayatri Vidya Parishad Institute of Health Care & Medical Technology, Andhra Pradesh.*

[7]*Assistant Professor, Bhaskar Medical College, Hyderabad.*

[8]*Professor HOD, Department of Biochemistry, Shadan Institute of Medical Sciences, Hyderabad.*

***Correspondence:**
Roya Rozati, Professor and HOD, Department of Obstetrics & Gynaecology, Shadan Institute of Medical Sciences, Medical and Research Director, Medical Health and Research Institute (MHRI), Hyderabad, Telangana, India.

Received: 01 Nov 2024; **Accepted:** 20 Dec 2024; **Published:** 03 Jan 2025

Citation: Roya Rozati, Wajeeda Tabasum, Gautam Mehdi Ayapati, et al. Infertility, Treatment and The Link to Cancer. Gynecol Reprod Health. 2025; 9(1): 1-7.

ABSTRACT

Background: *Ovarian, Breast, and Endometrial cancers are linked to various risk factors, including low parity, infertility, early menarche, and late menopause.*

The objective of this study is to evaluate the potential link between infertility and cancer in patients and to examine whether this association is due to genetic factors or the effects of treatments received.

Methodology: *It is a retrospective, hospital-based study conducted at MHRI Hospital and Research Centre in Hyderabad from January 2019 to January 2024. The study included 105 women with endometrial cancer, 950 with ovarian cancer, and 60 with breast cancer, all of whom had a history of infertility were 135 patients.*

Results: *Our study enrolled 1,115 patients, diagnosed with ovarian (n=950), endometrial (n=105), and breast cancer (n=60). Among the cohort of Cancer patients, 135 patients reported a history of infertility, Of which 67 patients have undergone treatment with Clomiphene Citrate, ovulation induction with more than 6 cycles of which 32 (48%) conceived and 35(52%) patients did not conceive and 68 patients had undergone IVF treatment between 2-6 cycles, and of which 22 (32%) patients have successfully conceived and 46 (68%) patients did not conceive. Regarding IVF outcomes, 22 women successfully conceived following multiple cycles. This study revealed variability in reproductive outcomes, with ovulatory disorders, polycystic ovary syndrome (PCOS), and unexplained infertility identified as the most prevalent causes of infertility.*

The mean age at cancer diagnosis was 50-55 years for ovarian cancer, 44-49 years for breast cancer, and 55-60 years for endometrial cancer. Among the infertile patients, 10 had Male factor, 32 had ovulatory disorders, 33 had PCOS, 20 had Obesity, 16 had Endometriosis and 24 had unexplained infertility.

Conclusion: *This study highlights the complex interplay between infertility, fertility treatments, and cancer risk. A notable proportion of ovarian cancer patients reported a history of infertility, particularly those with ovulatory dysfunction, polycystic ovary syndrome*

(PCOS), and unexplained infertility both of which may contribute to both infertility and an increased risk of cancer. While ovulation induction with Clomiphene Citrate and IVF yielded partial success in achieving pregnancy, infertility remained a persistent challenge for many, underscoring the variability in reproductive outcomes may be due to Genetic background.

The findings suggest that prolonged infertility, particularly when associated with hormonal imbalances such as those seen in PCOS and ovulatory disorders, may elevate the risk of certain malignancies. Further research is required to explore the long-term effects of fertility treatments, particularly Clomiphene Citrate, on cancer risk. Additionally, studies should investigate the mechanisms by which infertility, especially in the context of hormonal dysregulation, may contribute to carcinogenesis, particularly in ovarian, endometrial, and breast cancers.

Keywords
Infertility, Assisted Reproductive Technology, *In vitro* Fertilization, Intracytoplasmic sperm injection, Fertility Drugs, Cancer.

Introduction
Infertility, defined as the inability to conceive after 12 months of regular, unprotected intercourse, affects approximately 20-25% of couples over the course of their lifetime [1]. Approximately 17% of infertility cases remain unexplained without an identified cause [2]. Infertility has been identified as a potential risk factor for several gynecological malignancies, such as Ovarian, Breast, and Endometrial cancers. Emerging evidence highlights a complex molecular relationship between infertility and cancer in women. Infertility has been linked to an elevated risk of specific cancers, including ovarian, endometrial, and breast cancers [3]. Dysregulations in the uterine molecular environment may contribute to the development of cancer by promoting abnormal cell growth, impairing DNA repair mechanisms, and disrupting hormonal balance. This is possibly due to lower parity and the use of exogenous hormones during infertility treatment. Lower parity is associated with a higher number of lifetime ovulatory cycles, which may increase the risk of ovarian cancer, Breast, and Endometrial, while parity is thought to reduce this risk by limiting the number of ovulatory cycles [4]. Unraveling the shared molecular mechanisms between infertility and cancer holds the potential to provide valuable insights into both conditions, enhancing diagnostic and therapeutic approaches [5].

The number of lifetime ovulatory cycles and consequently influences exposure to ovarian hormones, the number of ovulatory cycles reduces the risk of ovarian cancer, Breast, and Endometrial Cancer. Estrogen levels progressively increase during the follicular phase, peaking just before ovulation, and remain elevated throughout the luteal phase. In contrast, progesterone levels are low before ovulation and rise markedly following ovulation, during the luteal phase. In anovulatory cycles, ovulation fails to occur, and as a result, the luteal phase is absent. Women with infertility attributable to ovulatory disorders have fewer ovulatory cycles than fertile women, leading to reduced cumulative exposure to luteal-phase hormones over their lifetime. Furthermore, the use of exogenous hormones in infertility treatments, including gonadotropins and Clomiphene Citrate may modulate cancer risk, although the evidence remains inconclusive [6].

The prevalence of infertility is influenced by a combination of genetic, environmental, nutritional, and physiological factors. Key risk factors associated with subfertility include obesity, anovulation, excessive tobacco use, endometriosis, and nulliparity [7,8].

Assisted reproductive technologies (ARTs) utilize medications and procedures that may lead to ovarian trauma during oocyte retrieval and induce multiple ovulations. These interventions result in elevated levels of sex hormones, including estrogen, progesterone, and gonadotropins [9]. Since many female reproductive malignancies, such as breast and gynecologic cancers, are hormone-dependent, a potential association between ARTs and an increased risk of hormone-driven cancers is biologically plausible.

The long-term risks associated with fertility medications, particularly in relation to cancer, are a significant concern. Fertility treatments can induce multiple ovulations and alter steroidogenesis, even though they operate through various mechanisms. Given that certain cancers, including reproductive and breast cancers, are hormone-dependent, this offers a physiological basis for a potential link between the use of fertility medications and an elevated risk of these cancers. Despite these concerns, the safety of fertility treatments, particularly those involving hormone-based ovarian stimulation, remains a subject of ongoing debate. However, there is limited evidence regarding the long-term safety and potential cancer risks associated with these treatments.

Fertility Drugs
Ovarian stimulating agents commonly used in the treatment of female infertility include selective estrogen receptor modulators (such as clomiphene citrate [CC]), GnRH analogs/agonists, human menopausal gonadotropin (hMG), progesterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and human chorionic gonadotropin (hCG). These medications are typically administered alone or in combination during the follicular phase of the menstrual cycle as part of assisted reproductive technology (ART) treatments. Changes in endogenous hormone levels resulting from the use of fertility drugs have raised significant concerns regarding the safety of these treatments. With the rising incidence of infertility and the subsequent increased use of fertility medications in recent years, investigating the long-term effects of these drugs has become critically important.

Breast Cancer
the most common malignancy among adult women worldwide, is a leading cause of cancer-related deaths. Women receiving hormone therapy are considered at higher risk for breast cancer due to the potential effects of hormone stimulation drugs. These medications

may activate gonadotropin-releasing hormones, increase estrogen levels, and potentially trigger the steroid receptor-related oncogenic pathways that promote tumor progression. Fertility medications, such as clomiphene citrate (CC) is of particular concern.

Ovarian Cancer

Ovarian cancer is a multifactorial disease with a complex etiology, frequently diagnosed at advanced stages. There is an Increased risk due to low parity [10], late onset of menopause [11], Oral contraceptive use [12].

Endometrial Cancer

Endometriosis is the subtype of infertility with more agreement and is associated with the risk of Cancer.

Clomiphene Citrate

Clomiphene citrate and other fertility drugs have been hypothesized to contribute to defects in epithelial lining and ovarian capsule damage, potentially increasing the risk of cancer development, particularly ovarian cancer [13]. Repeated ovulation induced by these drugs may lead to trauma to the ovarian surface epithelium and invagination of the underlying stroma, predisposing women to malignant transformation [14]. Additionally, the hormonal changes associated with these drugs may play a role in increasing the risk of breast cancer [15]. The proposed link between ovulation-stimulating drugs, epithelial disruption, and ovarian cancer warrants further investigation to elucidate the underlying mechanisms [16]. It is a selective estrogen receptor modulator, that inhibits the negative feedback on gonadotropin release, thereby promoting estrogen production and inducing ovulation. Gonadotropins, including FSH, LH, and hCG, bind directly to receptors on ovarian follicular cells, stimulating ovarian activity. Clomiphene acts by blocking estrogen receptors in the hypothalamus, leading to an increase in gonadotropin secretion from the pituitary gland, which in turn enhances ovulation. This results in elevated levels of both estradiol and progesterone [17]. The increased hormone levels may promote breast cell proliferation, potentially establishing an inverse relationship between clomiphene. Clomiphene citrate (CC), the most commonly used ovulation induction drug, is known to increase the risk of ovarian hyperstimulation, and its long-term use may be associated with an increased risk of both ovarian and endometrial cancers [18]. As the number of women undergoing infertility treatments involving ovarian stimulation agents increases, the long-term effects of ovulation-inducing drugs on the risk of ovarian, breast, and endometrial cancers have become an important area of concern.

Materials and Methodology

This retrospective, hospital-based study was conducted at the MHRI Hospital and Research Centre in Hyderabad between January 2019 and January 2024. The study received approval from the institutional Ethics Committee, with the registration number ECR/1609/Inst/TG/2021. MHRI Hospital serves as a tertiary referral center, receiving patients from various institutions, including MNJ Cancer Hospital, Basavatarkaam Indo-American Cancer Hospital, Medicover Cancer Hospital, Apollo Hospital, and KIMS Hospital. We retrospectively recruited Endometrial Cancer (n = 105), Ovarian Cancer (n = 950), and Breast Cancer (n = 60), with 135 patients reporting a history of infertility. The study population consisted of women who presented to the IVF unit and underwent at least one treatment cycle. Infertility status was assessed at baseline and through follow-up questionnaires administered at regular intervals. Participants were queried regarding their attempts to conceive over the course of one year without success.

All participants were asked in the questionnaires that collected comprehensive demographic and clinical information, including age, marital status, history of infertility, details of infertility treatments received, duration of infertility treatment, the number of IVF cycles undertaken, and the number of cycles involving clomiphene citrate or gonadotropins. Additional data included the type of infertility diagnosis (e.g., tubal block, endometriosis, PCOS, anovulation, or obesity), the number of cycles of IVF or ovulation induction treatments administered, and whether infertility persisted despite treatment. In cases where a participant did not respond to this question, it was assumed that she had not used ovulation-induction drugs. If a participant answered affirmatively, she was classified as having used ovulation-induction therapy at least once during the follow-up period. Women who reported using ovulation-induction treatments were further asked to specify the type of medication used clomiphene citrate (CC). Comprehensive data were collected regarding demographic characteristics, including age for all participants. Additionally, detailed information was gathered on the type of infertility, the number of treatment cycles completed, and the corresponding treatment outcomes.

A total of 135 women, who were treated for infertility between January 2019 and January 2024 were followed for the development of cancer. Among them, 950 cases of ovarian cancer, 60 cases of breast cancer, and 105 cases of endometrial cancer were identified.

The study received approval from the institutional Ethics Committee, with the registration number ECR/1609/Inst/TG/2021.

Results

This study enrolled a total of 1,115 cancer patients across various cancer types ie Ovarian, Breast, and Endometrial Cancer, with detailed reproductive histories collected for each participant. The distribution of cancer types among the enrolled patients was as follows Endometrial Cancer (n = 105), Ovarian Cancer (n = 950), and Breast Cancer (n = 60). Among the cohort, 135 patients reported a history of infertility, Of which 67 patients have undergone treatment with Clomiphene Citrate, ovulation induction with more than 6 cycles ,of which 32 conceived (48%) and 35(52%) patients did not conceive have higher incidence of cancer and 68 patients had undergone IVF treatment between 2-6 cycles, and of which 22 (32%)patients have successfully conceived and 46(68%) patients did not conceive are at higher risk of cancer.

Regarding IVF outcomes, 22 women successfully conceived following multiple cycles. The study revealed variability in

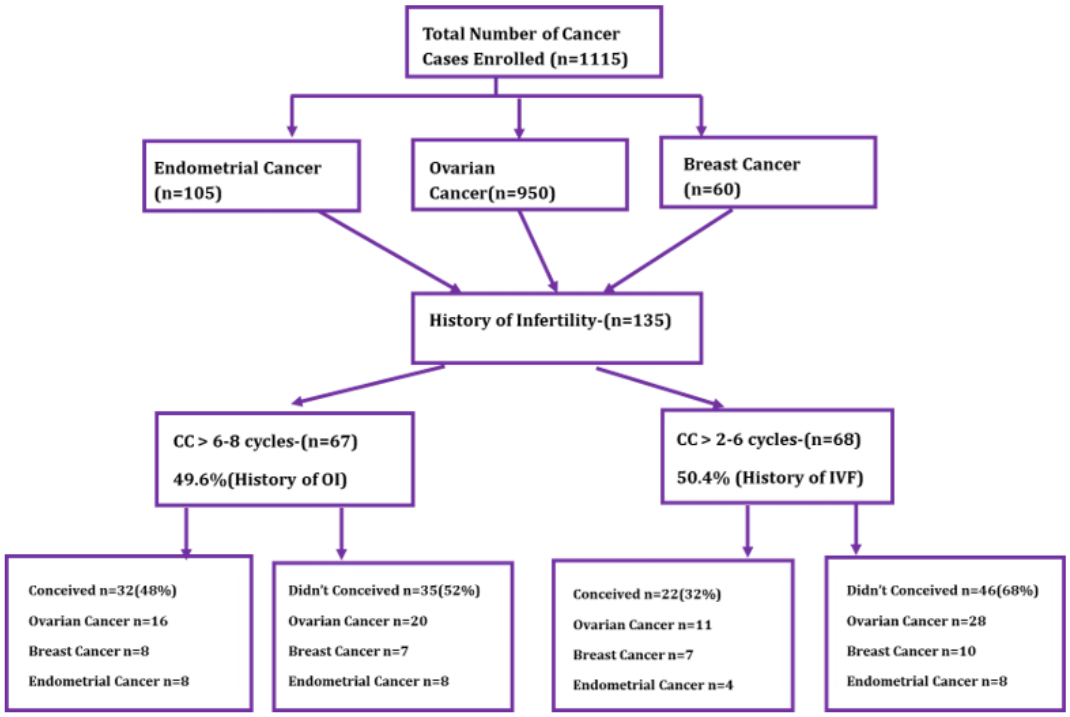


Figure 1: Enrollment and Screening of Cancer Subjects based on the history of infertility Opting for IVF treatment.

reproductive outcomes, with ovulatory disorders polycystic ovary syndrome (PCOS) and unexplained infertility identified as the most prevalent causes of infertility.

The mean age at cancer diagnosis was 50-55 years for ovarian cancer, 44-49 years for breast cancer, and 55-60 years for endometrial cancer. Among the infertile patients, 10 had Male factor, 32 had ovulatory disorders, 33 had PCOS, 20 had Obesity 16 had Endometriosis, and 24 had unexplained infertility.

These findings underscore the challenges faced by women with a history of cancer and infertility in achieving pregnancy, particularly following extended cycles of ovulation induction and IVF treatment. The data also suggest that fertility outcomes may vary significantly depending on the number of treatment cycles and the type of cancer as Depicted in flow chart 1.

Table 1 represents the Sociodemographic features of 135 patients with a past History of Infertility out of 1115 cancer cases. It represents the average age of cancer onset varies by cancer type, with ovarian cancer having the earliest onset at 50-55 years, followed by breast cancer at 44-49 years, and endometrial cancer at 55-60 years. These findings suggest that reproductive factors, including hormonal exposure and the age of reproductive cessation, may influence the timing of cancer onset. Regarding infertility, the cohort shows diverse underlying causes Male factor (10 patients) Ovulatory disorders (32 patients) and polycystic ovary syndrome (PCOS) (33 patients) were the most prevalent causes of infertility, followed by obesity (20 patients), endometriosis (16 patients), and unexplained infertility (24 patients). The duration of infertility may be a critical factor in the increased risk of cancer development, especially for ovarian and endometrial cancers, where prolonged anovulation and altered, hormonal environments could contribute to carcinogenesis. The higher prevalence of PCOS, ovulatory disorders and Unexplained infertility may also suggest a hormonal imbalance that could contribute to both infertility and an increased risk of specific cancers. These findings further suggest that infertility, which is often linked to hormonal disorders such as PCOS, ovulatory dysfunction, and unexplained infertility, may not only impair reproductive success but also be a potential risk factor for the development of certain malignancies. The relationship between infertility and subsequent cancer risk.

Table 2 Infertility treatment taken by 135 patients with a past History of Infertility out of 1115 cancer cases. Regarding fertility treatment, 67 patients in the cohort underwent ovulation induction with clomiphene citrate for more than 6-8 cycles. Among those who received treatment, 32 patients successfully conceived, yielding para 1 was 11 and para 2 was 21, reflecting a partial success rate for ovulation induction. However, 35 patients who underwent the same treatment did not achieve conception, despite prolonged exposure to clomiphene citrate has higher incidence of cancer, indicating persistent infertility despite therapeutic intervention. This discrepancy may highlight the heterogeneous nature of infertility and response to treatment, as well as the possibility that infertility, regardless of treatment success, may still be linked to an elevated risk of certain cancers. These findings suggest the need for further investigation into the long-term effects of fertility treatments—especially clomiphene citrate—on cancer risk and the potential mechanisms by which infertility treatments may contribute to carcinogenesis, particularly in ovarian, breast, and endometrial cancers.

Table 1: Baseline Characteristics of the subjects according to History of Infertility among 1115 Women with Ovarian, Breast, and Endometrial cancer and the treatment Outcome.

S.No	Characteristic	Number of Patients
1	**Duration Of Infertility**	**7-15 years**
2	**Causes of Infertility**	
	Male factor	10 (7.4%)
	Ovulatory Disorders	32 (23.7%)
	PCOS	33(24.4%)
	Obesity	20 (15%)
	Endometriosis	16 (11.8%)
	Unexplained Infertility	24 (17.7%)
3	**Age of Onset of Cancer**	
	Ovarian Cancer	50 -55 years
	Breast Cancer	44-49 years
	Endometrial Cancer	55-60 years

Table 2: Infertility treatment with History of Clomiphene Citrate taken with Cancer.

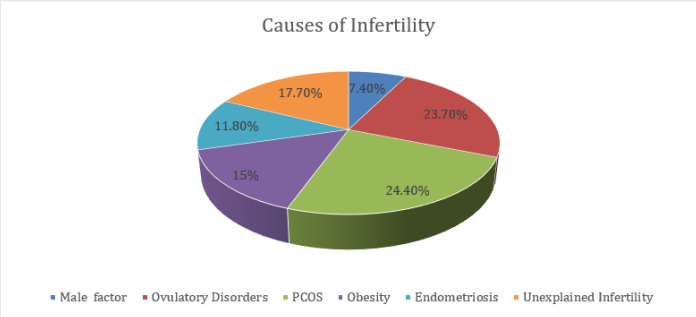
Condition	Conceived	Did not Conceived	p- Value
History of Infertility	(n=135)		
Ovulation Induction with Clomiphene Citrate 50 >6-8 Cycles	67		
Ovarian Cancer	16 (50%)	20 (57.1%)	0.82
Breast Cancer	8 (25%)	7 (20%)	
Endometrial Cancer	8 (25%)	8 (22.8%)	
Conceived with Clomiphene Citrate 50 >6-8 Cycles	32(48%)	35(52%)	

The table 3 provides the No of the Infertile patients taken IVF treatment out of 1115 Cancer cases. Among the 950 ovarian cancer patients, 68 undergone for in vitro fertilization (IVF) as part of their fertility treatment. Of those undergoing IVF, 22 (32%) patients successfully conceived, while 46 (68%) patients remained infertile and did not achieve conception, despite IVF intervention are at higher risk of cancer. These findings suggest that, although IVF can provide a potential pathway for fertility in cancer patients, success rates may be variable, with some individuals not achieving pregnancy despite utilizing assisted reproductive technologies. The number of IVF patients is relatively small, which may limit the generalizability of the findings; however, these results emphasize the importance of individualized treatment plans in managing fertility preservation and conception in cancer patients.

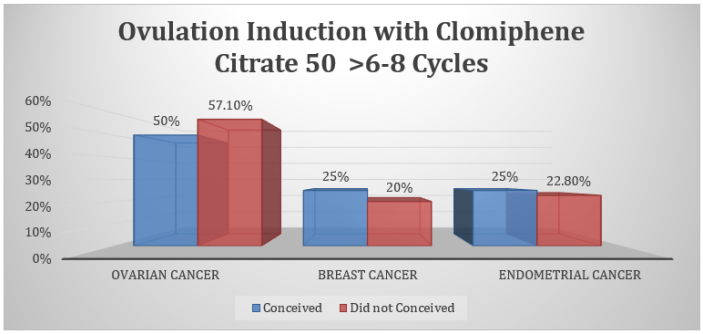
Table 3: Reproductive Treatment with the History of IVF and Cancer.

Condition	Conceived	Did not Conceived	P Value
Ovarian Cancer	11 (50%)	28 (61%)	0.63
Breast Cancer	7 (31.8%)	10 (21.7%)	
Endometrial Cancer	4 (18.2%)	8 (17.3%)	
Conceived	22(32%)	46(68%)	
Patients underwent for IVF	(n=68)		

Graph 1: Patients with Cancer incidence with the past history of Infertility and their causes

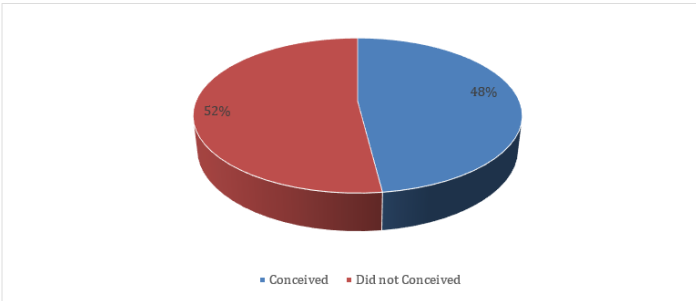


Graph 2A Ovulation Induction with Clomiphene Citrate 50 >6-8 Cycles



Graph 2B Ovulation Induction with Clomiphene Citrate 50 >6-8 Cycles

Patients Conceived and not Conceived



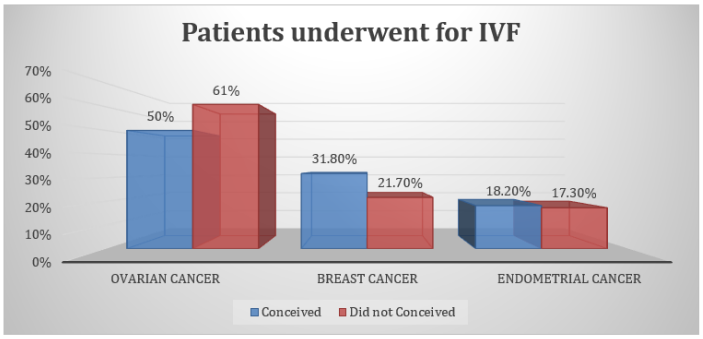
Discussion

In this study we examined the reproductive outcomes and fertility treatment patterns in cancer patients, specifically focusing on ovarian, breast, and endometrial cancers. A total of 1,115 patients were enrolled, with ovarian cancer patients (n = 950), followed by endometrial cancer (n = 105) and breast cancer (n = 60). The findings revealed significant insights into the complex relationship between infertility, ovulation induction, and in vitro fertilization (IVF) treatments in terms of cancer, while also highlighting the potential links between infertility and an elevated risk of cancer development. Our finding of this study is that 50% of ovarian cancer patients reported a history of infertility. This is consistent with existing literature, which suggests that infertility may be associated with an increased risk of ovarian cancer [19].

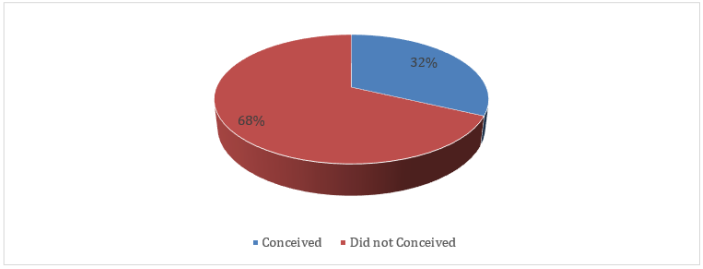
Infertility due to conditions like polycystic ovary syndrome (PCOS), ovulatory dysfunction, and endometriosis has been recognized as a risk factor for ovarian cancer [20].

In PCOS and ovulatory disorders, which were the most common

Graph 3A: Patients who underwent for IVF



Graph 3B Patients underwent IVF Conceived and not Conceived



causes of infertility in this cohort 33 and 32 patients, respectively), are associated with hormonal imbalances, such as elevated levels of estrogen, which may contribute to ovarian carcinogenesis [21]. Similarly, prolonged anovulation and unopposed estrogen exposure, commonly seen in women with infertility, have been implicated in increasing the risk of endometrial cancer [22].

Of which 67 patients have undergone treatment with Clomiphene Citrate, ovulation induction with more than 6 cycles, of which 32 conceived (48%) and 35(52%) patients did not conceive had undergone treatment with Clomiphene citrate who did not conceive are at a higher incidence of Cancer, further underscores the role of reproductive history in cancer risk. Nulliparity has long been established as a risk factor for both ovarian and endometrial cancers, with the absence of pregnancy leading to prolonged exposure to endogenous hormones such as estrogen, which may increase cancer risk [23]. These findings reinforce the need for further exploration of the interplay between infertility, hormonal imbalances, and the development of gynecological cancers. While CC is an effective treatment for many women with anovulatory infertility, there are ongoing concerns about its long-term use, particularly its potential association with ovarian cancer risk [24]. And 68 patients have undergone IVF treatment for 2-6 cycles. Of these, 22 (32%) were successfully conceived, 11 were Ovarian Cancer patients, 7 were Breast Cancer and 4 were Endometrial Cancer while 46 (68%) remained infertile and did not Conceive were Ovarian Cancer patients 28(61%), 10 (21.7%) were Breast Cancer and 8 (17.3%)were Endometrial Cancer. This suggests a heterogeneous response to treatment, where some women benefit from CC, while others do not, possibly due to factors such as the severity of infertility, the type of underlying disorder, or the impact of cancer treatments on ovarian reserve and function [25].

The potential association between prolonged CC use and ovarian cancer remains contentious. Some studies suggest that prolonged ovulation induction with CC may increase the risk of ovarian cancer [26], while other studies fail to establish a definitive link [19]. The findings from this study underscore the need for further research to investigate the long-term effects of ovulation induction on cancer risk, particularly in populations with pre-existing infertility or cancer treatment histories.

Among cancer patients in this study, 14 opted for IVF, with 6 achieving successful pregnancies (1-2 children) and 8 remaining infertile despite IVF treatment. The overall IVF success rate of approximately 45% in this cohort is consistent with previously reported success rates for cancer patients undergoing IVF, which typically range from 20-60%. However, IVF success in cancer patients is influenced by numerous factors, including age, type of cancer, prior treatments, and ovarian reserve [27]. This study's findings highlight the variable IVF outcomes in cancer patients and emphasize the importance of individualized treatment planning.

Conclusion

Our study shows the intricate relationship between infertility, cancer therapies, and reproductive outcomes. While fertility treatments, such as clomiphene citrate and *in vitro* fertilization (IVF), present promising options for cancer patients seeking to conceive, the success rates associated with these treatments remain highly variable. These outcomes are influenced by a range of factors, including the patient's age, cancer type, and prior oncological treatments. Moreover, given the potential long-term risks of fertility treatments particularly concerns regarding an increased risk of ovarian cancer it is critical that future research investigates the enduring effects of these interventions. This will be essential for both improving fertility outcomes and assessing the potential carcinogenic risks associated with fertility-preserving therapies in cancer survivors.

Funding

The work was supported by the Indian Council of Medical Research.

References

1. Zegers-Hochschild F, Adamson GD, de Mouzon J, et al. The international committee for monitoring assisted reproductive technology (ICMART) and the world health organization (WHO) revised glossary on ART terminology, 2009. Human reproduction. 2009; 24: 2683-2687.
2. Pisarska MD, Chan JL, Lawrenson K, et al. Genetics and Epigenetics of Infertility and Treatments on Outcomes. J clin Endocrinol Metab. 2019; 104: 1871-1886.
3. Cetin I, Cozzi V, Antonazzo P. Infertility as a cancer risk factor - a review. Placenta. 2008; 169-177.
4. Yang HP, Murphy KR, Pfeiffer RM, et al. Lifetime number of ovulatory cycles and risks of ovarian and endometrial cancer among postmenopausal women. Am J Epidemiol. 2016; 183: 800-814.
5. Yang Q, Ciebiera M, Bariani MV, et al. Comprehensive Review of Uterine Fibroids: Developmental Origin, Pathogenesis, and Treatment. Endocr Rev. 2022; 43: 678-719.
6. Kroener L, Dumesic D, Al-Safi Z. Use of fertility medications and cancer risk: a review and update. Curr Opin Obstet Gynecol. 2017; 29: 195-201.
7. Momenimovahed Z, Taheri S, Tiznobaik A, et al. Do the fertility drugs increase the risk of cancer? A review study. Frontiers in endocrinology. 2019; 10: 313.
8. Katzke VA, Kaaks R, Kühn T. Lifestyle and cancer risk. The Cancer Journal. 2015; 21: 104-110.
9. Diakosavvas M, Fasoulakis Z, Ntounis T, et al. A Potential pathogenic link between cancer of female reproductive system and infertile women treated with assisted reproduction techniques. *in vivo*. 2021; 35: 1393-1339.
10. Moorman PG, Palmieri RT, Akushevich L, et al. Ovarian cancer risk factors in African-American and white women. Am J Epidemiol. 2009; 170: 598-606.
11. Tsilidis KK, Allen NE, Key TJ, et al. Oral contraceptive use and reproductive factors and risk of ovarian cancer in the European Prospective Investigation into Cancer and Nutrition. Br J Cancer. 2011; 105: 1436-1442.
12. Beral V, Doll R, Hermon C, et al. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet. 2008; 371: 303-314.
13. Mannava LL. A Comparative Study on Ovulation Induction with Clomiphene Citrate Versus Letrozole in Women with Infertility: A Prospective Randomized Trial at Infertility Clinic, KVG Medical College and Hospital Sullia (Master's thesis, Rajiv Gandhi University of Health Sciences (India)).
14. Choi JH, Wong AS, Huang HF, et al. Gonadotropins and ovarian cancer. Endocrine reviews. 2007; 28: 440-461.
15. Brinton LA, Scoccia B, Moghissi KS, et al. Long-term relationship of ovulation-stimulating drugs to breast cancer risk. Cancer Epidemiol Biomarkers Prev. 2014; 23: 584-593.
16. Jensen A, Guleria S, Albieri V, et al. Fertility treatment and risk of ovarian cancer in a large nationwide cohort of infertile Danish women. International Journal of Cancer. 2024.
17. Sovino H, Sir-Petermann T, Devoto L. Clomiphene citrate and ovulation induction. Reprod Biomed Online. 2002; 4: 303-310.
18. Weiss NS, Braam S, König TE, et al. How long should we continue clomiphene citrate in anovulatory women?. Human Reproduction. 2014; 29: 2482-2486.
19. Luo X, Zhang Y, Sun J. Infertility as a risk factor for ovarian cancer: A population-based cohort study. Journal of Ovarian Research. 2017; 10: 15.
20. McGuire V, Bandera EV. Infertility and cancer risk: An overview. Cancer Epidemiology, Biomarkers & Prevention. 2012; 21: 1843-1849.
21. Coveney CM, Collins RL, Poynton RR. Polycystic ovary syndrome and the risk of ovarian cancer: A systematic review and meta-analysis. Journal of Clinical Endocrinology & Metabolism. 2019; 104: 2585-2592.
22. Missmer SA, Cramer DW. Endometriosis and ovarian cancer: A review of the literature. Human Reproduction Update. 2004; 10: 1-13.
23. Ali AT. Reproductive factors and the risk of endometrial cancer. Int J Gynecol Cancer. 2014; 24.
24. Hart R, Doherty DA, Schilling C. Clomiphene citrate and its association with ovarian cancer risk: A retrospective cohort study. The Lancet Oncology. 2017; 18: 1216-1223.
25. Kogan EA, Diamond MP. Ovarian reserve and fertility treatment in cancer survivors. Fertility and Sterility. 2015; 103: 939-945.
26. Grodin JL, Garcia RI, Mandel MP. Clomiphene citrate and ovarian cancer: A review of current evidence. Fertility and Sterility. 2015; 104: 519-525.
27. Anderson RA, Cameron DA, Telfer EE. Fertility preservation and reproductive outcomes in young women with cancer: A review. Human Reproduction Update. 2018; 24: 544-559.