

Correlation between Fertility Drug and the Likelihood of Gynecological Cancer - A Systematic Review

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ABSTRACT

Background: There is increasing use of fertility drugs for ovulation induction and ovarian stimulation in assisted reproductive treatment like In Vitro Fertilization. For the treatment of subfertility, several medications are used to grow more eggs these drugs used to stimulate their ovaries may fuel cancer risk. In this review, recent literature regarding the correlation between fertility drug and cancer risk is reviewed to find out whether the medicines used to stimulate ovulation increase the risk of any gynecological cancer in women.

Main body: Broad controversy exists in the literature about fertility treatment-induced cancer, although clinical trials are generally more focused. In order to present comprehensive strategies, the author has attempted to synthesize findings from Forty-seven research papers. The purpose of this study is to present a systematic review of the available evidence-based research paper concerning the relationship between fertility drug and gynecological cancers.

Conclusion: The result of this study shows support for the correlation between fertility drugs and certain cancer risk, the correlation should continue to be monitored because the included studies had several limitations and multiple differences in the way they were conducted. However, we suggest the need to counsel women about their potential risk of Uterine/ Endometrial cancer and Breast Cancer in the future before any treatment procedure.

Keywords: Cancer, Clomiphene citrate, Female infertility, Fertility drugs, Gonadotropin, Ovulation induction

ABBREVIATIONS: WHO: World Health Organization; IVF: In Vitro Fertilization; CC: Clomiphene Citrate; HMG: Human Menopausal Gonadotropin; FSH: Follicle Stimulating Hormone; HCG: Human Chorionic Gonadotropin; ART: Artificial Reproduction Technology; IRR: Individual Research Result; OI: Ovulation Induction.

BACKGROUND

Reproductive health is a priority global health area, According to WHO One in every four couples in developing nations had been seen as influenced by infertility. The rate of primary female infertility is ranged from 1.9 to 2.6% and secondary female infertility ranged from 7.3 to 17% with the highest rates in Central and Eastern Europe, followed by South Asia at 12.2% and Sub-Saharan Africa. This data consolidated information between 1990 and 2010, providing a 5-year projection of infertility [1]. According to this data, the highest rates of infertility were concentrated through Africa and Central/Eastern Europe [2]. Simi et al. explored the significance of early detection of female infertility in [3-5]. World Health Organization ICD-11 describes female infertility as a Disease of the reproductive system defined by the

failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [6]. All clinical studies will begin after at least one year according to the World Health Organization (WHO).

In recent years, an incredible interest has been arisen to find the correlation between infertility treatments and cancer development, mainly breast, uterus, and ovarian cancer [7]. The importance of understanding any existing correlation between fertility medications and cancer risk is crucial because the use of these treatments has become very common, with approximately 1 million in vitro fertilization (IVF) cycles reported per year worldwide furthermore to an obscure number of ovulation induction cycles. This paper evaluates the association of fertility drugs and gynecological cancer risk [8,9].

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Ovulation-inducing agents have been broadly used to treat infertility issues, either alone such as anti-estrogens (e.g. clomiphene citrate [CC]), or as part of IVF cycles including human menopausal gonadotropin (hMG), follicle-stimulating hormone (FSH), and human chorionic gonadotropin (hCG). Infertile women with normal ovulatory function, who have been exposed to excessive CC and/or gonadotropin administration, continually raised estrogen and progesterone concentrations, and numerous ovulatory cycles may be more prone to changes in the ovarian tissue than those with ovulatory disorders. This review systematically analyzes the 47 most significant research papers published on this topic to summarize the correlation between infertility drugs and gynecological cancers.

This study aimed to create a comprehensive picture of the association between infertility drug and the risk of ovarian, endometrial, cervical, and breast cancer in women. The highlight

of this paper was we only concentrate on cohort or case-control study of large population and single cancer researches [10].

MATERIAL AND METHODS

This paper presented a review of the scientific literature concerning the relationship between the use of fertility drugs and the risk of gynecological cancers. We searched digital databases including Pubmed, MEDLINE, and Google. The survey was completed using keywords such as "infertility", "ovarian stimulation consequences", " ovarian cancer risk", "gynecological cancer and fertility drug", "gynecological cancer risk", " Endometrial Cancer", "fertility drugs", "infertility treatment and cancer risk", variously associated together (Table 1). The criteria for entering the study included either case-control or cohort study. Initially 84 articles were selected by checking the keywords. The fertility drug used is In vitro fertilization (IVF) Procedure and clomiphene citrate, the gonadotropins, human chorionic gonadotropin (hCG), and human menopausal

Table 1: Study of Fertility drug effect and ovarian cancer.

Reference & Year	Country	Study Duration	Study Population	Study Design	Medication	Research Finding(s)
Trabert et al [4]-2013	United States	1965-88 with follow-up through 2010	9825	Cohort	Clomiphene citrate gonadotropins	No correlation between fertility drugs and ovarian cancer risk. Overweight is associated with Ovarian cancer risk However, their study suggests that Use of fertility drug and failure to attain pregnancy was related to ovarian cancer risk
Modan et al [5]-1998	Israel	1964-1974	2496	Cohort	Clomiphene citrate hMG	suggest that treatment with ovulation-inducing drugs doesn't increase the risk for ovarian cancer
Bjørnholt et al [6]-2015	Denmark	1963-2006	96545	Cohort	Gonadotropins clomiphene citrate human chorionic gonadotropins	No correlation between fertility drugs and ovarian cancer risk. But they observed an increased risk for serious borderline ovarian tumors after the use of progesterone.
Stewart et al [7]-2013	Australia	1982-2002	21646	Cohort	IVF	No Evidence for ovarian cancer growth following IVF in women who conceive an offspring. Meanwhile unsuccessful women have some risk.
Sanner et al. [8]-2009	Sweden	1961-75	2768	Cohort	clomiphene citrate gonadotropins	An increased risk of ovarian cancer gonadotropins and borderline tumors after clomiphene treatment.
Franceschi et al [9] 1994	Italy	Since 1992	195 cases 1339 controls	Case-Control	gonadotropins	No association between ovulation stimulation drugs and cancer risk.
Asante et al [10]-2013	USA	1999-2012	1900 cases- 1028 control- 872	Case-control	gonadotropins	No Correlation between fertility drug use and risk of ovarian tumors
Kurta et al [11] 2012	USA	2003-2008	902 cases Controls, N=1802	Case-control	clomiphene citrate follicle-stimulating hormone (FSH), human chorionic gonadotropin (hCG), gonadotropin, and human menopausal gonadotropin (hMG)	No Correlation between fertility drug use and risk of ovarian Tumors

Leeuwen et al [12]-2011	Netherlands	1983-1995	19146	Cohort	IVF	Ovarian stimulation for IVF may increase the risk of borderline ovarian tumors
Rizzuto et al [13]-2019		1990-2013	4,684,724	Cohort and Case-control	IVF	Infertility drugs may increase the risk of ovarian cancer slightly in subfertile women treated with infertility drugs.
Brinton et al [22]-2004		1965-88	12,193	Cohort	clomiphene citrate gonadotropins	No Correlation between fertility drug use and risk of ovarian tumors
Parazzini et al [24]-2001	Italy	1992-99	Cases 1031 Controls 2411	Case-control	no information was available	Observed a moderate association between fertility drugs and ovarian cancer risk
Vassard et al. [39]-2019	Denmark	1994-2015	Cases 58472 Controls 625330	Case-control	IVF	Observed an association between ART treatment and the risk of ovarian cancer among women with endometriosis
Lundberg et al. [47]-2019	Sweden	women born 1942-1992	2,882,847	Cohort	Not specified	Ovarian cancer incidence was higher in women diagnosed with endometriosis
Williams CL et al. [52]-2018	Great Britain	1991-2010	255 786	Cohort	ART	Increased risks of invasive and borderline ovarian cancer were found

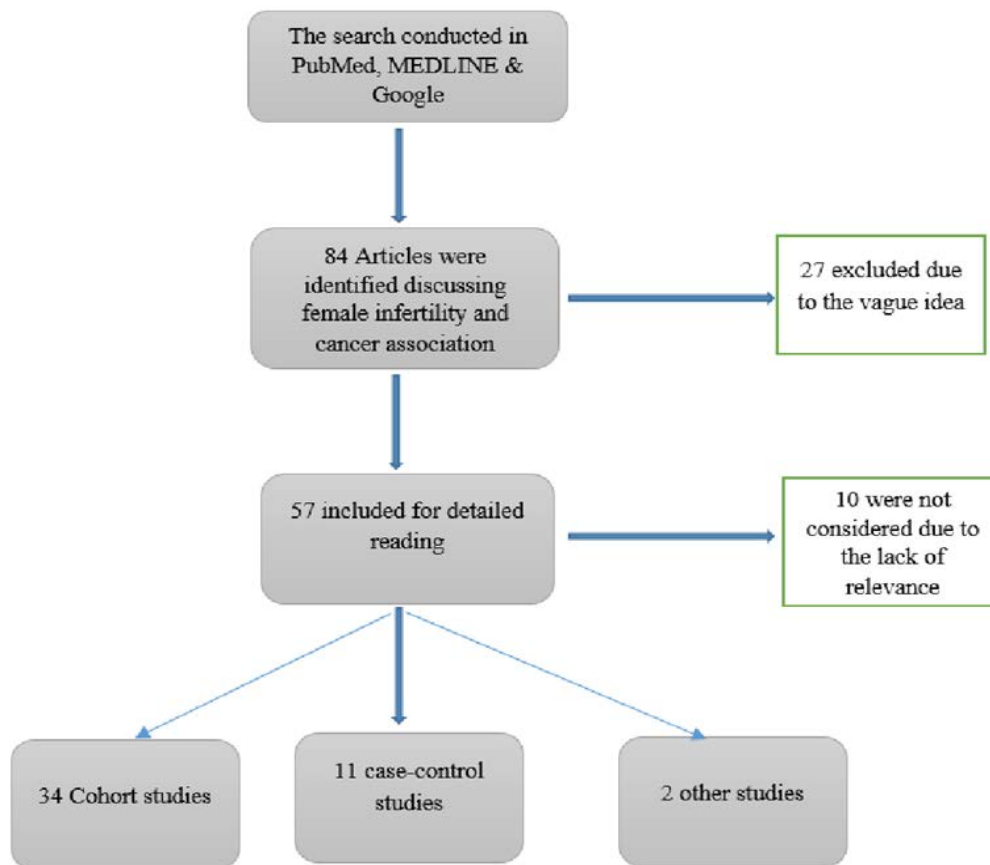


Figure 1: Flow chart demonstrating methodology of articles searched, filtered & included.

gonadotropin (hMG), alone or in combination. 46 were selected for the research paper based on relevance and clear findings. Figure 1 shows the flowchart of the inclusion methodology.

No study design restrictions and periods have been applied in this research. A general concern is that the medication of infertility has changed over the years. Specific fertility drugs that are currently in the commonplace, such as gonadotropins, were not broadly used until the late 1980s. Therefore, a few studies might not have caught exposure to this study. Furthermore, Cohort studies also have

inherent advantages and limitations because in most of the studies data are collected via interview or answering the questionnaires, numerous cohort studies are restricted by an absence of long-term follow-up, prompting lower apparent occurrence of disease as cancers may occur many years after the medications. Reference lists of the most significant papers were likewise analyzed and examined the full versions of all relevant studies. The strength of this study includes the large size of the cohort and the long and complete follow-up, providing sufficient power for subgroup analyses (Tables 2-4) [11-13].

Table 2: Study of Fertility drugs effect and Uterine /endometrial cancer.

Reference & Year	Country	Study Duration	Study Population	Study Design	Medication	Research Finding(s)
Modan et al. [5]- 1998	Israel	1964-1974	2496	Cohort	Clomiphene citrate hMG	suggested that the chance of association between infertility drug and the development of endometrial cancer can't be avoided
Reigstad et al. [14]- 2017	Norway	2004-2014	1,353,724	Cohort	clomiphene citrate and ART exposure	Clomiphene citrate appears associated with an increased risk of Endometrial cancer.
Jensen et al. [15]- 2009	Denmark	1965-1998	54,362	Cohort	clomiphene citrate gonadotropins human chorionic gonadotropin	Correlation between fertility drug (clomiphene citrate, human chorionic gonadotropin) and the risk of uterine cancer was observed. (Exception:- gonadotropin was not associated with risk)
Althuis et al [16]- 2005	USA	1965-1988	8,431	Cohort	clomiphene citrate	The association between clomiphene use and uterine cancer was observed
Kessous et al [17]- 2016		1988-2013	106,031	Cohort	IVF and ovulation induction (OI)	Observed an association between IVF history and uterine cancer
Brinton [18]- 2013	USA	1965-88	12 193	Cohort	Clomiphene gonadotropins	No association between fertility drugs and endometrial cancer risk
Venn et al. [21]- 2001	Australia		29,700	Cohort	IVF	Observed an increased incidence of uterine cancer in women with a history of infertility
Sponholtz et al. [20]- 2017	USA	1995-2013	47,555	Cohort	IUI	Observed an association between endometrial cancer and fertility drug
Parazzini et al. [23]- 2010	Italy	1992-2006	454 cases 908 Controls	case-control	Clomiphene gonadotropins	Observed an increase in the risk of endometrial cancer with the duration of fertility drug usage.
Benshushan et al. [25]- 2001	Israel	1989-1992	128 cases 255 controls	case-control	clomiphene citrate	No evidence found for proving the association of ovulation-inducing agents, including clomiphene citrate and a higher risk of endometrial cancer.
Silva et al [54]- 2009	British	20 years	7355	Cohort	clomiphene	Women consuming ≥ 2250 mg of clomiphene having a 2.6-fold increase in the risk of Uterine cancer

Table 3: Study of Fertility drugs effect and breast cancer.

Reference & Year	Country	Study Duration	Study Population	Study Design	Medication	Research Finding(s)
Modan et al [5]- 1998	Israel	1964-1974	2496	Cohort	Clomiphene citrate Hmg	suggest that treatment with ovulation-inducing drugs doesn't increase the risk for breast cancer
Brinton et al. [19]- 2014	USA	1989-2010	9,892	Cohort	Clomiphene gonadotropins	Observed an association between gonadotropins and breast cancer risk among nulligravid women

Burkman et al.[26]-2003	USA	1994-1998	4,575 case 4,682 control	case-control	human menopausal gonadotropin (hMG) clomiphene citrate	Observed an adverse effect of fertility drug on the risk of breast cancer
Gauthier et al. [27]-2004	Europe	1990-1991	98997	Cohort	Clomid(CC), Ondogyne Neopergonal, menotropin, gonadotropin, chorionic gonadotropin	Fertility drug does not influence breast cancer risk overall
Geva et al. [28]-2006	Israel	1964-1984	120,895	Cohort and nested case-control study.	clomiphene citrate, gonadotropins	Observed a Significant Risk of breast cancer for women treated with clomiphene citrate
Jensen et al.[29]-2007	Denmark		54,362	Cohort	gonadotrophins, clomiphene, human chorionic gonadotrophin	No strong association between breast cancer risk and use of fertility drugs
Pappo et al.[30]-2008	Israel	1986-2003	3,375	Cohort	IVF	Observed an association between IVF therapy and breast cancer development
Orgeas et al.[31]-2009	Sweden	1961-1976	1135	Cohort	clomiphene citrate gonadotropins	Observed that high-dose clomiphene citrate therapy may have an elevated risk for breast cancer
Stewart et al. [51]-2012	Australia	1983-2002	21,025	Cohort	IVF	Observed that Commencing IVF treatment at a young age is associated with an increased rate of breast cancer.
Ricci et al. [32]-1999	Italy	1983-1991	3 415 cases 2916 controls	case-control	Not specified	No association between fertility drug treatment and breast cancer risk.
Krul et al. [33]-2015	Netherlands	1983-95	12,589	Cohort	IVF	Observed an association between IVF therapy and breast cancer development
Reigstad et al. [34]-2015	Norway	1984-2010	808,834	Cohort	IVF	Observed an association between IVF therapy and breast cancer development
Van den et al. [35]-2016	Netherlands	1983-1995	19,158	Cohort	IVF	No association between fertility drug treatment and breast cancer risk.
Cooley et al. [36]-2012	USA		MCF- 10A, MCF-7 and HCC 1937 cell lines	cell lines	hCG, estrogen, progesterone and clomiphene citrate	Observed minimal direct effects of infertility treatment on breast cell multiplication
Bernstein et al. [37]-1995	USA	1983-1988	744 case-control pair	case-control	human chorionic gonadotropin (hCG)	Observed that hCG may be a means for reducing breast cancer risk.
Katz et al. [38]	Israel	1984-2002	7162	Case-Control	IVF	Observed that Women who start IVF after the age of 30 appear to be at increased risk of developing breast cancer

RESULTS AND DISCUSSIONS

For decades, researchers are trying to discovering the uncovered causes of cancer and the means of prevention. All the gynecological cancers are dangerous especially breast cancer has been the most common life-threatening cancers among women worldwide [14,15]. Infertility has long been perceived as a risk factor for different cancers, including breast, ovary, and

Gynecologic cancers. More recently, concern has been raised for the impacts of medications used to treat infertility, especially since these fertility drugs stimulate ovulation and raise different Hormone levels. Researchers worldwide have been involved with several pieces of research to clarify the effects of fertility drug exposures on the risk of various gynecologic cancers [16].

Analysis of Ovarian Cancer Studies

The Correlation between fertility drugs including those associated with in vitro fertilization (IVF) and cancers is an ongoing concern of both health providers and patients. Gynecological cancers are related to several hormonal and reproductive risk factors. The association among PCOS and endometrial cancer, as well as between endometriosis and ovarian cancer, are genuinely well defined [17-20].

In several years, researchers have investigated the association between borderline ovarian tumors and fertility drugs. Ovarian cancer is rare and the most deadly gynecological cancer worldwide [21-23]. Many pieces of research have shown that an increased risk of ovarian cancer is related to the intake of clomiphene citrate and gonadotropin [24].

Trabert et al. [4] reported that there is a correlation between Clomiphene citrate, gonadotropins, and ovarian cancer risk. They are also able to find Overweight is associated with ovarian cancer risk significantly. However, their study suggests that Use of fertility drugs and failure to attain pregnancy was related to ovarian cancer risk. A 1998 study by Modan et al. [5] suggested that fertility drug doesn't increase the risk of cancer. Additionally another study by Bjørnholt et al. [6] provided the same result. Stewart et al. [7] concluded that there is no proof of an expanded danger of ovarian cancer growth following IVF in women who conceive an offspring. There is some vulnerability concerning the impact of IVF in ladies who remain nulliparous they have an increased chance of Risk.

Although some studies have shown an increased risk [25-28], most studies do not show an overall increase of ovarian cancer in women exposed to fertility drugs [28]. However, some suggest a possible increased risk within subgroups, including sub fertile women, and women who are not conceived even after the medication. Reviewing the recently documented literature [29-31], demonstrate a significantly increased risk of invasive and borderline ovarian cancer. Two studies suggested an increased risk of ovarian cancer associated with endometriosis [32,33].

Analysis of Uterine /Endometrial Cancer Studies

Endometrial cancer is one of the hormone-related cancers. Death rates for uterine cancer began to increase around 2000 in the wake of increasing occurrence rates. According to the recent statistics, excess weight increases endometrial cancer risk by 50%. The results of several cohort studies showed an increase in uterine cancer among women who used ovulation-inducing drugs [31-35]. In this study, we have selected 11 relevant types of research. Out of 11 nine studies shown a Correlation between fertility drugs and the risk of uterine/endometrial cancer.

Reviewing the literature yields suggested that the chance of association between infertility drugs and the development of endometrial cancer can't be avoided [36]. According to a cohort of 1,353,724 women, the incidence of endometrial cancer increases in women who have a history of clomiphene citrate drug usage more than 6 cycles. A cohort study that lasted for 33-years revealed that uterine cancer is associated with the usage of clomiphene citrate and one exception point they reported is gonadotropin was not associated with risk [15]. This is consistent with the finding of Althuis's study. Kessous et al. [37] have attempted to pursue the conclusion that, an association between IVF history and uterine cancer are existing. In a retrospective study, Sponholtz et al [20] communicate that fruitful women were less likely to develop endometrial cancer (IRR 0.77, 95% CI 0.57, 1.05) than nulliparous women.

A study by Venn et al. [21] the incidence of uterine cancer increases in women who have a history of infertility. The results of a case-control study stated the duration of the use of fertility drugs was positively associated with endometrial cancer risk. There have been a few studies that did not show any association between fertility drugs including clomiphene citrate and a higher risk of endometrial cancer [38-40]. A 20 years British cohort study of 7355 women concluded that consumption of more than 2,250 mg of clomiphene is associated with a 2.6-fold increase in the risk of uterus cancers relative to those who were not treated.

Analysis of Breast Cancer Studies

Breast cancer is the leading cause of cancer death in women aged 20 to 59 years [41-43]. From 2005 to 2014, in general, breast cancer incidence rates expanded. Although the relationship between breast cancer and ovulation-inducing drugs is not clear, it appears that these drugs increase breast cell multiplication. Some studies reported that breast cancer diagnosed within the initial 2 years following infertility treatment is similar in cancer characteristics compared with those happening in patients without earlier fruitlessness treatment [45,45].

Most recent studies have shown an association between the risk of breast cancer and fertility drug usage when comparing women undergoing fertility treatment [46-48]. Although few recent studies found no association of fertility drugs with breast cancer risk. Treatment with ovulation-inducing drugs is not associated with an increased risk of a breast cancer diagnosis is the conclusion of one early study. The use of gonadotropins, due to ovulation disorders, increases breast cancer risk among nulliparous women [49]. A case-control study of 4,575 cases and 4,862 controls aged between 35 to 64 found that extensive use of fertility drugs could initiate some negative effect; the relative risk of breast cancer in women with an hMG use for more than 6 months was between 2.07 to 3.8.

The author of this cohort study provided the information that there is no evidence of an association between fertility drug and breast cancer risk but a family history of cancer can affect. An Israeli study on the effect of ovulation-inducing drugs discloses that for barren ladies treated with clomiphene citrate, breast cancer risk is elevated. They have adopted a cohort and nested case-control study of 20 years to reach into this conclusion. A Danish cohort study of 54,362 women with infertility problems, however, did show no strong association between breast cancer and ovulation-inducing fertility drugs, but they suggested a long term follow up of among nulliparous women exposed to gonadotropin, this suggestion support the result of Brinton et al. [19].

Some previous studies have also revealed an increased risk of breast cancer in women who used fertility drugs [50,51]. Orgeas et al. [31] convey that cancer risk is associated with high-dose clomiphene citrate for women treated with nonovulatory causes. An IVF cohort study of women aged 20-44 years reported that risk of breast cancer was associated with women they had their first delivery at a late age (HR=1.56,95% CI 1.01-2.40) [51]. A breast cell proliferation study supported minimal direct effects of infertility treatment on breast cell multiplication.

The result of a registry-based cohort study of 808,834 women showed that the risk of breast cancer increased in individuals who gave birth following IVF [95 % CI 1.07-1.71] [34]. These data agree with a recent 2 IVF cohort studies comprised of 12589 women [52]. A 12-year long cohort study of 19,158 IVF treated women revealed that the risk of breast cancer in IVF-treated women was not significantly different from that in the general population and from the risk in the non-IVF group. The result of a case-control study of 18 years showed that an increased risk of breast cancer was associated with women who undergo IVF treatment after the age of 30 years [38]. Meanwhile, many researchers could not show a positive relationship between fertility treatment and breast cancer.

Analysis of Cervical Cancer studies

A few studies assessing the risk of cervical cancer following fertility treatment have consistently shown no increased risk of cervical cancer compared to both the general population and infertile women as controls. A subset of studies has discovered a decreased incidence of cervical cancer in IVF patients, although the mechanism behind this phenomenon is unclear but perhaps related to better access to care with more frequent cervical cytology screening in women experiencing fertility medication. Twenty four years of case-control study disclose that they can find a lower risk of cervical cancer in IVF treated women [40]. A cohort study of Swedish women showed that IVF treated women had a decreased rate of cervical cancer [41]. Overall the results of the present study suggest that fertility drug is not a risk factor for cervical cancer [53-57].

CONCLUSION

This study intended to learn the association between the use of fertility drug and gynecological cancers. Because of the correlation between hormonal and reproductive factors, women's cancers have been got much more attention to found the association between the use of fertility drugs and cancer in recent years. Even though this association is hypothetically justifiable, the unpredictable and various elements that are engaged with the beginning of cancer growth make it hard to decide the precise relationship between the use of these medications and cancer by fertility treatment. According to the results of this study, there is no absolute correlation between the use of fertility drugs and cervical cancer, and only some observational studies have studied and pointed to this relationship so we suggest a long term follow-up for reaching the conclusion. As reported by this review 82% of studies show a strong association between the ovulation-inducing drug and Uterine /Endometrial Cancer. In the case of breast cancer, 63% research paper says we cannot completely neglect the association between fertility drug and risk of cancer. Generally, most studies show that fertility treatments do not increase the risks of ovarian cancer but at the same time some most recent studies show the association. There is, however, limited evidence that the use of fertility treatments may quietly increase the risk of borderline ovarian cancer. So the

correlation between fertility drug and gynecological cancers is still an open question.

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Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of Data and Material

Not applicable

Competing Interests

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Authors' Contributions

MS analyzed and interpreted the 47 research data regarding the correlation between fertility treatment and Gynecological cancers.

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