Fertility drugs and cancer: a guideline

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Methodological limitations in studying the association between the use of fertility drugs and cancer include the inherent increased risk of cancer in women who never conceive, the low incidence of most of these cancers, and that the age of diagnosis of cancer typically is many years after fertility drug use. Based on available data, there does not appear to be a meaningful increased risk of invasive ovarian cancer, breast cancer, or endometrial cancer following the use of fertility drugs. Several studies have shown a small increased risk of borderline ovarian tumors; however, there is insufficient consistent evidence that a particular fertility drug increases the risk of borderline ovarian tumors, and any absolute risk is small. Given the available literature, patients should be counseled that infertile women may be at an increased risk of invasive ovarian, endometrial, and breast cancer; however, use of fertility drugs does not appear to increase this risk. (Fertil Steril® 2016;106:1617–26. ©2016 by American Society for Reproductive Medicine.)

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The use of fertility drugs that may cause alterations in endogenous hormones and multiple ovulations has raised concerns about the long-term safety of such medications. Although some clinical studies have suggested a link between fertility drugs and the risk of cancer, the results of these studies are difficult to interpret. A variety of methodological limitations exist, including the lack of proper controls, recall bias, failure to control for confounders that are known to influence cancer risk, including the inherent increased risk of cancer in infertility patients, and the lack of long-term follow-up. In addition, the incidence of these cancers is low, and in general they do not occur until much later in life, which makes it difficult to establish a causal link. However, the importance of understanding any existing relationship between fertility medications and cancer risk is crucial because the use of these medications has become quite common, with approximately 1 million in vitro fertilization (IVF) cycles reported per year worldwide in addition to an unknown number of ovulation induction cycles. This guideline evaluates the association of fertility drugs and cancer risk.

This clinical practice guideline was based on a systematic review of the literature. The search was restricted to PubMed MEDLINE citations of human subject research published in the English language from 1966 to December 18, 2015, using a combination of the following words or word phrases: breast, cancer risk, cancer risk, cancer, cause, cervical, chorionic gonadotropin, clomid, clomifen, clomifene, clomiphene, clomiphene/adverse effects [MeSH], colon, colonic neoplasms/chemically induced[MeSH], colonic neoplasms/epidemiology[MeSH], colonic neoplasms/etiology[MeSH], drug, drugs, endometri*, endometrial neoplasms/chemically induced[MeSH], endometrial neoplasms/etiology[MeSH], endometrial, endometrioid, endometrium, fertility agents, female/adverse effects[MeSH], fertility, fertilization in vitro/adverse effects[MeSH], follicle stimulating hormone/adverse effects[MeSH], FSH, genotoxic*, genotoxic*, genotoxicity, gonadotrophin, gonadotrophins, gonadotropin, gonadotropins, gonadotropins/adverse effects[MeSH], hCG, hMG, human/adverse effects[MeSH], infertility, IVF, letrozole, LH, luteinizing hormone, mammary, medical treatment, medication, medicine, melanoma, melanoma/chemically induced[MeSH], melanoma/epidemiology[MeSH], melanoma/etiology[MeSH], menotropins/adverse effects [MeSH]. neoplasms [MeSH], neoplasms/chemically induced[MeSH], neoplasms/epidemiology*[MeSH], ovar*, ovarian neoplasms/etiology[MeSH], ovarian neo plasms/chemically induced[MeSH], ovarian stimulation, ovarian, ovary, ovulation induction, ovulation induction/adverse effects[MeSH], thyroid neoplasms/chemically induced[MeSH], thyroid neoplasms/epidemiology[MeSH], thyroid neoplasms/etiology[MeSH], thyroid, treatment, treatments, uter*, uterine cervical neoplasms/chemically induced[MeSH], uterine cervical neoplasms/epidemiology[MeSH], uterine cervical neoplasms/etiology[MeSH], uterine, uterus.

Studies were eligible if they met one of the following criteria: primary evidence (clinical trials) that assessed the effectiveness of a procedure correlated

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with an outcome measure, meta-analyses, and relevant articles from bibliographies of identified articles. A total of 1,332 studies were identified in an electronic search and from examination of reference lists from primary and review articles, 113 of which were selected for inclusion in this systematic review.

The quality of the evidence was evaluated using the following grading system:

1) Level I: Evidence obtained from at least one properly designed randomized, controlled trial.
2) Level II-1: Evidence obtained from well-designed controlled trials without randomization.
3) Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
4) Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
5) Level III: Systematic reviews, meta-analyses, opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

The strength of the evidence was evaluated as follows:

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

METHODOLOGICAL LIMITATIONS OF EPIDEMIOLOGIC STUDIES

To study the relationship between fertility drugs and cancer, observational studies, such as case-control and cohort studies, are typically utilized since randomized trials would not be practical to address this issue. Case-control studies are particularly common as this method is efficient in the study of rare outcomes. However, this study design suffers from inherent methodological limitations, including selection bias that may contribute to the uncertainty about this relationship. Women who take fertility drugs are a heterogeneous group with many underlying diagnoses for infertility such as hypothalamic amenorrhea, anovulation, polycystic ovary syndrome (PCOS), male-factor infertility, tubal factor infertility, unexplained infertility, and endometriosis-related infertility. Certain subgroups, which are known to be independently associated with increased cancer risk (for example, nulliparity, endometriosis, and anovulation) are over-represented in the study population (1–6). Conversely, the use of certain hormonal medications, such as oral contraceptives that are known to be associated with a decreased risk of cancer, may be over-represented in the control population. Furthermore, detection bias is also potentially problematic as infertility patients may undergo more surveillance by ultrasound and laparoscopy than is typical for a control population. This bias may lead to higher detection rates of cancers in the study population compared with controls.

Cohort studies also have inherent advantages and limitations. While a cohort study can potentially minimize selection bias, it may be limited by recall bias and/or the ability to precisely identify and quantitate exposure. "Fertility drugs" are pharmacologically and physiologically distinct agents. In addition, many cohort studies are limited by a lack of long-term follow-up, leading to lower perceived incidence of disease as cancers may occur many years after the medication was used and thus there is difficulty establishing a causal link. Lack of distinction between clomiphene citrate (CC), gonadotropins (follicle-stimulating hormone [FSH] and/or luteinizing hormone [LH]), and human chorionic gonadotropin (hCG) in the study design can also lead to bias and a false-positive *or* false-negative finding. Additionally, retrospective studies rely on two main strategies to determine the drug, dose, and duration of fertility therapy: chart reviews and patient recall. Chart reviews confirm exposure via medical records, whereas patient recall may suffer from poor reliability or bias. The accurate recall of fertility drug usage may be questioned in women with cancer as individuals attempt to look for reasons why they developed cancer. These limitations as well as others must be considered when evaluating the evidence supporting or refuting an association between the use of fertility drugs and cancer.

Another general concern is that the treatment of infertility has changed over the years. Specific fertility medications that are now commonplace, such as gonadotropins, were not widely used until the late 1980s. As a result, some studies may not have captured exposure to this class of medication, and long-term follow-up is limited. In addition, salpingectomy prior to IVF is now an accepted treatment for those with severe tubal disease, and this may have implications for the incidence of "ovarian" cancers, given the newer theories that some ovarian cancers may originate in the fallopian tube (7).

Ovarian Cancer

Ovarian cancer is rare and accounts for about 3% of all cancers in women, with approximately 20,000 cases diagnosed annually in the United States (8). Parity is inversely related to the risk of ovarian cancer (odds ratio [OR] 0.65, 95% confidence interval [CI] 0.48–0.88) (9); therefore, women with infertility are felt to be at an increased risk for ovarian cancer. Several theories suggest the plausibility that fertility drugs could alter the incidence of ovarian cancer, especially ovarian epithelial tumors. The "incessant ovulation" theory suggests that prolonged and uninterrupted years of ovulation *increase* cancer risk. This is supported by the observations that the risk for ovarian cancer in gravid women and/or women who have utilized chronic ovarian suppression is decreased. Fertility drugs, which often lead to multiple ovulatory sites within the ovary during a single cycle, are thus hypothesized to increase the risk of ovarian cancer, while oral contraceptives reduce the risk by reducing the number of epithelial disruptions associated with ovulations and epithelial repair (10). However, current evidence has challenged the dogma that the ovary is the primary origin of ovarian cancer. The most recent theory suggests that more aggressive ovarian cancers

may originate in other pelvic organs and involve the ovary secondarily (11). For example, there is good evidence to suggest that the fallopian tube is the primary origin of high-grade serous ovarian cancers (7). Therefore, the theory of incessant ovulation linking fertility drugs and all ovarian cancers has been called into question.

There are other potential theories about how fertility drugs can potentially lead to ovarian cancer. In vitro studies have demonstrated that approximately half of all ovarian epithelial tumors express gonadotropin receptors (12). Moreover, FSH, LH, and estradiol stimulate ovarian epithelial cell proliferation and inhibit apoptosis in ovarian epithelial cancer cell lines (13). Interestingly, CC potentiates the antiproliferative effect of some chemotherapeutic agents in estrogen receptor–negative ovarian cancer cell lines (14). However, study of cancer lines in vitro does not provide a definitive mechanism of how fertility drugs may alter the risk of ovarian cancer. In addition, it is not known if limited exposure during fertility treatment could alter lifetime risk, or if a pregnancy resulting from fertility treatments will negate any potential increase in risk.

OVARIAN CANCER

Invasive Ovarian Cancer

When considering the relationship between fertility drugs and invasive ovarian cancer, several methodologic issues arise. Women with infertility, nulliparity, and late menopause have been shown to be at increased risk for developing invasive ovarian cancer independent of treatment for fertility issues (15, 16). In addition, ovarian cancer is a rare disease and the onset typically occurs many years after reproductive age, necessitating long-term follow-up. Studies evaluating this association published in the early 1990s suggested that fertility drugs may be associated with an increased incidence of ovarian cancer (17, 18). Although these studies raised a significant amount of concern, they had several limitations: 1) use of a non-ideal fertile control population; 2) few observations of cancers in the groups studied; 3) use of imprecise outcomes such as combining benign and malignant ovarian neoplasms; 4) recall bias; 5) inability to identify the specific medications that were administered or the duration of their use; 6) no information regarding dose response; 7) no controlling for confounding variables; and 8) usage and indications for fertility medications have changed since the first associations were reported (17–19). These limitations make interpretation of the data difficult.

Subsequent studies have used better methodology to evaluate if there is a causal relationship between fertility drug use and invasive ovarian cancer (2–5, 15, 16, 20–47). In addition, there have been several systematic reviews and/or meta-analyses that have evaluated this relationship (48–55).

The majority of studies have shown no significant increase in the development of invasive ovarian cancer following the use of fertility drugs when compared with infertile controls and/or with the general population (1–5, 15, 16, 20–25, 29, 32, 34, 45, 47, 56–60). A large cohort study of more than 87,000 women evaluated and/or treated for infertility showed no increase in the risk of ovarian cancer following ever-use of fertility drugs when compared with those who received no treatment (hazard ratio [HR] 0.90, 95% CI 0.45–1.79), or following IVF (HR 1.58, 95% CI 0.75–3.29) (22). Another cohort study of more than 54,000 women with infertility found no increase in the rate of invasive ovarian cancer with CC (adjusted rate ratio [ARR] 1.14, 95% CI 0.79–1.64) or gonadotropin use (ARR 0.83, 95% CI 0.50–1.37) when compared with never users with a median follow-up of 16 years (56).

There have been a few studies that showed an increase in the risk of ovarian cancer following treatment with fertility drugs. One study of over 25,000 women found that the overall risk of invasive ovarian cancer was not increased following IVF when compared with the general population (standardized incidence ratio [SIR] 1.30, 95% CI 0.86–1.88) (43), but the risk was increased when follow-up was $\geq$15 years (SIR 3.54, 95% CI 1.62–6.72) (43). The SIR is obtained by dividing the observed number of cases of cancer by the "expected" number of cases that would occur in a community. Another study showed an increase in the risk of invasive ovarian cancer following the use of fertility drugs (SIR 1.91, 95% CI 1.18–2.91). However, when cancer cases diagnosed within 1 year of treatment were excluded, no significant increase in invasive ovarian cancer risk was noted (SIR 1.46, 95% CI 0.83–2.36) (59). Another study evaluated the incidence of cancer in a population of consecutive women who delivered a baby at a single institution over a 25-year period. Those who underwent IVF, as identified in the prenatal database, had an increased incidence of ovarian cancer compared with those who did not have fertility treatments (HR 3.9, 95% CI 1.2–12.6) (27).

Several systematic reviews have also evaluated this association and have not found a significant increase in invasive ovarian cancer following fertility drug exposure when compared with an infertile control group (48, 50, 52, 53, 55) or when compared with the general population (48, 51–53). The largest systematic review was performed by the Cochrane Collaboration and included 11 case-control and 14 cohort studies, with a total of 182,972 women (53). Due to the extreme heterogeneity among studies, they were not able to perform a true meta-analysis to derive an overall relative risk. The group identified 7 out of the 11 case-control studies with no increased risk compared with controls of similar age, and 7 out of the 14 cohort studies which demonstrated no increased risk of invasive ovarian cancer in women who used fertility drugs compared with subfertile controls (53). The Cochrane group identified two cohort studies that reported an increased incidence of invasive ovarian cancer in subfertile women treated with any fertility drug compared with the general population. One study had an SIR of 5.0 (95% CI 1.0 to 15) based on three cancer cases; the other study reported an OR of 2.09 (95% CI 1.39 to 3.12), based on 26 cases (53). Overall, the collaboration group concluded that there was no convincing evidence that fertility drugs were associated with an increased risk of invasive ovarian cancer.

Risk of Ovarian Cancer with the Use of Specific Fertility Drugs

Individual fertility drugs, including CC, gonadotropins, and hCG, have not been associated with an increased risk of

developing invasive ovarian cancer. The largest study to address the risk of cancer associated with specific fertility drug usage reviewed data on 54,362 women followed in all Danish fertility clinics during 1963–1998 (56). There was no overall increased risk of epithelial ovarian cancer in women treated with gonadotropins (risk ratio [RR] 0.83, 95% CI 0.50–1.37), CC (RR 1.14, 95% CI 0.79–1.64), hCG (RR 0.89, 95% CI 0.62–1.29), or gonadotropin-releasing hormone (GnRH) agonist (RR 0.80, 95% CI 0.42–1.51), either individually or when combined. Additionally, there was no association with the number of cycles of use, duration of follow-up, or parity. Other studies showed similar findings with no increased risk for ovarian cancer following the use of gonadotropins, CC, combined therapy, and other infertility drugs (4, 5, 23, 29, 32, 38). One study in 9,825 women evaluated for infertility found no increase in the risk for invasive ovarian cancer following the use of gonadotropins or CC, except in the 517 women who remained nulligravid after CC use (RR 3.63, 95% CI 1.36–9.72) (4).

BORDERLINE OVARIAN TUMORS

Borderline ovarian tumors, also known as tumors of low malignant potential, account for approximately 15% of all ovarian neoplasms (61). In contrast to invasive ovarian cancer, borderline ovarian tumors are indolent in their disposition, are more likely to be diagnosed in women of reproductive age, and have a favorable prognosis with more than 95% of women surviving 5 years beyond diagnosis (1). While there is very little support for an association between fertility drug use and invasive ovarian cancer, several studies have shown a link between fertility drugs and borderline ovarian tumors (1, 18, 33, 38, 43, 52, 62, 63). One of the largest studies looking at incidence of borderline ovarian tumors in IVF patients evaluated a cohort of infertility patients identified through a hospital registry and compared those who underwent IVF with infertility patients who did not undergo IVF (1). Out of the 7,544 women who underwent IVF, there were 17 women diagnosed with borderline ovarian tumors compared with 14 cases identified in 14,095 women in the non-IVF infertility group. The rate of borderline ovarian tumors in women undergoing IVF was higher with an HR of 2.46 (95% CI 1.20–5.04), which translates into 11 additional cases of borderline tumors per 10,000 women. Unlike invasive ovarian cancer, prior birth, hysterectomy, sterilization, or endometriosis did not affect the incidence of borderline tumors. Another study compared the incidence of borderline ovarian tumors in a cohort of >19,000 women undergoing IVF with 6,000 women with subfertility who did not undergo IVF and with the general population, with a mean follow-up of 14.7 years (43). The incidence of borderline ovarian tumors was higher in the IVF cohort when compared with the general population (SIR 1.76, 95% CI 1.16–2.56) as well as compared with the subfertility group (HR 4.23, 95% CI 1.25–14.33), whereas the rate of invasive ovarian cancer was not increased (HR 1.51, 95% CI 0.65–3.54) when compared with the subfertile group.

Despite this evidence, some studies have not demonstrated an increased risk of borderline ovarian tumors with the use of fertility drugs (64–66). The largest study addressing this question was a retrospective case-cohort study of 96,545 Danish women with infertility followed for a median of 11 years, which identified 142 women with borderline ovarian tumors (66). Overall, the use of fertility drugs did not increase the risk for borderline ovarian tumors (RR 1.0, 95% CI 0.67–1.51). While no association was observed for CC, gonadotropins, hCG, or GnRH agonists, progesterone use was associated with an increased risk of borderline tumors (RR 1.82, 95% CI 1.03–3.24).

The largest systematic review evaluating the risk of borderline ovarian tumors following the use of fertility drugs identified three case-control and three cohort studies (53). Three studies were included that reported a 2–3-fold increased risk for borderline ovarian tumors with fertility drug use (62–64). However, the authors were not able to perform a true meta-analysis giving an overall relative risk due to the extreme heterogeneity among studies (53). Nonetheless, when individual drug use was evaluated, there was no significant increased risk for borderline ovarian tumors with CC alone, CC and gonadotropins, or gonadotropins alone (53). Interpreting and summarizing the results of the existing observational studies addressing the association between fertility drugs and borderline ovarian tumors remain a challenge, given the rarity of such tumors and the significant methodological issues which make studies prone to confounding and bias.

Summary statements:

- Based on the available data, we can be reasonably reassured that there is no meaningful increased risk of invasive ovarian cancer following the use of fertility drugs in infertile women. (Grade B)
- Based on the available data there is fair evidence that the risk of invasive ovarian cancer is not different with one fertility drug compared with another. (Grade B)
- While several studies have shown a small increase in the absolute risk of borderline ovarian tumors after fertility treatments, there is insufficient consistent evidence that a particular fertility drug increases the risk of borderline ovarian tumors. (Grade C)
- It is important to note that any absolute increase in risk is small, and these tumors are indolent and generally have a favorable prognosis. (Grade B)
- There is insufficient evidence to recommend against the use of fertility medications to avoid borderline ovarian tumors. (Grade C)

BREAST CANCER

The causes of breast cancer are unknown and, likely, multifactorial and complex. One unifying theory for breast cancer development suggests that exposure to endogenous estrogen (earlier menarche, later menopause) increases risk (67). However, this increase in ovulatory events is also associated with an increase in exposure to progesterone. The data regarding the association of progesterone exposure and breast cancer are contradictory. While progesterone is protective to the

endometrium, it appears to be mitogenic to the breast (68, 69). However, parity, a state of high progesterone levels, is associated with a lower risk of breast cancer (70). The use of fertility drugs may result in higher estrogen, *and* progesterone, and therefore has been postulated to be associated with an increase in breast cancer, especially with prolonged use. However, it must be remembered that fertility drug use results in high levels of hormones for short periods of time, so prolonged exposure must involve numerous cycles of fertility drugs. Despite the biological plausibility, the results are conflicting; some studies show a possible increased or decreased risk, while others show no effect. In addition, several confounding factors are present when evaluating the relationship between breast cancer and fertility drug therapy. Nulliparity, late age at first birth, late age at menopause, and infertility are considered risk factors for development of breast cancer (29) and are also characteristics of the infertile population. These characteristics can also lead to detection bias in studies evaluating these issues. As with other cancers, length of follow-up in most studies may not capture the age at which disease detection commonly occurs. As a result, the data are difficult to interpret.

A distinction should be made between "fertility medications" in the study of their associations with cancer. Clomiphene citrate is structurally and functionally similar to tamoxifen (71), and when administered continuously, tomoxifen lowers the risk of breast cancer (72). Furthermore, CC causes apoptosis in breast cancer cell lines in vitro (73). The action of this agent in the laboratory, however, does not resolve the clinical issue of recurrent CC cycles for ovulation induction. The mechanism for a putative increased or decreased risk of breast cancer with the use of gonadotropins is unknown other than the obvious increase in both estradiol and progesterone in these cycles.

Many studies have evaluated the relationship between fertility drugs and breast cancer (22–24, 27, 29, 30, 32, 35, 37, 39, 41, 44, 45, 47, 58, 60, 74–91) as well as seven systematic reviews or meta-analyses (48, 51, 87, 88, 92–94). The majority of the studies and all the systematic reviews/meta-analyses have either shown no significant increase in the risk of breast cancer or a decrease in risk following infertility treatment when compared with either women with infertility who did not undergo treatment with fertility medications or the general population (22–24, 27, 29, 30, 32, 35, 37, 41, 44, 45, 47, 48, 51, 58, 60, 74–84, 86–89, 91–94). A large cohort study evaluated the incidence of breast cancer in an infertile population and found that the incidence was not significantly higher in those who underwent IVF compared with those who did not (HR 1.10, 95% CI 0.88–1.36) (89). Another large cohort study with 30 years' follow-up found that ever use of CC or gonadotropins was not associated with an increased risk for breast cancer compared with never use (HR 1.05, 95% CI 0.90–1.22 and HR 1.14, 95% CI 0.89–1.44, respectively) (76). Another cohort study with >30 years follow-up showed that ovulation induction with CC (SIR 1.21, 95% CI 0.91–1.58), gonadotropins (SIR 0.4, 95% CI 0.11–1.6), or CC and gonadotropins (SIR 0.93, 95% CI 0.48–1.63) was not associated with an increased risk of breast cancer when compared with expected rates in the general population (29).

While the majority of studies fail to show an association, subset analyses in some studies show conflicting data regarding risk of breast cancer in relation to low or high cumulative dose of CC (29, 60, 91, 95), hormonal cause of infertility (29, 91), and age at first infertility treatment (83, 89, 96). One concern is that length of follow-up in most studies is relatively short, and in some studies a higher risk of breast cancer has been observed with follow-up of >10 years (75, 85, 92), but in two studies with >30 years of follow-up, no association was noted (29, 76).

Summary statement:

- There is fair evidence that fertility drugs are not associated with an increased risk of breast cancer. (Grade B)

ENDOMETRIAL CANCER

Type 1 endometrial cancer is the most common uterine cancer and is associated with unopposed estrogen. Progesterone is protective. It is, therefore, plausible to suggest that fertility drugs could either increase the incidence of endometrial cancer due to increased estrogen production or decrease the incidence of endometrial cancer secondary to the protective progestational effect seen with ovulation. As with investigation to determine the risk of fertility drugs on other types of cancer, studies addressing the risk of endometrial cancer are also limited by methodological issues. Most cohort studies have small numbers of outcomes, short or incomplete follow-up, and inadequate methods to control for potential confounders such as anovulation, hormonal therapy, obesity and associated hyperinsulinemia, and hysterectomy. In addition, many studies do not reflect current practice patterns as they evaluate infertility populations that were treated well before IVF became a common treatment for infertility.

Several studies have shown an increase in the incidence of endometrial cancer in women with infertility, most notably in those with ovulatory dysfunction, progesterone deficiency, and/or obesity (29, 32, 37, 97, 98). When evaluating the relationship between fertility drug use and subsequent development of endometrial cancer, nine studies and three systematic reviews were included for this guideline (22, 24, 29, 32, 37, 48, 55, 97–101). The majority of studies showed that the overall use of fertility drugs, specifically CC, gonadotropins, and IVF treatment, was not associated with a significant increased risk for endometrial cancer (22, 24, 29, 32, 37, 97, 99, 100). A large, retrospective study of 12,193 women evaluated for infertility and followed for an average of 26 years showed no significant increase in the risk of endometrial cancer with CC (HR 1.39, 95% CI 0.96–2.01), gonadotropins (HR 1.34, 95% CI 0.76–2.37), or CC and gonadotropins (HR 1.77, 95% CI 0.98–3.19) when compared with non-users (100). Another study in 2,431 women diagnosed with infertility and followed for more than 20 years showed that the incidence of endometrial cancer following treatment with either CC (SIR 1.07, 95% CI 0.39–2.33) or human menopausal gonadotropin (hMG) (SIR 2.16, 95% CI 0.43–6.32) was not increased compared with the

general population, while treatment with CC and hMG was associated with an increased risk (SIR 5.0, 95% CI 2.15–9.85) (29). However, in a subsequent multivariable analysis there was no significant increase noted in any of these comparisons. One case-control study showed an increased risk of endometrial cancer following the use of fertility drugs when compared to a general female population matched for age and study center, although there is no information provided regarding the type of fertility drugs used (OR 3.26, 95% CI 1.07–9.95) (101). In this study, the risk of endometrial cancer was higher with last use less than 25 years before interview and age at first use <30 years. One systematic review reported an increased risk for endometrial cancer with fertility drug use only when compared with the general population (RR 2.04, 95% CI 1.22–3.43), but not when the study group was compared with an untreated infertility cohort (RR 0.45, 95% CI 0.18–1.14) (55).

Summary statement:

- Overall, there is fair evidence that fertility drugs are not associated with an increased risk of endometrial cancer. (Grade B)

OTHER CANCERS

Thyroid Cancer

Thyroid cancer is more common in women than men, especially during the reproductive years. Other factors associated with an increase in thyroid cancer risk include high parity and use of exogenous hormones such as oral contraceptives and hormone replacement therapy (102). Six studies were included for analysis (37, 102–106). The majority of studies evaluating the association between fertility drug use and thyroid cancer show no significant effect. The three largest studies have conflicting results. Two studies showed a nonsignificant increase in the incidence of thyroid cancer following ever use of CC: one had an RR 1.42 (95% CI 0.5–3.7), which did not vary with dose or duration of therapy and had no effect following the use of gonadotropins (RR 1.1, 95% CI 0.2–4.9) (103); and the other had an HR 1.57 (95% CI 0.89–2.75) based on 55 patients (104). Another showed a significant increase in thyroid cancer with ever use of CC (RR 2.29, 95% CI 1.08–4.82), significant risk with 1–5 cycles of CC and ≥5-year use, no increased risk with gonadotropins, and an increased risk with progesterone based only on three patients (102).

Malignant Melanoma

The incidence of malignant melanoma has increased during the last 50 years, especially in women, and has been associated with low parity, late age at first birth, and use of oral contraceptives (107). Several studies and one systematic review have evaluated the risk of malignant melanoma following the use of fertility drugs (30, 37, 103, 104, 107–112). All but one showed no significant overall increased risk of malignant melanoma with the use of fertility drugs. Notably, in the subanalysis, one study showed women who underwent IVF and became parous had a higher risk of invasive melanoma compared with those women who underwent IVF and remained nulliparous (HR 3.61, 95% CI 1.79–7.26), although there was no overall association with IVF (113). In another study, although there was not an overall association, use of gonadotropins and GnRH among parous women was significantly associated with invasive melanoma (107). The use of CC was associated with an increased risk of melanoma in two studies (23, 104). However, there was no significant association noted in other studies (103, 107, 109, 111, 112).

Colon Cancer

Three studies that examined the use of fertility drugs and colon cancer were included for this guideline (103, 104, 114). One study evaluated the risk of colon cancer in 8,422 women following the use of fertility drugs and found no association with CC (RR 0.83, 95% CI 0.4–1.9) (103). A second study with a median follow-up of 21 years evaluated the incidence of colorectal cancer in 19,158 women who received ovarian stimulation for IVF, compared with 5,950 women who underwent subfertility treatments other than IVF (tubal surgery [stimulated or unstimulated], intrauterine insemination, CC, or withdrew from the waiting list for IVF) and the general population identified in the national cancer registry (114). There was no increase in the incidence of colorectal cancer in the IVF group compared with controls (SIR 1.00, 95% CI 0.80–1.23); however, the incidence of colorectal cancer was lower in the non-IVF group (SIR 0.58, 95% CI 0.36–0.88).

Non-Hodgkin Lymphoma

One study evaluated the risk for non-Hodgkin lymphoma following the use of fertility drugs and showed an increased risk with ovulation induction therapy (HR 2.86, 95% CI 1.14–7.20) but not with use of CC alone (23).

Cervical Cancer

Several studies evaluated the risk of cervical cancer following the use of fertility medications and found no increased risk when compared to the general population as well as patients with infertility (24, 27, 35–37, 47, 51, 55, 59, 81, 103, 115). Two studies noted a significant decrease in the incidence of cervical cancer following IVF (47, 81). One study noted a significant decrease in cervical cancer following the use of CC (RR 0.4, 95% CI 0.2–0.8) (115).

Summary statements:

- Overall, there is fair evidence that fertility drugs are not associated with an increased risk of invasive thyroid cancer. (Grade B)
- Overall, there is insufficient evidence that fertility drugs are associated with an increased risk of melanoma. (Grade C)
- Overall, there is fair evidence that fertility drugs are not associated with an increased risk of colon cancer. (Grade B)

- Based on a single study, there is insufficient evidence that fertility drugs are associated with an increased risk of lymphoma. (Grade C)
- Overall, there is fair evidence that fertility drugs are not associated with an increased risk of cervical cancer. (Grade B)

SUMMARY

- The data assessing the association between fertility drugs and cancer are limited and principally come from observational studies (Level 2-2 or lower).
- Methodological issues include small sample sizes, heterogeneous treatment regimens, inadequate information about duration and dose of treatment, retrospective analyses, and short follow-up periods.
- Overall, there is fair evidence that women with infertility have an increased risk of breast, ovarian, and endometrial cancer. (Grade B)
- Based on available data, we can be reasonably reassured that there is no meaningful increased risk of invasive ovarian cancer following the use of fertility drugs in infertile women. (Grade B)
- Based on the available data there is fair evidence that the risk of invasive ovarian cancer is not different with one fertility drug compared with another. (Grade B)
- While several studies have shown a small increase in the absolute risk of borderline tumors after fertility treatments, there is insufficient consistent evidence that a particular fertility drug increases the risk of borderline ovarian tumors. (Grade C)
- It is important to note that any absolute increase in risk is small, and borderline ovarian tumors are indolent and generally have a favorable prognosis. (Grade B)
- There is fair evidence that fertility drugs are not associated with an increased risk of breast cancer. (Grade B)
- Overall, there is fair evidence that fertility drugs are not associated with an increased risk of endometrial cancer. (Grade B)
- Overall, there is fair evidence that fertility drugs are not associated with an increased risk of invasive thyroid cancer. (Grade B)
- Overall, there is insufficient evidence that fertility drugs are associated with an increased risk of melanoma. (Grade C)
- Overall, there is fair evidence that fertility drugs are not associated with an increased risk of colon cancer. (Grade B)
- Based on a single study, there is insufficient evidence that fertility drugs are associated with an increased risk of lymphoma. (Grade C)
- Overall, there is fair evidence that fertility drugs are not associated with an increased risk of cervical cancer. (Grade B)

RECOMMENDATIONS

- Given the available literature, patients should be counseled that infertile women may be at an increased risk of invasive ovarian, endometrial, and breast cancer; however, use of fertility drugs does not appear to increase this risk.
- While several studies have shown a small increase in the absolute risk of borderline ovarian tumors after fertility treatments, there is insufficient consistent evidence that a particular fertility drug increases the risk of borderline ovarian tumors.
- It is important to note that borderline ovarian tumors are indolent and generally have a favorable prognosis, and any absolute increase in risk related to fertility drugs is small. Therefore, there is insufficient evidence to recommend against the use of fertility medications to avoid borderline ovarian tumors.

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