Fertility drugs and cancer: a guideline

Practice Committee of the American Society for Reproductive Medicine

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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 increased risk of cancer because of factors (endometriosis and unopposed estrogen) associated with infertility, the low incidence of most of these cancers, and that the diagnosis of cancer is typically several years after fertility drug use. On the basis of available data, there does not appear to be an association between fertility drugs and breast, colon, or cervical cancer. There is no conclusive evidence that fertility drugs increase the risk of uterine cancer, although women with infertility are at higher risk of uterine cancer. There are insufficient data to comment on the risk of melanoma and non-Hodgkin lymphoma associated with fertility drug use. Women should be informed that there may be an increased risk of invasive and borderline ovarian cancers and thyroid cancer associated with fertility treatment. It is difficult to determine whether this risk is related to underlying endometriosis, female infertility, or nulliparity. (Fertil Steril® 2024;122:406–20. ©2024 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Fertility, fertility drugs, cancer, reproductive health, reproductive science

RECOMMENDATIONS

- Women should be informed that there may be an increased risk of ovarian cancer associated with fertility treatment. Given significant heterogeneity between studies, it is difficult to approximate the effect size; however, the overall risk is likely to be small. In addition, it is difficult to determine whether this risk is related to underlying endometriosis, female infertility, or nulliparity, which has previously been associated with an increased risk of ovarian cancer (strength of evidence, B; strength of recommendation, weak/moderate).
- Women should be informed that there may be an increased risk of borderline ovarian tumors associated with assisted reproductive technology. This increase in risk may be because of underlying infertility or nulliparity (strength of evidence, B/C; strength of recommendation, weak/moderate).
- Women should be informed that there does not appear to be an increased risk of breast cancer associated with assisted reproductive technology. Prolonged (>10 cycles) of clomiphene should be avoided (strength of evidence, B; strength of recommendation, weak/moderate).
- Women should be informed that there is no conclusive evidence that fertility treatments increase the risk of endometrial/uterine cancer. Underlying risk factors associated with infertility are more likely to be associated with endometrial cancer (strength of evidence, B; strength of recommendation, moderate).
- Women should be informed that there may be an increased risk of thyroid cancer associated with fertility treatment, specifically clomiphene use among those most heavily exposed (strength of evidence, C; strength of recommendation, weak).
- Women should be informed that fertility drugs are not associated with an increased risk of colon cancer (strength of evidence, B/C; strength of recommendation, weak/moderate).
- Women should be informed that there are insufficient data to determine whether fertility drugs are associated with an increased risk of non-Hodgkin lymphoma (strength of evidence, C; strength of recommendation, weak).
- Women should be informed that fertility drugs are not associated with an increase in the risk of cervical cancer (strength of evidence, B/C; strength of recommendation, weak/moderate).
- Women should be informed that there are insufficient data to determine whether fertility drugs are associated with an increased risk of malignant melanoma (strength of evidence, C; strength of recommendation, weak).

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

Received March 27, 2024; accepted March 28, 2024; published online May 3, 2024.
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Fertil Steril® Vol. 122, No. 3, September 2024 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2024.03.026

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 patients with infertility; and the lack of long-term follow-up. Women with infertility are more likely to have endometriosis, a risk factor for ovarian cancer, and oligomenorrhea, a risk factor for endometrial cancer. 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 (OI) cycles. This guideline is an update and replaces the published document "Fertility Drugs and Cancer: A Guideline," published in 2016 (1).

MATERIALS AND METHODS

This clinical practice guideline followed a methodological protocol established by American Society for Reproductive Medicine (ASRM) staff and executive leadership, the ASRM Practice Committee, and an independent consulting epidemiologist. The ASRM Practice Committee identified the necessity to update the previously published 2016 guideline on "Fertility Drugs and Cancer" and empaneled a task force of experts to engage in its development (1). The members of the task force applied the Population, Interventions, Comparisons, and Outcomes framework to formulate focused questions.

A comprehensive systematic review of the literature using the MEDLINE database through PubMed was conducted to identify peer-reviewed studies. The searches were restricted to include articles published since the previous guideline and included the date range of December 8, 2015 (the end date of the original 2016 data search), to November 30, 2022, using a combination of the following words or word phrases: fertility; infertility; medication; drug; drugs; medicine; medical treatment; treatment; treatments; cancer; endometri*; endometrial; endometrium; endometrioid; mammary; breast; ovary; ovarian; ovar*; uterus; uterine; uter*; cervical; thyroid; colon; melanoma; IVF; clomid; clomiphene; clomifene; clomifen; genotoxic*; cancer risk; cause; FSH; genotoxic*; genotoxicity; cancer risk; gonadotropin; gonadotropins; gonadotrophin; gonadotrophins; hcg; hmg; LH; luteinizing hormone; letrozole; ovarian stimulation; ovulation induction; fertilization in vitro/adverse effects [MeSH]; ovulation induction/adverse effects[MeSH]; fertility agents; female/adverse effects[MeSH]; neoplasms [MeSH]; neoplasms/chemically induced[MeSH]; neoplasms/epidemiology*[MeSH]; endometrial neoplasms/chemically induced [MeSH]; endometrial neoplasms/etiology[MeSH]; ovarian neoplasms/chemically induced[MeSH]; ovarian neoplasms/etiology[MeSH]; uterine cervical neoplasms/chemically induced[MeSH]; uterine cervical neoplasms/etiology[MeSH]; uterine cervical neoplasms/epidemiology[MeSH]; thyroid neoplasms/chemically induced[MeSH]; thyroid neoplasms/etiology[MeSH]; thyroid neoplasms/epidemiology[MeSH]; colonic neoplasms/chemically induced[MeSH]; colonic neoplasms/etiology[MeSH]; colonic neoplasms/epidemiology [MeSH]; melanoma/chemically induced[MeSH]; melanoma/etiology[MeSH]; melanoma/epidemiology[MeSH]; clomiphene/adverse effects[MeSH]; follicle-stimulating hormone/adverse effects[MeSH]; gonadotropins/adverse effects [MeSH]; chorionic gonadotropin; human/adverse effects [MeSH]; and menotropins/adverse effects[MeSH]. Articles were subsequently culled for English language. The literature search yielded 1,077 articles, of which 52 studies met the inclusion criteria for this update. This guideline's summary statements and recommendations were based on included studies.

Per inclusion/exclusion criteria that the task force agreed on (Table 1), studies included for assessment were randomized controlled trials (RCTs); systematic reviews or meta-analyses of RCTs; systematic reviews or meta-analyses of a combination of RCTs, controlled trials without randomization, and cohort studies; controlled trials without randomization; cohort studies; and case-control studies. Descriptive studies, case series, case reports, letters, nonsystematic reviews, opinions on the basis of clinical experience, and reports of expert committees were excluded from this guideline.

TABLE 1

Inclusion/exclusion criteria.

Include	Exclude
RCTs; systematic reviews or meta-analyses of RCTs; systematic reviews or meta-analyses of a combination of RCTs, controlled trials without randomization, and cohort studies; controlled trials without RCTs, controlled trials without randomization; and case-control studies	Descriptive studies, case series, case reports, letters, nonsystematic reviews, opinions on the basis of clinical experience, and reports of expert committees
Human studies	Animal studies
English	Non-English
Studies with a comparison group	Studies without a comparison group
Studies that assess cancer outcome/incidence in women after exposure to infertility treatment	Studies that assessed the prevalence of cancer in offspring of patients with infertility

Note: RCT = randomized controlled trial.

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The titles and abstracts of potentially relevant articles were screened and reviewed initially according to the preliminary inclusion/exclusion criteria determined by task force members. All reviewed the full articles of all citations that potentially matched the predefined selection criteria. Final inclusion or exclusion decisions were made on examination of the articles in full detail. Disagreements about inclusion were discussed and resolved by consensus or arbitration after consultation with an independent reviewer/epidemiologist.

Quality of evidence

A methodological specialist extracted data from included studies into an evidence table for outcomes identified by the task force, including study population of patients with exposure to infertility treatment vs. controls, type of fertility medication used (follicle-stimulating hormone [FSH], human menopausal gonadotropin, letrozole, gonadotropin-releasing hormone [GnRH], or clomiphene citrate [CC]), outcomes including type of cancer (breast, ovarian, borderline ovarian tumor [BOT], thyroid, melanoma, colorectal, or uterine cancer) and subsequent incidence/odds of cancer diagnosis. Task force members critically assessed the strengths and limitations of available evidence to rate the quality of each study and assign a quality grade on the basis of the rating scale below, which was recorded in the evidence table (Supplemental Table 1, available online).

Assessment of the quality of the evidence allowed the task force to make distinctions among studies (Table 2). The quality of the evidence was evaluated using the following grading system. The task force chair reviewed grades of quality assigned by task force members and provided oversight throughout the entire development process. If no grade was assigned, the task force chair determined a grade of quality on the basis of a study's strengths and limitations. The study design was evaluated, and the quality of the methodology was assessed on the basis of components including blinding, allocation concealment, appropriate control groups, intention-to-treat analysis, generalizability, and risk of bias. The consulting epidemiologist and chair of the task force confirmed agreement with the expert task force's assessment of quality on the basis of the following definitions.

The task force summarized data from the evidence table in narrative form to include the characteristics, quality, benefit, and conclusions of studies relevant to answering each treatment related to the question. The expert task force convened via email to review the literature and summarize findings. The task force chair presented these summaries of evidence and draft conclusions to the ASRM Practice Committee for deliberation of the strength of the evidence and the strength of the recommendations and approval of summary statements and recommendations. The quality of the evidence informed the strength of the guideline's evidence (Table 3). The strengths of recommendations in this guideline were based on both the quality and strength (confidence/certainty) of evidence, risks, benefits, and expert judgment of the Practice Committee and task force. Patient perspective and feedback were elicited during review and before the publication of a guideline.

TABLE 2

Rating for quality of evidence.

Quality of evidence	Definition
High quality	✓ Target population clearly identified ✓ Sufficient sample size for the study design ✓ Clear description of the study design ✓ Appropriate control(s) ✓ Generalizable results ✓ Definitive conclusions ✓ Minimal risk of bias ✓ Limitations do not invalidate conclusions ✓ Evidence primarily on the basis of well-designed systematic reviews or meta-analyses of RCTs
Intermediate quality	✓ Target population ✓ Sufficient sample size for the study design but could benefit from larger studies ✓ Control group identified ✓ Reasonably consistent results in which limitations do not invalidate ✓ Fairly definitive conclusions ✓ Low risk of bias ✓ Evidence primarily on the basis of small RCTs; systematic reviews or meta-analyses of a combination of RCTs, controlled trials without randomization, and cohort studies; controlled trials without randomization; and/or well-designed observational studies
Low quality	✓ Insufficient sample size for the study design ✓ Discrepancies among reported data ✓ Errors in study design or analysis ✓ Missing significant information ✓ Unclear or inconsistent results ✓ High risk of bias because of multiple flaws so that conclusions cannot be drawn ✓ High uncertainty about validity of conclusions

Note: RCT = randomized controlled trial.

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TABLE 3

Rating for strength of evidence.

Strength of evidence	Definition
Grade A	High confidence in evidence. Larger or further study very unlikely to change reported effect. Most evidence supported by well-constructed RCTs or extremely strong and consistent observational studies with generalizable results, sufficient sample sizes for the study design, adequate controls, definitive conclusions, and minimal risk of bias
Grade B	Moderate confidence in evidence. Larger or further studies not likely to change reported effect but may more precisely identify magnitude of effect. Most evidence comprises RCTs with potential weaknesses including small sample size or generalizability or moderately strong and consistent observational studies with reasonably consistent results, sufficient sample sizes for the study designs, identified appropriate controls, fairly definitive conclusions, and low risk of bias
Grade C	Low confidence in evidence. Evidence lacking to support reported effect. Evidence comprises observational studies with significant methodological flaws and/or inconsistent findings on the basis of poor evidence, inconsistent results, insufficient sample size for study design, conclusions that cannot be drawn, and/or high risk of bias

Note: RCT = randomized controlled trial.

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Not all topics are appropriate for a systematic review. In some cases, literature is yet to be available, and documents on the basis of expert consensus should summarize suggested best practices in the context of available literature. The ASRM guidelines, however, follow a rigorous developmental process on the basis of documented, verifiable systematic reviews of the scientific literature. The ASRM task force guideline development follows a strict methodology to objectively evaluate available scientific literature on their assigned topic to make evidence-based recommendations. Included evidence related to the association of fertility drugs and cancer was searched for and collected systematically, objectively assessed, and described clearly and succinctly to inform readers relying on the ASRM guidelines with trusted recommendations that were guided by the quality of available evidence. These evidence-based recommendations are intended to optimize patient care and help guide medical practice in the field of reproductive medicine.

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 because randomized trials would not be possible to address this issue. Case-control studies are particularly common because this method is efficient in studying rare outcomes. However, this study design has 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 several 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, known to be independently associated with increased cancer risk (e.g., nulliparity, endometriosis, and anovulation), are overrepresented in the study population (2–7). 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 overrepresented in the control population. Furthermore, detection bias is also potentially problematic because patients with infertility 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 than in controls.

Cohort studies also have inherent advantages and limitations. Although a cohort study can potentially minimize selection bias, it may be limited by recall bias and/or the ability to identify and quantitate exposure precisely. "Fertility drugs" are pharmacologically and physiologically distinct agents. In addition, several cohort studies are limited by a lack of long-term follow-up, leading to a lower perceived incidence of disease because cancers may occur several years after the medication was used and, thus, there is difficulty in establishing a causal link. Lack of distinction between CC, gonadotropins (FSH and/or luteinizing hormone [LH]), and human chorionic gonadotropin in the study design can also lead to bias and a false-positive *or* false-negative finding. Additionally, retrospective studies rely on 2 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 have poor reliability or bias. The accurate recall of fertility drug usage may be questioned in women with cancer because individuals attempt to find reasons why they developed cancer. These limitations, as well as others, should 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 before 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 (8). Overall, the most significant limitations in the existing literature include duration of follow-up, conflicting results, recall bias, selection of appropriate control groups, and controlling for important confounding factors such as nulliparity and underlying infertility diagnoses. As such, it is difficult to assess a directly causal relationship between exposure to infertility treatments and the outcome of cancer(s) because associations may or may not be because of unreported/unmeasured confounder(s).

OVARIAN CANCER

Ovarian cancer is rare and accounts for approximately 3% of all cancers in women, with approximately 20,000 cases diagnosed annually in the United States (9). Parity is inversely related to the risk of ovarian cancer (odds ratio [OR], 0.65; 95% confidence interval [CI], 0.48–0.88) (10); therefore, women with infertility are felt to be at an increased risk of ovarian cancer. In addition, endometriosis, which is present in 20%–30% of women with infertility, increases the risk of ovarian cancer nearly twofold (standardized rate ratio [SRR], 1.93; 95% CI, 1.68–2.22) (11).

There are several mechanisms by which 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 of ovarian cancer in gravid women and/or women who have used 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, whereas oral contraceptives reduce the risk by reducing the number of epithelial disruptions associated with ovulations and epithelial repair (12). 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 originate in other pelvic organs and involve the ovary secondarily (13). For example, good evidence suggests that the fallopian tube is the primary origin of high-grade serous ovarian cancers (8). Therefore, the theory of incessant ovulation linking fertility drugs and all ovarian cancers has been questioned.

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 (14). Moreover, FSH, LH, and estradiol stimulate ovarian epithelial cell proliferation and inhibit apoptosis in ovarian epithelial cancer cell lines (15). Interestingly, CC potentiates the antiproliferative effect of some chemotherapeutic agents in estrogen receptor-negative ovarian cancer cell lines (16). However, the 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 unknown whether limited exposure during fertility treatment could alter lifetime risk or a pregnancy resulting from fertility treatments will negate any potential increase in risk.

INVASIVE OVARIAN CANCER

As the 2016 guideline "Fertility Drugs and Cancer" acknowledged, the risk of ovarian cancer after infertility treatment has been suggested for several years (1). However, at the time of the publication, there was not sufficient evidence to conclude whether there was an association between fertility treatment and invasive ovarian cancer. After the publication of this guideline, several additional studies have been published in this area that demonstrate an association.

In 2015, one of the first large observational studies was published by Luke et al. (17). This group specifically investigated patients who underwent assisted reproductive technologies (ARTs) in New York, Texas, or Illinois. It linked these patients to their respective state cancer registries in the years after ART. The mean number of years of follow-up was 4.87 years, and the study reported 48 cases of ovarian cancer in 113,226 women who underwent ART (17). This study noted a nonsignificant increase in the expected number of ovarian cancer cases on the basis of age-specific cancer rates in the general population (SRR, 1.18; 95% CI, 0.87–1.56). This study contained overall low numbers of ovarian cancer cases within a relatively short period of follow-up. A Danish, nationwide, population-based cohort study (1994–2015) linked ART cycle data with data from the Danish Cancer Register. The population consisted of 58,472 ART-treated women and 625,330 untreated women (all with no previous malignancies). A total of 393 women (0.06%) were diagnosed with ovarian cancer during follow-up (mean, 9.7 years). Women treated with ART had an increased risk of ovarian cancer (hazard ratio [HR], 1.20; 95% CI, 1.10–1.31), which diminished over time (18).

The observed increase in risk may be attributable to underlying endometriosis. Previous studies have indicated that the presence of endometriosis confers a higher risk of ovarian cancer (19). In a 2021 meta-analysis, Kvaskoff et al. (11) found a positive association between endometriosis and ovarian cancer risk (SRR, 1.93; 95% CI, 1.68–2.22), with the risk highest for clear cell (SRR, 3.44; 95% CI, 2.82–4.42) and endometrioid (SRR, 2.33; 95% CI, 1.82–2.98) ovarian cancer types (11). Further analysis of the Danish cohort study showed that the risk of ovarian cancer was only increased among women with endometriosis (HR, 3.78; 95% CI, 2.45–5.84), whereas no increased risk was found among ART-treated women with other female causes of infertility. This study concluded that ART treatment without the presence of endometriosis was not associated with an increased risk of ovarian cancer (18).

Other studies have been less clear if patient factors specifically, or the ART treatment itself, place patients at increased risk of ovarian cancer. In 2016, a study was published comparing the incidence of long-term female malignancies in a cohort of women with and without a history of fertility treatments (including IVF and OI) (n = 3,239) (20). A total of 106,031 women met the study inclusion criteria, with 4.1% (n = 4,363) having a history of fertility treatments. During the follow-up period, patients with a history of IVF had a significantly increased risk of ovarian cancer compared with patients after OI and those with no history of fertility treatments, even when controlling for age and obesity (adjusted

HR [aHR], 3.9; 95% CI, 1.2–12.6; $P = .022$, and aHR 4.6; 95% CI, 1.4–14.9; $P = .011$, respectively). It is important to note that the investigators did not control for infertility diagnosis or the presence of endometriosis and were ambiguous regarding whether the aHR calculations compared IVF patients with OI vs. patients without subfertility. Similarly, Williams et al. (21) performed a data linkage cohort study in Great Britain in 2018, where all patients who had undergone ART from 1991 to 2010 were linked to a national cancer registry. A total of 255,786 women contributed 2,257,789 person-years of follow-up in this study, and the observed first diagnoses of ovarian, breast, and corpus uteri cancers in cohort members were compared with age, sex, and expected rates of cancer in this period. There was an increased risk of invasive ovarian cancer (264 observed cases vs. 188.1 expected; standardized incidence ratio [SIR], 1.40; 95% CI, 1.24–1.58; absolute excess risk, 3.4 cases per 100,000 person-years; 95% CI, 2.0–4.9). Increased risks of ovarian tumors were noted to be limited to women with endometriosis, low parity, or both. This study found no increased risk of any ovarian tumor in women treated because of only male factor or unexplained infertility.

Another large population-based register study was conducted in 2019 of 1,340,097 women with a first live birth in Sweden between 1982 and 2012 to assess the relationship between ART treatments, infertility, and incidence of ovarian cancer (22). This study found that women who gave birth after ART had a higher incidence of ovarian cancer (aHR, 2.43; 95% CI, 1.73–3.42) than those without infertility. Compared with women with infertility diagnoses and non-ART births, women with ART births also had a higher incidence of ovarian cancer (aHR, 1.79; 95% CI, 1.18–2.71). The investigators of this study concluded that at least part of the risk of ovarian cancer seems to be because of the underlying infertility and not the treatment per se.

Finally, a Cochrane review was published in 2019 to evaluate the risk of invasive ovarian cancer in women treated with ovarian-stimulating drugs for subfertility (23). The overall group size was 4,684,724, with 13 case-control and 24 cohort studies included. The investigators of the meta-analysis found that there were few studies suggesting that infertility drugs increase the risk of ovarian cancer slightly in women with subfertility treated with infertility drugs compared with that in the general population or women with subfertility not treated. This conclusion was in contrast to the Cochrane review in 2013, which demonstrated no convincing evidence of an increase in the risk of invasive ovarian tumors with fertility drug treatment (24). The risk found in the most recent Cochrane review was slightly higher in nulliparous than in multiparous women treated with infertility drugs. However, it was also noted that few studies have been conducted, the number of cancers is very small, and information on the dose or type of fertility drugs used is insufficient.

Further studies have been performed in special populations with more reassuring results. BRCA1 and BRCA2 mutation carriers do not appear to have an increased risk of epithelial ovarian cancers, no matter the modality of treatment used (25). When comparing carriers who were treated for infertility with those not treated for infertility, fertility treatments were not associated with epithelial ovarian cancer risk (age-adjusted OR, 0.63; 95% CI, 0.38–1.05) regardless of treatment type (with CC, OR, 0.87 [95% CI, 0.46–1.63]; with gonadotropin, OR, 0.59 [95% CI, 0.26–1.31]; with IVF, OR, 1.08 [95% CI, 0.57–2.06]). A study was performed in 2016 to assess possible ovarian cancer risk in oocyte donors (26). This retrospective cross-sectional survey of women who had donated oocytes between 1990 and 2012 was performed, with 429 of 569 donors screened responding to self-administered questionnaires. There were no reports of ovarian or uterine cancer and only 1 case of breast cancer in the cohort, with a mean follow-up time after the donation of 11.2 years. This study is reassuring regarding the risk of ovarian cancer in oocyte donors; however, further large studies are needed to ensure this risk is minimal.

Summary statement

- There is weak/moderate evidence that fertility treatment is associated with ovarian cancer. Given significant heterogeneity between studies, it is difficult to approximate the effect size; however, the overall risk is likely to be small (approximately 3 more cases per 100,000 person-years). In addition, evidence suggests that at least some of this risk is related to underlying endometriosis, female infertility, or nulliparity, which has previously been associated with an increased risk of ovarian cancer.

Recommendation

- Women should be informed that there may be an increased risk of ovarian cancer associated with fertility treatment. Given significant heterogeneity between studies, it is difficult to approximate the effect size; however, the overall risk is likely to be small. In addition, it is difficult to determine whether this risk is related to underlying endometriosis, female infertility, or nulliparity, which has previously been associated with an increased risk of ovarian cancer (strength of evidence, B; strength of recommendation, weak/moderate).

BORDERLINE OVARIAN TUMORS

Borderline ovarian tumors are unique, recognized as an intermediate between malignant and benign tumors, with a low malignant potential and accounting for 15% of all ovarian neoplasms (27). In contrast to ovarian cancer, BOTs do not grow invasively (28), are diagnosed in women at an earlier age, and have a favorable prognosis, with more than 95% of women surviving 5 years beyond diagnosis (2). With an increasing demand for infertility treatment, there is still little evidence of an association between fertility drug use and ovarian cancer. Of note, several studies have shown a link between fertility drugs and BOTs (2, 22, 29–35). One of the most extensive register-based study on 1,340,097 performed in Sweden between 1982 and 2012 suggested that women who have underwent ART have a higher risk of BOT (aHR, 1.91; 95% CI, 1.27–2.86) (22). They also acknowledged that part

of that risk seems to be because of the underlying infertility and not the treatment per se because the increased risk was smaller than that in other women with infertility who did not undergo ART treatment (aHR, 1.48; 95% CI, 0.90–2.44) (22). Another large study investigating the incidence of BOT in ART patients evaluated a cohort of patients with infertility identified through a hospital registry and compared those who underwent ART with patients with infertility who did not undergo ART (2). Of the 7,544 women who underwent ART, 17 were diagnosed with BOTs, compared with 14 of 14,095 women in the non-ART infertility group (2). The rate of BOTs in women who underwent ART was higher, with an HR of 2.46 (95% CI, 1.20–5.04), translating into 11 additional cases of borderline tumors per 10,000 women. Unlike invasive ovarian cancer, previous birth, hysterectomy, sterilization, or endometriosis did not affect the incidence of borderline tumors (2, 18). Another study compared the incidence of BOTs in a cohort of >19,000 women who underwent ART with that in 6,000 women with subfertility who did not undergo ART and that in the general population, with a mean follow-up of 14.7 years (32). The incidence of BOTs was higher in the ART cohort than in the general population (SIR, 1.76; 95% CI, 1.16–2.56) and the subfertility group (HR, 4.23; 95% CI, 1.25–14.33), whereas the rate of invasive ovarian cancer did not increase (HR, 1.51; 95% CI, 0.65–3.54) compared with that in the subfertility group (32).

Despite these reports, several studies have not demonstrated an increased risk of BOTs with the use of ART treatments (18, 25, 36–39). A large 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 BOTs (38). Overall, the use of ART treatments did not increase the risk of BOTs (relative risk [RR], 1.0; 95% CI, 0.67–1.51). Although no evident association was observed for CC, gonadotropins, human chorionic gonadotropin, or GnRH agonists, progesterone use was associated with an increased risk of BOTs (RR, 1.82; 95% CI, 1.03–3.24). A large systematic review evaluating the risk of BOTs after the use of ART treatments identified 3 case-control and 3 cohort studies (38). Three studies were included that reported a two- to threefold increased risk of BOTs with fertility drug use (34–36). However, the investigators were not able to perform a true meta-analysis, giving an overall RR because of the extreme heterogeneity among studies (24). Nonetheless, when individual drug use was evaluated, there was no significant increased risk of BOTs with CC alone, CC and gonadotropins, or gonadotropins alone (24). An updated version of the original 2013 Cochrane review on the risk of ovarian cancer and BOT in women using ART treatments compared with the general population or women with infertility not treated concluded that the link between ART treatments and ovarian cancer remains controversial (23). They analyzed the data of 13 case-control and 24 cohort studies, including a total of 4,684,724 women. Although some studies suggested a slight increase in the risks of ovarian cancer and BOT, none provided moderate- or high-certainty evidence (23). In addition, the review underlined the lack of studies conducted, very small incidence, and lack of information on the dose or type of fertility drugs used (23).

Interpreting and summarizing the existing evidence reported by observational studies addressing the association between fertility drugs and BOTs remain a challenge, given the rarity of such tumors and significant methodological issues that make studies prone to confounding and bias.

Summary statements

- There is weak evidence that fertility treatment, specifically ART, increases the risk of BOTs.
- There is weak evidence that at least some of the increase in risk is because of underlying infertility or nulliparity.

Recommendation

- Women should be informed that there may be an increased risk of BOTs associated with ART. This increase in risk may be because of underlying infertility or nulliparity (strength of evidence, B/C; strength of recommendation, weak/moderate).

BREAST CANCER

Breast cancer remains the most frequent female malignancy, affecting 1 in 8 women's lifetimes. The causes are unknown and, likely, multifactorial and complex. Most breast cancers are estrogen and progesterone sensitive, and several hormonal aspects could play a significant role in its etiology. This led to a common hypothesis for breast cancer development, suggesting that endogenous estrogen exposure (in the case of early menarche, delayed menopause) increases its risk (40). However, this increase in ovulatory events is also naturally associated with an increase in exposure to progesterone. Evidence regarding the association of progesterone exposure and breast cancer is contradictory. Although progesterone seems protective of the endometrium, it appears to be mitogenic to the breast (41, 42). Of note, parity, a state of high progesterone levels, is associated with a lower risk of breast cancer (43).

Considering the increased incidence of breast cancer worldwide, determining whether the use of ART treatments increases the risk of breast cancer is a matter of great public health concern. However, studies investigating breast cancer risks in women who underwent ART treatments are inconsistent (3, 21, 44–51). The common belief is that ART treatments may induce temporary high estrogen *and* progesterone blood levels and, therefore, have been suggested to be linked with an increase in breast cancer incidence, especially with repeated and prolonged use. However, ART treatment results in short exposure to high hormonal blood levels, and therefore, prolonged exposure should involve numerous cycles of ART treatment. Despite the biologic plausibility, the results are conflicting; some studies show a possible increased or decreased risk, whereas others show no effect. In addition, several confounding factors are present when evaluating the relationship between breast cancer and ART treatments. Nulliparity, advanced age at first delivery, delayed menopause, and infertility are considered risk factors for

breast cancer incidence (52) and, at the same time, characteristics of the population with infertility. These characteristics can also lead to detection bias in studies evaluating these issues. As with other cancers, follow-up duration 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 ART treatments in studying their associations with cancer. Clomiphene citrate is structurally and functionally similar to tamoxifen (53), and when administered continuously, tamoxifen lowers the risk of breast cancer (54). Furthermore, CC causes apoptosis in breast cancer cell lines in vitro (55). The action of this agent in the laboratory, however, does not resolve the clinical (56) issue of recurrent CC cycles for OI. 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 levels in these cycles.

Several studies (17, 20, 52, 57–88) and 7 systematic reviews or meta-analyses (46, 50, 67, 81, 83, 89, 90) have evaluated the relationship between ART treatment and breast cancer. Most studies and all systematic reviews/meta-analyses have shown either no significant increase in the risk of breast cancer or a decrease in risk after infertility treatment compared with that in either women with infertility who did not undergo treatment with fertility medications or the general population (17, 20, 45, 46, 50, 52, 57–61,64, 65, 67–84,86, 89–91). Gennari et al. (46) conducted a meta-analysis of 20 studies and reported that hormonal treatments for infertility are not associated overall with an increased breast cancer risk. A large cohort study evaluated the incidence of breast cancer in a population with infertility and found that the incidence was not significantly higher in those who underwent IVF than in those who did not (HR, 1.10; 95% CI, 0.88–1.36) (83). Another large cohort study with 30 years' follow-up found that the ever use of CC or gonadotropins was not associated with an increased risk of 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) (71). Another cohort study with >30 years' follow-up showed that OI 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) were not associated with an increased risk of breast cancer compared with the expected rates in the general population (52).

A historical cohort (OMEGA) study with complete follow-up through December 2013 for 96% of the cohort included 19,158 women who started IVF treatment between 1983 and 1995 (IVF group) and 5,950 women who started other fertility treatments between 1980 and 1995 (non-IVF group) from all 12 IVF clinics in the Netherlands investigated the long-term risk of breast cancer after ART (91). They report that breast cancer risk among ART-treated women was not significantly higher than that in non–ART-treated women or those in the general population (91). Similarly, a recent case-control comparison, dating from 2011 to 2013, investigating 928 cases and 928 controls, reported no statistically significant relationship between infertility and OI drugs and the risk of breast cancer, except for the substantial increases in the risk of breast cancer among patients who had used fertility drugs for >6 months (51).

Other investigators reviewing a total of 95 articles reported no significant increase in the risk of breast or other cancers in women using ART treatments. They also noted a significant protective factor when achieving pregnancy at an earlier age (48). There are reports that pregnancy using ART treatment (all types of ART treatments) in women with a history of breast cancer is feasible and does not seem detrimental to the cancer outcome. These investigators studied 198 women who were diagnosed with breast cancer between 2000 and 2009 and had a pregnancy after the oncologic diagnosis (49). More reassuring evidence was provided by Coddington et al. (92) who investigated death from all causes in women who delivered between 2004 and 2013, with or without ART treatment history. Their data indicate that the death rates within 5 years of delivery do not differ between the 2 groups (93).

On the contrary, other reports showed an increased risk of breast cancer in women who underwent ART treatment. A study from Norway comparing 16,626 ART-exposed women with 972,208 non–ART-exposed women reported an increased risk of breast cancer (aHR, 1.20; 95% CI, 1.01–1.42) (47). Although the absolute risk increase was small, it is important to stress that a large portion of the study population was young and follow-up time was relatively short (47). Similar claims were reported by investigators examining women in the United States who accessed fertility and routine gynecologic medical care between 2003 and 2016 (93). Of note, that the absolute cancer risk was low, follow-up limited, and data-based with known limitations (93). Similarly, a study performed in the United Kingdom that investigated 255,756 women with ART treatment and compared with the general population incidence showed no increased risk of invasive breast cancer but an increased risk of in situ breast cancer (21). This finding was limited to women with endometriosis, low parity, or both, and therefore, this could be confounded by the underlying patient characteristics (21).

Although most studies fail to show an association, subset analyses in some studies show conflicting data regarding the risk of breast cancer in relation to low or high cumulative doses of CC (52, 68, 85, 94), hormonal cause of infertility (52, 85), and age at first infertility treatment (78, 83, 95). One concern is that the 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 (46, 47, 71); however, in 2 studies with >30 years of follow-up, no association was noted (52, 84).

Despite the limitations of the evidence available, the implications of these from a public health perspective are reassuring because they confirm that there does not appear to be an increased risk of breast cancer associated with ART treatments because it does not translate into a detectable overall increased risk for this, quite large, population of women with infertility.

Summary statements

- Four high-/intermediate-quality studies showed no association, whereas 1 intermediate-quality study showed an

increased risk of breast cancer in patients who underwent ART.
- A meta-analysis reported an increase in breast cancer risk associated with prolonged (>10 cycles) clomiphene use.

Recommendation

- Women should be informed that there does not appear to be an increased risk of breast cancer associated with ART treatments. Prolonged (>10 cycles) clomiphene use should be avoided (strength of evidence, B; strength of recommendation, weak/moderate).

UTERINE CANCER

Type 1 endometrial cancer is the most common uterine cancer and is associated with unopposed estrogen. Progesterone is known to be protective. It is, therefore, plausible that fertility drugs could either increase the incidence of endometrial cancer because of increased estrogen production or decrease the incidence of endometrial cancer secondary to the protective progestational effect observed with ovulation. As with investigations to determine the risk of fertility drugs on other types of cancer, studies addressing the risk of endometrial cancer are also limited by methodological design. Most cohort studies have small numbers of outcomes, short or incomplete follow-up, and inadequate methods to control for potential confounders such as anovulation, hormone therapy, obesity, hyperinsulinemia, and hysterectomy. In addition, many studies do not reflect current IVF practice patterns. 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 (51, 59, 61, 96, 97).

For this guideline, 9 studies, including 4 systemic reviews and meta-analyses, were used to determine the relationship between fertility drugs and subsequent development of endometrial cancer (17, 20, 21, 48, 87, 93, 98–100). An Israeli population-based cohort study found that women with a history of fertility treatment had a significantly higher risk of uterine cancer even after adjusting for age and obesity (HR, 4.6; 95% CI, 1.4–14.9) (20). However, a subsequent study using a health insurance claims database found that underlying infertility itself increased the risk of uterine cancer (93). Additionally, a study using the Society for Assisted Reproductive Technology Clinic Outcome Reporting System database found no increase in the risk of uterine cancer in women who underwent IVF compared with that in age-matched controls (SIR, 0.76; 95% CI, 0.57–1.01) (17). Finally, a 2017 Cochrane meta-analysis, including 6 studies using women with subfertility as the control group, found that fertility drugs were not associated with an increased risk of endometrial cancer (RR, 0.96; 95% CI, 0.67–1.37; 156,774 participants; very-low-quality evidence) (99).

Pooled analysis of 5 studies of 92,849 women with subfertility exposed to CC indicated a positive association with endometrial cancer (RR, 1.32; 95% CI, 1.01–1.71). Four studies of 19,614 women with subfertility who required CC found an increased risk compared with that in a general population control group (RR, 1.87; 95% CI, 1.00–3.48). The overall evidence, although low-quality, suggests that OI with CC in women with subfertility is associated with an increased risk of endometrial cancer, especially at cumulative doses of >2,000 mg and with a high number (>7) of treatment cycles (RR, 1.69; 95% CI, 1.16–2.47) (99). These findings are consistent with previous conclusions that this association may largely be because of underlying risk factors such as PCOS, anovulation, and obesity in women who require CC for OI rather than exposure to the drug itself. The evidence regarding exposure to gonadotropins was inconclusive.

Summary statements

- Underlying infertility increases the risk of uterine cancer. When women with subfertility are used as controls, the use of fertility drugs is not associated with an increased risk of endometrial cancer.
- Low-quality evidence suggests that exposure to CC as an ovary-stimulating drug in women with subfertility is associated with an increased risk of endometrial cancer, especially at cumulative doses of >2,000 mg and >7 cycles. This may largely be because of underlying risk factors in women who require treatment with CC, such as PCOS, rather than exposure to the drug itself. The evidence regarding exposure to gonadotropins and endometrial cancer risk is inconclusive.

Recommendation

- Women should be informed that there is no conclusive evidence that fertility treatments increase the risk of endometrial/uterine cancer. Underlying risk factors associated with infertility are more likely to be associated with endometrial cancer (strength of evidence, B; strength of recommendation, moderate).

THYROID CANCER

Thyroid cancer is the seventh most common cancer in women and affects women 3 times more often than men. A previous study has shown an association between thyroid cancer risk, high parity, and the use of exogenous hormones such as oral contraceptives and hormone replacement therapy (101).

Four studies, including a systemic review and meta-analysis assessing the association between fertility drugs and thyroid cancer, were included in this updated guideline (48, 93, 102, 103). In a retrospective study of 8,422 women with infertility, fertility medication use was not associated with a significant increase in the risk of thyroid cancer (RR, 1.42; 95% CI, 0.5–3.7) (104). In a cohort of 12,193 women with infertility (285,332 person-years, 55 thyroid cancers), CC was not statistically significantly associated with thyroid cancer risks (HR, 1.57; 95% CI, 0.89–2.75) (103). However, a Danish cohort study of 54,362 women with infertility showed a significant association between CC use and thyroid cancer, on the basis of 29 cases (RR, 2.29; 95% CI, 1.08–4.82) (101). A subsequent systematic review and meta-analysis found a

significant positive association between thyroid cancer risk and the use of fertility drugs among women with infertility (RR, 1.35; CI, 1.12–1.88; $P = .005$) (102). However, women with infertility who do not receive fertility medications are still at higher risk of thyroid cancer than those without infertility (0.21% vs. 0.16%; aHR, 1.59; CI, 1.11–2.30) (93).

Summary statement

- Evidence for an association between fertility drugs and thyroid cancer is mixed. In some studies, clomiphene was associated with a significantly increased risk, with a higher risk among nulligravid women or those with infertility than among fertile women.

Recommendation

- Women should be informed that there may be an increased risk of thyroid cancer associated with fertility treatment, specifically clomiphene use among those most heavily exposed (strength of evidence C; strength of recommendation, weak).

COLON CANCER

Two studies and a comprehensive review examining the use of fertility drugs and colon cancer were included in this guideline (48, 103, 105). One study of 9,982 women examined the relationship between ovulation-stimulating drugs and cancer risk other than breast and gynecologic malignancies (103). Neither CC nor CC plus gonadotropins was shown to be associated with colorectal cancer during 30 median years of follow-up (HR, 0.83; CI, 0.52–1.33) and particularly after 15 years of follow-up (HR, 1.34; CI, 0.77–2.34). A second study using national cancer registry data 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 IVF waiting list) and the general population (105). There was no increase in the incidence of colorectal cancer in the IVF group compared with that in controls (SIR, 1.00; 95% CI, 0.80–1.23); furthermore, the incidence of colorectal cancer was lower in the non-IVF group (SIR, 0.58; 95% CI, 0.36–0.88) than in the general population.

Summary statements

- A few intermediate-quality studies specifically assessed the risk of colon cancer in patients who underwent fertility treatment. All studies showed no increase in colon cancer risk for fertility treatment, including after 15 years of follow-up.

Recommendation

- Women should be informed that fertility drugs are not associated with an increased risk of colon cancer (strength of evidence, B/C; strength of recommendation, weak/moderate).

NON-HODGKIN LYMPHOMA

Two studies have evaluated the risk of non-Hodgkin lymphoma among women with infertility. One study showed an increased risk with OI treatment (HR, 2.86; 95% CI, 1.14–7.20) compared with that in women in the population but no statistically significant increase with the use of CC alone (57). Conversely, a large retrospective cohort study showed no increased risk of non-Hodgkin lymphoma among patients with infertility compared with that in controls without infertility (HR, 0.93; 95% CI, 0.73–1.19) (20).

Recommendation

- Women should be informed that there are insufficient data to determine whether fertility drugs are associated with an increased risk of non-Hodgkin lymphoma (strength of evidence, C; strength of recommendation, weak).

CERVICAL CANCER

Multiple studies have evaluated the risk of cervical cancer after the use of fertility medications and found no increased risk when compared with that in the general population as well as patients with infertility (20, 48, 58, 60, 61, 76, 88, 90, 104, 106–110). Three studies have shown a significant decrease in the incidence of cervical cancer after IVF (76, 90, 111). One study noted a significant decrease in the incidence of cervical cancer after the use of CC (RR, 0.4; 95% CI, 0.2–0.8) (109).

Summary statements

- Most studies have shown no increased risk of cervical cancer after the use of fertility medications; 4 studies showed a decreased risk.

Recommendation

- Women should be informed that fertility drugs are not associated with an increased risk of cervical cancer (strength of evidence, B/C; strength of recommendation, weak/moderate).

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, late age at menopause, early menarche, and use of oral contraceptives (112, 113). The risk of melanoma is not increased in women with an infertility diagnosis compared with that in women without infertility (93). Several studies, including 2 review articles, have evaluated the risk of malignant melanoma after the use of fertility drugs (17, 61, 97, 103, 104, 112, 114–118). All but 1 showed no significant overall increased risk of malignant melanoma. A Western Australia cohort study showed that women who underwent IVF and became parous had a higher risk of invasive melanoma than those who underwent IVF and remained nulliparous (HR, 3.61; 95% CI, 1.79–7.26), although there was no overall

association with IVF (HR, 1.16; 95% CI, 0.83–1.62) (119). In another study, although there was not an overall association, the use of gonadotropins (RR, 2.29; 95% CI, 1.16–4.52) and GnRH (RR, 3.26; 95% CI, 1.50–7.09) among parous women was significantly associated with invasive melanoma (112). The use of CC was associated with an increased risk of melanoma in 2 studies (57, 103). There was no significant association noted between CC and melanoma in other studies (104, 112, 115, 117, 118).

Summary statements

- Studies evaluating the risk of melanoma after ART have been inconclusive, with some showing no increased risk, some suggesting a nonsignificant increased risk, and others finding a significantly increased risk. Inconsistent results may be because of the small numbers of cases, short follow-up, inadequate control groups, and confounding factors such as age.

Recommendation

- Women should be informed that there are insufficient data to determine whether fertility drugs are associated with an increased risk of malignant melanoma (strength of evidence, C; strength of recommendation, weak).

OVERALL SUMMARY

- There is weak/moderate evidence that fertility treatment is associated with ovarian cancer. Given significant heterogeneity between studies, it is difficult to approximate the effect size; however, the overall risk is likely to be small. In addition, evidence suggests that at least some of this risk is related to underlying endometriosis, female infertility, or nulliparity, which has previously been associated with an increased risk of ovarian cancer.
- There is weak evidence that fertility treatment, specifically ART, increases the risk of BOTs.
- There is weak evidence that at least some of the increase in risk is because of underlying infertility or nulliparity.
- Four high-/intermediate-quality studies showed no association, whereas 1 intermediate-quality study showed an increased risk of breast cancer in patients who underwent ART.
- A meta-analysis reported an increase in breast cancer risk associated with prolonged (>10 cycles) clomiphene use.
- Underlying infertility increases the risk of uterine cancer. When women with subfertility are used as controls, the use of fertility drugs is not associated with an increased risk of endometrial cancer.
- Low-quality evidence suggests that exposure to CC as an ovary-stimulating drug in women with subfertility is associated with an increased risk of endometrial cancer, especially at cumulative doses of >2,000 mg and >7 cycles. This may largely be because of underlying risk factors in women who require treatment with CC, such as PCOS, rather than exposure to the drug itself. The evidence regarding exposure to gonadotropins and endometrial cancer risk was inconclusive.
- Evidence for an association between fertility drugs and thyroid cancer is mixed. In some studies, clomiphene was associated with a significantly increased risk, with a higher risk among nulligravid women or those with infertility than among fertile women.
- A few intermediate-quality studies specifically assessed the risk of colon cancer in patients who underwent fertility treatment. All studies showed no increase in colon cancer risk for fertility treatment, including after 15 years of follow-up.
- Most studies have shown no increased risk of cervical cancer after the use of fertility medications; 4 studies showed a decreased risk.
- Studies evaluating the risk of melanoma after ART have been inconclusive, with some showing no increased risk, some suggesting a nonsignificant increased risk, and others finding a significantly increased risk. Inconsistent results may be because of the small numbers of cases, short follow-up, inadequate control groups, and confounding factors such as age.

Acknowledgments

This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committee and Board of Directors of the American Society for Reproductive Medicine have approved this report.

This document was reviewed by the ASRM members, and their input was considered in the preparation of the final document. The following members of the ASRM Practice Committee participated in the development of this document: Clarisa Gracia, M.D., M.S.C.E.; Paula Amato, M.D.; Jake Anderson Bialis M.B.A.; Tommaso Falcone, M.D.; Rebecca Flyckt, M.D.; Jessica Goldstein, R.N.; Karl Hansen, M.D., Ph.D.; Micah Hill, D.O.; Sangita Jindal, Ph.D.; Suleena Kalra, M.D., M.S.C.E.; Tarun Jain, M.D.; Alan Penzias, M.D.; Bruce Pier, M.D.; Richard Reindollar, M.D.; Jared Robins, M.D., M.B.A.; Chevis N Shannon, Dr.P.H., M.P.H., M.B.A.; Anne Steiner, M.D., M.P.H.; Cidgem Tanrikut, M.D.; Michael Thomas, M.D.; and Belinda Yauger, M.D. The Practice Committee acknowledges the special contribution of Paul Pirtea, M.D.; Bruce Pier, M.D.; Leslie Appiah, M.D.; Benjamin Harris, M.D.; Jeffrey Hayes, Ph.D.; and Suleena Kalra, M.D., M.S.C.E., in the preparation of this document. All Committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. The members of the Committee who were found to have conflicts of interest on the basis of the relationships disclosed did not participate in the discussion or development of this document.

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Medicamentos para la fertilidad y el cáncer: una guía

Las limitaciones metodológicas en el estudio de la asociación entre el uso de medicamentos para la fertilidad y el cáncer incluyen el riesgo inherentemente mayor de cáncer en mujeres que nunca concibieron, el riesgo mayor de cáncer debido a factores (endometriosis y estrógenos sin oposición) asociados con la infertilidad, la baja incidencia de la mayoría de estos cánceres y que el diagnóstico de cáncer se produce típicamente varios años después del uso de medicamentos para la fertilidad. Sobre la base de los datos disponibles, no parece haber una asociación entre los medicamentos para la fertilidad y el cáncer de mama, colon o cuello uterino. No hay evidencia concluyente de que los medicamentos para la fertilidad aumenten el riesgo de cáncer uterino, aunque las mujeres con infertilidad tienen un riesgo mayor de cáncer uterino. No hay datos suficientes para comentar sobre el riesgo de melanoma y linfoma no Hodgkin asociado con el uso de medicamentos para la fertilidad. Se debe informar a las mujeres que puede haber un mayor riesgo de cánceres de ovario invasivos y limítrofes, y cáncer de tiroides asociado con el tratamiento de fertilidad. Es difícil determinar si este riesgo está relacionado con la endometriosis subyacente, la infertilidad femenina o la nuliparidad.