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Fertility Drugs and the Risk of Breast and Gynecologic Cancers

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Abstract

The evaluation of cancer risk among patients treated for infertility is complex, given the need to consider indications for use, treatment details, and the effects of other factors (including parity status) that independently affect cancer risk. Many studies have had methodologic limitations. Recent studies that have overcome some of these limitations have not confirmed a link between drug use and invasive ovarian cancers, although there is still a lingering question as to whether borderline tumors might be increased. It is unclear whether this merely reflects increased surveillance. Investigations regarding breast cancer risk have produced inconsistent results. In contrast, an increasing number of studies suggest that fertility drugs may have a special predisposition for the development of uterine cancers, of interest given that these tumors are recognized as particularly hormonally responsive. Additional studies are needed to clarify the effects on cancer risk of fertility drugs, especially those used in conjunction with in vitro fertilization. Because many women who have received such treatments are still relatively young, further monitoring should be pursued in large well-designed studies that enable assessment of effects within a variety of subgroups defined by both patient and disease characteristics.

Keywords

infertility; ovulation-inducing drugs; cancer; risk

There has been concern about the long-term effects of fertility drugs ever since they were first prescribed in the early 1960s. Although nulliparity has been extensively linked to cancers of the breast, ovary, and endometrium, and most studies suggest this association is largely attributable to infertility,[1] the effects of causes of infertility and associated treatments on cancer risk are poorly understood. Several clinical reports of cancers among exposed women and several epidemiologic studies suggest a link, but the precise relationships have been difficult to understand fully. The importance of clarifying effects is emphasized by the facts that the numbers of women treated annually have nearly doubled between 1973 and

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1991[2] and that by 2025 an estimated 5.4 to 7.7 millionwomen 15 to 44 years of age will have been exposed to such drugs in the United States.[3]

An association between fertility drugs and elevated cancer risks derives biological credibility from the fact that the most commonly used medications, clomiphene citrate and gonadotropins, are effective at stimulating ovu-lation, a factor implicated in the etiology of both ovarian[4] and breast[5] cancers. Second, these drugs raiseboth estradiol and progesterone levels,[6] hormones that affect the development and growth of breast and gynecologic cancers. Further, some epidemiological studies have linked the use of these drugs with an increased incidence of various cancers.

Epidemiological Approaches Used in Previous Studies

Studies to clarify the relationships are difficult to undertake, with the interpretation of results of many of the existing investigations hindered by a variety of methodological limitations. Although some clinical studies have suggested a link between fertility drugs and the risk of various cancers, the absence of comparison groups in such studies precludes definitive conclusions. Case-control studies have been undertaken, but such studies rely on patient reports of exposure to infertility treatment, which can be imprecise or reflect the influence of selective recall. Cohort studies that provide more definitive results have relied on both retrospective and prospective approaches to evaluate relationships of medication use to subsequent cancers. These studies also are usually hindered by imprecise information on indications for drug use (i.e., causes of infertility)[7] that can independently affect cancer risk. For example, anovulation has been linked to increased risks of endometrial[8–11] and possibly breast[8,12–18] cancers, endometriosis has been linked to ovarian[19–23] and breast[20,22] cancers, and tubal factors to ovarian cancers.[23–26]

Further, case-control studies usually focus on an unselected sample of cases diagnosed in the general population (rather than on, for example, a group of infertile women), resulting in low rates of use of fertility medications. Thus, even though case-control studies may start with a large number of subjects, their ability to evaluate specific associations may be limited. For example, in a population-based case-control study of breast cancer,[27] which included 4,566 cases and 4,676 controls, <5% of the study subjects reported prior fertility drug use (184 cases and 200 controls). An additional complexity of case-control studies is that some have used hospitalized women as the control group. Because hospitalized women are likely to have better access to and more utilization of medical services compared with controls selected from the general population, studies using hospital controls may derive different risk estimates than those using controls selected from the general population.

As a result of the limitations of case-control studies, more credibility regarding the relationship of fertility treatments to cancer risk has derived from prospective or cohort studies, reviewed in Table 1, that define exposures prior to the onset of disease. Most cohort studies, however, are limited by small numbers of cancers and lack of information on other cancer predictors. Many cohort studies have had short follow-up periods; thus effects that require long latency intervals may remain undetectable. Participants in these studies are often still young and have not yet reached the age of peak cancer incidence.

The unavailability of appropriate comparison groups is also problematic for cohort studies. In many of these studies, the disease experience of cohorts of infertile women is compared with the experience of the general population through the calculation of standardized incidence ratios (SIRs). SIRs compare the number of observed cancers in the cohort to the number expected based on incidence rates in the general population. These comparisons take into account age, race, and calendar time, but usually there is no information regarding other cancer predictors. Of notable concern is the inability to adjust for parity, a recognized risk factor for breast, endometrial, and ovarian cancers.[1] Thus comparisons of cancer rates among infertile women (with or without ovulation induction) to cancer rates in the general population can be difficult to interpret.

Cohort studies are most informative if they allow internal comparisons that enable adjustment for a variety of potential cancer risk factors. Through the calculation of relative risks (RRs) rather than SIRs, disease risks can be compared between treated and untreated women while holding constant (or controlling for) other cancer predictors. Few cohort studies, however, have had access to data on all pertinent risk factors. In most cases, when covariate data are available, they are limited to data abstracted from medical records, with only a few studies having attempted direct administration of questionnaires to study subjects.[28,29] Because of the large numbers of women usually required for evaluation of longterm effects of fertility treatments, several studies have collected extensive risk factor information only from cancer cases and a sample of nondiseased subjects, either through nested case-control studies within the cohort[30] or from case-cohort investigations.[31,32]

Although cohort studies are generally preferred for the evaluation of effects of fertility drugs, they are not without their inherent limitations. Losses to follow-up are common in prospective studies. Although poor rates of response to questionnaires are a particular concern for case-control studies, they are also problematic for cohort studies if information on potential confounding variables is attempted through questionnaires. Surveillance bias can also come into play in both case-control and cohort studies if women who receive fertility drugs are under close medical scrutiny.[33]

When interpreting reported disease associations, we must give particular consideration to the strengths and limitations of the individual studies, as discussed next.

Ovarian Cancer

Clinical Reports

Numerous clinical reports have expressed concern about a potential link between the use of fertility drugs and ovarian cancer risk.[34–42] The association has biological credibility, given that “incessant ovulation” and associated alterations in endogenous hormones during the reproductive years are plausible explanations for several factors that alter disease risk, including nulliparity and oral contraceptive use.[4,43]

Cohort Studies

In the 1990s, an epidemiological study raised major concern regarding a potential link between the use of fertility medications and ovarian cancer risk. This study[26] consisted of a

meta-analysis of 12 ovarian cancer case-control studies, only 3 of which provided information regarding drug use (focusing on 526 cases and 966 controls). There was scant information about the type of drug or the extent of its use. Self-reported prior use of fertility medications was associated with an odds ratio (OR) of 2.8 [95% confidence interval (CI), 1.3 to 6.1] as compared with women who had no history of infertility. This risk was limited to nulligravid women, who experienced a 27-fold increase in risk associated with drug use (95% CI, 2.3 to 315.6). Although the report caused great medical and lay concern, several editorials and literature reviews disputed the conclusion of markedly increased risk,[44–47] pointing out that the risk estimate was based on only 12 exposed cases and 1 exposed control. Moreover, drug use among gravid women was associated with a nonsignificant OR of 1.4 (95% CI, 0.52 to 3.6).

Further concern was raised following publication of results from a retrospective cohort study of 3837 women evaluated for infertility in a Seattle practice between 1974 and 1985 who were followed for cancer incidence through a regional cancer registry.[32] Clomiphene use, as documented in medical records, was associated with an adjusted 2.3-fold increased risk (95% CI, 0.5 to 11.4), based on nine ovarian cancers. Five of the nine women with cancer had taken the drug for ≥12 monthly cycles, resulting in a RR of 11.1 (95% CI, 1.5 to 82.3). An enhanced risk associated with long-term treatment was observed in both those with and without ovulatory abnormalities. A large proportion of the observed tumors were borderline (5 of the 11 in the cohort).

These two studies prompted several other investigations, including cohort studies in Australia,[18,48] Israel,[14,16,49,50] the United States,[28,51] the Netherlands,[29] the United Kingdom,[52,53] Denmark,[54] and Sweden.[55–57] Most of these studies failed to provide confirmation of a link between fertility drug use and ovarian cancers. However, as shown in Table 2, several of the investigations were limited by extremely small numbers of events.

Of studies that have assessed relationships with earlier treatment protocols (in the era before in vitro fertilization [IVF]), the most comprehensive ones were conducted in the United States,[28] Denmark,[54] and the United Kingdom.[52] In the U.S. study, 45 ovarian cancers developed among 12,193 infertile women followed for a median of 18.8 years. This study involved detailed collection of information on drug exposures, causes of infertility, and potential cancer risk factors from both medical records and questionnaires, allowing subjects who had undergone a bilateral oophorectomy to be eliminated from those at risk.[28] The results were largely reassuring, showing no risk increases associated with ever use of either clomiphene or gonadotropins. However, there were nonsignificant risk increases (range of RRs: 1.5 to 2.5) associated with use of either clomiphene or gonadotropins among the subjects followed for the longest periods of time (i.e., ≥15 years).

In the Danish study,[54] among 54,362 women diagnosed from 1963 to 1998, there were 156 ovarian cancer cases identified through linkage with the Danish Cancer Registry. In internal analyses, there was no evidence of increased ovarian cancer risk associated with clomiphene, the most commonly used fertility drug during the period of subject accrual (RR: 1.14; 95% 0.79 to 1.64) or with a variety of other fertility drugs documented in medical records.

Finally, in a study of 7355 women in the United Kingdom evaluated for infertility between 1963 and 1991 and in whom 21 ovarian cancers were identified, there was no evidence of a significant link between fertility drug use and ovarian cancer, although this study was somewhat more limited than others in not being able to adjust for most other risk factors.[52]

Although these previously discussed studies focused on women exposed to ovulation-inducing agents at earlier times, several other studies have concentrated on exposures received during IVF. One study that derived data from 15 California clinics, published to date only in abstract form,[51] in which 50 ovarian cancers developed among 51,371 women, found no evidence for an association of fertility drugs with ovarian cancer risk, even when dose, formulation, and number of treatment cycles were considered.

Among 29,666 women referred to 10 Australian IVF clinics, 13 ovarian cancers were observed during follow-up.[18] The investigators had detailed information on indications for drug use but only limited information on patient characteristics. The overall SIR was 0.99, with no higher risk for the women who received at least one IVF treatment cycle (0.88) as compared with those who received no drug treatment (1.16). Women with unexplained infertility were at a significantly increased risk compared with the general population, but within this subgroup there was no difference in risk between treated and untreated women.

In a cohort of 25,152 women treated for subfertility in the Netherlands, 17 ovarian cancers developed.[29] Strengths of this study included detailed information on causes of sub-fertility and drug exposures from medical records, as well as on cancer risk predictors obtained through completed questionnaires from many of the study subjects. Results showed no difference in risk between treated and untreated subjects, even when the number of cycles or ampoules received were considered.

The latest results regarding IVF and ovarian cancer risk derive from several studies in Sweden,[55–57] all of which focused on cancer developing among women who gave birth following IVF treatment. One of these observed only one ovarian cancer developing after IVF[57]; and the other two studies had more power to evaluate effects. Although seemingly focused on the same populations of women, the studies derived discrepant results, possibly due to differences in analytical approaches. One investigation[55] found a significantly elevated risk of ovarian cancer following IVF treatments (OR: 2.09; 95% CI, 1.39 to 3.12); the other[56] found no overall effect of IVF but a significantly increased risk of invasive ovarian cancer associated with exposure to gonadotropins (RR: 5.28; 1.70 to 16.47).

Case-Control Studies

Although reassuring results regarding the effects of fertility drugs on ovarian cancer risk have emerged from several casecontrol studies, most have been limited by the small number of subjects reporting prior drug use.[23,58–62] For example, in the largest study,[61] based on 1031 cases and 2411 hospital controls, only 1.1 to 1.5% of the subjects reported fertility drug use, resulting in only 15 cases and 26 controls with relevant exposures.

To derive larger numbers, Ness and others[23] undertook a meta-analysis of eight studies involving data on 1060 cases and 1337 controls. In this study, after adjustment for types of

infertility, the risk associated with drug use was somewhat higher among nulligravid women (1.8) and among those who had ≥4 months of exposure (RRs: 1.5–1.7), but none of these risks was statistically significant.

Subgroups of Interest

Although the results of the most recent studies are much more reassuring than early studies, several observations indicate a need for further monitoring. These include the findings in two studies[23,28] of modest risk increases with either extended follow-up or increased drug exposure. Given that these medications became available in the United States beginning in the early 1960s, women who were subsequently exposed to them are now entering the age range of highest ovarian cancer incidence. Thus additional follow-up data are needed to evaluate their effects.

Several investigations[23,26,28] have noted higher risks associated with fertility drug use among nulligravid women, suggesting the possibility of an enhanced effect of the medications among women with certain indications for use. However, other investigations have not confirmed this relationship.[62] A possible additional subgroup of interest with respect to effects of fertility drugs are women at high genetic risk for ovarian cancer. Women with BRCA mutations exposed to fertility drugs have been evaluated for breast but not ovarian cancer risk.[63]

Disease Heterogeneity

It has also been questioned whether fertility medications might have a preferential effect on certain ovarian tumor types. Clear cell,[64,65] malignant germ cell,[66] and granulosa cell[42] tumors have been linked by case reports to the use of ovulation-inducing drugs. Gonadotropins have been shown to induce granulosa cell tumors in rodents[67] and stimulate cells in human in vitro models,[68] and clomiphene has been shown to increase granulosa, theca, and luteal cells in a rat model.[69] Epidemiological studies of these rare tumor types are not available, but several descriptive analyses in Finland[70,71] fail to provide support for an effect of fertility drug use on granulosa cell tumors.

That fertility drugs might preferentially affect the risk of borderline ovarian tumors is suggested by both cohort[32,56,72] and case-control[23,73] investigations, with associated risk ratios in the range of 3 to 5. The relationship has been found to predominate among nulligravid women,[23] users of clomiphene,[56] and users of gonadotropins.[23,72,73] These findings, in conjunction with case reports of ovarian cancer developing in women during or shortly after treatment with ovulation-inducing agents,[34–38,40,42,74] have led to speculations that ovarian stimulation may induce growth in existing highly differentiated indolent tumors. Alternatively, the findings simply could reflect more intensive medical surveillance among infertile women.

Breast Cancer

The epidemiology of breast cancer has been extensively studied, with many investigations supporting the notion of an important etiologic role for endogenous as well as exogenous hormones.[75] Surprisingly, few studies have addressed the potential relationships to breast

cancer risk of fertility drugs, despite their recognized effects on ovulation and hormone patterns[76] and clinical reports that have suggested an association.[41,77–81]

Despite the biological plausibility of a relationship between the use of these hormonal agents and breast cancer risk, the literature remains quite confusing, with some studies showing a possible increased risk associated with the drugs,[30,49] others showing the opposite effect,[82,83] and still others showing no substantial relationship.[14,29,52,53,84,85] Many of these results derive from the same cohort studies that addressed relationships with ovarian cancer, and they are plagued by the same methodological problems previously mentioned. A few, however, merit specific discussion.

Cohort Studies

One of the earliest studies addressing breast cancer relationships was that of Rossing and others,[82] the cohort study that raised substantial concern regarding effects on ovarian cancer risk. For breast cancer (Table 3), the opposite relationship was observed, namely a nonsignificantly reduced risk of invasive and in situ breast cancer associated with clomiphene use (adjusted RR: 0.5; 95% CI, 0.2 to 1.2). This estimate, however, was based on only 12 exposed cases, and there was no indication of any further risk reduction with extended duration of use. A chemopreventive effect of clomiphene would be of interest given that it is a selective estrogen receptor modulator (SERM) and thus could have properties similar to tamoxifen, another SERM.[86] Additional epidemiological support of a reduced risk of breast cancer associated with clomiphene use was provided by results from the Nurses Health Study II,[83] which showed a RR of 0.40 (95% CI, 0.2 to 0.7) associated with the use of clomiphene among women treated for ovulatory infertility. Risk decreased significantly with duration of use of clomiphene, with users of ≥10 months having a RR of 0.21 compared with nonexposed women. The findings were based on self-reports of both drug use as well as causes of infertility.

In contrast to these results, a more recent study from Israel, which included 131 breast cancers, found a significantly increased SIR of 1.4 associated with exposure to clomiphene.[30] Given concerns that this might merely reflect confounding by such factors as parity, the authors conducted a nested case-control study within their cohort to obtain additional information on covariates. The excess risk associated with clomiphene persisted and even became stronger after adjustment for a variety of breast cancer risk factors. Women who received more than four cycles of clomiphene were also noted to be at increased breast cancer risk (SIR: 1.90; 95% CI, 1.08 to 3.35) in a Swedish cohort,[57] but this was based on only 12 exposed cases and unadjusted for other breast cancer risk factors.

An additional Israeli study, focused on women giving birth after IVF treatment, also noted an increased risk associated with self-reported exposure to ovulation induction drugs (RR: 1.65; 95% CI, 1.15 to 2.36).[49] Additional information on types of drugs used was not available in this investigation.

In contrast to these studies showing either reduced or increased risks associated with fertility drug use, studies conducted in both the United States (292 breast cancer cases)[84] and Denmark (331 cases)[31] have noted no substantial relationships. However, in the U.S. study,

there was some evidence of an increase in risk of invasive breast cancer with follow-up time, with a significant excess risk seen for clomiphene users with 20 or more years of follow-up (RR: 1.6; 95% CI, 1.0 to 2.5). In the Danish study,[31] no increased risk was seen for clomiphene or gonadotropins, but subjects who were prescribed progestins were found to have more than a twofold increased risk.

Another large study, embedded in the French E3N Cohort Study in France,[85] which focused on 92,555 women, 6602 of whom reported infertility problems, found no overall association between self-reports of exposure to fertility drugs and breast cancer risk (with 183 breast cancers occurring among the infertile women), but it did note increased risks associated with treatment among those with a family historyof breast cancer. However, these risks were based on relatively small numbers and require a cautious interpretation.

Although most of the investigations of breast cancer have focused on older fertility treatment protocols, a few have assessed IVF effects, including investigations in Australia,[18] the Netherlands,[29] Sweden,[55,87] and Israel.[88] These studies for the most part have failed to find an overall difference in risk between exposed and unexposed subjects. However, one of the studies in Israel[88] found higher risks among women who received IVF at age 40 or beyond or those who had four or more cycles of treatment. In the Australian study,[18] a twofold increased risk of breast cancer was observed within 1 year of last treatment. This prompted the suggestion that ovulation-inducing drugs might promote the rapid growth of preexisting tumors, similar to the short-term transient increase in breast cancer following a recent pregnancy.[89] However, several other studies that have assessed the detailed timing effects of last drug use found no support for a promotional effect by either clomiphene or gonadotropins.[29,84]

Case-Control Studies

The few case-control studies that have addressed the relationship of fertility drug use to breast cancer risk have for the most part not found any substantial associations.[90–92] Most of these studies, however, were limited by small numbers of cancers, imprecise information on patterns of or indications for drug use, or incomplete ability to control for other correlates of risk, including well-recognized reproductive risk factors. One large study, involving ≥4500 breast cancer cases, was able to carefully control for potential confounding variables but had to rely on self reports of infertility and had few women exposed to fertility drugs.[93] Although this study found no association of risk related to the use of clomiphene, there was some indication of a risk elevation among women with long-term use of gonadotropins (risks ranging from 2.7 to 3.8 for use of at least ≥6 months or six cycles). The authors speculated that this might be due to increases in serum estrogen and progesterone levels, although whether hormone increases that would result from such exposure could substantially affect subsequent breast cancer risk has been questioned.[94]

Disease Heterogeneity

Only a few studies have focused on whether breast cancers that occur among patients exposed to fertility drugs exhibit unusual clinical characteristics. One study[95] showed that breast cancers developing subsequent to fertility drug use are more advanced and have

worse prognostic features (e.g., they are estrogen or progesterone receptor negative). The diagnosis of aggressive tumors predominated within 2 years of drug exposure and appeared similar to pregnancy-associated breast cancers evaluated in the same investigation. However, other investigations have not confirmed poorer prognostic features in patients exposed to fertility drugs.[83,96] An evaluation of breast cancer mortality in the Australian study also failed to show any appreciable differences between those who did and did not receive IVF.[97]

Apart from the one French study that evaluated effects of fertility drugs among women with a family history of breast cancer,[85] scant attention has focused on familial or genetic modifications. One study evaluated the relationships of fertility drugs among carriers of BRCA1 or BRCA2 mutations but found no unusual effects.[63] An additional study assessed whether fertility drug use might increase mammographic densities, one of the strongest identified risk factors for breast cancer, but found no notable relationships.[98]

Endometrial Cancer

Endometrial cancers are well recognized as hormonally sensitive.[99] Surprisingly, there has not been as much focus on this cancer site as on ovarian and breast cancers, but several recent reports indicate that of the three cancer sites that endometrial cancer may be the one most strongly influenced by fertility drug use. However, as with the other cancers, results are not entirely consistent, with a number of studies showing no associations.[16,18,29,48,53] However, these studies involved relatively short follow-up times, as well as small numbers, as did the one previous case-control study that addressed the topic.[100]

Cohort Studies

There is, however, some consistency in several of the larger cohort studies of increased risks of endometrial cancer related to either fertility drug use in general or more specifically to the use of clomiphene (Table 4). The possibility of a relationship was first raised in one of the earlier Israeli cohorts in which a significant twofold increased risk was noted for fertility drug use.[11] An increased risk of self-reported exposure to ovulation induction drugs was also noted in the Jerusalem Perinatal Study, although interpretation of the effect was hindered by the fact that the study was restricted to parous women and that the increased risk (3.32; 95% CI: 1.31 to 8.42) was based on only five exposed women.[49]

Several studies that have addressed relationships with clomiphene use have noted some risk elevation. In a U.S. cohort, ever use of clomiphene was associated with a RR of 1.8 (95% CI, 0.9 to 3.3), with significant risks seen for subjects with higher dosages and longer follow-up periods.[101] In a study in the United Kingdom, a slight increase was observed for any use of ovarian stimulants, with the highest risk seen in those with a total cumulative dose of clomiphene of ≥2250 mg (RR: 2.62; 95 CI, 0.94 to 6.82).[52]

Although not all studies have found an increased risk of uterine cancers associated with clomiphene,[102] it is of interest that the SERM clomiphene is structurally similar to tamoxifen,[6] a drug that has been repeatedly linked with increases in endometrial cancer risk.[103] The biological plausibility of a relationship is also supported by a clinical report of

three cases of adenomatous hyperplasia of the endometrium, a precursor condition, occurring among women exposed to ovulation-inducing agents.[104]

Less information is available on effects of drugs other than clomiphene. However, a recent cohort study in Denmark noted a significantly increased risk of uterine cancer associated with gonadotropin exposure.[102]

Disease Heterogeneity

Venn and others[18] reported an increased incidence of uterine sarcomas in their IVF-exposed population, based on four observed cases, resulting in an SIR of 8.56 (95% CI, 3.21 to 22.8). This finding requires further follow-up, although this will be difficult given the rarity of the tumor. Along these lines, it would be of particular interest to evaluate whether there are differences between type 1 (endometrioid) and type 2 (nonendometrioid) uterine tumors, given the evidence that the former are especially hormonally responsive.[105]

Conclusions

The evaluation of cancer risk among patients treated for infertility is complex given the need to consider indications for use, details of the treatment protocols, and effects of other factors that could have independent effects on risk (including whether the fertility treatment is successful and produced a pregnancy, a major protective factor for breast and gynecologic cancers). Many of the available studies to address these issues have also had small numbers and/or short follow-up times.

Although most of the available studies have focused on effects of older treatment protocols (most notably clomiphene exposures), more recent studies are beginning to focus on the long-term effects of drugs used in IVF. Because the women who have received such treatments in the past are still relatively young, it may be some time before we have sufficient follow-up to resolve relationships fully. Interpretation of effects will depend on the availability of detailed information on a wide array of fertility treatments (including clomiphene, gonadotropins, gonadotropin-releasing hormone agonists and antagonists, and progestational agents). These studies will clearly need to be large for the evaluation of rare tumors and should incorporate special efforts to evaluate some of the subgroups that have been suggested to possibly be more susceptible (e.g., nulligravidas) and focus on the possibility of heterogeneous effects within broader disease categories (including whether relationships vary by tumor histology and markers). Fortunately, there are several ongoing studies in the United States, Israel, and several Scandinavian countries, whose emerging results in the near future should bring additional clarity to the issue of how use of a broad spectrum of fertility drugs may have an impact on the subsequent occurrence of breast, gynecologic, and other cancers.

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Table 1

Cohort Studies Evaluating the Relationship of Fertility Drug Use to Breast and Gynecologic Cancers

Location	Study	No. of Subjects	Years Evaluated	Average Years of Follow-Up	Measure of Association	No. of Ovarian Cancers	No. of Breast Cancers	No. of Uterine Cancers
United States (Seattle)	Rossing et al[32,82]	3837	1974–1985	12.3	SIR, RR	11	27	
Australia (Melbourne)	Venn et aI[48]	10,358	1978–1992	6.5	SIR, RR	6	34	5
Israel (Tel Hashomer)	Modan et al[11]	2496	1964–1974	21.4	SIR	12	59	21
Israel (Soroka University Hospital, Beer Sheba, Tel Aviv, Israel)	Potashnik et al[16]	1197	1960–1984	17.9	SIR	2	20	2
Australia (10 IVF centers)	Venn et al[18]	29,700	before 1994	8.5	SIR	13	143	12
United States	Crouqhan-Minihane et al[51]	51,371	1965–1998	5.6	SIR, RR	50		
The Netherlands	Klip et al[29]	25,152	1980–1995	5.6	SIR, RR	17	116	14
United Kingdom (Hallam Medical Center, London)	Doyle et al[53]	5556	1974–1989	7.9	SIR, RR	6	55	4
Israel (Chaim Sheba, Tel Hashomer, Assuta Medical Centers, Tel Aviv)	Dor et al[14]	5026	1981–1991	3.6	SIR	1	11	2
Israel (Liz Maternity Center, Tel Aviv)	Lerner-Geva et al	1082	1984–1992	6	SIR	3	5	
United States (5 clinical sites)	Brinton et al[21,84] Althuis et al[101]	12,193	1965–1988	18.8	SIR, RR	45	292	39
France (E3N cohort study)	Gauthier et al[85]	92,555 (6602 infertile women)	1990–1995				2571 (183)	
Israel (5 clinics)	Lerner-Geva et al[30]	5788	1964–1984	20.9	SIR, RR		131	
United States (Nurses' Health Study)	Terry et al[83]	116,671 (5798 with ovulatory infertility)			HR		1,357 (69)	
Denmark	Jensen et al[31,54,102]	54,362	1963–1998	8.8	SIR, RR	156	331	83
Sweden	Kristiansson et al	8716	1982–2002	6.2	SIR, RR	317	3,083	79
Israel (Jerusalem Perinatal Sudy)	Calderon-Marqalit et al[49]	15,030	1974–1976	?	RR	43	530	44
Israel (Hadassah Hebrew University Medical Center)	Katz et al[96]	7162	1984–2002	12.9	OR		41	
Israel (Assaf Harofeh Medical Center, Tel Aviv)	Pappo et al[88]	3375	1986–2003	8.1	SIR		35	
United Kingdom	dos Santos Silva et al[52]	7355	1963–1991	21.4	SIR	21	177	31
Sweden	Orgeas et al[57]	1135	1961–1976		SIR, RR		54	
Sweden (3 major clinics in Stockholm, Gothenburg, Uppsala)	Sanner et al[56]	2768	1961–1975	33.3	SIR, RR	29		

Location	Study	No. of Subjects	Years Evaluated	Average Years of Follow-Up	Measure of Association	No. of Ovarian Cancers	No. of Breast Cancers	No. of Uterine Cancers
Sweden (3 major clinics in Stockholm, Gothenburg, Uppsala)	Kallen et al[55]	24,058	1982–2006		SIR	62	112	5

SIR, standardized incidence ratio; RR, relative risk.

Table 2

Findings from Cohort Studies Regarding the Relationship of Fertility Drug Use to Ovarian Cancer Risk

Study	Primary Exposure of Interest	No. of Cancers in Exposed	No. of Cancers in Unexposed	SIR in Exposed (95% CI)	SIR in Unexposed (95% CI)	RR (Exposed versus Unexposed)	Comments
Rossing et al[32]	Clomiphene	9	2	Not provided	Not provided	2.3 (0.5–11.4)	RR of 11.1 (1.5–82.3) for those with 12+ cycles (based on 5 exposed patients)
Venn et al[48]	IVF treatment	3	3	1.7 (0.55–5.27)	1.62 (0.52–5.02)	1.45 (0.28–7.55)	
Potashnik et al[16]	Fertility drugs	1	1	0.68(0.01–3.80)	1.35 (0.02–7.49)		
Venn et al[18]	IVF treatment	7	6	0.88(0.42–1.84)	1.16(0.52–2.59)		Registry match; no RR reported
Doyle et al[53]	Ovarian stimulation Treatments	4	2	0.84(0.23–2.15)	1.67 (0.20–6.05)	0.59(0.12–3.00)	
Dor et al[14]	IVF treatment	1		0.57 (0.01–3.20)			Historical cohort analysis; no untreated group
Lerner-Geva et al[50]	IVF treatment	3		5.0(1.02–14.6)			Registry match; no untreated group; SIR decreased to 1.67 (0.02–9.27) when cases developing within 1 year were excluded
Brinton et al[21]	Clomiphene	15	30			0.82 (0.4–1.5)	Somewhat higher risks with extended follow-up and among women who remained nulligravid
Calderon-Margalit et al[49]	Self-reported exposure to ovulation induction drugs	1	42			0.61 (0.08–4.42)	Restricted to parous women
Jensen et al[54]	Clomiphene treatment (33% of subcohort)	58	98			1.14(0.79–1.64)	
Sanner et al[56]	Hormonal infertility Treatment	16	13	0.71 (0.31–1.39)	0.90(0.52–1.44)		Significant RRs of invasive cancer associated with gonadotropins (5.28; 1.70–16.47)
dos Santos Silva et al[52]	Ovarian stimulation Treatments	12	8	1.10(0.57–1.93)	0.78(0.34–1.53)	1.42 (0.53–3.99)	
Källén et al[55]	IVF treatment	26				2.09(1.39–3.12)	Calculated ORs, also assessed risks associated with IVF occurring after cancer diagnoses

SIR, standardized incidence ratio; CI, confidence interval; RR, relative risk; IVF, in vitro fertilization; OR, odds ratio.

Table 3

Findings from Cohort Studies Regarding the Relationship of Fertility Drug Use to Breast Cancer Risk

Study	Primary Exposure of Interest	No. of Cancers in Exposed	No. of Cancers in Unexposed	SIR in Exposed (95% CI)	SIR in Unexposed (95% CI)	RR (Exposed versus Unexposed)	Comments
Venn et al[48]	IVF treatment	16	18	0.88(0.55–1.46)	0.98(0.62–1.56)	1.11 (0.56–2.20)	Registry match
Rossing et al[82]	Clomiphene	15	12	Not provided	Not provided	0.5(0.2–1.2)	Reduction in risk associated with clomiphene use did not increase with duration of use
Potashnik et al[16]	Fertility drugs	16	4	1.65 (0.94–2.68)	0.80(0.21–2.04)		No dose-response relationship with number of clomiphene cycles
Venn et al[18]	IVF treatment	87	56	0.91 (0.74–1.13)	0.95(0.73–1.23)		Registry match; no untreated group
Doyle et al[53]	Ovarian stimulation treatments	43	11	1.16(0.84–1.56)	1.15(0.57–2.05)	0.95(0.47–1.92)	
Dor et al[14]	IVF treatment	11		0.69(0.46–1.66)			Registry match; no untreated group
Lerner-Geva et al[50]	IVF treatment	5		1.02 (0.33–2.39)			Registry match; no untreated group; SIR decreased to 0.82 (0.22–2.10) when cases developing within 1 year were excluded
Brinton et al[84]	Clomiphene	108	184	1.29(1.1–1.6)	1.28(1.1–1.5)	1.02(0.8–1.3)	Somewhat higher risks with extended follow-up and among women who remained nulligravid
Gauthier et al[85]	Self-reported information on infertility treatment	183	2388			0.95(0.82–1.11)	Similar RR for IVF treatment
Lerner-Geva et al	Hormonal treatment for infertility	73	58	1.06(0.81–1.36)	1.21 (0.95–1.53)	1.11 (0.79–1.57)	Higher RR for women exposed to clomiphene (1.49; 1.15–1.93), with results confirmed by a nested case-control study
Terry et al[83]	Self-reported information on drugs to induce ovulation	32	29			0.60 (0.42–0.85) Drug use among women with ovulatory infertility versus no infertility	Observed inverse relation of risk with months of clomiphene use (HR: 0.25; 0.09–0.75 for 10+ months use)
Jensen et al[31]	Clomiphene treatment (31% of subcohort)	102	229			1.08(0.85–1.39)	Increased RR (3.36; 1.3–8.6) associated with progesterone exposure
Kristiansson et al[87]	IVF treatment	24	3059	4.31 (2.89–6.43)	4.12(3.97–4.27)	0.93(0.48–1.43)	Restricted to women giving birth after IVF; also compared

Study	Primary Exposure of Interest	No. of Cancers in Exposed	No. of Cancers in Unexposed	SIR in Exposed (95% CI)	SIR in Unexposed (95% CI)	RR (Exposed versus Unexposed)	Comments
							postconception 1 −3 years as start of followup period 3 years as start of followup period
Calderon-Marqalit et al[49]	Self-reported exposure to ovulation induction drugs	32	498			1.65(1.15–2.36)	Restricted to parous women
Katz et al[96]	IVF treatment	28					In case-control analyses, observed increased OR for women receiving IVF after age 30 (1.24; 1.03–1.48)
Pappo et al[88]	IVF treatment	35		1.4(0.98–1.96)			Higher risks associated with treatment at age 40+ years; hormonal infertility and 4+ IVF cycles
dos Santos Silva et al[52]	Ovarian stimulation treatments	102	72	1.26(1.03–1.53)	0.99(0.78–1.25)	1.27(0.93–1.75)	
Orgéas et al[57]	Hormonal treatment	54		1.01 (0.77–1.31)			SIR of 3.00(1.35–6.67) for women with nonovulatory infertility who received 4+ cycles of clomiphene
Källén et al[55]	IVF treatment	91				0.76(0.62–0.94)	Calculated ORs; also assessed risks associated with IVF occurring after cancer diagnoses

SIR, standardized incidence ratio; CI, confidence interval, RR, relative risk; IVF, in vitro fertilization; HR, hazard ratio; OR, odds ratio.

Table 4

Findings from Cohort Studies Regarding the Relationship of Fertility Drug Use to Uterine Cancer Risk

Study	Primary Exposure of Interest	No. of Cancers in Exposed	No. of Cancers in Unexposed	SIR in Exposed (95% CI)	SIR in Unexposed (95% CI)	RR (Exposed versus Unexposed)	Comments
Venn et aI[48]	IVF treatment	2	3	2.22 (0.55–0.87)	3.48(1.12–10.8)	0.65 (0.11–3.94)	Registry match
Venn et al[18]	IVF treatment	5	7	1.09(0.45–2.61)	2.47 (1.18–5.18)		Registry match; no RR reported
Doyle et al[53]	Ovarian stimulation treatments	3	1	1.21 (0.25–3.53)	1.68(0.04–9.37)	0.72 (0.06–8.62)	
Althuis et al[101]	Clomiphene	19	20	2.14(1.3–3.3)	1.24(0.8–1.9)	1.79(0.9–3.4)	Somewhat higher risks for women using higher dosages, with extended follow-up, and who remained nulligravid
Dor et al[14]	IVF treatment	2		2.25 (0.25–8.11)			Registry match; no untreated group
Calderon-Margalit et al[49]	Self-reported exposure to ovulation induction drugs	5	39			3.32 (1.31–8.42)	Restricted to parous women
dos Santos Silva et al[52]	Ovarian stimulation treatments	18	12	2.31 (1.37–3.64)	1.66(0.86–2.90)	1.39(0.63–3.16)	Women given 2250+ mg of clomiphene had a RR of 2.62 (0.94–6.82)
Jensen et al[102]	Clomiphene	29	54			1.36(0.83–2.23)	Higher risks for those with 6+ cycles. Also elevated RR for those exposed for multiple cycles to gonadotropins or hCG

SIR, standardized incidence ratio; CI, confidence interval; RR, relative risk; IVF, in vitro fertilization; hCG, human chorionic gonadotropin.