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# LONG-TERM EFFECTS ON WOMEN OF ASSISTED REPRODUCTION

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Abstract

The long-term health sequelae for women from assisted reproductive technology (ART) have not been studied extensively. There are a number of reasons that women's health may be compromised after ART procedures, including the consequences of the increased incidence of multiple births, operative deliveries, and preterm infants, the possible adverse effects of the drug regimens used for ovarian stimulation, and the instrumentation involved in ART procedures. In this paper we review the existing literature in these areas. It emphasizes the effects of the drugs used for ovarian stimulation, and in particular the incidence of cancer among women who have undergone ART. The review indicates that there is cause for concern about the long-term effects on women from ART treatments. It highlights the lack of research undertaken in almost all areas related to women's long-term health after ART. In the area of ART and cancer, it draws attention to the lack of conclusive evidence in relation to the posited association between fertility treatments and cancer, resulting from the limited number of very large studies and the need for longer follow-up periods. We make a number of recommendations regarding further research that is needed to address the current shortcomings in the published literature.

**Keywords:** Reproductive Techniques, Fertility Agents, Women's Health, Neoplasms

Women undergoing assisted reproduction are exposed to a range of drugs and procedures with the potential to cause adverse effects either in the immediate or longer term. These interventions include the drugs involved in ovarian stimulation and ovulation induction, instrumentation involved in egg retrieval and the reintroduction of embryos, and exposure to the culture medium in which the embryos develop. Women also may be affected by complications of pregnancy, poor pregnancy outcomes, and adverse perinatal outcomes that stem from the initial interventions. This paper first reviews the limited information available on the long-term physical sequelae of the various components of assisted reproduction technologies (ART). This review is followed by a detailed review of the research to date on the incidence of cancer among women who have undergone ART assisted conception.

## EFFECTS OF OVULATION INDUCTION

Clomiphene citrate, human menopausal gonadotropin (hMG), follicle-stimulating hormone (FSH), and gonadotropin-releasing hormone (GnRH) agonists are used

in ART cycles to stimulate the ovaries to produce one or more follicles and oocytes. There are four major areas where adverse effects of ovarian stimulation and ovulation induction have been identified. These are: ovarian hyperstimulation syndrome; bone loss due to GnRH agonists; adverse reproductive outcomes, such as ectopic and heterotopic pregnancies, early pregnancy loss, and multiple pregnancies; and the development of cancers, especially of the ovary.

### Ovarian Hyperstimulation Syndrome

The major immediate adverse health outcome of ovulation induction, including ovulation induction without IVF/GIFT, is ovarian hyperstimulation syndrome (OHSS). Although milder symptoms of ovarian stimulation are very common and form a continuum with symptoms that may be experienced with spontaneous ovulation (peritoneal fluid accumulation, ovarian bleeding, enlargement of the ovaries, and mood swings), ovarian hyperstimulation syndrome is characterized by massive ovarian enlargement and fluid accumulation in the peritoneal, pleural, and occasionally, pericardial cavities. Most ovulation-inducing drugs can cause ovarian hyperstimulation, and the incidence is believed to be greater when GnRH analogues are used in conjunction with gonadotropins for ovulation induction.

Mild cases occur in up to 23% of cycles. The moderate form is reported by Schenker and Ezra (68) as occurring in 3% to 4% of cases. Estimates of the incidence of severe OHSS vary from 0.1%–0.2% (68) to 1%–5% (53).

One long-term follow-up study in Israel has followed 1,107 women treated with hMG/human chorionic gonadotropin (hCG) (3,464 treatment cycles) between 1962 and 1982. In this group there were no deaths among the women treated and the incidence of severe OHSS was 0.25% (29). A number of serious, potentially life-threatening but rare side effects of severe OHSS have been the subject of case reports. These include stroke, cerebrovascular accident, tension ascites, ovarian torsion, adult respiratory distress syndrome, venous and arterial thromboembolism, peripheral gangrene, hypercoagulation, and serious impairment of liver or renal function. Several deaths have been reported (68). To our knowledge, there have been no reports of long-term follow-up of women who have experienced OHSS to determine the sequelae of these more immediate complications.

### Bone Loss

Agents used for ovulation induction, particularly the GnRH agonists, have been shown to be associated with significant bone loss when used as treatment for endometriosis (16). Although the regimens of treatment differ between GnRH agonists in assisted conception and GnRH agonists for endometriosis, the loss of trabecular bone appears to be dose- and duration-dependent as well as dependent on potency and route of administration (16). Recovery of the bone loss is slow following cessation of treatment.

Depending on the age of the woman, speed of recovery, and whether recovery is complete, bone loss as a result of treatment with GnRH agonists may increase women's risk of osteoporosis later in life. As yet there have been no long-term studies that have considered this possibility.

## EFFECTS OF INSTRUMENTATION

The surgical procedures involved with egg retrieval and embryo transfer are associated with a number of real, although infrequent, complications with potential long-term implications. These include pelvic infection from either the aspiration needle

or laparoscopy, complications of anesthesia, ovarian trauma associated with the puncture of follicles for egg retrieval, and visceral and vascular injuries resulting from laparoscopy.

### Pelvic and Other Infections

The incidence of pelvic sepsis requiring antibiotics or hospital admission for treatment after transvaginal egg retrieval procedures has been estimated in the range of 0.15% (when povidine iodine has been used for vaginal cleansing and oral antibiotics have been administered afterward) to 1.2% (when neither preventive measure has been used) (72). Infection may result from contamination from the embryo culture medium, with infection with hepatitis B and HIV/AIDS both having been reported in the literature (68). Infection may, in severe cases, result in pelvic adhesions, hysterectomy, and/or oophorectomy, with resultant loss or reduction in fertility.

### Complications of Anesthesia

Schenker and Ezra (68) have summarized the complications of regional and general anesthesia. They estimate the incidence of complications of general anesthesia as 2–3 per 1,000 and list hypoxia, aspiration pneumonia, pulmonary edema, pneumothorax, hypotension, gastric perforation, and death as possible complications. The use of general anesthesia with ART is now restricted to gamete intrafallopian tube transfers (GIFT), and regional anesthesia is not used at all (D. Healy, personal communication).

### Visceral, Vascular, and Ovarian Injuries

Complications of transvaginal oocyte retrieval include blood vessel injury, bladder injury, and intestinal injury, which are relatively rare but severe, with death a possible outcome. Dicker et al. (19) report complications, including acute abdominal pain because of severe tubo-ovarian abscess, rupture of endometrioma, and hemoperitoneum requiring laparotomy occurring in 0.38% of 3,556 transvaginal, ultrasonically guided oocyte retrievals. Schenker and Ezra (68) estimate that laparoscopic injuries occur in between 1 and 30 per 1,000 cases, with injuries to the uterus being the most common with an incidence of 10–30 per 1,000.

## LONG-TERM SEQUELAE OF COMPLICATIONS OF PREGNANCY AND POOR PREGNANCY OUTCOMES

Poor pregnancy outcomes, including spontaneous abortion and ectopic and heterotopic pregnancies, remain more common in women with ART-related pregnancies than among those who conceive unassisted. Those among whom pregnancy is maintained experience a higher rate of complications of pregnancy and birth, including pregnancy-induced hypertension, bleeding, placenta praevia, gestational diabetes mellitus, multiple gestation, preterm prelabor and rupture of the membranes, preterm birth, cesarean birth, and postpartum hemorrhage. Pregnancy complications are discussed in more detail elsewhere in this issue.

### Spontaneous Abortion

The raised incidence of spontaneous abortion of pregnancies conceived with ART remains at over 20%. It has not decreased despite the increasing proportion of women undergoing procedures as the result of male factor infertility (42). It is also unlikely that these raised incidence rates are the result of better identification of

early spontaneous abortion. As well as the pregnancy loss itself, there are small but additional risks for women resulting from spontaneous abortion. If surgical evacuation of the uterus is required, risks of infection and other surgical complications are encountered.

Spontaneous abortion is associated with an increased risk of preterm birth in subsequent pregnancies, especially birth before 32 weeks gestation, with the relative risk increasing with the number of prior spontaneous abortions. This may be due to a common cause for spontaneous abortion and preterm birth. Given a very similar association between induced abortion and subsequent preterm birth, the possibility that the procedure of emptying the uterus may be a causal factor cannot be excluded (47).

### Ectopic and Heterotopic Pregnancies

Ectopic and heterotopic pregnancies present the possibility of reduced future fertility for those women who experience this pregnancy outcome. Schenker and Ezra (68) estimate the incidence of ectopic pregnancy as between 3.0% and 5.5% and the incidence of heterotopic pregnancy as 0.5% to 1.2%. In Australia, the incidence of ectopic pregnancy following ART conceptions fell from above 5% prior to 1990 to 2.5% in 1995, possibly due to the increasing proportion of women using these procedures due to male factor infertility (42). Comparative population data on ectopic pregnancies in all Australian pregnancies are not available.

### Complications of Pregnancy

It is unclear from the existing literature whether the long-term outcomes for these conditions differ between those women using ART and those conceiving unassisted.

### Perinatal Mortality and Multiple Gestation

Compared to the 1.4% of multiple pregnancies among all Australian births in 1995, among IVF pregnancies in 1995 in Australia and New Zealand 19.4% were multiple pregnancies, of which 17.7% were twin pregnancies and 1.7% were triplets. Twin pregnancies were reported in 20.0% of GIFT pregnancies, triplets in 2.7% of pregnancies, and one quadruplet pregnancy was reported (42). The high rates of multiple births contribute to increased fetal and neonatal death rates and also increase the risks of pregnancy to the mother (49).

In Australia the perinatal outcome for infants conceived by IVF and GIFT is substantially worse than that for the Australian population as a whole. In 1995, fetal death rates after IVF (21.2 per 1,000 births) and GIFT (20.2 per 1,000 births) (42) were higher than for all Australian births (5.3 per 1,000 births in 1995). The neonatal death rates after IVF (10.9 per 1,000 live births) and GIFT (9.5 per 1,000 live births) (42) were also higher than for all Australian births (3.1 per 1,000 live births). Multiple births were an important factor contributing to the higher death rates after IVF and GIFT, but singleton births after ART also had higher death rates.

Preterm birth of less than 37 weeks' gestation occurred in 12.1% of singleton IVF pregnancies and 12.5% of GIFT pregnancies in 1995 (36), compared with 6.4% in all Australian pregnancies in 1995. There were also higher rates of low birth weight (less than 2,500 g) in IVF singleton births (10.1%) and GIFT singleton births (13.5%) (42) than in all Australian births (6.3% in 1995). Very low birth weight (less than 1,500 g) was also more common in IVF (7.3%) and GIFT (7.6%) births (42) than in all Australian births (1.3% in 1995). Again, multiple births contributed to the higher rates after ART, but very low birth weight occurred in 2.9% of

singleton IVF births and 4.6% of singleton GIFT births in 1995 (42). These outcomes are found across maternal age groups and across different types of infertility in the pooled Australian and New Zealand data (1;2;3;54;55;56;57;58;59).

### Cesarean Delivery

The rate of delivery by cesarean section for Australian singleton IVF pregnancies was 35.5% in 1995, almost double that for all singleton Australian births (19.0%) (42). The cesarean rate for twin and triplet IVF pregnancies was higher again at 58.5% and 91.2%, respectively. The cesarean rate in GIFT pregnancies was 31.6% for singletons, 57.4% in twin pregnancies, and 92.3% in triplet pregnancies. Cesarean delivery poses small but real additional mortality and morbidity risks for the mother (61;69).

A widely recognized sequel of cesarean delivery is the increased risk of uterine rupture in a subsequent pregnancy, especially if the first cesarean was carried out in association with the need for a classic cesarean or was very preterm. Two systematic reviews have identified long-term adverse effects of cesarean delivery. The first, which dealt with psychosocial outcomes, found less immediate and long-term satisfaction with the birth, a lower likelihood of ever breastfeeding, a longer time to first interaction with the infant, less positive reactions to the infants after birth, and less interaction with them at home (21). The other, a review of cohort studies, found prior cesarean delivery to be a risk factor for lower fertility, ectopic pregnancy, and possibly miscarriage, complications in the next pregnancy and birth, and health problems in the next infant (33). Both reviews drew attention to problems with the existing primary research. Two prospective studies have shown an increased prevalence of depression after cesarean birth (10;25).

Poor perinatal outcomes place a burden on the mother of the affected infant(s) and her family. The longer-term consequences for mothers, their families, and affected children are thoroughly discussed in a study of triplets and higher order births by Botting and colleagues (9). Similar, though less severe, problems exist for mothers of twins and their families.

As a result of preterm and very preterm birth, live born infants conceived as a result of ART have an increased chance of requiring admission to neonatal intensive care and special care. The factors of preterm birth and multiple gestation usually predict significant increases in morbidity in the perinatal period, increased rates of hospitalization in the first year of life, and higher rates of postnatal death, as well as disabilities and impairments in surviving infants (22;43;44;52;67;73). Long-term adverse effects on the parents of such infants are largely unknown.

There is relatively good evidence that there is no overall increase in birth defects among children conceived by ART (42), despite earlier findings suggesting significantly higher rates of spina bifida and transposition of the great vessels after IVF (41). However, there remains a need for subgroup analyses and multivariate analysis of large samples of children conceived by ART.

## CANCER AFTER TREATMENT WITH FERTILITY DRUGS

Interest in the question of whether fertility drugs are associated with an increased cancer risk has increased in the last few years. Findings from epidemiological studies, however, have not provided consistent answers. Common problems in the reported studies include small numbers of women with both previous exposure to fertility drugs and cancer, the difficulty in distinguishing the separate effects of infertility

from the effects of treatment or nulliparity, a lack of appropriate comparison groups, and a lack of complete information about fertility drug treatment or cause of infertility. Here we review those studies that explicitly aimed to examine the relationship between fertility drug exposure and cancer. Other studies of the relationship between infertility and cancer (12;14;27;28;62) have also produced inconsistent findings.

Although fertility drugs have been used in the treatment of anovulatory infertility for over 35 years, their use in ART to induce multiple folliculogenesis in ovulatory women is more recent (32). Different combinations of drugs and higher doses are used in ART compared with conventional ovulation induction. The effect of these different drug regimens is to stimulate the ovary to produce many oocytes: the mean number produced in ART cycles is approximately nine but can range from zero to 60. More than 90% of women having ART in Australia have normal ovulatory patterns. Only one of the observational studies (74), summarized in Table 1, has specifically examined whether the use of fertility drugs with ART is associated with an increased cancer risk. Because ART was developed relatively recently, the duration of follow-up may be too short to expect any evidence of fertility drugs initiating the development of cancer. Evidence of an increased risk of cancer in the short to medium term, however, might suggest a promoting effect of fertility drugs on the growth rate of pre-existing early stage tumors.

### Ovarian Cancer

Two major hypotheses about epithelial ovarian carcinogenesis are consistent with a role for fertility drugs. The first is that incessant ovulation with repeated trauma to the epithelium or repeated mitotic stimulation of the epithelium is carcinogenic (23;24). The second is that it is persistent exposure to high levels of circulating gonadotropins that is the important factor (71). A study of the incidence of ovarian cancer after ART may contribute to our understanding of the relative importance of these mechanisms.

Case reports and case series (4;5;6;7;13;20;30;31;35;37;38;45;46) have given detailed reports of ovarian cancer in women who have been treated with fertility drugs but suggest only the possibility of an association. Willemsen et al. (78) reported a case series of 12 patients in whom granulosa cell ovarian tumors were detected after ovarian stimulation with clomiphene citrate or gonadotropins. Eight of the 12 patients returned to normal ovulatory cycles after surgical removal of their tumors and five conceived spontaneously during the follow-up period. This report emphasizes the need for a thorough investigation of the cause of infertility, to rule out the presence of cancer, before fertility drug treatment is commenced.

Whittemore et al. (77), with the Collaborative Ovarian Cancer Study Group, analyzed data from 12 North American case-control studies of ovarian cancer. Information on fertility drug use was available in 3 of the 12 studies. Women who had taken fertility drugs had an increased odds ratio (OR) of invasive epithelial ovarian cancer and ovarian cancer of low malignant potential (borderline tumors), relative to women with no clinical history of infertility. The association with invasive ovarian cancer was very high in nulliparous women (OR = 27.0; 95% CI, 2.3–315.6) but not in parous women. The small number of women who had been treated with fertility drugs limited the power of the study. Inadequate data on causes of infertility also made it impossible to separate the effects of fertility drug treatment from the effects of ovulation disorders that independently may be associated with an increased risk of ovarian cancer.

**Table 1.** Comparison of the Use of Fertility Drugs with Assisted Reproductive Technology and Increased Risk of Cancer

| Study | Design | Study population | Comparison[a] | Tumor type | SIR[b] | RR[b] | OR[b] | 95% CI[b] |
|---|---|---|---|---|---|---|---|---|
| Whittemore et al. (77) | Reanalysis of pooled data from 3 case-control studies | Cases from U.S. hospital diagnoses (1977–81); controls from hospitals and general population (622 cases of invasive cancer, 1,101 controls; 88 cases of borderline tumors, 752 controls) | Infertile fertility drug users vs. nonusers with no clinical history of infertility | Invasive ovarian | | | 2.8 | 1.3–6.1 |
| | | | | Borderline ovarian | | | 4.0 | 1.1–13.9 |
| Rossing et al., (63;64;65;66) | Case-cohort | 3,867 U.S. women evaluated for infertility (1974–85). | Infertile fertility drug users vs. infertile nonusers | Borderline & invasive ovarian | | 2.3 | | 0.5–11.4 |
| | | | | Invasive & in situ breast | | 0.5 | | 0.2–1.2 |
| | | | | Invasive & in situ cervix | | 0.4 | | 0.2–0.8 |
| | | | | Melanoma | | 2.2 | | 0.5–10.2 |
| | | | Infertile fertility drug users vs. general female population | Borderline & invasive ovarian | 3.1 | | | 1.4–5.9 |
| | | | | Invasive & in situ breast | 0.9 | | | 0.6–1.4 |
| | | | | Invasive & in situ cervix | 0.5 | | | 0.4–0.7 |
| | | | | Melanoma | 1.8 | | | 0.9–3.1 |
| Modan et al. (50) | Cohort | 2,496 infertile Israeli women diagnosed 1964–74. Of these, 1,309 treated with fertility drugs. | Infertile fertility drug users vs. general female population | Invasive ovarian | 1.7 | | | 0.6–3.6 |
| | | | | Invasive & in situ breast | 1.1 | | | 0.7–1.6 |
| | | | | Invasive & in situ endometrial | 6.8 | | | 3.5–11.5 |
| Franchesci et al. (26) | Case-control | 195 cases from Italian hospital admissions (1992–3); 1,339 hospital controls. | Fertility drug users vs. nonusers | Invasive ovarian | | | 0.7 | 0.2–3.3 |
| La Vecchia et al. (39) | Case-control | As for reference 26 above. Data from one region extended to 208 cases and 873 controls. | Fertility drug users vs. nonusers | Invasive ovarian | | | 1.1 | 0.4–3.6 |

(*Continued*)

**Table 1.** (*Continued*)

| Study | Design | Study population | Comparison[a] | Tumor type | SIR[b] | RR[b] | OR[b] | 95% CI[b] |
|---|---|---|---|---|---|---|---|---|
| Sushan et al. (70) | Case-control | 164 cases of invasive and 36 cases of borderline ovarian cancer reported to the Israel cancer registry (1990–93); 408 controls from general population. | Fertility drug users vs. nonusers | Invasive ovarian | | | 1.3 | 0.6–2.7 |
| | | | | Borderline ovarian | | | 3.5 | 1.2–10.1 |
| Mosgaard et al. (67) | Case-control | 746 cases from the Danish cancer registry (1989–94); 1,721 controls from general population. | Parous infertile fertility drug users vs. parous infertile nonusers | Invasive ovarian | | | 0.6 | 0.2–1.3 |
| | | | Nulliparous infertile fertility drug users vs. nulliparous infertile nonusers | | | | 0.8 | 0.4–2.0 |
| Venn et al. (74) | Cohort | 10,358 women in an Australian IVF program (1979–92); of these 5,564 treated with fertility drugs. | Infertile fertility drug users vs. infertile nonusers | Invasive ovarian | | 1.5 | | 0.3–7.6 |
| | | | | Invasive breast | | 1.1 | | 0.6–2.2 |
| | | | | Invasive uterine | | 0.7 | | 0.1–3.9 |
| | | | | Invasive & in situ cervix | | 1.6 | | 0.9–3.2 |
| | | | | Melanoma | | 0.9 | | 0.3–2.5 |
| | | | Infertile fertility drug users vs. general female population | Invasive ovarian | 1.7 | | | 0.6–5.3 |
| | | | | Invasive breast | 0.9 | | | 0.6–1.5 |
| | | | | Invasive uterine | 2.2 | | | 0.6–8.9 |
| | | | | Invasive & in situ cervix | 0.6 | | | 0.4–0.9 |
| | | | | Melanoma | 1.1 | | | 0.7–1.8 |
| Braga et al. (11) | Case-control | 2,569 cases from Italian hospital admissions (1991–94); 2,588 hospital controls. | Fertility drug users vs. nonusers | Breast | | | 1.43 | 0.9–2.3 |

Abbreviations: SIR = standardized incidence ratio; RR = relative risk; OR = odds ratio; CI = confidence interval.
[a] Nonusers of fertility drugs included infertile and fertile women unless otherwise specified.
[b] SIR, RR, OR, and 95% CI values given to two decimal places in some papers have been reduced to one decimal place here.

Rossing et al. (63) conducted a case-cohort study of women who had had infertility investigations. Case-cohort studies are similar to nested case-control studies in that they follow up a defined cohort of individuals but collect detailed information only on exposures and covariates for the individuals who developed the disease of interest (cases) and a subsample of the cohort who did not develop the disease. The incidence of ovarian cancer in this study was determined by record linkage with the regional cancer registry for a follow-up period of between 6 and 16 years. A total of 11 cases of ovarian cancer were identified: four invasive tumors, two granulosa cell tumors, and five borderline ovarian tumors. A comparison of cancer incidence in the infertile cohort with age-standardized general population incidence rates gave a standardized incidence ratio (SIR) of 2.5 (95% CI, 1.3–4.5) for all ovarian tumors. The relative risk (RR) of ovarian tumors in women who had been treated with clomiphene citrate, which included women without ovulation disorders, compared with infertile women who had not had clomiphene was not significantly increased. Women who had had clomiphene citrate treatment for 12 or more cycles, however, had a relative risk of ovarian tumors of 11.1 (95% CI, 1.5–82.3) compared with women who had not used the drug. There was no such association for women who had had clomiphene for less than a year. The small number of tumors and the inclusion of borderline tumors limited the inferences that could be drawn from this study.

Cancer incidence in a cohort of 2,496 infertile Israeli women who were followed for between 17 and 27 years has been described by Modan et al. (50). There were more ovarian cancers in the cohort than expected (SIR = 1.6, 95% CI, 0.8–2.9), although the difference was not statistically significant. Women who had been treated with fertility drugs had a similar incidence of ovarian cancer as those who were untreated.

Three case-control studies have examined previous fertility drug treatment in women with invasive ovarian cancer. Franceschi et al. (26) found no association between ovarian cancer and the use of fertility drugs. The very small number of women who had had fertility drug treatment meant this study was unable to look at the effects of different types of fertility drugs or cause of infertility. Updated data from one of the regions in this study also failed to show any association (39).

A case-control study of ovarian cancer was reported by Shushan et al. in 1996 (70) included living women with invasive or borderline ovarian tumors reported to the Israel cancer registry and control subjects who were selected from the general female population. Of all women with ovarian cancer reported to the registry, 25% had died and 30% of those living were lost to follow-up or were unable to participate. Assessment of exposure to fertility drugs came from women's self-report and showed a higher prevalence of fertility drug use than the Italian case-control study described above. Exposure to fertility drugs was not significantly associated with ovarian cancer (invasive and borderline combined). A significant association was found, however, for borderline ovarian tumors alone; adjusted OR = 3.52 (95% CI, 1.23–10.09).

Analysis of all ovarian tumors by type of fertility drugs suggested that exposure to hMG had the largest effect, adjusted OR = 3.19 (95% CI, 0.86–11.82), but the finding was not statistically significant. Exposure to 12 or more cycles with clomiphene citrate was not associated with ovarian cancer (OR = 1.44, 95% CI, 0.34–5.82). Some of the limitations with this study include the exclusion of women who had died, reliance on self-report of fertility drug exposures without verification using medical records, and a lack of data on cause of infertility.

In a recent Danish case-control study from Mosgaard et al. (51), fertility drugs had been used by 20.7% of the living patients and 23.8% of the control subjects. Among parous and nulliparous infertile women, fertility drugs were not associated with ovarian cancer. No significant association was found with ovarian cancer for any particular fertility drug type. Although no association was found between fertility drugs and ovarian cancer, the data suggested that infertility was significantly associated with ovarian cancer in nulliparous women (OR = 2.71; 95% CI, 1.33–5.52) when compared with nulliparous women with no history of infertility. The effect of infertility was not seen for parous women (OR = 1.14; 95% CI, 0.6–2.17).

Parazzini et al. (60) recently described a case-control study of 93 Italian women with borderline ovarian tumors and 273 hospital control subjects. Four of the cases (4.3%) and none of the control subjects had ever used fertility drugs: the difference was statistically significant (Fisher exact test, $P = 0.004$).

To date, only one study has examined the incidence of cancer in a cohort of women who have had ART treatment. Record linkage with population-based cancer registries was used by two of us and our colleagues to determine the incidence of cancer in an Australian cohort of women who had been in an IVF program (74). The duration of follow-up ranged from 1 to 15 years. Women who had had IVF treatment with ovarian stimulation to induce multiple folliculogenesis comprised over half the cohort. Exposure to fertility drugs in this cohort was characteristic of the regimens used routinely to induce superovulation, and relatively few women exposed to fertility drugs had ovarian disorders (6.2%). Women who had not been exposed to fertility drugs with IVF were those who had been referred for treatment but had chosen not to continue for a range of reasons such as pregnancy occurring without IVF, other treatment options pursued, financial constraints, relationship difficulties, and concerns about risks and discomforts associated with treatment.

Three cases of ovarian cancer were observed in the women exposed to fertility drugs compared with 1.77 expected (SIR = 1.7; 95% CI, 0.55–5.27). In the unexposed group, three cases were observed and 1.85 expected (SIR = 1.62; 95% CI, 0.52–5.02). All IVF patients combined gave a SIR = 1.66 (95% CI, 0.75–3.69). Fertility drugs did not appear to be associated with an increased risk of ovarian cancer, but the proportional hazards model used to derive the RR estimate proved to be unstable due to the small number of cases of ovarian cancer (75). Examination of the relationship between cause of infertility and cancer risk showed significantly more cases of ovarian cancer among IVF patients with unexplained infertility than expected from age-standardized general population rates (SIR = 6.98; 95% CI, 2.90–16.8), regardless of treatment with fertility drugs.

Our study was limited by the small number of ovarian cancer cases observed, the relatively short follow-up time after exposure to fertility drugs, and the lack of data on important covariates, including parity. We were unable to establish whether potential confounding factors, such as parity and oral contraceptive use, were distributed differently among the women exposed and unexposed to fertility drugs.

### Breast Cancer

Theoretical concerns about fertility drugs and breast cancer are based on the role of endogenous and exogenous hormones in tumor development (36). Estrogen and progesterone have each been implicated in mechanisms of breast cancer development. Patients undergoing ART with ovarian stimulation and multiple ovulation have increased serum estradiol and progesterone concentrations compared with the spontaneous ovulation cycle. Case reports have appeared in the literature (8;40).

IVF patients have been found to have the same incidence of breast cancer as the general female population of the same age (74). Sixteen cases of invasive breast cancer were observed in women exposed to fertility drugs compared with 17.9 expected (SIR = 0.89; 95% CI, 0.55–1.46), and 18 were observed in the unexposed group compared with 18.3 expected (SIR = 0.98; 95% CI, 0.62–1.56). There was no increase in breast cancer risk in women exposed to fertility drugs compared with those who were not treated. No significant association was found between breast cancer risk and number of stimulated IVF treatment cycles or cause of infertility.

The case-cohort study described by Rossing et al. (66) found 27 cases of breast cancer (in situ and invasive tumors combined) in women with infertility compared with 28.8 cases expected (SIR = 0.9; 95% CI, 0.6–1.4). Women who had had treatment with clomiphene citrate had a nonsignificantly reduced risk of breast cancer compared with women who had not had clomiphene citrate (RR = 0.5; 95% CI, 0.2–1.2). The authors postulated that the finding might be explained by the similarity between clomiphene citrate and tamoxifen, a drug currently in use for the treatment of breast cancer.

Modan et al. (50) found 59 cases of breast cancer in their infertile cohort compared with 48.8 expected (SIR = 1.3; 95% CI, 0.96–1.6). The SIR for women who had had fertility drugs was less than for those who were untreated.

An Italian multicenter case-control study of breast cancer (11) showed no increase in breast cancer risk in women exposed to fertility drugs. Only a small proportion of patients (1.8%) and control subjects (1.2%) had ever used fertility drugs.

### Other Cancers

The incidence of other cancers in women who have had fertility drug treatment has been described in the cohorts studied by Rossing et al. (64;65), Venn et al. (74), and Modan et al. (50). Two studies (65;74) found that women seeking infertility treatment had a significantly lower incidence of carcinoma in situ (CIS) and invasive cancer of the cervix than the general population. The explanation for this finding is not clear, although some have been proposed (65). Before they registered with the IVF program, women in the IVF cohort (74) had the same incidence of CIS of the cervix as expected from general population incidence rates. After joining the program, the incidence of CIS was less than expected. This might reflect the outcome of increased cervical screening at the time of infertility investigations. An increase in the detection and treatment of low-grade cervical abnormalities in frequently screened infertile women would be expected to reduce the incidence of high-grade abnormalities compared with the general population.

Rossing's study (65) found a significantly reduced risk of cervical cancer in women who had used clomiphene citrate compared with women who had not used the drug. Incidence of cervical cancer was not reduced in women exposed to fertility drugs with ART.

Case reports of uterine cancer after fertility drug treatment have appeared in the literature (6;76). Endometrial cancer has been shown in previous studies to be increased by the unopposed action of estrogens (15) and to be more common in women with polycystic ovarian disease (18).

Cancer of the uterus was significantly more common among IVF patients than expected. The risk of uterine cancer did not differ significantly between women exposed and those unexposed to fertility drugs, but was greater in women with

unexplained infertility compared with women with known causes (RR = 6.34; 95% CI, 1.06–38.0). Modan et al. (50) also found an increased incidence of endometrial cancer in infertile women compared with the general population (SIR = 4.8; 95% CI, 3.0–7.5). The SIR was greater in women who had had fertility drug treatment than in those who were untreated, but the difference was partly explained by the greater proportion of treated women who had hormonal disorders characterized by unopposed estrogen.

Findings on the incidence of melanoma in women seeking infertility treatment differed between the two cohorts. In Australia, which has the highest incidence of melanoma, IVF patients had the same incidence as the general population (74). Exposure to fertility drugs was not associated with a significantly increased risk. Rossing's study (64), on the other hand, suggested a greater than expected incidence of melanoma in women attending North American infertility clinics compared with the general population and an increased risk among women who had had 12 or more treatment cycles with clomiphene citrate (RR = 2.2; 95% CI, 0.5–10.2). Neither association was statistically significant.

In the cohort of IVF patients, the incidence of all invasive cancers combined was found to be no greater than expected.

## CONCLUSIONS

The literature shows substantial possibilities of long-term adverse effects on women and children of ART, and thus, cause for concern. However, it is also evident that, with the exception of studies of ovarian and, to a lesser extent, breast cancer, there is a dearth of systematic long-term studies of physical and mental health effects on women in particular.

There is a need to conduct systematic and regular investigations of the physical, emotional, and social effects of ART treatments, including both qualitative and quantitative methods. Survey and/or interviews with participants can be used to allow those who have undergone ART treatments to identify problems and issues that they believe require further study. These may become the bases for specific research studies. They also would have the benefit of providing feedback to ART units, which can be used for improving service provision, and of providing a context for debriefing, problem resolution and, if necessary, further treatment for women. The cooperation of ART units is required to encourage ART participants to participate in follow-up studies and to endeavor to provide and maintain contact details required to facilitate such follow-up studies.

Those countries that provide ART services, and in which pregnancy-associated mortality and/or morbidity data are routinely collected, should consider including ART procedure–related mortality and major morbidity among women who do not become pregnant using these procedures in the proposed expanded definitions of pregnancy-associated mortality/severe morbidity.

Specific research studies required are longitudinal follow-up studies of the physical, emotional, and social health of women who are treated with ovulation-induction agents, particularly GnRH agonists, and those women who experience OHSS, pelvic infections, or visceral, vascular, or ovarian injuries. Careful consideration will need to be given to the choice of control groups for such studies, taking into account the possible role of infertility itself as well as treatment-associated problems. Specific large-scale studies of subgroups of congenital malformations

are required also, with multivariate analysis being employed in the analysis of relevant data.

More studies of cancer after ART are needed with longer-term follow-up and efforts to account for the effects of covariates that have been difficult to measure in many of the completed studies. The role of cancer screening and the possibility of increased ascertainment of cancer in women who have had ART should also be examined. Large cohort and case-control studies are needed to overcome the problem of low statistical power that has plagued studies of fertility drugs and cancer; collaboration between infertility clinics will be essential in achieving this goal. A reanalysis of pooled data from completed epidemiological studies may also be an option for the future.

## REFERENCES


1. AIHW National Perinatal Statistics Unit and Fertility Society of Australia. *Assisted conception, Australia and New Zealand, 1989.* Sydney: AIHW National Perinatal Statistics Unit, 1991.
2. AIHW National Perinatal Statistics Unit and Fertility Society of Australia. *Assisted conception, Australia and New Zealand, 1990.* Sydney: AIHW National Perinatal Statistics Unit, 1992.
3. AIHW National Perinatal Statistics Unit and Fertility Society of Australia. *Assisted conception, Australia and New Zealand, 1991.* Sydney: AIHW National Perinatal Statistics Unit, 1993.
4. Atlas, M., & Menczer, J. Massive hyperstimulation and borderline carcinoma of the ovary. *Acta Obstetricia et Gynecologica Scandinavica,* 1982, 61, 261–63.
5. Bandera, C., Cramer, D., Friedman, A., & Sheets, E. Fertility therapy in the setting of a history of invasive epithelial ovarian cancer. *Gynecologic Oncology,* 1995, 58, 116–19.
6. Banford, P., & Steele, S. Uterine and ovarian carcinoma in a patient receiving gonadotropin therapy. Case-report. *British Journal of Obstetrics and Gynaecology,* 1982, 89, 962–64.
7. Ben-Hur, H., Dgani, R., Lancet, M., et al. Ovarian carcinoma masquerading as ovarian hyperstimulation syndrome. *Acta Obstetricia et Gynecologica Scandinavica,* 1986, 65, 813–14.
8. Bolton, P. Bilateral breast cancer associated with clomiphene. *Lancet,* 1977, 2, 1176.
9. Botting, B. J., McFarlane, A. J., & Price, F. V. (eds.). *Three, four or more: A study of triplet and higher order births*. London: HMSO, 1990.
10. Boyce, P., & Todd, A. L. Increased risk of postnatal depression after emergency caesarean section. *Medical Journal of Australia,* 1992, 157, 172–74.
11. Braga, C., Negri, E., La Vecchia, C., et al. Fertility treatment and the risk of breast cancer. *Human Reproduction,* 1996, 11, 300–03.
12. Brinton, L., Melton, J., Malkasian, G., Bond, A., & Hoover, R. Cancer risk after evaluation for infertility. *American Journal of Epidemiology,* 1989, 129, 712–22.
13. Carter, M., & Joyce, D. Ovarian carcinoma in a patient hyperstimulated by gonadotropin therapy for in vitro fertilization: A case report. *Journal of In Vitro Fertilization and Embryo Transfer,* 1987, 4, 126–28.
14. Cowan, L., Gordis, L., Tonascia, J., & Jones, G. Breast cancer incidence in women with a history of progesterone deficiency. *American Journal of Epidemiology,* 1981, 114, 209–17.
15. Creasy, G., Kafrissen, M., & Upmalis, D. Review of the endometrial effects of estrogens and progestins. *Obstetrical and Gynecological Survey,* 1992, 47, 654–78.
16. Dawood, M. Y. Hormonal therapies for endometriosis: Implications for bone metabolism. *Acta Obstetricia et Gynecologica Scandinavica,* 1994, 159(Suppl.), 22–34.
17. Day, P., Lancaster, P., & Huang, J. *Australia's mothers and babies, 1995*. Sydney: AIHW National Perinatal Statistics Unit, 1997. Perinatal statistics series, no. 6.

18. de Waart, F. Uterine corpus. In D. Schottenfeld & J. Fraumeni (eds.), *Cancer epidemiology and prevention*. Philadelphia: Saunders, 1982, 901–08.
19. Dicker, D., Ashkenazi, J., Feldberg, D., et al. Severe abdominal complications after transvaginal ultrasonographically guided retrieval of oocytes for in vitro fertilization and embryo transfer. *Fertility and Sterility,* 1993, 59, 1313–15.
20. Dietl, J. Ovulation and ovarian cancer (letter). *Lancet,* 1991, 338, 445.
21. DiMatteo, M. R., Morton, S. C., Lepper, H. S., et al. Cesarean childbirth and psychosocial outcomes: A meta-analysis. *Health Psychology,* 1996, 15, 303–14.
22. Doyle, L. W. In-vitro fertilisation: A neonatal paediatrician's perspective. *Australian New Zealand Journal of Obstetrics and Gynaecology,* 1990, 30, 676–70.
23. Fathalla, M. Incessant ovulation: A factor in ovarian neoplasia? *Lancet,* 1971, 2, 163.
24. Fathalla, M. Factors in the causation and incidence of ovarian cancer. *Obstetrical and Gynecological Survey,* 1972, 27, 751–68.
25. Fisher, J., Astbury, J., & Smith, A. Adverse psychological impact of operative interventions: A prospective longitudinal study. *Australian and New Zealand Journal of Obstetrics and Gynaecology,* 1997, 31, 728–38.
26. Franceschi, S., La Vecchia, C., Negri, E., et al. Fertility drugs and risk of epithelial ovarian cancer in Italy. *Human Reproduction,* 1994, 9, 1673–75.
27. Gammon, M., & Thompson, W. Infertility and breast cancer: A population-based case-control study. *American Journal of Epidemiology,* 1990, 132, 708–16.
28. Gammon, M., & Thompson, W. Polycystic ovaries and the risk of breast cancer. *American Journal of Epidemiology,* 1991, 134, 818–24.
29. Golan, A., Ron, R., Herman, A., et al. Ovarian hyperstimulation syndrome: An update review. *Obstetrical and Gynecological Survey,* 1989, 44, 430–40.
30. Goldberg, G., & Runowicz, C. Ovarian carcinoma of low malignant potential, infertility and induction of ovulation: Is there a link? *American Journal of Obstetrics and Gynecology,* 1992, 166, 853–54.
31. Grimbizis, G., Tarlatzis, B., Bontis, J., et al. Two cases of ovarian tumours in women who had undergone multiple ovarian stimulation attempts. *Human Reproduction,* 1995, 10, 520–23.
32. Healy, D., Trounson, A., & Andersen, A. Female infertility: Causes and treatment. *Lancet,* 1994, 343, 1539–44.
33. Hemminki, E. Impact of caesarean section on future pregnancy: A review of cohort studies. *Paediatric and Perinatal Epidemiology,* 1996, 10, 366–79.
34. Hurst, T., Shafir, E., & Lancaster, P. *Assisted conception, Australia and New Zealand, 1996.* Sydney: AIHW National Perinatal Statistics Unit, 1997. Assisted conception series, no. 3.
35. Karlan, B., Marrs, R., & Lagasse, L. Advanced-stage ovarian carcinoma presenting during infertility evaluation. *American Journal of Obstetrics and Gynecology,* 1994, 171, 1377–78.
36. Kelsey, J., & Gammon, M. Epidemiology of breast cancer. *Epidemiologic Reviews,* 1990, 12, 228–40.
37. Komatsu, T., Konishi, I., Mandai, M., et al. Peritoneal papillary serous carcinoma arising in an infertile woman during ovulation-induction therapy: Immunohistochemical expression of LH/hCG receptors. *Gynecologic Oncology,* 1995, 56, 470–74.
38. Kulkarni, R., & McGarry, J. Follicular stimulation and ovarian cancer (letter). *British Medical Journal,* 1989, 299, 740.
39. La Vecchia, C., Negri, E., Parazzini, F., & Franceschi, S. Fertility drugs and breast and ovarian cancer (letter). *Lancet,* 1995, 346, 1628.
40. Laing, R., Glaser, M., & Barrett, G. A case of breast carcinoma in association with in vitro fertilization. *Journal of the Royal Society of Medicine,* 1989, 82, 503.
41. Lancaster, P. A. L. Congenital malformations after in vitro fertilization (letter). *Lancet,* 1987, 2, 1392–93.
42. Lancaster, P., Shafir, E., Hurst, T., & Huang, J. *Assisted conception, Australia and New Zealand, 1994 and 1995*. Sydney: AIHW National Perinatal Statistics Unit, 1997.

43. Leslie, G. I., Bowen, J. R., Arnold, J. D., & Saunders, D. M. In-vitro fertilisation and ventilator use in a tertiary perinatal centre. *Medical Journal of Australia,* 1992, 157, 165–67.
44. Levene, M. Assisted conception and its implications for paediatricians. *Archives of Disease in Childhood,* 1991, 66, 1–3.
45. Lopes, P., & Mensier, A. Cancer de l'ovaire après procreation medicalement assistée. *La Presse Medicale,* 1992, 21, 677.
46. Lopes, P., & Mensier, A. Ovarian cancer and assisted reproductive technology (editiorial). *European Journal of Obstetrics, Gynaecology, and Reproductive Biology,* 1993, 51, 171–73.
47. Lumley, J. The association between spontaneous abortion, prior induced abortion and preterm birth in first singleton births. *Prenatal and Neonatal Medicine,* 1998, 3, 21–24.
48. Lunenfeld, B., Blankstein, J., Kotev-Wmeth, S., et al. Drugs used in ovulation induction: Safety of patient and offspring. *Human Reproduction,* 1986, 1, 435–39.
49. McFarlane, A. J., Price, F. V., & Draw, E. G. Antenatal care. In B. J. Botting, A. J. McFarlane, & F. V. Price, (eds.), *Three, four or more: A study of triplet and higher order births*. London: HMSO, 1990.
50. Modan, B., Ron, E., Lerner-Geva, L., et al. Cancer incidence in a cohort of infertile women. *American Journal of Epidemiology,* 1998, 147, 1038–42.
51. Mosgaard, B., Lidegaard, O., Kjaer, S., Schou, G., & Andersen, A. Infertility, fertility drugs, and invasive ovarian cancer: A case-control study. *Fertility and Sterility,* 1997, 67, 1005–12.
52. National Health and Medical Research Council. *Perinatal morbidity*. Canberra: NHMRC, 1994.
53. National Health and Medical Research Council. *Long-term effects on women of assisted conception*. Canberra: NHMRC, 1995.
54. National Perinatal Statistics Unit and Fertility Society of Australia. *In vitro fertilization pregnancies, Australia, 1980-1983*. Sydney: National Perinatal Statistics Unit, 1984.
55. National Perinatal Statistics Unit and Fertility Society of Australia. *In vitro fertilization pregnancies, Australia and New Zealand, 1979-1984*. Sydney: National Perinatal Statistics Unit, 1985.
56. National Perinatal Statistics Unit and Fertility Society of Australia. *In vitro fertilization pregnancies, Australia and New Zealand, 1979-1985*. Sydney: National Perinatal Statistics Unit, 1987.
57. National Perinatal Statistics Unit and Fertility Society of Australia. *IVF and GIFT pregnancies, Australia and New Zealand, 1986*. Sydney: National Perinatal Statistics Unit, 1987.
58. National Perinatal Statistics Unit and Fertility Society of Australia. *IVF and GIFT pregnancies, Australia and New Zealand, 1987*. Sydney: National Perinatal Statistics Unit, 1988.
59. National Perinatal Statistics Unit and Fertility Society of Australia. *IVF and GIFT pregnancies, Australia and New Zealand, 1988*. Sydney: National Perinatal Statistics Unit, 1990.
60. Parazzini, F., Negri, E., La Vecchia, C., et al. Treatment for fertility and risk of ovarian tumors of borderline malignancy. *Gynecologic Oncology*, 1998, 68, 226–28.
61. Petitti, D. B. Maternal mortality and morbidity in cesarean section. *Clinics in Obstetrics and Gynecology,* 1985, 28, 763–69.
62. Ron, E., Lunenfeld, B., Menczer, J., et al. Cancer incidence in a cohort of infertile women. *American Journal of Epidemiology,* 1987, 125, 780–90.
63. Rossing, M., Daling, J., Weiss, N., Moore, D., & Self, S. Ovarian tumors in a cohort of infertile women. *New England Journal of Medicine,* 1994, 331, 771–76.
64. Rossing, M., Daling, J., Weiss, N., Moore, D., & Self, S. Risk of cutaneous melanoma in a cohort of infertile women. *Melanoma Research,* 1995, 5, 123–27.
65. Rossing, M., Daling, J., Weiss, N., Moore, D., & Self, S. In situ and invasive cervical carcinoma in a cohort of infertile women. *Fertility and Sterility,* 1996, 65, 19–22.

66. Rossing, M., Daling, J., Weiss, N., Moore, D., & Self, S. Risk of breast cancer in a cohort of infertile women. *Gynecologic Oncology,* 1996, 60, 3–7.
67. Saunders, D. M., & Lancaster, P. The wider perinatal significance of the Australian in-vitro fertilization data collection program. *American Journal of Perinatology,* 1989, 6, 252–57.
68. Schenker, J. G., & Ezra, Y. Complications of assisted reproductive techniques. *Fertility and Sterility,* 1994, 61, 411–22.
69. Schuitemaker, N., van Roosmalen, J., Dekker, G., van Dongen, P., van Geijn, H., & Gravenhorst, J. B. Maternal mortality after cesarean section in The Netherlands. *Acta Obstetrica et Gynecologica Scandinavica,* 1997, 76, 332–34.
70. Shushan, A., Paltiel, O., Iscovich, J., et al. Human menopausal gonadotropin and the risk of epithelial ovarian cancer. *Fertility and Sterility,* 1996, 65, 13–18.
71. Stadel, B. The etiology and prevention of ovarian cancer. *American Journal of Obstetrics and Gynecology,* 1975, 123, 772–74.
72. Sultan, K. M., Neal, G. S., Grifo, J. A., et al. *Incidence of pelvic infection following transvaginal oocyte aspiration for in vitro fertilisation and embryo transfer*. Presented at the VIIIth World Congress on IVF and Alternate Assisted Reproduction, Kyoto, Japan, September 12–15, 1993.
73. van Duivenboden, Y. A,, Merkus, J. M., & Verlove-Vanhorick, W. M. Infertility treatment: Implications for perinatology. *European Journal of Obstetrics, Gynaecology, and Reproductive Biology,* 1991, 42, 201–04.
74. Venn, A., Watson, L., Lumley, J., et al. Breast and ovarian cancer incidence after infertility and in vitro fertilisation. *Lancet,* 1995, 346, 995–1000.
75. Venn, A., Watson, L., Lumley, J., et al. Fertility drugs and breast and ovarian cancer (letter). *Lancet,* 1995, 346, 1627–28.
76. Waterstone, J., & Parsons, J. Endometrial stromal sarcoma two years after a successful in vitro fertilization treatment cycle. *Human Reproduction,* 1992, 7, 72.
77. Whittemore, A., Harris, R., Itnyre, J., & the Collaborative Ovarian Cancer Group. Characteristics relating to ovarian cancer risk: Collaborative analysis of 12 U.S. case-control studies, II: Invasive epithelial ovarian cancers in white women. *American Journal of Epidemiology,* 1992, 136, 1184–203.
78. Willemsen, W., Kruitwagen, R., Bastiaans, B., Hanselaar, T., & Rolland, R. Ovarian stimulation and granulosa-cell tumour. *Lancet,* 1993, 341, 986–88.