Tumour incidence in Swedish women who gave birth following IVF treatment

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BACKGROUND: Possible effects on maternal tumour incidence of a full-term pregnancy following IVF treatment with indicated supraphysiologic steroid and peptide hormonal levels in pregnancy remain uncertain. METHODS: National registries were used to compare incidence of non-invasive and invasive tumour disease in Swedish women with live birth following IVF treatment with women with live birth without IVF. RESULTS: The study had a mean follow-up period of 6.2 years in the IVF group and 7.8 years in the non-IVF group, and the mean gestation period (s.d.) for IVF and non-IVF group was 271.0 (21.1) days and 278.5 (14.1) days, respectively. In a multivariate Poisson regression analysis, adjusted rate ratios of 0.70 (0.52–0.92) and 0.93 (0.58–1.43) among IVF women were found for the risk of carcinoma in situ (CIS) of the cervix and breast cancer, respectively. When date of conception plus 1 and 3 years were used as start of follow-up, the rate ratios of CIS of the cervix increased to 0.77 (0.57–1.03) and 0.86 (0.60–1.19), respectively, and the corresponding figures for breast cancer decreased to 0.91 (0.58–1.42) and 0.74 (0.40–1.26). CONCLUSION: Following a relatively short follow-up period, there is little if any increased risk of premenopausal cancer development in women who gave birth after IVF treatment. The women who gave birth after IVF treatment had a decreased incidence of CIS of the cervix and breast cancer, but only the former was statistically significant. However, further studies are necessary to include longer follow-up times.

Key words: IVF/National registries/tumour incidence

Introduction

Assisted reproduction technology (ART) is a common recommendation with successively increased use and success rates for couples having subfertility problems. The number of reported initiated treatment cycles of ART in 2000 increased in Europe by 8% to 142 174 treatment cycles and in the USA by 13.5% to 99 989 treatment cycles, both compared with 1999 levels. In European countries with complete registration, this corresponded to 856 initiated treatment cycles per million inhabitants (ASRM/SART, 2004; Nyboe Andersen et al., 2004). Short-term effects of ART treatment on women have been studied and reported in detail, with small side-effect incidences, for example ovarian hyperstimulation syndrome in 1.1% of all stimulated cycles (Nyboe Andersen et al., 2004). However, concerns have been raised about the long-term effects of ART treatment, particularly ovarian stimulation treatment, regarding subsequent risk of tumour disease, especially tumours of the breast, uterus and ovary.

Long-term effects of ovarian stimulation treatment have been studied in cohort studies where infertile women exposed to ovarian stimulation treatment were compared with infertile women who did not receive such treatment or had ART without ovarian stimulation, for example artificial insemination (Venn et al., 1995, 1999; Dor et al., 2002; Doyle et al., 2002). These studies displayed incidence rates of cancer of the breast or ovary not significantly different in women who received hormonal ovarian stimulation and those who did not, and the incidences were no greater than expected based on national cancer rates. However, a statistically significant increased incidence rate was displayed of uterine cancer among infertile women who did not receive ovarian stimulation, and a decreased incidence of carcinoma in situ (CIS) of the cervix among infertile women, whether or not they received ovarian stimulation, as compared with that of the general population (Venn et al., 1999).

Women treated with ovarian stimulation to induce multiple folliculogenesis have been shown to have supraphysiological levels of steroid and peptide hormones not only during the phase of stimulation but also during a subsequent pregnancy (Kristiansson et al., 1996, 1999; Lagiou et al., 2003). Possible negative or positive long-term effects of these changes in the hormonal milieu during a full-term pregnancy following ovarian stimulation treatment on the incidence or development of
invasive and non-invasive tumours remain uncertain. Thus, a full-term pregnancy achieved following ovarian hyperstimulation may affect incidence of tumours under hormonal influence separately from the effects of ovarian hormonal stimulation per se.

The aim of this study was to compare the incidences of invasive and non-invasive tumours in women following pregnancy and live birth as a result of IVF treatment, with pregnancy and live birth without such treatment.

Materials and methods

Data collection

In Sweden, every individual has a unique census registration number that permits accurate record linkages between health care databases. The Swedish National Board of Health and Welfare is responsible for official statistics about deliveries, assisted reproduction, cancer incidence and causes of death. Data on all deliveries in Sweden from 1973 are reported to the Swedish Medical Birth Registry, which contains individual data collected during pregnancy, delivery and the neonatal period. The proportion of deliveries not reported to the registry was estimated to be 0.5–2% per year (Cnattingius et al., 1990). In addition, there is a complete register on information from all IVF clinics in Sweden from 1986 onwards, and the proportion of non-reporting is assumed to be negligible. Smaller numbers of IVFs were recorded between 1982 and 1985.

The law obliges all health care providers in Sweden to report a tumour diagnosis to the National Cancer Registry, founded in 1958. The overall reporting to the registry is estimated to be 96% of all diagnosed cases (www.sos.se/sose/sosomsos/statist.htm). The register includes diagnosis of neoplastic solid tumours, neoplastic blood tumours, in situ malignant tumours and benign tumours located, for example in the ovaries. Since 1958, tumours have been coded by site, according to International Classification of Diseases and Health Related Diseases, seventh revision (ICD-7) and histologically, according to WHO/HS/CANC/24.1. The histological types of the selected tumours were malignant, in situ malignant and benign. A code in the register classifies a case as benign or non-benign.

The Swedish Cause of Death Registry was used to identify women who died during the follow-up period.

Study population

Women with live birth following pregnancy achieved by IVF treatment in a stimulated cycle, without or with ICSI, were allocated to the IVF group. Women with live birth without such treatment (not in the register of IVF treatment) were allocated to the non-IVF group. To keep the IVF group as homogeneous as possible from a hormonal stimulation point of view, women with IVF treatment with ovum transfer in a natural cycle or frozen–thawed embryo transfer were excluded. Women diagnosed with an invasive tumour before the first conception leading to birth were also excluded. We did not take into account women with repeated pregnancies following in-vitro fertilization, because the number of cases among women with multiple pregnancies were too few. The categorization of exposure was IVF or non-IVF where IVF could be multiple IVF pregnancies.

Tumour cases were ascertained by record linkage. Groups of all invasive and all non-invasive tumours were formed, and women with multiple tumours registered were only counted once. Average time (years) between date of conception and date of invasive tumour was 4.9 for IVF-group and 6.0 for non-IVF group. For non-invasive tumour the average time was 2.7 for IVF and 3.1 for non-IVF group.

The effect of emigration/immigration was diminished by only including in the cohort women born in Sweden, as fewer women from foreign countries may be found among women treated with IVF.

Follow-up began at the time of first conception leading to a delivery and continued until date of tumour diagnosis, death, or the end of the observation period (31 December 2001), whichever came first. Date of conception was estimated from ultrasonographic measurement in gestational week 18 or, when not available, from the date of last menstrual period. IVF treatment was handled as a time-dependent variable, that is person-years were allocated to the non-IVF group until an IVF pregnancy occurred (Breslow and Day, 1987).

The ovarian hyperstimulation principle used during the study period was standardized and uniform. Administration of gonadotrophins promoted the development of a large number of ovarian follicles resulting in high circulating levels of, for example, estradiol and the possibility of recovering many oocytes by follicle aspiration.

Statistical methods

Crude and standardized incidence rates per 10 000 person-years for the IVF and the non-IVF groups were calculated, with all women in the study included. Age and age plus conception year adjusted incidence rates for the non-IVF group with 95% confidence intervals (95% CI) were calculated directly, standardized to the distribution of age and conception year in the IVF population (Armitage and Colton, 1998). The standardization calculations were based on age- and year-specific rates in 1-year classes.

Poisson regression was used to obtain estimates of relative risks with 95% CI to compare IVF and non-IVF groups, adjusting for the following time-dependent variables: age at follow-up, calendar year at follow-up, number of siblings and multiple births, as well as age at first conception leading to a delivery (Breslow and Day, 1987). Because of substantial differences between IVF and non-IVF groups in the distributions of conception age and conception year, only women with a first conception from age 25 to 39 and from 1989 to 2001 were included in the Poisson model to minimize the risk of residual confounding. The ages and years included contained at least 100 first IVF conceptions per year and age, respectively. The categorization of the factors used in the model was 21–24, 25–29, 30–34, 35–39 and 40–43 for age at follow-up, 1-year classes for year at follow-up and age at first conception leading to a delivery, none/any for number of siblings and yes/no for multiple births. For studied tumour types, age standardized incidence rates per 10 000 women based on 5-year age classes diverged at most by 0.05 as compared with rates per 10 000 based on 1-year age classes. Risk time was allocated to the non-sibling category for a subject until the next possible conception and to the one child category until the date of a possible multiple birth. All estimates of the rate ratio IVF group/non-IVF group were calculated including all factors in the model. Incidence rate ratios from the Poisson model was calculated using date of conception plus 1 and 3 years as the time origin of the exposure to remove possible differences in health status at the time of conception. This means that we did not include cases within 1 and 3 years from date of conception. It could be that a woman entering an IVF treatment is generally more aware of a good health status at the time of conception than the average woman becoming pregnant without IVF. The pregnancy conceived without IVF treatment could be unplanned in contrast to women undergoing an IVF treatment. Information was not available on oral contraceptive use, family occurrence of cancer or smoking. Statistical analyses were performed using the SAS program package (SAS Institute Inc., Cary, NC, USA).

The ethics committees of Uppsala University and Karolinska Institutet, Sweden approved this study.
Results

The cohort consisted of 647,704 women between 21 and 43 years of age registered with a first pregnancy (IVF or non-IVF) from 1 January 1981 until 31 December 2001 resulting in 1,269,967 deliveries. In this cohort, 8716 women had 9323 deliveries following pregnancies achieved by IVF treatment, of whom 7645 had IVF for their first delivery, whereas 1071 had had a previous delivery without IVF treatment.

Demographic characteristics of women included are summarized in Table I. Distribution of location of non-invasive and invasive tumours in IVF group and non-IVF group is presented in Table II. There were at least 10 cases of tumours in the breast, ovary, cervical uterus and body of uterus, and these were therefore included in further analyses.

The incident numbers of cases and crude, age-standardized and age/year-standardized numbers of cases per 10,000 person-years of non-invasive tumours in IVF group and non-IVF group are summarized in Table III. The incidence of non-invasive CIS of the cervix per 10,000 person-years was lower in the IVF group than in the non-IVF group. In the combined group of all non-invasive tumours, the difference between IVF group and non-IVF group was smaller, and when CIS of the cervix was excluded, the incidence was slightly higher for the IVF group.

The lower rates for the age-standardized rates for CIS of the cervix as compared with the corresponding crude rate for the non-IVF group is attributable to the IVF women being generally older as compared with the non-IVF group, showing the inverse relationship between age and tumour incidence of CIS of the cervix.

The incident numbers of cases and crude, age-standardized and age/year-standardized numbers of cases per 10,000 person-years of invasive tumours in IVF group and non-IVF group are summarized in Table III. The standardized incidence of invasive tumour of the breast per 10,000 person-years was lower in the IVF group than in the non-IVF group but with overlapping confidence intervals. In the aggregated groups of invasive tumours, the standardized rate of invasive tumours in the IVF group was slightly lower, although slightly higher when breast cancer was excluded.

A multivariate Poisson regression analysis was performed to take into account the possible confounding factors collected in the study, adjusting for age at follow-up, age at first conception, calendar year at follow-up, number of siblings and multiple births. The material used for the Poisson regression analysis comprised 7681 IVF women with an average age at first conception (SD) of 32.8 (3.5) years and an average number of person-years (SD) of 6.2 (3.0). The number of non-IVF women was 253,793 with an average age at first conception (SD) of 29.3 (3.2) years and an average number of person-years (SD) of 7.8 (3.6).

The incidence rate ratio of non-invasive CIS of the cervix in the IVF group was 0.70 (0.52–0.92) of that in the non-IVF group (Table IV). The incidence rate ratio of all non-invasive tumours was also lower in IVF group, 0.76 (0.60–0.96) than in the non-IVF group. After date of conception plus 1 and 3 years were used as start of follow-up, the rate ratio increased.

As regards invasive tumours, the multivariate analysis displayed a lower, statistically non-significant, incidence rate ratio of invasive breast tumour in the IVF group as compared with the non-IVF group (Table IV). The incidence rate ratio of breast cancer in the IVF group was 0.93 (0.59–1.43) of that in the non-IVF group, that is, a decreased risk in the IVF group of 7%, although not statistically significant. The rate ratio of invasive tumour of the breast displayed a further decrease to 26% in the IVF group after date of conception plus 1 and 3 years were used as start of follow-up, although still not statistically significant. The incidence rate ratio for the aggregated group of invasive tumours suggested that the overall cancer rates for the IVF and non-IVF groups were very similar.

Discussion

In this prospective cohort study, using reliable national registers, a lower incidence of cancer of the breast and CIS of the cervix is identified among IVF women as compared with non-IVF women. However, only the latter was statistically significant. In multivariate regression analyses taking possible confounders measured into account, the association was stronger for CIS of the cervix, although when inclusion in the study was prolonged 1 and 3 years the association became stronger for breast cancer and weaker for CIS of the cervix. Regarding ovarian tumours, the incidence was slightly lower for the IVF group than in the non-IVF group. In the combined group of all non-invasive tumours, the difference between IVF group and non-IVF group was smaller, and when CIS of the cervix was excluded, the incidence was slightly higher for the IVF group.
cancer and uterine cancer, too few cases and too short follow-up time prevented further analysis. We did not find any statistically significant differences between IVF and non-IVF women for the aggregated invasive tumour groups.

To the best of our knowledge, no previous study has examined the incidence of tumour disease in women following full-term pregnancy achieved after IVF treatment. The results must be interpreted with caution although cohort studies are inherently stronger methodologically than case–control data in establishing an association (Kashyap et al., 2004). However, the present results more strongly indicate no increased risk of tumour disease in women who gave birth to a child as a result of IVF treatment than in women without such treatment. This is in accordance with findings in studies of women undergoing IVF treatment, irrespective of whether or not there was a subsequent pregnancy, where the incidence of cancer was no greater than in women referred for IVF but not treated or in women from the general population (Venn et al., 1995, 1999; Doyle et al., 2002).

In the context of tumour development and tumour progression, this study is limited by the short time of follow-up (an average 6.2 years in the IVF group and 7.8 years in the non-IVF group for the adjusted Poisson regression analysis), although the follow-up time was no shorter than presented in previous studies of tumour risk and ART (Venn et al., 1999; Dor et al., 2002; Doyle et al., 2002).

The complete explanation for the displayed lower incidences of cancer of the breast and CIS of the cervix will probably include factors not measured in this study, and so, the reasons for the different rates of cancer incidence between the groups here are a matter of speculation.

An association between social inequalities and incidence of breast cancer and dysplasia of the cervix including CIS has been suggested (Parikh et al., 2003; Henderson et al., 1996).

### Table III. Absolute number and rate per 10,000 person-years, standardized by age and conception year, of women diagnosed with a non-invasive or invasive tumour presented by location and as IVF and non-IVF groups

<table>
<thead>
<tr>
<th>Location</th>
<th>ICD-7 code</th>
<th>Exposure</th>
<th>Number</th>
<th>Rate (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-invasive tumour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical uterus</td>
<td>171</td>
<td>IVF</td>
<td>63</td>
<td>11.31 (8.83–14.47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-IVF crude</td>
<td>13,931</td>
<td>18.75 (18.45–19.07)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age standardized</td>
<td></td>
<td>16.91 (16.57–17.26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age and conception year</td>
<td>29</td>
<td>16.96 (16.59–17.34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>standardized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All, excluding cervical</td>
<td></td>
<td>IVF</td>
<td>29</td>
<td>5.20 (3.62–7.49)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-IVF crude</td>
<td>3364</td>
<td>4.53 (4.38–4.68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age standardized</td>
<td></td>
<td>4.58 (4.40–4.77)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age and conception year</td>
<td>454</td>
<td>4.54 (4.35–4.74)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>standardized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td>IVF</td>
<td>92</td>
<td>16.51 (13.46–20.25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-IVF crude</td>
<td>17,295</td>
<td>23.28 (22.94–23.63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age standardized</td>
<td></td>
<td>21.43 (21.05–21.82)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age and conception year</td>
<td>21.43</td>
<td>21.01–21.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>standardized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive tumour</td>
<td></td>
<td>Breast</td>
<td>1701–1709</td>
<td>24 (4.31 (2.89–6.43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-IVF crude</td>
<td>3059</td>
<td>4.12 (3.97–4.27)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age standardized</td>
<td>5,906</td>
<td>5.96 (5.73–6.20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age and conception year</td>
<td>5,96</td>
<td>9.33 (7.11–12.25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>standardized</td>
<td></td>
<td>6.97 (6.79–7.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All</td>
<td>13.64</td>
<td>8.41 (8.16–8.67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All, excluding breast</td>
<td>14.42</td>
<td>8.49 (8.21–8.77)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All</td>
<td>14.42</td>
<td>10.85–11.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All</td>
<td>14.42</td>
<td>10.46–14.79</td>
</tr>
</tbody>
</table>

### Table IV. Rate ratios of non-invasive and invasive tumour incidence by IVF/non-IVF from multivariate Poisson regression analysis with 95% confidence interval (95% CI) standardized by age at follow-up, age at first conception, calendar year at follow-up, number of parities and multiple births

<table>
<thead>
<tr>
<th>Tumour location</th>
<th>Date of conception</th>
<th>Date of conception plus 1 year</th>
<th>Date of conception plus 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate ratio ([95% CI]) (Number of cases IVF/Non-IVF)</td>
<td>Rate ratio ([95% CI]) (Number of cases IVF/Non-IVF)</td>
<td>Rate ratio ([95% CI]) (Number of cases IVF/Non-IVF)</td>
</tr>
<tr>
<td>Non-invasive tumour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIS of the cervix</td>
<td>0.70 [0.52–0.92] (52/3526)</td>
<td>0.77 [0.57–1.03] (49/3157)</td>
<td>0.86 [0.60–1.19] (35/2328)</td>
</tr>
<tr>
<td></td>
<td>0.76 [0.60–0.96] (76/4421)</td>
<td>0.84 [0.65–1.06] (71/3948)</td>
<td>0.87 [0.64–1.16] (48/2890)</td>
</tr>
<tr>
<td>Invasive tumour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>0.93 [0.58–1.43] (21/7111)</td>
<td>0.91 [0.58–1.42] (19/691)</td>
<td>0.74 [0.40–1.26] (13/617)</td>
</tr>
<tr>
<td></td>
<td>1.06 [0.81–1.36] (67/2069)</td>
<td>1.01 [0.76–1.32] (58/1941)</td>
<td>1.00 [0.71–1.36] (41/1565)</td>
</tr>
</tbody>
</table>

CIS, carcinoma in situ.

*Calculated from date of conception, date of conception plus 365 days and date of conception plus 1095 days.
Higher social class has been found to be positively associated with breast cancer risk and negatively with risk of cervical cancer including CIS of the cervix. Thus, in this study, social class does not necessarily explain the suggested decreased risk of breast cancer and CIS of the cervix.

Parallel to the ‘healthy patient effect’ (Venn et al., 2001), IVF women could have delayed tumour incidence as compared with the general population. Women who chose IVF treatment might be more aware of risks or be more health conscious at the time of conception as compared with non-IVF women, all variables related to decreased risk of illness. Nevertheless, the indicated decreased risk of cancer of the breast was more evident when date of conception plus 1 and 3 years were used as start of follow-up, although the opposite was observed for CIS of the cervix. For CIS of the cervix, the decreased risk diminished suggesting that a ‘healthy patient effect’ could be an explanation of the decreased risk for IVF women. In addition, human papilloma virus (HPV) infection has been found to be closely associated with CIS of the cervix, and HPV infection was found to be significantly less frequent in IVF women than in controls (Schiffman et al., 1996; Lundqvist et al., 2002). There is evidence in favour of socio-demographic differences between the IVF and non-IVF women in this study because only women accepted for IVF treatment were women in couples in a solid, lasting relationship (National Board of Health and Welfare, 1998), the infertility investigation for IVF included a thorough diagnostic investigation before and during the treatment cycle, and about half the couples had to pay for the IVF treatment privately. We have not found any publications about socio-demographic characteristics of sub-fertile/infertile and fertile women. No typical psychological profile in infertile couples was found in a study from Germany (Wischmann et al., 2001).

Examples of demographic risk factors for breast cancer are early age at menarche, nulliparity, late full-term pregnancy, higher social class and increasing age. Such factors known to exert protective effects on breast cancer development are early full-term pregnancy, increasing number of births, longer periods of anovulation and more physical activity (Bernstein et al., 1994).

For IVF women, in this study, determinants of increased risk of breast cancer are older age, late full-term pregnancy and fewer deliveries whereas no protective factors could be stated. Considering these factors, the absence of an increased incidence of premenopausal breast cancer in this study suggests a possible protective effect of the IVF pregnancy.

The long-term protective effect on breast cancer risk of an early full-term pregnancy seems to be triggered by an intrinsic rather than an extrinsic mechanism (Russo and Russo, 2000). Full differentiation of the mammary gland is a gradual process and the result of complex interactions of ovarian, pituitary and placental hormones (Russo et al., 2001). The supraphysiologic levels of steroid and peptide hormones in pregnancy might have exerted such a protective biologic effect in IVF women (Russo and Russo, 1999, 2000). Treatment with clomiphene citrate also gives raised hormone levels in the subsequent pregnancy and appears to reduce the risk of breast cancer in infertile women (Bell et al., 1989; Rossing et al., 1996). The same effect could explain why increased progesterone levels were associated with a lower incidence of maternal breast cancer among women pregnant without IVF treatment (Peck et al., 2002).

Infertile women, who did or did not receive fertility drugs, exhibited a lower incidence of CIS of the cervix than found in the general population (Venn et al., 1995). This is in accordance with a 0.70 rate ratio of CIS of the cervix in our multivariate regression analysis when possible confounders were taken into account. In contrast to the case with breast cancer, the incidence of CIS of the cervix did not further decrease when we prolonged the time for inclusion in the study. This finding is in line with the theory of non-hormonal aetiologic factors being of importance to the development of CIS of the cervix.

In conclusion, there appears to be little if any increased risk of premenopausal cancer development in women who gave birth after IVF treatment. The women who gave birth after IVF treatment had a decreased incidence of CIS of the cervix and breast cancer, the former statistically significant. Probable explanations are non-measured confounding factors, a hormonal protective biologic mechanism of the breast and lower incidence of HPV infection. Our results are reassuring for women undergoing IVF treatment, but further studies are necessary to include longer follow-up times. The average follow-up time of 7 years in our study may be too short to reveal any possible carcinogenic effects of IVF treatment. This also prevents us from being able to draw any conclusions about post-menopausal women.

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