

No increased risk of relapse of breast cancer for women who give birth after assisted conception

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STUDY QUESTION: Is childbirth after IVF associated with a risk of relapse in breast cancer?

SUMMARY ANSWER: Women who had been diagnosed with breast cancer and completed treatment had no increased risk of relapse if they gave birth after conceiving with IVF.

WHAT IS KNOWN ALREADY: Pregnancy and childbirth have not been shown to increase the risk of relapse in breast cancer. Ovarian stimulation during IVF increases the oestrogen levels and could theoretically increase the risk of relapse in breast cancer.

STUDY DESIGN, SIZE, DURATION: This is a retrospective register study, using national Swedish register data from the National Patient Register, the Medical Birth Register, the Swedish National Cancer Register, the National Breast Cancer Register, the National Quality Registry of Assisted Reproduction (Q-IVF), the National IVF Dataset, the Swedish Prescribed Drug Register and the Cause of Death Register. All women diagnosed with breast cancer who were between 20 and 44 years of age during the years 1982 to 2014 and identified in the cancer registries were assessed.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women, previously diagnosed with breast cancer, who had given birth after IVF (29 after completed breast cancer treatment and 8 after fertility preservation) were compared with a matched control group who had given birth after spontaneous conception. Matching was done in a ratio 1:4, based on T-stage (size of the tumour) and year of diagnosis +/-5 years.

MAIN RESULTS AND THE ROLE OF CHANCE: We found 26 114 women that had been diagnosed with breast cancer when 20–44 years old and of those 860 had subsequently given birth, 823 after spontaneous and 37 after IVF conception. Follow-up time was similar between the groups, ranging from 2.6 to 24.0 years, with a mean follow-up time of 10.3 (SD 4.2) years in the IVF group and 10.7 (SD 4.4) years in the control group. There were no relapses (0/37) in the IVF group. The relapse rate for the matched controls was 36/148 (24.8%). Ten women who suffered relapse died due to breast cancer.

LIMITATIONS, REASONS FOR CAUTION: This is reassuring data; however, the result is based on a few cases. The poor coverage of important prognostic variables in the register resulted in uncertain comparability of the groups. The main limitation in this study is the extent of missing data on tumour-related variables, due to poor coverage from the early years of the National Breast Cancer Register. It is possible that the women accepted for IVF had a less aggressive breast cancer and were generally healthier than women delivering after conceiving spontaneously and therefore had a lower risk of relapse. Other limitations are the lack of information on the anticancer therapies used and type of disease relapse, plus the older of the two IVF registers did not hold information on unsuccessful IVF cycles, leaving only cycles leading to birth, to be analysed.

WIDER IMPLICATIONS OF THE FINDINGS: We found no indication that women who had been diagnosed with breast cancer had an increased risk of relapse if they gave birth after conceiving with IVF. Based on our findings, there is no evidence to advise against IVF treatment in this group of women. More detailed registry data would be valuable for future studies, enabling proper matching of tumour characteristics between groups.

STUDY FUNDING/COMPETING INTEREST(S): The study was financed by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (ALFGBG-720291), The Assar Gabrielsson Fund (FB 15-20), The Breast Cancer Fund and the Swedish Association of Local Authorities and Regions, SKL. There are no conflicts of interest to declare.

Key words: assisted reproduction / ART / IVF / breast cancer / relapse / childbirth

WHAT DOES THIS MEAN FOR PATIENTS?

For women who have gone through treatment for breast cancer, the ability to become pregnant can be reduced and there might be a need for assisted reproduction such as IVF (*in vitro* fertilisation). Earlier studies have shown that pregnancy and childbirth, including after IVF, are safe and not associated with an increased risk of the breast cancer recurring (relapse). In our study, we compared the relapse rate for women with previous breast cancer who had given birth after IVF with those who had given birth after spontaneous conception and found no increased risk for the IVF group. None of the 37 women who had undergone IVF prior to giving birth had a relapse, while there were 36 relapses among the 148 women with spontaneous conception. Ten women who suffered relapse died due to breast cancer. With the present careful selection of patients diagnosed with breast cancer to be offered IVF, the risk of relapse is not increased after childbirth following IVF compared with spontaneous conception.

Introduction

Breast cancer is the most common cancer among women worldwide, and the incidence is rising. Incidence rates are generally higher in high-income countries and is 110/100 000 women in Europe (WHO, Global Cancer Observatory/ European Health Information Gateway, 2018). Every year, more than 8000 people in Sweden are diagnosed with breast cancer (National Board of Health and Welfare, 2013), making it the second most common cancer form in the population and the most common among women, where it constitutes one-third of all cancers. The median age at diagnosis is 60 years, but women of childbearing age are also affected. About 10% of the women diagnosed with breast cancer are between 20 and 44 years of age (National Board of Health and Welfare, 2016). Survival in breast cancer has improved significantly in recent decades and the relative 5-year survival is around 90% (Fredholm et al., 2009; National Board of Health and Welfare, 2013). Thus, there is a population of women who have undergone breast cancer treatment (surgery, radiation, chemotherapy and/or hormone modulating treatment) that are still of childbearing age and may have a wish to conceive. In these women, fertility may be impaired for several reasons. Chemotherapy drugs have a toxic effect on the reproductive organs (Petrek et al., 2006) and many women are treated with anti-oestrogen for several years after initial treatment to reduce the risk of relapse, during which time pregnancy is contraindicated. Since these women might have had to postpone pregnancy attempts because of their cancer and subsequent treatments, many of them also reach an age where natural fertility is reduced. The chance to conceive spontaneously is reduced by half after breast cancer treatment (Ives et al., 2007; Van den Berg et al., 2018; Andersson et al., 2018), and thus, some women will be treated with ART. The protocol for IVF treatments includes ovarian stimulation, with highly increased oestrogen levels giving a theoretical risk of relapse in breast cancer. Several studies have investigated the risk of relapse of breast cancer in women who subsequent to breast cancer diagnosis but before treatment have undergone fertility preservation (Azim et al., 2008; Kim et al., 2016; Rodriguez et al., 2018) and found no elevated risk for relapse compared with women who had not gone through this procedure. Fewer studies have been published concerning women undergoing ART and

giving birth after completed breast cancer treatment (Goldrat et al., 2015). The international multi-centre study by Goldrat et al. (2015) evaluated the risk for relapse in 25 women who had undergone ART (ovulation induction, IVF with own or donated gametes) after breast cancer treatment and found no elevated risk compared with women who conceived naturally; 2/25 (8%) compared with 10/173 (5.8%) suffered distant recurrences, and 1 and 11 women died in the ART and spontaneous conception groups, respectively.

The aim of this national register-based study was to assess the risk of relapse in breast cancer in women who have given birth after ART compared with women who have delivered after spontaneous conception. The ART group includes both IVF and embryo transfer after completed breast cancer treatment as well as fertility preservation in connection with the breast cancer diagnosis.

Materials and Methods

Design

This is a retrospective, population-based, matched cohort study. The study base included women with breast cancer who subsequent to diagnosis and treatment had given birth. Each woman exposed to ART with ovarian stimulation was matched with four women from the study base.

Data sources

The National Patient Register (NPR) started in 1964 and included all diagnoses for patients admitted to hospital. Since 2001, diagnoses for outpatient visits (excluding primary care) have been included. Surgical interventions have been reported to the register since the start, while reporting of medical interventions began in 2006. Reporting to this register is mandatory by law. The registry has been shown to have a high validity (Ludvigsson et al., 2011).

The Swedish National Cancer Register (NCR) started in 1958 and includes data on all cancers diagnosed in Sweden. Cancer diagnoses are reported to the register through six regional cancer centres. It includes information about tumour type, size, histopathology and proliferation.

The *National Breast Cancer Register* is operated by the Stockholm County Council and started in 2007. Since 2008, all regions in Sweden are included. It is a source of information on what treatments and diagnoses have been given to each patient with a breast cancer diagnosis (C50* in ICD 10 (International Classification of Disease). The register covers 99% of all invasive and *in situ* breast cancer diagnoses but has a lower coverage for oncological treatments. Available variables are, for example, preoperative diagnoses, other invasive tumours, TNM stage (Tumour size, tumour positive Nodes, Metastases), time to treatment and complications.

The *National Quality Register for Assisted Reproduction (Q-IVF)* started in 2007 and includes all started IVF cycles in both private and public IVF clinics in Sweden. The National Board of Health and Welfare holds a previous research dataset on live births after IVF from 1982 to 2006, hereafter named *the National IVF dataset*. Since the National IVF Dataset does not hold information on IVF stimulations in women who have had unsuccessful IVF, only women who have given birth after breast cancer were included in this study.

The *Swedish Prescribed Drug Register* started in 2005 and is maintained by the National Board of Health and Welfare through the E-health Authority, to which all prescribed and redeemed medical drugs are reported. From this register, we were able to identify patients who had received hormonal drugs (oestrogens and/or progestogens) from the date of breast cancer diagnosis and onwards.

The *Medical Birth Register (MBR)* was used to identify those who gave birth, both before and after breast cancer diagnosis. This register includes all births in Sweden since 1973, reported from the delivery wards. It includes data from the antenatal care including demographic variables, obstetric diagnoses as well as diagnoses of the newborn. The registry was validated in 1990 and was found to have high validity (Cnattingius *et al.*, 1990).

From the *Cause of Death register*, also maintained by the National Board of Health and Welfare and with a complete coverage since 1961, we retrieved information on deaths caused by breast cancer. It is based on death certificates and lists up to four diagnosed causes of death.

Patients

Through the NPR, the NCR and the National Breast Cancer Register, we identified women, aged 20 to 44 years, diagnosed with breast cancer (malignant tumour in the female breast, diagnosis code 174 in ICD9 (1987–1996) and diagnosis code C50 in ICD10 (from 1997 and onwards) during the period 1982 to 2014. These patients were cross-linked by unique personal identification numbers, given to all citizens living in Sweden, to all other registers used in the present study.

Exposure

Exposure was defined as having undergone IVF treatment with controlled ovarian stimulation using gonadotrophins, either as fertility preservation before start of cancer treatment or after completed treatment for breast cancer. At fertility preservation, the hormonal stimulation and oocyte aspiration takes place directly after diagnosis of breast cancer, oocytes or embryos are cryopreserved and embryo transfer and subsequent childbirth occurs after completed treatment for breast cancer. Otherwise, both stimulation(s) and embryo transfer take place after treatment for breast cancer.

Each exposed individual was matched to four women who had given birth after spontaneous conception, and they constituted the control group. Matching variables were calendar year (+/– 5 years) at breast cancer diagnosis and tumour size (T-stage at diagnosis; T1 (tumour <2 cm), T2 (<5 cm), T3 (>5 cm) or information on T-stage missing). Where T-stage was a missing variable, matching was done with controls whose T-stage was also missing.

Outcome

The primary outcome was relapse in breast cancer. Relapse as a variable in the National Breast Cancer Register has until recently been reported in only one region in Sweden; Stockholm-Gotland. To identify relapse within the entire study cohort, we created a coding template (Supplementary Table S1), based on the typical patterns of ICD diagnoses in the NPR, that indicated relapse in breast cancer (Supplementary Table S2). The template was cross-checked against the Stockholm-Gotland part of the National Breast Cancer Register, with registered relapse cases as the true outcome. Two independent authors reviewed all Stockholm-Gotland cases in which the template was not in agreement with the true relapse outcomes. Any disagreement in the judgement of relapse between the two authors was resolved in consensus. The coding template was modified accordingly to achieve the optimal sensitivity and specificity.

Variables

Potential confounding factors affecting breast cancer and the risk of relapse were accounted for through available register data. From the Swedish Prescribed Drug Register, we identified prescription of hormonal drugs after breast cancer diagnosis. One or more retrievals of a prescribed hormonal drug were defined as use. Smoking 3 months prior to pregnancy and BMI at the start of pregnancy were retrieved from the MBR. The National Breast Cancer Register provided information on TNM stage (Tumour size, Nodes, Metastases), histological type and hormone receptor status as well as age when diagnosed and type of treatment (surgery, radiation, chemotherapy). To define the time from diagnosis to exposure with IVF, we used data from the National Breast Cancer Register, NCR, MBR, the National IVF dataset and Q-IVF.

Statistical methods

Descriptive statistics were used to present mean values, SD, median, minimum and maximum values as well as the percentage distribution. For continuous variables number (*n*), mean (SD) and median (minimum; maximum) are presented. For comparison between groups, Fisher's exact test was used for dichotomous variables, using SAS 9.4 (SAS Institute, Cary, NC, USA).

Ethical approval

The study has been approved by the Regional Ethical Committee at the University of Gothenburg (Dnr 240-15).

Results

In all, 26 114 women, aged 20–44 years, diagnosed with breast cancer from 1982 to 2014 were identified. Out of these, 860 had undergone pregnancy and childbirth after the cancer diagnosis. In total,

823 women had given birth after spontaneous conception and 37 women had given birth after IVF (exposed group). These 37 women represented two different cohorts, 29 (78%) who underwent their IVF treatment after the cancer treatment was completed and 8 (22%) who had undergone fertility preservation, implying ovarian stimulation close to the time of breast cancer diagnosis, while embryo transfer and childbirth took place after completed cancer treatment. After matching, the control group included 148 women.

Demographics

Background factors, tumour characteristics and prescription of hormones are presented in Table 1.

Mean age at diagnosis was 32.5 and 31.7 years for the IVF group and the control group, respectively. The mean time from cancer diagnosis to childbirth was 4.9 years in the IVF group and 3.8 years in the control group. Smoking and BMI at the beginning of pregnancy were similarly distributed between groups.

TNM stage was reported in only one-third of the subjects. Oestrogen and progesterone receptor positivity was also poorly reported; only one-fifth of the subjects had this information. None of the subjects were reported as having metastatic disease at the time of diagnoses. The highest reported N-stage was N1, meaning one to three positive lymph nodes. Only one individual (2.7%) in the exposed group was diagnosed with positive lymph node(s) compared with 21 (14.2%) in the unexposed group. However, the number of cases with missing information about positive lymph nodes was substantial (Table 1).

A rather large proportion of women had been prescribed and redeemed hormonal contraceptives after breast cancer diagnosis (18.9% in both groups). There was a higher rate of using other hormonal drugs in the IVF group, probably related to the IVF treatment.

Primary outcome

The coding template for relapse showed a 90% concordance with the reported relapses in the Stockholm-Gotland part of the National Breast Cancer Register. The ability to correctly identify relapses among 'true' relapses according to the Stockholm-Gotland part of the National Breast Cancer Register was 611/646 (sensitivity 0.95) and to correctly identify individuals without relapse was 1034/1183 (specificity 0.87).

There were no relapses among the 37 women with IVF births, but 36 (24.3%) among controls ($P = 0.0002$). Among the 36 patients with relapse, 10 had died due to the breast cancer diagnosis. Follow-up time was similar between the groups, ranging from 2.6 to 24.0 years, with a mean follow-up time of 10.3 (SD 4.2) years in the IVF group and 10.7 (SD 4.4) years in the non-IVF group.

Discussion

The present study showed no elevated risk for relapse of breast cancer after IVF childbirth compared with childbirth after spontaneous conception in women previously treated for breast cancer. None of the women in our study who had a child born after IVF suffered relapse, neither among those giving birth after completed breast cancer treatment nor among those who underwent fertility preservation, while relapse occurred in 24.3% of women who conceived spontaneously. This is in line with the expected relapse risk for this group of patients

(Nordenskjöld et al., 2018). There are several possible explanations for the large difference in relapse rate between the IVF and the spontaneous conception groups. More women in the spontaneous conception group had spread of cancer to axillar lymph nodes, albeit to a maximum of one to three positive nodes. Further, two-thirds of the entire study population had missing data regarding T- and N-stage and receptor (oestrogen/progesterone/human epidermal growth factor receptor 2) status was only partly available in the register. It is thus likely that patients with a favourable prognosis have been carefully selected, although no formal criteria for such selection before acceptance to IVF exist in Sweden, which could have affected the risk of relapse.

Time from breast cancer diagnosis to childbirth was a mean of 4.8 years for the IVF group and 3.9 years in the control group. A longer disease-free survival before pregnancy and childbirth could imply a lower relapse risk for the IVF group.

The IVF women were matched with four controls, and matching was done with the variables tumour size (T-stage) and calendar year at diagnosis, considered to be the two most important matching variables. Treatment strategies for cancer tend to shift over time, and T-stage is an important prognostic variable. Further matching was not possible due to the small sample size.

Several large studies and meta-analyses have compared the risk of relapse between patients going through a pregnancy after breast cancer treatment and non-pregnant patients. A Danish study from 2008 (Kroman et al., 2008) found no negative influence of pregnancy on survival after breast cancer. In a meta-analysis, including 19 cohort studies covering 1828 cases and 23 736 control women, pregnant women had a reduced risk of death, also after controlling for the 'healthy mother effect' (Hartman et al., 2016). A large Canadian study also demonstrated safety for pregnancy after breast cancer with a significantly higher survival rate 6 months or more after breast cancer compared to women with no pregnancy (Iqbal et al., 2017). In two large studies from Lambertini and co-workers (Lambertini et al., 2018b, 2019), no difference in disease-free survival was found between pregnant and non-pregnant women, demonstrating evidence of long-term safety. Thus, although pregnancy after breast cancer seems safe, a survey among breast cancer physicians reported that up to 30% of physicians were not aware of this knowledge and thought that pregnancy would increase the risk of recurrence (Lambertini et al., 2018a). Further, guidelines concerning pregnancy after breast cancer have been carefully written, however not discouraging pregnancy following breast cancer (Peccatori et al., 2013).

Three studies reporting the effect of fertility preservation before breast cancer treatment found no elevated risk for this procedure (Azim et al., 2008; Kim et al., 2016; Rodriguez et al., 2018). The Swedish study reported no higher relapse risk among women in the Stockholm-Gotland region who had undergone fertility preservation when diagnosed with breast cancer ($n = 188$) compared with age-matched controls ($n = 378$) (incident rate ratio, for relapse in the exposed group was 0.59 (95% confidence interval 0.34–1.04)). Their result remained unchanged after adjusting for T- and N-stage, oestrogen receptor positivity and chemotherapy treatment. That study covered partly the same population as our study but focused on relapse after fertility preservation in one region while our study has a nationwide coverage and the majority had performed IVF as in fertility treatment and not as fertility preservation. A retrospective multi-centre study (Goldrath et al., 2015) of women who underwent

Table 1 Demographic variables in the ART and no ART groups.

| Variable | *ART (n = 37) | No ART (n = 148) |
|--|------------------------------|------------------------------|
| Age at BC diagnosis | 32.5 (3.7) 33.0 (22.4; 38.3) | 31.7 (4.8) 31.8 (20.0; 44.1) |
| T-stage | | |
| T1 | 7 (18.9%) | 28 (18.9%) |
| T2 | 5 (13.5%) | 20 (13.5%) |
| T3 | 1 (2.7%) | 4 (2.7%) |
| Not reported | 24 (64.9%) | 96 (64.9%) |
| N-stage | | |
| N0 | 11 (29.7%) | 32 (21.6%) |
| N1 | 1 (2.7%) | 21 (14.2%) |
| Not reported | 25 (72.6%) | 95 (64.2%) |
| M-stage | | |
| M0 | 10 (27.0%) | 40 (27.0%) |
| Mx | 3 (8.1%) | 13 (8.8%) |
| Not reported | 24 (64.9%) | 95 (64.2%) |
| Oestrogen receptor | | |
| Positive | 2 (5.4%) | 12 (8.1%) |
| Negative | 5 (13.5%) | 13 (8.8%) |
| Not reported | 30 (81.1%) | 123 (83.1%) |
| Progesterone receptor | | |
| Positive | 2 (5.4%) | 9 (6.1%) |
| Negative | 5 (13.5%) | 16 (10.8%) |
| Not reported | 30 (81.1%) | 123 (83.1%) |
| HER2 receptor | | |
| Amplified, therapeutic indication | 0 (0%) | 5 (3.4%) |
| Not amplified | 7 (18.9%) | 20 (13.5%) |
| Not reported | 30 (81.1%) | 123 (83.1%) |
| Childbirth before BC | 4 (10.8%) | 70 (47.3%) |
| Smoking at 3 months before pregnancy | 3 (9.7%) | 21 (14.2%) |
| BMI closest to first pregnancy after BC diagnosis (kg/m ²) | 25.1 (4.7) | 23.4 (3.3) |
| Not reported | 25.2 (18.6; 35.2) | 22.9 (16.2; 36.4) |
| Time from BC diagnosis to child birth (years) | 7 (18.9%) | 23 (15.5%) |
| 4.9 (2.6) | 4.5 (1.2; 10.3) | 3.8 (2.2) |
| 4.5 (1.2; 10.3) | 5.44 (4.39) | 3.5 (0.8; 11.0) |
| Follow-up time (childbirth to end) | 4.72 (0.55; 18.02) | 5.90 (4.67) |
| 5.44 (4.39) | 5.35 (−2.09; 21.07) | |
| Medications after BC diagnosis | | |
| G03A (hormonal contraceptives for systemic use) | 7 (18.9%) | 28 (18.9%) |
| G03B (androgens) | 0 (0%) | 0 (0%) |
| G03C (oestrogens) | 15 (40.5%) | 15 (10.1%) |
| G03D (progestogens) | 27 (73.0%) | 25 (16.9%) |
| G03E (androgens and female sex hormones in combination) | 0 (0%) | 0 (0%) |
| G03F (progestogens and oestrogens in combination) | 3 (8.1%) | 2 (1.4%) |

For categorical variables, *n* (%) is presented. Percentage distribution refers to the entire group. For continuous variables Mean (SD)/Median (Min; Max)/*n* is presented. BC; breast cancer, HER2 human epidermal growth factor receptor 2.

*ART: includes having undergone IVF treatment with controlled ovarian stimulation using gonadotropins, as fertility preservation either before start of cancer treatment (*n* = 8) or after completed treatment for breast cancer (*n* = 29). At fertility preservation, the hormonal stimulation and oocyte aspiration takes place directly after diagnosis of breast cancer; oocytes or embryos are cryopreserved, and embryo transfer and subsequent childbirth occurs after completed treatment for breast cancer. Otherwise, both stimulation(s) and embryo transfer take place after treatment for breast cancer.

ART compared with women who conceived spontaneously showed no elevated risk of relapse.

Strengths

Using national registries gives a low risk of selection bias. The present study contributes safety data on both fertility preservation and ART after completed breast cancer treatment, the latter being reported in few previous studies.

Limitations

The main limitation in this study is the extent of missing data on tumour-related variables, due to poor coverage from the early years of the National Breast Cancer Register. When important prognostic variables such as T- and N-stages and receptor status are missing in more than half of the cases, a valid comparison cannot be guaranteed. Further, since there is no diagnosis code in ICD for relapse in breast cancer, nor any nationwide covering registry entry for relapse in cancer, our primary outcome had to be defined by means of a self-created coding template. However, we found a satisfactory concordance with the reported relapse cases in the only region that does report relapse as a register variable.

Other limitations are the lack of information on anticancer therapies and type of disease relapse, which were not possible to retrieve. Further, the older of the two IVF registers did not hold information on unsuccessful IVF cycles, leaving only cycles leading to birth, to be analysed.

There is a possibility that some individuals among the controls may have undergone IVF stimulations after breast cancer, not resulting in childbirth, but then conceived naturally. We find this scenario to be unlikely, but it cannot be ruled out.

Conclusion

In conclusion, we found no relapse in breast cancer after IVF childbirth, including IVF after completed breast cancer treatment and fertility preservation at the time of diagnosis. This is reassuring data; however, the result is based on few cases. The poor coverage of important prognostic variables in the register resulted in uncertain comparability of the groups; childbirth after IVF versus after spontaneous conception.

Supplementary data

Supplementary data are available at *Human Reproduction Open* online.

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Authors' roles

A.S. and C.B. were responsible for the conception and design of the study. E.R. and A.F. created the coding template for the primary outcome. E.R. drafted/wrote the first manuscript, and all the authors revised and approved the final version. All authors contributed to the analyses and interpretation of data.

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Conflict of interest

None.

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