ORIGINAL ARTICLE: ENVIRONMENT AND EPIDEMIOLOGY

Ovarian stimulation and risk of breast cancer in Swedish women

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Objective: To investigate whether ovarian stimulation for treating infertility is associated with the risk of breast cancer.
Design: Nationwide register-based cohort study.
Setting: Not applicable.
Patient(s): In a cohort of 1,340,211 women who gave birth 1982–2012, we investigated the relationship between assisted reproductive technology (ART) and incidence of breast cancer. Associations between any ovarian stimulation since 2005 and breast cancer incidence were studied in a separate cohort of 1,877,140 women born 1960–92. Both cohorts were followed through 2012.
Intervention(s): None.
Main Outcome Measure(s): Hazard ratios (HRs) and 95% confidence intervals (CIs) for breast cancer.
Result(s): There was no increased risk of breast cancer in women who gave birth after ART compared with women who gave birth after spontaneous conception (adjusted HR, 0.84; 95% CI, 0.74–0.95). The incidence of breast cancer was not increased among women who received controlled ovarian stimulation or among women who received other hormonal fertility treatments since 2005, regardless of live birth (adjusted HR, 0.86; 95% CI, 0.69–1.07; and adjusted HR, 0.79; 95% CI, 0.60–1.05, respectively).
Conclusion(s): No increased incidence of breast cancer was found among women who had gone through ovarian stimulations, including ART. These results are consistent with other studies and reassuring given the widespread and increasing use of ART. (Fertil Steril® 2017;■:■–■. Copyright ©2017 The Authors. Published by Elsevier Inc. on behalf of the American Society for Reproductive Medicine. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Key Words: Infertility, assisted reproduction, in vitro fertilization, ovarian stimulation, breast cancer

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Concerns have been expressed about the long-term safety of the hormonally potent drugs used for ovarian stimulation, in particular in relation to the increasing use of assisted reproductive technologies (ART). Clomiphene citrate or low-dose gonadotropins have commonly been used to induce ovulation in women with ovulatory disorders. For ART, high doses of gonadotropins are required to stimulate multiple follicular development in controlled ovarian stimulation (COS), while spontaneous ovulation is suppressed using GnRH agonists or antagonists.

Since ovarian stimulation influences endogenous estrogen levels, these treatments have been suspected to increase cancer risk (1). Several forms of breast cancer are estrogen sensitive, with established hormone-related risk factors such as age at menarche and menopause, oral contraceptives, and hormone therapy use (2). However, results from previous studies of breast cancer risk after ART have been inconsistent. Many studies suffer from low power due to small sample sizes or short follow-up (3). It is also debated whether observed associations have been due to COS or the underlying fertility problems.

Most previous studies have not found an increased risk of breast cancer after ovarian stimulation (4–7). In a previous Swedish study, women who had given birth after ART had a slightly lower risk of breast cancer (8). Furthermore, a systematic review and

Received February 9, 2017; revised and accepted May 4, 2017.
F.E.L. has nothing to disclose. A.N.I. has nothing to disclose. K.R.-W. has nothing to disclose. C.B. has nothing to disclose. K.G.-D. has nothing to disclose. A.L.V.J. has nothing to disclose.
Funded by the EU-FP7 Health program (agreement 259679), the Swedish Research Council (K2011-69X-21871-01-6 and SIMSAM 340-2013-5867), and the Strategic Research Program in Epidemiology Young Scholar Awards, Karolinska Institutet. The funding sources were not involved in designing the study, collecting, analyzing and interpreting data, writing the manuscript, or deciding to submit the article for publication.
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Fertility and Sterility® Vol. ■, No. ■, ■ 2017 0015-0282

http://dx.doi.org/10.1016/j.fertnstert.2017.05.010

meta-analysis concluded that there was no clear association between ovarian stimulation and breast cancer (3).

However, a recent cohort study from Norway found an increased risk of breast cancer in women who gave birth after ART (9). In addition, some studies have shown an increased risk of breast cancer within certain subgroups of patients (10–14). In a previous study, we have shown an association between COS and mammographic breast density, a marker for breast cancer risk (15).

The objectives of the present population-based cohort study were to investigate the associations between ovarian stimulation by ovulation induction or COS and breast cancer incidence and to assess the role of the underlying infertility for the studied associations.

MATERIALS AND METHODS

The present cohort study used information on ART treatments from several Swedish registers. First, information on live births after ART treatment was recorded by the National Board of Health and Welfare during the years 1982–2006, including all ART clinics in Sweden. Since 2007, all ART treatments in Sweden, regardless of pregnancy outcome, are recorded in the National Quality Registry for Assisted Reproductive Technology (Q-IVF). In addition, the Prescribed Drug Register (PDR) contains data on all prescribed drugs dispensed in Sweden since July 2005, including those used for ovarian stimulation. Diagnoses related to infertility have been recorded in the National Inpatient Register since 1964, with complete nationwide coverage since 1987 (16), and in the National Outpatient Register since 2001.

Study Populations

The Swedish Multi-Generation Register (MGR) links all persons who were born after 1932 and residing in Sweden 1961 or later to their parents. Using the personal identity number assigned to all Swedish residents, we linked these registers and several other Swedish national population registers to establish two cohorts: [1] a parous population of women who had their first live birth between 1982 and 2012 (n = 1,535,678) and [2] women born 1960–92 (ages 20–45 between 2005 and 2012; n = 2,338,869). From the parous population (Supplemental Fig. 1), we excluded women who had invalid personal identification numbers (n = 1,876), did not reside in Sweden at the start of pregnancy (n = 189,110), or had a previous diagnosis of malignant disease (n = 4,481), leaving a cohort of 1,340,211 women. The cohort of women born 1960–92 (Supplemental Fig. 2) included 1,877,140 women after excluding those with invalid personal identification numbers (n = 2,592) and those who had died (n = 28,484), emigrated (n = 356,111), been diagnosed with malignant diseases (n = 14,718), or given birth to four or more children (n = 59,824) before start of follow-up. Due to overlap, 1,061,510 women were included in both cohorts.

Exposure Information

For each woman, diagnoses related to infertility were identified using the National Patient Registers. In addition to the diagnosis "female infertility," we included the following diagnoses commonly associated with impaired female fertility: ovarian dysfunction (including polycystic ovary syndrome and premature ovarian insufficiency); absent, scanty, or rare menstruation; and endometriosis (diagnosis codes in Supplemental Table 1).

In the cohort of parous women, ART births were identified using information from the National Board of Health and Welfare for the years 1982–2006 and the Q-IVF for 2007–12. Both fresh and frozen ETs from standard IVF and intracytoplasmic sperm injection (ICSI) were included. Women with no ART births were subdivided into two groups, those with and without an infertility-related diagnosis.

In the cohort born 1960–92, we used the PDR to identify all ovarian stimulation treatments 2005–12. COS was defined as dispensations of gonadotropins (either hMG or FSH) and down-regulation (using either GnRH-agonist or antagonist) in the PDR with a maximum of 90 days between dispensations, or stimulation for ART recorded in Q-IVF. Ovulation induction was defined as dispensations of either clomiphene citrate or gonadotropins without down-regulation in the PDR. Women with no ovarian stimulation were further divided into two groups, those with and without an infertility-related diagnosis.

Breast Cancer

Since 1958, the Swedish Cancer Register (SCR) records occurrences of cancer in all Swedish residents with an estimated completeness of >95% for solid tumors (16). Recorded information includes date of diagnosis, tumor site and morphology, with diagnoses coded using the current version of the International Classification of Diseases (ICD) and also translated to version 7 (ICD-7).

In the present study, breast cancers were defined according to ICD-7 code 170 and pathoanatomical diagnosis code 096. Women with a first diagnosis of breast cancer during follow-up were considered cases. Women with any diagnosis of malignant diseases (ICD-7, codes 140–205) before start of follow-up were excluded, and those with a malignancy other than breast during the study period were censored at date of diagnosis. By combining information in the MGR with the SCR, family history of breast cancer was defined as having a biological mother or sister with breast cancer.

Covariates

Date of childbirth and the woman's parity were obtained from the MGR. Gestational length was obtained from the Medical Birth Register (MBR). Where this information was missing, 280 days was used. Start of pregnancy was calculated by subtracting the gestational length from the birthdate of each child. Body mass index (BMI, kg/m^2) was calculated from height and weight at start of pregnancy, available from the MBR (missing for the years 1990–91).

The woman's date and country of birth were obtained from the Total Population Register, highest achieved level of education from the Education Register, date of death from the Cause of Death Register, and any migrations in or out of Sweden from the Total Population Register.