ORIGINAL ARTICLE: MENTAL HEALTH, SEXUALITY, AND ETHICS

Depression, anxiety, and antidepressant treatment in women: association with in vitro fertilization outcome

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Objective: To investigate associations between depression, anxiety, and antidepressants before in vitro fertilization (IVF) and IVF cycle outcomes, including pregnancy, live birth, and miscarriage.
Design: Nationwide register-based cohort study.
Setting: Not applicable.
Patient(s): Nulliparous women undergoing their first IVF cycle recorded in the Swedish Quality Register of Assisted Reproduction, January 2007 to December 2012 (n = 23,557).
Intervention(s): Not applicable.
Main Outcome Measure(s): Associations between diagnoses of depression/anxiety, antidepressants, and IVF cycle outcome evaluated using logistic regression to produce adjusted odds ratios (AOR) and 95% confidence intervals (CI).
Result(s): In total, 4.4% of women had been diagnosed with depression/anxiety and/or dispensed antidepressants before their IVF first cycle. The odds for pregnancy and live birth were decreased (n = 1,044; AOR = 0.86; 95% CI, 0.75–0.98; and AOR = 0.83; 95% CI, 0.72–0.96, respectively). For women with a prescription for a selective serotonin reuptake inhibitor (SSRI) only (n = 829), no statistically significant associations were found. Women with non-SSRI antidepressants (n = 52) were at reduced odds of pregnancy (AOR = 0.41; 95% CI, 0.21–0.80) and live birth (AOR = 0.27; 95% CI, 0.11–0.68). Women with a depression/anxiety diagnosis with no antidepressant (n = 164) also had reduced odds of pregnancy (AOR = 0.58; 95% CI, 0.41–0.82) and live birth (AOR = 0.60; 95% CI, 0.41–0.89). Among the women who became pregnant (39.7%), there were no statistically significant associations between exposure and miscarriage except for the women taking non-SSRI antidepressants (AOR = 3.56; 95% CI, 1.06–11.9).
Conclusion(s): A diagnosis of depression/anxiety and/or treatment with antidepressants before IVF was associated with slightly reduced odds of pregnancy and live birth. Women with the presence of depression/anxiety without antidepressants had a more pronounced reduction in odds, implying that the underlying disorder is important for the observed association. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Antidepressants, depression, epidemiology, in vitro fertilization, IVF outcome

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Received November 20, 2015; revised and accepted January 26, 2016.
C.E.C. has nothing to disclose. A.V. has nothing to disclose. H.O. has nothing to disclose. V.J. has nothing to disclose. A.S. has nothing to disclose. C.B. has nothing to disclose. A.S. has nothing to disclose. K.-G.N. has nothing to disclose. S.C. has nothing to disclose. A.N.I. has nothing to disclose.
Supported by the EU-FP7 Health Program (agreement 259679), the Swedish Research Council (K2011-69X-21871-01-6), the Strategic Research Program in Epidemiology Young Scholar Awards, Karolinska Institutet, and the European Society of Contraception and Reproductive Health.
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Fertility and Sterility® Vol. ■, No. ■, ■ 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.01.036

The use of in vitro fertilization (IVF) has grown rapidly in the last two decades, and Sweden is ranked fifth in Europe for utilization, with 3.5% of all deliveries attributable to assisted reproductive technology (ART) (1). The pregnancy rate per cycle has been estimated at around 28% but varies due to a number of factors including the cause of infertility and maternal age (1).

Women receiving fertility treatment have a high prevalence of depression and anxiety symptoms (2), and up to 11% have been found to have a diagnosis of major depression and 15% of any anxiety disorder (3). These rates are higher than those found among women overall in Sweden, where the prevalence of major depression and generalized anxiety disorder has been reported to be around 7% and 11%, respectively (4). Although some studies report that symptoms of depression and anxiety are associated with decreased pregnancy rates after fertility treatment (5–11), other studies find no association with treatment outcome (12–17). However, two Nordic register-based studies have suggested a possible healthy patient effect: women undergoing fertility treatment were less likely to have been hospitalized for psychiatric conditions, including depression, before infertility treatment compared with the general population (18, 19). For those who did receive a depression diagnosis before their ART treatment, Sejbaek et al. (19) found these women underwent fewer ART treatments and were less likely to achieve a live birth when compared with women without a depression diagnosis. Furthermore, there are studies that focus on psychiatric illness in individuals who remain childless that report differing conclusions (20, 21).

Today, selective serotonin reuptake inhibitors (SSRIs) constitute the most commonly prescribed class of antidepressant for treatment of depression and anxiety (22). Treatment with SSRIs has increased both in general (23), among women of reproductive age, and during pregnancy (24), with reports that 3% of women fill a prescription for an SSRI in the 3-month period before conception (25, 26). Still, little is known about the effect of SSRIs on fertility and the ability to conceive. The prevalence of SSRI medication among patients undergoing ART has been estimated at 4%, but the pregnancy rate among these women has only been explored in a limited number of small studies reporting inconsistent results (27–30). An association between SSRI medication and miscarriage has been reported (31). However, recent large studies conclude that this association may be due to confounding by indication and/or lifestyle factors associated with the underlying depression (32–34).

By using a Swedish nationwide cohort of 23,557 nulliparous women undergoing their first fresh IVF cycle with embryo transfer (ET) as recorded in the National Quality Registry of Assisted Reproduction, we evaluated the odds of pregnancy, live birth, and miscarriage among women diagnosed with depression or anxiety and those treated with antidepressants. Our hypothesis was that depression and anxiety negatively influences pregnancy and the live-birth rates.

MATERIALS AND METHODS

Data Sources and Study Population

In Sweden, all individuals are assigned a unique personal identification number (PIN) at birth or at immigration that enables the linkage of population registries at the individual level (35). The National Quality Register of Assisted Reproduction (Q-IVF; http://www.ucr.uu.se/qivf/) was initiated in 2007 and includes data on all IVF treatments and outcomes in Sweden, including cycles using intracytoplasmic sperm injection (ICSI). Women undergoing cycles recorded in the Q-IVF were linked to the following national population registers: the Total Population Register, the National Patient Register (36), the Prescribed Drug Register (37), the Longitudinal Integration Database for Health Insurance and Labor Market Studies (containing socioeconomic data for individuals registered in Sweden), and the Medical Birth Register (38).

In Q-IVF, 36,117 women have contributed 102,510 cycles to the register between January 1, 2007, and December 31, 2012. Only IVF cycles with ET were included in this study, therefore 15,226 (15%) with a cycle start date but no ET were excluded. The reason for this exclusion is that failure to reach ET in many cases may be due to male factor infertility resulting in failed fertilization or failed embryo cleavage and thus is not relevant to our present research question. Of the remaining cycles, the first recorded cycle per woman was selected (n = 34,064). To ensure that only nulliparous women were included, women who had previously delivered an infant as recorded in the Medical Birth Register were excluded (n = 8,780). Women with first cycles performed with frozen embryos (n = 1,415) were also excluded because it was assumed that the majority of these women had a fresh cycle performed before start of the Q-IVF. Cycles without data recorded on cycle outcome were considered lost to follow up and were excluded (n = 312). The final number of nulliparous women contributing their first fresh IVF cycle to this study was 23,557 women (Fig. 1).

Outcome

Three IVF cycle outcomes were considered: pregnancy, live birth, and miscarriage, as reported in the Q-IVF. Pregnancy was defined as a record of a positive pregnancy test. If information on pregnancy test was missing, recorded data on the fetus were used as an indication of pregnancy.

Exposure

Antidepressant dispensations in the 6 months before IVF cycle start recorded in the Prescribed Drug Register were identified using the Anatomical Therapeutic Chemical (ATC) classification system code N06, and categorized as either an SSRI antidepressant (all N06AB antidepressants: fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, and escitalopram) or a non-SSRI antidepressant (N06AA: clomipramine, trimipramine, amitriptyline, nortriptyline; N06AG: moclobemide; N06AX: tryptophan, mianserin, mirtazapine, bupropion, venlafaxine, reboxetine, duloxetine, agomelatine). In general, prescriptions for antidepressants are filled for 3 to