GYNECOLOGY

The effect of antidepressants on fertility

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BACKGROUND: Information on the effects of different pharmaceuticals on fertility is sparse. Human and animal models indicate that antidepressant use could have a negative effect on fertility through alteration of levels of the neurosteroid, allopregnanolone.

OBJECTIVE: The objective of this study is to assess the effects of antidepressants on the natural fertility in women.

STUDY DESIGN: A secondary analysis of data from Time to Conceive, a prospective cohort study, was conducted. Women ages 30 to 44 years without a history of infertility, early in their attempts to conceive, were followed with standardized pregnancy testing until pregnancy was detected. Medication use was assessed at enrollment, daily for up to 4 months, and then monthly. For this analysis, discrete time regression models were created to calculate the association between antidepressant use and fecundability. Potential confounders—age, body mass index, caffeine, alcohol use, and education—were included in all models.

RESULTS: Ninety-two (9.6%) of 957 women reported antidepressant use while attempting to conceive. Women taking antidepressants were more likely to be non-Hispanic Caucasian (91% vs 75%, $P < .01$) and to consume alcoholic beverages (74% vs 61%, $P < .01$). Antidepressant use at enrollment had an adjusted fecundability ratio (FR) of 0.86 (95% confidence interval [CI], 0.63—1.20). However, time-varying analyses suggested that antidepressant use in a given cycle is associated with a reduced probability of conceiving in that cycle (adjusted FR, 0.75; 95% CI, 0.53—1.06). After adjusting for history of depression or restricting the analysis to women who reported a history of depression, the association between antidepressant use and decreased fecundability remained [adjusted FR, 0.66 (95% CI, 0.45—0.97) and (adjusted FR, 0.64; 95% CI, 0.43—0.94), respectively].

CONCLUSION: Our data suggest that antidepressants may reduce the probability of a woman with a history of depression to conceive naturally. Future studies are needed to differentiate the extent to which this association is due to the antidepressant itself versus the underlying depression.

Key words: antidepressants, depression, fertility, fecundability

Antidepressants are the first line of treatment for unipolar major depression[1] and a number of other psychiatric disorders, such as obsessive compulsive disorder.[2] In 2011, antidepressants were the most dispensed drug in the United States, accounting for over 260 million prescriptions.[3] Antidepressants were disproportionately used by women,[4] the majority of reproductive age, compared with men.[5] Although there has been significant research on the teratogenicity of antidepressants, little is known about their direct impact on fertility.

The three most commonly prescribed classes of antidepressants increase allopregnanolone,[6] a progesterone derivative considered a neurosteroid that is produced and is neuroactive in the brain. Allopregnanolone is a positive allosteric modulator of the gamma aminobutyric acid ($GABA_A$) receptor. Its presence enhances the activity of GABA, which is the main inhibitory neurotransmitter in the central nervous system, including the hypothalamus.

Research on rodents suggests that an antidepressant-induced increase in allopregnanolone levels could lead to dysregulation of the hypothalamic-pituitary-ovarian (HPO) axis. Incubation of hypothalamic tissue with allopregnanolone suppresses GnRH release in a concentration-dependent manner. The effects are blocked with the addition of a GABA-antagonist, suggesting that allopregnanolone increases GABA activity, suppressing GnRH release.[7] Accordingly, injection of allopregnanolone into the hypothalamus of rats has been shown to decrease circulating LH levels and result in fewer oocytes at oestrus.[6] The results of animal models have been consistent in humans. Intravenous administration of allopregnanolone in healthy, fertile women decreases follicle-stimulating hormone (FSH) and LH levels[8] and subsequently decreases rates of ovulation. This dysregulation in allopregnanolone could inhibit the pulsatile action of GnRH needed to sustain proper synchronization of ovulation, resulting in infertility.

The above evidence suggests that antidepressants may contribute to changes in the HPO axis through their GABAergic action. HPO axis dysfunction can manifest in numerous ways, including anovulation or luteal phase defects, which can negatively affect a woman's ability to conceive. We hypothesized that antidepressant use would impair natural fertility, which we examined by analyzing the effect of antidepressants on fecundability, the probability of conceiving in a menstrual cycle.

Materials and Methods

This study is a secondary analysis of Time to Conceive (TTC), an ongoing prospective time-to-pregnancy cohort study approved by the institutional review board at the University of North Carolina. A detailed description of the TTC study has been published previously.[9] In brief, women were recruited to the study via community-based fliers, informational emails, internet, radio, television and print advertising, and community blogs. English-speaking women 30 to 44 years old, who had been attempting to conceive for less than 3 months, were eligible to participate.

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Women with a history of infertility, polycystic ovary syndrome, pelvic inflammatory disease, endometriosis, pelvic radiation, or a partner with a history of infertility were excluded. Our analysis includes women enrolled between April 2008 and July 2015. Information was collected via web-based questionnaires and daily diaries. At enrollment, women provided demographic information, medical and surgical history, obstetric, gynecologic, and menstrual history, information on behaviors, height and weight, and pregnancy history, as well as partner demographics. Women were asked if they had a history of anxiety or depression (yes/no). The question was not restricted to any specific type of depression or anxiety. The Cerner Multum drug database system was embedded to identify and record over-the-counter and prescription medication use. This comprehensive database included dosing information and drug names, both generic and brand names.

While attempting to conceive, women completed an online daily diary for 4 months or until pregnancy was detected. The daily diary collected information on vaginal bleeding, intercourse, pregnancy test results, and medication use. If the woman did not conceive in the first 4 months of enrollment, she completed an online questionnaire monthly thereafter, which also collected information on medication use. The women were followed for twelve months or until pregnancy was achieved. Pregnancy tests (sensitivity = 20 mIU hCG/mL) were provided with standardized instructions. For this analysis, a positive pregnancy test was our primary outcome of interest.

Antidepressants were categorized by class via mechanism of action. A comprehensive list of traditional antidepressants was constructed. Our list included selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors, serotonin antagonist and reuptake inhibitors, norepinephrine reuptake inhibitors, norepinephrine/dopamine reuptake inhibitors, tri and tetracyclic antidepressants (TCAs), monoamine oxidase inhibitors, and other antidepressants. Adjunct antidepressants and other psychotropic medications with antidepressant action were excluded.

Statistical analysis

Women were categorized by antidepressant use (yes/no). Antidepressant use was categorized by 1) use at enrollment, 2) use at any given time during the study, and 3) use in a given menstrual cycle. Bivariate analyses, with χ^2 tests, were used to compare demographics and potential covariates (age, race, education level, pregnancy history, menstrual cycle regularity and length, frequency of intercourse, previous contraceptive use, body mass index [BMI], partner age, smoking status, alcohol use, and caffeine use) between the antidepressant users (at any given time in the study) and non-users.

Discrete-time survival models were constructed to assess the relationship between 1) antidepressant use at enrollment and fecundability and, as antidepressant use of an individual woman could vary over time, 2) antidepressant use in a given cycle and fecundability in that given cycle. All analyses were restricted to the first nine cycles of attempt, due to few women remaining after that time. All models accounted for both the right censoring and left truncation (due to women enrolling in cycles 1, 2, 3, or 4 of their pregnancy attempt) present in the data. In these models, a fecundability ratio (FR) less than 1.0 suggested reduced fecundability.

In all adjusted models we included both the covariates strongly associated with fecundability or antidepressants and those identified in multiple prior studies as related to fecundability. These covariates were age, Caucasian race (yes/no), BMI, education level, and alcohol use (yes/no). Maternal age was collapsed into three categories (30−34, 35−37, and 38−44 years of age), and BMI was categorized into 4 groups ($\leq$18.4, 18.5−24.9, 25.0−29.9, and $\geq$30 kg/m^2). Additional analyses adjusted for history of anxiety/depression as reported in the baseline questionnaire and restricted analysis to those women, who reported a history of anxiety/depression. In an attempt to explore the extent to which underlying anxiety/depression may play a role in the relationship between antidepressants and fertility, we analyzed the relationship between history of anxiety/depression, as reported in the baseline questionnaire and fecundability.

Results

A total of 957 women and 3355 menstrual cycles were included in this analysis. Of the analysis cohort, 70% of women were 30 to 34 years old, 18% were 35 to 37 years old, and 12% were 38 to 44 years old. Participants tended to be Caucasian (76%), highly educated (72% with some graduate education or more), and normal weight (62%). Six hundred twenty-two (65%) of subjects conceived during their first 9 cycles of attempt. Analysis was restricted to the first nine cycles due to high levels of drop-out past this point.

Ninety-two (9.6%) women reported antidepressant use at some point during enrollment. Antidepressant use was reported by 7.6% of women in the first cycle of attempt, 9.0% in the second, 8.9% in the third, 8.2% in the sixth, and 11.0% in the eighth. The most frequently used antidepressants were SSRIs and all antidepressants, except one report of TCAs, were reuptake inhibitors. Women taking antidepressants were more likely to be non-Hispanic Caucasian (91% vs 75%, $P < .01$) and to consume alcoholic beverages (74% vs 61%, $P < .01$). There were no differences in other variables analyzed (Table 1). Menstrual cycle length and history of regular menstrual cycles did not differ at baseline by antidepressant use. Antidepressant users at enrollment reported on average 2.18 [standard deviation (SD) 1.25] acts of intercourse per week, which did not differ significantly from non-users at that time with 2.38 (SD 1.59) act per weeks ($P = .27$. Women reporting a history of depression had similar fecundability to those who did not (adjusted FR, 1.03; 95% CI, 0.82−1.24).

Initial models suggested minimal to no effect of antidepressants on fecundability (Figure 1) when analyzing baseline antidepressant use; women who were taking antidepressants at enrollment had an adjusted FR of 0.86 (95%