Major depression, antidepressant use, and male and female fertility

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Objective: To determine if maternal major depression (MD), antidepressant use, or paternal MD are associated with pregnancy outcomes after non-IVF fertility treatments.
Design: Cohort study.
Setting: Clinics.
Patient(s): Participants in two randomized trials: PPCOS II (clomiphene citrate versus letrozole for polycystic ovary syndrome), and AMIGOS (gonadotropins versus clomiphene citrate versus letrozole for unexplained infertility).
Intervention(s): Female and male partners completed the Patient Health Questionnaire (PHQ-9). Female medication use was collected. PHQ-9 score ≥ 10 was used to define currently active MD.
Main Outcome Measure(s): Primary outcome: live birth. Secondary outcomes: pregnancy, first-trimester miscarriage. Poisson regression models were used to determine relative risks after adjusting for age, race, income, months trying to conceive, smoking, and study (PPCOS II versus AMIGOS).
Result(s): Data for 1,650 women and 1,608 men were included. Among women not using an antidepressant, the presence of currently active MD was not associated with poorer fertility outcomes (live birth, miscarriage), but rather was associated with a slightly increased likelihood of pregnancy. Maternal antidepressant use ($n = 90$) was associated with increased risk of miscarriage, and male partners with currently active MD were less likely to achieve conception.
Conclusion(s): Currently active MD in the female partner does not negatively affect non-IVF treatment outcomes; however, currently active MD in the male partner may lower the likelihood of pregnancy. Maternal antidepressant use is associated with first-trimester pregnancy loss, which may depend upon the type of antidepressant.
Clinical Trial Registration Numbers: NCT00719186 and NCT01044862. (Fertil Steril® 2018;109:879–87. ©2018 by American Society for Reproductive Medicine.)
Key Words: Infertility, depression, antidepressant

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Depression, as defined by the presence of moderate or severe depressive symptoms, affects 7.4% of Americans aged 18–39 years and is more common among women (9.3%) than men (5.8%) (1). Studies have shown that depression is even more common in women with infertility (2), with one study reporting a

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41% prevalence of depression in women seeking fertility treatments (3). Furthermore, it has been reported that women with depression are less likely to conceive and have a lower live birth rate after in vitro fertilization (IVF) treatment (odds ratio [OR] 0.86, 95% confidence interval [CI] 0.75–0.98; and OR 0.83, 95% CI 0.72–0.96; respectively) (4). Studies in couples undergoing non-IVF treatments are limited and are necessary to more adequately counsel patients, because a majority of patients with infertility elect to undergo non-IVF procedures. The effects of depression outcomes can not be directly extrapolated from the IVF literature as many techniques used in IVF could potentially overcome many of the proposed mechanisms regarding the effect of depression on fertility, including sexual function, libido, and sperm quality.

Similar to their female counterparts, men seeking fertility treatments also have an increased prevalence of depression (5), with one study reporting a 49.1% prevalence of depression in men undergoing IVF treatments (6). Although most studies investigating depression, fertility, and pregnancy outcomes focus on the female partner, there is a developing body of literature regarding the effect of depression on semen parameters. Studies have demonstrated a decrease in sperm concentration (7, 8); however, data indicating whether or not this translates to poorer fertility treatment outcomes are lacking. Furthermore, studies accounting for the potential effect of both female and male partner depression as well as female antidepressant use are lacking.

Treatment of depression with the use of antidepressant medication is common. An estimated 9.2% of reproductive-age American women (18–39 year old) are currently using an antidepressant (9). Antidepressant use in pregnancy has been associated with an increased risk of pregnancy complications, including miscarriage (10, 11), but many of these studies did not account for the effect of the underlying depression, nor did they control for other risk factors or elective terminations. Furthermore, there are limited data on antidepressant use, fertility potential, and fertility treatment outcomes. Although it is generally thought that the benefits obtained from antidepressant use outweigh these risks (9), the effects on pregnancy outcome may be based on the type of antidepressant medication used, such as selective serotonin reuptake inhibitors (SSRIs) and non-SSRI medications (4). A review by Domar et al. in 2013 revealed that although there were no statistically significant differences in pregnancy rates among infertile women using an SSRI medication in any of the studies under review, there was also no clear evidence of benefit (12). A majority of the studies were conducted in couples pursuing IVF, and therefore it is possible that technologies used during IVF treatments could overcome the effect of depression for all subjects and so no difference is noted with the use of antidepressant treatment. It is unclear whether antidepressant use in the absence of these technologies would improve fertility treatment outcomes.

Many infertile couples pursue non-IVF fertility treatments, and therefore the present study sought to fill the gaps in the literature by evaluating the effect of depression and antidepressant use in couples pursuing non-IVF fertility treatments. Furthermore, we aimed to evaluate the effect of depression in the female partner as well as the male partner, which are not frequently reported together in the literature. We hypothesized that women and men with currently active major depression (MD) would have decreased fertility and poorer pregnancy outcomes compared with those without currently active MD, and that women using antidepressants who do not demonstrate currently active MD would have improved pregnancy outcomes compared with women continuing to have currently active depression, possibly depending upon the type of antidepressant used.

MATERIALS AND METHODS

Institutional Review Board approval was obtained at all sites participating in each Reproductive Medicine Network trial. Female and male participants in the Pregnancy in PCOS II (PPCOS II) (13) and Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) (14) randomized trials were included in this secondary analysis. Briefly, PPCOS II included 750 couples (female ages 18–40 years) in which the female partner was diagnosed with polycystic ovary syndrome (PCOS) by the presence of ovulatory dysfunction and either evidence of hyperandrogenism or polycystic ovaries on ultrasound, and without evidence of other infertility factors, including a sperm concentration of $\geq$14 million/mL in the male partner. Subjects were randomized to treatment with either clomiphene citrate (CC) or letrozole for ovulation induction. hCG testing was performed 2 weeks after the midluteal visit and was confirmed with serum testing. Pregnancy was defined as positive serum hCG level >10 mIU/mL. The AMIGOS trial included 900 couples (female ages 18–40 years) diagnosed with unexplained infertility (with a sperm concentration of $\geq$5 million/mL in the male partner) who were randomly assigned to ovarian stimulation with gonadotropins, CC, or letrozole in conjunction with intrauterine insemination (IUI). Study subjects underwent serum hCG testing two weeks after the date of IUI. Pregnancy was defined when hCG levels rose between two consecutive serum samples. For both studies, participants who conceived were followed until a viable intrauterine pregnancy was observed (fetal heart motion visualized with the use of ultrasound), and outcomes were tracked through delivery.

In both trials, both partners completed the Patient Health Questionnaire (PHQ-9) at enrollment, which is a validated self-administered instrument that scores each of the nine Diagnostic and Statistical Manual of Mental Disorders, 4th edition, depression criteria as 0 (not at all) to 3 (nearly every day). Compared with the Mental Health Professional Interview as standard, a PHQ-9 score $\geq$10 has a sensitivity of 88% and specificity of 88% for MD. PHQ-9 scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression, respectively (15). Women were queried about medication use throughout both primary trials; however, data regarding medication use in the male partner was not collected during either study.

Analysis

PHQ-9 scores were calculated for both partners. Currently active major depression (MD) was defined as PHQ-9 score