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Major depression, antidepressant use and male and female fertility

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Abstract

Objective—To determine if maternal major depression (MD), anti-depressant use, or paternal MD are associated with pregnancy outcomes following non-IVF fertility treatments.

Design—Cohort study

Setting—Clinics in the Reproductive Medicine Network

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Clinical trial registration: PPCOSII: NCT00719186 and AMIGOS: NCT01044862

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Patients—Participants in two randomized trials: PPCOS II (clomiphene citrate versus letrozole for PCOS), and AMIGOS (gonadotropins versus clomiphene citrate versus letrozole for unexplained infertility).

Intervention—Female and male partners completed the patient health questionnaire (PHQ-9). Female medication use was collected. PHQ-9 ≥ 10 was used to define currently active MD.

Main outcome measure—Primary outcome: live birth. Secondary outcomes: pregnancy, first trimester miscarriage. Poisson regression models were used to determine relative risk after adjusting for age, race, income, months trying to conceive, smoking and study.

Results—Data for 1,650 females and 1,608 males were included. Among women not using an antidepressant, the presence of currently active MD (N=72) was not associated with poorer fertility outcomes (live birth, miscarriage); but rather was associated with a slightly increased likelihood of pregnancy (RR 1.38; 95% CI 1.07–1.78). Maternal antidepressant use (N=90) was associated with increased risk of miscarriage (RR 1.87; 95% CI: 1.18–2.99), Male partners with currently active MD (N=34) were less likely to achieve conception (RR 0.44; 95% CI 0.20–0.98).

Conclusion—Currently active MD in the female partner does not negatively impact 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, but may depend upon the type of antidepressant.

Keywords

infertility; depression; antidepressant

INTRODUCTION

Depression, as defined by the presence of moderate or severe depressive symptoms, affects 7.4% of Americans between the ages of 18–39 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 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 following IVF treatment (OR 0.86, 95% 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, as a majority of patients with infertility elect to undergo non-IVF procedures. The effects of depression outcomes cannot 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 anti-depressant medication is common. An estimated 9.2% of reproductive age, American women (18–39 years 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), however, 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. While 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 (SSRI) 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 thus it is possible that technologies used during IVF treatments could overcome the effect of depression for all subjects and thus no difference was noted with 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 thus our 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 is not frequently reported together in the literature. We hypothesized that women and/or men with currently active major depression (MD) would have decreased fertility and poorer pregnancy outcomes when compared to those without currently active MD, and women using anti-depressants who do not demonstrate currently active MD would have improved pregnancy outcomes compared to women continuing to have currently active depression, potentially depending upon the type of anti-depressant used.

MATERIALS AND METHODS

IRB approval was obtained at all sites participating in each Reproductive Medicine Network trial (PPCOS II and AMIGOS). Female and male participants in the Pregnancy in PCOS II (PPCOSII) (13) and Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) (14) randomized trials were included in this secondary analysis. Briefly, PPCOSII included 750 couples (female age 18–40 years) in which the female partner was diagnosed with PCOS by the presence of ovulatory dysfunction and either 1) evidence of hyperandrogenism or 2) polycystic ovaries on ultrasound, and were without evidence of other infertility factors, including a sperm concentration of at least 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

two weeks after the mid-luteal visit and was confirmed with serum testing. Pregnancy was defined as positive serum HCG level above 10 mIU/mL. The AMIGOS trial included 900 couples (female age 18–40 years) diagnosed with unexplained infertility (inclusive of couples with a sperm concentration of at least 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 on 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 9 DSM-IV depression criteria as “0” (not at all) to “3” (nearly every day). Using the mental health professional interview as standard criteria, a PHQ-9 score ≥ 10 has a sensitivity of 88% and specificity of 88% for major depression. 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 ≥ 10. PHQ-9 scores and reported antidepressant use were used to stratify female subjects into 4 groups to account for the effect of currently active depression as well as the antidepressant: 1) no currently active MD, no antidepressant use, 2) no currently active MD, using an antidepressant, 3) presence of currently active MD, no antidepressant use, and 4) presence of currently active MD, using an antidepressant. Antidepressant use was then further stratified by the type of antidepressant used as follows: 1) no antidepressant use, 2) any antidepressant use, 3) only selective serotonin reuptake inhibitor (SSRI) use, 4) only non-SSRI use and 5) both SSRI and non-SSRI use.

The primary outcome tested was live birth. Secondary outcomes of interest included pregnancy and first trimester pregnancy loss. First trimester pregnancy loss was defined as cessation of pregnancy up to 13 weeks gestation. Multi-gestation pregnancies with loss or reduction of one gestation but live birth of the other was classified as a live birth rather than a pregnancy loss. Live birth was defined as the delivery of a viable infant.

Bivariate analysis was conducted to examine the association between covariates and 1) categories of female MD and antidepressant use and 2) male MD. Parametric tests (Student’s t test, ANOVA) were used to compare normally distributed data, non-parametric tests (Kruskal Wallis) were used to compare non-normally distributed data and Chi-square was used to compare proportions. Poisson regression models were subsequently constructed, adjusting for covariates that significantly differed between study groups as well as variables that have been previously demonstrated to affect outcome as identified in the literature. To assess the relationship between primary outcomes and female MD and antidepressant use our model included age, race, income, months trying to conceive, current smoking and

study. To avoid over-correction, BMI was not included in the model due to its significant correlation with the variable "study." Covariates used for analysis of female data by antidepressant use (and type) were the same, with the addition of PHQ-9 score to account for severity of depression. Poisson regression models were similarly used to assess the relationship between MD in the male partner and the primary outcomes adjusting for male age, BMI, and current smoking status and female age, antidepressant use, months trying to conceive, and PHQ-9 score. Power analysis revealed that our study had 80% power to detect a 14% difference in live birth rate for female subjects and a 22% difference in live birth rate for male subjects (alpha = 0.05, two-sided test).

Continuous data are presented as mean (standard deviation). Categorical data are presented as number (percentage). Associations are presented as relative risk (RR) with 95% confidence interval (CI). P value < 0.05 was considered statistically significant. STATA version 12 (StataCorp Inc.) was used for statistical analysis.

RESULTS

Demographics

Data were available for 1,650 females and 1,608 males and of those, PHQ-9 scores were available for 92% (n=1520) and 93% (n=1489) of females and males, respectively. A majority of female subjects were Caucasian (79.52%), nulliparous (79.94%), highly educated (85.1% with at least some college education), non-smokers (88.97%), with an average (standard deviation) age of 30.68 (4.56) years, BMI 30.66 (8.88) kg/m2 and had been trying to conceive for an average of 37.83 (31.82) months. The average PHQ-9 score for all female subjects was 2.8 (3.51) with 5.96% of women exhibiting currently active MD as defined as PHQ-9 score ≥ 10. Of all female study participants, 5.72% indicated they were using an antidepressant medication. A majority of women reporting antidepressant use scored below 10 on the PHQ-9 (no currently active major depression), however, 18.0% of women reporting antidepressant use met our criteria for currently active major depression at the time of enrollment into the study. A majority of male subjects were Caucasian (77.7%), married (89.55%), highly educated (72.42% with at least some college education), non-smokers (61.26%), with an average age of 33.02 (5.74) years and BMI 29.50 (6.57) kg/m2. The average PHQ-9 score for male subjects was 1.49 (2.65) with 2.28% of men exhibiting currently active MD. The presence of female partner currently active MD, male partner currently active MD and antidepressant use did not differ between treatment groups within each individual study.

Female Participants

Covariates by female MD status and antidepressant use (group 1: no currently active MD, no antidepressant use; group 2: no currently active MD, using an antidepressant; group 3: presence of currently active MD, no antidepressant use; and group 4: presence of currently active MD, using an antidepressant) are presented in Table 1. Significant differences among the groups were noted for age, BMI, months attempting conception, AMH, smoking status, income and study (PPCOSII vs AMIGOS). Participants with currently active MD (groups 3 and 4) tended to have a higher BMI and were more frequently enrolled in the PPCOSII trial.

When stratified by study and thus diagnosis (PPCOSII or AMIGOS, i.e. PCOS versus unexplained infertility) there was a highly significant difference in the prevalence of currently active MD among our female subjects (11.02% vs 1.63%, respectively; $p < 0.001$). The average PHQ-9 scores for groups 1 through 4 were: 2.10, 3.33, 12.78 and 13.13, respectively. The live birth rates were 25.39%, 23.29%, 27.78% and 25% for groups 1–4, respectively.

Among women who were not using an antidepressant, the presence of currently active MD was not associated with poorer fertility outcomes; rather the presence of currently active MD was associated with a slightly increased likelihood of pregnancy (RR 1.38; 95% CI 1.07–1.78), Table 2. In women without currently active MD, antidepressant use was associated with an increased likelihood of first trimester loss (RR 1.87; 95% CI: 1.18–2.99), an association that was not demonstrated in women with currently active MD. Despite these associations, there were no significant differences in live birth rates for any of the groups.

Associations with antidepressant type are presented in table 3. The live birth rates for groups 1–5 were 24.93%, 23.33%, 28.07%, 8%, and 37.5%, respectively. Participants reporting any antidepressant use were more likely to experience a first trimester loss compared to non-users (RR 1.92; 95% CI 1.22–3.02). Specifically, the use of non-selective serotonin reuptake inhibitors (non-SSRI) alone (N=6) was associated with an increased risk of first trimester loss (RR 3.45; 95% CI: 1.99–5.98) compared to antidepressant non-use, whereas use of SSRI medications alone was not associated with a statistically significantly lower live birth or pregnancy rate, or increased first trimester loss. Compared to those using an SSRI alone, participants reporting use of a non-SSRI tended to have lower pregnancy (RR 0.45; 95% CI 0.21–1.00) and live birth rates (RR 0.16; 95% CI 0.02–1.10), and increased pregnancy loss (RR 1.99; 95% CI 0.97–4.09), however, these differences were not statistically significant.

Sensitivity analysis was performed using various PHQ-9 score cutoffs to define currently active MD. Lowering the PHQ-9 cutoff (i.e. PHQ-9 of ≥ 5 to define currently active major depression) weakened the association between pregnancy and currently active MD, suggesting that the higher the PHQ-9 score, the more likely subjects were to conceive. A weakened association between miscarriage and the use of antidepressants in subjects screening without currently active MD was also observed. This suggests that subjects using an antidepressant whose depression was well controlled had a decreased risk of miscarriage compared to those that were not as well controlled.

Male Participants

Demographics of male subjects by MD status are presented in Table 1. Unlike their female counterparts, there were no significant differences noted between men with or without currently active MD in regards to age, BMI, smoking, study (AMIGOS vs PPCOSII), or months trying to conceive. Furthermore, sperm concentration, female partner age and female partner antidepressant use did not differ between the male subjects with and without currently active MD, however, the PHQ-9 score for female partners of men with currently active MD was higher than in female partners of men without currently active MD (female partner PHQ-9 score: 4.24 vs 2.61, p=0.002, for men with and without currently active MD, respectively) although the prevalence of currently active major depression in the female

partner did not differ between groups (p=0.06). The average PHQ-9 scores for men with and without currently active MD were 13.41 (4.24) and 1.21 (1.83), and live birth rates were 8.82% and 24.67%, respectively. After adjusting for age, BMI, current smoking, months trying to conceive, female partner age, female partner PHQ-9 score and female partner antidepressant use, male partners with currently active MD (N=34) were less likely to have a partner achieve conception (RR 0.44; 95% CI 0.20–0.98) (Table 4). It is notable that the pregnancy rates for men with currently active major depression differed between studies (10.5% vs 20% in AMIGOS and PPCOSII, respectively), although this difference did not reach statistical significance and is likely secondary to other associated factors that are intrinsic to a diagnosis of unexplained infertility.

Sensitivity analysis was performed for male partner data and demonstrated that decreasing the PHQ-9 score cutoff to define currently active major depression weakened the association between depression and treatment outcome (pregnancy and live birth). This suggests that the worse the male depression, the worse the fertility treatment outcome.

Discussion

In this study of infertile couples undergoing non-IVF fertility treatments, 5.96% of women had currently active major depression and 5.72% used antidepressants. Approximately 2.28% of male partners had currently active MD as determined by the PHQ-9. Women with currently active MD did not demonstrate lower pregnancy or live birth rates compared to women without currently active MD. Women taking antidepressants were at a higher risk of experiencing miscarriage, with this finding in our study largely explained by use of non-SSRI drugs. Partners of men with currently active MD were less likely to conceive.

The prevalence of depression was lower in this infertile cohort than expected. Previously published studies have demonstrated up to a 41% prevalence of depression in women seeking fertility treatment (3) and a 49.1% prevalence in males undergoing IVF treatment (6). Factors that could account for the variations in reported prevalence include the use of different methods of measuring and quantifying symptoms of depression. Our study utilized the PHQ-9 score, which has been shown to have 88% sensitivity and 88% specificity for detection of major depression (15). Similarly, another study using the PHQ-9 score to assess infertile women preparing to undergo IVF also reported a low prevalence of major depression (2%) using a PHQ-9 score of ≥ 10 for classification, although data was not collected for male partners (16). There are several other depression screening methods reported in studies assessing infertile populations, with the highest prevalence of depression noted in studies using the “NIH Patient Reported Outcome Measurement Information System (PROMIS) screening tool” (41% prevalence of depression in female subjects (3)) and the “Self-Rating Depression Scale” (49.1% prevalence of depression in male subjects (6)). It is also possible that the difference in prevalence is due to differing patient populations rather than as a result of the screening tool itself. Furthermore, it has been demonstrated in the literature that women who screened positive for depression were significantly less likely to pursue fertility treatments (OR 0.55 95% CI: 0.31 – 0.95) (3) and thus they may also be less likely to enroll in a fertility treatment study. Lastly, it may be that

enrolling in a study that provides fertility treatments without cost decreases stress and therefore has a positive impact on depression.

Our study did not demonstrate decreased pregnancy or live birth rates in women with currently active MD. Similar to our findings, a study of 202 women undergoing their first IVF procedure showed no difference in live birth rate in women with pre-procedure depression (17) and two meta-analysis by Mathiessen et al. (18) and Boivin et al. (19) demonstrated no significant association between pre-ART treatment depression and clinical pregnancy rate nor emotional distress and ART outcomes. In comparison to the above mentioned studies, our study was conducted in subjects undergoing non-IVF procedures only, which further supports the existing literature and suggests that the absence of poorer fertility treatment outcomes in the IVF literature is not due to the ability of IVF technology to overcome the effect of depression on fertility outcomes. Studies in non-infertile populations have reported similar results. A study of natural fertility in a non-infertile cohort did not demonstrate a decreased pregnancy rate in women reporting depression (20). A similar population based study evaluating the association between major depression inventory (MDI) scores and fecundability did find an association between MDI score and self-reported fecundability, but only for women with severe depression (FR 0.62; 95% CI: 0.43 – 0.91) and not for women demonstrating mild (FR 1.00; 95% CI: 0.79 – 1.26) or moderate (FR 0.94; 95% CI: 0.69 – 1.28) depression (21). Similarly, a study including only cases of depression requiring hospitalization (implying increased severity) reported lower mean number of live births after ART procedures compared to those without depression (22). Thus variation in outcomes reported in the literature could be due to differences in the severity of depression, methods of pregnancy detection, inclusion of women with depression and anxiety (4), or antidepressant use (17).

Interestingly, women with currently active MD who were not receiving antidepressant therapy had a slightly higher pregnancy rate compared to subjects without MD, but no difference in live birth rate. In the above mentioned study assessing the association between MDI scores and fecundability (21), the authors found that although severe depression was associated with decreased fecundability, when stratified by psychotropic medication use, the subjects who were not currently receiving medications but had used them in the past did not have a lower pregnancy rate (FR 1.18; 95% CI: 0.80 – 1.76), suggesting that previous treatment may improve pregnancy rates compared to those that were either never treated or who were currently receiving treatment. Unfortunately, our study did not directly assess previous antidepressant use and thus the effect of previous use cannot be determined. Furthermore, studies assessing non-pharmacologic treatments have demonstrated improvement in depression scores (23,24) and a meta-analysis assessing the effect of psychosocial interventions for infertile couples with depressive symptoms, anxiety, infertility stress and/or marital dysfunction found that psychosocial interventions for couples pursuing fertility treatments improved clinical pregnancy rates (25). Data regarding non-pharmacologic treatments for depression such as psychotherapy and mind-body programs were not collected during our study and therefore the effect of these interventions cannot be assessed.

Our study did not demonstrate an increase in pregnancy rate among women whose depression was well controlled (i.e. not currently active) on antidepressant medication. This is similar to the findings outlined in a review by Domar et al demonstrating that there were no statistically significant differences in pregnancy rates among women using SSRI medications in any of the studies under review (12), although the majority were conducted in an IVF population. The findings of our study further support that antidepressant medications do not seem to improve fertility treatment outcomes even in the absence of IVF technologies.

Our study did demonstrate an increased risk of first trimester pregnancy loss among women treated with antidepressants. This finding is consistent with multiple recent studies (11), and two meta-analyses (26, 27) which demonstrated increased risk of spontaneous abortion (RR 1.45, 95% CI: 1.19 – 1.77) in women using anti-depressants. Unlike the meta-analyses, our study showed that increased risk of loss was only associated with non-SSRI use (and not with SSRI use). This suggests that perhaps the lack of consensus in the literature in regard to antidepressant use and fertility outcomes may be due in part to non-stratification by antidepressant type. Cesta et al showed that risk of miscarriage increased with non-SSRI dispensation within 6 months prior to IVF (OR 3.56, 95% CI: 1.06 – 11.9) but not with SSRIs (4). The authors of that study concluded that women on non-SSRI antidepressants likely had a more severe disorder, and were more likely to continue taking the medication during pregnancy.

Women with male partners with currently active major depression were less likely to conceive following non-IVF fertility treatment and this effect may vary by infertility diagnosis and severity of male depression. We found a non-statistically significant difference in conception rates in men with currently active MD between studies (AMIGOS and PPCOSII). It is likely, however, that there are other factors affecting pregnancy rates in each of the studies, such as female infertility factors and innate differences in conception rates by infertility diagnosis, that likely have a larger effect than factors related to MD in males. Similarly, a study of Chinese men (N=202) demonstrated that male depression was an independent predictor of IVF failure (6). Depression may cause sexual dysfunction due to reduced libido, erectile dysfunction or delayed or inhibited ejaculation (28–31), with the incidence of symptoms being associated with the severity of depression (32). A study of over 2,000 men showed that intercourse frequency is decreased when depression is present in the male partner and that frequency decreases with severity (33). Our sensitivity analysis also supports that fertility treatment outcomes may be poorer in males with currently active depression that is more severe. It is possible that intercourse frequency may contribute to the differences in fertility treatment outcomes seen in our study; however, subjects in our study were instructed to have intercourse 2–3 times per week (PPCOS II) or they underwent intrauterine insemination procedures (AMIGOS). Alternatively, depression and antidepressant use may negatively impact sperm parameters including concentration, motility, morphology and DNA integrity (10,11). In our study we did not observe significant differences in sperm concentration between men with or without currently active MD; however, we did not collect data on sperm morphology, DNA integrity or male antidepressant use.

Our study does have limitations. Our study was a secondary analysis of two randomized controlled trials which include different populations of subjects (PCOS vs unexplained infertility). Combining data from two patient populations; however, potentially makes our findings more generalizable. Data regarding other, non-pharmacologic treatments for depression and indication for antidepressant use in women are lacking in our study, as well as information on use of treatments for depression in the male partner. The absolute difference in live birth rate for men with currently active MD was 15.85%, however, our study was only powered to detect a 22% difference. Although a difference in miscarriage rate was noted in women using non-SSRIs, the number of subjects was low (N=6) and thus definitive conclusions cannot be made. The strengths of our study include the utilization of two multi-center studies with a large sample size, prospective collection of outcomes after assessment of MD at baseline, collection of data on MD for both partners and adequate power to detect a clinically meaningful difference in live birth rate for women with currently active MD.

Conclusions

Currently active major depression in infertile women undergoing non-IVF fertility treatments does not appear to negatively impact treatment outcomes; however, currently active major depression in their male partners may lower the likelihood of pregnancy. Antidepressant use in infertile women undergoing non-IVF fertility treatments does not increase pregnancy rates and is associated with an increased risk of first trimester pregnancy loss, specifically in those that are treated with a non-SSRI antidepressant; however, further studies are needed to confirm this finding.

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Table 1

Demographics of female and male subjects by major depression status and antidepressant use in the female partner.

	FEMALE SUBJECTS						MALE SUBJECTS	
	PHQ-9 < 10 No antidepressant (N=1359)	**PHQ-9 < 10 On antidepressant (N=73)**	**PHQ-9 ≥ 10 No antidepressant (N=72)**	**PHQ-9 ≥ 10 On antidepressant (N=16)**	**P value**	**PHQ-9 < 10 (N=1455)**	**PHQ-9 ≥ 10 (N=34)**	**P value**
Age, average (SD)	30.77 (4.48)	31.03 (4.56)	28.42 (4.59)	30 (3.39)	0.0002	33.05 (5.76)	32.71 (5.45)	0.83
BMI, average (SD)	30.14 (8.75)	32.22 (8.32)	36.7 (9.32)	37.58 (7.59)	0.0001	29.34 (6.48)	31.00 (7.16)	0.19
Months trying to conceive, average (SD)	36.14 (29.94)	45.07 (39.89)	51.26 (43.17)	26.19 (17.86)	0.006	37.30 (30.42)	37.18 (31.96)	0.73
AMH (female), average (SD)	5.07 (5.63)	4.70 (3.6)	6.03 (4.58)	6.30 (5.85)	0.01	5.05 (5.51)	3.83 (3.85)	0.2
PHQ-9 score, average (SD)	2.10 (2.38)	3.33 (2.65)	12.78 (2.62)	13.13 (3.90)	0.0001	1.21 (1.83)	13.41 (4.24)	0.0001
Race, N (%)					0.4			0.6
white	1096 (80.65%)	66 (90.41%)	56 (77.78%)	14 (87.5%)		1156 (79.45%)	28 (82.35%)	
black	138 (10.15%)	2 (2.74%)	9 (12.5%)	1 (6.25%)		190 (13.06%)	5 (14.71%)	
other	125 (9.2%)	5 (6.85%)	7 (9.72%)	1 (6.25%)		109 (7.49%)	1 (2.94%)	
History smoking, N(%)	495 (36.42%)	39 (53.42%)	42 (58.33%)	7 (43.75%)	< 0.0001	694 (47.8%)	19 (55.88%)	0.35
Current smoking, N(%)	139 (10.23%)	12 (16.44%)	17 (23.61%)	1 (6.25%)	0.002	260 (17.91%)	9 (26.47%)	0.2
Eduction, N(%)					0.22			0.83
8th grade or less	6 (0.44%)	-	-	-		17 (1.17%)	-	
some high school	37 (2.72%)	1 (1.37%)	2 (2.78%)	1 (6.25%)		82 (5.65%)	1 (2.94%)	
high school graduate	146 (10.74%)	7 (9.59%)	14 (19.44%)	2 (12.5%)		280 (19.3%)	7 (20.59%)	
some college	371 (27.3%)	24 (32.88%)	27 (37.5%)	5 (31.25%)		422 (29.08%)	13 (38.24%)	
college graduate	510 (37.53%)	31 (42.47%)	23 (31.94%)	6 (37.5%)		444 (30.6%)	9 (26.47%)	
graduate degree	289 (21.27%)	10 (13.7%)	6 (8.33%)	2 (12.5%)		206 (14.2%)	4 (11.76%)	
Income (household), N(%)					< 0.0001			0.43
< $25,000	83 (6.11%)	5 (6.85%)	14 (19.44%)	1 (6.25%)		102 (7.01)	5 (14.71)	
$25,000 to $49,999	272 (20.01%)	14 (19.18%)	20 (27.78%)	1 (6.25%)		279 (19.18)	9 (26.47)	
$50,000 to $74,999	319 (23.47%)	27 (36.99%)	16 (22.22%)	6 (37.5%)		356 (24.47)	6 (17.65)	
$75,000 to $100,000	263 (19.35%)	14 (19.18%)	7 (9.72%)	4 (25%)		282 (19.38)	5 (14.71)	
> $100,000	207 (15.23%)	8 (10.96%)	2 (2.78%)	1 (6.25%)		213 (14.64)	4 (11.76)	
Previous live birth, N(%)	278 (20.46%)	17 (23.29%)	12 (16.67%)	4 (25%)	0.75	281 (19.31)	11 (32.35)	0.06

	FEMALE SUBJECTS						MALE SUBJECTS	
	PHQ-9 < 10 No antidepressant (N=1359)	**PHQ-9 < 10 On antidepressant (N=73)**	**PHQ-9 ≥ 10 No antidepressant (N=72)**	**PHQ-9 ≥ 10 On antidepressant (N=16)**	**P value**	**PHQ-9 < 10 (N=1455)**	**PHQ-9 ≥ 10 (N=34)**	**P value**
Study, N(%)					< 0.0001			0.93
AMIGOS	771 (56.73%)	35 (47.95%)	11 (15.28%)	2 (12.5%)		824 (56.63%)	19 (55.88%)	
PPCOS II	588 (43.27%)	38 (52.05%)	61 (84.72%)	14 (87.5%)		631 (43.37%)	15 (44.12%)	
Partner PHQ-9 ≥ 10, N (%)	26 (2.05%)	1 (1.56%)	4 (7.02%)	0	0.09	70 (4.89)	4 (12.12)	0.06
Sperm concentration (million per mL), average (SD)	72.63 (65.96)	69.76 (61.01)	86.85 (79.60)	73.86 (29.01)	0.36	73.59 (66.37)	73.65 (74.77	0.94
Partner age, average years (SD)	32.96 (5.61)	33.92 (6.11)	32.17 (6.69)	31.93 (3.35)	0.26	30.75 (4.52)	30.44 (4.94)	0.75
Female antidepressant use, N(%)	-	-	-	-		75 (5.38%)	1 (3.13%)	0.32

Table 2

Fertility treatment outcomes by major depression status and antidepressant use in the female partner.

	PHQ-9 < 10 No antidepressant (N=1359)		PHQ-9 < 10 On antidepressant (N=73)		PHQ-9 ≥ 10 No antidepressant (N=72)		PHQ-9 ≥ 10 On antidepressant (N=16)	
	N (%)	**RR**	**N (%)**	**RR**	**N (%)**	**RR**	**N (%)**	**RR**
Achieved pregnancy	497 (36.57%)	reference	31 (42.47%)	1.13 (0.85 – 1.50)	31 (43.06%)	1.38 (1.07 – 1.78)	6 (37.5%)	0.94 (0.50 – 1.79)
1st trimester miscarriage	110 (22.13%)	reference	14 (45.16%)	1.87 (1.18 – 2.99)	5 (16.12%)	0.85 (0.37 – 1.96)	2 (33.33%)	1.40 (0.47 – 4.17)
Live birth	345 (25.39%)	reference	17 (23.29%)	0.88 (0.56 – 1.40)	20 (27.78%)	1.22 (0.84 – 1.78)	4 (25%)	0.91 (0.39 – 2.13)

*RR (95%CI) adjusted for age, income, months trying to conceive, current smoking, study, race

- Denominator for 1st trimester miscarriage = only subjects who conceived

- Denominator for live birth = all subjects

Table 3

Fertility treatment outcomes by female subject use of antidepressant medication.

	No antidepressant use (N=1484)		Any antidepressant use (N=90)		SSRI use (N=57)		Non-SSRI use (N=25)		Both SSRI and non-SSRI use (N=8)	
	N (%)	**RR**	**N (%)**	**RR**	**N (%)**	**RR**	**N (%)**	**RR**	**N (%)**	**RR**
Achieved pregnancy	539 (36.32%)	reference	37 (41.11%)	1.04 (0.80 – 1.37)	27 (47.37%)	1.23 (0.91 – 1.65)	6 (24%)	0.55 (0.26 – 1.16)	4 (50%)	1.27 (0.64 – 2.53)
1st trimester miscarriage	118 (21.89%)	reference	16 (43.24%)	1.92 (1.22 – 3.02)	11 (40.74%)	1.73 (1.00 – 3.0)	4 (66.67%)	3.45 (1.99 – 5.98)	1 (25%)	1.15 (0.19 – 7.06)
Live birth	370 (24.93%)	reference	21 (23.33%)	0.84 (0.55 – 1.27)	16 (28.07%)	1.04 (0.66 – 1.64)	2 (8%)	0.16 (0.02 – 1.08)	3 (37.5%)	1.45 (0.60 – 3.52)

* RR (95%CI) adjusted for PHQ-9 score, age, income, months trying to conceive, current smoking, study, race

- Denominator for 1st trimester miscarriage = only subjects who conceived

- Denominator for live birth = all subjects

Table 4

Fertility treatment outcomes by major depression status in the male partner.

	PHQ-9 < 10 (N=1455)		PHQ-9 ≥ 10 (N=34)	
	N (%)	**RR**	**N (%)**	**RR**
Achieved pregnancy	527 (36.22%)	reference	5 (14.71%)	0.44 (0.20 – 0.98)
1st trimester miscarriage	121 (22.96%)	reference	0	
Live birth	359 (24.67%)	reference	3 (8.82%)	0.39 (0.13 – 1.16)

* RR (95%CI) adjusted for age, BMI, months trying to conceive, current smoking, female age, female PHQ-9 score, femaleantidepressant use

- Denominator for 1st trimester miscarriage = only subjects who conceived

- Denominator for live birth = all subjects