What is a person with depression who wants to have a baby to do?

It is well established that infertility, and the process of going through fertility treatment, is associated with psychological distress, and with depression in particular (1). Of course, one of the primary methods used to treat depression is medication. In the U.S. antidepressants are one of the most frequently prescribed types of mediation, with selective serotonin reuptake inhibitors (SSRIs) being the most common class. This begs the question, should fertility treatment patients (or pregnant women) struggling with depression be treated with antidepressant medications? What are the risks versus the benefits?

A review of the literature quickly provides the impression that these patients may be stuck between a rock and a hard place. On one hand, some research suggests that depression itself is a risk factor for a range of negative fertility treatment or pregnancy-related outcomes. Thus, the conventional wisdom has been that the benefits conferred by antidepressant medication during the perinatal periods outweigh the risks of untreated depression. But a recent review suggests the converse is true: the association between depression and pregnancy complications is weak at best, and antidepressant medications do not appear to improve pregnancy outcomes but instead carry their own set of risks such as worse in vitro fertilization outcomes and miscarriage (2). Given these disparate views, the question remains as to how best to treat prospective parents with depression.

The study by Evans-Hoeker and colleagues (3) sought to address this critical topic, evaluating the degree to which depression or antidepressant medication use impacts three important outcomes: achieved pregnancy, first trimester miscarriage, and live birth. The study built on past research by examining couples utilizing non-in vitro fertilization treatments and by including the effect of depression in the male partner (in addition to the female partner). The authors reported three main findings. First, results showed that women with current depression who were not using any antidepressant medications had an increased likelihood of pregnancy. Second, women taking non-SSRI antidepressant medications had an increased risk of first trimester miscarriage as compared to those not taking antidepressants. Third, women with a depressed male partner were less likely to conceive following fertility treatment.

The study results were also notable in terms of what was not found. For example, there was no evidence that depression was associated with increased risk of miscarriage or decreased live-birth rate (depression in women was actually positively associated with pregnancy rate). This fits with evidence that depression itself does not lead to worse fertility treatment or pregnancy outcomes (2, 4). Further, no differences were found between women taking SSRIs and non-medicated women on any of the three main outcomes. Finally, the data indicated that the negative impact on miscarriage was limited to non-SSRI antidepressants. While intriguing, this result was based on a notably small subsample ($N = 6$) and does not address the question of mechanism (a direct effect of the medication, or the byproduct of additional risk factors in those requiring these types of medications, such as more severe depression, treatment-resistant depression, or comorbid diagnoses).

The authors identified important limitations of this study, but two issues in particular warrant further attention. First, the study is a secondary analysis of data from two very different patient groups: couples in which the female partner had polycystic ovarian syndrome (PCOS) who received ovulation induction treatment and were instructed to have intercourse, and couples with unexplained infertility who received a form of ovarian stimulation treatment followed by intrauterine insemination. While the authors argued that combining the samples increased the generalizability of the findings and included study as a covariate (3), the differences between the samples made this a very unique dataset, with the potential for differences between the groups to impact the overall pattern of findings.

Second, this study sample had a strikingly low rate of depression. These are members of couples who have one of two very stressful conditions, and who have been trying to conceive for an average of 3.2 years. Yet only 5.96% of women and 2.28% of men scored in the depressed range (for reference, this is even lower than the annual prevalence rate in the U.S. of 8.4% for women and 5.2% for men) (1). Moreover, there was a major difference in the prevalence of depression between the two groups. Only 1.6% of women in the unexplained fertility group were categorized as currently depressed (3). Not only is this surprisingly low, but it means that 75 of the 88 women with depression in the study (85%) were in the PCOS group. The authors address some of the possible explanations for the low depression rate (e.g., perhaps depressed individuals are less likely to enroll in a fertility treatment study). Regardless, these issues make the depression-related analyses feel specific to the PCOS group and underscore limitations related to the data's interpretability and generalizability.

Stepping back, it is worth recognizing an element not included in this study: non-pharmacological treatment approaches to depression such as cognitive-behavioral therapy. Indeed, the authors note that data for psychological treatments was not collected, and thus we cannot know if any of the depression or outcome data was influenced by participants also engaging in such interventions during the course of data collection. This is unfortunate as there is a huge body of evidence demonstrating that CBT is equivalent to antidepressant medication for individuals with mild to moderate depression, and superior to medication in preventing relapse (2). In addition, a recent meta-analysis demonstrated that psychosocial interventions (i.e., cognitive-behavioral therapy, and mind/body interventions) have the potential to reduce psychological distress and to improve fertility treatment pregnancy outcomes (5).

So where does that leave us regarding the use of antidepressant medications during fertility treatment and pregnancy? It seems more work is required to parse the implications for different medications at different levels of depression severity in different fertility treatment populations. Meanwhile, the best we can do is provide psychoeducation about what is known

(and not known) at this time and make individualized and collaborative medication decisions with each patient. Beyond that, it is important to remember that psychological interventions may be the best first line of treatment as they are the only validated option that has the potential to help without the accompanying risk of pregnancy-related harm.

Sarah R. Holley, Ph.D.
Department of Psychology, San Francisco State University and Department of Psychiatry, University of California, San Francisco, California

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