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ETHICS CASE
Weighing Risks and Benefits of Prescribing Antidepressants during Pregnancy
Commentary by Benjamin C. Silverman, MD, and Anne F. Gross, MD

Rebecca, a 27-year-old recently married woman, visits her doctor, Dr. Krieger, after testing positive on a home pregnancy test. Rebecca hadn't been planning to get pregnant, but she has decided to continue the pregnancy and to raise the child. In reviewing Rebecca's medical chart, Dr. Krieger remembers that for the past 8 years she has been renewing Rebecca's prescription for Paxil. Rebecca had psychiatrists in the past, but had asked Dr. Krieger to prescribe the Paxil for the past several years, since she has been on a stable dose and feeling very well. Dr. Krieger asks Rebecca if she is still taking the drug and whether it has helped her depression.

"Yes, I still take it every day, and it's helped me so much," Rebecca explains. "Before taking it, I just felt so down. I had trouble concentrating at work, and when I came home I would spend the whole night slumped on the couch. I didn't want to be around anyone or do any of the things I enjoyed before. I tried seeing a therapist and taking a bunch of other antidepressants"—she'd been on Prozac, Lexapro, and Effexor—"but nothing seemed to work before Paxil. It let me actually connect with my friends and my husband and actually enjoy things like working in my garden and traveling. I can't even think about what my life would be like without it."

"I'm so glad to hear how well it's worked for you," Dr. Krieger responds. "However, there is some evidence that Paxil may put your fetus at an increased risk for a congenital heart defect. Other studies say there is no risk. But better safe than sorry—I don't think it's a good idea to take the Paxil during your pregnancy."

Rebecca is visibly upset by this plan. "I want my baby to be healthy, but some evidence of increase risks doesn't seem all that significant. I can't imagine going back to feeling the way I did—and I can't imagine being depressed would help my pregnancy or my baby either."

Dr. Krieger is sympathetic to Rebecca's concern about her depression recurring but is also concerned about the potential effects of Paxil on the fetus. Rebecca is due for a prescription refill, and Dr. Krieger needs to decide whether to renew the prescription or not.

Commentary
In this case, Dr. Krieger faces the question: should she renew Rebecca's paroxetine (Paxil) prescription or not? This is both a clinical and ethical question. We will start with the clinical perspective in order to then best consider the ethical challenges.

Major depressive disorder is a common illness, occurring more frequently in women than men [1]. Approximately 5-15 percent of women will have a major depressive episode during pregnancy [2, 3]. Women who have a history of prior depressive episodes are more likely to experience a major depressive episode during their pregnancies [4]. It is common for women who are on antidepressant treatment to consider discontinuing the medication during prenatal planning or when they find out they are pregnant due to information regarding risks of the antidepressant to the fetus [4, 5]. At the same time, women with histories of depression who discontinue antidepressant medications during pregnancy have been shown to have higher rates of relapse in depressive symptoms than women who continue taking medication [6].

The risk of antidepressant medication to the fetus must be weighed against the risk of recurrence of depression to the mother and its effect on the fetus. Women who suffer from depression during pregnancy have been found to more frequently use tobacco, alcohol, or other harmful substances and less frequently receive prenatal care [7]. This can lead to low birth weight, growth retardation, preterm delivery, preeclampsia, prematurity, and respiratory distress [4, 7, 8, 9].

Rebecca, who has a history of major depressive disorder, with multiple failed medication trials, has had her depression stabilized by the use of paroxetine (Paxil). She has been taking paroxetine consistently for the last 8 years and reports that her depression is well controlled; she is able to spend time with friends and family and enjoy pleasurable activities. From her perspective, the "pros" of continuing to take antidepressants are abundantly clear. In essence, we can imagine she might not even be pregnant and facing this positive life event if not for antidepressants (i.e., she was able to form relationships and have a social life only after her depression abated with paroxetine treatment). Given Rebecca's years-long history of clinical stability on paroxetine, the risk of clinical destabilization must be weighed against the risk of paroxetine exposure to the fetus.

Dr. Krieger attempts to explain the "cons" of continuing to take antidepressant treatments to Rebecca. In brief, the data on the safety of antidepressants during pregnancy are limited, as there are no randomized placebo-controlled trials. No studies indicate that antidepressant medications are without risks; selective serotonin reuptake inhibitors (SSRIs) (a class of medications that includes paroxetine) and tricyclic antidepressants (TCAs) may increase the likelihood of low birth weight, respiratory distress, and preterm birth [8]. In general, SSRIs and TCAs have not been associated with increased risk of congenital malformations [8]. In 2005, a meta-analysis did not identify an association between SSRIs and congenital malformations [10]. In December 2005, however, the Food and Drug Administration (FDA) issued a warning that paroxetine use in pregnant women may double the risk of fetal heart defects and labeled paroxetine a category D risk—more risky than other SSRIs, which are in category C [11]. This risk is associated with paroxetine exposure during the first trimester, when organogenesis is occurring. In the literature, there is controversy regarding the data that was used in support of the FDA warning [12],

and studies have been conflicting on the risk of paroxetine exposure in pregnancy [7, 13]. Two meta-analyses reported an increased risk for congenital malformations [14] and cardiac malformations [15] with paroxetine exposure. Other studies disagree and found no increased risk of congenital or cardiac malformations with paroxetine exposure [10, 13, 16]. A recent systematic review and meta-analysis of the literature found that antidepressant exposure was not associated with congenital malformations overall, but was associated with an increased risk of cardiovascular malformations and septal heart defects [13]. In this study, paroxetine (but not fluoxetine) was associated with an increased relative risk for cardiovascular malformations; however, the relative and absolute risks were small and did not reach clinical significance.

Rebecca appears to understand the increased risk of congenital heart defects; she understands that the risk is relatively small and appears to be concerned about the risk of recurrence of depression if she were to switch to another antidepressant or stop antidepressants altogether. The concerns that Rebecca has expressed to her physician are appropriate: those with a history of major depressive disorder have a risk of approximately 25 percent of relapse during pregnancy with treatment as compared to risk of 68 percent of relapse if medications are discontinued [6], and the absolute risk of fetal cardiac malformations associated with paroxetine use during pregnancy are low [7, 13]. Other subjective potential "cons" of discontinuing antidepressant treatment, i.e., Rebecca's recollection of what it felt like to be depressed, is difficult for Dr. Krieger to truly quantify in a risk-benefit analysis.

Given that Rebecca was already taking paroxetine, it is quite likely that the fetus has already had exposure to it during organogenesis. The risk of cardiac malformations is associated with first-trimester exposure to paroxetine, so the decision about whether or not to prescribe paroxetine should take into account current gestational age. The benefits of stopping paroxetine treatment now might be minimal if organogenesis has already occurred, in which case the risk of depression relapse might more obviously outweigh the benefits of stopping the antidepressant.

The decision of whether to continue the paroxetine needs to consider Rebecca's prior episodes of depression, including history of psychosis, mania, suicidal ideation, suicidal plans or attempts, prior psychiatric hospitalizations, current support system, current psychological and psychiatric treatment, prior relapses when paroxetine was discontinued, and any prior pregnancies during which she had depressive or postpartum illness. Treatment decisions must weigh the risks of untreated depression during the pregnancy but also other possible longer-term effects—for example, women who experience depression during pregnancy may have reservations about future pregnancies. Guidelines do exist in the literature about the use of paroxetine during pregnancy and include confirming an accurate diagnosis, appropriate dose with adjustments as needed, an ultrasound or fetal echocardiogram, and a slow taper off of paroxetine if the medication is going to be discontinued, inasmuch as paroxetine is associated with a withdrawal syndrome when abruptly stopped [8].

Rebecca's case raises important questions about autonomy. As a basic principle of medical ethics, we understand autonomy to reflect an individual's right to self-determination, i.e., the patient has the right to choose or refuse her or his own treatment. In modern medicine, the principle of autonomy has often been held above other ethical principles, as we have shifted toward a patient-centered view of health care and away from a paternalistic tradition in which the physician's word reigns supreme [17]. Respect for autonomy forms the basis for informed consent, in which physicians provide information to patients and allow them to make their own appropriately informed decisions.

Ethical dilemmas arise when patients and physicians face situations in which one ethical principle conflicts with another, perhaps leading to different actions or outcomes. In Rebecca's case, Dr. Krieger faces a situation in which respecting Rebecca's autonomy (i.e., permitting her choice to continue on antidepressants which are potentially harmful to her unborn fetus) might conflict with Dr. Krieger's sense of what would be best for the fetus (i.e., her duties of beneficence—doing what is in the best interests of the fetus—and nonmaleficence—not doing harm to the fetus).

An important question for Dr. Krieger to answer in this case is who is her patient—Rebecca, the unborn fetus, or both? How does she weigh a desire to respect Rebecca's autonomy with a desire to respect the principles of beneficence and nonmaleficence to and autonomy of the fetus? This challenge has been discussed at length in the literature, particularly on the topic of a complicated pregnancy and maternal-fetal conflict [18, 19]. If carrying a pregnancy to term were to be life-threatening to a woman, for example, do we prioritize beneficence and nonmaleficence toward the woman and abort the fetus or prioritize beneficence and nonmaleficence to the fetus and allow it to progress to term to give it the greatest chance at life? (A separate and important area of ethical consideration that is beyond the scope of this paper but relevant to decisions about how to balance these interests concerns the personhood and rights, or lack thereof, of the fetus. This distinction sits at the center of the ethical debate over abortion, which has been explored in depth in the literature [20].) As in Rebecca's case, the practical decisions are rarely actually so binary.

As described above, it is seemingly clear that respecting Rebecca's autonomous choices (with a caveat about if she is or can actually be truly informed about them, which we will discuss below) would lead Dr. Krieger to continue prescribing the antidepressant. It is much less clear, however, based on the medical details, how respecting the principles of beneficence or nonmaleficence toward the fetus might proceed. Would exposure to the slight risk of cardiac malformation be better or worse than exposure to a depressed mother, which can have significant medical sequelae as described above? If organogenesis had already occurred, would this shift the decision toward continuing the antidepressant? If Rebecca's previous episodes involved suicidal intent, plans, or actions (which could be lethal to both her and the fetus), perhaps the decision balance shifts toward continuing the antidepressant?

We must additionally consider whether Rebecca's preference can truly be categorized as informed and therefore autonomous. The elements of informed consent include understanding the indications, risks, benefits, alternatives, and consequences of no treatment for any particular medical therapy or decision. In this case, the information is unclear. The risks are uncertain. The data are conflicting. The medical evidence is constantly changing. Can a layperson (or even an educated expert, in the absence of clear and convincing medical evidence) truly understand these risks and benefits? Does this uncertainty push the physician to prioritize the principles of beneficence and nonmaleficence toward the fetus over Rebecca's autonomy, however complete or incomplete it may be? Would it matter if Rebecca had or had not attended college? Or if she were illiterate? Or if she had attended medical school? Appropriately or not, such details might influence the physician's view of the patient's autonomy, perhaps shifting toward or away from a more paternalistic response (i.e., to ignore Rebecca's choice in favor of "protecting" the fetus).

Making a decision in this case necessitates that more information be gathered, including details about Rebecca's prior history of depression and the fetus's stage of organ development and current health. With this further clarification, Rebecca and Dr. Krieger must each make a value-based determination about two matters: whether a high risk of depression in the mother is more or less dangerous to the fetus than a slightly increased risk of birth defect and whether absolute protection of the fetus is more important than preventing the mother's suffering. In Dr. Krieger's case, this means coming to terms with whom she considers to be her patient(s)—mother, fetus, or both—and if both, prioritizing one above the other. It is quite possible that Rebecca and Dr. Krieger will not come to the same conclusions, in which case, we believe neither has the moral right to compel the other to act in violation of a strongly held value (e.g., Dr. Krieger's autonomy also comes into play and holds some weight in the decision). If disagreement persists, Dr. Krieger would be advised to obtain additional consultation about how to proceed or refer Rebecca to another clinician who might be more aligned with her own value-based decision in this scenario. Further consultation might include bringing other viewpoints into the conversation, including those of Rebecca's spouse, other family, other treaters, spiritual advisors, and so on.

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