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Antipsychotics during Pregnancy: Pros and Cons

Mary V. Seeman

Department of Psychiatry, University of Toronto, Ontario, Canada

***Corresponding Author:** Mary V. Seeman MD, Department of Psychiatry, University of Toronto, Ontario, Canada, Email: mary.seeman@utoronto.ca

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Abstract

Background: As a general rule, medical professionals agree that it is best to avoid all drugs during pregnancy. Sometimes, however, drugs are essential to a woman's health and well-being and to the safety of her fetus.

Aim: The aim of this article is to review the pros and cons of pregnant women with schizophrenia remaining on antipsychotic medication.

Method: The medical database, PubMed, was initially searched for literature in English of the last 5 years using the search terms: "pregnancy" and "antipsychotics". Forty-four papers were selected.

Results: There is no easy answer to the question of the wisdom of continuing antipsychotics during pregnancy. The reviewed literature suggests that the decision depends on the woman's previous experience, the severity of her illness, her stage of pregnancy, and the specifics of the drug she is taking.

Conclusion: As long as the woman is well-informed and competent to make decisions, she needs to carefully weigh benefits against risks to make the final determination. Whatever the decision, close clinical monitoring is warranted throughout pregnancy and the postpartum period.

Keywords: Schizophrenia; Adverse Effects; Antipsychotic Discontinuation; Pregnancy

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Introduction

Long-term antipsychotic (AP) treatment is considered essential in the management of schizophrenia, an illness that, without treatment, manifests as irrational thinking, perceptual errors, poor judgement, and severe subjective distress. Nonetheless, many individuals with this diagnosis do not adhere to their AP regimen because of unwelcome side effects such as weight gain, sedation, movement disorders and many other complications [1]. In addition, patients suffering from this disorder frequently do not believe that they require medication. They may be tormented by their symptoms but may attribute them to causes other than illness. Adherence to medication is, therefore, poor, and this is especially so in women during pregnancy. The rate of adherence to any mental health treatment drops off during pregnancy [2] because of fear of harm to the fetus. For the same reason, many physicians do not prescribe APs to pregnant women. In a 2014 study in the

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United Kingdom, only 38% of women on 2nd generation APs at the beginning of gestation and 19% on 1st generation APs were still being prescribed the drug in their third trimester [3]. Since adherence to prescribed drugs in the AP-taking population is generally estimated at about 50% [4], one might reasonably conclude that considerably fewer than one third of women with schizophrenia take an AP throughout pregnancy. This is a problem because, for most people with schizophrenia, AP discontinuation is a major predictor of relapse in terms of symptom exacerbation, hospital admission, self-harm and, too frequently, suicide [5,6]. For pregnant women with schizophrenia, however, there are considerations other than relapse. There is the possibility, for the mother, of pregnancy-specific side effects, and, for the child, congenital malformations, and impaired development. This literature review examines the pros and cons of AP continuation during gestation.

Method

The English language psychiatric literature of the last 5 years was searched on PubMed with the following search terms: pregnancy AND antipsychotics. The original search yielded 430 abstracts. The articles that included mention of pregnancy and fetal complications, as well as those that addressed postpartum psychosis and infant development were retained. Whenever there was overlapping information, the more recent article was cited. In order to streamline the articles retained for the final draft of this paper, I selected those most frequently referenced by later reviews, which, thus, made for the inclusion of a few classic papers published prior to 2014. This method allows for a measure of subjectivity in the conclusions reached.

Findings

Adverse events

Women with schizophrenia are known to experience adverse events during pregnancy in the form of symptom exacerbation, emergence of new symptoms, emergency room visits, psychiatric hospitalization, family break ups, victimization, and suicide attempts [7]. Approximately 12% of women with schizophrenia are hospitalized during their pregnancy [8]. They are even more vulnerable to relapse during their immediate postpartum period than during pregnancy [8-11]. Stress (illness symptoms, domestic turmoil, unstable housing and lack of financial and emotional resources) impacts not only the mother but, via impaired maternal self-care, poor maternal nutrition and increased use of alcohol or other substances, undermines the health, growth and development of the fetus and neonate. Birth complications can exert unfavorable longterm effects on the child's future and even pose threats to the child's life. As an example, preterm birth, which is a relatively prevalent adverse birth outcome in women with schizophrenia, is associated with cerebral palsy, visual, hearing, speech, neuromotor, cognitive and behavioral impairment in the child [12]. Fetal distress during labor and delivery increases the risk of cardiovascular disorders, neurological deficits, mobility disturbance, and cerebral palsy [13]. Another adverse outcome commonly found in this population, intrauterine growth restriction, has been associated with growth retardation, neurodevelopmental deficits, metabolic syndrome, and cardiovascular disease in later years [14]. Even continued prescription of APs during pregnancy is no guarantee of freedom from psychotic relapse. Approximately 50% of women with schizophrenia experience a relapse of symptoms when pregnant, whether they are taking their prescriptions or not [15]. This is probably due to the added stress of pregnancy in a population that is markedly disadvantaged by poverty, low family and social support, inadequate housing, and few personal or financial resources. This is also a group characterized by high levels of comorbidity and substance use, and relatively poor attendance at prenatal care. Women with schizophrenia, whether treated or not, have rates of obesity, diabetes, thyroid disease, epilepsy, anemia, infections, and substance use disorders that are

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significantly higher than rates in the general population [7, 16]. These disadvantages culminate in a multitude of events during pregnancy that can cause harm to both mother and fetus [17,18]. The clinical question is whether AP treatment reduces the frequency of such events, or whether it contributes to the harm. Heun Johnson et al. [16] have determined that comorbidities and substance use are responsible for approximately half the increased risk for adverse birth outcomes in this population. Comorbidities and substance use raise the risk of gestational diabetes by 7%, the risk for obstetric complications by 15% and the risk for poor fetal outcomes by 2%. Poverty, psychotic symptoms, social isolation, risk behaviors, the consequences of mental illness stigma, and the use of AP drugs account for the other half of the increased risk [19]. This makes it difficult to decide about the wisdom of APs during pregnancy. These drugs do reduce psychotic symptoms, but psychotic symptoms are only one among the many problems facing women with schizophrenia when they are pregnant. Moreover, APs often introduce problematic adverse effects of their own. Some physicians routinely stop 1st generation AP prescription even before pregnancy, when a woman with schizophrenia first expresses the wish to conceive. This is because 1st generation drugs markedly reduce fertility - much less of a problem with 2nd generation APs [20]. Once a woman with schizophrenia becomes pregnant, many physicians avoid all drugs during the critical first trimester as a guard against the possibility of fetal congenital defects. This is the case despite the fact that, with the exception of risperidone [21,22], there is little evidence that APs increase the rate of congenital anomalies [23,24]. As pregnancy continues, estrogen levels steeply rise. Estrogens are known to offer protection against psychotic relapse [25] so that APs become less necessary at this time and doses may often be safely reduced [26], although this depends on the stage of pregnancy [27] and the specifics of the AP under consideration. CYP1A2 enzymatic activity decreases during pregnancy while CYP2D6 activity increases [28]. This means that the doses of olanzapine and clozapine, both drugs metabolized principally by CYP1A2, may need to be decreased whereas the doses of other APs, especially those metabolized by CYP2D6, may need, by contrast, to be increased. There will also be individual variation depending on the person's slow or rapid metabolizer status, especially for drugs chiefly metabolized via CYP2D6 [29]. Theoretically, the less AP in the mother's circulation at the time of delivery, the safer the labor, with fewer drug-induced obstetrical complications. The infant is then born wide awake and free of adverse effects. Neonates exposed to AP in utero can experience withdrawal symptoms such as agitation, feeding disorders, hypotonia, hypertonia, respiratory distress, somnolence, and tremor after delivery. Neonate extrapyramidal symptoms are also seen, most commonly with the use of first-generation APs [30, 31]. Should the clinical decision be to reduce AP dose during pregnancy or stop drugs altogether, reduction is best done gradually, under close monitoring. There are known dangers to abrupt discontinuation [32].

Specific AP-induced side effects

Maternal complications of AP specific to pregnancy are gestational diabetes mellitus, pre-eclampsia, and venous thromboembolism [15]. Although weight gain as a result of AP is not specific to pregnancy, it carries extra risks in pregnancy by increasing the likelihood of gestational diabetes [33]. Individuals with schizophrenia show an increased risk for diabetes even without APs, but the risk is further increased once APs are started [34]. During pregnancy, olanzapine and quetiapine are the main AP culprits that lead to gestational diabetes [35], a condition that significantly raises the risk of developing type 2 diabetes in later life. Adult diabetes, in turn, contributes to the risk of cardiovascular disease and premature mortality [36]. In a study of 2741 women in Australia exposed to AP during pregnancy, those with the greatest antipsychotic exposure had the highest rates of both gestational diabetes and gestational hypertension [37].

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Cause and effect are not clear, however, because women with severe mental illness who remain untreated or who discontinue these drugs during pregnancy also show many pregnancy complications such as placental abnormalities, antepartum hemorrhage, or preeclampsia, significantly more often than other women [22].

Adverse effects for the infant

Although there is little evidence for congenital defects as a complication of AP, other complications for infants such as prematurity, intrauterine growth retardation or distress, suboptimal birth weights, low Apgar scores, and neonatal hypoglycemia are associated with the use of these drugs. The rate of stillbirth may also be increased [38].

Discussion

Many factors such as poverty, family support, domestic relationships, smoking, substance abuse, body weight, and the specifics of the AP drug being taken [39], as well as its dose, affect the rate of drug complications during pregnancy. Decisions about dose reduction or discontinuation are, therefore, difficult to make and may not apply to all women with schizophrenia who are pregnant; some women may have such severe illness symptoms that thoughts of even very gradual dose reduction are impossible to entertain [40,41]. Cooper et al. [42] conducted focus groups among prescribing physicians in the UK about AP reduction in general (not restricted to pregnancy). Their qualitative results suggested that there was inadequate evidence about who among patients was best suited for dose reduction. Practitioners also found a lack of guidance as to how this procedure could be safely done. Maintenance of the AP dose was seen as the easier, less hazardous alternative. This research group advocate shared decision making because patients have important experiences to share with care providers, experiences that can throw light on the safety or danger of dose reduction or discontinuation. When discussing these options during pregnancy, clinicians must be aware of the serious risk of postpartum psychosis in women with schizophrenia who are undermedicated [8-11]. Should the decision be to lower the dose substantially or to discontinue APs, there must be a built-in strategy for resuming them immediately after delivery. Besides the risk of postpartum psychosis, there is also the risk of mother's re-emerging psychopathology interfering with maternal/infant bonding, critical for the infant's healthy development [43]. The alternate risk, whose magnitude is still largely unknown, is the possibility that APs during pregnancy can result in delayed infant neurological and motor development, generalized cognitive deficits and learning difficulties [44].

Conclusion

In conclusion, the decision whether or not a woman with a diagnosis of schizophrenia should continue or stop AP treatment when pregnant lends itself to no easy answer. The patient, the baby's father, the patient's family should probably all have a say, although the final decision is the woman's as long as she is judged competent to make it. The pros and cons must be explained clearly and many times. Whatever the decision, the mother's progress during pregnancy, as well as the infant's progress after birth, need to be carefully monitored.

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