ADHD and Pregnancy

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Attention deficit hyperactivity disorder (ADHD) has been increasingly recognized and treated in children and adults in recent years. As a result, a growing number of women enter their reproductive years treated with medication for ADHD or are diagnosed and start medication during their reproductive years. A common question in perinatal psychiatry regards the risk-benefit profile of pharmacotherapy for ADHD, particularly with stimulants. At this time, there are no guidelines to inform the treatment of ADHD across pregnancy and the postpartum period. Concerns about in utero exposure to stimulants are based primarily on the impact these medications might have on fetal growth. While stimulants do not appear to be associated with major congenital malformations, more human data regarding potential behavioral teratogenicity are needed in order to understand both the short- and long-term risks. Severity of illness, presence of comorbid disorders, and degree of impairment have an impact on treatment decisions. Crucial considerations include driving safety and ability to function in occupational roles. While most women can successfully avoid the use of stimulant medication during pregnancy, there are cases in which the benefits of stimulant treatment outweigh known and putative risks of in utero medication exposure.

(Am J Psychiatry 2014; 171:723–728)

Attention deficit hyperactivity disorder (ADHD) is estimated to affect 4.4% of adults in the United States (1). It is associated with an elevated risk of poorer general and mental health, substance abuse, impaired work performance, and financial distress (2). Approximately half of adults who had childhood ADHD continue to have the disorder and associated impairments (1). There is a growing appreciation that girls with ADHD have a substantial likelihood of continuing to have the disorder in adulthood. Biederman et al. (3) assessed a cohort of girls and demonstrated with longitudinal follow-up that a majority are still affected by ADHD more than a decade later, with approximately one-third continuing to meet full criteria for the disorder, approximately another third meeting partial criteria, and 10% experiencing impaired functioning. A diagnosis of ADHD is also associated with a higher risk of subsequent diagnoses of mood, anxiety, and substance use disorders (4).

Considerations in Pregnancy

There have been no systematic studies evaluating the course of ADHD across pregnancy and the postpartum period. It is possible that the perinatal period has an impact on the course of ADHD as a result of hormonal changes or other factors. It is plausible that women experience greater distraction from other areas as they focus increasingly on a life transition to motherhood. Treatment decisions are affected by pregnancy, as the wish to avoid medication exposure during pregnancy motivates many women to discontinue stimulants during pregnancy and while breastfeeding. Little is known about the impact of treatment decisions on occupational functioning, interpersonal relationships, course of comorbid illnesses, and quality of life.

Neurocognition, Memory, and Executive Functioning During Pregnancy

It is debatable whether women experience neurocognitive changes across pregnancy. There have been observations that neurocognitive functions, including memory, may be negatively affected by pregnancy, and pregnant women are more likely than nonpregnant women to assess their memory as impaired (5, 6). Indeed, it is widely believed that there is a syndrome of "pregnancy brain" with memory impairment during pregnancy, the hypothesis being that changes in sex hormone production lead to worsening cognition (7). We lack studies assessing women with ADHD during pregnancy, but there have been small animal and human studies from which to draw. Some suggest impaired neurocognitive functioning during pregnancy, although these results are inconsistent, and no clear relationships have been elucidated between changes in any one hormone and cognition during pregnancy.

For example, in a study of 19 pregnant women (8), participants performed better on verbal memory tasks after delivery than they did 2 months before delivery. No associations were found between sex hormones and cognitive performance, although higher levels of progesterone were associated with a higher rate of negative mood states.

This article is featured in this month's AJP Audio and is an article that provides Clinical Guidance (p. 728)

A young professional planning a pregnancy seeks advice on managing her ADHD symptoms.

"Ms. A," a 28-year-old woman, presents for a perinatal psychiatry consultation. She has long been treated with methylphenidate for attention deficit hyperactivity disorder (ADHD) and is now planning pregnancy. She is an attorney and states that her job is difficult when she does not take her medication. She recalls a long history of trouble with attention and distractibility, starting in elementary school. As a bright child, she was initially able to achieve good grades with little effort. As her school years continued and the workload increased, however, she experienced more difficulty with her grades, and in high school she was diagnosed with ADHD. She was started on methylphenidate, with good results. She was able to complete college and law school, although she had some difficulty studying for and passing the state bar examination. Even with treatment and testing accommodations, she failed twice and needed to take time off to study before passing the examination on her third attempt.

Ms. A has been trying to conceive for 1 year. About 9 months ago, she discontinued methylphenidate and noted greater difficulty completing her work and found that she was making more errors. A colleague noticed and asked if everything was all right, which prompted her to restart methylphenidate. She did not notice any difficulty driving without the methylphenidate, although she does report that she is "not the best driver" and has had three minor accidents over the past several years. She has a history of major depressive episodes. She reports that when her ADHD has been untreated, she has noted an increased burden of depressive and anxious symptoms, which she attributes to feelings of poor self-efficacy and guilt about not being able to perform at her potential.

After a detailed discussion with her psychiatrist, Ms. A decided to continue methylphenidate while trying to conceive, in order to preserve her occupational functioning, and to discontinue the drug after she became pregnant. She monitored her menstrual cycle, and after 6 more months of trying to conceive, she became pregnant. She discontinued methylphenidate at around 6 weeks of gestation. She used public transportation as often as possible after learning that untreated ADHD is associated with a higher risk of motor vehicle accidents. At one point during the second trimester, Ms. A had an unavoidable and unplanned increase in work stress and workload. She and her psychiatrist decided on a short-term plan of using low doses of methylphenidate during the weekdays for 2 weeks until she was able to get through a particularly demanding time. She experienced some periods, lasting several days at a time, of low mood and frustration that were triggered by feeling overwhelmed at work, but she was able to function well enough to continue without methylphenidate.

Ms. A gave birth at term to a healthy baby boy. She opted to breastfeed and remain off of methylphenidate for 3 months. After 3 months, her maternity leave ended, and on returning to work, she discontinued breastfeeding and restarted methylphenidate.

However, in another study (9), in which women were assessed in the third trimester and again postpartum (N=55) and compared with nonpregnant comparison women (N=21), investigators found lower verbal memory and processing speed scores for women during pregnancy and the postpartum period relative to the comparison subjects. Prolactin levels were associated with verbal memory and executive functioning scores during pregnancy, while estrogen and cortisol were negatively associated with attention scores in the postpartum period. The timing of such impairments varies among studies (e.g., throughout pregnancy, in late pregnancy only), as does whether such findings extend to the postpartum period (6, 10, 11). A meta-analysis on this topic (12) demonstrated that study findings have been inconsistent, and overall there may be impairments among both pregnant and postpartum women on some specific neurocognitive tests of memory, particularly those that draw on executive functioning.

In some animal studies, higher progesterone and estrogen levels have been demonstrated to improve memory. For example, pregnant rats have been reported to outperform nonpregnant female rats on tests of memory and cognition (13). Other animal studies have shown morphological brain changes during pregnancy in the absence of functional memory impairment (14).

The inconsistencies in the literature suggest that neurocognitive impairments associated with pregnancy are subtle and unlikely to be experienced universally by pregnant and postpartum women. It is possible that women with preexisting ADHD constitute a vulnerable subgroup for neurocognitive worsening during pregnancy.

Clinical Implications and Treatment Considerations

Many women can stop ADHD medications for pregnancy without ill effects. For others, functional impairment may be severe, with potentially severe consequences. Some ADHD patients are at risk of motor vehicle accidents. It has been documented that treatment with stimulants for ADHD improves driving capability, which is a key functional outcome (15). Also, untreated ADHD may be associated with moderate to severe impairment in occupational or school functioning. Recommendations to reduce a woman's workload during the pregnancy or to increase structure and organization at work or school with some external

supports may improve functioning sufficiently during a pregnancy to allow the avoidance of medication. Employers may be able to offer accommodations in consideration of a pregnancy.

Reproductive Safety Profiles of ADHD Medications

The baseline rate of congenital malformations in the United States is approximately 3% of all pregnancies (16). In most cases, the causes are unknown. A number of medications are used to treat ADHD, including stimulants and non-stimulant medications, such as bupropion and atomoxetine. In general, stimulants have greater efficacy for ADHD than non-stimulants (17–19).

Stimulants

Although several systematic reviews have assessed the literature on stimulant use during pregnancy (20, 21), this literature has important limitations. Notably, stimulants often represent drugs of abuse rather than prescribed treatment for a specific indication. The lack of comprehensive data on use or misuse and associated variables greatly constrains our ability to derive a reproductive safety profile for stimulants.

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The data pertaining to stimulants suggest a potential impact on fetal growth rather than a risk of teratogenicity (22–24). In one study, pregnancy and neonatal outcomes were reported for women who had a diagnosis of ADHD (N=153) (24). The use of concomitant medications was common, reflecting the comorbidity that has been consistently reported. The medications most commonly used in this group were methylphenidate (82.4%), risperidone (29.4%), selective serotonin reuptake inhibitors (16.4%), and imipramine (4.6%). The most frequent delivery complication was neonatal hypoxia (15.6%). The most frequent side effect occurring during pregnancy was decreased maternal appetite (34.9%). It is difficult to discern whether neonatal effects such as hypoxia are attributable to stimulant use, but this result warrants further study. The report of low appetite is consistent with the side effect profile of stimulants, as well as with the observation of decreased body weight among pregnant animals exposed to methylphenidate (25). Other studies also suggest that first-trimester exposure to methylphenidate does not increase the risk of congenital abnormalities beyond the rate in the general population. In a recent report, Dideriksen et al. (22) reported congenital anomalies occurring in four of 180 exposed pregnancies, or 2.2%. In a study of 39 mothers who used methylphenidate as a substance of abuse (23), there were relatively high rates of prematurity, growth retardation, and withdrawal. There was no control group, and exposures also included alcohol, cigarettes, and other drugs of abuse.

The timing of stimulant exposure may determine the impact on fetal growth. In a large prospective study (N=42,101) in which 237 pregnant women were treated with dextroamphetamine to prevent excessive weight gain (26), birth weights were not significantly affected when the drug was discontinued before week 28 of gestation but were 4% lower on average when the drug was discontinued after week 28. Neonatal length and head circumference were not affected, and there was no association with any type of malformation.

Behavioral teratogenicity. Animal studies in rats and zebra fish have suggested that prenatal exposure to amphetamines is associated with changes in dopaminergic transmission and receptor expression in regions of the brain, as well as postpubertal decreased motor activity (27, 28). Studies in humans are few and are limited to stimulant use in the context of substance abuse. In studies of outcomes after prenatal cocaine exposure, after controlling for confounding variables, children have generally not been found to experience consistent impairment on standard cognitive tests and visual habituation, and no effects have been found on language skill development (29). Lower psychomotor scores in the early months of life were not independently associated with cocaine exposure but rather with concurrently used substances, and no detrimental effects have been observed on motor development during the later years of early childhood (29). However, in later childhood, the heaviest maternal cocaine use was associated with subtle deficits in executive functioning (30).

Breastfeeding and stimulants. Only limited data are available to inform patients on the use of stimulants during breastfeeding. Because stimulant use in late pregnancy has the potential to negatively affect fetal growth, conceivably exposure via breast milk could affect infant growth and have adverse effects on appetite and sleep. In a report of three breastfeeding mother-infant pairs in which the mothers were taking dextroamphetamine (31), no adverse events were observed. In two of the infants, the plasma level of dextroamphetamine was low but detectable, while in the third it was undetectable. The mean infant dose assessed was 5.7% of the maternal dose, below the 10% cutoff usually cited in the breastfeeding literature as relatively low. The estimated infant dose was lower (0.16%−0.2%) in two other case reports of infants who

were breastfed while the mothers were treated with methylphenidate (32, 33).

Bupropion

Bupropion may be a reasonable option for women who have had a good response to it, for those with comorbid depression, and for those seeking a pharmacological treatment for smoking cessation. Compared with the number of reports regarding other antidepressants (especially the selective serotonin reuptake inhibitors), fewer studies are available regarding its reproductive safety; however, the amount of data available for bupropion exceeds that for other medications used in the treatment of ADHD. Published reports regarding its safety during pregnancy are relatively reassuring, but as noted above, bupropion is not as efficacious as stimulants in the treatment of ADHD (17–19).

Prospective birth outcome data from the Bupropion Pregnancy Registry suggest that birth defect rates with bupropion exposure are similar to the general population rate (34). In the registry, 3.6% (24/675) of the cohort experienced a congenital anomaly after first-trimester exposure. The rate of birth defects with second-trimester exposure was 2.1%. There was no clear pattern of type of birth defects.

In one prospective study of 136 women who used bupropion in the first trimester (35), there was no evidence of higher rates of malformations compared with a group of women who used other antidepressants and a group who had no exposure to teratogens. In an epidemiological study of women who used antidepressants in pregnancy (36), outcomes were compared for women who used bupropion in the first trimester (N=1,213), women who used other antidepressants in the first trimester (N=4,743), and women who used bupropion after the first trimester (N=1,049). Results did not support teratogenic effects of first-trimester bupropion exposure. A small increase in the risk of cardiovascular left outflow defects was reported in a retrospective case-control study from a birth defect registry (37). The absolute risk was approximately 2 out of 1,000 pregnancies.

The literature on bupropion use during breastfeeding is limited to small case reports. In a report of two infants whose mothers breastfed while using bupropion (38), neither had detectable levels of bupropion or metabolites in their serum. In the case of a 14-month-old infant who was breastfed while the mother was treated with bupropion (39), milk-to-maternal-plasma ratios were reported as low, and bupropion and its metabolites were undetectable in the baby's plasma. In a third report (40), urine levels of bupropion were assessed in four infants who were breastfed while their mothers were treated with bupropion. One of the infants had detectable levels of urinary bupropion, and had also been premature. The estimated bupropion dose that the infants were exposed to was 5.7% of the weight-adjusted maternal dose, which is considered compatible with breastfeeding. There is also a case report (41) of a baby who was breastfed while the mother was using bupropion and had a possible seizure as reported by the mother.

Atomoxetine and Guanfacine

No systematic studies in human pregnancy have been conducted for these two agents. In a report on the use of guanfacine to treat hypertension associated with preeclampsia (42), 23 of 30 women experienced a good response to the drug as an antihypertensive, and six of 30 infants were reported to have been small for gestational age, although it is not possible to discern a potential risk of guanfacine in this context.

Psychotherapies for ADHD

Psychotherapeutic approaches for ADHD have been investigated. Cognitive behavioral therapy (CBT) has been demonstrated to have a significant impact on symptoms. CBT and "coaching" strategies can help improve functioning and assist patients in tailoring their routines in ways to cope with ADHD (43–46). For some women, such strategies may be adequate to sustain functioning during pregnancy.

Summary and Recommendations

Impairment associated with severe ADHD during pregnancy may have serious consequences, such as psychosocial and financial stressors associated with the untreated disorder when it affects domains such as relationships and occupational functioning. There is also the risk of injury and mortality associated with impaired driving.

Medications may be part of the treatment strategy for women who are trying to conceive or are pregnant or breastfeeding. It is imperative that the benefit of a medication be robust enough to justify any potential exposure during pregnancy. Women approaching childbearing may have had medication-free trials and know in advance how their functioning might be affected if they stop ADHD medications during pregnancy. For women who have not had one, a medication-free trial is warranted, ideally with psychotherapy targeting ADHD symptoms.

For women who have been successfully treated with medications for ADHD and are assessing whether to continue or discontinue medications during pregnancy, key questions in determining the risk of the untreated disorder include:

1. How have you functioned in the past at work (or school) without the use of medications?

2. How is your driving when not treated with medications for ADHD? Have you had a history of accidents?

If impairments in work functioning and driving are noted, it is important to explore what accommodations can be made for a pregnancy. For example, can the patient avoid driving? Can the patient implement strategies at work that would minimize the effect of ADHD symptoms, such as changes to her workload or schedule or strategies she might learn through CBT?

A woman who is planning pregnancy might discontinue medication while she is trying to conceive, or might instead wait until she is pregnant to discontinue medications. None of the medications have been demonstrated to have clear risks in very early pregnancy. Women with more severe ADHD may either elect to make major life changes to minimize the impact of ADHD on impairment in their lives or choose to continue using medication. Most available data on stimulant use during pregnancy are derived from use in other contexts, such as substance abuse and weight management during pregnancy, the outcomes of which may not be generalizable to women who use stimulants as prescribed for the treatment of ADHD. The main finding with stimulants is that fetal growth may be reduced when stimulants are used in late pregnancy. Long-term outcomes, including behavioral teratogenicity, have not been adequately studied.

For other non-stimulant medications, such as guanfacine and atomoxetine, even fewer data are available regarding use in pregnancy. More data are available for bupropion, with relatively reassuring information about pregnancy outcomes from prospective studies, except for an inconsistently reported risk of cardiovascular malformation with first-trimester exposure.

Nonpharmacological strategies such as CBT are recommended in order to allow women to function as well as possible during pregnancy either without medication or while using the minimum amount required to maintain functioning. In some cases, such as when a woman has a history of impaired driving when not using medication and there are no alternatives to driving, a stimulant used sparingly on an as-needed basis might be the best and safest option. Since stimulants do have a quick onset, intermittent use is an option, which is not the case with bupropion and atomoxetine, which require daily dosing. Collaborative decision making between patients and their providers is crucial when so many variables and unknowns are involved.

Received May 24, 2013; revision received July 18, 2013; accepted Aug. 5, 2013 (doi: 10.1176/appi.ajp.2013.13050680). From the Department of Psychiatry, Harvard Medical School, Boston; and the Perinatal and Reproductive Psychiatry Program, Massachusetts General Hospital, Boston. Address correspondence to Dr. Freeman (mfreeman@partners.org).

Dr. Freeman has received research support from or served on advisory boards or as a consultant for Forest, GlaxoSmithKline, Lilly, Otsuka/Lundbeck, Pamlab, and Takeda and has served as a medical editor for DSM Nutritional Products.

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Clinical Guidance: ADHD and Pregnancy

Medications for attention deficit hyperactivity disorder (ADHD) have not been demonstrated to have clear risks in early pregnancy, but fetal growth may be reduced when stimulants are used in late pregnancy. Treatment suggestions offered by Freeman include cognitive-behavioral therapy, which may allow pregnant or breastfeeding women with ADHD to function reasonably well with less or no medication. For some women with more severe ADHD symptoms who wish to forego medication, it may help to anticipate and accommodate their expected impairments, such as lower work performance and poor driving. Others may choose to continue medication or to use it intermittently, since stimulants take effect quickly.