Attention-deficit/hyperactivity disorder in pregnancy and the postpartum period

Olivia Scoten, BHSc; Katarina Tabi, PhD; Vanessa Paquette, PharmD; Prescilla Carrion, MSc; Deirdre Ryan, MB; Nevena V. Radonjic, MD, PhD; Elizabeth A. Whitham, MD; Catriona Hippman, PhD

Attention-deficit/hyperactivity disorder is a childhood-onset neurodevelopmental disorder that frequently persists into adulthood with 3% of adult women having a diagnosis of attention-deficit/hyperactivity disorder. Many women are diagnosed and treated during their reproductive years, which leads to management implications during pregnancy and the postpartum period. We know from clinical practice that attention-deficit/hyperactivity disorder symptoms frequently become challenging to manage during the perinatal period and require additional support and attention. There is often uncertainty among healthcare providers about the management of attention-deficit/hyperactivity disorder in the perinatal period, particularly the safety of pharmacotherapy for the developing fetus. This guideline is focused on best practices in managing attention-deficit/hyperactivity disorder in the perinatal period. We recommend (1) mitigating the risks associated with attention-deficit/hyperactivity disorder that worsen during the perinatal period via individualized treatment planning; (2) providing psychoeducation, self-management strategies or coaching, and psychotherapies; and, for those with moderate or severe attention-deficit/hyperactivity disorder, (3) considering pharmacotherapy for attention-deficit/hyperactivity disorder, which largely has reassuring safety data. Specifically, providers should work collaboratively with patients and their support networks to balance the risks of perinatal attention-deficit/hyperactivity disorder medication with the risks of inadequately treated attention-deficit/hyperactivity disorder during pregnancy. The risks and impacts of attention-deficit/hyperactivity disorder in pregnancy can be successfully managed through preconception counselling and appropriate perinatal planning, management, and support.

Key words: ADHD, amphetamine, atomoxetine, breast milk, buproprion, clonidine, dextroamphetamine, guanfacine, lactation, lisdexamfetamine, mental health, methylphenidate, nonstimulants, pharmacotherapy, postpartum, pregnancy, stimulants, therapy, viloxazine

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that involves impaired attention and executive functioning, such as the ability to concentrate and plan, and/or impulse control and hyperactivity. It is common globally, affecting 3% to 7% of children,[1] and ADHD symptoms persists into adulthood in about 75% of affected females.[2] The prevalence of ADHD among adult women is 3.2%,[3,4] and it is 4.4% among gender-diverse adults who were assigned female at birth.[5] It is not uncommon for ADHD to be untreated in adulthood with only ~10% of adults with ADHD receiving treatment.[3] It frequently co-exists with other neurodevelopmental disorders, including tic disorders, autism spectrum disorders, intellectual disabilities, spe-

From the Faculty of Medicine, University of British Columbia (UBC), Vancouver, BC, Canada (Ms Scoten); the Department of Psychiatry, UBC, Vancouver, BC, Canada (Dr Tabi, Ms. Carrion, and D. Ryan); the Department of Obstetrics & Gynaecology, UBC, Vancouver, BC, Canada (Dr Hippman); Reproductive Mental Health Program, BC Women's Hospital, Vancouver, BC, Canada (Dr Tabi, Ms Carrion, Dr Ryan, and Dr Hippman); BCCH Centre for Mindfulness, BC Children's Hospital, Vancouver, BC, Canada (Dr Tabi); BC Women's Health Research Institute, Vancouver, BC, Canada (Dr Tabi and Dr Hippman); Department of Pharmacy, BC Women's and Children's Hospital, Vancouver, BC, Canada (Dr Paquette); Department of Psychiatry, SUNY Upstate Medical University, Syracuse, NY (Dr Radonjic); Private practice, Newport Beach, CA (Dr Whitham); and Faculty of Nursing, University of Calgary, Calgary, AB, Canada (Dr Hippman).

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Corresponding author: Catriona Hippman, PhD. catriona.hippman@ubc.ca

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cific developmental disorders of communication, learning, and motor development, and behavioural problems, such as oppositional defiant disorder.[6] Furthermore, it commonly coexists with other psychiatric illnesses[4]; around 10% of adults with recurrent depression and/or anxiety disorders have ADHD.[7,8] We know from clinical experience that treatment of depression and anxiety will likely be inadequate to restore optimal quality of life and functioning for those with unaddressed ADHD. This is supported by the finding that individuals with ADHD who stopped their psychostimulant medication during pregnancy had a significant increase in depressive symptoms, despite remaining on their antidepressant medication.[9] Thus, for individuals with co-existing depression or anxiety, it is particularly important for ADHD to be adequately managed for a greater chance of treating the depression and/or anxiety to remission. Unlike depression, which is most often episodic in nature, ADHD is a chronic condition preceding pregnancy. Thus, there is no formal diagnosis of perinatal ADHD. However, we see in clinical practice that ADHD symptoms often become more challenging to manage as birthing individuals deal with the increased demands of pregnancy and parenting. The aim of this review was to summarize the current literature regarding ADHD in pregnancy and the postpartum period and to offer clinical guidance on the diagnosis and management of this condition in the perinatal period.

Attention-deficit/hyperactivity disorder signs and symptoms

Individuals with ADHD may predominantly experience symptoms of inattention, hyperactivity or impulsivity, or a combination of these[10] (Table 1). Adults with ADHD are more likely to present with inattentive symptoms.[11] When ADHD is suspected, the first step is to have patients complete part A of the Adult ADHD Self-Report Scale (ASRS-V1.1),[12] which asks patients to indicate the frequency of a variety of symptoms. A screen is positive when a patient checks often or very often for 4 or more of the 6 questions.

TABLE 1
Diagnostic Criteria for ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[10]

There must be:
- an ongoing pattern of inattentive and/or hyperactive-impulsive symptoms—at least 6 mo;
- multiple inattentive and/or hyperactive-impulsive symptoms—5 or more (for age ≥17 y; 6 or more are required for age <17 y);
- several inattentive and/or hyperactive-impulsive symptoms with an onset before the age of 12 y;
- several inattentive and/or hyperactive-impulsive symptoms that are present in 2 or more settings (eg, home, work);
- evidence that inattentive and/or hyperactive-impulsive symptoms interfere with or reduce the quality of functioning (eg, interpersonal, occupational)

Symptoms are not better explained by:
- oppositional behavior, defiance, hostility, or failure to understand tasks or instructions;
- another mental disorder (eg, psychotic disorder, mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal)

Inattentive symptoms	Hyperactive-impulsive symptoms
1. Poor attention to detail	1. Frequent fidgeting (eg, tapping a desk)
2. Difficulty concentrating or sustaining attention on tasks	2. Finds it difficult to sit still for prolonged periods
3. Seems preoccupied, difficulty in shifting focus even when spoken to directly	3. Feeling of inner restlessness or agitation
4. Difficulty with completing tasks (gets distracted/side-tracked)	4. Often loud and disruptive
5. Organizational challenges (eg, resulting in chronic lateness—for appointments or deadlines, messiness, disorganized work)	5. Always on the go, difficult for others to keep up
6. Reluctance to engage in tasks that require sustained mental effort (eg, preparing reports, reviewing lengthy papers)	6. Often talks excessively
7. Difficulty keeping track of personal belongings/items required for task completion	7. Frequently interrupts others (difficulty restraining themselves from sharing their perspectives or waiting their turn in conversation)
8. Easily distracted	8. Highly impatient (eg, difficulty waiting in line)
9. Frequently forgetful	9. Often intrudes into others' activities (eg, may take over what others are doing)

Predominantly inattentive type: 5 or more symptoms of inattention for at least 6 mo, but <5 symptoms of hyperactivity-impulsivity.
Predominantly hyperactive-impulsive type: 5 or more symptoms of hyperactivity-impulsivity for at least 6 mo, but <5 symptoms of inattention.
Combined type: 5 or more symptoms of inattention AND 5 or more symptoms of hyperactivity-impulsivity for at least 6 mo.

ADHD, attention-deficit/hyperactivity disorder.

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If a patient screens positive for ADHD, further investigation is warranted to assess if they meet the full diagnostic criteria (Table 1 contains a summary and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, criteria).[10] These investigations may include having the patient complete part B of the ASRS to further elucidate their symptoms; asking someone who knows the patient well (eg, parent, spouse) to complete the ASRS with the patient in mind to gain insights into how their symptoms are perceived by and impact those around them; and using a functional impairment scale, such as the Weiss Functional Impairment Rating Scale- Self (WFIRS-S), which was developed and validated to measure ADHD-specific impairment.[13] Studies have found that adults with ADHD often display difficulties in managing their home (eg, cooking, cleaning) and keeping track of their children's schedules and appointments.[14]

There is a lack of systematic research that evaluated the course of ADHD symptoms throughout the perinatal period. However, there is evidence that neurocognitive functions may be negatively affected during pregnancy in general. Impaired memory, disorientation, confusion, and reading difficulties have subjectively been reported among pregnant individuals.[15,16] Certain objective measures of cognitive function, particularly pertaining to memory and executive functioning, show impairments during pregnancy[15,17,18] and the postpartum period,[19] although findings are inconsistent.[20,21] It has been suggested that women with a preexisting diagnosis of ADHD may be particularly vulnerable to worsening cognition during pregnancy.[22]

During pregnancy, there are many medical appointments to coordinate, in addition to obtaining the necessary items and preparing the home environment for the baby. If the pregnancy is complicated by conditions, such as gestational diabetes, which has been found to be more common in individuals with ADHD,[23] there is an additional need to adhere to particular diets and regimes. It has been suggested that ADHD symptoms may interfere with the effective completion of these tasks because they involve planning, organization, financial oversight, and time management.[24] Furthermore, the rates of unplanned pregnancy and early parenthood (ie, younger age) have been shown to be significantly higher among individuals with ADHD,[2,25–27] which may contribute additional stress to these patients in the perinatal period.

ADHD in pregnancy has been associated with impairment in a variety of life domains, particularly occupational and interpersonal domains, and inattentive symptoms were the most important predictors of impairment in daily functioning.[24] This is supported by our clinical observations that ADHD symptoms frequently become difficult to manage during the perinatal period and require additional support and attention. Parenting with ADHD may be overwhelming, particularly if the individual has not previously learned organizational skills to compensate for their symptoms. Parents with ADHD have been found to experience greater parental distress in the first year postpartum than new parents without ADHD.[28] Further research is needed to explore the course of ADHD symptom severity and associated functional impairment in pregnancy and the postpartum period. However, taken together, current evidence suggests that special attention needs to be given to caring for pregnant patients with ADHD.

Managing attention-deficit/hyperactivity disorder in the perinatal period

The risks and impacts of ADHD during pregnancy can be successfully managed through preconception counselling and appropriate perinatal planning, management and support.

Preconception counselling includes the following:

- Discussing risks associated with untreated or undertreated ADHD (eg, driving risks[29]) and ways to minimize symptoms and optimize functioning across all life domains (school, occupation, family).[30]
- Reviewing pharmacologic and nonpharmacologic treatment options and potentially changing medication regimens before becoming pregnant (see section on Treatment and self-management).
- Reinforcing the importance of seeking help if ADHD symptoms worsen during pregnancy.[9,24]

Planning, management, and support include the following:

1. Asking all pregnant people about a personal history of ADHD or other neurodevelopmental disorders or psychiatric illnesses.
2. Developing a management plan that involves the pregnant person and their family or support network, psychiatry, obstetrics, and primary care. Planning needs to incorporate ongoing monitoring, and, if necessary, adjustment of medications throughout the perinatal period.
3. Addressing factors that may worsen functioning in the perinatal period, such as stress, inadequate nutrition (particularly prioritizing eating throughout the day), and sleep deprivation.

Treatment and self-management

Treatment of ADHD frequently involves a combination of behavioural therapy and medications, most commonly psychostimulants. Table 2 contains a list of treatments commonly used for ADHD. For mild to moderate ADHD during pregnancy or the postpartum period among women and gender diverse birthing people, psychoeducation, self-management strategies, coaching, and psychotherapies are recommended as first-line interventions. Pharmacotherapy may also be required for pregnant or postpartum women and gender diverse birthing people with moderate to severe ADHD.[31,32] When treating a pregnant or postpartum person, it is important to consider the presence of ADHD, along with any other psychiatric illness, because the treatment of these

TABLE 2
Treatments commonly used to treat ADHD in the perinatal period

Severity of Symptoms	Treatment and Self-Management
Mild to moderate	A. Psychoeducation B. Self-management or coaching C. Psychotherapies i. Cognitive behavioral therapy (CBT) ii. Mindfulness-based interventions iii. Dialectical behavior therapy
Moderate to severe	Treatment for mild to moderate symptoms plus: D. Pharmacotherapy (medications) i. Stimulants a. Amphetamine-based stimulants b. Methylphenidate-based stimulants ii. Nonstimulants

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conditions will not be as successful if the ADHD is not addressed at the same time.[9]

Psychoeducation

Psychoeducation has been shown to decrease disorganization and inattention and increase self-confidence among adults with ADHD.[33] We are unaware of research on psychoeducation for ADHD in the perinatal period, however, psychoeducation in the perinatal period has been shown to be effective for other mental health conditions, including perinatal depression.[34,35] The goal of psychoeducation for ADHD in the perinatal period is to help pregnant people and their families understand the symptoms they are experiencing and the underlying disorder, to learn about available treatment modalities, and to reinforce existing coping strategies that have proven to be effective. The goal is to promote understanding and personal management of their disorder.[35,36] Specific topics that are important to cover in psychoeducation for ADHD include:

- Information about the disorder[36]
- Prevalence[1,3,4]
- Signs and symptoms[11]
- Risk and protective factors[37–41]
- Highly co-occurring conditions[4,6–8]
- Treatment options[31,42–44]
- Benefits and potential risks of treatment (particularly related to pharmacotherapy in the perinatal period)[45–47]
- Anticipated improvements with treatment[48–50]

Self-management or coaching

In self-management, patients are supported to make changes in how they structure their lives to minimize the impact of ADHD symptoms and foster a high quality of life. Coaching helps individuals with ADHD manage their behaviour and improve functioning in various areas of their lives with support and accountability from coaches. Coaches help individuals set realistic goals, develop plans to accomplish these goals, and tailor their daily routines to better cope with ADHD. Coaching for ADHD has been shown to improve attention, time management, concentration, impulsivity, self-esteem, quality of life, and overall task completion.[48,51–53]

Strategies to consider:

1. Establishing routines, structures, and habits
2. Using lists, calendars, and timers
3. Self-care, including taking breaks, sleep hygiene, regular nutritious meals, and exercise
4. Reducing workload during pregnancy or implementing additional structure or external supports in the workplace
5. Taking public transport or making alternative transportation arrangements to avoid driving.

Implementing the above strategies may be particularly helpful if patients wish to avoid the use of medications during pregnancy.[22] Driving ability in particular is a crucial safety consideration in the context of severe or untreated ADHD. Treatment with stimulants has been shown to improve driving capability.[54] Alternative transportation arrangements are strongly recommended for pregnant people with a history of, or a high risk for, driving impairment.

Psychotherapies

There is currently a scarcity of research that evaluated the efficacy of psychotherapies for the treatment of ADHD in the perinatal period. Thus, the following categories summarize the research that has been conducted largely among adults with ADHD and that has been extrapolated to the perinatal population.

Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) focuses on how thoughts can affect emotions, which, in turn can affect behavior and physiological bodily responses. Targeted CBT treatments have been developed specifically for ADHD and help people to develop their executive functioning skills. These treatments support the establishment of more adaptive cognitions related to time management, organization, and planning, and teach more adaptive behavioural skills. There are also CBT programs that focus on emotional self-regulation, stress management, and impulse control.

Of the psychotherapy options for ADHD, CBT has been the most extensively studied and has been found to be the most effective for the treatment of ADHD and co-existing anxiety and depression in adults.[42]

CBT for adults with ADHD has been shown to be effective in both group[49,55–57] and individual settings.[58–61] Literature suggests that the effectiveness of CBT for ADHD is further increased when used in combination with medication.[62]

Mindfulness-based interventions (MBIs): mindfulness can be described as a cultivation of awareness that involves paying attention in the present moment,

nonjudgmentally, and with kind acceptance. MBIs are standardized evidence-based programs, the most extensively studied programs being the 8-week group-based Mindfulness-Based Cognitive Therapy (MBCT) and Mindfulness-Based Stress Reduction (MBSR) programs.[63,64] Mindfulness can be described as a cultivation of awareness that involves paying attention in the present moment, nonjudgmentally, and with kind acceptance.

Evidence for the use of mindfulness for managing ADHD in the general adult population is rapidly increasing with the understanding of its mechanisms at both the behavioral and neuronal levels. At a neuroscientific level, 3 main neural networks have been involved in both ADHD and in mindfulness, namely the default mode network, salience network, and central executive network.[65–71] On the behavioral level, studies show that MBIs help people with ADHD most profoundly in the following areas: inattention symptoms, emotion regulation, executive function and overall quality of life.[65,72–75] Furthermore, various clinical guidelines recommend MBIs as a nonpharmacologic intervention for adults with ADHD (eg, The Canadian Resource Alliance (CADDRA) Canadian ADHD Practice Guidelines,[76] and National Institute of Health and Care Excellence guidelines in the United Kingdom[77]).

When we consider the unique circumstances of becoming a parent, literature looking at mindfulness and other mental health diagnoses during the perinatal period suggests great improvement in self-compassion, parental self-efficacy, and various dimensions of mindfulness, including observing, acting with awareness, without judgment or nonreactivity.[78–80]

Thus, although MBIs were introduced relatively recently and evidence for their use in managing ADHD in the perinatal population is still emerging, they seem increasingly promising.

Dialectical behavior therapy (DBT): there are 4 modules in DBT, namely (1) mindfulness skills, (2) distress tolerance, (3) interpersonal effectiveness skills, and (4) emotion regulation skills. DBT can be delivered individually or in a group setting.

DBT has been modified to suit the needs of adult patients with ADHD with elements of each module targeting aspects of ADHD. The mindfulness module addresses poor concentration, the distress tolerance module addresses disorganization, the interpersonal skills module addresses troubled interpersonal relationships that are common for those with ADHD, and the emotion modulation module addresses affective lability.[81] After treatment with DBT, patients showed decreased ADHD symptoms, improved neuropsychological functioning, and reduction of co-existing anxiety and depression.[82–84]

Pharmacotherapy

For moderate to severe ADHD, the gold standard of treatment involves a combination of psychotherapy and medication. First-line medications for the treatment of ADHD are psychostimulants, particularly amphetamine-based stimulants (amphetamine, dexamphetamine, lisdexamfetamine), and methylphenidate.[31] Nonstimulant options include bupropion, atomoxetine, guanfacine, clonidine, and viloxazine.[31,43]

Stimulant medications are typically the first choice to treat ADHD because they work for 70% to 80% of people with ADHD[85,86] and have been shown to be more effective than nonstimulant medications.[44] A recent meta-analysis that examined the comparative efficacy of ADHD medications proposed methylphenidate for children and adolescents and amphetamines for adults as the preferred first choice of pharmacotherapy.[50]

When stimulants do not work or patients experience severe side effects, nonstimulant medications are second-line treatment options. The most commonly used nonstimulant medication, atomoxetine,[87] is a norepinephrine modulator that is significantly more efficacious than placebo in treating ADHD in adults.[43] Another nonstimulant option, bupropion, is a norepinephrine and dopamine reuptake inhibitor, which has been shown to be more effective than placebo in adults with ADHD.[50] Recently, viloxazine extended release, a serotonin—norepinephrine modulating agent that was approved in the 1970s in the United Kingdom for the treatment of depression,[88] has received FDA approval in the United States for the treatment of ADHD in children and adults. It has also been shown to be significantly more efficacious than placebo in the treatment of ADHD in adults.[43] This same meta-analysis demonstrated that the alpha-2 adrenoreceptor agonist, guanfacine, is more effective than placebo in adults with ADHD, but there are no randomized controlled trials on the use of clonidine, another alpha-2 adrenoreceptor agonist, for the treatment of ADHD in adults.

Pharmacotherapy during pregnancy: unfortunately, it is common for care providers to advise patients to stop their ADHD medications if they are contemplating pregnancy or are pregnant.[9] This is particularly prevalent in cases where ADHD co-exists with other conditions and the patient is taking more than 1 psychiatric medication.

As is the case for the treatment of other psychiatric illnesses in the perinatal period, it is imperative that the risks of exposure to medications to treat ADHD in pregnancy are weighed against the risks of untreated or inadequately treated ADHD in pregnancy. Methylphenidate, dextroamphetamine, and atomoxetine have all been shown to cross the placenta in rat and mice models,[89–91] and it is generally thought that the medications used to treat ADHD cross the placenta in humans, leading to exposure to the developing fetus.[92] However, discontinuing psychostimulant treatment during pregnancy can lead to worse mental health outcomes and significant impairments in functioning in the pregnant individual.[9,93] This may subsequently have negative impacts on the developing fetus or baby, because untreated ADHD has been shown to be associated with increased risks for spontaneous abortion and preterm birth.[94]

Furthermore,[89–92] the research that has been conducted on the potential teratogenicity of ADHD medications, which has mainly focused on the use of stimulants, is largely reassuring

TABLE 3
Summary of the evidence regarding fetal, neonatal, or infant risks associated with the use of medications for the treatment of ADHD while pregnant or breastfeeding

Psychostimulants for the treatment of ADHD

Medication	Dosage range[95]	Fetal or neonatal risk	Hale lactation risk category[95]	Breastfeeding	Additional considerations or monitoring
Amphetamine mixed salts (Adderall XR®)	Usual starting dose: 10 mg po qam Titration: Titrate dose by 5 mg weekly up to 50 mg	Overall Amphetamines do not seem to be associated with major congenital malformations, including cardiac malformations, or other significant adverse obstetrical or developmental outcomes.[46,96–100] Congenital malformations Possible increased risk for gastroschisis (aOR, 3.0; 95% CI, 1.2–7.4);[101] one study, possible confounding by indication, small absolute risk given rarity of gastroschisis (population prevalence of 0.05%[102]), and other studies have not found this association. Obstetrical outcomes Possible increased risk for preeclampsia (aRR, 1.29; 95% CI, 1.11–1.49),[103–105] but this risk seems to be small, and other studies have not found this association. Possible increased risk for preterm birth when stimulant use continues in the second half of pregnancy, but this risk seems to be small (aRR, 1.30; 95% CI, 1.10–1.55).[103] Long-term outcomes Data are limited, inconsistent, and potentially impacted by confounding factors.[97] However, a recent, large, well-controlled study demonstrated no increased risks for the use of methylphenidate, amphetamine, dexamphetamine, lisdexamfetamine, modafinil, atomoxetine, or clonidine during pregnancy on the long-term outcomes; neurodevelopmental psychiatric disorders, impairments in vision or hearing, epilepsy, seizures, or growth impairment.[100]	L3	Overall Based on very limited data, at doses prescribed for therapeutic indications, amphetamine use during breastfeeding does not seem to adversely affect infants.[96,106,107] Amphetamine is present in human milk and has been detected in the serum and urine of infants exposed to amphetamines via breastfeeding.[106,108] Recommendation Monitor infant carefully for irritability, insomnia, and feeding difficulty.	Information provided here is related to therapeutic use of amphetamines during pregnancy and lactation and does not apply to nonprescribed amphetamine use in persons with stimulant use disorder. Nonprescribed use of amphetamines during pregnancy and breastfeeding is not recommended because of associated maternal, fetal, and neonatal harm.
Dextroamphetamine (Dexedrine®)	Usual starting dose and titration: Immediate release: 5 mg po BID, increase by 5 mg weekly increments to a maximum of 50 mg per d Spansule: 10 mg po qam, increase by 5 mg	Please see amphetamine for information on fetal or neonatal risk in pregnancy.	L3	Please see amphetamine for information about breastfeeding while taking dextroamphetamine. The one case series (N=4) of dextroamphetamine use while breastfeeding was	

Scoten. Attention-deficit/hyperactivity disorder in the perinatal period. Am J Obstet Gynecol 2024. *(continued)*

TABLE 3
Summary of the evidence regarding fetal, neonatal, or infant risks associated with the use of medications for the treatment of ADHD while pregnant or breastfeeding *(continued)*

Psychostimulants for the treatment of ADHD

	increments weekly to a maximum of 50 mg per d			consistent with the data for amphetamine use.[109]
Lisdexamfetamine (Vyvanse®)	Usual starting dose: 20–30 mg po qam Titration: Increase by 10 mg weekly to a maximum of 70 mg daily	Limited published information on the use of lisdexamfetamine in pregnancy. Lisdexamfetine is a prodrug that is converted to dextroamphetamine.[110] Please see amphetamine for information on fetal or neonatal risk in pregnancy.	L3	There are no published studies specifically on lisdexamfetamine while breastfeeding. Please see amphetamine for information that is likely applicable to breastfeeding while taking lisdexamfetamine.
Methylphenidate (Ritalin®, Ritalin SR®, Biphentin®, Concerta®, Foquest®)	Please refer to the CADDRA Guidelines for dosing recommendations for each specific brand: https://www.caddra.ca/	Overall Methylphenidate does not seem to be associated with major congenital malformations or other significant adverse obstetrical or developmental outcomes.[93,99,100,111–114] Congenital malformations Possible increased risk for cardiac malformations (OR, 1.59; 95% CI, 1.02–2.49),[115] but this risk seems to be small (absolute risk of 1.7%) and other studies have not found this association. Possible increased risk for gastroschisis (aOR, 3.0; 95% CI, 1.2–7.4);[101] one study, possible confounding by indication, small absolute risk given rarity of gastroschisis (population prevalence of 0.05%[102]), and other studies have not found this association. Obstetrical outcomes Possible increased risk for preeclampsia (aRR, 1.29; 95% CI, 1.11–1.49),[103,105] but this risk seems to be small, and other studies have not found this association. Possible increased risk for preterm birth (aOR, 1.3; 95% CI, 1.1–1.6)[47] (aRR, 1.3; 95% CI, 1.1–1.55),[103] but this risk seems to be small. Possible increased risk for spontaneous abortion but confounding by indication cannot be ruled out.[116] Possible increased risk for poor neonatal adaptation (13/55 = 23.6% vs 48/355 = 13.5%; P=.05), but this difference was only just statistically significant.[117] Possible increased risk for NICU admission (aOR, 1.5; 95% CI, 1.3–1.7), and central nervous system disorders (aOR, 1.9; 95% CI, 1.1–3.1),[47] however, there were substantial	L2	Overall Based on very limited data, at doses prescribed for therapeutic indications, methylphenidate use during breastfeeding does not seem to adversely affect infants.[93,119–122] Methylphenidate is present in human milk and has been detected in the serum of infants exposed to methylphenidate via breastfeeding— —although at very low levels.[119–122] Recommendation Monitor infant carefully for irritability, insomnia, and feeding difficulty.[96]

Scoten. Attention-deficit/hyperactivity disorder in the perinatal period. Am J Obstet Gynecol 2024. *(continued)*

TABLE 3
Summary of the evidence regarding fetal, neonatal, or infant risks associated with the use of medications for the treatment of ADHD while pregnant or breastfeeding *(continued)*

Psychostimulants for the treatment of ADHD				
		differences between the background characteristics in the exposed and unexposed groups, thus posing a challenge for interpretation and increasing risk for confounding. Long-term outcomes Data are limited and likely impacted by confounding factors.[118] However, a recent, large, well-controlled study demonstrated no increased risks for the use of methylphenidate, amphetamine, dexamphetamine, lisdexamfetamine, modafinil, atomoxetine, or clonidine during pregnancy on the long-term outcomes; neurodevelopmental psychiatric disorders, impairments in vision or hearing, epilepsy, seizures, or growth impairment.[100]		
Nonstimulants for the treatment of ADHD				
Atomoxetine (Strattera®)	Usual starting dose: 40 mg po daily Titration: Dose is usually adjusted every 7–14 d; to 60 then 80 mg/d Total maximum dose is recommended as the lesser of 1.4 mg/kg/d or 100 mg/d	Overall Atomoxetine does not seem to be associated with major congenital malformations, including cardiac malformations, or other significant adverse obstetrical or developmental outcomes, although data are limited.[18,100,103,123,124] Obstetrical outcomes Possible increased risk for spontaneous abortion but confounding by indication cannot be ruled out.[116] Long-term outcomes A recent, large, well-controlled study demonstrated no increased risks for the use of methylphenidate, amphetamine, dexamphetamine, lisdexamfetamine, modafinil, atomoxetine, or clonidine during pregnancy on the long-term outcomes; neurodevelopmental psychiatric disorders, impairments in vision or hearing, epilepsy, seizures, or growth impairment.[100]	L4	Overall—caution is advised There are no published studies of atomoxetine while breastfeeding. Based on the pharmacokinetics of the drug (low molecular weight, long half-life), it will likely be present in human milk. The effects on a nursing infant are unknown and references caution its use during breastfeeding at this time.[95,96,116]
Bupropion (Wellbutrin®)	SR: Usual starting dose: 100–150 mg po daily Maintenance dose: 100–150 mg po BID XL: Usual starting dose: 150 mg po daily Maintenance dose: 150–300 mg po daily Maximum dose: 450 mg per d[125]	Overall Bupropion does not seem to be associated with major congenital malformations, or other significant adverse obstetrical outcomes, although data are limited.[126–131] Congenital malformations A small absolute increase in the risk of 2 cardiovascular malformations have been associated with first-trimester exposure to bupropion monotherapy, but confounding by indication cannot be ruled out, and other studies have not found these associations. 1) Left ventricular outflow tract obstruction heart defects	L3	Overall—caution is advised Very limited data (21 cases).[96,140–145] Bupropion is present in human milk and has been detected in the serum of infants exposed to bupropion via breastfeeding—although at very low levels (sometimes undetectable)[95] Generally, no adverse events reported, but there have been 2 case reports of seizures in breastfed infants.[142,143] Recommendation

Scoten. Attention-deficit/hyperactivity disorder in the perinatal period. Am J Obstet Gynecol 2024. *(continued)*

TABLE 3
Summary of the evidence regarding fetal, neonatal, or infant risks associated with the use of medications for the treatment of ADHD while pregnant or breastfeeding *(continued)*

Nonstimulants for the treatment of ADHD

		(incidence 0.279% vs 0.07% with exposure to other antidepressants[132,133]), and 2) ventricular septal defects (aOR, 2.9; 95% CI, 1.5–5.5) Possible increased risk for diaphragmatic hernia (aOR, 2.77; 95% CI, 1.34–5.71)[134]; 1 study, possible confounding by indication,[135] small absolute risk given rarity of diaphragmatic hernia (population prevalence of 0.012%–0.031%[136,137]), and other studies have not found this association. Obstetrical outcomes Possible increased risk for spontaneous abortion.[128] Possible increased risk for poor neonatal adaptation, but this has been reported in only 1 case, specifically presenting with seizures because of prolonged hypoglycemia as a consequence of severe hyperinsulinism.[138] Long-term outcomes Further research is needed to clarify possible increased risk for ADHD[139] and to disentangle likely confounding by indication.		Monitor infant carefully for vomiting, diarrhea, jitteriness, sedation, and/or seizures.
Clonidine[a]	Usual starting dose: 0.05–0.1 mg po QHS Titration: Increase by 0.1 mg BID – TID to a max of 0.4 mg per d[146]	Overall Clonidine could be considered as an adjunct agent in the treatment of ADHD following a risk-benefit discussion, acknowledging the limited information on both safety in pregnancy and efficacy for the treatment of ADHD in adults. Very limited published information indicates that clonidine is likely not associated with adverse pregnancy or developmental outcomes.[100,147–152] Congenital malformations There are studies documenting the use of clonidine during pregnancy for the treatment of hypertension or hyperemesis gravidarum, which have found no increased risk for major or minor malformations.[147–151] One case report of clonidine for the treatment of hypertension throughout pregnancy led to an infant born with Roberts syndrome.[152] Long-term outcomes A recent, large, well-controlled study demonstrated no increased risks for the use of methylphenidate, amphetamine, dexamphetamine, lisdexamfetamine, modafinil, atomoxetine, or clonidine during pregnancy on	L3	Overall—caution is advised Little published data are available regarding clonidine use while breastfeeding, but the majority of cases reported were not associated with any adverse effects for the infants.[153,154] However, there is one case report of an infant developing drowsiness, hypotonia, suspected generalized seizures, and episodes of apnea. The infant was exposed to 0.15 mg daily during pregnancy and the early postpartum period. All symptoms resolved with 24 hours of breastfeeding cessation.[153,155,156] Clonidine is found in human milk and is also detectable in infant serum following exposure via breastfeeding.[95,153,156] The M:P ratio has been reported as 2 with a RID up to 7.1%.[95] Infants should be monitored for drowsiness and hypotonia.

Scoten. Attention-deficit/hyperactivity disorder in the perinatal period. Am J Obstet Gynecol 2024. *(continued)*

TABLE 3
Summary of the evidence regarding fetal, neonatal, or infant risks associated with the use of medications for the treatment of ADHD while pregnant or breastfeeding *(continued)*

Nonstimulants for the treatment of ADHD				
		the long-term outcomes; neurodevelopmental psychiatric disorders, impairments in vision or hearing, epilepsy, seizures, or growth impairment.[100]		
Guanfacine (Intuniv XR®) (Approved in Canada for treatment in children and adolescents aged 6–17 y only[95])[a]	Usual starting dose: 1 mg once daily. Titration: Titrate dose by 1 mg/wk based on response and as tolerated to the recommended target dose range: 0.05 to 0.12 mg/kg/d or 1 to 7 mg/d[157]	Overall Guanfacine could be considered in the treatment of ADHD following a risk-benefit discussion acknowledging the very limited information on its safety in pregnancy and the limited data on its efficacy for the treatment of ADHD in adults. Alternative agents would be preferred. There are no published studies of guanfacine in pregnancy specifically for the treatment of ADHD. The only published study that evaluated guanfacine in pregnancy was for the treatment of hypertension in 30 patients with preeclampsia. No congenital malformations were reported, however, all patients were outside the first trimester, so this cannot be assessed from this study. Six of the infants (20%) had low birth weight but all were reported to later develop normally.[158]	Not rated	Overall—caution is advised There are no published studies of guanfacine while breastfeeding.
Viloxazine ER[a] (Qelbree®) (Not currently available in Canada; approved in the United States for treatment in children and adolescents aged 6 and older)	Usual starting dose: 200 mg po once daily Titration: titrate by 200 mg increments at weekly intervals based on response and tolerability; maximum daily dose: 600 mg/d.[159]	Overall Viloxazine could be considered as an agent in the treatment of ADHD following a risk-benefit discussion, acknowledging that there is no information published on its safety in pregnancy and there is limited data on its efficacy for the treatment of ADHD in adults. Alternative agents would be preferred. There are no published studies of viloxazine in pregnancy.	Not rated	Overall—caution is advised There are no published studies of viloxazine while breastfeeding.

Approval for, and accessibility to, these medications will vary by jurisdiction. Drug products and dosing listed are based mainly on products available in Canada. Please refer to local guidelines for availability of drug products and their respective dosing.

ADHD, attention-deficit/hyperactivity disorder; *aOR,* adjusted odds ratio; *aRR,* adjusted risk ratio; *BID,* bis in die (twice a day); *CADDRA,* Canadian ADHD Resource Alliance; *CI,* confidence interval; *NICU,* neonatal intensive care unit; *po,* per os (orally); *qam,* quaque die ante meridiem (every morning/every day before noon); *QHS,* quaque hora somni (daily at bedtime); *RID,* relative infant dose.

[a] Limited data are available on the efficacy, safety, and tolerability of clonidine, guanfacine, and viloxazine for the treatment of ADHD in adults.

Scoten. Attention-deficit/hyperactivity disorder in the perinatal period. Am J Obstet Gynecol 2024.

(Table 3[18,46,47,95–159]). The majority of studies do not find an increased risk for congenital malformations.[46,93,96–98,103,111–114,117,158,160,161] Select studies have suggested a slightly increased risk for cardiac defects[99,115,123,162] with methylphenidate use, however, this risk seems to be small (absolute risk of 1.7% relative to a baseline risk of 1.07%), and other studies have not found this association. One study found an increased risk for gastroschisis with the use of ADHD medications in early pregnancy,[101] however, the absolute risk was small. Atomoxetine and bupropion do not seem to be associated with major congenital malformations, although data are limited.[103,123] The only published study that evaluated guanfacine in pregnancy was for the treatment of hypertension in which no congenital malformations were reported.[158] There are studies documenting the use of clonidine during pregnancy for the treatment of hypertension or hyperemesis gravidarum, which have found no increased risk for major or minor malformations.[147–149] There are no data available on the safety of viloxazine in the perinatal context.

There is some evidence that ADHD medications in pregnancy might increase the risk for pregnancy and birth complications, such as preeclampsia,[103–105] preterm birth,[47,103] low birth weight,[158] poor neonatal adaptation,[117] neonatal intensive care unit admissions,[47] and central nervous system disorders.[47] However, much of the existing evidence comes from small studies that examined the illicit use of stimulants or the use of different medications in combination, and several other studies found no such effects.[47,98,105,117,161] Furthermore, the magnitude of documented risks is arguably not clinically meaningful and there is evidence that these risks may be elevated in ADHD in general instead of being directly attributable to the medication.[47,105]

The available evidence on the safety of ADHD pharmacotherapy in pregnancy is reassuring, particularly for the stimulants. Because of limited studies, further research is needed to evaluate the second-line, nonstimulant agents during pregnancy. There also remains a gap on the long-term outcomes of ADHD pharmacotherapy in pregnancy. Table 3[18,46,47,95–159] provides our summary and recommendations based on the evidence that is currently available.

Pharmacotherapy during breastfeeding: Research on the safety of ADHD medications in breastfeeding (refer to the Box[163,164] regarding language) is scarce and largely limited to case reports. Generally, relative infant doses (RIDs) in human milk below 10% are considered safe for breastfeeding.[165] Methylphenidate is only secreted in small amounts in human milk with RIDs of <1% found in all cases, and it is generally not detected in the blood of breastfed infants; in addition, no adverse effects have been reported in infants.[119–122] Thus, it is broadly considered safe during breastfeeding.[45,46,93] Amphetamines are transferred more readily into human milk, although reports of medical treatment with amphetamines during breastfeeding showed RIDs below the 10% threshold, low but detectable amounts in infant plasma, and no notable adverse effects on early development.[106,107,109,120]

Because methylphenidate and amphetamines increase the levels of dopamine, an inhibitor of the hormone prolactin, it is thought that they may impact milk production, particularly in those who have not yet established lactation.[166] Both methylphenidate and amphetamines have indeed been shown to reduce serum prolactin levels in postpartum people,[167–170] however, most of these studies did not report on the corresponding effects on milk production, and 1 study that reported this outcome did not find that amphetamine interfered with milk supply.[106] It has further been suggested that prolactin levels may not impact milk production in those who have already established lactation.[166] Thus, caution may need to be exercised, and a review of medications may be indicated for individuals being treated with stimulants who would like to breastfeed but are having difficulty establishing lactation.

Bupropion displays RIDs compatible with breastfeeding, is generally not detected in infant blood, and no medical problems have mostly been reported in breastfed infants,[140,141,171] however, there have been 2 case reports of seizures in infants exposed to bupropion via human milk.[142,143] There is little safety data on the use of atomoxetine in breastfeeding, however, practice caution against its use during breastfeeding based on the pharmacokinetic properties of the drug.[95,96] As mentioned previously, further research on the safety of medications in the treatment of ADHD while breastfeeding would allow patients and clinicians to have more confidence in evidence-informed shared decision-making for ADHD pharmacotherapy in this context.

We suggest practicing caution in terms of breastfeeding if a patient is taking multiple medications (eg, antidepressants, benzodiazepines, and ADHD medications) and considering alternative infant feeding options in these cases. Overall, the decision to breastfeed while taking medication to treat ADHD should be the subject of a risk-benefit analysis, conducted in consultation with the treating physician, and the infant's development should be carefully monitored.

Pharmacotherapy—general principles: The consensus is that the magnitude of documented risks is very low and that treatment with medications should not be stopped if they are required for the daily functioning of the pregnant or breastfeeding person.[45] Because stimulants have a rapid effect, intermittent use on an as-needed basis with the goal of maximizing functioning while reducing overall fetal or infant exposure has been suggested as a possible solution.[22] Another possibility is switching from stimulants to bupropion (an antidepressant) in the perinatal period, particularly for individuals requiring treatment for cooccurring depression, given the available safety data for this drug in the perinatal period.[31] However, it is important to consider that bupropion is not as efficacious as stimulants for the treatment of ADHD.[172] For general principles regarding medication management for ADHD in the perinatal period, refer to Table 4.

TABLE 4
General principles regarding ADHD medication management for women and gender diverse birthing individuals during pregnancy and while breastfeeding

Preconception	• If taking a psychostimulant, consider a trial of gradually discontinuing the medication before pregnancy if it is not likely to severely impact daily functioning. • If unable to discontinue the medication, continue with the current medication or reduce to the lowest effective dose or consider intermittent use or consider switching to a nonstimulant option. • Engage the patient in a risk-benefit discussion regarding the choice of medication and lowest effective dose.
Pregnancy	• If taking a psychostimulant, engage the patient in a risk-benefit discussion regarding continuing their currently well-tolerated, effective dose or considering intermittent use. • Monitor pregnancy carefully, including fetal growth, blood pressure checks, and ensuring appropriate weight gain.
At birth and during breastfeeding	• If taking methylphenidate or bupropion, maintain therapeutic dose at the time of delivery and during breastfeeding. • If taking an amphetamine derivative, discuss breastfeeding safety. Consider intermittent use and timing feeding or pumping to achieve the lowest concentration in human milk or other feeding options. • Monitor infant early development carefully; ensure infants are gaining weight appropriately and meeting appropriate milestones.

ADHD, attention-deficit/hyperactivity disorder.

Scoten. Attention-deficit/hyperactivity disorder in the perinatal period. Am J Obstet Gynecol 2024.

Conclusions: approaching attention-deficit/hyperactivity disorder in the perinatal period

Key points

- The rate of ADHD is approximately 3.2% in adult women, and 4.4% among gender-diverse adults who were assigned female at birth.[5]
- Although ADHD is a chronic condition instead of being an episodic one, during the perinatal period, there may be an exacerbation of symptoms that can be successfully managed through preconception counselling and appropriate perinatal planning, management, and support.
- Clinical features of ADHD in pregnant and postpartum women and gender diverse birthing people are the same as those outside the perinatal period among women and gender diverse people assigned female at birth. However, further research is needed to explore the course of ADHD symptom severity and the associated functional impairment in pregnancy and the postpartum period.
- ADHD often co-exists with other psychiatric illnesses (eg, perinatal depression and/or anxiety) and neurodevelopmental disorders.[4,6]
- ADHD is primarily managed through behavioral therapy and medications. Mild to moderate ADHD may be successfully treated with nonpharmacologic treatments, including self-management strategies. Medications—most frequently stimulants—may also be required for moderate to severe ADHD.
- Nonpharmacologic treatments include psychoeducation, self-management or coaching, CBT, MBIs, and DBT. Of the nonpharmacologic options for ADHD treatment, CBT has been studied the most and shown to be the most effective.[42,53] Given that the evidence base for nonpharmacologic treatments for ADHD is largely comprised of studies in adults with ADHD outside pregnancy and the postpartum period, further research in the perinatal population is needed.
- When deciding whether to treat ADHD with medications during pregnancy, it is important to weigh risks associated with ADHD medications in pregnancy against the risks associated with untreated or inadequately treated ADHD in pregnancy. Although pharmacologic studies of ADHD in pregnancy are limited, particularly for non-stimulants, the available safety data for ADHD medications in pregnancy is largely reassuring.
- Research on the safety of ADHD medications in breastfeeding is scarce. The decision to breastfeed while taking medications should be made collaboratively and the infant's development should be closely monitored.[45,93]

Box
The importance of inclusive language

Not every person who is lactating will be comfortable with the term breastfeeding. It is important for healthcare providers to ask people which term they prefer to use when discussing the act of feeding their baby. Other options may include chestfeeding or nursing. We encourage clinicians to be sensitive to patient language preferences and be aware of inclusive language options.[163,164] In the interests of plain language writing, we use the terms breastfeeding and human milk in this guideline, but the messages are intended to apply to individuals of all genders.

Scoten. Attention-deficit/hyperactivity disorder in the perinatal period. Am J Obstet Gynecol 2024.

Recommendations

1. Encourage people with a diagnosis of ADHD to plan their pregnancy.
2. Work with women and gender diverse birthing people with ADHD to develop an individualized treatment plan to optimize their mental health in the perinatal period. This includes education about the signs and symptoms of deteriorating mental health and strategies for supporting mental wellness—

particularly prioritizing sleep and nutrition.

3. Consider referral to a general psychiatrist or specialist reproductive psychiatrist if you:
   - have concerns about the safety of ADHD medications in pregnancy or breastfeeding; and/or
   - would like support with ongoing management of your patient with ADHD in the perinatal period.
4. For patients with ADHD whose treatment plan might include medications in pregnancy or while breastfeeding:
   - Engage in shared decision-making with the patient and the patient's partner or family member(s) as appropriate;
   - Discuss the importance of balancing the risks of using ADHD medications during pregnancy or breastfeeding against the risks of potential ADHD symptom exacerbation if the patient does not use ADHD medications;
   - Ensure the medication regimen for ADHD is titrated to the lowest effective dose and the minimum number of medications; and
   - If using ADHD medications while breastfeeding, monitor the baby for adverse effects, such as, irritability, insomnia, and feeding difficulties. ■

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