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SYSTEMATIC REVIEW

Associations of Prescribed ADHD Medication in Pregnancy with Pregnancy-Related and Offspring Outcomes: A Systematic Review

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Abstract

Background Increasing numbers of reproductive-aged women are using attention-deficit/hyperactivity disorder (ADHD) medications. Findings from studies exploring the safety of these medications during pregnancy are mixed, and it is unclear whether associations reflect causal effects or could be partially or fully explained by other factors that differ between exposed and unexposed offspring.

Objectives The aim of this systematic review was to evaluate the adverse pregnancy-related and offspring outcomes associated with exposure to prescribed ADHD medication during pregnancy with a focus on how studies to date have handled the influence of confounding.

Methods We searched PubMed, Embase, PsycINFO, and Web of Science up to 1 July 2019 without any restrictions on language or date of publication. We included all observational studies (e.g., cohort studies, case–control studies, case–crossover studies, cross-sectional studies, and registry-based studies) with pregnant women of any age or from any setting who were prescribed ADHD medications and evaluated any outcome, including both short- and long-term maternal and offspring outcomes. Two independent authors then used the Newcastle–Ottawa Scale to rate the quality of the included studies.

Results Eight cohort studies that estimated adverse pregnancy-related and offspring outcomes associated with exposure to ADHD medication during pregnancy were included in the qualitative review. The included studies had substantial methodological differences in data sources, type of medications examined, definitions of studied pregnancy-related and offspring outcomes, types of control groups, and confounding adjustment. There was no convincing evidence for teratogenic effects according to the relative risk of pregnancy-related and offspring outcomes, and the observed differences in absolute risks were overall small in magnitude. Adjustment for confounding was inadequate in most studies, and none of the included studies adjusted for ADHD severity in the mothers.

Conclusion The current evidence does not suggest that the use of ADHD medication during pregnancy results in significant adverse consequences for mother or offspring. However, the data are too limited to make an unequivocal recommendation. Therefore, physicians should consider whether the advantages of using ADHD medication outweigh the potential risks for the developing fetus according to each woman's specific circumstances. Future research should attempt to triangulate research findings based on a combination of different designs that differ in their underlying strengths and limitations and should investigate specific confounding factors, the potential impact of timing of exposure, and potential long-term outcomes in the offspring.

1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting 5% of children and adolescents and about 2.5% of adults worldwide; it is well-established that impairing ADHD persists into adolescence and adulthood in many individuals [1, 2]. In particular, girls with ADHD in childhood have a substantial likelihood of also continuing to be diagnosed with ADHD in adulthood [3, 4]. Meta-analytic evidence from double-blind randomized controlled trials (RCTs) shows that stimulant ADHD medications are highly, and nonstimulants moderately, efficacious in the short term to reduce the core symptoms of ADHD in

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Key Points

Increasing numbers of reproductive-age women are using attention-deficit/hyperactivity disorder (ADHD) medications, but the safety of these medications during pregnancy remains unclear.

At present, the few available studies indicate that the absolute risks of adverse pregnancy-related and offspring outcomes associated with ADHD medication use during pregnancy are low. The studies, particularly the most methodologically rigorous studies, also suggest that there is no clear evidence to indicate that prenatal exposure to ADHD medication results in clinically significant adverse effects.

More studies are still needed to evaluate both the consequences of using ADHD medication during different specific pregnancy periods and the longer-term outcomes in offspring, with various study designs to adjust for confounding.

children, adolescents, and adults [5]. As with all medication and some nonpharmacological approaches, ADHD medications may be associated with adverse events, which in most cases can be managed without stopping the medication when effective [6]. The most recent ADHD treatment guideline was written by the National Institute for Health and Care Excellence (NICE) in the UK [7]. This guideline recommends methylphenidate as the first-line treatment, lisdexamfetamine or other amphetamines as second-line treatment, and atomoxetine or guanfacine (both nonstimulant medications) as third-line treatments for school-aged children and adolescents. In adults, methylphenidate or lisdexamfetamine (or other amphetamines) and atomoxetine are recommended as first- and second-line treatment, respectively. According to the updated ADHD guildline from American Academy of Pediatris (AAP), behavior therapy is recommended as the first-line treatment for preschoolers, while the combination therapy with both behavior therapy and medication treatment is recommended for elementary school-aged children (6–11 years of age) and preferred for adolescents (12–18 years of age) [8]. However, to our knowledge, there are no specific recommendations for adults with ADHD in the USA.

Appropriate treatment for ADHD is an important public health issue, as the disorder is associated with high rates of psychiatric [9, 10] and somatic [11, 12] comorbidity as well as increased risk for poor educational, occupational, and social outcomes [9, 13, 14]. A recent large, population-based study using prescription databases from 13 countries and one special administrative region identified a sharp increase in ADHD medication prescriptions during the last decade, though this varied substantially across countries [15]. Research has also found that the prescribing prevalence of ADHD medication has increased more rapidly among adults than among children and adolescents [16, 17], particularly in women [18]. A growing number of women, therefore, enter their reproductive years while receiving medication for ADHD or are diagnosed and start medication during their reproductive years.

Given these trends, there is a need to accurately understand the potential effects of maternal pharmacotherapy during pregnancy on pregnancy-related outcomes and offspring development. This need is particularly salient given the historical context of research on prenatal stimulant exposure. Amidst a period of increased cocaine (an illicit stimulant) use in the 1980s in the USA, preliminary research showing adverse birth outcomes led to dire predictions regarding the medical, behavioral, and social outcomes of the so-called crack babies [19–22]. However, subsequent research showed that such predictions were largely unfounded, as infants, children, and adolescents prenatally exposed to cocaine ultimately demonstrated physical development and cognitive and academic outcomes comparable to those in similar nonexposed youth [21, 23–25]. Studies that observed differences (e.g., behavioral and cognitive problems) generally indicated that potential causal effects of stimulant exposure are modest in magnitude [26, 27]. This broader historical context highlights that the current limited research on ADHD pharmacotherapy in pregnancy needs to be carefully reviewed in detail.

Fetal exposure to common ADHD medications in animals has shown limited evidence of adverse effects at or below the equivalent maximum recommended human dose (MRHD) on a mg/m^2 basis. In mice, methylphenidate was shown to pass the placenta with ensuing pharmacologically significant concentrations in the fetal brain [28]. Additionally, mice exposed to 5 mg/kg methylphenidate in utero had decreased anxiety-related behaviors and increased impulsivity and compulsivity [29, 30]. However, gestational exposure to methylphenidate in rats and rabbits at or below the MRHD did not demonstrate significant adverse effects in the exposed fetuses [31–33]. In contrast, pregnant rabbits given methylphenidate at 40 times the MRHD had an increased incidence of fetal spina bifida [33]. In pregnant rats given seven times the MRHD of methylphenidate, increased incidences of fetal skeletal variations and maternal toxicity were observed, and rats exposed to four times the MRHD had offspring with decreased body weight gain [33]. Additionally, offspring to pregnant rats treated with twice the MRHD during gestation displayed elevated expression of dopamine markers in the brain and decreased preference and motivation for sucrose [34]. Similar to methylphenidate, amphetamines have also been shown to pass the placenta in mice [35], and exposure to amphetamines in mice during gestation at doses 41 times the MRHD had embryotoxic and teratogenic effects [36]. Yet, no embryotoxic or teratogenic effects was observed in

rabbits given the drug at seven times the human dose [37] or in rats given 12.5 times the MRHD [38]. Atomoxetine and its metabolites were shown to pass the placenta in pregnant rats, although with substantially less exposure in fetal tissue than in maternal tissue [39]. According to unpublished data, atomoxetine at a dose approximately 23 times the MRHD reduced the rate of live births and increased resorption [40]. Thus, the existing animal literature suggests stimulant and nonstimulant ADHD medication well above MRHD is associated with adverse outcomes, but relatively few adverse effects have been documented at doses equivalent to MRHD.

In humans, observational studies have provided some information regarding the safety of ADHD medication use during pregnancy. The pooled estimates from a recent meta-analysis [41] of eight cohort studies demonstrated that exposure to ADHD medication during pregnancy was associated with an elevated risk of neonatal intensive care unit (NICU) admission but not of other adverse pregnancy-related and offspring outcomes. However, it is important to consider whether these findings could reflect a causal effect of prenatal ADHD medication exposure or, alternatively, systematic differences between exposed and unexposed pregnancies. In particular, observational treatment studies need to account for confounding by indication, that is, patients who are medicated are usually more symptomatic and have more comorbid conditions than those who are not on medication. Therefore, patients exposed and unexposed to a particular intervention or treatment might not be comparable, limiting the ability to draw causal inference. Providing a clear and comprehensive covariate selection is necessary for a better interpretation of the results from observational studies [42]. Consequently, it is important to evaluate the extent to which available observation studies have adjusted for the relevant confounders to block confounding by indication.

We could not find any specific clinical guidelines regarding the use of ADHD medication during pregnancy. The general guidance on the use of psychotropics in pregnancy from the British Association of Psychopharmacology (BAP) [43] highlights that data on the safety of ADHD medications used in the perinatal period are limited. The BAP recommends that the decision as to whether medication should be continued during pregnancy and breastfeeding, and the choice of medication, should be based on the general principles of the guidance. Therefore, there is a need for high-quality evidence to support guidelines for the use of ADHD medication during pregnancy.

We reviewed observational studies exploring associations between prescribed ADHD medication in pregnancy and pregnancy-related and offspring outcomes. To contribute to such evidence, this systematic review aimed to extend the previous meta-analysis [41] in four important ways. First, the present study appraised and synthesized the available evidence on the safety of ADHD medication use during pregnancy using qualitative methods with a focus on methodological considerations. Given the substantial heterogeneity across included studies regarding data sources, types of medications examined, definitions of pregnancy-related and offspring outcomes, and types of control groups, the results from the previous meta-analysis should be interpreted with great caution. Second, although the previous meta-analysis highlighted substantial variation in confounding adjustment across studies, we compared the confounding control strategies across studies and discuss the potential influences of confounding on the pooled estimates (e.g., confounding by indication via maternal ADHD). Third, we report absolute risks of outcomes (e.g., by calculating risk differences [RDs]), which is important for a better understanding of the real-world population effects of ADHD medications, instead of solely reporting relative risks. Finally, we highlight and discuss limitations related to control of potential confounders and provide directions for future studies to address these limitations, given the potential for confounding factors (whether measured, unmeasured, or unknown) to bias the estimates from observational studies.

2 Methods

2.1 Search Strategy and Selection of Studies

We applied the standard methodological guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement [44]. We systematically searched PubMed, Embase, PsycINFO, and Web of Science using a prespecified search strategy to identify all studies in humans published up to 1 July 2019, evaluating associations with ADHD medication use during pregnancy. Detailed information on the search terms and syntax for each database are reported in Table S1 in the electronic supplementary material (ESM). We did not impose any restrictions on language or date of publication. Two authors (LL and AS) also searched the reference lists of selected papers to retrieve any possible additional pertinent publications that could have been missed in the electronic search.

We included all pertinent observational studies on humans, including cohort studies, case–control studies, case-crossover studies, cross-sectional studies, and registry-based studies; studies including pregnant women of any age or from any setting; and studies evaluating any outcome, including both short- and long-term maternal and offspring outcomes. We excluded studies focused on illicit medication use, as well as reviews, books, guidelines, and case reports.

2.2 Data Extraction

The authors LL and AS extracted the data from the studies. Disagreements were resolved by consensus or, when necessary, by a third reviewer (HL). LL and AS extracted the following data from each study for the qualitative synthesis:

name of the first author; publication year; study country; data source and sample size; information on the main exposure, including specific ADHD medications, source of information, exposure window; information on exposure to other medications during pregnancy; outcomes assessed; information on confounder adjustment, including specific measured covariates included and the use of methods to adjust for unmeasured confounding; absolute RD; and main conclusion. Wang et al. [45] identified three types of data sources: administrative database/registry, ad hoc disease registry, and ad hoc clinical sample.

2.3 Assessment of Study Quality

The authors LL and AS used the Newcastle–Ottawa Scale (NOS) [46] to independently rate the quality of the included studies, and initial discrepancies were resolved by consensus. The NOS is a validated tool for evaluating the quality of observational studies and includes three categories to evaluate studies: selection (definition/representativeness of exposed subjects, selection of nonexposed subjects), comparability (controls or adjustment for confounding factors), and outcome (assessment of outcome, adequate nonresponse rate or follow-up time). A higher score on the NOS represents a higher-quality study, and the maximum score a study can receive is 9.

3 Results

Figure 1 shows the study selection process. Table S2 in the ESM presents a list of all excluded studies with reasons for exclusion. After removing duplicate records, LL and AS screened 1311 records by reviewing titles and abstracts, removing 1259 because they were not relevant, and then evaluated the full-text articles of the remaining 52 records in detail. Ultimately, our qualitative review included eight published research studies based on original data [47–54].

Table 1 shows the main characteristics of the eight included studies. All were cohort studies and were conducted across several countries: Denmark, Israel, Germany, England, Canada, the USA, Sweden, and Australia. Of the eight studies, seven (87.5%) obtained data from an administrative database/registry [47, 48, 50–54] and one (12.5%) obtained data from an ad hoc clinical sample [49]. Therefore, administrative databases/registries comprising large numbers of participants were the most commonly used data source for the studied associations. Of note, no research has studied ADHD medication use during pregnancy in developing

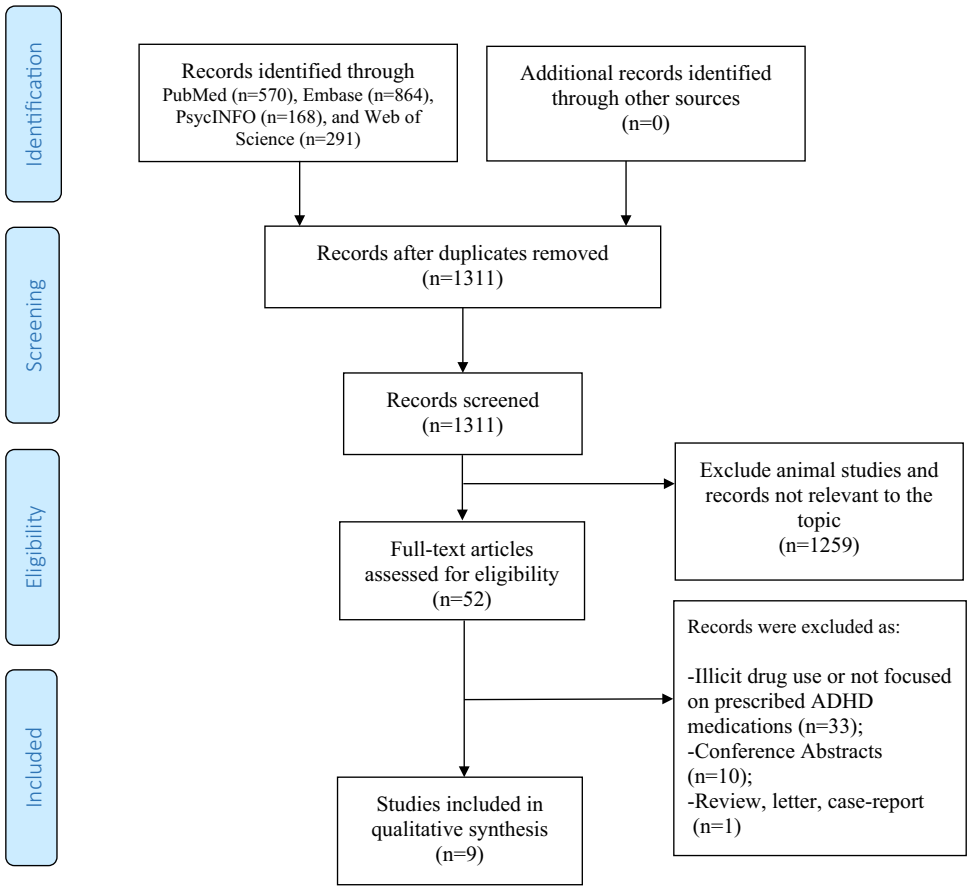

Fig. 1 PRISMA flow diagram for inclusion of the studies examining the association between ADHD medication use during pregnancy and outcomes in the offspring. *ADHD* attention-deficit/hyperactivity disorder, *PRISMA* Preferred Reporting Items for Systematic Review and Meta-Analyses

countries. All studies analyzed relatively large samples, ranging from approximately 700 to 2 million offspring. The exposure definitions varied across studies, and the prevalence of exposure ranged between 0.004 and 0.58%. The studies examined a variety of ADHD medications, including amphetamine, atomoxetine, dextroamphetamine, lisdexamfetamine, methylphenidate, and modafinil. Six studies defined exposure using prescription records [47, 48, 50, 51, 53, 54], one study defined exposure according to maternal reports of medication use [49], and one study defined exposure according to prescription records or maternal reports [52]. Five studies focused on exposure occurring anytime during pregnancy [47, 49, 50, 52, 54], and three studies focused on exposure occurring early in pregnancy only [48, 51, 53]. None of the identified studies evaluated exposure later in pregnancy specifically, nor did they consider variations in dosage or duration of exposure.

All studies accounted for confounding by adjusting for a number of measured characteristics. These characteristics varied widely across studies but included calendar year, pregnancy characteristics (e.g., parity), sociodemographic characteristics (e.g., age, region, ethnicity, educations), proxies for maternal healthcare utilization, maternal mental and physical health (e.g., psychiatric conditions, body mass index), maternal substance use (e.g., alcohol and nicotine), and maternal co-occurring medication use (see Table 2). Of particular importance, only one measured confounder was considered across all of the included studies (i.e., maternal age), and no study included maternal ADHD severity as a measured covariate.

Five of eight studies used alternative comparisons groups in addition to comparing exposed and unexposed pregnancies to rule out the influence of confounding [47, 48, 50, 52, 54]. Specifically, Hærvig et al. [50] compared exposed and unexposed pregnancies in the same woman (i.e., sibling comparison); Bro et al. [47] compared mothers with ADHD prescribed ADHD medications and mothers with ADHD but not prescribed ADHD medications; Cohen et al. [48] evaluated pregnancies exposed to stimulant ADHD medications compared with pregnancies exposed to atomoxetine (a nonstimulant ADHD medication); Nörby et al. [52] evaluated pregnancies with prescribed ADHD medication during pregnancy compared with those with prescribed ADHD medication before or after pregnancy only; and Poulton et al. [54] evaluated pregnancies with prescribed ADHD medication exposure before, during or after pregnancy compared with unexposed pregnancies.

The included studies evaluated associations with a wide variety of pregnancy outcomes, including pregnancy losses (miscarriages, stillbirths), pregnancy complications (e.g., preeclampsia, gestational diabetes, postpartum hemorrhage), and birth and neonatal outcomes (e.g., perinatal death, congenital malformations, birth weight, gestational age, Apgar score) (Table 1). No study evaluated associations with long-term outcomes.

Table 3 presents the RDs (i.e., difference in risk of an adverse outcome between an exposed and an unexposed group) of pregnancy-related and offspring outcomes in the ADHD medication-exposed group versus the reference group. The RDs for pregnancy complications, congenital malformations, and labor and delivery outcomes were overall small in magnitude, with a range from 0.03% for cardiovascular malformation to 9.84% for NICU admission (mean ± standard deviation 2.07 ± 2.33%). The relatively high risk for NICU admission might present a combination of the risk for a variety of pregnancy-related adverse outcomes, including preterm birth, low birth weight, and birth defects or a health condition requiring special care [55, 56]. The RDs were even smaller in the five studies [47, 48, 50, 52, 54] that used alternative comparisons groups to rule out the influence of unmeasured confounding (e.g., unexposed siblings). In these studies, RDs ranged from 0.01% for major malformation to 3.90% for cesarean delivery (mean 0.97 ± 1.02%).

The studies varied in quality, with NOS ratings ranging from 5 to 9. As shown in Table S3 in the ESM, all studies used well-defined exposures and outcomes with reasonable and strict selection criteria. However, most included studies with one or no star in "comparability" did not consider maternal ADHD and unmeasured factors (e.g., genetic factors) as potential confounders [48–54].

Regarding the relative risk (i.e., the ratio between the risk of an adverse outcome in exposed and unexposed groups), conflicting evidence was found for the association between maternal ADHD medication use during pregnancy and adverse pregnancy and offspring outcomes. Some studies suggested a small increased risk of low Apgar scores [47], preeclampsia [48], preterm birth [48], miscarriage [49, 50], cardiac malformations [51], admission to a NICU [52, 54], and central nervous system (CNS)-related disorder [52], but other available studies [47, 49, 52–54] failed to detect similar associations.

4 Discussion

4.1 Overall Summary

Large studies from several countries explored several important pregnancy-related outcomes. There is no conclusive evidence to support that ADHD medication use in pregnancy increases the risk of pregnancy-related and offspring outcomes. For example, the pooled estimates from a recent meta-analysis [41] of these studies only demonstrated a statistically significant association with NICU (relative risk 1.88; 95% confidence interval 1.70–2.08),

Table 1 Overview of cohort studies included in the systematic review

Study, country, data source (sample size)	Exposure	Co-medicine in different exposure groups	Adjusted for confounders	Outcomes and main conclusion	NOS
Hærvig et al. [50], Denmark, administrative database/registry (1,054,494)	Drugs: MPH 393 (0.04%), modafinil 45 (0.004%), ATX 42 (0.004%) Measurement: Redeemed prescriptions recorded in national prescription registry Time window: 28 days before first day of LMP to end of pregnancy	During pregnancy: anxiety medicine 27 (5.5%), SSRI 104 (21.7%) Before/after pregnancy: NA Nonexposure: anxiety medicine 7591 (0.7%), SSRI 21,129 (2.0%)	Measured: Age, region, ethnicity Unmeasured: compared exposed and unexposed pregnancies of same woman to account for unchanged factors between pregnancies: gene, early-life exposure	Outcomes: Abortion, miscarriage, stillbirth, congenital malformations Main conclusion: ADHD medication in pregnancy associated with different indicators of maternal disadvantage and increased risk of induced abortion and miscarriage	8
Pottegard et al. [53], Denmark, administrative database/registry (2442)	Drugs: MPH 222 (9.09%) Measurement: redeemed prescriptions recorded in national prescription registry Time window: 14 days before beginning of first trimester to end of first trimester	During pregnancy: antipsychotics 20 (9.0%), antidepressants 76 (34.2%), anxiolytics 6 (2.7%), NSAIDs 14 (6.3%) Before/after pregnancy: NA Nonexposure: antipsychotics 139 (6.3%), antidepressants 768 (34.6%), anxiolytics 58 (2.6%), NSAIDs 139 (6.3%)	Measured: Maternal age, smoking status, BMI, length of education, calendar year of completion of pregnancy, concomitant use of antipsychotics, antidepressants, anxiolytics, and NSAIDs Unmeasured: NA	Outcomes: Major malformations, cardiac malformations Main conclusion: First-trimester MPH exposure does not appear to be associated with a substantial increased risk of major congenital malformations	7
Bro et al. [47], Denmark, administrative database/registry (989,932)	Drugs: MPH/ATX 186 (0.02%) Measurement: Redeemed prescriptions recorded in national prescription registry Time window Spontaneous abortion: from 30 days before estimated day of conception to day before abortion or gestational age Live births, stillbirths: from 30 days before estimated day of conception until day before birth	During pregnancy: antipsychotics 17 (9.1%), antidepressants 57 (30.6%), antiepileptics 7 (3.8%) Before/after pregnancy: NA Nonexposure: antipsychotics 25 (9.1%), antidepressants 35 (12.7%), antiepileptics 10 (3.6%)	Measured: Maternal age, smoking, parity, education, cohabitation, comorbidity and comedication Unmeasured: Compared with women with ADHD who did not take MPH/ATX	Outcomes: Spontaneous abortion, birth weight, gestational age, small for gestational age, low birth weight, Apgar score < 10 Main conclusion: MPH/ATX was associated with a higher risk of SA, but results indicated that it may at least partly be explained by confounding by indication. MPH/ATX was associated with low Apgar scores, an association not found among women with ADHD who did not use MPH/ATX	9
Diav-Citrin et al. [49], Israel, Germany, England, Canada; ad hoc clinical sample (764)	Drugs: MPH 382 (50%) Measurement: Structured questionnaire administered to women who contacted teratology information services before outcome of pregnancy was known Time window: Conception to end of pregnancy	During pregnancy: NA Before/after pregnancy: NA Nonexposure: NA	Measured: Maternal age, gestational age, year at initial contact Unmeasured: NA	Outcomes: Major congenital anomalies, miscarriages and elective termination of pregnancy, preterm birth Main conclusion: MPH does not seem to increase the risk for major malformations. Further studies required to establish pregnancy safety and possible associations with miscarriages	5

Table 1 (continued)

Study, country, data source (sample size)	Exposure	Co-medicine in different exposure groups	Adjusted for confounders	Outcomes and main conclusion	NOS
Cohen et al. [48], USA, administrative database/registry (1,466,792)	Drugs: AMP/DEX 3331 (0.23%), MPH 1515 (0.10%), ATX 453 (0.03%) Measurement: Medicaid insurance prescription records Time window: LMP to LMP plus 140 days	During pregnancy: atypical antipsychotic 18,080 (1.2%), antidepressant 138,074 (9.5%), benzodiazepine 45,483 (3.1%), opioid 323,505 (22.1%), triptan 16,202 (1.1%), NSAID 244,501 (16.7%), acetaminophen 389,759 (26.7%), anticonvulsant or lithium 18,186 (1.2%) Before/after pregnancy: NA Nonexposure: atypical antipsychotic 876 (16.5%), antidepressant 2639 (49.8%), benzodiazepine 1063 (20.1%), opioid 2140 (40.4%), triptan 184 (3.5%), NSAID 1290 (24.3%), acetaminophen 2240 (42.3%), anticonvulsant or lithium 680 (12.8%)	Measured: Demographic characteristics, maternal and pregnancy characteristics, certain chronic conditions, indications for stimulants, other psychiatric and pain conditions, proxies for healthcare utilization intensity, and cotreatment with psychiatric and pain medication Unmeasured: ATX used as negative control exposure (ATX is a nonstimulant ADHD medication)	Outcomes: Preeclampsia, placental abruption, small for gestational age, preterm birth Main conclusion: Psychostimulant use during pregnancy associated with small increased relative risk of preeclampsia and preterm birth. The absolute increases in risks are small, so women with significant ADHD should not be counseled to suspend their ADHD treatment based on these findings	9
Nörby et al. [52], Sweden, administrative database/registry (964,734)	Drugs: MPH/AMP/DEX/LIS/modafinil/ATX 1591 (0.2%) Measurement: Self-reported use recorded in the medical birth register or filled prescription recorded in the prescribed drug register Time window: 1 month before pregnancy to end of pregnancy	During pregnancy: opioids 15.0%, antiepileptics 9.7%, psycholeptics 34.9%, antidepressants 31.8%, alimemazine 4.1%, promethazine 28.1% Before/after pregnancy: opioids 12.1%, antiepileptics 3.2%, psycholeptics 15.1%, antidepressants 20.0%, alimemazine 1.3%, promethazine 18.6% Nonexposure: opioids 4.4%, antiepileptics 0.5%, psycholeptics 2.3%, antidepressants 3.3%, alimemazine 0.1%, promethazine 7.7%	Measured: Year of birth, maternal age, primiparity, BMI, maternal smoking, noncohabitating with father, mother born outside Nordic countries, maternal use of opioids, antiepileptics, psycholeptics, antidepressants, alimemazine, or promethazine during pregnancy Unmeasured: compared with ADHD medication use before or after pregnancy	Outcomes: Gestational age, small for gestational age, large for gestational age, Apgar score < 7 at 5 min, birth defects, perinatal death, NICU admission, respiratory disorders, hyperbilirubinemia, hypoglycemia, feeding difficulties, CNS-related disorders, withdrawal symptoms for therapeutic drugs Main conclusion: ADHD medication during pregnancy associated with higher risk for neonatal morbidity, especially CNS-related disorders such as seizures. Large differences in background characteristics between treatment women and controls mean the extent to which this can be explained by the ADHD medication per se is unclear	8

Table 1 (continued)

Study, country, data source (sample size)	Exposure	Co-medicine in different exposure groups	Adjusted for confounders	Outcomes and main conclusion	NOS
Huybrechts et al. [51], USA, Nordic countries; administrative database/registry (1,813,894)	Drugs: MPH 2072 (0.11%), AMP/DEX 5571 (0.31%) Measurement: Medicaid insurance prescription records Time window: First 90 days of pregnancy	During pregnancy MPH exposed: anticonvulsants 302 (14.6%), antidepressants 1033 (49.9%), anxiolytics 43 (2.1%), antipsychotics 375 (18.1%), barbiturates 39 (1.9%), benzodiazepines 336 (16.2%), other hypnotics 245 (11.8%) AMP/DEX exposed: anticonvulsants 833 (15.0%), antidepressants 2537 (45.5%), anxiolytics 128 (2.3%), antipsychotics 749 (13.4%), barbiturates 130 (2.3%), benzodiazepines 1315 (23.6%), other hypnotics 678 (12.2%) Before/after pregnancy: NA Nonexposure: anticonvulsants 35,644 (2.0%), antidepressants 155,155 (8.6%), anxiolytics 7187 (0.4%), antipsychotics 22,661 (1.3%), barbiturates 18,023 (1.0%), benzodiazepines 54,893 (3.1%), other hypnotics: 63,265 (3.5%)	Measured: Demographic characteristics, obstetric characteristics, psychiatric conditions, chronic comorbid medical conditions, markers of general comorbidity, and prescribed medications Unmeasured: NA	Outcomes: Major congenital malformations, cardiac malformations Main conclusion: Findings suggest a small increase in risk of cardiac malformations associated with intrauterine exposure to MPH but not to amphetamines. This information is important when weighing risks and benefits of alternative treatment strategies for ADHD disorders in women of reproductive age and during early pregnancy	

Table 1 (continued)

Study, country, data source (sample size)	Exposure	Co-medicine in different exposure groups	Adjusted for confounders	Outcomes and main conclusion	NOS
Poulton et al. [54], Australia, administrative database/registry (30,305)	Drugs: MPH/DEX 175 (0.58% for ADHD medication) Measurement: Prescription records in pharmaceutical drugs of addiction system Time window: 1 year before expected delivery date	During pregnancy: NA Before/after pregnancy: NA Nonexposure: NA	Measured: Maternal age, infant year of birth, preexisting diabetes mellitus, preexisting hypertension, smoking, parity, multiple pregnancy Unmeasured: Compared with women treated before or after pregnancy	Outcomes: Gestational diabetes, instrumental vaginal delivery, postpartum hemorrhage, birthweight < 2500 g, birthweight > 4000 g, 5-min Apgar < 7, perinatal death, spontaneous labor onset, cesarean delivery, active resuscitation, neonatal admission > 4 h, preeclampsia, preterm birth, 1-min Apgar < 7 Main conclusion: Compared with no treatment, ADHD stimulant treatment at any time was associated with small increases in risk of some adverse pregnancy outcomes; treatment before, or before and during pregnancy, associated with additional adverse outcomes, even after a treatment-free period of several years. None of these associations can be confidently attributed to stimulant treatment; in all cases, ADHD per se or correlates of it could be responsible for the association	8

ADHD attention-deficit/hyperactivity disorder, *AMP* amphetamine, *ATX* atomoxetine, *BMI* body mass index, *CNS* central nervous system, *DEX* dextroamphetamine, *LIS* lisdexamfetamine, *LMP* last menstrual period, *MPH* methylphenidate, *NA* not available, *NICU* neonatal intensive care unit, *NOS* Newcastle–Ottawa Scale, *NSAID* nonsteroidal anti-inflammatory drug, *SA* spontaneous abortion, *SSRI* selective serotonin reuptake inhibitor

Table 2 Confounders and risk factors evaluated in studies of included studies

Variables	Hærvig et al. [50]	Pottegard et al. [53]	Bro et al. [47]	Diav-Citrin et al. [49]	Cohen et al. [48]	Nörby et al. [52]	Huybrechts et al. [51]	Poulton et al. [54]
Maternal age	×	×	×	×	×	×	×	×
Region	×				×	×		
Ethnicity	×	×			×		×	
Education		×	×					
BMI		×			×	×		
Cohabitation			×			×		
Year of conception					×			
Year of delivery						×	×	×
Year at initial contact				×				
Gestational age				×				
Parity/multiparty			×		×	×	×	×
Multifetal pregnancy					×		×	×
Smoking status		×	×		×	×		×
Alcohol use					×			
Other drug abuse or dependence					×	×		
Psychiatric conditions			×		×		×	
Chronic comorbid medical conditions			×		×		×	×
Marker of general comorbidity					×		×	
Prescribed medications/co-medications		×	×		×	×	×	
Proxies for healthcare utilization intensity					×			

BMI body mass index

with only two studies contributing to the pooled estimates. The results of the current study demonstrate that the absolute RDs were overall small in magnitude, particularly for studies using alternative comparisons groups to rule out confounding. Further, because of the limited number of studies and control for confounding, it is currently unclear whether these small associations are due to a causal effect of prenatal exposure to ADHD medication or confounding. Moreover, no study evaluated associations with long-term offspring outcomes. Given the absence of scientific evidence, physicians should weigh the advantages of using ADHD medication against the potential risks for the developing fetus offspring according to the unique situation of each pregnant woman or woman of childbearing age.

4.2 Methodological Considerations

Several noncausal pathways could account for observed associations between maternal ADHD medication use during pregnancy and pregnancy-related and offspring outcomes. Given that RCTs of ADHD medication use during pregnancy are unfeasible, any advances in our knowledge of the potential risks and benefits needs to rely on evidence from observational studies. The findings of the current systematic review highlight two methodological considerations that need to be addressed in future observational studies.

First, although all individual studies included in this systematic review accounted for confounding by adjusting for measured characteristics in the regression models, the included confounding factors varied substantially across studies, and few studies provided a clear rationale for their covariate selection. In addition, inadequate adjustment for confounding was found in most studies, and none of the included studies adjusted for ADHD severity, which is known to be related to co-occurring conditions and widely varying courses of treatment [57]. Because of these limitations, it is currently unclear whether any of the observed associations reflect a causal effect or confounding. Clearly, more research is needed, and future studies should use well-designed measured confounding selection strategies to identify all relevant confounding, which would be consistent with recent methodological recommendations for observational studies [58].

Second, only five of eight included studies used methods that target unmeasured confounding factors [47, 48, 50, 52, 54]. Sibling comparisons is a widely used family-based quasi-experimental design, especially in studies of associations between prenatal exposures and later health outcomes

Table 3 Risk difference of maternal and neonatal outcomes in the attention-deficit/hyperactivity disorder medication-exposed group versus the reference group

Outcomes	Study	No exposure (*A*)		Exposure during pregnancy (*B*)		Alternative comparison groups (*C*)		RD (*B* − *A*), %	RD (*C* − *A*), %
		N	*N* (%) with outcome	*N*	*N* (%) with outcome	*N*	*N* (%) with outcome		
Pregnancy complications									
Preeclampsia	Cohen et al. [48]	1,461,493	54,467 (3.73)	4846	256 (5.28)	453	22 (4.86)[a]	1.55	1.13
	Poulton et al. [54]	25,249	1509 (5.98)	175	13 (7.43)	4881	311 (6.37)[b]	1.45	0.39
Diabetes	Poulton et al. [54]	25,249	817 (3.24)	175	4 (2.29)	4881	122 (2.50)[b]	− 0.95	− 0.74
Postpartum hemorrhage	Poulton et al. [54]	10,749	169 (1.57)	78	2 (2.56)	2073	35 (1.69)[b]	0.99	0.12
Placental abruption	Cohen et al. [48]	1,461,493	20,676 (1.41)	4846	88 (1.82)	453	11 (2.42)[a]	0.41	1.01
Labor and delivery outcomes									
Spontaneous abortion	Hærvig et al. [50]	1,054,014	114,389 (10.86)	480	54 (11.25)	706	83 (11.76)[c]	0.39	0.90
	Bro et al. [47]	989,471	114,672 (11.59)	186	18 (9.67)	275	26 (9.45)[d]	− 1.92	− 2.14
	Diav-Citrin et al. [49]	382	27 (7.07)	383	54 (14.10)	–	–	7.03	–
Instrumental vaginal delivery	Poulton et al. [54]	25,225	3677 (14.57)	175	31 (17.71)	4878	692 (14.19)[b]	3.14	− 0.38
Cesarean delivery	Poulton et al. [54]	25,237	5564 (22.04)	175	52 (29.71)	4880	1266 (25.94)[b]	7.67	3.90
Active neonatal resuscitation	Poulton et al. [54]	20,750	1683 (8.11)	159	21 (13.21)	3992	394 (9.87)[b]	5.10	1.76
Preterm birth/gestational age	Bro et al. [47]	989,471	34,211 (3.46)	186	3 (1.61)	275	10 (3.64)[d]	− 1.85	0.18
	Diav-Citrin et al. [49]	343	23 (6.71)	293	26 (8.87)	–	–	2.16	–
	Cohen et al. [48]	1,461,493	163,772 (11.21)	4846	635 (13.10)	453	56 (12.36)[a]	1.89	1.15
	Nörby et al. [52]	953,668	52,182 (5.47)	1591	144 (9.05)	9475	682 (7.20)[e]	3.58	1.73
	Poulton et al. [54]	25,245	1832 (7.26)	175	19 (10.86)	4880	403 (8.26)[b]	3.60	1.00
Low birth weight	Bro et al. [47]	989,471	23,691 (2.39)	186	1 (1.98)	275	8 (2.90)[d]	− 0.41	0.51
	Poulton et al. [54]	25,235	1676 (6.64)	175	20 (11.43)	4873	353 (7.24)[b]	4.79	0.60
Small for gestational age	Bro et al. [47]	989,471	65,499 (6.62)	186	4 (2.15)	275	18 (6.55)[d]	− 4.47	− 0.07
	Cohen et al. [48]	1,451,493	42,526 (2.92)	4846	178 (3.67)	453	20 (4.42)[a]	0.75	1.46
	Nörby et al. [52]	953,668	21,789 (2.28)	1591	43 (2.70)	9475	222 (2.34)[e]	0.42	0.06
Large for gestational age	Nörby et al. [52]	953,668	39,273 (4.11)	1591	78 (4.90)	9475	422 (4.50)[e]	0.79	0.39
High birth weight	Poulton et al. [54]	25,235	2539 (10.06)	175	20 (11.43)	4873	481 (9.87)[b]	1.37	− 0.19
Low Apgar scores	Bro et al. [47]	989,471	50,184 (5.07)	186	8 (4.30)	275	8 (2.91)[d]	− 0.77	− 2.16
	Nörby et al. [52]	953,668	12,592 (1.32)	1591	38 (2.38)	9475	177 (1.86)[e]	1.06	0.54
	Poulton et al. [54]	25,179	640 (2.54)	174	5 (2.87)	4767	133 (2.79)[b]	0.33	0.25
Stillbirth/perinatal death	Hærvig et al. [50]	1,054,014	3677 (0.35)	480	2 (0.42)	706	1 (0.14)[c]	0.07	− 0.21
	Bro et al. [47]	989,471	3517 (0.36)	186	0	275	1 (0.04)[d]	− 0.36	− 0.32
	Nörby et al. [52]	953,668	4268 (0.45)	1591	8 (0.50)	9475	38 (0.41)[e]	0.05	− 0.04
	Poulton et al. [54]	25,233	233 (0.92)	175	2 (1.14)	4870	47 (0.97)[b]	0.22	0.05
NICU admission	Nörby et al. [52]	953,668	79,530 (8.34)	1591	259 (16.27)	9475	1105 (11.66)[e]	7.93	3.32
	Poulton et al. [54]	25,239	4305 (17.06)	175	47 (26.9)	4879	1019 (20.89)[b]	9.84	3.83

Table 3 (continued)

Outcomes	Study	No exposure (*A*)		Exposure during pregnancy (*B*)		Alternative comparison groups (*C*)		RD (*B* − *A*), %	RD (*C* − *A*), %
		N	*N* (%) with outcome	*N*	*N* (%) with outcome	*N*	*N* (%) with outcome		
Congenital malformations									
Major malformation	Hærvig et al. [50]	1,054,014	41,238 (3.91)	480	3 (0.63)	–	–	− 3.28	–
	Pottegard et al. [53]	2220	86 (3.87)	222	7 (3.15)	–	–	− 0.72	–
	Bro et al. [47]	989,471	39,557 (4.00)	186	2 (1.08)	275	7 (2.55)[d]	− 2.92	1.45
	Diav-Citrin et al. [49]	358	13 (3.6)	309	10 (3.23)	–	–	− 0.41	–
	Nörby et al. [52]	953,668	20,736 (2.17)	1591	48 (3.02)	9475	205 (2.16)[e]	0.85	− 0.01
	Huybrechts et al. [51]	1,797,938	62,966 (3.50)	7643	348 (4.55)	–	–	1.05	–
Cardiovascular malformation	Pottegard et al. [53]	2220	32 (1.44)	222	3 (1.35)	–	–	− 0.09	–
	Diav-Citrin et al. [49]	358	3 (0.84)	247	2 (0.81)	–	–	− 0.03	–
	Huybrechts et al. [51]	1,797,938	22,910 (1.27)	7643	125 (1.63)	–	–	0.36	–
Other perinatal morbidity among infants									
Respiratory disorders	Nörby et al. [52]	953,668	35,479 (3.72)	1591	92 (5.78)	9475	511 (5.39)[e]	2.06	1.67
Hyperbilirubinemia	Nörby et al. [52]	953,668	42,948 (4.50)	1591	91 (5.71)	9475	511 (5.39)[e]	1.21	0.89
Hypoglycemia	Nörby et al. [52]	953,668	23,965 (2.51)	1591	66 (4.15)	9475	326 (3.44)[e]	1.64	0.93
Feeding difficulties	Nörby et al. [52]	953,668	9837 (1.03)	1591	34 (2.14)	9475	130 (1.37)[e]	1.11	0.34
CNS-related disorders	Nörby et al. [52]	953,668	2885 (0.30)	1591	16 (1.01)	9475	40 (0.42)[e]	0.71	0.12
Withdrawal symptoms for therapeutic drugs	Nörby et al. [52]	953,668	124 (0.01)	1591	7 (0.44)	9475	10 (0.11)[e]	0.43	0.10

ADHD attention-deficit/hyperactivity disorder, *CNS* central nervous system, *NICU* neonatal intensive care unit, *RD* risk difference

[a]Alternative comparison groups including women exposed to atomoxetine (a nonstimulant ADHD medication) during pregnancy

[b]Alternative comparison groups including women who used ADHD medication before or after pregnancy

[c]Alternative comparison groups including women with discordant exposure to ADHD medication across pregnancies

[d]Alternative comparison groups including women diagnosed with ADHD who did not take ADHD medications

[e]Alternative comparison groups including women who used ADHD medication before or after pregnancy only

[59, 60]. Siblings share approximately 50% of their segregating genes and often have similar early-life environments. A contrast of siblings discordant for prenatal ADHD medication use automatically accounts for genetic and environmental factors shared by siblings [61]. One sibling-comparison study [50] examined the associations between ADHD medication use during pregnancy and the risk of miscarriage, suggesting that confounding by familial factors could account for the associations observed in the studied population. However, because only a small portion ($n = 706$) of all observed pregnancies ($n = 1{,}054{,}494$) contributed to the main information in these analyses (i.e., siblings discordant for both maternal ADHD medication exposure and studied outcomes are most informative in the sibling comparisons), the findings should be interpreted with caution. In addition to the substantial reduction in sample size and statistical power and the high attenuation of associations due to random measurement error, sibling comparisons do not by design account for factors that vary across pregnancies, which must be considered, as their confounding influence will be inflated when comparison is restricted to exposure discordant siblings. Sibling-comparison studies also assume no carryover effects [62] from the exposed siblings (ADHD medication use during pregnancy) to unexposed siblings (without ADHD medication during other pregnancies). More sibling-comparison studies from different countries, with larger samples, and focusing on other perinatal and long-term outcomes are still needed to replicate and extend the available evidence.

The timing of exposure design compares offspring outcomes following maternal ADHD medication use before or after pregnancy with those following maternal ADHD medication use during pregnancy. This design accounts for confounding factors shared by women who are prescribed ADHD medication around the time of pregnancy. Observing similar risk of outcomes across different exposure time periods before, during, and after the pregnancy is inconsistent with a causal hypothesis, as treatment before or after pregnancy but not during pregnancy is unlikely to have a specific intrauterine influence [63]. Nörby et al. [52] reported somewhat increased risks for NICU admissions, CNS-related disorders, and preterm birth in offspring exposed to maternal ADHD medication during pregnancy compared with both nonexposed infants and those born to mothers who took ADHD medication before or after pregnancy. However, Poulton et al. [54] found that treatment for ADHD at any time (before, before and during, or only after the index pregnancy) was similarly associated with a somewhat increased risk of cesarean delivery, neonatal resuscitation, and NICU admission. Poulton et al. [54] did not directly evaluate use during pregnancy compared with use before or after pregnancy, so the study had limited ability to assess whether ADHD medication use during pregnancy had an effect over and above indications for ADHD treatment around the time of pregnancy. The main limitations of the timing of exposure design are that preconception exposure is assumed to have no intrauterine influence, and some important confounding factors (e.g., severity of the underlying condition) are not automatically adjusted for by the design. More studies are needed to examine associations with exposure during specific trimesters rather than using a broad measure covering exposure during any time point across the pregnancy period.

Restricting the analyses to the target patient group with or without treatment is often used as a strategy to evaluate associations between treatments and outcomes; the approach targets confounding by indication by directly accounting for the underlying condition. Bro et al. [47] examined the rate of adverse pregnancy outcomes after exposure to ADHD medication during pregnancy compared with unmedicated women diagnosed with ADHD. This study found a small increased risk of spontaneous abortion in both treated and untreated women, whereas an increased risk of low Apgar score was only found in those exposed to ADHD medication during pregnancy. It is important to note that Bro et al. [47] did not directly compare exposed pregnancies and those with ADHD diagnosis but without prescribed ADHD medications, indicating that the study had a limited ability to disentangle the effects of the medication from the effects of the underlying disease. A major limitation of this design is that treated and nontreated individuals typically differ on measures of severity and in their comorbidity profiles, meaning that confounding by indication remains a serious threat to validity in the design.

The active comparator design compares the effect of the target medication with another active drug used in clinical practice for the same underlying condition. The purpose of the design is to mitigate confounding by indication and other unmeasured patient characteristics (e.g., healthy initiator, frailty). One study [48] evaluated the safety of psychostimulant (amphetamine, dextroamphetamine) use during pregnancy by using atomoxetine, a nonstimulant ADHD medication, as an active comparator. The study found that psychostimulant use during pregnancy was associated with a small increased risk of preeclampsia and preterm birth compared with atomoxetine use during pregnancy. This finding suggests that previously observed associations between maternal psychostimulant use during pregnancy and risk of adverse pregnancy outcomes were not solely due to confounding by factors associated with taking either medication. The main limitation of the design is that the interpretation of results rested on the assumption that there are no unmeasured factors that differentiate the different study drug initiators. For future studies, it is important to note that the baseline characteristics of the two treatment groups should be balanced, by using the same approaches to covariate selection, or choosing an appropriate active comparator

group receiving a drug with the same or a similar indication makes the treatment groups similar in terms of treatment indications [64].

No previous study has used paternal ADHD medication use as a negative control to explore the role of unmeasured confounding. The negative control design examines the impact of unmeasured confounding by comparing the associations with outcomes separately for maternal ADHD medication using during pregnancy and paternal ADHD medication use during the same pregnancy period. It is based on the assumptions that there is no direct association between the father's exposure during the pregnancy period and the child's outcome and that the shared confounders are equally associated with the mother's and the father's exposures [65]. Any observed association between paternal medication use and offspring outcomes could be taken to suggest that an observed association between maternal medication use and offspring outcome is influenced by confounding to some extent. Several paternal comparison studies [65–68] have examined the associations between paternal antidepressant use during the pregnancy period and risk of autism spectrum disorder (ASD) or ADHD in offspring. Most of these studies, including a meta-analysis [68], reported positive associations, which indicates that the observed associations between maternal antidepressant use during pregnancy and risk of ASD or ADHD in offspring are at least partly due to familial confounding.

Obviously, because the above-mentioned study designs are reliant upon varying assumptions, each has the potential to address differing sources of confounding to differing extents. Given that none of them is likely to completely eliminate bias from confounding, future efforts should attempt to triangulate research findings based on a combination of different designs that differ in their underlying assumptions and limitations [69].

4.3 Current Knowledge Gaps

A number of significant research questions related to the risks and benefits of maternal ADHD medication use during pregnancy need to be addressed in future research. First, rodent studies suggested dose-dependent associations between fetal exposure to common ADHD medications and adverse outcomes in offspring. Future human studies should also explore whether the associations observed in humans depend on dose. Second, the available studies used administrative data or register-based data from Europe and the USA. Similar data are also available in Asian countries [70, 71], and these data should be used in future research to test for generalizability of findings regarding the safety of ADHD medication use during pregnancy. Third, several studies used methods that helped account for unmeasured confounding in combination with measured covariates to study ADHD medication use during pregnancy and pregnancy-related and offspring outcomes, but whether observed associations in these studies are causal remains unclear, which requires studies that more rigorously account for confounding. Fourth, future research is needed to further elucidate the long-term impact of ADHD medication use during pregnancy on offspring, including neurodevelopmental delays and children's long-term psychosocial health. The fetal origins hypothesis [72] proposes that the period of gestation has significant impacts on the developmental health and wellbeing outcomes for an individual, ranging from infancy to adulthood, but there are no studies of the long-term associations with ADHD medication exposure during pregnancy. Fifth, more studies need to assess whether some periods during pregnancy are particularly sensitive. Most studies used measures of ADHD medication exposures that did not tap into specific periods during pregnancy, which is potentially problematic given that some research indicates that exposure during early pregnancy (first trimester or first 90 days of pregnancy) may be more harmful because of the immaturity of the blood–brain barrier [73]. Exposure during the second and third trimester may also be important to consider given that these are sensitive periods for fetal growth and brain development [74]. Clearly, more studies evaluating the implications of ADHD medication use during specific pregnancy periods are still needed.

4.4 Clinical Implications

The current systematic review extends the findings from previous studies by documenting relatively small absolute risks associated with ADHD medication during pregnancy for pregnancy-related and offspring outcomes, along with considerable heterogeneity in the quality (e.g., adjustment for confounding) of the extant literature. Women with ADHD appear to be at a slightly higher risk of adverse pregnancy outcomes regardless of current medication status, highlighting a need for increased obstetric surveillance in this group. There is no solid evidence that ceasing medication during pregnancy reduces the risk of adverse outcomes. More research is needed to provide clear recommendations for updated guidelines regarding the use of ADHD medication in pregnancy. Decisions about whether to continue medication in pregnancy should be made case by case, weighing the need for medication for daily life functioning against the slightly increased risk of adverse pregnancy outcomes.

5 Conclusions

This systematic review suggests that there is no convincing evidence to indicate that prenatal exposure to ADHD medication results in clinically significant adverse effects. However, more research is needed before solid clinical recommendations can be made. In particular, research needs to seek converging evidence from studies using a variety of samples and designs with different strengths and limitations. Moreover, future research needs to assess the potential impact of timing of exposure and potential long-term outcomes in the offspring.

Compliance with Ethical Standards

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Conflict of interest HL has served as a speaker for Evolan Pharma and Shire and has received research grants from Shire, all outside the submitted work. SC has received honoraria and reimbursement of travel and accommodation expenses for lectures from the nonprofit associations Association for Child and Adolescent Central Health, Canadian ADHD Alliance Resource (CADDRA), and BAP and from Healthcare Convention for educational activity on ADHD. BD has received reimbursement of travel and accommodation expenses for CADDRA and Children and Adults with Attention-Deficit/Hyperactivity Disorder. LL, ACS, AB, ZC, PQ, AV, and ASÖ have no conflicts of interest that are directly relevant to the content of this article.

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