Perinatal Outcomes After Treatment With ADHD Medication During Pregnancy

Ulrika Nörby, MSc Pharm, PhD,[a,b] Birger Winbladh, MD, PhD,[c] Karin Källén, PhD[a]

abstract

OBJECTIVES: To analyze perinatal outcomes after maternal use of attention-deficit/hyperactivity disorder (ADHD) medication during pregnancy.

METHODS: The study included singletons born between 2006 and 2014 in Sweden. Data on prescription drug use, pregnancies, deliveries, and the newborn infants' health were obtained from the Swedish Medical Birth Register, the Prescribed Drug Register, and the Swedish Neonatal Quality Register. We compared infants exposed to ADHD medication during pregnancy with infants whose mothers never used these drugs and infants whose mothers used ADHD medication before or after pregnancy. Analyses were performed with logistic regression.

RESULTS: Among 964 734 infants, 1591 (0.2%) were exposed to ADHD medication during pregnancy and 9475 (1.0%) had mothers treated before or after pregnancy. Exposure during pregnancy increased the risk for admission to a NICU compared with both no use and use before or after pregnancy (adjusted odds ratio [aOR], 1.5; 95% confidence interval [CI], 1.3–1.7; and aOR, 1.2; 95% CI, 1.1–1.4, respectively). Infants exposed during pregnancy had more often central nervous system–related disorders (aOR, 1.9; 95% CI, 1.1–3.1) and were more often moderately preterm (aOR, 1.3; 95% CI, 1.1–1.6) than nonexposed infants. There was no increased risk for congenital malformations or perinatal death.

CONCLUSIONS: Treatment with ADHD medication during pregnancy was associated with a higher risk for neonatal morbidity, especially central nervous system–related disorders such as seizures. Because of large differences in background characteristics between treated women and controls, it is uncertain to what extent this can be explained by the ADHD medication per se.

[a]*Centre of Reproduction Epidemiology, Tornblad Institute, Department of Clinical Sciences, Lund University, Lund, Sweden;* [b]*Department of E-health and Strategic IT, Health and Medical Care Administration, Stockholm County Council, Stockholm, Sweden; and* [c]*Department of Clinical Sciences and Education, Karolinska Institutet and Sachs' Children's and Youth Hospital, Stockholm, Sweden*

Dr Nörby planned and designed the study and drafted the initial manuscript; Dr Källén planned and designed the study, was responsible for the data collection and the statistical analysis, and reviewed and revised the manuscript; Dr Winbladh acted as scientific advisor during all stages of the study process and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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Address correspondence to Ulrika Nörby, MSc Pharm, PhD, Department of E-health and Strategic IT, Health and Medical Care Administration, Stockholm County Council, PO Box 17533, SE-118 91 Stockholm, Sweden. E-mail: ulrika.norby@sll.se

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WHAT'S KNOWN ON THIS SUBJECT: The use of medications for treatment of attention-deficit/hyperactivity disorder has increased rapidly during the last decade, including among pregnant women. Until now, the knowledge concerning the fetal safety of these drugs is limited, especially regarding neonatal symptoms.

WHAT THIS STUDY ADDS: Infants exposed to attention-deficit/hyperactivity disorder medication in utero had an increased risk for preterm birth, admission to a NICU, and central nervous system–related disorders. There was no association between the exposure and congenital malformations, after adjustment for maternal factors.

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The use of attention-deficit/hyperactivity disorder (ADHD) medication has increased rapidly during the last 10 years, both in the general population and among pregnant women.[1–4] In the United States, ~1% of pregnant women use drugs for treatment of ADHD, which ranks these medications among the most commonly used prescription drugs during pregnancy.[4] Until now, data concerning fetal safety of ADHD drugs are limited, especially when it comes to neonatal disorders.[1,5–8]

Stimulant drugs (mainly methylphenidate and different amphetamine products) are the first-line pharmacological treatments of ADHD.[3,9,10] Methylphenidate has not been linked to an increased rate of congenital malformations[5,7,8] but has been associated with a higher risk for miscarriage and low Apgar scores.[1,6]

For amphetamine, it is difficult to evaluate existing data because most studies were undertaken among pregnant women with illicit drug use or who used amphetamine as an anorectic drug.[11,12] However, amphetamine does not seem to increase the risk of structural malformations,[13,14] although authors of a few human studies report a higher rate of some birth defects.[15–17] An association has been found, however, with low birth weight, preterm birth, smaller head circumference, and problems in the newborn infant like poor feeding, tachypnea, and lethargy.[11,18–23]

There is sparse information regarding fetal effects for the nonstimulant ADHD drug atomoxetine. The substance is a presynaptic inhibitor of noradrenaline reuptake, and theoretically it might cause similar effects as antidepressant drugs (for example, neonatal adaption problems).[24]

In this study, we aimed to increase the knowledge concerning perinatal outcomes after in utero exposure to prescribed ADHD medication by analyzing data on a population level from Swedish health and neonatal quality registers. To be able to adjust for the impact of the ADHD condition per se, infants exposed during pregnancy were compared with infants whose mothers used ADHD medication before or after the pregnancy in addition to the general population.

METHODS

Data Sources and Study Population

Data were obtained from 4 registers in Sweden: the Medical Birth Register (MBR),[25] the Prescribed Drug Register (PDR),[26] the Swedish Neonatal Quality Register (SNQ),[27] and the Perinatal Revision South Register (PRS).[28] We identified singleton births recorded in the MBR between July 1, 2006, and December 31, 2014. Linkage from the MBR to the other registers was achieved via Swedish personal identification numbers, which are assigned to each resident in the country. The study design is displayed in Fig 1.

The MBR comprises data on antenatal care, delivery, and pediatric examination of the newborn infant for >97% of all births in Sweden.[25] At the initial visit at the antenatal clinic, which in 90% of the cases takes place in the first trimester,[25] the pregnant woman is interviewed by a midwife. Data are collected on the woman's family situation, previous pregnancies, weight, height, smoking habits and medication use. Furthermore, the MBR includes information on gestational length, birth weight, Apgar scores, congenital malformations, and neonatal diagnoses from delivery and neonatal records. Gestational age (GA) is in >95% of the pregnancies in Sweden, based on ultrasound estimation.[29] Congenital malformations and other neonatal diagnoses are coded in the MBR according to the *International Classification of Diseases, 10th Revision* (ICD-10). The data are reported from the clinics to the MBR no later than 1 month after the birth of the child.

In the PDR, data are stored on all prescription drugs dispensed at Swedish pharmacies.[26] Substance, brand name, formulation, and date of dispensing are recorded. The register does not include drugs used for inpatient care in hospitals. In both the PDR and MBR, drug exposure is classified per the Anatomical Therapeutic Chemical Classification System.

The neonatal quality registers SNQ[27] and PRS[28] contain detailed information on infants admitted to NICUs at birth or within the first 28 days of life. They cover the infants' diagnoses, duration of stay, and treatment. Since 2012, the SNQ includes all 37 NICUs in Sweden. Before that, information on neonatal care for the south region in Sweden was only recorded in the PRS. The diagnoses in the SNQ and PRS are registered as ICD-10 codes or via checkboxes in the infant's medical records.

Drug Exposure

We collected information on drug exposure from the MBR and PDR. The following drugs for treatment of ADHD were analyzed (Anatomical Therapeutic Chemical codes are shown in parentheses): the stimulant substances methylphenidate (N06BA04), amphetamine (N06BA01), dexamphetamine (N06BA02), lisdexamfetamine (N06BA12), modafinil (N06BA07), and the nonstimulant substance atomoxetine (N06BA09). The use of ADHD medication was allocated into 3 categories: use during pregnancy (self-reported use according to the MBR and/or registered in the PDR during pregnancy or 1 month before), use but not during pregnancy (ADHD medication registered in the PDR anytime during the study period, except during the interval 1 month

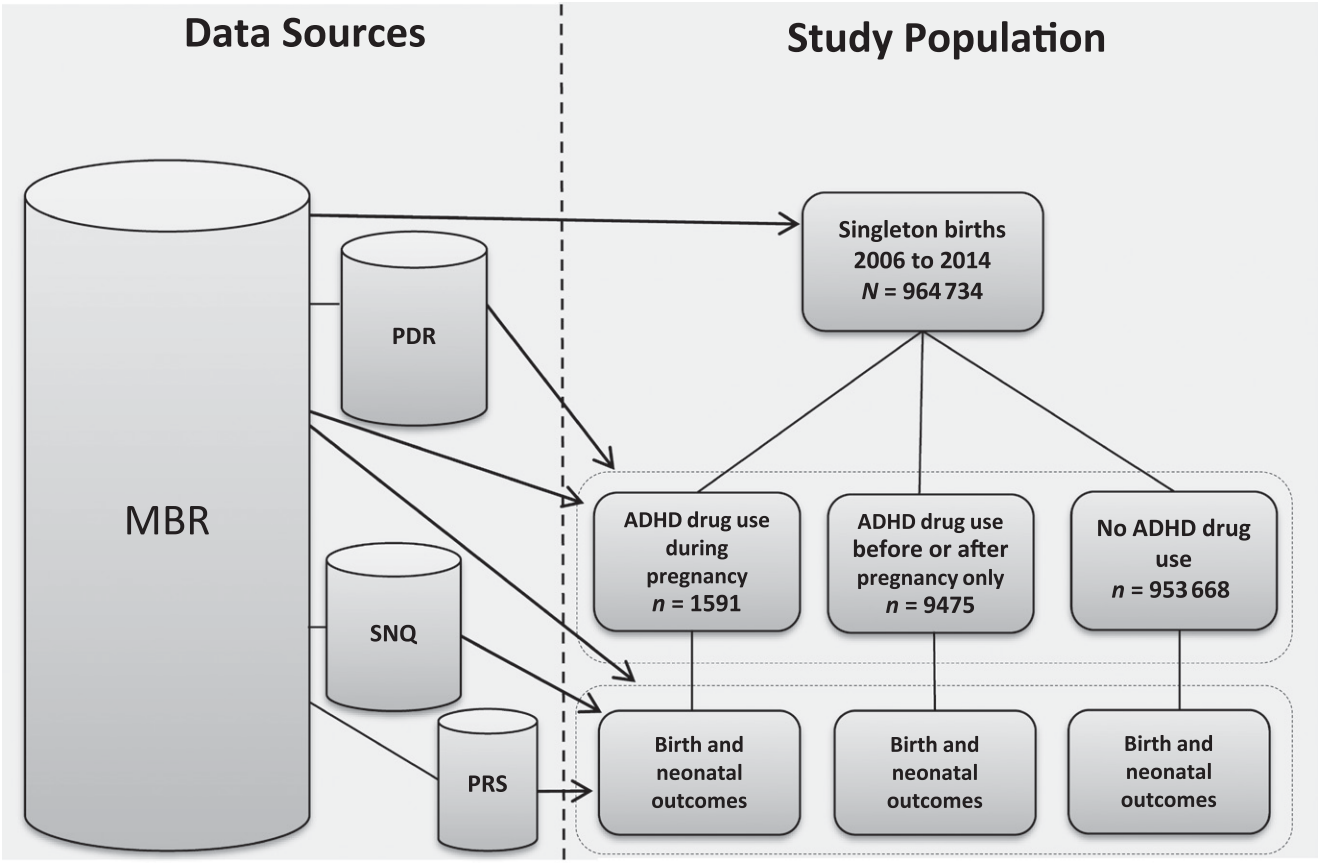

FIGURE 1
Flowchart of data sources and study design.

before pregnancy until delivery); and no use (no records of ADHD medication).

We also obtained information on the use of antiepileptics (N03A), opioids (N02A), psycholeptics (N05), antidepressants (N06A), alimemazine (R06AD01), and promethazine (R06AD02, R06AD52) because these drugs might cause similar perinatal effects as ADHD medication.

Perinatal Outcomes

From the MBR, data were acquired on GA, fetal weight for GA and sex (birth weight *z* scores),[30] Apgar scores at 5 minutes and perinatal death.

We collected data on birth defects from the MBR, SNQ, and PRS. Birth defects were defined as ICD-10 diagnoses beginning with Q, excluding these minor conditions: preauricular appendix, patent ductus arteriosus in a preterm infant, single umbilical artery, tongue tie, undescended testicle, hip dislocation or subluxation, and nevus. The following neonatal outcomes were also obtained from all 3 registers: any respiratory disorder (ICD-10 codes P220, P221, P228/checkbox, P240–P249), transient tachypnea or other respiratory disease (P228/checkbox/P221), persistent pulmonary hypertension of the newborn (PPHN) (P293B/checkbox), respiratory distress syndrome (RDS) (P220), hypoglycemia (P704; P707A, P704B/checkbox), hyperbilirubinemia (P590–P599/checkbox), feeding difficulties (P92/checkbox), disorders related to the central nervous system (CNS) (P909, P941 and P942, P910–P919), and withdrawal symptoms from therapeutic use of drugs in newborn (P962).

Admission to and duration of stay at a NICU, treatment with continuous positive airway pressure (CPAP), and ventilator (checkboxes) were identified via the SNQ and PRS.

Statistical Methods

We used logistic regression analyses to obtain odds ratios (ORs) for dichotomous outcomes for ADHD medication during pregnancy versus ADHD medication before or after pregnancy and versus no ADHD medication, respectively. When so specified in the tables and in the text, crude and adjusted odds ratios (aORs) are displayed. First, we selected a set of variables that we considered to be possible confounders because they all were known to be associated with both the exposure (ADHD medication)

and most of the outcomes. Prefatory analyses were performed to choose the most efficient way to represent these covariates in the analyses (linear, second-degree polynomial, or division into class variables). For each outcome studied, we first included all considered possible confounders in a multiple model. In order not to overfit the models, the final aORs were obtained from a restricted model, including variables with $P < .2$ only. The eligible factors were as follows: year of child birth (linear); maternal age (linear continuous variable); primiparity (versus multiparity); BMI (linear); maternal smoking (ordinal scale: 1 = no, 2 = 1–9 cigarettes per day, 3 = ≥10 cigarettes per day); living together with the child's father (no versus yes); mother born outside the Nordic countries (yes versus no); and maternal use of opioids (yes versus no), antiepileptics (yes versus no), psycholeptics (yes versus no), antidepressants (yes versus no), and alimemazine or promethazine (yes versus no) during pregnancy. Detailed lists of the factors included in the final models are available in Supplemental Tables 4–7. Missing data were replaced by the overall means.

Furthermore, a subanalysis was performed to investigate if the associations between ADHD medication and need of neonatal care and CNS disorders, respectively, were mediated by GA.

Statistical analyses were conducted by using SPSS version 22 and 23 (IBM SPSS Statistics; IBM Corporation, Armonk, NY) and Gauss version 10 (Aptech Systems Inc, Maple Valley, WA).

Ethics

The study was approved by the regional ethical review board in Lund (dnr. 2013/342-31/5).

RESULTS

The study population consisted of 964 734 singleton births. Among them, 1591 (0.2%) were exposed to ADHD medication during pregnancy. Stimulant drugs constituted 1464 of the exposures (~90% methylphenidate), whereas 165 infants were born to mothers who used atomoxetine. Most women were treated with ADHD medication during early pregnancy: 251 (15.8%) of the infants were exposed during the last 90 days of the pregnancy. Women who used ADHD medication before or after (but not during) pregnancy gave birth to 9475 (1.0%) of the infants.

Background Characteristics

There were substantial differences in background characteristics between women who used ADHD medication and women who did not use these drugs (see Table 1). Women treated with ADHD drugs were younger, more often nulliparous, smokers, obese, more frequently lived without the father of the child, and they also used other medications to a larger degree. These differences were seen both when comparing women who used ADHD medication during and before or after pregnancy with nonusers, but the differences were more pronounced for women who were treated with ADHD drugs during their pregnancies (Table 1). When comparing women who used ADHD medication before and after their pregnancies, respectively, there were expected differences in age, parity, and year of delivery; otherwise, the groups seemed to be similar (Supplemental Table 8).

Birth and Neonatal Outcomes

Table 2 displays the results concerning GA and birth weight for the 3 subcohorts. Exposure to ADHD medication during pregnancy was associated with a higher frequency of moderately preterm birth and with being large for gestational age (LGA), defined as >2 SDs above the mean birth weight for GA; aOR, 1.3 (95% confidence interval [CI], 1.1–1.6) and 1.3 (95% CI, 1.0–1.7), $P = .02$, respectively, compared with no use of ADHD medication.

There was no statistically significant increased risk for low Apgar scores, birth defects, or perinatal death among infants exposed during pregnancy when we controlled for maternal characteristics (Table 3).

However, exposure during pregnancy was linked to a higher rate of admission to the NICU compared with no use of these drugs: aOR, 1.5 (95% CI, 1.3–1.7) and number needed to harm, 13 (see Table 3). The risk increase was also significant compared with infants whose mothers used these drugs before or after pregnancy: aOR, 1.2 (95% CI, 1.1–1.4). For infants treated at the NICU, the median duration of stay was 7 days both for infants exposed to and infants not exposed to ADHD medication.

Use of ADHD medication during pregnancy was also associated with a higher frequency of CNS-related disorders; aOR, 1.9 (95% CI, 1.1–3.1) versus no use and aOR, 1.8 (95% CI, 1.0–3.3), $P = .05$ versus use before or after pregnancy (Table 3). Altogether, 16 infants exposed to ADHD medication were diagnosed with CNS disorders; 7 infants had unspecified CNS conditions, 6 infants had seizures, 2 had congenital hypotonia, and 1 had hypoxic ischemic encephalopathy with seizures. Moreover, 7 infants had withdrawal symptoms because of therapeutic drugs in the cohort exposed during pregnancy; 6 of them were also diagnosed with CNS disorders. Several infants with withdrawal symptoms had been exposed to other drugs (for example, psycholeptics) in addition to ADHD medication.

The results regarding admission to a NICU and CNS disorders were almost identical when adjusted for GA. The results were also similar when all

TABLE 1 Background Characteristics of the Study Population

Characteristic	ADHD Medication During Pregancy,[a] *N* = 1591	ADHD Medication Before or After but Not During Pregnancy,[b] *N* = 9475	No ADHD Medication, *N* = 953 668	ADHD Medication During Pregnancy Versus No ADHD Medication[c]
	%	%	%	OR (95% CI)
Year of child birth				
2006–2010	22.8	60.5	54.7	0.2 (0.2–0.3)
2011–2014	77.2	39.5	45.3	4.1 (3.6–4.6)
Maternal age, y				
<20	12.3	7.8	2.0	6.9 (5.9–8.0)
35+	14.2	13.6	21.7	0.6 (0.5–0.7)
Parity				
Primipara	60.8	53.2	51.4	1.5 (1.3–1.6)
Multipara	39.2	46.8	48.1	0.7 (0.6–0.8)
BMI				
BMI <18.5	2.2	2.5	2.2	1.1 (0.8–1.5)
BMI >30	17.6	16.2	11.4	1.7 (1.5–1.9)
Missing information	7.2	9.2	7.9	
Maternal smoking				
Yes	33.5	26.4	5.9	8.0 (7.2–8.9)
Missing information	4.1	4.6	4.6	
Maternal country of birth				
Sweden	93.1	91.8	75.2	4.5 (3.7–5.4)
Other Nordic	1.4	1.4	2.2	0.6 (0.4–0.9)
Non-Nordic	5.2	6.6	21.0	0.2 (0.2–0.3)
Not living with father of child	31.2	20.1	6.0	7.1 (6.4-7.5)
Maternal disease				
Diabetes	0.9	1.0	0.6	1.7 (1.0*–2.8)
Gestational diabetes	1.3	1.0	1.1	1.1 (0.7–1.7)
Hypothyroidism	2.8	2.1	1.8	1.5 (1.1–2.1)
Essential hypertension	0.4	0.4	0.4	0.9 (0.4–2.1)
Severe preeclampsia	1.1	0.9	0.9	1.2 (0.8–2.0)
Crohn's disease	0.1	0.3	0.3	0.5 (0.1–1.8)
Cesarean delivery	22.5	20.4	16.6	1.5 (1.3–1.6)
Use of other neurotropic drugs				
Opioids (N02A)	15.0	12.1	4.4	3.8 (3.3–4.4)
Antiepileptics (N03A)[d]	9.7	3.2	0.5	23.5 (18.9–27.9)
Psycholeptics (N05)	34.9	15.1	2.3	22.4 (20.2–24.9)
Antidepressants (N06A)	31.8	20.0	3.3	13.8 (12.4–15.3)
Alimemazine (R06AD01)	4.1	1.3	0.1	56.6 (43.7–73.3)
Promethazine (R06AD02, R06AD52)	28.1	18.6	7.7	4.7 (4.2–5.2)

[a] Exposure information acquired from self-reported use in early pregnancy or any prescription during pregnancy or 1 mo before.
[b] Any prescription during the study period except during the interval 1 mo before pregnancy until delivery.
[c] Reference = total population minus analyzed variable.
[d] Pregabalin, a substance classified as an antiepileptic but mainly used for other indications like anxiety and neuropathic pain, has previously been shown to be prescribed frequently to women with ADHD medication.[31]
* $P < .05$.

outcomes were analyzed, excluding atomoxetine (Supplemental Tables 9 and 10).

DISCUSSION

To our knowledge, this is the largest study to date in which perinatal outcomes after maternal use of prescribed ADHD medication during pregnancy are analyzed. Authors of previous studies have included smaller samples[1,5,7,8,32] or focused on pregnant women with illicit use of amphetamine or methamphetamine.[18,33,34] Our results revealed weak to modest associations between in utero exposure to ADHD medication and neonatal morbidity. Because women who used these drugs during pregnancy in many ways differed from the average pregnant population, it is uncertain to what extent these associations can be explained by the ADHD medication itself.

Newborn infants exposed to ADHD medication in utero were more often admitted to a NICU, but there was no association with any of the individual neonatal diagnoses analyzed, apart from CNS-related disorders. Concerning respiratory symptoms, which were the most common diagnoses among the infants, we would have been able to detect a relative risk ratio of 1.4 (80% power and a significance level of 0.05) for the comparison of ADHD medication during pregnancy versus no ADHD medication. There was, however, no sign of an increased occurrence of

TABLE 2 GA and Birth Weight Among Infants Exposed to ADHD Medication During Pregnancy Compared With Infants Whose Mothers Used ADHD Medication Before or After Pregnancy and With Infants Whose Mothers Never Used These Drugs

Outcome	ADHD Medication During Pregnancy,[a] *N* = 1591	ADHD Medication Before or After Pregnancy,[b] *N* = 9475	No ADHD Medication, *N* = 953 668	ADHD Medication During Pregnancy Versus ADHD Medication Before or After Pregnancy[c]		ADHD Medication During Pregnancy Versus No ADHD Medication[c]	
	n (%)	*n* (%)	*n* (%)	Crude OR (95% CI)	aOR (95% CI)	Crude OR (95% CI)	aOR (95% CI)
GA, wk							
<32	19 (1.2)	121 (1.3)	12 435 (1.3)	1.0 (0.6–1.6)	0.8 (0.5–1.3)	0.9 (0.6–1.5)	0.9 (0.6–1.5)
32–36	125 (7.9)	561 (5.9)	39 747 (4.2)	1.4 (1.1–1.7)	1.2 (1.0–1.4)	1.9 (1.6–2.3)	1.3 (1.1–1.6)
37–41	1365 (85.8)	8283 (87.4)	838 318 (87.9)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
≥42	82 (5.2)	510 (5.4)	63 168 (6.6)	1.0 (0.8–1.2)	1.0 (0.8–1.3)	0.8 (0.6–1.0*)	0.9 (0.7–1.2)
Birth wt[d]							
SGA	43 (2.7)	222 (2.3)	21 789 (2.3)	1.2 (0.8–1.6)	1.0 (0.7–1.4)	1.2 (0.9–1.6)	0.9 (0.6–1.2)
AGA	1470 (92.4)	8831 (93.2)	892 606 (93.6)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
LGA	78 (4.9)	422 (4.5)	39 273 (4.1)	1.1 (0.9–1.4)	1.2 (0.9–1.6)	1.2 (1.0–1.5)	1.3 (1.0–1.7*)

AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age.

[a] Exposure to ADHD medication according to self-reported use in early pregnancy or any prescription during pregnancy or 1 mo before.

[b] Any ADHD medication dispensed from a pharmacy during the study period except during the interval 1 mo before pregnancy until delivery.

[c] The factors considered to be potential confounders were as follows: year of birth, maternal age, primiparity, BMI, maternal smoking, noncohabiting with father, mother born outside the Nordic countries, and maternal use of opioids, antiepileptics, psycholeptics, antidepressants, alimemazine, or promethazine during pregnancy. All were simultaneously entered into the introductory multiple logistic regression analyses. The final aORs were obtained from a restricted model after elimination of all variables with $P \geq .2$. A detailed list of the factors included in the final models is available in Supplemental Table 4.

[d] Sex-specific birth wt *z* score; SGA = 2 SDs below mean, LGA = 2 SDs above mean.

* $P < .05$.

respiratory problems after exposure to ADHD drugs during pregnancy after adjustment for maternal factors.

For some of the less frequent diagnoses, it is possible that our study cohort was too small to detect an increased risk. Feeding difficulties, hypoglycemia, low Apgar scores, and withdrawal symptoms did, for example, show a tendency toward an association with ADHD medication during pregnancy, but this did not reach significance. Low Apgar scores linked to ADHD medication during pregnancy were also seen in a Danish study.[6]

Stimulant drugs affect dopamine, noradrenaline, and serotonin, which are key neurotransmitters in the CNS.[18,35] Therefore, our finding of an increased frequency of CNS disorders among infants exposed to ADHD medication in utero might be explained by the pharmacological and toxicological properties of the substances. Methamphetamine use during pregnancy has previously been shown to increase the rate of CNS stress with nonoptimal reflexes, poorer quality of movement, lower arousal and excitability, and more hypotonicity among newborn infants.[34] On the other hand, we cannot rule out that the association between ADHD medication and CNS symptoms in our study was a random finding.

In addition, in concordance with previous studies,[1,5,7,8,32] we could not detect any association between ADHD medication and overall rate of congenital malformations. However, the absence of a significant association does not mean that no association exists. There was an indication of an elevated OR for malformations, and it almost reached statistical significance even after adjustment for maternal characteristics. Our material was also not large enough to study specific malformations. Additionally, it should be mentioned that we included malformations diagnosed

TABLE 3 Perinatal Morbidity Among Infants Exposed to ADHD Medication During Pregnancy Compared With Infants Whose Mothers Used ADHD Medication Before or After Pregnancy and With Infants Whose Mothers Never Used These Drugs

Outcome	ADHD Medication During Pregnancy,[a] $N = 1591$	ADHD Medication Before or After Pregnancy,[b] $N = 9475$	No ADHD Medication, $N = 953\,668$	ADHD Medication During Pregnancy Versus ADHD Medication Before or After Pregnancy[c]		ADHD Medication During Pregnancy Versus No ADHD Medication[c]	
	n (%)	*n* (%)	*n* (%)	Crude OR (95% CI)	aOR (95% CI)	Crude OR (95% CI)	aOR (95% CI)
Apgar score <7 at 5 min	38 (2.4)	177 (1.9)	12 592 (1.3)	1.3 (0.9–1.8)	1.0 (0.7–1.5)	1.8 (1.3–2.5)	1.2 (0.8–1.6)
Birth defects (weeded)[d]	48 (3.0)	205 (2.2)	20 736 (2.2)	1.4 (1.0–1.9*)	1.3 (0.9–1.8)	1.4 (1.0–1.9*)	1.2 (0.9–1.6)
Perinatal death	8 (0.5)	38 (0.4)	4268 (0.4)	1.3 (0.6–2.7)	1.1 (0.5–2.5)	1.1 (0.6–2.3)	0.9 (0.4–1.8)
NICU admission	259 (16.3)	1105 (11.7)	79 530 (8.3)	1.5 (1.3–1.7)	1.2 (1.1–1.4)	2.1 (1.9–2.4)	1.5 (1.3–1.7)
Any respiratory disorder	92 (5.8)	511 (5.4)	35 479 (3.7)	1.1 (0.9–1.4)	1.0 (0.8–1.2)	1.6 (1.3–2.0)	1.0 (0.8–1.2)
Transient tachypnea or other respiratory disease	70 (4.4)	346 (3.7)	25 198 (2.6)	1.2 (0.9–1.6)	1.0 (0.8–1.4)	1.7 (1.3–2.2)	1.1 (0.9–1.4)
PPHN	7 (0.4)	49 (0.5)	3065 (0.3)	0.9 (0.4–1.9)	0.8 (0.4–1.8)	1.4 (0.7–2.9)	0.9 (0.4–2.8)
RDS	13 (0.8)	82 (0.9)	5101 (0.5)	0.9 (0.5–1.7)	1.0 (0.6–2.0)	1.5 (0.9–2.7)	1.0 (0.6–1.8)
CPAP	60 (3.8)	332 (3.5)	22 287 (2.3)	1.1 (0.8–1.4)	0.9 (0.7–1.3)	1.6 (1.3–2.1)	1.0 (0.8–1.3)
Ventilator treatment	15 (0.9)	90 (0.9)	5257 (0.6)	1.0 (0.6–1.7)	1.0 (0.6–1.7)	1.7 (1.0–2.9)	1.2 (0.7–2.1)
Hyperbilirubinemia	91 (5.7)	511 (5.4)	42 948 (4.5)	1.1 (0.9–1.3)	1.0 (0.8–1.3)	1.3 (1.0–1.6)	1.1 (0.9–1.4)
Hypoglycemia	66 (4.1)	326 (3.4)	23 965 (2.5)	1.2 (0.9–1.6)	1.0 (0.7–1.3)	1.7 (1.3–2.2)	1.2 (0.9–1.5)
Feeding difficulties	34 (2.1)	130 (1.4)	9837 (1.0)	1.6 (1.1–2.3)	1.1 (0.8–1.7)	2.1 (1.5–2.9)	1.3 (0.9–1.8)
CNS-related disorders	16 (1.0)	40 (0.4)	2885 (0.3)	2.4 (1.3–4.3)	1.8 (1.0–3.3*)	3.4 (2.0–5.5)	1.9 (1.1–3.1)
Withdrawal symptoms from therapeutic drugs	7 (0.4)	10 (0.1)	124 (0.0)	4.2 (1.6–11.0)	—	34.0 (15.8–72.9)	2.1 (0.9–4.7)

—, not analyzed because of low number of infants.

[a] Exposure to ADHD medication according to self-reported use in early pregnancy or any prescription during pregnancy or 1 mo before.

[b] Any ADHD medication dispensed from a pharmacy during the study period except during the interval 1 mo before pregnancy until delivery.

[c] The factors considered to be potential confounders were as follows: year of birth, maternal age, primiparity, BMI, maternal smoking, noncohabiting with father, mother born outside the Nordic countries, and maternal use of opioids, antiepileptics, psycholeptics, antidepressants, alimemazine, or promethazine during pregnancy. All were simultaneously entered into the introductory multiple logistic regression analyses. The final aORs were obtained from a restricted model after elimination of all variables with $P \geq .2$. A detailed list of the factors included in the final models is available in Supplemental Table 5.

[d] ICD-10 diagnoses beginning with Q, excluding the following minor conditions: preauricular appendix, patent ductus arteriosus in a preterm infant, single umbilical artery, tongue tie, undescended testicle, hip dislocation or subluxation, and nevus.

* $P < .05$.

mainly during the neonatal period. An increased risk of conditions detected later might thereby be missed. Because the diagnostic delay most likely is the same in the exposed and unexposed groups, this would not have a substantial effect on the estimated overall OR for malformations.

We found an increased rate of moderately preterm birth among infants exposed to ADHD medication during pregnancy, which earlier has been demonstrated after illicit use of amphetamines among pregnant women.[22,36] Exposure to ADHD drugs was also linked to being LGA, a somewhat unexpected result that we have not been able to find in other publications. This could potentially be related to a larger weight gain during pregnancy among the women who used ADHD medication, but the registers do not include this parameter.

In the current study, we include a population-based, prospectively collected cohort with high coverage of data and the possibility to adjust for many important confounders. Still, the profound differences in background characteristics between women who used ADHD medication compared with women who did not use these drugs complicate the interpretations. Because women who were treated with ADHD drugs before or after pregnancy also clearly differed from nonusers, the underlying disease or lifestyle aspects might be important factors that are difficult to control for. For example, the registers used in this study do not provide information on alcohol or illicit drug use, but it can be suspected that a considerable number of the women had addiction problems. A Swedish report from the National Board of Health and Welfare stated that 26% of women between 26 and 34 years of age who used methylphenidate were diagnosed with substance abuse and/or dependency.[31] Because the

rate of care at a NICU and of CNS symptoms after exposure to ADHD medication during pregnancy was also increased compared with use of these drugs before or after pregnancy, a real association with exposure in utero is supported. However, it is also possible that women who were treated during pregnancy had more severe ADHD symptoms that could have resulted in residual confounding by indication.

Concerning the diagnosis of ADHD, the registers used in this study do not provide such information. Because only psychiatrists and specialists in pediatric neurologic rehabilitation can prescribe the stimulant drugs in Sweden, reasonable precision and uniformity in the diagnosis of ADHD is likely.

A limitation with our methodology is that we do not know whether the drugs were actually ingested. We believe that compliance to treatment with ADHD drugs might be even more complicated than for other continuous drug therapy. It seems that ∼1 out of 10 patients occasionally interrupt their treatment (for example, during weekends) (K. Wide, MD, PhD, personal communication, 2016). The real exposure is therefore probably lower, but this would only slightly affect the calculated ORs. It might also be that exposure during late pregnancy is higher than estimated because women who temporarily interrupted their treatment did not need a refill after 3 months.

An important aspect seen in both this and other studies[1,6] is that women treated with ADHD drugs frequently use other psychoactive medications, are more often young and single, and have other characteristics that imply that they are a vulnerable group. In a recent publication, Eddy et al[37] showed that symptoms of ADHD like inattention and impulsivity can impair daily function in pregnant women. It is possible that this might result in poorer adherence to antenatal care, an unhealthier lifestyle, and increased maternal stress that in turn can affect the fetus negatively. These factors must be taken into consideration and be carefully balanced against the potentially increased risk for neonatal morbidity associated with the drugs when decisions are made concerning treatment during pregnancy.

Additional research is needed to further elucidate the impact of ADHD medication on the newborn child. A larger sample with more infants exposed to only ADHD drugs would yield clearer answers. More studies are also needed to find out whether there is a difference between the various stimulant drugs and between stimulants and atomoxetine.

CONCLUSIONS

Exposure to ADHD medication in utero was associated with an increased risk for moderately preterm birth, admission to a NICU, and for CNS-related disorders in infants. These findings warrant attention but are hardly reasons to abstain from ADHD medication during pregnancy if treatment is crucial for the woman.

ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
aOR: adjusted odds ratio
CI: confidence interval
CNS: central nervous system
CPAP: continuous positive airway pressure
GA: gestational age
ICD-10: *International Classification of Diseases, 10th Revision*
LGA: large for gestational age
MBR: Medical Birth Register
OR: odds ratio
PDR: Prescribed Drug Register
PPHN: persistent pulmonary hypertension of the newborn
PRS: Perinatal Revision South Register
RDS: respiratory distress syndrome
SNQ: Swedish Neonatal Quality Register

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