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Association Between Methylphenidate and Amphetamine Use in Pregnancy and Risk of Congenital Malformations
A Cohort Study From the International Pregnancy Safety Study Consortium

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IMPORTANCE Given the rapidly increasing use of stimulant medications during pregnancy and among women of reproductive age who may become pregnant inadvertently, there is a need to better understand their safety.

OBJECTIVE To examine the risk of congenital malformations associated with intrauterine exposure to stimulants.

DESIGN, SETTING, AND PARTICIPANTS Cohort study of the Medicaid-insured population in the United States nested in the 2000-2013 US Medicaid Analytic eXtract, with follow-up of safety signals detected in the Medicaid Analytic eXtract data using the Nordic Health registries (2003-2013) (Denmark, Finland, Iceland, Norway, and Sweden). A total of 1 813 894 publicly insured pregnancies in the United States and 2 560 069 singleton pregnancies in the 5 Nordic countries ending in live births were included. Relative risks were estimated accounting for underlying psychiatric disorders and other potential confounders. Relative risk estimates for the US and Nordic data were pooled using a fixed-effects meta-analytic approach. The study was conducted from July 1, 2015, to March 31, 2017.

EXPOSURES Methylphenidate and amphetamines dispensed during the first trimester.

MAIN OUTCOMES AND MEASURES Major congenital malformations and subgroup of cardiac malformations.

RESULTS In the US data, of the 1 813 894 pregnancies evaluated, 35.0 per 1000 infants not exposed to stimulants were diagnosed as having congenital malformations, compared with 45.9 per 1000 infants for methylphenidate and 45.4 for amphetamines. For cardiac malformations, the risks were 12.7 (95% CI, 12.6-12.9), 18.8 (95% CI, 13.8-25.6), and 15.4 (95% CI, 12.5-19.0) per 1000 infants, respectively. The adjusted relative risks for methylphenidate were 1.11 (95% CI, 0.91-1.35) for any malformation and 1.28 (95% CI, 0.94-1.74) for cardiac malformations. No increased risks were observed for amphetamines: 1.05 (95% CI, 0.93-1.19) for any malformations and 0.96 (95% CI, 0.78-1.19) for cardiac malformations. Findings were confirmed in sensitivity analyses accounting for proxies of unmeasured confounders and increasing the specificity of the exposure and outcome definitions. Replication of the analyses for methylphenidate using the Nordic data including 2 560 069 pregnancies yielded a relative risk of 1.28 (95% CI, 0.83-1.97) for cardiac malformations, resulting in a pooled estimate of 1.28 (95% CI, 1.00-1.64).

CONCLUSIONS AND RELEVANCE These findings suggest a small increase in the risk of cardiac malformations associated with intrauterine exposure to methylphenidate but not to amphetamines. This information is important when weighing the risks and benefits of alternative treatment strategies for attention-deficit/hyperactivity disorder in women of reproductive age and during early pregnancy.

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Supplemental content

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inattention and/or hyperactivity-impulsivity with negative effects on social, academic, and/or occupational functioning.[1,2] Although originally defined as a childhood disorder, it is increasingly recognized that ADHD can persist into or even emerge in adulthood.[3,4] The cross-national prevalence of ADHD has been estimated at approximately 3% in children,[5] adolescents,[5] and adults.[6] Stimulants, including amphetamines and methylphenidate, are considered first-line medications for managing ADHD.[2] In recent years, use of these medications in adults, including women of reproductive age, has increased substantially.[7-10] They thus represent an increasingly frequent drug exposure during pregnancy.[11,12]

Data regarding the safety of stimulant medications in early pregnancy are limited. Animal studies suggest that amphetamines at very high doses may increase the risk of cardiac and other malformations.[13,14] Human studies generally have not found an increased risk for malformations when these medications are used medically, although data are limited.[14,15] Although very high doses of methylphenidate have also been associated with certain malformations, most animal studies using relevant doses do not indicate a teratogenic effect[16,17]; corresponding data in humans are sparse and conflicting.[18-21] Two recent cohort studies (<250 exposed pregnancies each) failed to detect an association between use of methylphenidate in early pregnancy and overall or cardiac malformations,[19,20] while another study found an increased risk of cardiac malformations (relative risk [RR], 1.81; 95% CI, 0.59-4.21), although the estimate was imprecise.[21]

Given the rapidly increasing use of stimulant medications during pregnancy and among women of reproductive age who may become pregnant inadvertently, there is a need to better understand their safety. We therefore undertook a study to examine the potential association between first-trimester exposure to stimulants and major congenital malformations, as well as the most common type of major malformation—congenital cardiac defects. In the primary analysis we used a nationwide cohort of pregnancies linked to offspring of Medicaid beneficiaries in the United States. To follow up on potential safety signals from the primary analysis, we replicated the analyses using data from 5 Nordic nationwide health registries (Denmark, Finland, Iceland, Norway, and Sweden).

Key Points

Question What is the risk of congenital malformations associated with intrauterine exposure to stimulant attention-deficit/hyperactivity disorder medications?

Findings Results from this cohort study including 1.8 million pregnancies nested in US Medicaid Analytic eXtract (2000-2013), with replication of initial safety signals in 2.5 million singleton pregnancies in the Nordic Health registries (2003-2013), suggest a potential small increased risk of cardiac malformations associated with methylphenidate use (pooled relative risk, 1.28; 95% CI, 1.00-1.64); an increase in the risk of this malformation type was not found for amphetamines. Neither methylphenidate nor amphetamines were associated with an increased risk for malformations overall.

Meaning This study provides important information when weighing the risks and benefits of alternative treatment strategies for attention-deficit/hyperactivity disorder in women of reproductive age and during early pregnancy and illustrates the unique opportunity provided by the International Pregnancy Safety Study network to rapidly follow-up on initial safety signals.

Methods

Data Source and Cohort

The primary analyses were conducted using the pregnancy cohort nested in the 2000-2013 nationwide Medicaid Analytic eXtract. To be eligible for the study, pregnant women aged 12 to 55 years were required to be continuously enrolled in Medicaid from 3 months before the date of their last menstrual period (LMP) to 1 month after delivery; their live-born infants were required to be enrolled for the first 3 months of life or until death. Pregnancies with exposure to a known teratogenic medication during the first trimester (n = 3562) and pregnancies with a fetal chromosomal abnormality (n = 3156) were excluded.

Validation analyses were conducted using information from the nationwide health registries in the Nordic countries, which contain prospectively collected health information on all inhabitants. Reporting is mandatory and regulated by national laws.[22] The Nordic cohorts consisted of all pregnancies resulting in singleton live births. Each participating country contributed data from different periods according to data availability (Denmark, 2005-2012; Finland, 1996-2010; Iceland, 2003-2012; Norway, 2005-2012; and Sweden, 2006-2013). Further information on the Nordic cohort is provided in eAppendix 1 in the Supplement. The study was conducted from July 1, 2015, to March 31, 2017.

Use of the US data for this research was approved by the Brigham and Women's Hospital institutional review board, which granted a waiver of informed consent. Use of the Nordic data was approved by the Regional Ethical Research Board in Stockholm, Sweden, the National Bioethics Committee in Iceland, the Steering Committee of the Drugs and Pregnancy Project, the authorities overseeing health registries for the Finnish National Institute for Health and Welfare and the Finnish National Social Insurance Institute, and the Danish Data Protection Agency. Each authority waived informed patient consent in approving use of data from its respective country. No ethics approval was required in Norway.

Primary Analyses: US Cohort

Stimulants

A pregnancy was considered exposed if a woman filled a prescription for a stimulant during the first 90 days of pregnancy (ie, the period of embryogenesis). Two different exposure groups were considered: (1) methylphenidate and (2) amphetamine and dextroamphetamine (referred to hereafter as *amphetamines* for brevity). A pregnancy was considered unexposed if a woman did not fill a prescription for any ADHD medication from 3 months before the LMP to the end of the first trimester.

Congenital Malformations

Inpatient and outpatient *International Classification of Diseases, Ninth Revision* diagnoses and procedure codes in the maternal and infant health records were used to identify congenital malformations. The maternal record was considered since Medicaid claims are sometimes recorded under the mother's name before her infant's eligibility has been processed. An infant was considered to have a major congenital malformation if any of 13 specific malformation groups (central nervous system, ear, eye, cardiovascular, other vascular, respiratory, oral cleft, gastrointestinal, genital, urinary, musculoskeletal, limb, and other) were present (eTable 1 in the Supplement provides details on the outcome algorithm). The subgroup of cardiovascular malformations was also evaluated separately.

Covariates

A broad range of known or possible risk factors, including proxies for putative risk factors not directly measured, was considered in adjusting analyses for confounding. These factors included demographic characteristics (age, race/ethnicity, year of delivery), obstetric characteristics (multiparity, multiple gestations), psychiatric conditions, chronic comorbid medical conditions, markers of general comorbidity, and prescribed medications. A complete list of psychiatric and neurologic conditions and chronic maternal illnesses considered in the adjusted analyses is provided in eTable 2 and eTable 3 in the Supplement. The Obstetric Comorbidity Index score,[23,24] number of distinct prescriptions for medications other than stimulants, number of distinct diagnoses, and number of outpatient visits, hospitalizations, and emergency department visits were used as general markers of the burden of illness. Concomitant medications included other psychotropic medications, antidiabetic and antihypertensive medications, suspected teratogens, as well as proxies for drug abuse or dependence (eTables 2 and 3 in the Supplement). Maternal morbidity and concomitant medication use were measured starting 3 months before pregnancy and continuing to the end of the first trimester. General markers of the burden of illness were assessed during the 3 months before pregnancy to avoid the possibility that measures of intensity of health care use were affected by early awareness of possible pregnancy complications.

Statistical Analysis

We compared baseline characteristics of women who received vs did not receive stimulants. We calculated the prevalence of any congenital malformation and the subgroup of cardiac malformations in their infants as well as unadjusted RRs (ie, prevalence ratios) with 95% CIs.

Analyses were performed with 2 levels of adjustment: (1) adjustment for psychiatric and neurologic conditions and use of psychotropic medications to control for the possible effect of the underlying indication and associated factors, and (2) adjustment for all potential confounding variables (eTable 2 and eTable 3 in the Supplement). Adjustment for possible confounders was achieved through fine stratification (50 strata) of the propensity score (PS), which was estimated using logistic regression.[25] We assessed whether baseline characteristics in the weighted population were balanced using the standardized mean difference (absolute value <0.1). Adjusted RRs were estimated using generalized linear models (PROC GENMOD procedure with weight statement and log link function). Analysis was conducted with SAS, version 9.4 (SAS Institute).

Sensitivity and Exploratory Analyses

The robustness of our primary findings was tested in sensitivity analyses. First, using the high-dimensional PS algorithm,[26] we selected 200 empirically identified confounders and combined them with the investigator-identified covariates described above to estimate an empirically enriched PS. Second, to reduce the possibility of exposure misclassification, we required women to have filled a prescription for a stimulant at least twice during the first trimester. Third, we redefined the outcome using diagnosis and procedure claims from infant records only.

Exploratory analyses were conducted to further test potential safety signals emerging from the study. We examined the association of stimulant use with specific cardiac defects (eTable 4 in the Supplement). We redefined cardiovascular malformations by excluding cases of patent ductus arteriosus (*International Classification of Diseases, Ninth Revision* code, 747.0x) and patent foramen ovale/osteum secundum type atrial septal defect (*International Classification of Diseases, Ninth Revision* code, 745.5x), as these defects may be of limited clinical significance.

Validation Analyses: Nordic Cohort

A positive association identified in a single observational study, typically in the context of multiple comparisons, should be considered a safety signal that requires confirmation in a separate study. We therefore replicated our analyses for methylphenidate using information from the Nordic registries. Because of the small number of pregnancies with exposure to amphetamines in the Nordic cohort (n = 99), no inferential analyses could be pursued for this exposure. Whenever possible, the same design and analytic approach were used, but certain differences were present given the characteristics of the respective data sets (**Table 1**). The complete list of covariates considered in the Nordic analyses is provided in eTable 5 in the Supplement. Multivariable logistic regression analyses were conducted to generate adjusted risk estimates for each of the Nordic countries separately. The RRs then were pooled using a fixed-effects meta-analytic approach because a homogeneous treatment effect is expected across countries in the adjusted analyses. Finally, the estimate based on the US data was combined with the estimate based on the Nordic data using a similar meta-analytic approach.

Results

Primary Analyses

A total of 1 813 894 pregnancies ending in live birth (referred to hereafter as *women*) in the United States met the cohort selection criteria. Among these, 2072 women (0.11%) filled a prescription for methylphenidate and 5571 women (0.31%) filled

Table 1. Main Differences in the Design and Analytic Approach Between the US and Nordic Analyses

Study Characteristic	US Study	Nordic Study
Cohort	Live births	Live singleton births
Exclusions	Known teratogens	Gestational wk ≤22 or >44
		Birth weight <300 or >7000 g
Exposure window	First trimester: LMP to LMP + 90 d	First trimester: LMP to LMP + 97 d
Reference group	No exposure from 3 mo before LMP to LMP + 90 d	No exposure from LMP to LMP + 97 d
Outcome assessment	First 3 mo of life	First year of life, except Norway (first 3 mo of life)
Covariate assessment	*ICD-9*	*ICD-9* and *ICD-10*
	3 mo before LMP to LMP + 90 d	Maternal nonpsychiatric: 1 y before LMP to delivery
	Healthcare utilization: 3 mo before LMP to LMP	Maternal psychiatric: 5 y before LMP to delivery
		Concomitant drug use: 90 d before LMP to LMP + 97 d
Confounding adjustment	Fine stratification on the propensity score	Multivariate regression

Abbreviations: *ICD-9*, *International Classification of Diseases, Ninth Revision*; *ICD-10*, *International Classification of Diseases, Tenth Revision*; LMP, last menstrual period.

a prescription for an amphetamine during their first trimester. There were 1 797 938 women without exposure to any ADHD medication during the 3 months before their LMP or during the first trimester (eFigure in the Supplement).

Compared with nonusers, women who received stimulants were younger and more likely to be white, to have a psychiatric or neurologic diagnosis, use other psychotropic medications, and use prescription opioids. Comparisons between methylphenidate and amphetamine users showed more homogeneous baseline characteristics (**Table 2**; eTables 2 and 3 in the Supplement).

Malformations were diagnosed in 62 966 infants who were not exposed to a stimulant during the first trimester (35.0 malformations per 1000 infants). The prevalence was higher among methylphenidate-exposed (n = 95; 45.9 per 1000) and amphetamine-exposed (n = 253; 45.4 per 1000) infants. The prevalence of cardiovascular malformations was increased among methylphenidate-exposed infants (18.8 vs 12.7 per 1000 unexposed infants) and to a lesser degree among amphetamine-exposed infants (15.4 per 1000) (**Table 3**). Accordingly, in unadjusted analyses, the RRs for any malformation and for cardiovascular malformations were elevated for both methylphenidate and amphetamine exposure (**Figure 1**; eTable 6 in the Supplement). After adjustment for psychiatric morbidity, the associations with malformations overall were reduced for both methylphenidate (RR, 1.16; 95% CI, 0.95-1.41) and amphetamines (RR, 1.18; 95% CI, 1.04-1.33). The risk for cardiovascular malformations remained slightly elevated for methylphenidate (RR, 1.27; 95% CI, 0.93-1.73), but not for amphetamines (RR, 1.07; 95% CI, 0.86-1.32) (Figure 1; eTable 6 in the Supplement). Stratification on the PS ensured that comparisons were made between groups with nearly identical measured characteristics (Table 2, all absolute standardized mean differences <0.1). In fully adjusted analyses, the associations with malformations overall and with cardiovascular malformations were null for amphetamines: 1.05 (95% CI, 0.93-1.19) for any malformations and 0.96 (95% CI, 0.78-1.19) for cardiac malformations. The fully adjusted RRs for methylphenidate were 1.11 (95% CI, 0.91-1.35) for any malformation and 1.28 (95% CI, 0.94-1.74) for cardiac malformations. These results remained unchanged after adjustment for an additional 200 empirically identified confounders using the high-dimensional PS algorithm (Figure 1; eTable 6 in the Supplement). The findings were not markedly affected, after accounting for the width of the CI, when we changed the exposure definition to dispensing of medication 2 or more times during the first trimester or when we defined the outcome based only on claims from the infant record (eTable 6 in the Supplement).

When exploring the risk of specific cardiac defects for methylphenidate, we found the most strongly increased risk for conotruncal defects (adjusted RR, 3.44; 95% CI, 1.54-7.65), but this finding is based on less than 11 exposed events (eTable 7 in the Supplement). None of the specific cardiac defects were associated with amphetamine use. When we removed (1) patent ductus arteriosus and (2) patent ductus arteriosus and patent foramen ovale/osteum secundum type atrial septal defects, the associations strengthened somewhat for methylphenidate: 1.32 (95% CI, 0.96-1.82) and 1.50 (95% CI, 1.05-2.14), respectively (eTable 8 in the Supplement) but remained null for amphetamines.

Validation Analyses

The Nordic cohort included 2 560 069 pregnancies ending in a singleton live birth. Among these, 1402 infants (0.05%) were exposed to methylphenidate. Characteristics of exposed and unexposed women are summarized in eTable 9 in the Supplement. The prevalence of malformations among infants exposed to methylphenidate was somewhat lower than that observed in the US cohort: 38.5 per 1000 infants for any malformation and 17.1 per 1000 infants for cardiovascular malformations. The prevalence among unexposed infants was somewhat higher in the Nordic countries: 37.8 per 1000 infants for any malformation and 13.3 per 1000 infants for cardiovascular malformations (eTable 10 in the Supplement). The unadjusted RRs of 1.14 (95% CI, 0.87-1.49) for any malformation and 1.49 (95% CI, 1.00-2.23) for cardiovascular malformations were attenuated after adjustment for potential confounding variables: 0.99 (95% CI, 0.74-1.32) and 1.28 (95% CI, 0.83-1.97), respectively. Among the 24 cardiovascular defects in exposed infants, 2 were conotruncal defects (eTable 11 in the Supplement).

Pooling the adjusted estimates for first-trimester methylphenidate exposure from the US and the Nordic data resulted in RRs of 1.07 (95% CI, 0.91-1.26) for any malformation and 1.28 (95% CI, 1.00-1.64) for cardiovascular malformations (**Figure 2**).

Discussion

In a nationwide cohort of 1 813 894 publicly insured pregnant women who gave birth in the United States, we found a 28% increased prevalence of cardiac malformations after

Table 2. Cohort Characteristics of Women With Exposure to Stimulants During the First Trimester and Women Without Exposure to Any Stimulant[a]

Characteristic	Methylphenidate, No. (%)					Amphetamines, No. (%)				
	Unadjusted		Adjusted[b]		Standardized Difference	Unadjusted		Adjusted[b]		Standardized Difference
	Methylphenidate	Unexposed	Methylphenidate	Unexposed		Amphetamines	Unexposed	Amphetamines	Unexposed	
Total No.	2072	1 797 938	2072	1 790 294	NA	5571	1 797 938	5570	1 781 473	NA
Age, mean (SD), y	21.9 (6.2)	24.3 (5.8)	21.9 (6.2)	22.0 (6.1)	−0.02	23.9 (6.0)	24.3 (5.8)	23.9 (6.0)	23.5 (6.0)	0.06
Race/ethnicity										
White	1492 (72.0)	710 245 (39.5)	1492 (72.0)	1 319 148 (73.7)	−0.04	4635 (83.2)	710 245 (39.5)	4634 (83.2)	1 509 496 (84.7)	−0.04
Black	331 (16.0)	590 905 (32.9)	331 (16.0)	272 276 (15.2)	0.02	409 (7.3)	590 905 (32.9)	409 (7.3)	123 113 (6.9)	0.02
Hispanic	72 (3.5)	264 861 (14.7)	72 (3.5)	54 986 (3.1)	0.02	142 (2.5)	264 861 (14.7)	142 (2.5)	39 055 (2.2)	0.02
Other	177 (8.5)	231 927 (12.9)	177 (8.5)	143 884 (8.0)	0.02	385 (6.9)	231 927 (12.9)	385 (6.9)	109 810 (6.2)	0.03
Multiple gestation	60 (2.9)	62 380 (3.5)	60 (2.9)	53 800 (3.0)	−0.01	163 (2.9)	62 380 (3.5)	163 (2.9)	51 027 (2.9)	0
Psychiatric and neurologic conditions										
ADHD	1089 (52.6)	10 170 (0.6)	1089 (52.6)	918 557 (51.3)	0.03	3145 (56.5)	10 170 (0.6)	3144 (56.4)	983 577 (55.2)	0.02
Depression	444 (21.4)	89 873 (5.0)	444 (21.4)	413 404 (23.1)	−0.04	1109 (19.9)	89 873 (5.0)	1108 (19.9)	393 803 (22.1)	−0.05
Anxiety	362 (17.5)	65 228 (3.6)	362 (17.5)	328 150 (18.3)	−0.02	1129 (20.3)	65 228 (3.6)	1128 (20.3)	370 387 (20.8)	−0.01
Alcohol abuse or dependence	20 (1.0)	7550 (0.4)	20 (1.0)	20 579 (1.1)	−0.02	41 (0.7)	7550 (0.4)	41 (0.7)	15 898 (0.9)	−0.02
Drug abuse or dependence	58 (2.8)	17 901 (1.0)	58 (2.8)	51 687 (2.9)	−0.01	132 (2.4)	17 901 (1.0)	132 (2.4)	51 241 (2.9)	−0.03
Smoking	135 (6.5)	62 254 (3.5)	135 (6.5)	123 878 (6.9)	−0.02	595 (10.7)	62 254 (3.5)	595 (10.7)	193 524 (10.9)	−0.01
Chronic maternal illness										
Diabetes	40 (1.9)	36 602 (2.0)	40 (1.9)	36 026 (2.0)	−0.01	101 (1.8)	36 602 (2.0)	101 (1.8)	31 822 (1.8)	0
Hypertension	51 (2.5)	41 610 (2.3)	51 (2.5)	44 741 (2.5)	0	187 (3.4)	41 610 (2.3)	187 (3.4)	54 623 (3.1)	0.02
Psychotropic medications										
Anticonvulsants	302 (14.6)	35 644 (2.0)	302 (14.6)	253 340 (14.2)	0.01	833 (15.0)	35 644 (2.0)	833 (15.0)	295 249 (16.6)	−0.04
Antidepressants	1033 (49.9)	155 155 (8.6)	1033 (49.9)	919 848 (51.4)	−0.03	2537 (45.5)	155 155 (8.6)	2536 (45.5)	882 546 (49.5)	−0.08
Antipsychotics	375 (18.1)	22 661 (1.3)	375 (18.1)	301 514 (16.8)	0.03	749 (13.4)	22 661 (1.3)	748 (13.4)	285 283 (16.0)	−0.07
Benzodiazepines	336 (16.2)	54 893 (3.1)	336 (16.2)	309 708 (17.3)	−0.03	1315 (23.6)	54 893 (3.1)	1314 (23.6)	419 872 (23.6)	0
Other hypnotics	245 (11.8)	63 265 (3.5)	245 (11.8)	215 082 (12.0)	−0.01	678 (12.2)	63 265 (3.5)	678 (12.2)	224 236 (12.6)	−0.01
Other concomitant medication										
Antidiabetics	23 (1.1)	15 556 (0.9)	23 (1.1)	19 752 (1.1)	0	69 (1.2)	15 556 (0.9)	69 (1.2)	22 229 (1.3)	0
Antihypertensives	175 (8.4)	46 949 (2.6)	175 (8.4)	143 925 (8.0)	0.01	422 (7.6)	46 949 (2.6)	421 (7.6)	120 704 (6.8)	0.03
Opioids	655 (31.6)	355 764 (19.8)	655 (31.6)	589 741 (32.9)	−0.03	2386 (42.8)	355 764 (19.8)	2385 (42.8)	765 743 (43.0)	0
Suspected teratogens[c]	332 (16.0)	163 453 (9.0)	332 (16.0)	293 790 (16.4)	−0.01	929 (16.7)	163 453 (9.1)	929 (16.7)	297 237 (16.7)	0
Markers of comorbidity, mean (SD)										
No. of generic drugs	3.8 (3.5)	1.7 (2.4)	3.8 (3.5)	3.9 (3.5)	−0.03	3.9 (3.5)	1.7 (2.4)	3.9 (3.5)	4.2 (3.6)	−0.06
No. of diagnoses	4.9 (4.1)	2.7 (3.2)	4.9 (4.1)	5.1 (4.1)	−0.04	5.1 (4.3)	2.7 (3.2)	5.1 (4.3)	5.4 (4.4)	−0.05
No. of outpatient visits	7.5 (9.9)	2.9 (4.1)	7.5 (9.9)	7.6 (8.7)	0	6.0 (7.3)	2.9 (4.1)	6.1 (7.3)	6.9 (7.7)	−0.12

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; NA, not applicable; PS, propensity score.

[a] Data obtained from Medicaid Analytic eXtract, 2000-2013.

[b] To account for PS, the untreated observations were weighted using the distribution of the treated among 50 PS strata. Observations from the nonoverlapping regions of the PS distributions were trimmed.

[c] Suspected teratogens included fluconazole, methimazole, danazol, propylthiouracil, progestins, angiotensin-converting enzyme inhibitors, and corticosteroids. Women exposed to known teratogens (warfarin, antineoplastic agents, lithium, isotretinoin, misoprostol, thalidomide) were excluded from the cohort.

Table 3. Prevalence of Congenital Malformations and Cardiovascular Malformations in Women With and Without Stimulant Exposure[a]

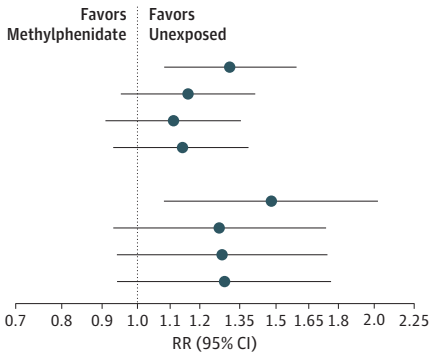
Exposure	No. of Events	Total No.	Prevalence/ 1000 Births	95% CI
Any congenital malformation				
Unexposed	62 966	1 797 938	35.0	34.8-35.3
Amphetamine	253	5571	45.4	40.3-51.2
Methylphenidate	95	2072	45.9	37.7-55.7
Cardiovascular malformations				
Unexposed	22 910	1 797 938	12.7	12.6-12.9
Amphetamine	86	5571	15.4	12.5-19.0
Methylphenidate	39	2072	18.8	13.8-25.6

[a] Data obtained from Medicaid Analytic eXtract, 2000-2013.

Figure 1. Comparison of the Risk of Malformations Between Stimulant-Exposed and -Unexposed Women

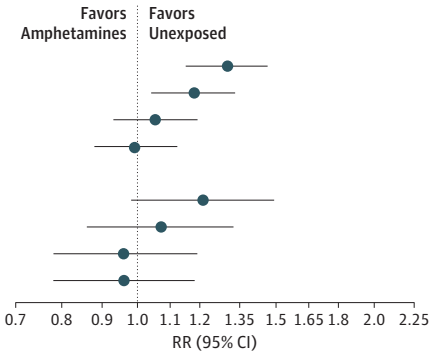
A Methylphenidate

Outcome	RR (95% CI)
Any congenital malformation	
Unadjusted	1.31 (1.08-1.59)
Adjusted for psychiatric morbidity	1.16 (0.95-1.41)
Fully adjusted	1.11 (0.91-1.35)
hdPS adjusted	1.14 (0.93-1.38)
Cardiovascular malformations	
Unadjusted	1.48 (1.08-2.02)
Adjusted for psychiatric morbidity	1.27 (0.93-1.73)
Fully adjusted	1.28 (0.94-1.74)
hdPS adjusted	1.29 (0.94-1.76)



B Amphetamines

Outcome	RR (95% CI)
Any congenital malformation	
Unadjusted	1.30 (1.15-1.46)
Adjusted for psychiatric morbidity	1.18 (1.04-1.33)
Fully adjusted	1.05 (0.93-1.19)
hdPS adjusted	0.99 (0.88-1.12)
Cardiovascular malformations	
Unadjusted	1.21 (0.98-1.49)
Adjusted for psychiatric morbidity	1.07 (0.86-1.32)
Fully adjusted	0.96 (0.78-1.19)
hdPS adjusted	0.96 (0.78-1.18)



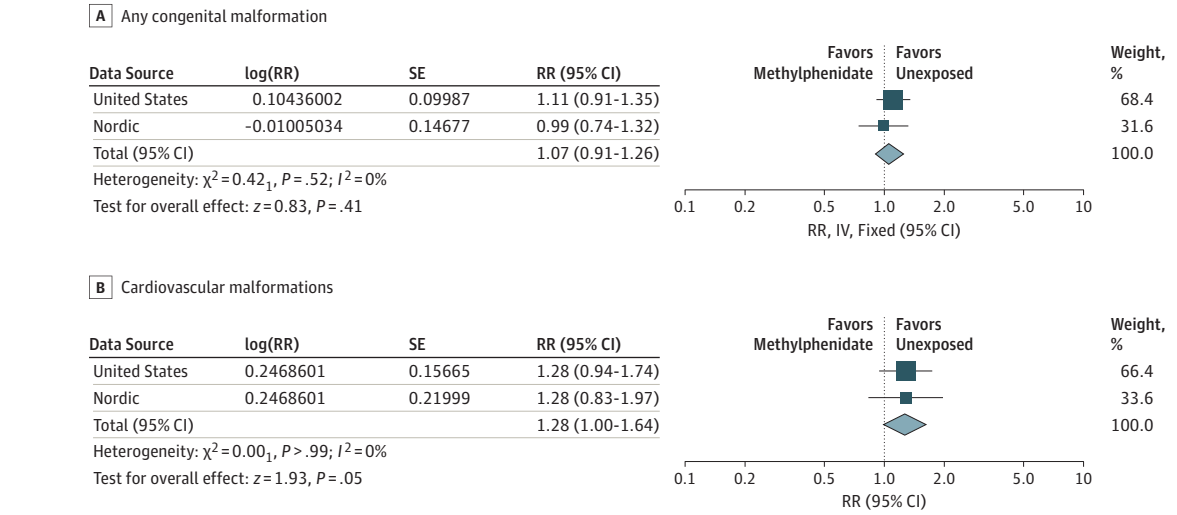
Data obtained from Medicaid Analytic eXtract 2000-2013. hdPS indicates high-dimensional propensity score; RR, relative risk.

first-trimester exposure to methylphenidate. After replication of these analyses in a cohort of 2 560 069 women who gave birth in the Nordic countries, the RR increase remained at 28% (95% CI, 0%-64%) based on pooled data. Since cardiac malformations affect approximately 10 infants per 1000 births, this increase corresponds to 3 additional infants born with congenital cardiac malformations for every 1000 women who receive methylphenidate during the first trimester of pregnancy. No association was observed for methylphenidate and congenital malformations overall or for amphetamines and any congenital or cardiac malformations.

Our study expands the evidence base regarding the safety of methylphenidate use in pregnancy by reporting on the outcomes of 2072 pregnancies exposed to this medication during the first trimester in the Medicaid Analytic eXtract primary cohort and 1402 in the Nordic validation cohort, allowing us to detect a small increase in the risk of cardiac malformations that prior studies[19,20] may have been underpowered to detect (eAppendix 2 in the Supplement provides a summary of existing evidence).

This is the first study to issue from the International Pregnancy Safety Study (InPreSS) consortium, a collaboration among research groups with access to health care databases with demonstrated ability to study the safety of medications in pregnancy: nationwide Medicaid data that cover close to 50% of pregnancies in the United States and the national registries

Figure 2. Meta-analytic Pooled Estimate for Methylphenidate-Exposed vs -Unexposed Women From US and Nordic Cohorts



Relative risk (RR) of any congenital malformation (A) and cardiovascular malformations (B).

in the 5 Nordic countries that cover nearly all pregnancies resulting in live births or stillbirths in these countries.[22,27-30] In this initial InPreSS study, we used the collaborative network to follow up on a potential safety signal initially identified in the US cohort. The opportunity to rapidly follow up on initial safety signals is likely to reduce the widespread dissemination of alarming early findings that are not confirmed or substantially weakened in subsequent studies.

Although a goal of InPreSS is to achieve sufficient statistical power through pooling, its priority is to maintain the highest possible methodologic standards to obtain valid estimates. Deviations from the commonly agreed upon protocol at the level of each data-contributing center are allowed to take advantage of the best available information in each country's data.

This study has several strengths, including use of prospectively collected data from 6 countries, with independent ascertainment of exposure and outcome and no risk of recall bias. Nevertheless, nonadherence to dispensed stimulants may have resulted in misclassification of exposure and thus biased the relative estimates toward the null. However, when we increased the specificity of the exposure definition by requiring that medication be dispensed to women at least twice during the etiologically relevant time window, our findings were not notably affected. Similarly, misclassification of the outcome is possible. In the primary analyses, we opted to use a specific outcome definition at the cost of sensitivity to increase the likelihood that the RR estimates would be unbiased. Although surveillance bias due to closer monitoring of infants of women treated with stimulants cannot be ruled out entirely, we would expect the resulting differential misclassification to be of similar magnitude for the different types of stimulants. The fact that we found no increased risk of malformations in infants exposed to amphetamines argues against substantial surveillance bias. Sensitivity analyses in which we tried to further increase the specificity of the outcome definition by restricting to infant claims or by excluding diagnoses that might be recorded due to increased use of cardiac imaging but are clinically insignificant, the strength of the association increased for methylphenidate, whereas the association remained null for amphetamines. These findings provide additional support for our main conclusions.

Residual confounding can never be completely excluded in a nonrandomized study. This is less of a concern for null findings (ie, amphetamines) but might have contributed to the small increased risk of cardiovascular malformations observed with methylphenidate. However, the balance in baseline characteristics observed after PS weighting suggests that there was no confounding by measured covariates or their correlates in adjusted analyses. The consistent findings in high-dimensional PS analyses suggest that there also was no confounding by proxies of unmeasured covariates. Moreover, it seems unlikely that residual confounding would affect the findings for methylphenidate but not for amphetamines since both medications are used similarly. Regardless, residual confounding by factors associated with ADHD severity remains a possible alternative explanation, especially in light of the small size of the observed risk increase and the shift in the estimates toward the null upon adjustment for measured confounders.

Limitations

Both cohorts were restricted to live births, which could have resulted in underestimation of the RR due to selection bias. This bias would occur if the likelihood of a malformation was higher among stimulant-exposed pregnancies and if the likelihood of a non-live birth was higher among affected exposed pregnancies than among affected nonexposed pregnancies.[31,32] Although unlikely, this possibility cannot be excluded since methylphenidate has been associated with an increased risk of miscarriage and elective termination in a small prospec-

tive study.[20] It has been shown previously, however, that differences in the proportion of non-live births among women who received vs those who did not receive stimulants within the levels of covariates used in the adjustment would have to be greater than seems plausible to fully account for a null finding, as was observed with amphetamines.[27]

Conclusions

Women with mild to moderate ADHD symptoms may be able to forego treatment during pregnancy and function well. However, if symptoms are more severe and interfere significantly with daily functioning, continuing pharmacologic treatment during pregnancy may be important. Considering the high rate of unplanned pregnancies among young women, the potential for accidental exposure to stimulants in early pregnancy is also high. Our findings suggest that there might be a small increase in the risk of cardiac malformations associated with intrauterine exposure to methylphenidate. Although the absolute risk is small, it is nevertheless important evidence to consider when weighing the potential risks and benefits of different treatment strategies for ADHD in young women of reproductive age and in pregnant women.

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