

First-Trimester Exposure to Methylphenidate: A Population-Based Cohort Study

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ABSTRACT

Objective: The use of methylphenidate to treat attention-deficit/hyperactivity disorder has risen dramatically in Western countries, and it is increasingly used by adults, including women of childbearing age. Very little is known about potential hazards of in utero exposure to methylphenidate. We conducted this study to estimate the risk of major congenital malformations following first-trimester in utero exposure to methylphenidate.

Method: Data from 2005 to 2012 were extracted from the Danish National Patient Register, the Danish National Prescription Registry, the Medical Birth Registry, and the Danish Civil Registration System. Exposure was defined as having redeemed 1 or more prescriptions for methylphenidate within a time window defined as 14 days before the beginning of the first trimester up to the end of the first trimester. Each exposed subject was propensity score-matched to 10 unexposed subjects with respect to maternal age, smoking status, body mass index, length of education, calendar year of completion of pregnancy, and concomitant use of antipsychotics, antidepressants, anxiolytics, and nonsteroidal anti-inflammatory drugs.

Results: We included 222 exposed and 2,220 unexposed pregnancies in the analysis. There was no statistically significant increase in major malformations (point prevalence ratio=0.8; 95% CI, 0.3–1.8) or cardiac malformations (point prevalence ratio=0.9; 95% CI, 0.2–3.0). Sensitivity analyses using different definitions of exposure or previous users of methylphenidate as the unexposed comparison cohort yielded comparable results.

Conclusions: First-trimester in utero exposure to methylphenidate does not appear to be associated with a substantially (ie, more than 2-fold) increased overall risk of major congenital malformations.

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The issue of methylphenidate use during pregnancy has become increasingly relevant as the prevalence of attention-deficit/hyperactivity disorder (ADHD) among adults has risen over the last decade.^{1,2} It is estimated that between 30% and 70% of children with ADHD will experience symptoms as adults.³ Estimates of the prevalence of adult ADHD have been reported to be around 3%–4%, ranging from 1% to 7% in different countries, with the highest prevalence among developed countries.^{4,5} Methylphenidate was approved for use in adults by the US Food and Drug Administration in 2008, but it does not yet hold this indication in Europe.^{6,7} Some guidelines recommend the use of methylphenidate in adults suffering from ADHD,⁸ including a recommendation on off-label use from the National Institute for Health and Clinical Excellence in the United Kingdom.⁹ A recent study¹⁰ showed that in Denmark many women in the fertile age range are prescribed methylphenidate: Among women aged 18–40 years, 4 to 8 per 1,000 persons use methylphenidate (Figure 1).

Safety data on the use of methylphenidate during pregnancy are scarce and give little guidance for the prescribing physician. Labeling for use during pregnancy is “C” (“animal data have shown adverse effect on the fetus”) in the United States,⁶ while the UK Summary of Product Characteristics⁷ states that “there is a limited amount of data from the use of methylphenidate in pregnant women” and that “methylphenidate is not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy.” A recent review¹ identified 180 first-trimester exposed pregnancies from various uncontrolled or small controlled studies, with no apparent excess risk of congenital malformations. No large controlled study of malformations following in utero methylphenidate exposure exists, and we thus performed a register-based nationwide cohort study of first-trimester use of methylphenidate in Denmark from 2005 to 2012.

METHOD

The analysis was performed as a cohort study. We compared the prevalence proportion of malformations in a cohort of pregnancies exposed to methylphenidate in the first trimester to a propensity score-matched cohort of pregnancies during which the mother had never used psychostimulants.

Data Sources

We used data from 4 Danish nationwide registries: the Danish National Patient Register, the Danish National Prescription Registry, the Danish Medical Birth Registry, and the Danish Civil Registration System. Data were obtained for the period of January 1, 1995, to December 31, 2012.

The Danish National Patient Register¹¹ contains data on all hospitalizations in Denmark since 1977 and outpatient visits since 1995. Discharge diagnoses are coded according to *ICD-10* since 1994. Virtually all medical care in Denmark is furnished by the national health authorities,

- First-trimester exposure to methylphenidate does not appear to be associated with a substantially increased overall risk of congenital malformations.
- The current data are too sparse to allow risk estimates of specific malformations.

whereby this data resource allows true population-based studies, covering all inhabitants of Denmark.

The Medical Birth Registry¹² contains information on all pregnancies in Denmark, both hospital births and home births. Information stored in the registry includes basic data on the children (gestational age, weight, height, Apgar score, referral to neonatal care unit, etc), complications, and procedures performed during the delivery. Until 1997, data were collected through birth reports sent to the National Board of Health. From 1997, the registry is primarily based on the Danish National Patient Register, but supplied with birth reports on home births and stillborn children.

The Danish National Prescription Registry¹³ contains data on all prescription drugs dispensed in Denmark since 1995. Prescription data include the date of dispensing, substance, brand name, and quantity. Drugs are categorized according to the Anatomical Therapeutic Chemical code, a hierarchical classification system developed by the World Health Organization for purposes of drug use statistics.¹⁴

The Danish Civil Registration System¹⁵ contains data on vital status (date of death) and migration to and from Denmark, which we used for censoring purposes. All data sources were linked by use of the personal identification number, a unique identifier assigned to all Danish individuals. All linkage was performed anonymously within Statistics Denmark, a governmental institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes.^{16,17}

Pregnancies

Pregnancies were identified using the Medical Birth Registry. As this registry includes only pregnancies resulting in births, either stillborn or live born, pregnancies terminated prior to birth, that is, both spontaneous and elective abortions, were not included in our material. As malformations are incompletely registered in stillborn children, we included only pregnancies resulting in live births (the infant survived ≥ 1 day). Exploratory analysis showed that maternal use of methylphenidate was very rare (1 subject) prior to January 1, 2005. Also, we required the possibility of 6 months of follow-up for the child after birth, to be able to assess malformations that were not detected at birth. Therefore, we included only pregnancies completed after January 1, 2005, and before July 1, 2012. Children who died within the first 6 months were, however, still included in the analysis. To assess drug exposure, we defined a period corresponding to the first trimester for each pregnancy. We did so using information

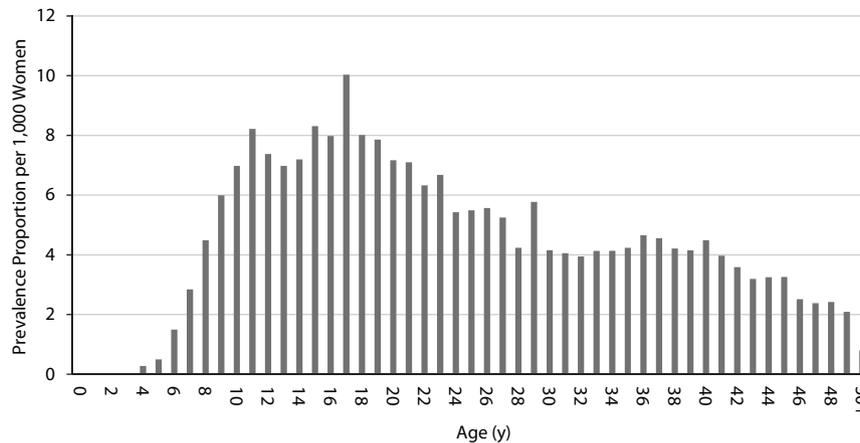
from the Danish Medical Birth Registry: We took the date of completion of the pregnancy and subtracted the gestational age at completion as estimated in the registry. The resulting date estimates the date of the end of the last menstruation. We therefore defined the first trimester as an interval from the 15th day to the 84th day from this date. We excluded multiple gestation pregnancies, pregnancies in which the mother migrated to or from Denmark within 5 years prior to the initiation of the pregnancy, and pregnancies in which the child migrated from Denmark within 6 months after being born. Additionally, we excluded pregnancies during which the mother had used certain drugs that are rarely used during pregnancy but known to be teratogenic. These drugs were vitamin K antagonists (B01AA), tetracyclines (J01AA), angiotensin-converting enzyme inhibitors (C09A and C09B), retinoids (D05BB, D10AD, and D10BA), and selected antiepileptic drugs: carbamazepine (N03AF01), oxcarbazepine (N03AF02), phenytoin (N03AB02), valproic acid (N03AG01), and phenobarbital (N03AA02).^{18,19} Use of these drugs was defined as having redeemed a prescription within 180 days before pregnancy to the end of the pregnancy.

Cohorts

To be included in the cohort of pregnancies exposed to methylphenidate in the first trimester, the mother was required to redeem 1 or more prescriptions for methylphenidate (ATC, N06BA04) within a time window defined as 14 days before the beginning of the first trimester up to the end of the first trimester. The unexposed cohort included pregnancies in which the mother had not redeemed a prescription for a psychostimulant (ATC, N06BA) at any time point prior to the end of the pregnancy. Using the above definitions, some pregnancies failed to be included in either cohort. This was intentional, as to avoid bias from misclassification, and was subject to sensitivity analyses (see Analysis).

Matching

The limiting factor in terms of statistical precision would be the number of first-trimester exposed women. From preliminary analyses of age-specific methylphenidate user prevalences and age-specific birth rates, we had calculated the expected number of exposed women to be on the order of 400. As the expected number of outcomes would therefore be low, we chose to analyze the data by use of propensity scores,²⁰ which estimate the likelihood of being treated, conditional on other covariates. For each pregnancy in the exposed cohort, we matched 10 pregnancies from the unexposed cohort. We used sequential balanced nearest-neighbor matching technique²¹ to match exposed and unexposed subjects on propensity score, allowing a maximum caliper of 0.05. This ensures that for each exposed subject, half of the individually matched unexposed subjects have propensity scores above the index subject, and half have propensity scores below. The following variables were included in the calculation of the propensity score: maternal age, maternal smoking status during first trimester, maternal body mass index

Figure 1. Prevalence of Methylphenidate Use Among Females in Denmark in 2010^a

^aAdapted with permission from Pottgård et al.¹⁰

(5% missing values were handled by imputation of mean value), calendar year of completion of pregnancy, length of education (grouped into 7–10 years, 11–12 years, ≥ 13 years, and unknown), and concomitant use of each of the following drugs: antipsychotics (N05A), antidepressants (N06A), anxiolytics (N05B), and nonsteroidal anti-inflammatory drugs (M01A excluding M01AX). Concomitant use of these drugs was defined as 1 or more prescriptions for the given drug within 40 days before the beginning of the first trimester up to the end of the first trimester.

Endpoints

The 2 study endpoints were major malformations and major cardiac malformations. We classified major malformations and subgroupings according to the European Surveillance of Congenital Anomalies (EUROCAT) system guide v1.3,²² based on *ICD-10* discharge diagnoses from the Danish National Patient Register. Furthermore, we calculated the mean gestational age and birth weight.

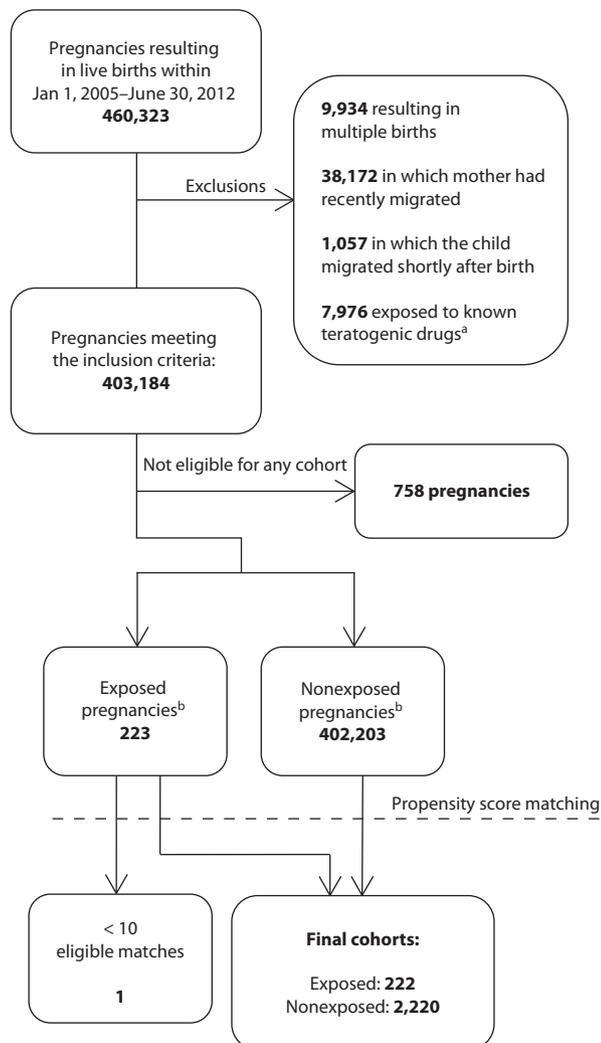
Analysis

Our main outcome measure was the point prevalence ratio, equivalent to the risk ratio, for major malformations and major cardiac malformations, calculated by comparing the exposed to the unexposed pregnancies. We furthermore applied a range of supplementary/sensitivity analyses. First, we performed subgroup analyses, stratifying by maternal age and by excluding pregnancies with concomitant use of psychostimulants other than methylphenidate (ATC, N06BA) or any of the abovementioned confounder drugs. Second, we changed the eligibility criteria for entering the unexposed cohort from never-use to previous use of methylphenidate. Previous use was defined as having redeemed 2 or more prescriptions for methylphenidate at any time prior to 180 days before the beginning of the first trimester, but no prescriptions for any psychostimulant (ATC, N06BA), within a time window defined as 180 days before the beginning of the first trimester up to the end of the pregnancy. In this analysis, we matched exposed to

unexposed in a ratio of 1:1. Last, we applied alternative criteria to define pregnancies that entered the exposed cohort: (1) more restrictive criteria, requiring 2 or more prescriptions within 14 days before the beginning of the first trimester up to the end of the first trimester, and (2) less restrictive criteria, requiring 1 or more prescriptions for methylphenidate within 40 days before the beginning of the first trimester up to the end of the first trimester.

RESULTS

From 460,323 pregnancies resulting in live births, we identified 240 exposed pregnancies in the period. Of these, 7 were excluded due to recent migration, 10 were excluded from analysis due to concomitant treatment with drugs with documented teratogenic potential, and 1 was excluded from analysis because she could not be matched with 10 unexposed subjects within the allowed caliper. A total of 222 subjects exposed to methylphenidate in the first trimester were matched to 2,220 unexposed subjects (Figure 2). Among the 222 exposed pregnancies, 6 women each contributed with 2 pregnancies. The exposed and unexposed cohorts were well balanced on all variables included in the propensity score model (Table 1), with the exception of a slightly higher prevalence of use of antipsychotics among the exposed. Compared to a random sample of 10,000 unexposed pregnancies, the cohorts were significantly younger, were less educated, smoked more, and had substantially higher consumption of drugs (ie, antipsychotics, antidepressants, anxiolytics, nonsteroidal anti-inflammatory drugs). Among the exposed, we observed 7 (3.2%) major malformations, 3 (1.4%) of which were cardiac. Among the unexposed, the corresponding numbers were 86 (3.9%) and 32 (1.4%). These rates are comparable to those observed in the random sample of unexposed pregnancies (3.7% and 1.1%, respectively). Comparison of the exposed and unexposed cohorts yielded overall point prevalence ratios of 0.8 (95% CI, 0.3–1.8) for all major malformations and 0.9 (95% CI, 0.2–3.0) for cardiac malformations (Table 2). There was no sign of aggregation of single malformations.

Figure 2. Flowchart Showing Included Pregnancies

^aVitamin K antagonists (B01AA), tetracyclines (J01AA), acetylcholinesterase inhibitors (C09A and C09B), retinoids (D05BB, D10AD, and D10BA), and selected antiepileptic drugs: carbamazepine (N03AF01), oxcarbazepine (N03AF02), phenytoin (N03AB02), valproic acid (N03AG01), and phenobarbital (N03AA02).

^bSee "Cohorts" in Method section for definition.

Sensitivity analyses stratifying by maternal age and excluding users of potentially confounding drugs did not result in materially different risk estimates (Table 2). Covariates were still well balanced among exposed and unexposed subjects within these subgroups (data not shown). Changing the comparison to previous users or applying other entry criteria to the exposed cohort also returned similar risk estimates (Table 3).

DISCUSSION

This is the first population-based study of the use of methylphenidate in pregnancy. We identified 240 women exposed to methylphenidate in the first trimester of pregnancy in Denmark from 2005 to 2012, among whom 222 entered the final cohort for analysis. We found no indication of increased overall risk of major congenital malformations. This finding is in accordance with 4 previously published studies that in

total evaluated 180 women exposed in the first trimester and found 4 major malformations, corresponding to a rate of 2.2% (95% CI, 0.6–5.6).¹ These previously reported cohort data, the majority of which are reported in the Swedish Birth Registry comprising 104 in utero exposed women, are mainly uncontrolled and thus have little or no potential to address confounding.^{18,23–25} The data in the Swedish Birth Registry have recently been updated and now comprise a total of 220 first-trimester exposed children, among whom 5 congenital malformations are described.²³

We used propensity score–matched controls and included maternal age, smoking status, body mass index, calendar year of birth date, length of education, and concomitant use of antipsychotics, antidepressants, antiepileptics, anxiolytics, and nonsteroidal anti-inflammatory drugs in the first trimester. Our analyses were robust, as various sensitivity analyses using less or more restrictive criteria for definition of exposure to methylphenidate or previous methylphenidate users for comparison did not change the results. We found a somewhat lower rate of exposure to methylphenidate during pregnancy than expected from total population estimates of methylphenidate use. On the basis of population estimates of the use of methylphenidate in women between the ages of 18 and 40 years between 2005 and 2012, about 400 exposed cases were expected.¹⁰ However, it is quite plausible that many women, on their own initiative or on the basis of physicians' advice, who are contemplating pregnancy or are accidentally exposed in the first trimester of pregnancy will discontinue treatment and not redeem prescriptions. The source of drug information most commonly used by health care professionals during pregnancy in Denmark states that, due to insufficient safety data, methylphenidate should be avoided during pregnancy.²⁶

With the addition of our data to the previously reported cohort data and the updated data from the Swedish Birth Registry, 518 first-trimester exposed pregnancies have now been reported, with no signs of excess risk of major congenital malformations.¹ The European Medicines Agency guidelines suggest that at least 1,000 first-trimester exposed women be evaluated with no sign of excess risk before a reassuring statement can be included in the Summary of Product Characteristics.²⁷ While the quantity and quality of the data at hand are short of this regulatory requirement, they still offer some reassurance to the treating clinician and the pregnant woman receiving methylphenidate.

The strength of our study is that it comprises data from an entire national cohort of more than 460,000 pregnancies from 2005 to 2012, using high-quality and validated registry data for identification of exposure and outcome.^{12,13} More than 99% of all births in Denmark have been recorded in the Medical Birth Registry, and completeness of the National Prescription Registry has been estimated to be 98%.^{13,28} The diagnoses of malformations have been found to have a predictive value of 88% for congenital malformations, with a completeness of 90%, and misclassification was probably random.²⁹ It is, however, conceivable that some newborns exposed to methylphenidate in utero will be more diligently

Table 1. Characteristics of Included Pregnancies

Characteristic	Methylphenidate Exposed (n = 222)	Unexposed (n = 2,220)	Random Sample (n = 10,000)
Maternal age, median (IQR), y	26 (22–30)	25 (22–30)	30 (27–34)
Maternal BMI, median (IQR) ^a	23.7 (20.8–28.7)	23.9 (20.9–28.1)	23.2 (21.0–26.6)
Maternal smoking status, n (%)			
Yes	113 (50.9)	1,100 (49.5)	1,512 (15.1)
No	102 (45.9)	1,035 (46.6)	8,303 (83.0)
Unknown	7 (3.2)	85 (3.8)	185 (1.8)
Maternal length of education, n (%)			
7–10 y	125 (56.3)	1,242 (55.9)	1,567 (15.7)
11–12 y	42 (18.9)	447 (20.1)	1,476 (14.8)
≥ 13 y	52 (23.4)	498 (22.4)	6,852 (68.5)
Unknown	3 (1.4)	33 (1.5)	105 (1.1)
Drug exposure, n (%) ^b			
Antipsychotics	20 (9.0)	139 (6.3)	33 (0.3)
Antidepressants	76 (34.2)	768 (34.6)	280 (2.8)
Anxiolytics	6 (2.7)	58 (2.6)	37 (0.4)
NSAIDs	14 (6.3)	139 (6.3)	324 (3.2)
Gestational age at birth, mean (CI), d	275 (274–277)	277 (276–277)	279 (278–279)
Birth weight, mean (CI), g	3,346 (3,263–3,428)	3,373 (3,348–3,398)	3,522 (3,510–3,533)
Low Apgar score, n (%) ^c	5 (2.3)	19 (0.9)	57 (0.6)
Endpoints, n (%)			
Major malformations	7 (3.2)	86 (3.9)	369 (3.7)
Cardiac malformations	3 (1.4)	32 (1.4)	111 (1.1)

^a5.6% of the exposed and unexposed cohorts had missing values.

^bDefined as having redeemed ≥ 1 prescription within 40 days prior to the first trimester up to the end of the first trimester.

^cApgar score < 7 after 5 minutes.

Abbreviations: BMI = body mass index, CI = confidence interval, IQR = interquartile range, NSAID = nonsteroidal anti-inflammatory drug.

Table 2. Fetal Outcomes and Point Prevalence Ratios (PPRs) Comparing the Exposed to the Unexposed Cohort, Overall, and by Subgroup

Subgroup	Events/No. of Pregnancies		PPR (95% CI)
	Exposed	Unexposed	
All			
Major malformations	7/222	86/2,220	0.8 (0.3–1.8)
Cardiac malformations	3/222	32/2,220	0.9 (0.2–3.0)
Maternal age < 30 y			
Major malformations	6/161	63/1,637	1.0 (0.3–2.2)
Cardiac malformations	2/161	19/1,637	1.1 (0.1–4.4)
Maternal age ≥ 30 y			
Major malformations	1/61	23/583	0.4 (0.0–2.6)
Cardiac malformations	1/61	13/583	0.7 (0.0–4.9)
No use of confounding drugs ^a			
Major malformations	5/125	53/1,346	1.0 (0.3–2.5)
Cardiac malformations	3/125	17/1,346	1.9 (0.4–6.6)

^aAtomoxetine (ATC, N06BA09), modafinil (N06BA07), dexamphetamine (N06BA02), antipsychotics (N05A), antidepressants (N06A), anxiolytics (N05B), and nonsteroidal anti-inflammatory drugs (M01A excluding M01AX).

scrutinized for malformations.³⁰ If this is the case, it will only strengthen our conclusion that methylphenidate is safe in pregnancy. Our results are consistent and robust with respect to rates of malformations observed in a large sample of unmatched unexposed pregnancies and alterations in the definition of the exposure window. By the matching procedure, we could adjust for a variety of parameters that could affect the malformation rate, and we could exclude pregnancies in which the mother had used drugs with documented teratogenic potential. In the study period, the determination of length of pregnancy is based on a first-trimester nuchal translucency scan performed in

Table 3. Sensitivity Analyses

Sensitivity Analysis	Events/No. of Pregnancies		PPR (95% CI)
	Exposed	Unexposed	
Comparing to previous users			
Major malformations	7/203	10/203	0.7 (0.2–2.0)
Cardiac malformations	3/203	3/203	1.0 (0.1–7.5)
More restrictive entry criteria ^a			
Major malformations	3/94	37/940	0.8 (0.2–2.6)
Cardiac malformations	1/94	11/940	0.9 (0.0–6.3)
Less restrictive entry criteria ^b			
Major malformations	9/271	135/2,710	0.7 (0.3–1.3)
Cardiac malformations	5/271	37/2,710	1.4 (0.4–3.4)

^aTwo or more prescriptions filled within 14 days before the beginning of the first trimester up to the end of the first trimester.

^bOne or more prescriptions for methylphenidate within 40 days before the beginning of the first trimester up to the end of the first trimester. Abbreviation: PPR = point prevalence ratio.

weeks 11–14, so we expect the gestational age at birth and the calculated date of initiation of pregnancy to be quite precise. We had complete follow-up in national registers, as we excluded people who emigrated.

The weakness of this registry-based study is primarily that we have no information on whether pregnant women who redeemed a prescription for methylphenidate during the first trimester continuously took the medication or had 1 or more “drug holidays.” Such bias would result in a conservative bias toward the null. Our estimate on cardiac malformations is inherently hampered by the sample size and outcome frequency. While we did not detect a statistically significant signal, the analysis is based on 3 cases of cardiac malformations in the exposed cohort. This specific malformation should be subject to future studies.

Due to the number of exposed cases, the statistical power is insufficient for a meaningful stratified analysis with respect to other specific malformations.

CONCLUSION

Methylphenidate exposure during the first trimester of pregnancy does not appear to be associated with a substantially (ie, more than 2-fold) increased overall risk of congenital malformation. However, the current data are too sparse to allow risk estimates of specific malformations. While insufficient to exclude some excess risks of major malformations, our findings offer some reassurance to pregnant women who receive, and their treating physicians who prescribe, methylphenidate. Other possible unwanted outcomes such as excess risk of miscarriage, preterm birth, low birth weight, neonatal complications, and postnatal neurodevelopmental issues remain unaccounted for.

Drug names: atomoxetine (Strattera), carbamazepine (Carbatrol, Equetro, and others), methylphenidate (Focalin, Daytrana, and others), modafinil (Provigil), oxcarbazepine (Trileptal and others), phenytoin (Dilantin, Phenytek, and others), valproic acid (Depakene, Stavzor, and others).

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