Atomoxetine in Early Pregnancy and the Prevalence of Major Congenital Malformations: A Multinational Study

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ABSTRACT

Objective: Most research on safety of attention-deficit/hyperactivity disorder (ADHD) medications during pregnancy concerns central nervous system stimulants, while little is known about the safety of atomoxetine, a primary treatment alternative. We assessed the prevalence of major congenital malformations overall, and cardiac malformations and limb malformations specifically, after first-trimester exposure.

Methods: In this cohort study, we included all approximately 2.4 million pregnancies ending in live births recorded in the population-based nationwide health registers of Denmark, Iceland, Norway, and Sweden (2003–2017) and approximately 1.8 million publicly insured pregnancies ending in live births recorded in the US Medicaid Analytic eXtract (MAX, 2001–2013) health care claims database. We compared the prevalence of major congenital malformations in the newborn among pregnancies exposed and unexposed to atomoxetine. For each country, we calculated prevalence ratios (PRs), crude and stratified by propensity scores (PSs). We pooled the country-specific PS strata to obtain a PR adjusted for potential confounding factors.

Results: We identified 368 pregnancies exposed to atomoxetine during the first trimester in the 4 Nordic countries and 622 in the US. The pooled crude PR for any major congenital malformation was 1.18 (95% CI, 0.88–1.60), and the adjusted PR was 0.99 (95% CI, 0.74–1.34). For cardiac malformations, the adjusted PR was 1.34 (95% CI, 0.86–2.09). For limb malformations, the adjusted PR was 0.90 (95% CI, 0.38–2.16).

Conclusions: After atomoxetine exposure in early pregnancy, we observed no increase in major congenital malformations overall and, although with some uncertainty due to sample size, no statistically increased risk estimates for cardiac malformations and limb malformations.

J Clin Psychiatry 2023;84(1):22m14430

To cite: Bröms G, Hernandez-Diaz S, Huybrechts KF, et al. Atomoxetine in early pregnancy and the prevalence of major congenital malformations: a multinational study. *J Clin Psychiatry.* 2023;84(1):22m14430.

To share: https://doi.org/10.4088/JCP.22m14430

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Treatment for attention-deficit/hyperactivity disorder (ADHD) is increasingly common among women of reproductive age.[1–4] Previous studies on ADHD medication use in pregnancy and risk of congenital malformations[5–8] have focused on central nervous system (CNS) stimulants, mainly methylphenidate and amphetamines. Data on the potential teratogenicity of in utero exposure to atomoxetine, a selective norepinephrine reuptake inhibitor also used to treat ADHD,[9,10] are very limited.[11] Two studies[7,12] that reported on atomoxetine as one ADHD medication of several in a variable defined by exposure to any ADHD medication raised no concerns, and likewise for a recent study[13] that reported separately on atomoxetine and the risk of major malformations in general. In studies of rabbits and rats,[14] high doses of atomoxetine (25–100 mg/kg/d compared to

Clinical Points

- Treatment for attention-deficit/hyperactivity disorder (ADHD) is increasing among women of reproductive age, but little is known about atomoxetine treatment in pregnancy.
- When considering whether or not to continue atomoxetine treatment in pregnancy, the individual's need of treatment can be weighed against the absence of an increase in major congenital malformations overall in this study, although the risk estimates for cardiac and limb malformations were uncertain due to sample size.

the recommended dose in humans of 1.2–1.8 mg/kg/d) have been associated with reduced fetal and postnatal viability in rodents, particularly with increased frequency of cardiovascular malformations and incomplete ossification of bones.

In light of the limited safety information, discontinuation of atomoxetine in preparation for pregnancy may be the clinically preferred option.[15] However, the health consequences of following discontinuation for the mother and child have, to our knowledge, not been well studied either.[16,17] Untreated symptoms of impulsivity and inattention may lead to impaired relationships and professional lives among pregnant women with ADHD, and hyperactivity has been linked to unhealthy prenatal lifestyle choices, such as continuation of smoking.[18,19] Furthermore, exposure to ADHD medication may occur inadvertently in yet undetected pregnancies during the first trimester, coinciding with the time that the fetus is most vulnerable to developing congenital malformations.

Aims of the Study

In this study, we assessed the association between atomoxetine use in early pregnancy and overall major congenital malformations, and cardiac and limb malformations specifically. The study was conducted as part of the International Pregnancy Safety Study (InPreSS), which combines register data from the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) and the US.

METHODS

According to the data availability in each country, we identified all liveborn singletons in Denmark (2005–2012), Iceland (2003–2017), Norway (2005–2017), and Sweden (July 2006–2016) and all liveborn infants in the US Medicaid Analytic eXtract (MAX; 2001–2013). We compared the prevalence of major congenital malformations among infants born to women exposed to atomoxetine in the first trimester to the prevalence among infants born to women not exposed to any ADHD drug during the period extending from 3 months before their last menstrual period (LMP) to the end of the first trimester. Data from Finland were ultimately not included in this study, as no patients were exposed to atomoxetine during the period for which data were available (2002–2012).

Data Sources and Study Population

We obtained data on births, filled drug prescriptions, malformations, and potential confounders from the national health registers of each Nordic country. These registers prospectively collect data on all residents. Reporting to the registers is mandatory and regulated by national laws.[20] The Nordic countries are considered relatively similar in terms of population composition, access to health care/medications, and availability of health registers.[21–23] A personal identification number assigned to all residents upon birth or immigration enables data linkage on an individual level among the registers. In the medical birth registers, all pregnancies leading to live births or stillbirths are recorded from week 22 or from week 28, depending on the country and year.[24]

We also included data from the US pregnancy cohort nested in the nationwide MAX health care claims database. Medicaid covers approximately 50% of deliveries in the US.[25] To be eligible for the study, pregnant women aged 12–55 years were required to be continuously enrolled in Medicaid from 3 months before the date of their LMP to 1 month after delivery, and their liveborn infants were required to be enrolled for the first 3 months of life or until death.

The Nordic health registers and the MAX pregnancy cohort have been used previously to study drug safety during pregnancy.[26] They were combined recently to study the safety of CNS stimulants.[8] We applied the same general design and analytic strategy to each country's dataset but allowed certain differences. For example, each participating country contributed data for different periods according to the availability of data from the registers.

Ascertainment of Exposure

The Nordic prescription registers include detailed information on dispensed drugs, including the date a prescription was filled and Anatomic Therapeutic Chemical (ATC) code.[27,28] The MAX database includes data on claims for filled prescriptions, including date, by substance name. A pregnancy was considered exposed if a prescription for atomoxetine was filled during a women's first trimester, from date of LMP to the end of 3 months of pregnancy. Women with exposed pregnancies were compared to women without filled prescriptions for ADHD medication in the first trimester or during the 3 months before. Pregnancies in which women were exposed to methylphenidate or amphetamines in this time period were excluded from the analyses.

Major Congenital Malformations

From the Nordic birth, patient, and cause-of-death registers, we retrieved data on major congenital malformations diagnosed within 1 year after birth for all countries except Norway, where the ascertainment period was 3 months. The Nordic patient registers record information on diagnoses and hospital contacts for inpatient and outpatient care. To

define a major congenital malformation, we required at least 1 inpatient diagnosis or 2 outpatient diagnoses coded according to the *International Statistical Classification of Diseases and Related Health Problems*, *10th revision* (*ICD-10*) (Supplementary Table 1).

In the MAX database, major congenital malformations were identified from maternal and infant health records within 3 months after birth. Maternal records were considered because Medicaid claims are sometimes recorded under the mother's name before her infant's eligibility has been determined.[29] To identify a malformation, we required 1 of the following: at least 2 inpatient or outpatient *ICD-9* diagnoses, 1 diagnosis followed by corrective surgery identified from procedure codes, or 1 diagnosis if the infant died within 3 months (Supplementary Table 1).

Major congenital malformations were considered as a group and by the organ-specific subgroups of cardiac malformations and limb malformations, defined as shown in Supplementary Table 1. We excluded pregnancies in which a fetal chromosomal abnormality was detected in the infant during the first year of life (first 3 months in Norway and in the US) (Supplementary Table 1).

Covariates

We used a common list of covariates in each country to adjust for potential confounding. Some variation was allowed, depending on data availability. A complete list of covariates included in the adjusted analyses is provided in Supplementary Table 2. In the Nordic countries, maternal diagnoses were identified from *ICD-10* codes in the patient and birth registers in the period extending from 1 year before LMP to end of the first trimester. In the US MAX, diagnoses were identified from claims for each condition during the 3 months before LMP to end of the first trimester. In both the Nordic countries and the US MAX, maternal exposure to medications other than atomoxetine was determined based on filled prescriptions in the period extending from 3 months before LMP to the end of the first trimester.

Covariates included maternal characteristics such as maternal age, calendar year of delivery, obstetric and medical characteristics, psychiatric conditions, hypertension, pregestational diabetes, chronic renal disease, and obesity. In the Nordic countries, smoking (except for Icelandic data, in which this information is not available) and Nordic/non-Nordic country of birth were included. Similarly, race/ethnic group and tobacco use were included from the US MAX. Medication use that was considered was of psychotropics and potential teratogens. Exposure to medications previously associated with teratogenic effects was an exclusion criterion for the US MAX and was adjusted for in the analyses for the Nordic countries. General markers of the burden of illness were assessed during the 3 months before pregnancy to characterize baseline health care needs.

Statistical Analyses

Data from the contributing countries were analyzed at each study center and later pooled at Karolinska Institutet, Stockholm, Sweden, using a meta-analytic approach. We calculated the prevalence ratio (PR) of major congenital malformations among infants born to women who had been treated with atomoxetine in early pregnancy, compared to infants of untreated women. In each national data set, a propensity score was obtained by fitting a logistic regression model that predicted the probability of exposure using the aforementioned covariates. Observations from non-overlapping regions of the propensity score distributions were excluded. We created propensity score strata based on the distribution among treated women, aiming for 50 strata. We weighted the observations for untreated women using the distribution obtained for treated women. Each country reported crude frequencies of malformations for treated and untreated women, as well as a set of results by propensity score–weighted individual strata to be pooled according to the Mantel-Haenszel method and presented as adjusted PRs. Countries were analyzed separately, but since the Nordic populations and registers are similar, we combined their data in the presentation of results.

A predefined sensitivity analysis was performed to assess the possibility of exposure misclassification. We widened the exposure window to include pregnancies in which women had filled at least 1 prescription during the period extending from 30 days before LMP to the end of the first trimester for the Nordic cohorts. The corresponding analysis for the US was for women with a "days' supply" extending into the first trimester (ie, date of prescription fill + duration of prescription overlapped with the first trimester).

All analyses were conducted using SAS software, version 9.4 (SAS Institute; Cary, North Carolina).

RESULTS

Among 2,440,606 pregnancies in the Nordic countries ending in live births, 368 women had filled a prescription for atomoxetine during their first trimester. Of 1,797,938 pregnancies ending in live births in the MAX database, 622 were exposed to atomoxetine in the first trimester. Women who used atomoxetine were younger and more often smokers and obese than women who did not use atomoxetine. Key characteristics of the women included in the analysis from Nordic countries and from the US are presented in Table 1.

Any Malformation

There were 89,005 infants (37 per 1,000) with major malformations in the unexposed groups in the Nordic countries and 63,047 (35 per 1,000) in the US MAX (Table 2). For pregnancies exposed to atomoxetine, the corresponding prevalence was 52 per 1,000 infants in the Nordic countries and 37 per 1,000 infants in the US MAX. There were no cases of malformations among the exposed in Denmark or in Iceland. The crude PR was 1.42 (95% CI, 0.91–2.20) in the Nordic countries and 1.06 (95% CI, 0.71–1.58) in the US. Considering the propensity score lowered the PRs to 1.16 (95% CI, 0.75–1.80) in the Nordic

Table 1. Cohort Characteristics of Infants Born to Women Who Filled Prescriptions for Atomoxetine in Early Pregnancy and Infants Born to Women Without Prescriptions for any ADHD Drug (ie, Population)

	Nordic Countries		US MAX	
	Atomoxetine, n (%)	Population, n (%)	Atomoxetine, n (%)	Population, n (%)
Total	368 (100)	2,440,606 (100)	622 (100)	1,797,938 (100)
Maternal age, y				
<19	69 (18.8)	46,797 (1.9)	247 (39.7)	410,211 (22.8)
20–24	99 (26.9)	335,295 (13.7)	138 (22.2)	616,976 (34.3)
25–29	99 (26.9)	769,287 (31.5)	122 (19.6)	436,483 (24.3)
30–34	71 (19.3)	824,591 (33.8)	70 (11.3)	215,686 (12.0)
35–39	23 (6.3)	389,433 (16.0)	35 (5.6)	93,875 (5.2)
≥40	7 (1.9)	75,203 (3.1)	<11	24,707 (1.4)
Hypertension	<5	9,229 (0.4)	12 (1.9)	41,610 (2.3)
Obesity				
Yes	42 (12.1)	206,218 (9.0)	12 (2.1)	39,148 (2.2)
Missing, n[a]	21	151,181		
Depression	148 (40.2)	100,045 (4.1)	171 (27.5)	89,873 (5.0)
Tobacco				
Yes	128 (36.0)	195,071 (8.4)	49 (7.9)	62,254 (3.5)
Missing, n[a]	13	109,977	…	…
ADHD	207 (56.3)	5,357 (0.2)	279 (44.9)	10,170 (0.6)
Antidepressants	148 (40.2)	100,045 (4.1)	373 (60.0)	155,155 (8.6)
Antipsychotics	69 (18.8)	19,579 (0.8)	181 (29.1)	22,661 (1.3)
Antihypertensives	21 (5.7)	25,766 (1.1)	61 (9.8)	46,949 (2.6)
Opioids	43 (11.7)	95,818 (3.9)	212 (34.1)	355,764 (19.8)

[a]Infants of women with missing values are not included in the denominator of the proportions.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, MAX = Medicaid Analytic eXtract.

Table 2. Comparison of the Risk of Major Malformations Between Infants Born to Women Exposed to Atomoxetine in Early Pregnancy and Infants Born to Women Without Exposure to any ADHD Drug

Variable	Events in Infants to Women Exposed to Atomoxetine, No. (per 1,000)	Events in Infants to Women Without Exposure, No. (per 1,000)	Crude PR (95% CI)[a]	Adjusted PR (95% CI)[a]
Any major malformation				
Nordic countries	19 (52)	89,005 (37)	1.42 (0.91–2.20)	1.16 (0.75–1.80)
US MAX	23 (37)	63,047 (35)	1.06 (0.71–1.58)	0.90 (0.60–1.36)
All countries	42 (42)	152,052 (36)	1.18 (0.88–1.60)	0.99 (0.74–1.34)
Cardiac malformations				
Nordic countries	6 (16)	30,591 (13)	1.30 (0.59–2.88)	1.11 (0.50–2.45)
US MAX	14 (23)	22,583 (13)	1.79 (1.07–3.01)	1.49 (0.87–2.55)
All countries	20 (20)	53,174 (13)	1.61 (1.04–2.49)	1.34 (0.86–2.09)
Limb malformations				
Nordic countries	5 (14)	9,627 (4)	3.45 (1.44–8.23)	2.87 (1.20–6.85)
US MAX	0 (0)	11,481 (6)	…	…
All countries	5 (5)	21,108 (5)	1.01 (0.42–2.43)	0.90 (0.38–2.16)

[a]A propensity score was obtained by fitting a logistic regression model that predicted the probability of exposure using the covariates listed in Supplementary Table 2. Each country reported crude results as well as results by the propensity score–weighted individual strata to be pooled according to the Mantel-Haenszel method and presented as crude and adjusted PRs, respectively.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, MAX = Medicaid Analytic eXtract, PR = prevalence ratio.

countries and to 0.90 (95% CI, 0.60–1.36) in the US cohort. Pooling estimates across all countries yielded a crude PR of 1.18 (95% CI, 0.88–1.60) and an adjusted PR of 0.99 (95% CI, 0.74–1.34).

Cardiac and Limb Malformations

For cardiac malformations, the crude and adjusted PRs were 1.30 (95% CI, 0.59–2.88) and 1.11 (95% CI, 0.50–2.45) in the Nordic countries and 1.79 (95% CI, 1.07–3.01) and 1.49 (95% CI, 0.87–2.55) in the US MAX. The pooled estimates yielded a crude PR of 1.61 (95% CI, 1.04–2.49) and an adjusted PR of 1.34 (95% CI, 0.86–2.09).

For limb malformations, the adjusted PR estimate in the Nordic countries was 2.87 (95% CI, 1.20–6.85). As there were no cases of limb malformation in the US, the pooled PR decreased to 0.90 (95% CI, 0.38–2.16). Extending the definition of timing of exposure to include 30 days before LMP in the Nordic countries and filled prescriptions with a days' supply overlapping with the first trimester in the US did not change the results markedly, except for cardiac malformations in the US MAX (crude PR = 2.14 [95% CI, 1.44–3.18] and adjusted PR = 1.90 [95% CI, 1.28–2.82]), resulting in a pooled adjusted estimate of 1.43 (95% CI, 1.01–2.03) (Supplementary Table 3).

DISCUSSION

In this multinational study including over 4 million births in Nordic countries and the US, we did not observe a meaningful association between maternal atomoxetine use and major congenital malformations overall. The relative risk estimate for cardiac malformations was slightly increased, but the association was estimated imprecisely. The elevated risk observed for limb malformations in the Nordic countries was not found in the US, which had no malformations of this type among exposed pregnancies. Both the exposure and the outcomes were rare, resulting in limited precision and some remaining uncertainty despite the large size of the study; nevertheless, large increases in specific congenital malformations appear implausible.

Very few studies have reported on the risk of congenital malformations in offspring of women taking atomoxetine in early pregnancy. Concerning other ADHD medications, one study from our group[8] reported slightly increased risks of cardiac malformation associated with methylphenidate use in early pregnancy. Given their different mechanisms of action,[9] methylphenidate and atomoxetine would not necessarily share a teratogenic profile, acknowledging the limited knowledge about the pathophysiology of congenital malformations. In our study, the adjusted risk of cardiac malformations in offspring of atomoxetine users was increased by almost 50% in the US data, with a higher risk estimate in the sensitivity analysis using an extended time period to define atomoxetine exposure. This resulted in a slightly elevated pooled relative risk. This finding may accord with early animal studies reporting an association with cardiovascular malformations.[14] However, the risk estimate was not increased in the Nordic data with either exposure definition, which along with the lack of increase of congenital malformations in general associated with atomoxetine is reassuring.

Incomplete ossification as seen in animal studies on atomoxetine[14] is not expected to be associated with malformations.[30] However, while there was an increased risk of limb malformations observed in the Nordic countries, it is reassuring that there were no exposed cases of limb malformations in the US data.

Strengths and Limitations

Drug safety studies of rare exposures and outcomes are challenging. The current study took advantage of a collaboration within the InPreSS consortium, which aims at pooling data from the 5 Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) and the US to increase statistical precision in pregnancy safety studies. Our study overlaps with previous studies using Swedish and Danish data[7,12,13] to some extent, but with its multicountry approach is significantly larger. Nevertheless, it was still limited by imprecise risk estimates. Data use agreements did not allow pooling of individual data in the same data set, but they did allow us to analyze data on an aggregate level. We created propensity score–based strata in each country, which were pooled using the Mantel-Haenszel method. This approach allowed us to include information from countries without exposed cases, for which a country-specific relative risk could not be calculated. These countries otherwise would have been excluded, potentially biasing the result of a conventional meta-analysis. For example, including the US data (in which there were no exposed cases with limb malformations) in the meta-analysis allowed us to validate and likely refute the high risk of limb malformations observed in the Nordic data.

The population-based data from the Nordic countries and the US MAX data, which cover close to 50% of pregnancies in the United States, were prospectively collected. Thus, recall bias was avoided. A common data model was used to strengthen the pooled analysis, although small deviations from the protocol were allowed to make use of the best available information.

However, the study also has limitations. Exposure to atomoxetine was defined by prescriptions filled in the first trimester and does not necessarily correspond to actual intake, which may bias results toward the null. Nevertheless, information on drugs dispensed to patients has been found to be more indicative of actual use than prescriptions alone.[31] Even exposure in a short time window or as a single dose may potentially result in congenital malformations, as in the case with thalidomide.[32] To explore the importance of temporal misclassification of exposure, we redefined the exposure time window in a sensitivity analysis, which yielded results qualitatively similar to those of the main analysis (Supplementary Table 3).

The outcome was defined by diagnoses of major congenital malformations in live born infants and did not include pregnancies that ended in stillbirth or spontaneous or therapeutic abortions. Unless there is a difference in the frequency of non-live births by both exposure status and outcome status, this definition of outcome could bias the results, ie, if atomoxetine-exposed pregnancies with a malformation more often end in non-live births than unexposed pregnancies with a malformation. Spontaneous abortions are notoriously difficult to assess, since most represent very early losses. Although not specific to atomoxetine exposure, previous studies from the Nordic countries[33,34] have reported that less than 5% of pregnancies with cardiac or limb malformations end in therapeutic abortion, and that for antidepressants, terminations and stillbirths because of malformations were similar among the exposed and the unexposed.

To minimize misclassification, we required at least 1 diagnosis from inpatient care or 2 from outpatient care in the Nordic data and 2 diagnoses or 1 followed by corrective surgery or death in the US data. In the US and in Norway, infants were followed for 3 months, while in the other countries, follow-up was until 1 year of age. With a longer follow-up, less evident malformations may be detected and minor congenital malformations or non-congenital diagnoses may be included, but this misclassification is likely to be equally distributed among exposed and unexposed

pregnancies. We excluded pregnancies in which a fetal chromosomal abnormality was detected in the infant. We did not consider it feasible to determine other genetic causes and exclude them from the analyses, given the small numbers and the limited possibility of determining genetic factors as the sole cause for a specific malformation in the registers.

We found no increased prevalence of major congenital malformations overall associated with atomoxetine use in early pregnancy. The increased prevalence of limb malformations in the Nordic countries was not observed in the US. Similarly, the increased prevalence of cardiac malformations in the US was not observed in the Nordic countries, although the pooled estimate was slightly increased. Given the low absolute risk of both of these outcomes, these results are reassuring from a public health perspective and provide important information in the consideration of whether to continue treatment with atomoxetine during pregnancy.

Submitted: February 18, 2022; accepted September 20, 2022.

Published online: January 16, 2023.

Relevant financial relationships: **Dr Bröms** has been a speaker for Takeda and has been involved in projects at Centre for Pharmacoepidemiology, Karolinska Institutet, partly financed by Janssen, Pfizer, and UCB, all unrelated to this project. **Dr Hernandez-Diaz** is an investigator on grants to her institution from Takeda for unrelated studies, has received personal consulting fees from UCB and Roche outside the submitted work, and has served as an epidemiologist with the North America AED pregnancy registry and as a scientific advisor for the National Pregnancy Registry for Psychiatric Medication and for Pregistry, which are funded by multiple companies. **Dr Huybrechts** reports being an investigator on research grants to her institution from Takeda and UCB for unrelated studies. **Mr Karlsson** is employed at the Centre for Pharmacoepidemiology, Karolinska Institutet, which receives grants from several entities (pharmaceutical companies, regulatory authorities, and contract research organizations) for performance of drug safety and drug utilization studies, with no relation to the work reported in this article. **Dr Nørgaard** is employed at the Department of Clinical Epidemiology, Aarhus University Hospital, which receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies has any relation to the present study. **Dr Reutfors** is employed at the Centre for Pharmacoepidemiology, Karolinska Institutet, which receives grants from several entities (pharmaceutical companies, regulatory authorities, and contract research organizations) for performance of drug safety and drug utilization studies, with no relation to the work reported in this article. **Dr Sørensen** is employed at the Department of Clinical Epidemiology, Aarhus University Hospital, which receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study. **Dr Zoega** is employed at the Centre for Big Data Research in Health, UNSW Sydney, which received funding from AbbVie Australia in 2020 to conduct research, unrelated to this study. AbbVie did not have any knowledge of, or involvement in, this study. **Dr Kieler** is employed at the Centre for Pharmacoepidemiology, Karolinska Institutet, which receives grants from several entities (pharmaceutical companies, regulatory authorities, and contract research organizations) for performance of drug safety and drug utilization studies, with no relation to the work reported in this article. **Drs Bateman**, **Einarsdóttir**, **Engeland**, **Furu**, **Gissler**, **Klungsøyr**, and **Lahesmaa-Korpinen**; **Mr Kristiansen**; and **Ms Mogun** report no conflicts of interest.

Funding/support: This study was supported by the Söderström-König Foundation (SLS-664411); the Swedish Society of Medicine (SLS-689141); and the Stockholm Region (clinical postdoc appointment SLL-20170670); partly supported by the Research Council of Norway through its Centres of Excellence funding scheme (Project# 262700); NordForsk as part of the Nordic Pregnancy Drug Safety Studies (NorPreSS; Project# 83539); the Research Council of Norway as part of the International Pregnancy Drug Safety Studies (InPreSS; Project# 273366); UNSW Scientia Award (to H.Z.); The Drugs and Pregnancy project, funded by the Finnish Institute for Health and Welfare (THL), the Finnish Medicines Agency (FIMEA), and the Social Insurance Institution of Finland (Kela); the National Institute of Child Health and Human Development (R21 HD092879); and the National Institute of Mental Health (R01 MH116194).

Role of the sponsor: The funding sources had no role in the design and conduct of the study or in the decision to publish.

Previous presentation: An oral presentation of this work (title: ADHD Drugs During Pregnancy and the Risk of Congenital Malformations: A Study from the International Pregnancy Safety Study [InPreSS] Consortium) was made at the International Conference of Pharmacoepidemiology and Drug Safety; Montreal, Canada; August 26-30 2017.

Ethical approval: The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (2015/1826-31/2); the National Bioethics Committee in Iceland (VSNb201860017/03.01); the Steering Committee of the Drugs and Pregnancy Project; the Norwegian Data Inspectorate and the Regional Ethics Committee for Medical Research of South/East Norway); and the Danish Data Protection Agency (2015-57-0002). The use of the US data was approved by the Institutional Review Board of Brigham and Women's Hospital, which granted a waiver of informed consent.

Additional information: The data in this study were obtained from national health registers in Denmark, Iceland, Norway, and Sweden and the US Medicaid Analytic eXtract and cannot be made publicly available in their entirety due to national laws and data privacy.

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Supplementary material: Available at Psychiatrist.com.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.

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CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Atomoxetine in Early Pregnancy and the Prevalence of Major Congenital Malformations: A Multinational Study

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DOI Number: https://doi.org/10.4088/JCP.22m14430

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1. **Table 1** Codes used to determine exposure and outcome status
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Supplementary tables for *Atomoxetine in early pregnancy and the prevalence of congenital malformations: A multinational study, Bröms et al.*

Supplementary Table 1. Codes used to determine exposure and outcome status			
	US MAX		**Nordic countries**
Codes used in outcome definition	**ICD-9**		**ICD-10**
Major congenital malformation	740-759		Q00.0 - Q89 Except: Q17.0, Q38.1, Q53, Q65.0-Q65.6, Q82.5, Q86.
Cardiac defects	745-747		Q20.0-Q26.4, Q26.8, Q26.9
Limb defects	754.5x, 755.x Except: 754.52, 754.53, 754.6x, 754.7x, 754.81, 754.82		Q66, Q68-Q74 Except: Q66.2-Q66.9, Q68.0, Q68.3-Q68.5
Chromosomal anomaly	758		Q90-99
Codes used in outcome definition	**ICD-9**	**CPT-4**	
Cardiac procedures and surgery codes	35.x, 36.x, 37.x (except 37.94), 38.x (except 38.18, 38.91, 38.92, 38.93, 38.94, 38.95, 38.98, 38.99), 39.x (except 39.27, 39.50, 39.95, 39.98)	00560, 00561, 00563, 33300-35190, 92992, 92993, 93530, 93531, 93532, 93533	
Codes used in exposure definition			**ATC**
Atomoxetine			N06BA09
Methylphenidate			N06BA04
Amphetamines			N06BA01-02, N06BA12

Supplementary tables for *Atomoxetine in early pregnancy and the prevalence of congenital malformations: A multinational study, Bröms et al.*

Supplementary Table 2. Main differences in the design and analytic approaches used for the US and Nordic data.		
	US MAX cohort	**Nordic cohorts/countries**
Cohort	Live births	Live singleton births
Exclusions	Medications previously associated with teratogenic effects: Warfarin, ACE-inhibitors, antineoplastic drugs, colchicine, lithium, isotretinoin, misoprostol, thalidomide, valproic acid, carbamazepine	Gestational weeks ≤22 or >44 weeks
		Birth weight <300 g or >7000 g
Exposure window	First trimester: LMP to LMP + 90 days	First trimester: LMP to LMP + 97 days
Reference group	No exposure from 3 months before LMP to LMP + 90 days	No exposure from LMP to LMP + 97 days
Outcome assessment	First 3 months of life	First year of life, except first 3 months of life in Norway
Covariate assessment	ICD-9	ICD-10
	3 months before LMP to LMP + 90 days: Hypertension, diabetes, chronic renal disease, migraine/headache, sleep disorder/anxiety, delirium, depression, bipolar disorder, psychosis, schizophrenia, personality disorder, reaction to severe stress and adjustment disorders, anxiety, alcohol use disorder, other substance use disorder, epilepsy or convulsions	1 year before LMP to delivery, ICD-10: Hypertension O10, O16, I10-15, diabetes A10, chronic renal disease N00-19, N25-262, delirium, depression, bipolar disorder, psychosis, schizophrenia, personality disorder, reaction to severe stress and adjustment disorders, anxiety F40-48, except F43, alcohol use disorder Z71.4, O35.4, F10, other substance use disorder F11-19, Z71.5, Z86.4, epilepsy or convulsions G40
	3 months before LMP to LMP + 90 days: Number of distinct non-ADHD prescription drugs, number of physician visits, hospitalizations, number of distinct diagnoses, number of emergency visits, maternal comorbidity index	90 days before LMP to LMP + 97 days, ATC codes for non-ADHD drug prescriptions 1 year before LMP to LMP + 97 days, ICD-10 codes for hospitalizations, number of distinct main diagnoses
	ADHD	ADHD, ICD-10: F90
	Race/Ethnic group	Mothers' country of birth as recorded in birth register, (Nordic/non-Nordic)
	State of delivery	Country of delivery
	3 months before LMP to LMP + 90 days: Benzodiazepines, other hypnotics, barbiturates, anxiolytics, anticonvulsants, antidepressants, antipsychotics, antidiabetics/insulin, antihypertensives, opiods, methadone, buprenorphine, naltrexone, naloxone, triptans, NSAIDs	90 days before LMP to LMP + 97 days, ATC codes for concomitant drug use: migraine/headache N02C, sleep disorder/anxiety N05C, depression N06A, benzodiazepines, other hypnotics, barbiturates, anxiolytics, N05B, N05C, except N05CH (melatonin), anticonvulsants N03, antipsychotics N05A, antidiabetics/insulin A10, antihypertensives C02-04, C07-09, opioids N02A, methadone N07BC02, buprenorphine N07BC01,

		naltrexone N07BB04, naloxone V03AB15, triptans N02C, NSAIDs M01A Potential teratogens: Danazol G03XA01, progestins G03D, methimazole, propylthiouracil H03BA, corticosteroids H02, fluconazole J02AC01 Medications previously associated with teratogenic effects: Warfarin B01AA03, ACE-inhibitors C09, antineoplastic drugs L01, colchicine M04AC01, lithium N05AN01, isotretinoin D05BB, misoprostol A02BB01, thalidomide L04AX02, valproic acid N03AG01, carbamazepine N03AF01
	3 months before LMP until LMP+90, date prescription was filled + duration of prescription. Potential teratogens: Danazol, progestins, methimazole, propylthiouracil, corticosteroids, fluxonazole	
	Obesity/overweight according to diagnostic codes, 3 months before LMP until LMP+90	Body mass index according to birth registers recorded at first antenatal visit, obesity BMI ≥30.0 kg/m^2
	Tobacco use according to diagnostic codes, 3 months before LMP until LMP+90	Smoking in the first trimester as recorded in the birth registers from first antenatal visit
	Preterm birth according to diagnostic codes	Preterm birth < 258 days, 37 weeks, as recorded in the birth registers Parity
Adjustment for confounding	Fine stratification on the propensity score	Fine stratification on the propensity score

ACE-inhibitors: Angiotensin converting enzyme inhibitors; ADHD: Attention deficit hyperactivity disorder; ATC: Anatomical Therapeutic Chemical Classification System; BMI: Body mass index; ICD: International Statistical Classification of Diseases and Related Health Problems; LMP: last menstrual period; NSAIDs: Non-steroidal anti-inflammatory drugs

Supplementary table 3. Comparison of the risk of major malformations between infants born to women exposed to atomoxetine in early pregnancy and infants born to women without exposure to any ADHD drug. Sensitivity analysis changed exposure period †

	Events in infants to women exposed to Atomoxetine N (per 1,000)	Events in infants to women without exposure N (per 1,000)	Crude PR (95% CI)	Adjusted PR (95% CI)
Any major malformation				
Nordic countries	22 (4.4)	89 005 (3.7)	1.20 (0.80 – 1.81)	1.00 (0.66 – 1.50)
US MAX	44 (4.9)	63 047 (3.5)	1.41 (1.05 – 1.87)	1.22 (0.92 – 1.63)
All countries	66 (4.7)	152 052 (3.6)	1.32 (1.04 – 1.67)	1.12 (0.89 – 1.42)
Cardiac malformations				
Nordic countries	7 (1.4)	30 591 (1.3)	1.11 (0.53 – 2.32)	0.83 (0.40 – 1.73)
US MAX	24 (2.7)	22 583 (1.3)	2.14 (1.44 – 3.18)	1.90 (1.28 – 2.82)
All countries	31 (2.2)	53 174 (1.3)	1.77 (1.25 – 2.51)	1.43 (1.01 – 2.03)
Limb malformations				
Nordic countries	6 (1.2)	9 627 (0.4)	3.02 (1.37 – 6.70)	2.48 (1.12 – 5.49)
US MAX	<11	11 481 (0.6)	0.18 (0.03 – 1.24)	0.17 (0.02 – 1.17)
All countries	7 (0.5)	21 108 (0.5)	1.01 (0.48 – 2.11)	0.86 (0.41 – 1.81)

†Nordic countries: Atomoxetine (LMP-30 days to LMP+97 days); US MAX: filled prescriptions with a days' supply overlapping with the first trimester
Numbers below 11 in the data from the US are not shown for integrity reasons.

ADHD: Attention deficit hyperactivity disorder
PR: prevalence ratio
MAX: Medicaid Analytic Extract
[a] A propensity score was obtained by fitting a logistic regression model that predicted the probability of exposure using the covariates listed in Supplementary table 2. Each country reported crude results as well as results by the propensity score-weighted individual strata to be pooled according to the Mantel-Haenszel method and presented as crude and adjusted PRs, respectively.