Title:

Antidepressant use in pregnancy and severe cardiac malformations: Danish register-based study

Running title:

Antidepressants and severe cardiac malformations

Line Kolding, MD, PhD[1,2]
Vera Ehrenstein, MPH, DSc, Professor[2,3]
Lars Pedersen, MSc, PhD, Professor[2,3]
Puk Sandager, MD, PhD, Associate Professor[1,2,4]
Olav B. Petersen, MD, PhD, Professor[5,6]
Niels Uldbjerg, MD, DMSc, Professor[1,2]
Lars H. Pedersen, MD, PhD, Professor[1,2,7,8]

[1] Department of Obstetrics and Gynecology, Aarhus University Hospital, Aarhus, Denmark
[2] Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
[3] Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus University, Aarhus, Denmark
[4] Centre for Fetal Diagnostics, Aarhus University Hospital, Aarhus University, Aarhus, Denmark
[5] Department of Obstetrics, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[6] Department of Clinical Medicine, University of Copenhagen, Copenhagen, Copenhagen, Denmark
[7] Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus, Denmark
[8] Department of Biomedicine, Aarhus University, Aarhus, Denmark

Corresponding:
Lars Henning Pedersen
Aarhus University Hospital
Palle Juul-Jensens Blvd. 99, 8200 Aarhus N, Denmark
Email: lhp@clin.au.dk
Phone: +45 50526512

ABSTRACT

Objective Studies restricted to live births may underestimate severe teratogenic effects. We address the limitation by including data from both prenatal and postnatal diagnoses of cardiac malformations.

Design Register-based study.

Setting Denmark.

Population 364,012 singleton pregnancies from 2007 to 2014.

Methods We used data from five nationwide registries. Exposure to antidepressants was measured using redeemed prescriptions.

Main Outcome Measures Pregnancies with cardiac malformations that end in miscarriage, termination, stillbirth, postnatal death or cardiac surgery <1 year of birth were classified as severe cardiac malformations (SCM). Propensity scores with adjusted prevalence ratios (PRs) were calculated.

Results SCM were reported in 972 / 364 012 pregnancies overall and in 16 / 4105 exposed. PRs for SCM were 1.09 (95%CI: 0.52–2.30) for selective serotonin reuptake inhibitors (SSRIs) and 2.13 (95%CI: 0.89–5.13) for venlafaxine. Among the venlafaxine-exposed pregnancies, there was a cluster of hypoplastic left heart syndromes (HLHS) (crude PR 17.4 (95%CI: 6.41–47.2)) of which none ended in a live birth. For HLHS, the absolute risk increase was 4.4 per 1000, the number needed to harm (NNH) was 225. PRs for cardiac malformations not classified as SCM were 1.38 (95%CI: 1.00–1.92) for SSRIs, and 1.73 (95%CI: 1.08–2.77) for venlafaxine.

Conclusions Pregnancy exposure to venlafaxine, but not SSRIs, is associated with an increased risk of SCM but with a low absolute risk. Potential mechanisms include direct effects or confounding by indication. Venlafaxine exposure is a marker for risk pregnancies for which fetal echocardiography may be considered.

Keywords pregnancy, antidepressants, SSRI, venlafaxine, prenatal ultrasound, selection bias

Tweetable abstract Exposure to venlafaxine, but not SSRIs, is associated with an increased risk of severe cardiac malformations, but with a low absolute risk.

INTRODUCTION

Depression affects 6%– 15% of pregnant women.(1, 2) Selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed antidepressants, followed by serotonin-norepinephrine reuptake inhibitors (SNRIs), primarily venlafaxine.(3) Up to 4.5% of pregnant women in Europe are prescribed an SSRI during pregnancy;(1, 4) prevalence of first trimester use is about 1.6% for SSRIs and 0.1% for venlafaxine.(3)

The monoaminergic systems are important for several aspects of fetal brain development. In addition to its neurotransmitter function in the brain, serotonin is a signaling molecule important for embryogenesis, involved in cell division, differentiation, migration, and synaptogenesis.(5, 6) Norepinephrine is crucial for embryonic heart development and survival, but its exact regulatory role and physiological targets are not fully understood.(7) Several studies, including a 2018 meta-analysis of 29 studies, showed that first-trimester exposure to SSRIs was associated with 1.4-fold increased risks of septal defects and right ventricular outflow tract defects,(8-10) and with 3.2- and 8.2-fold increased risks of tetralogy of Fallot (ToF) and Ebstein's anomaly.(11) However, not all studies showed these associations.(3, 12-15) With respect to venlafaxine and duloxetine, which inhibit receptors of both serotonin and noradrenaline, most evidence, including a systematic review (venlafaxine n=3186, duloxetine n=668), does not suggest an association,(16) except for one case-control study reporting an association between first-trimester exposure to venlafaxine and risk of several types of malformations, including a 3.1-fold increased risk of atrial septal defect (ASD) and a 4.1-fold increased risk of coarctation of aorta (CoA).(17)

A limitation of many studies of drug teratogenicity is lack of data on malformations among pregnancies ending in abortive outcomes. A drug that causes a lethal malformation may appear harmless or even protective in analyses restricted to live births if most exposed cases do not survive until being observed. (18) Five percent of fetuses with cardiac malformations and up to 22% fetuses with severe cardiac

87 malformations result in a pregnancy termination and are therefore not observed at birth.(19) In this
88 nationwide registry-based study in Denmark, we examined the association between first-trimester
89 exposure to antidepressants and risk of cardiac malformations using data on malformations among
90 clinically recognized pregnancies from gestational week 11 onwards, regardless of fetal survival.
91

92 **METHODS**

93 This prevalence study was set in Denmark, a prosperous country with universal access to health care.
94 (20) We used routinely collected data from five nationwide registries and databases: the Danish Fetal
95 Medicine Database,(21, 22) the Danish National Patient Registry,(23, 24) the Danish Medical Birth
96 Registry,(25) and the Danish Health Services Prescription Database,(26) all linked on individual level,
97 including exact mother-child linkage, via a unique identifier from the Danish Civil Registration
98 System.(22, 27)
99

100 The study population consisted of all clinically recognized singleton pregnancies with fetuses alive at
101 the nuchal scan from 11 completed gestational weeks, with estimated conception dates from 1
102 November 2007 through 1 February 2014. Pregnancies ending in a termination before week 22 were
103 identified in the Danish National Patient Registry, and pregnancies ending in a live or stillbirth from
104 week 22 onwards were identified in the Danish Medical Birth Registry. Gestational age at pregnancy
105 end was estimated from ultrasound measures in early pregnancy, or, if not available, calculated from
106 the date of the last menstrual period. Conception date was calculated by subtracting gestational age
107 from the date of pregnancy end and adding 14 days. Pregnancies with fetal chromosomal
108 abnormalities were excluded regardless of presence of other malformations.
109

110 Exposure to antidepressants was measured using redeemed prescriptions through linkage to the
111 Danish Health Services Prescription Database.(26) In the main analysis, first-trimester exposure was
112 defined as two or more redeemed prescriptions from 28 days before through 70 days after the

conception date.(28) The unexposed group was defined by absence of redemptions for an antidepressant in the same time window, combined with absence of former use. The "former use", taken to be a proxy for untreated depression, was defined by one or more redeemed prescription of an antidepressant from 365 to 183 days preconception and no redemptions between 182 days preconception through the first trimester (Appendix S1).(13) Pregnancies with one redeemed prescription in the first trimester were excluded from the main analyses and included in a sensitivity analyses in the exposed group, as described below. Medications were classified as any antidepressant, class-specific groups (SSRI, TCA and other) and agent-specific drugs (e.g. sertraline).

Data on prenatally diagnosed cardiac malformations came from the Danish Fetal Medicine Database, which contains data on malformations diagnosed prenatally from all first trimester screenings and second trimester malformation scans starting from week 11. The database was 95% complete during its period of coverage.(21, 22) Data on cardiac malformations diagnosed up to 1 year postnatally came from the Danish National Patient Registry.(23) Cardiac malformations were defined as malformations of the heart chambers, heart valves, great arteries, veins and septal defects and classified by severity into 1) severe cardiac malformations (SCM) defined as malformations that ended in a miscarriage or termination, stillbirth, postnatal death or cardiac surgery during the first year of life (arranged in hierarchy of termination>miscarriage>death (including stillbirth)>surgery), and 2) the remaining cardiac malformations (non-SCM). Indication for terminations after week 12 was classified as fetal (e.g., malformation) or non-fetal (e.g., severe disease of the mother) (Appendix 1).

Data on covariates, obtained from the available data sources, included maternal ethnicity (Afro-Caribbean, Asian, Caucasian, other), civil status (living with partner, yes/no), parity (nulliparous/multiparous), age at conception ($\leq$35, > 35 years), prepregnant body mass index (BMI, <25, 25– <30, $\geq$ 30 kg/m^2), smoking during pregnancy (yes/no), redeemed prescription of a known teratogen from 180 days preconception and through the first trimester, and, as measures of maternal morbidity, prescriptions of relevant medications redeemed in two years preconception

(antihypertensives, antidiabetic agents, antiepileptics, antipsychotics, anxiolytics, hypnosis and sedatives) and hospital diagnoses of depression or diabetes two years preconception.(23, 24)

We tabulated maternal characteristics according to first-trimester exposure to antidepressants. We used log-binomial regression to estimate the association between antidepressants and the cardiac malformation outcomes(29) by prevalence ratios (PRs) with 95% confidence intervals (CIs). We reported crude PRs; PRs adjusted for age, smoking, and depression diagnosis (hereafter, minimally adjusted) for non-SCM only because of sparse data; and PRs adjusted for all measured covariates using propensity-score fine stratification with 50 strata (hereafter, fully adjusted).(30)

Furthermore, we conducted a number of sensitivity analyses. First, we repeated the analyses excluding pregnancies exposed to other psychiatric medication and known teratogens. Second, to assess the impact of exposure misclassification, we defined first-trimester exposure by one or more redeemed prescription. Third, to assess the impact of selection bias due to exclusion malformations among terminated pregnancies, we repeated the analyses restricting the study population to live-born infants. Finally, we analyzed the time variation in the prevalence of cardiac malformations by calendar year.

Statistical analyses were performed with Stata (version 14, StataCorp, TX, USA) and SAS (version 9.4, SAS Inc., Cary, NC, USA). In all analyses, cell counts <5 were masked to comply with the Danish data protection regulations to avoid identification of individuals.

RESULTS

During the study period, we identified 366 489 eligible pregnancies. After excluding 2123 pregnancies with fetal chromosomal anomalies and 354 pregnancies with coding errors, the study population comprised 364 012 clinically recognized singleton pregnancies in completed gestational week 11

onwards, of which 96% had data from ultrasound examinations from the Danish Fetal Medicine Database starting in gestational week 12. The prevalence of first-trimester exposure to antidepressants was 1.1% (n=4105) based on ≥2 redeemed prescriptions and 3.2% (n=11 459) based on ≥1 redeemed prescription. The prevalence of former use was 1.8% (n=6326). The characteristics of the exposed pregnancies were more similar to those of the former users than to the unexposed pregnancies (Table 1), e.g. for smoking more than 22% smoked among both the exposed and the former used compared to 9.8% among the unexposed. The proportion of pregnancies terminated for any reason after week 11 was 6.0% among pregnancies with first trimester antidepressant exposure, 2.5% among unexposed pregnancies, and 3.9% among pregnancies with former use. The majority of terminations were due to non-fetal indications (Table 1).

There were 972 SCM and 3,361 non-SCM for a combined prevalence of 12 per 1000. There was no time variation in the prevalence of outcome (Figure S1 and Figure S2). Among the SCM, 236 (24%) pregnancies had been terminated prenatally and therefore would not have been captured in an analysis restricted to live births. The proportion of terminated malformations increased with severity (Table 2). The ratio between the cases diagnosed prenatally to the cases diagnoses postnatally showed substantial variation, e.g. the majority of hypoplastic left heart syndromes (HLHS) cases were diagnoses prenatally whereas virtually no cases of atrial septal defects (ASDs) were diagnosed in utero.

The fully adjusted PRs for SCM were 1.31 (95% CI: 0.78–2.22) for any antidepressant, 1.09 (95% CI: 0.52–2.30) for SSRIs, and 2.13 (95% CI: 0.89–5.13) for venlafaxine. Most PRs became attenuated in response both to improved covariate adjustment and to using untreated depression as the comparator, but the association with venlafaxine persisted (Table 3), even after exclusion of pregnancies exposed to other psychiatrics medication (Table S2). In the venlafaxine group, the majority of exposed cases were of the same type, HLHS, resulting in crude PR of 17.4 (95% CI: 6.41–47.2) and an increase in absolute risk of 4.4 per 1000 (95% CI: -0.2–9.1 per 1000). The fully adjusted PRs for non-SCM were

1.65 (95% CI: 1.31–2.08) for any antidepressant, 1.38 (95% CI: 1.00–1.92) for SSRIs, and 1.73 (95% CI: 1.08–2.77) for venlafaxine. For mirtazapine, the minimally adjusted PR for SCM was 3.62 (1.48–8.85) with no specific pattern of malformations. Class-specific and agent-specific estimates became attenuated by improved covariate adjustment, from crude to minimally adjusted, to fully adjusted (Table 4 and Table S3).

Sensitivity analyses, with exposure defined by ≥1 redeemed prescription during the first trimester, resulted in an increase in the number of both SCM and non-SCM exposed cases of cardiac malformations available for analysis: from 16 to 36, and from 75 to 177 cases (Table S1, S4, and S5). In a sensitivity analysis restricted live births, the number of cases of SCM was reduced from 972 to 736 with two or more redeemed prescriptions, and exposed SCM from 16 to 11 cases with two or more redeemed prescriptions. A typical analysis restricted to live births yielded the PRs for venlafaxine 0.62 (95% CI: 0.09–4.40) and for SSRIs 1.87 (95% CI: 1.00–3.48) (Table S6).
The number needed to harm (NNH) for venlafaxine was 307 for SCM and 225 for HLHS. For non-SCM, the NNH was 162 for SSRI and 90 for venlafaxine.

DISCUSSION

Main findings

In this population-based study including malformations detected among all clinically recognized pregnancies, regardless of fetal survival, first-trimester exposure to SSRIs was not associated with SCM. First-trimester exposure to venlafaxine was associated with a 2.1-fold increased PR of SCM and 1.7-fold increased PR of non-SCM, with evidence of clustering of a specific type of severe heart malformation, HLHS. First-trimester exposure to antidepressants overall and in specific classes (SSRI, TCA and other) was associated with a 1.4 to 2.7-fold increased PR of non-SCM. The confidence intervals were, however, wide and the results are potentially sensitive to random variation. Our

findings underscore the importance of inclusion of malformations among pregnancies that lead to termination of pregnancies or intrauterine demise for studies on medication that may cause severe malformations.(18)

Our findings that first trimester SSRIs were associated with non-SCM, but not with SCM, are in accordance with several previous studies, including a recent systematic review,(9) reporting an association between first trimester SSRIs and the prevalence of overall cardiac malformation and 1.4-fold increase in risk of specific cardiac malformations.(11, 31) Individual SSRIs have been associated with risks of septal defects (paroxetine(8, 31); sertraline(9, 10, 28); citalopram(28); fluoxetine(32)) and ventricular outflow tract obstruction defects (paroxetine(8, 10, 32)). However, far from all studies report such associations.(3, 12-14, 31) One other study reported an association between first trimester venlafaxine exposure and CoA and ASD.(17)

The association in our study between venlafaxine and an increased risk of SCM, in particular the marked association with HLHS, is a novel finding and a potential cause for concern. A recent paper including prenatal data from some regions, published after the conclusion of the present study, finds that venlafaxine had the highest proportion of elevated specific birth defects, among commonly prescribed individual antidepressants. Similar to our findings, venlafaxine was associated with an increased risk of HLHS with an aOR of 3.54 (95% CI: 1.21–10.40).(33)

For mirtazapine, we found a comparable increased risk of SCM but with no clear pattern of specific malformations which limits the interpretation. Few studies have investigated the potential risk of mirtazapine and found no associations.(34)

Strengths and Limitations

These results need to be interpreted with caution. Venlafaxine is often a second-line treatment used in patients with depression that is refractory to first-line agents, and is therefore potentially a marker of depression severity.(35) We attempted to reduce this confounding by comparing with former users, and in these analyses the associations with SCM and in particular HLHS persisted. Smoking is potentially

an important confounder, either per se or as a proxy for strong confounders. Reassuringly, an almost identical proportion of the exposed and the former users were smokers. Further, our proxy measure of depression (former users vs unexposed) was not associated with HLHS (PR 0.58 (95% CI 0.1–4.2) Table S7). This suggests that confounding by indication is unlikely to explain away the HLHS association.

The prevalence of antidepressant use and heart malformations reported here were consistent with those reported in earlier Nordic studies, i.e. first-trimester exposure to antidepressant and SSRIs (respectively, 3.2% and 2.4% measured by ≥2 redeemed prescriptions; respectively, 1.1% and 0.8% measured by ≥1 redeemed prescription(1, 3)) and prevalence of cardiac malformations per 1000 singleton pregnancies after excluding chromosome anomalies (12 vs. previously reported 5 to16 per 1000(3, 14, 36)). The low prevalence of malformations limits the power of the analyses, in particular in the analyses of the specific malformations. For example, the results on SCM is based on only 16 exposed cases of a total of 4105. Few misclassified cases could have changed the results. However, due to the nature of the definition of SCM, misclassification is less likely for such outcome as a group (i.e. a baby may have been coded as a stillborn even if it died right after birth but would still end up in the SCM group). The extent of selection bias was reduced in our study thanks to the completeness and nationwide coverage of the data sources, enabling the inclusion of nearly all eligible pregnancies and all diagnosed malformations both prenatally and up to one year of age. Any potential selection bias from non-random pregnancy loss before 11 weeks would require early detection of cardiac malformations, which is not feasible in the current routine clinical settings. We aimed to reduce misclassification of exposure by requiring two qualifying redeemed prescriptions during the first trimester, as was done in previous studies(10, 28). Although we used a validated definition for the cardiac malformations,(37) reliance on diagnostic codes masks some clinical details, e.g., codes do not discriminate between persistent foramen ovale and atrial septum defects. Several approaches were used to adjust for or assess the extent of confounding. The PRs tended to attenuate in

response to better confounding control, suggesting that some uncontrolled confounding (e.g. depression severity) could at least partially explain the observed associations. Importantly, we were not able to adjust for all potential confounders, e.g. alcohol and illicit drug use, and this must be taken into account when interpreting the results, particularly for outcomes that was associated with most types of antidepressants, e.g. non-SCM. We know of no specific association between. illicit drug use and venlafaxine compared to other types of antidepressants or with HLHS. We cannot rule out an upward surveillance bias if pregnant women with a history of depression tend to undergo a more thorough prenatal examination; however, this bias would not affect the severe outcomes of terminations, stillbirth, death or surgery. Table 3 illustrates the limitation of the prenatal data in cases of specific malformations (e.g. ASD) and the subsequent need to include all available data, prenatal and postnatal, in the evaluation of medication used in pregnancy.

Interpretation

Fetal echocardiography is offered to pregnancies with a significantly increased risk of fetal heart malformations, e.g. in our population in pregnancies with fetuses with a nuchal translucency>4 or tricuspid regurgitation. The underlying risks of these conditions are of the same magnitude as the risk estimates for venlafaxine in our study, for HLHS the relative risk is higher. Regardless of the underlying mechanisms behind the observed associations, e.g. confounding by indication (discussed in more detail below) or a direct effect on the developing heart, venlafaxine exposure is a marker for an increased risk of one of the most severe types of heart malformations. Because prenatal diagnosis of e.g. HLHS may be vitally important for obstetric management, we believe that women that use venlafaxine in pregnancy should be offered fetal echocardiography.

CONCLUSION

Using nationwide population-based data that include malformations of pregnancies that lead to termination of pregnancies or intrauterine demise, we corroborated previous findings that first-trimester exposure to SSRIs was associated with non-SCM but not SCM. A new finding in our study

298 suggests that first trimester venlafaxine was associated with an increased risk of HLHS, an association
299 that would have been missed in a study relying solely on pregnancies ending in a live birth. The results
300 are potentially important for clinical management of women with depression in the reproductive years
301 but, importantly, the absolute risk for e.g. HLHS is low and must be balanced against the potential
302 devastating effects of un- or undertreated depression during pregnancy. Regardless, venlafaxine
303 exposure is a marker for risk pregnancies for which fetal echocardiography may be considered.
304

Acknowledgements: Thanks to the Danish Fetal Medicine Study Group

This work was supported by: The University of Aarhus Denmark, Director Jacob Madsen and wife Olga Madsen's Foundation, Ove William Buhl Olesen and Mrs. Edith Buhl Olesen Memorial Foundation, Carl and Ellen Hertz's Foundation, Professor Ann Tabor's Foundation, the Solar Foundation of 1978, and Health Research Fund of Central Denmark Region. The funding sources had no role in the design and conduct of the study; the collection, analysis and interpretation of data; or the preparation, review, or approval of the manuscript.

Potential conflict of interest: None

Authors contribution: LK, LHP, LP, VE, PS, OBP, and NU was responsible for study concept and design, analysis and interpretation of data, drafting the manuscript and revising it for intellectual content, and study supervision. LP, LHP, LK, and VE analysed the data.

Ethical approval: This study received the required approvals from the Danish Data Protection Agency (Aarhus University J.nr. 2016-051-000001/KEA-2017-24), from the Research Committee of the Danish Fetal Medicine Database, and from the Board of the Danish Health Service Prescription Database.

REFERENCES

1. Charlton RA, Jordan S, Pierini A, Garne E, Neville AJ, Hansen AV, et al. Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions. BJOG : an international journal of obstetrics and gynaecology. 2015;122(7):1010-20.
2. Evans J, Heron J, Francomb H, Oke S, Golding J. Cohort study of depressed mood during pregnancy and after childbirth. BMJ. 2001;323(7307):257-60.
3. Furu K, Kieler H, Haglund B, Engeland A, Selmer R, Stephansson O, et al. Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design. BMJ. 2015;350:h1798.
4. Andrade SE, Reichman ME, Mott K, Pitts M, Kieswetter C, Dinatale M, et al. Use of selective serotonin reuptake inhibitors (SSRIs) in women delivering liveborn infants and other women of child-bearing age within the U.S. Food and Drug Administration's Mini-Sentinel program. Arch Womens Ment Health. 2016;19(6):969-77.
5. Gentile S. Early pregnancy exposure to selective serotonin reuptake inhibitors, risks of major structural malformations, and hypothesized teratogenic mechanisms. Expert opinion on drug metabolism & toxicology. 2015;11(10):1585-97.
6. Sadler TW. Selective serotonin reuptake inhibitors (SSRIs) and heart defects: potential mechanisms for the observed associations. Reprod Toxicol. 2011;32(4):484-9.

7. Peoples JNR, Maxmillian T, Le Q, Nadtochiy SM, Brookes PS, Porter GA, Jr., et al. Metabolomics reveals critical adrenergic regulatory checkpoints in glycolysis and pentose-phosphate pathways in embryonic heart. The Journal of biological chemistry. 2018;293(18):6925-41.
8. Berard A, Sheehy O. Paroxetine use during pregnancy and adverse pregnancy outcomes in the absence of detection bias. European Psychiatry. 2010;25.
9. Gao SY, Wu QJ, Sun C, Zhang TN, Shen ZQ, Liu CX, et al. Selective serotonin reuptake inhibitor use during early pregnancy and congenital malformations: a systematic review and meta-analysis of cohort studies of more than 9 million births. BMC medicine. 2018;16(1):205.
10. Louik C, Lin AE, Werler MM, Hernandez-Diaz S, Mitchell AA. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. N Engl J Med. 2007;356(26):2675-83.
11. Wemakor A, Casson K, Garne E, Bakker M, Addor MC, Arriola L, et al. Selective serotonin reuptake inhibitor antidepressant use in first trimester pregnancy and risk of specific congenital anomalies: a European register-based study. European journal of epidemiology. 2015;30(11):1187-98.
12. Wang S, Yang L, Wang L, Gao L, Xu B, Xiong Y. Selective Serotonin Reuptake Inhibitors (SSRIs) and the Risk of Congenital Heart Defects: A Meta-Analysis of Prospective Cohort Studies. J Am Heart Assoc. 2015;4(5).
13. Jimenez-Solem E, Andersen JT, Petersen M, Broedbaek K, Jensen JK, Afzal S, et al. Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformations: a nationwide cohort study. BMJ open. 2012;2(3).
14. Petersen I, Evans SJ, Gilbert R, Marston L, Nazareth I. Selective serotonin reuptake inhibitors and congenital heart anomalies: comparative cohort studies of women treated before and during pregnancy and their children. The Journal of clinical psychiatry. 2016;77(1):e36-42.
15. Reefhuis J, Devine O, Friedman JM, Louik C, Honein MA, National Birth Defects Prevention S. Specific SSRIs and birth defects: Bayesian analysis to interpret new data in the context of previous reports. BMJ. 2015;351:h3190.
16. Lassen D, Ennis ZN, Damkier P. First-Trimester Pregnancy Exposure to Venlafaxine or Duloxetine and Risk of Major Congenital Malformations: A Systematic Review. Basic Clin Pharmacol Toxicol. 2016;118(1):32-6.
17. Polen KN, Rasmussen SA, Riehle-Colarusso T, Reefhuis J, National Birth Defects Prevention S. Association between reported venlafaxine use in early pregnancy and birth defects, national birth defects prevention study, 1997-2007. Birth defects research Part A, Clinical and molecular teratology. 2013;97(1):28-35.
18. Levy A, Matok I, Gorodischer R, Sherf M, Wiznitzer A, Uziel E, et al. Bias toward the null hypothesis in pregnancy drug studies that do not include data on medical terminations of pregnancy: the folic acid antagonists. J Clin Pharmacol. 2012;52(1):78-83.
19. Svensson E, Ehrenstein V, Norgaard M, Bakketeig LS, Rothman KJ, Sorensen HT, et al. Estimating the proportion of all observed birth defects occurring in pregnancies terminated by a second-trimester abortion. Epidemiology. 2014;25(6):866-71.

20. Schmidt M, Schmidt SAJ, Adelborg K, Sundbøll J, Ehrenstein V, Sørensen HT. The Danish healthcare system and epidemiological research: from healthcare contacts to database records Clin Epidemiol (in press). 2019.
21. Ekelund CK, Kopp TI, Tabor A, Petersen OB. The Danish Fetal Medicine database. Clin Epidemiol. 2016;8:479-83.
22. Pedersen LH, Petersen OB, Norgaard M, Ekelund C, Pedersen L, Tabor A, et al. Linkage between the Danish National Health Service Prescription Database, the Danish Fetal Medicine Database, and other Danish registries as a tool for the study of drug safety in pregnancy. Clin Epidemiol. 2016;8:91-5.
23. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-90.
24. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. Scandinavian journal of public health. 2011;39:54-7.
25. Knudsen LB, Olsen J. The Danish Medical Birth Registry. Dan Med Bull. 1998;45(3):320-3.
26. Johannesdottir SA, Horvath-Puho E, Ehrenstein V, Schmidt M, Pedersen L, Sorensen HT. Existing data sources for clinical epidemiology: The Danish National Database of Reimbursed Prescriptions. Clin Epidemiol. 2012;4:303-13.
27. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. European journal of epidemiology. 2014;29(8):541-9.
28. Pedersen LH, Henriksen TB, Vestergaard M, Olsen J, Bech BH. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. BMJ. 2009;339:b3569.
29. Methods for estimating adjusted risk ratios. The Stata Journal, 2009;9(2):175-196: https://ageconsearch.umn.edu/bitstream/127328/2/sjart_st0162.pdf.
30. Desai RJ, Rothman KJ, Bateman BT, Hernandez-Diaz S, Huybrechts KF. A Propensity-score-based Fine Stratification Approach for Confounding Adjustment When Exposure Is Infrequent. Epidemiology. 2017;28(2):249-57.
31. Jordan S, Morris JK, Davies GI, Tucker D, Thayer DS, Luteijn JM, et al. Selective Serotonin Reuptake Inhibitor (SSRI) Antidepressants in Pregnancy and Congenital Anomalies: Analysis of Linked Databases in Wales, Norway and Funen, Denmark. PLoS One. 2016;11(12):e0165122.
32. Malm H, Artama M, Gissler M, Ritvanen A. Selective serotonin reuptake inhibitors and risk for major congenital anomalies. Obstetrics and Gynecology. 2011;118(1):111-20.
33. Anderson KN, Lind JN, Simeone RM, Bobo WV, Mitchell AA, Riehle-Colarusso T, et al. Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects. JAMA Psychiatry. 2020.
34. Smit M, Dolman KM, Honig A. Mirtazapine in pregnancy and lactation - A systematic review. Eur Neuropsychopharmacol. 2016;26(1):126-35.
35. Schueler YB, Koesters M, Wieseler B, Grouven U, Kromp M, Kerekes MF, et al. A systematic review of duloxetine and venlafaxine in major depression, including unpublished data. Acta Psychiatr Scand. 2011;123(4):247-65.

36. Olsen M, Videbaek J, Johnsen SP, Danish Register of Congenital Heart D. The Danish Register of Congenital Heart Disease. Scandinavian journal of public health. 2011;39(7 Suppl):50-3.
37. Agergaard P, Hebert A, Bjerre J, Sorensen KM, Olesen C, Ostergaard JR. Children diagnosed with congenital cardiac malformations at the national university departments of pediatric cardiology: positive predictive values of data in the Danish National Patient Registry. Clin Epidemiol. 2011;3:61-6.

Table 1. Characteristics of women and pregnancy outcomes.
Exposed with two or more redeemed prescriptions of antidepressants, unexposed and former use.

Characteristic	Exposed (n= 4105)	Unexposed (n= 353 581)	Former use (n= 6326)
Age at conception, years, mean (SD)	29.6 (5.5)	29.7 (5.1)	28.7 (5.6)
Parity, missing: 416 (10.1)/ 22 840 (6.5)/ 524 (8.3), n (%)			
0	1752 (42.7)	149 922 (42.4)	2809 (44.4)
>0	1937 (47.2)	180 819 (51.1)	2993 (47.3)
BMI, kg/m^2, missing: 411 (10.0)/ 20 730 (5.9)/ 492 (7.8), n (%)			
<25	1893 (46.1)	207 819 (58.8)	3156 (49.9)
25–29.9	824 (20.1)	66 252 (18.7)	1331 (21.0)
≥ 30	977 (23.8)	58 780 (16.6)	1347 (21.3)
Smoking in pregnancy, missing: 333 (8.1)/ 16,774 (4.7)/ 399 (6.3), n (%)	916 (22.3)	34 678 (9.8)	1402 (22.2)
Civil status, living with partner, missing: 16 (0.4)/ 512 (0.1)/ 20 (0.3), n (%)	3427 (83.5)	319 177 (90.3)	5357 (84.7)
Ethnicity, missing: 520 (12.6)/ 34 053 (9.6)/ 663 (10.5), n (%)			
Afro-Caribbean	16 (0.4)	3,512 (1.0)	38 (0.6)
Asia	54 (1.3)	11.161 (3.2)	120 (1.9)
Caucasian	3486 (85.0)	299 041 (84.6)	5405 (85.4)
Other	29 (0.7)	5814 (1.6)	100 (1.6)
Depression diagnosis*, n (%)	2005 (48.8)	12 941 (3,7)	1457 (23.0)
Diabetes**, n (%)	112 (2.7)	5811 (1.6)	127 (2.0)
Use of antihypertensive***, n (%)	61 (1.5)	1963 (0.6)	51 (0.8)
Use of known teratogen	96 (2.3)	3050 (0.9)	80 (1.3)
Use of other psychotropic medication***, n (%)			
Antiepileptics	247 (6.0)	1580 (0.5)	82 (1.3)
Antipsychotics	352 (8.6)	811 (0.2)	87 (1.4)
Anxiolytics, hypnosis, and sedatives	24 (0.6)	63 (0.0)	6 (0.1)
Termination ≥ week 12+0, n (%)	85 (2.2)	3179 (0.9)	72 (1.2)
Fetal indication ≥ week 12+0 – 22+0, n (%)	28 (0.7)	1385 (0.4)	26 (0.4)
Non-fetal indication ≥ week 12+0 – 22+0, n (%)	57 (1.4)	1794 (0.5)	46 (0.7)
Termination ≥ week 11+0, n (%)	247 (6.0)	8912 (2.5)	245 (3.9)
Miscarriage <week 22+0, n (%)	134 (3.3)	10 739 (3.0)	221 (3.5)
Stillborn, singleton ≥week 22+0, *n (%)*	19 (0.5)	1083 (0.3)	22 (0.4)
Live born, n (%)	3705 (90.3)	332 847 (94.1)	5838 (92.3)
Death postpartum < 1 year, n (%)	9 (0.2)	728 (0.2)	15 (0.3)
Cardiac surgery postpartum < 1 year, n (%)	10 (0.2)	617 (0.2)	11 (0.2)
SCM#, n (%)	16 (0.4)	935 (0.3)	21 (0.3)
Non-SCM#, n (%)	75 (1.8)	3221 (0.9)	65 (1.0)

* Diagnoses within two years prior to conception date
** Diagnoses within two years prior to conception date and/or antidiabetic agents one month prior to conception date throughout first trimester
*** Use of other medication one month prior to conception date throughout first trimester
# Severe cardiac malformations

435

Table 2. Pre- and postnatal diagnoses of specific cardiac malformations

	HLHS	HRHS	ToF	DORV	CoA	AVSD	VSD	ASD
Pregnancies	102	40	109	48	195	222	1049	1170*
Prenatal diagnosed, (%)	75 (73.5)	28 (70.0)	16 (14.7)	10 (20.8)	16 (8.2)	23 (10.4)	39 (3.7)	<5
Postnatal diagnosed (within 1 year), (%)	16 (15.7)	5 (12.5)	66 (60.6)	28 (58.3)	157 (80.5)	188 (84.7)	992 (94.6)	1165 (99.6)
Pre- and postnatal diagnosed, (%)	11 (10.8)	7 (17.5)	27 (24.8)	10 (10.8)	22 (11.3)	11 (5.0)	18 (1.7)	<5
Pregnancy outcome								
Termination, miscarriage, still born	73	27	13	9	5	18	8	<5
Live born	29	10*	96	39	190	204	1041	1167
Surgery within 1 year	18	10	82	34	111	39	145	50
Death within 1 year (includes surgery before death)	21	<5	11	5	<5	<5	18	17

Each pregnancy only contributes once, hierarchy of cardiac malformation: HLHS> HRHS> ToF> DORV> CoA> AVSD> VSD> ASD. Hierarchy of diagnoses: postnatal>prenatal if difference between postnatal and prenatal (with exception of diagnoses without further specification)

HLHS: Hypoplastic left heart syndrome. HRHS: Hypoplastic right heart syndrome. ToF: Tetralogy of Fallot. DORV: Double outlet right ventricle. CoA: Coarctation of aorta. AVSD: Atrioventricular septal defect. VSD: Ventricular septal defect. ASD: Atrial septal defect

* Number is rounded to nearest 10 or reported as <5 to comply with data protection regulations

Table 3. SCM[#] in first trimester exposed (≥ 2 prescriptions) compared with unexposed and former use

	Exposed versus unexposed		Exposed versus former use	
	Crude PR (95% CI)	Fully adjusted PR[¤] (95% CI)	Crude PR (95% CI)	Cases / Unexposed Cases / Former use
Unexposed	1.0	1.0	-	915/346 227*
Former use	-	-	1.0	21/6305
				Cases / Exposed
Antidepressant^ (N06A)	1.47 (0.90 – 2.42)	1.31 (0.78 – 2.22)	1.17 (0.61 – 2.25)	16/4105**
SSRI^^ (N06AB)	1.50 (0.83 – 2.72)	1.09 (0.52 – 2.30)	1.20 (0.58 – 2.48)	11/2767
Venlafaxine (N06AX16)	2.23 (0.93 – 5.37)	2.13 (0.89 – 5.13)	1.78 (0.67 – 4.70)	5/847
Other ^^^	-	-	-	0/629

[#] Severe cardiac malformations

^ AD: Imipramine (N06AA02), clomipramine (N06AA04), amitriptyline (N06AA09), nortriptyline (N06AA10), doxepin (N06AA12), dosulepin (N06AA16), fluoxetine (N06AB03), citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), fluvoxamine (N06AB08), escitalopram (N06AB10), isocarboxazid (N06AF01), nialamide (N06AG02), mianserin (N06AX03), mirtazapine (N06AX11), bupropion (N06AX12), venlafaxine (N06AX16), reboxetine (N06AX18), duloxetine (N06AX21), agomelatine (N06AX22)

^^ SSRI: Fluoxetine (N06AB03), citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), fluvoxamine (N06AB08), escitalopram (N06AB10)

^^^ Other: TCA (N06AA), isocarboxazid (N06AF01), nialamide (N06AG02), mianserin (N06AX03), mirtazapine (N06AX11), bupropion (N06AX12), duloxetine (N06AX21), agomelatine (N06AX22)

[¤] Variables included in the analysis with propensity score fine stratification: ethnicity, civil status, parity, age, BMI, smoking, exposure to teratogens, antihypertensives, antidiabetics, use of other psychotropic drugs, depression diagnosis, diabetes diagnosis

* No former use, no pregnancies with only one redeemed prescription

** The sum of the cases in the subcategories of antidepressants does not add up to the total because cases may contribute to multiple categories

Table 4. Non-SCM[#] in first trimester exposed (≥ 2 prescriptions) compared with unexposed and former use

	Exposed versus unexposed			Exposed versus former use		
	Crude PR (95% CI)	Minimally adjusted[¤] PR (95% CI)	Fully adjusted[¤¤] PR (95% CI)	Crude PR (95% CI)	Minimally adjusted [¤ ¤¤] PR (95% CI)	Cases / Unexpos Cases / Fo use
Unexposed	1.0	1.0	1.0	-	-	3119/346
Former use	-	-	-	1.0	1.0	65/632
						Cases / Ex
Antidepressant^ (N06A)	2.03 (1.62 – 2.54)	1.94 (1.52 – 2.47)	1.65 (1.31 – 2.08)	1.78 (1.28 – 2.47)	1.79 (1.29 – 2.50)	75/4105
TCA^^ (N06AA)	3.93 (2.07 – 7.48)	3.82 (1.99 – 7.34)	2.73 (1.38 – 5.40)	3.45 (1.74 – 6.85)	3.36 (1.68 – 6.71)	9/254
Nortriptyline (N06AA10)	3.87 (1.76 – 8.51)	3.64 (1.64 – 8.09)	2.98 (1.36 – 6.55)	3.39 (1.49 – 7.73)	3.21 (1.40 – 7.35)	6/172
SSRI^^^ (N06AB)	1.68 (1.25 – 2.28)	1.60 (1.17 – 2.19)	1.38 (1.00 – 1.92)	1.48 (1.00 – 2.17)	1.50 (1.02 – 2.20)	42/276
Fluoxetine (N06AB03)	2.72 (1.47 – 5.02)	2.51 (1.35 – 4.65)	2.69 (1.46 – 4.97)	2.39 (1.24 – 4.61)	2.40 (1.24 – 4.63)	10/408
Citalopram (N06AB04)	1.25 (0.74 – 2.11)	1.19 (0.70 – 2.02)	0.94 (0.51 – 1.74)	1.10 (0.62 – 1.95)	1.11 (0.63 – 1.97)	14/123
Sertraline (N06AB06)	1.85 (1.08 – 3.18)	1.75 (1.01 – 3.03)	1.70 (0.97 – 2.99)	1.62 (0.90 – 2.93)	1.63 (0.90 – 2.95)	13/780
Escitalopram (N06AB10)	2.16 (0.98 – 4.78)	2.11 (0.95 – 4.67)	1.97 (0.89 – 4.36)	1.90 (0.8 – 4.34)	1.94 (0.85 – 4.43)	6/308
Other AD^^^^ (N06AX)	2.69 (1.87 – 3.86)	2.53 (1.73 – 3.68)	1.97 (1.35 – 2.86)	2.35 (1.53 – 3.64)	2.29 (1.48 – 3.54)	29/119
Mirtazapine (N06AX11)	4.63 (1.96 – 10.92)	4.39 (1.86 – 10.38)	3.04 (1.16 – 7.97)	4.06 (1.66 – 9.89)	3.62 (1.48 – 8.85)	5/120
Venlafaxine (N06AX16)	2.23 (1.39 – 3.57)	2.06 (1.27 – 3.34)	1.73 (1.08-2.77)	1.95 (1.15 – 3.32)	1.90 (1.12 – 3.22)	17/847

[#] Severe cardiac malformations

^ AD: ATCs below + isocarboxazid (N06AF01), nialamide (N06AG02)

^^ TCA: Imipramine (N06AA02), clomipramine (N06AA04), amitriptyline (N06AA09), nortriptyline (N06AA10), doxepin (N06AA12), dosulepin (N06AA16) ^^^ SS fluoxetine (N06AB03), citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), fluvoxamine (N06AB08), escitalopram (N06AB10)

^^^^ Other AD: mianserin (N06AX03), mirtazapine (N06AX11), bupropion (N06AX12), venlafaxine (N06AX16), reboxetine (N06AX18), duloxetine (N06AX21), agomelatine (N06AX22)

[¤] Adjusted for smoking, age at conception, and depression diagnosis

[¤¤] Variables included in the analysis with propensity score fine stratification: ethnicity, civil status, parity, age, BMI, smoking, exposure to teratogens, antihypertensiv antidiabetics, use of other psychotropic drugs, depression diagnosis, diabetes diagnosis

[¤¤¤] Adjusted for smoking and age at conception

* No former use, no pregnancies with only one redeemed prescription

** The sum of the cases in the subcategories of antidepressants does not add up to the total because cases may contribute to multiple categories

451