

Combined use of selective serotonin reuptake inhibitors and sedatives/hypnotics during pregnancy: risk of relatively severe congenital malformations or cardiac defects. A register study

Margareta Reis,¹ Bengt Källén²

To cite: Reis M, Källén B. Combined use of selective serotonin reuptake inhibitors and sedatives/hypnotics during pregnancy: risk of relatively severe congenital malformations or cardiac defects. A register study. *BMJ Open* 2013;**3**:e002166. doi:10.1136/bmjopen-2012-002166

► Prepublication history for this paper are available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2012-002166>).

Received 27 September 2012
Revised 16 January 2013
Accepted 17 January 2013

This final article is available for use under the terms of the Creative Commons Attribution Non-Commercial 2.0 Licence; see <http://bmjopen.bmj.com>

ABSTRACT

Objectives: To investigate the proposed synergistic teratogenic effect of use of selective serotonin receptor inhibitors (SSRI) together with sedatives or hypnotics, primarily benzodiazepines, during pregnancy.

Design: Cohort study of congenital malformations after maternal use of SSRI, sedatives/hypnotics or the combination of the two drug categories.

Setting: Swedish national health registers.

Participants: A total of 10 511 infants born of women who had used SSRI drugs but no other central nervous system (CNS)-active drug, 1000 infants born of women who had used benzodiazepines and no other CNS-active drug, and 406 infants whose mothers had used both SSRI and benzodiazepines but no other CNS-active drug.

Results: None of the three groups showed a higher risk for any relatively severe congenital malformation or any cardiac defect when comparison was made with the general population risk (adjusted risk ratio (RR) for the combination of SSRI and benzodiazepines and a relatively severe malformation=1.17 (95% CI 0.70 to 1.73). Similar results were obtained for the combination of SSRI with other sedative/hypnotic drugs.

Conclusions: The previously stated increased risk associated with the combined use of these drug categories, notably for a cardiac defect, could not be replicated.

INTRODUCTION

The combined use of selective serotonin receptor inhibitors (SSRI) and sedatives/hypnotics, including benzodiazepines, in the first trimester of pregnancy is not uncommon.¹ The drug groups have been studied thoroughly with regard to possible malformation risks in the offspring. However, if the combination SSRI+sedatives/hypnotics have a synergistic effect with an increased

ARTICLE SUMMARY

Article focus

- Does the combined use of selective serotonin receptor inhibitors (SSRI) and benzodiazepine drugs during pregnancy increase the risk for a congenital malformation and notably a cardiovascular defect?

Key messages

- No significant risk increase of a relatively severe malformation or of a cardiovascular defect was seen for SSRIs alone, benzodiazepines alone, or for the combined use of the two drug categories.
- The combined use of SSRI and other sedatives/hypnotics did not increase this risk either.

Strengths and limitations of this study

- The strengths of the study are the large number of women studied; drug exposure information from interviews in early pregnancy; and ascertainment of malformations from multiple sources.
- A limitation of the study is that, in spite of the large number of women included, relatively few had a concomitant use of an SSRI and benzodiazepine and only five cardiovascular defects were identified.
- Another limitation is that fetuses which were aborted because of a prenatally diagnosed malformation could not be included in the study.

¹Department of Medical and Health Sciences, Clinical Pharmacology, Linköping University, Linköping, Sweden

²Tornblad Institute, University of Lund, Lund, Sweden

Correspondence to

Dr Margareta Reis;
Margareta.Reis@liu.se

malformation risk is a question that still remains open. One study, which was published in 2008, found that neither maternal use of an SSRI (or venlafaxine) alone nor of a benzodiazepine alone increased the risk for a congenital malformation. However, the combined use of the two drug categories did notably increase the risk for a cardiovascular defect.² As far as we know, it has not been studied since. It was thought to be of interest

to see if the observation could be replicated in a different material. We explored this problem using the Swedish Medical Birth Register.

MATERIAL AND METHODS

Data source

Data from the Swedish Medical Birth Register were used.³ Women giving birth between 1 July 1995 and 31 December 2008 (n=1 290 672) were interviewed by midwives at the first antenatal care visit, usually before the end of the first trimester. They were asked about all drug use since they became pregnant.⁴ The drug names were recorded in clear text and then transferred to ATC codes (Anatomical, Therapeutic, Chemical classification system). A total of 12 050 women reported the use of SSRI; 2014 the use of benzodiazepines; 1503 the use of hypnotic benzodiazepine receptor agonists (HBRA); and 1003 the use of other sedatives/hypnotics, the largest group of which used hydroxyzine (n=819). In order to remove possible confounding from other CNS-active drugs, women reporting the use of opioids, anticonvulsants, antipsychotics including lithium or other antidepressants than SSRI were excluded from the analyses.

Congenital malformations in the infants were identified from three registers: the Medical Birth Register, the Birth Defect Register (previously called the Register of Congenital Malformations) and the Patient Register (previously called the Hospital Discharge Register).⁵ Linkage between registers was made using the unique personal identification number every person living in Sweden has.

The malformation rate was 4.7% in all babies born during the time period. In order to reduce variability in the definition of malformations, a restriction was made in respect of relatively severe malformations. The following common and clinically less significant malformations with an inconsistent registration were excluded: preauricular tags, tongue tie, patent ductus arteriosus in preterm infants, single umbilical artery, undescended testicle, hip (sub)luxation or clicking hip and nevus. These exclusions reduced the population rate of congenital malformations to 3.3%. Subanalyses were made of infants with cardiovascular defects (excluding patent ductus at preterm birth and single umbilical artery). In these subanalyses, infants with known chromosome anomalies were excluded.

Statistical analysis

Analyses were performed with Mantel-Haenszel methodology and the approximate 95% confidence intervals (95% CI) of odds ratios (OR) with Miettinen's method. Adjustments were made for year of birth of the infant, maternal age (5 year classes), parity, smoking in early pregnancy and body mass index (BMI). These variables affect malformation rates in different ways according to the malformation studied. Information on the latter two

variables was obtained from the midwife interviews and was recorded in the Medical Birth Register. When the expected number of the outcome was below 10, a risk ratio (RR) was calculated as the observed number divided by the expected number (adjusted as above) and with a 95% CI based on exact Poisson distributions.

RESULTS

Maternal characteristics

Table 1 compares some maternal characteristics with all women in Sweden who gave birth during the same time period. It can be seen that women using SSRI but no sedatives or hypnotics are older, more often of first parity (have their first child), smoke more and are overweight or obese more often than other women, but they do not have an increased risk of previous miscarriages. This is true with some modifications also for women who used SSRI together with sedatives/hypnotics. These women seemed to smoke more often than women using only SSRI. Women using SSRI in combination with benzodiazepines seemed not to be of parity one or overweight/obese as often as women using SSRI alone. Some of these apparent differences may be random, but adjustments for these variables have been made with the exception of previous miscarriages.

Risk for a congenital malformation in the offspring

Table 2 summarises data on the occurrence of any relatively severe malformation and of any cardiovascular defect according to the maternal use of these drugs. The OR for any relatively severe malformation varied between 0.76 and 1.35. For cardiovascular defects, the numbers were low except for the two large groups of SSRI or benzodiazepines—the highest OR was for benzodiazepines, but it was not statistically significant.

The combination of SSRI and benzodiazepines was associated with 16 infants with a relatively severe malformation. These are listed in table 3. The only remarkable finding is three cases of hypospadias, but this can be random (RR=2.97, 95% CI 0.61 to 8.68).

Women using an SSRI also use many non-CNS active drugs in excess, some of which may have teratogenic effects: insulin (as an indicator of pre-existing diabetes), antihypertensive drugs and drugs used for thyroid disease.⁶ Exclusion of women who reported one or more of these drugs hardly changed the risk estimates. The risk for a cardiovascular defect after the combination of SSRI and benzodiazepines was still based on five cases and the RR was 1.09 (95% CI 0.36 to 2.55).

DISCUSSION

The present study was based on drug use as recorded in early pregnancy among more than one million women giving birth. The study was specifically directed to the question of possible teratological synergism between SSRI and sedatives/hypnotics and notably benzodiazepines. An advantage with the study, except for its size, was that

Table 1 Some characteristics of women using SSRI and/or sedatives/hypnotics during early pregnancy

Drug category	Number	Age <25 vs 25–34	Age ≥35 vs 25–34	Parity 1 vs ≥2	Any smoking	Any previous miscarriage	BMI ≥25
SSRI only*	10383	0.88 (0.83 to 0.95)	1.25 (1.17 to 1.33)	1.36 (1.29 to 1.43)	2.47 (2.27 to 2.70)	0.99 (0.94 to 1.05)	1.27 (1.20 to 1.33)
SSRI+benzodiazepine	400	0.92 (0.68 to 1.25)	1.44 (1.06 to 1.94)	1.04 (0.83 to 1.32)	4.98 (3.50 to 7.10)	0.96 (0.73 to 1.27)	0.92 (0.71 to 1.18)
SSRI+HBRA	305	0.98 (0.70 to 1.36)	1.14 (0.83 to 1.17)	1.40 (1.08 to 1.81)	5.48 (3.87 to 7.78)	0.94 (0.70 to 1.30)	1.19 (0.89 to 1.60)
SSRI+other sedative/hypnotic	221	0.83 (0.54 to 1.28)	1.42 (0.85 to 2.36)	1.63 (1.15 to 2.29)	4.94 (3.08 to 7.52)	0.97 (0.65 to 1.44)	1.31 (0.94 to 1.83)

For each variable, adjustments were made for all the other studied variables. ORs with 95% CIs within brackets comparing exposed women with all other women in the population (n=1 290 672).

*SSRI without sedatives and/or hypnotics but possibly with other concomitant medication.

BMI, body mass index; HBRA, hypnotic benzodiazepine receptor agonist; SSRI, selective serotonin reuptake inhibitor.

the information on drug use was based on interviews of the women early in pregnancy when the possible presence of congenital malformations was yet unknown. It is probable that some under-reporting or under-registration of drug use occurs, notably for drugs which may seem stigmatising like some CNS-active drugs. This will mean that some infants who were actually exposed were not identified and were included in the comparison group of non-exposed infants, but the proportion will be low and the effect on risk estimates negligible. Further, it is not certain that the women who reported the use of SSRI and a sedative/hypnotic had used both drug categories simultaneously. A larger problem is that the study is only based on infants born. In some cases, fetal diagnosis would have revealed the presence of severe congenital malformations and an induced abortion could have been performed. Such cases are registered, but Swedish legislation does not permit a registration of such abortions with personal identification number why a correlation to possible maternal drug use not can be made. If a drug causes a serious condition which is nearly always aborted (eg, anencephaly), this cannot be identified in the present study. If it causes a malformation which is sometimes but not always aborted (like spina bifida), the power to detect the association will be reduced but it will still be possible to identify it. It is, however, possible that maternal psychiatric disease affects the use of prenatal fetal diagnostics, even though most pregnant women in Sweden undergo routine sonography during pregnancy. This source of error will play a small role in the analysis of cardiac defects, notably mild defects like septal defects.

Women using CNS-active drugs during pregnancy differ from other women in many aspects. We adjusted for differences in maternal age and parity distribution, maternal smoking and BMI, but other unidentified confounders may exist, most notably the presence of maternal psychiatric diagnosis. Maternal non-obstetric diagnoses and, in particular, maternal psychiatric diagnoses are incompletely registered in the birth register. The use of sedatives/hypnotics together with SSRI may, for example, be more prevalent among women with anxiety or a panic syndrome than among women with depression. Another possible confounder is concomitant morbidity and drug use. We have shown that the rates of pre-existing diabetes, chronic hypertension, thyroid disease and asthma were higher than expected among women using antidepressant drugs.^{1–6} Among these conditions, the first three are known to affect malformation rate,^{6–9} while the association between maternal asthma and infant congenital malformations is weak.^{6–10} We therefore studied the confounding effect of the first three conditions by removing from the analysis women who had reported the use of such drugs—it hardly influenced the malformation risk. The maternal use of alcohol or illicit drug use could not be taken into consideration due to incomplete registration. However, the teratogenic effect of illicit drugs is generally low and

Table 2 Risks of a relatively severe malformation in infants and of a cardiovascular defect according to maternal drug use compared with infants born of women, unexposed to the respective drug groups, in the population

Drug group used	Total number	With relative severe malformation	OR/RR		With cardiovascular defect	OR/RR	
			95% CI	95% CI		95% CI	
All SSRI	12195	396	1.06	0.96 to 1.17	121	1.01	0.84 to 1.21
SSRI without sedative/hypnotic	10511	337	1.05	0.94 to 1.17	103	0.99	0.82 to 1.21
Benzodiazepine without SSRI	1000	37	1.10	0.79 to 1.54	13	1.30	0.75 to 2.24
HBRA without SSRI	776	22	0.86	0.57 to 1.72*	2	0.26	0.63 to 0.94*
Other sedative/hypnotic without SSRI	606	21	1.06	0.69 to 1.69	5	0.89	0.26 to 1.88*
SSRI with sedative/hypnotic	822	30	1.09	0.85 to 1.57	8	0.92	0.40 to 1.82*
Among them with benzodiazepine	406	16	1.17	0.70 to 1.93	5	1.14	0.37 to 2.67*
Among them with HBRA	309	8	0.76	0.37 to 1.54*	2	0.66	0.08 to 2.37*
Among them with other sedative/hypnotic	256	10	1.35	0.73 to 2.61*	3	1.26	0.26 to 3.68*

OR or RR with 95% CI after adjustment for year of birth, maternal age, parity, smoking and BMI.

*RR as observed over expected numbers with 95% CI from Poisson distributions.

HBRA, hypnotic benzodiazepine receptor agonist; OR, odds ratio; RR, risk ratio; SSRI, selective serotonin reuptake inhibitor.

both exposures are strongly correlated with maternal smoking, which was adjusted for.

The combination of SSRI and sedatives/hypnotics gave no indications of an increased risk compared with either drug group. Specifically, the risk with a combination of a benzodiazepine and an SSRI (based on 16 malformed infants) was not increased. Thus, the observation reported by Oberlander *et al* could not be replicated.² In our study, 406 exposed infants were included, whereas in the Oberlander *et al* study it was 359. In our study, there were 16 infants with relatively severe malformations, whereas in the Oberlander *et al* study there were 20 infants with major malformations. These two

concepts are not identical, but the two rates do not differ significantly. We found five cases with cardiovascular defects (4.6 expected), whereas Oberlander *et al.* found six. In both studies, the numbers are thus small, notably for cardiovascular defects. It can also be pointed out that in our material, the dominating SSRI drug was citalopram followed by sertraline (see table 3), whereas in the Oberlander *et al.* study it was paroxetine followed by sertraline and fluoxetine. The dominating benzodiazepine in our material was diazepam followed by oxazepam, but in the Oberlander *et al.* study it was lorazepam followed by clonazepam. This is a possible explanation to the discrepancy in results; another possibility is that

Table 3 Specification of infants exposed to SSRI and benzodiazepines and with a relatively severe malformation

Number	Malformation	SSRI	Benzodiazepine	Other drugs reported
1	Hypospadias	Citalopram	Alprazolam	–
2	Hypospadias	Fluoxetine	Alprazolam	Propranolol
3	Hypospadias+VSD	Paroxetine	Lorazepam	Paracetamol
4	VSD+ASD	Sertraline	Alprazolam	ASA+prometazine
5	VSD+ASD	Escitalopram	Oxazepam	Hydroxyzine
6	Pulmonary valve stenosis	Citalopram	Alprazolam	Zolpidem
7	Pulmonary valve stenosis	Paroxetine	Oxazepam	–
8	Laryngeal malformation	Fluoxetine	Alprazolam	Buspirone, B12
9	Pylorostenosis	Sertraline	Alprazolam	Meclozine
10	Duodenal atresia/stenosis	Citalopram	Oxazepam	–
11	Anorectal fistule	Sertraline	Aprazolam	–
12	Megacolon	Fluoxetine	Aprazolam	–
13	Pes equino-varus	Citalopram	Oxazepam	–
14	Polydactyly hand	Sertraline	Diazepam	Ranitidine
15	Down syndrome	Citalopram	Alprazolam	–
16	Down syndrome	Escitalopram	Oxazepam	Thyroxine, disulfiram

ASA, acetyl salicylic acid; ASD, atrium septum defect; VSD, ventricular septum defect.

one of the two estimates is randomly high or low. Further information on a large and independent material is needed to definitely settle the question.

To conclude, we found no evidence in our material of a synergistic teratogenic effect of the combination of SSRI and benzodiazepines or other sedatives/hypnotics. Further studies are recommended as the numbers of infants exposed to specific drug combinations were low and an existing synergism may have gone undetected.

Acknowledgements We thank the National Board of Health and Welfare for giving us access to the health registers we used in this study.

Contributors The two authors jointly planned the study. Data collection and analysis were made by BK who also drafted the article. MR revised the text critically, and both authors approved the final text.

Funding The study was supported by grants from Evy and Gunnar Sandberg's Foundation, Lund (BK) and the Swedish Medical Research Council (No. 2009-4740) (MR). The authors' work was independent of the funders.

Competing interests None.

Ethics approval The study was performed within the responsibilities of the National Board of Health and Welfare (BK), and therefore no ethical approval from outside ethical committees was needed.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. Reis M, Källén B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. *Psychol Med* 2010;10:1723–33.
2. Oberlander TF, Warburton W, Misri S, *et al*. Major congenital malformations following prenatal exposure to serotonin reuptake inhibitors and benzodiazepines using population-based health data. *Birth Defects Res B Dev Reprod Toxicol* 2008;83:68–76.
3. National Board of Health and Welfare. Centre for Epidemiology. The Swedish Medical Birth Register—a summary of content and quality. 2003. <http://www.socialstyrelsen.se/Publikationer2003/-112-3> (accessed 29 May 2012).
4. Källén B, Otterblad Olausson P. Monitoring of maternal drug use and infant congenital malformations. Does loratadine cause hypospadias? *Int J Risk Safety Med* 2001;14:115–19.
5. National Board of Health and Welfare. Centre for Epidemiology. Registration of congenital malformations in Swedish health registers. 2004. <http://www.socialstyrelsen.se/Publikationer2004/2004-112-1> (accessed 29 May 2012).
6. Källén B. *Drugs during pregnancy*. New York, NY: Nova Biomedical Books, 2009.
7. Yang J, Cummings EA, ÓConnel C, *et al*. Fetal and neonatal outcomes of diabetic pregnancies. *Obstet Gynecol* 2006;108:644–50.
8. Lennestål R, Otterblad Olausson P, Källén B. Maternal use of antihypertensive drugs in early pregnancy and delivery outcome, notably the presence of congenital heart defects in the infants. *Eur J Clin Pharmacol* 2009;65:615–25.
9. Wikner BN, Sparre LS, Stiller CO, *et al*. Maternal use of thyroid hormones in pregnancy and neonatal outcome. *Acta Obstet Gynecol* 2008;87:617–27.
10. Källén B, Otterblad Olausson P. Use of anti-asthmatic drugs during pregnancy. 3. Congenital malformations in the infants. *Eur J Clin Pharmacol* 2007;63:383–8.