



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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-002166
Article Type:	Research
Date Submitted by the Author:	27-Sep-2012
Complete List of Authors:	Reis, Margareta; Clinical Pharmacology, Department of Medical and Health Sciences Källén, Bengt; Tornblad Institute, Lund University
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Obstetrics and gynaecology, Mental health
Keywords:	Maternal medicine < OBSTETRICS, Depression & mood disorders < PSYCHIATRY, EPIDEMIOLOGY

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

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Short title

Sedatives/hypnotics + SSRI in early pregnancy. Risk of cardiac defects

Key words: SSRI, benzodiazepines, sedatives, hypnotics, congenital malformations, cardiac
defects.

Word count: 1851 (excluding Abstract, References, Tables, and Statements).

Abstract

Objectives: To investigate the proposed synergistic teratogenic effect of use of selective serotonin receptor inhibitors (SSRI) together with sedatives or hypnotics 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 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 RR for the combination of SSRI and benzodiazepines and a relatively severe malformation = 1.17 (95% CI 0.70-1.73). 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 verified.

Word count: 182.

Article summary

Article focus:

- Does the combined use of SSRI and benzodiazepine drugs during pregnancy increase the risk for a congenital malformation and notably a cardiovascular defect?

Key messages:

- Neither SSRIs alone or benzodiazepines alone, nor the combined use of the two drug categories increased significantly the risk for a relatively severe malformation or for a cardiovascular defect.
- Neither did the combined use of SSRI and other sedative/hypnotics.

Strengths and limitations

- 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 a 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.

INTRODUCTION

The combined use of selective serotonin receptor inhibitors (SSRI) and sedatives/hypnotics, including benzodiazepines, during early pregnancy is not uncommon. The drug groups have, respectively, been studied thoroughly with regards to possible malformation risks in the offspring. However, if the combination SSRI+ sedatives/hypnotics has a synergistic effect with an increased malformation risk is a question that still remains open. One study, which was published in 2008, found that neither maternal use of an SSRI alone nor of a benzodiazepine alone increased the risk for a congenital malformation. However, the combined use of the two drug categories did, notably the risk for a cardiovascular defect.[1] 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 verified 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 was used.[2] Women giving birth between July 1, 1995 and December 31, 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.[3] 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; 2,014 the use of benzodiazepines; 1,503 the use of hypnotic benzodiazepine receptor agonists (HBRA); and 1,003 the use of other

sedatives/hypnotics, the largest group of which was made up of 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).[4] 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 to 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). 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 outcome was below 10, a risk ratio (RR) was calculated instead as the observed number divided with 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 seem to smoke more often than women only using SSRI. Women using SSRI in combination with benzodiazepines seem not to be of parity 1 or be 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 summarizes data on the occurrence of any relatively severe malformation and of any cardiovascular defect according to maternal use of these drugs. The odds ratio for any relatively severe malformation varied between 0.76 and 1.35. For cardiovascular defects 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 0.61-8.68).

Women using SSRI drug also use many non-CNS active drugs in excess, some of which may have teratogenic effects: insulin (as an indicator of preexisting diabetes), antihypertensive drugs, and drugs used for thyroid disease.[5] 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 5 cases and the RR was 1.09 (95% CI 0.36-2.55).

DISCUSSION

The present study was based on drug use as recorded in early pregnancy among more than 1 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 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 stigmatizing 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. A larger problem is that the study is only based on infants born. In some cases, fetal diagnosis will have revealed the presence of severe congenital malformations and an induced abortion has 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 (e.g., 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 little role in the analysis of cardiac defects, notably mild such 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.[5, 6] Among these conditions, the first three are known to affect malformation rate,[5, 7-9] while the association between maternal asthma and infant congenital malformations is weak.[5, 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. 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 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. The observation reported by Oberlander et al. could thus not be verified.[1] In our study, 406 exposed infants were included, in the Oberlander et al. study 359. In our study there were 16 infants with relatively severe malformations, in the Oberlander et al. study there were 20 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), Oberlander et al. found six. In both studies, 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. material it was paroxetine followed by sertraline and fluoxetine (venlafaxine was also included among SSRI). The dominating benzodiazepine in our material was diazepam followed by oxazepam, but in the Oberlander et al. material it was lorazepam followed by clonazepam. This is a possible explanation to the discrepancy in results; another possibility is that 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 numbers of infants exposed to specific drug combinations were low and an existing synergism may have gone undetected.

Data sharing: No additional data available.

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Authorship: The two authors jointly planned the study, data collection and analysis was made by BK who also drafted the article. MR revised the text critically and both authors approved the final text.

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Competing interests: All authors declare that the answer to the questions on your competing interest for bmj.com/cgi/content/full/317/7154/291/DCI are all No and therefore have nothing to declare.

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

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.

Ethics: 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.

Data Sharing Statement: Data from the Swedish Medical Birth Register was used. Please see ref: National Board of Health and Welfare. Centre for Epidemiology. The Swedish Medical Birth Register – a summary of content and quality. 2003.

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Table 1: Some characteristics of women using SSRI and/or sedatives/hypnotics during early pregnancy. For each variable, adjustments were made for all other studied variables. Odds ratios (OR) with 95% confidence intervals within brackets comparing exposed women with all other women in the population (n=1,290,672).

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

HBRA = hypnotic benzodiazepine receptor agonist, SSRI = selective serotonin reuptake inhibitor.

* SSRI without sedatives and /or hypnotics but possibly with non-CNS active drugs

Table 2: Risk 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 respective drug groups, in the population. Odds ratios (OR) or risk ratios (RR) with 95% confidence intervals (95% CI) after adjustment for year of birth, maternal age, parity, smoking, and BMI. RRs are not presented when three or less observed cases.

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

HBRA = hypnotic benzodiazepine receptor agonist, SSR = selective serotonin reuptake inhibitor.

#Relative risk (RR) as observed over expected numbers with 95% CI from Poisson distributions.

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



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Manuscript ID:	bmjopen-2012-002166.R1
Article Type:	Research
Date Submitted by the Author:	04-Dec-2012
Complete List of Authors:	Reis, Margareta; Clinical Pharmacology, Department of Medical and Health Sciences Källén, Bengt; Tornblad Institute, Lund University
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Key words: SSRI, benzodiazepines, sedatives, hypnotics, congenital malformations, cardiac
defects.

Word count: 1851 (excluding Abstract, References, Tables, and Statements).

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 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 RR for the combination of SSRI and benzodiazepines and a relatively severe malformation = 1.17 (95% CI 0.70-1.73). 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.

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- Does the combined use of SSRI and benzodiazepine drugs during pregnancy increase the risk for a congenital malformation and notably a cardiovascular defect?

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- Neither SSRIs alone or benzodiazepines alone, nor the combined use of the two drug categories increased significantly the risk for a relatively severe malformation or for a cardiovascular defect.
- Neither did the combined use of SSRI and other sedative/hypnotics.

Strengths and limitations

- 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 a benzodiazepine and only five cardiovascular defects were identified.
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INTRODUCTION

The combined use of selective serotonin receptor inhibitors (SSRI) and sedatives/hypnotics, including benzodiazepines, in the first trimester of pregnancy is not uncommon.[2] The drug groups have, respectively, been studied thoroughly with regards to possible malformation risks in the offspring. However, if the combination SSRI+ sedatives/hypnotics have a synergistic effect with an increased 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, increased the risk for a cardiovascular defect.[1] 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 was used.[2] Women giving birth between July 1, 1995 and December 31, 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.[3] 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; 2,014 the use of benzodiazepines; 1,503 the use of hypnotic benzodiazepine receptor agonists (HBRA); and 1,003 the use of other

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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 outcome was below 10, a risk ratio (RR) was calculated instead as the observed number divided with 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 seem to smoke more often than women only using SSRI. Women using SSRI in combination with benzodiazepines seem not to be of parity 1 or be 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 summarizes data on the occurrence of any relatively severe malformation and of any cardiovascular defect according to maternal use of these drugs. The odds ratio for any relatively severe malformation varied between 0.76 and 1.35. For cardiovascular defects, 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.

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Women using SSRI drug also use many non-CNS active drugs in excess, some of which may have teratogenic effects: insulin (as an indicator of preexisting diabetes), antihypertensive drugs, and drugs used for thyroid disease.[5] 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 5 cases and the RR was 1.09 (95% CI 0.36-2.55).

DISCUSSION

The present study was based on drug use as recorded in early pregnancy among more than 1 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 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 stigmatizing 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 will have revealed the presence of severe congenital malformations and an induced abortion has 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 (e.g., 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 little role in the analysis of cardiac defects, notably mild such 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.[5, 6] Among these conditions, the first three are known to affect malformation rate,[5, 7-9] while the association between maternal asthma and infant congenital malformations is weak.[5, 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. 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 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. The observation reported by Oberlander et al. could thus not be replicated.[1] In our study, 406 exposed infants were included, in the Oberlander et al. study 359. In our study there were 16 infants with relatively severe malformations, in the Oberlander et al. study there were 20 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), Oberlander et al. found six. In both studies, 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. material 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. material it was lorazepam

followed by clonazepam. This is a possible explanation to the discrepancy in results; another possibility is that 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 numbers of infants exposed to specific drug combinations were low and an existing synergism may have gone undetected.

Data sharing: No additional data available.

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Authorship: The two authors jointly planned the study, data collection and analysis was made by BK who also drafted the article. MR revised the text critically and both authors approved the final text.

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Table 1: Some characteristics of women using SSRI and/or sedatives/hypnotics during early pregnancy. For each variable, adjustments were made for all other studied variables. Odds ratios (OR) with 95% confidence intervals within brackets comparing exposed women with all other women in the population (n=1,290,672).

Drug category	Number	Age <25 vs 25-34	Age ≥35 vs 25-34	Parity 1 vs ≥2	Any smoking	Any previous miscarriage	Body mass index ≥25
SSRI only*	10383	0.88 (0.83-0.95)	1.25 (1.17-1.33)	1.36 (1.29-1.43)	2.47 (2.27-2.70)	0.99 (0.94-1.05)	1.27 (1.20-1.33)
SSRI+benzodiazepine	400	0.92 (0.68-1.25)	1.44 (1.06-1.94)	1.04 (0.83-1.32)	4.98 (3.50-7.10)	0.96 (0.73-1.27)	0.92 (0.71-1.18)
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HBRA = hypnotic benzodiazepine receptor agonist, SSRI = selective serotonin reuptake inhibitor.

* SSRI without sedatives and /or hypnotics but possibly with non-CNS active drugs

Table 2: Risk 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 respective drug groups, in the population. Odds ratios (OR) or risk ratios (RR) with 95% confidence intervals (95% CI) after adjustment for year of birth, maternal age, parity, smoking, and BMI.

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

HBRA = hypnotic benzodiazepine receptor agonist, SSR = selective serotonin reuptake inhibitor.

#Relative risk (RR) as observed over expected numbers with 95% CI from Poisson distributions.

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

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

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Short title

Sedatives/hypnotics + SSRI in early pregnancy. Risk of cardiac defects

Key words: SSRI, benzodiazepines, sedatives, hypnotics, congenital malformations, cardiac
defects.

Word count: 1851 (excluding Abstract, References, Tables, and Statements).

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 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 RR for the combination of SSRI and benzodiazepines and a relatively severe malformation = 1.17 (95% CI 0.70-1.73). 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.

Word count: 182.

Article summary

Article focus:

- Does the combined use of SSRI and benzodiazepine drugs during pregnancy increase the risk for a congenital malformation and notably a cardiovascular defect?

Key messages:

- Neither SSRIs alone or benzodiazepines alone, nor the combined use of the two drug categories increased significantly the risk for a relatively severe malformation or for a cardiovascular defect.
- Neither did the combined use of SSRI and other sedative/hypnotics.

Strengths and limitations

- 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 a 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.

INTRODUCTION

The combined use of selective serotonin receptor inhibitors (SSRI) and sedatives/hypnotics, including benzodiazepines, in the first trimester of pregnancy is not uncommon.[2] The drug groups have, respectively, been studied thoroughly with regards to possible malformation risks in the offspring. However, if the combination SSRI+ sedatives/hypnotics have a synergistic effect with an increased 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, increased the risk for a cardiovascular defect.[1] 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 was used.[2] Women giving birth between July 1, 1995 and December 31, 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.[3] 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; 2,014 the use of benzodiazepines; 1,503 the use of hypnotic benzodiazepine receptor agonists (HBRA); and 1,003 the use of other

sedatives/hypnotics, the largest group of which was made up of 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).[4] 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 to 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 outcome was below 10, a risk ratio (RR) was calculated instead as the observed number divided with 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 seem to smoke more often than women only using SSRI. Women using SSRI in combination with benzodiazepines seem not to be of parity 1 or be 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 summarizes data on the occurrence of any relatively severe malformation and of any cardiovascular defect according to maternal use of these drugs. The odds ratio for any relatively severe malformation varied between 0.76 and 1.35. For cardiovascular defects, 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 0.61-8.68).

Women using SSRI drug also use many non-CNS active drugs in excess, some of which may have teratogenic effects: insulin (as an indicator of preexisting diabetes), antihypertensive drugs, and drugs used for thyroid disease.[5] 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 5 cases and the RR was 1.09 (95% CI 0.36-2.55).

DISCUSSION

The present study was based on drug use as recorded in early pregnancy among more than 1 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 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 stigmatizing 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 will have revealed the presence of severe congenital malformations and an induced abortion has 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 (e.g., 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 little role in the analysis of cardiac defects, notably mild such defects like septal defects.

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HBRA = hypnotic benzodiazepine receptor agonist, SSRI = selective serotonin reuptake inhibitor.

* SSRI without sedatives and /or hypnotics but possibly with non-CNS active drugs

Table 2: Risk 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 respective drug groups, in the population. Odds ratios (OR) or risk ratios (RR) with 95% confidence intervals (95% CI) after adjustment for year of birth, maternal age, parity, smoking, and BMI. **RRs are not presented when three or less observed cases.**

Drug group used	Total number	With rel. severe malformation	OR/RR	95% CI	With cardio-vascular defect	OR/RR	95% CI
All SSRI	12195	396	1.06	0.96-1.17	121	1.01	0.84-1.21
SSRI without sedative/hypnotic	10511	337	1.05	0.94-1.17	103	0.99	0.82-1.21
Benzodiazepine without SSRI	1000	37	1.10	0.79-1.54	13	1.30	0.75-2.24
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Other sedative/hypnotic without SSRI	606	21	1.06	0.69-1.69	5	0.89	0.26-1.88#
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HBRA = hypnotic benzodiazepine receptor agonist, SSR = selective serotonin reuptake inhibitor.

#Relative risk (RR) as observed over expected numbers with 95% CI from Poisson distributions.

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



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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-002166.R2
Article Type:	Research
Date Submitted by the Author:	16-Jan-2013
Complete List of Authors:	Reis, Margareta; Clinical Pharmacology, Department of Medical and Health Sciences Källén, Bengt; Tornblad Institute, Lund University
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Mental health, Paediatrics, Obstetrics and gynaecology
Keywords:	Depression & mood disorders < PSYCHIATRY, Paediatric pathology < PATHOLOGY, EPIDEMIOLOGY

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

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Short title

Sedatives/hypnotics + SSRI in early pregnancy. Risk of cardiac defects

Key words: SSRI, benzodiazepines, sedatives, hypnotics, congenital malformations, cardiac
defects.

Word count: 1851 (excluding Abstract, References, Tables, and Statements).

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 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 RR for the combination of SSRI and benzodiazepines and a relatively severe malformation = 1.17 (95% CI 0.70-1.73). 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.

Word count: 184

Article summary

Article focus:

- Does the combined use of SSRI and benzodiazepine drugs during pregnancy increase the risk for a congenital malformation and notably a cardiovascular defect?

Key messages:

- Neither SSRIs alone or benzodiazepines alone, nor the combined use of the two drug categories increased significantly the risk for a relatively severe malformation or for a cardiovascular defect.
- Neither did the combined use of SSRI and other sedative/hypnotics.

Strengths and limitations

- 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 a 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.

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, respectively, been studied thoroughly with regards to possible malformation risks in the offspring. However, if the combination SSRI+ sedatives/hypnotics have a synergistic effect with an increased 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, increased 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 was used.[3] Women giving birth between July 1, 1995 and December 31, 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; 2,014 the use of benzodiazepines; 1,503 the use of hypnotic benzodiazepine receptor agonists (HBRA); and 1,003 the use of other

sedatives/hypnotics, the largest group of which was made up of 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 to 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 outcome was below 10, a risk ratio (RR) was calculated as the observed number divided with 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 seem to smoke more often than women only using SSRI. Women using SSRI in combination with benzodiazepines seem not to be of parity 1 or be 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 summarizes data on the occurrence of any relatively severe malformation and of any cardiovascular defect according to maternal use of these drugs. The odds ratio for any relatively severe malformation varied between 0.76 and 1.35. For cardiovascular defects, 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 0.61-8.68).

Women using SSRI drug also use many non-CNS active drugs in excess, some of which may have teratogenic effects: insulin (as an indicator of preexisting 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 5 cases and the RR was 1.09 (95% CI 0.36-2.55).

DISCUSSION

The present study was based on drug use as recorded in early pregnancy among more than 1 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 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 stigmatizing 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 will have revealed the presence of severe congenital malformations and an induced abortion has 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 (e.g., 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 little role in the analysis of cardiac defects, notably mild such 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. 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 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. The observation reported by Oberlander et al. could thus not be replicated.[2] In our study, 406 exposed infants were included, in the Oberlander et al. study 359. In our study there were 16 infants with relatively severe malformations, in the Oberlander et al. study there were 20 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), Oberlander et al. found six. In both studies, 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. material 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. material it was lorazepam followed by clonazepam. This is a possible explanation to the discrepancy in results; another

possibility is that 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 numbers of infants exposed to specific drug combinations were low and an existing synergism may have gone undetected.

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Authorship: The two authors jointly planned the study, data collection and analysis was made by BK who also drafted the article. MR revised the text critically and both authors approved the final text.

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Competing interests: All authors declare that the answer to the questions on your competing interest for bmj.com/cgi/content/full/317/7154/291/DCI are all No and therefore have nothing to declare.

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

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.

Ethics: 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.

Data sharing: No additional data available.

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Table 1: Some characteristics of women using SSRI and/or sedatives/hypnotics during early pregnancy. For each variable, adjustments were made for all other studied variables. Odds ratios (OR) with 95% confidence intervals within brackets comparing exposed women with all other women in the population (n=1,290,672).

Drug category	Number	Age <25 vs 25-34	Age ≥35 vs 25-34	Parity 1 vs ≥2	Any smoking	Any previous miscarriage	Body mass index ≥25
SSRI only*	10383	0.88 (0.83-0.95)	1.25 (1.17-1.33)	1.36 (1.29-1.43)	2.47 (2.27-2.70)	0.99 (0.94-1.05)	1.27 (1.20-1.33)
SSRI+benzodiazepine	400	0.92 (0.68-1.25)	1.44 (1.06-1.94)	1.04 (0.83-1.32)	4.98 (3.50-7.10)	0.96 (0.73-1.27)	0.92 (0.71-1.18)
SSRI+HBRA	305	0.98 (0.70-1.36)	1.14 (0.83-1.17)	1.40 (1.08-1.81)	5.48 (3.87-7.78)	0.94 (0.70-1.30)	1.19 (0.89-1.60)
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HBRA = hypnotic benzodiazepine receptor agonist, SSRI = selective serotonin reuptake inhibitor.

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Table 2: Risk 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 respective drug groups, in the population. Odds ratios (OR) or risk ratios (RR) with 95% confidence intervals (95% CI) after adjustment for year of birth, maternal age, parity, smoking, and BMI.

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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	-
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sedatives/hypnotics during pregnancy: Risk of relatively severe congenital
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Short title

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Key words: SSRI, benzodiazepines, sedatives, hypnotics, congenital malformations, cardiac
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Word count: 184

Article summary

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Key messages:

- Neither SSRIs alone or benzodiazepines alone, nor the combined use of the two drug categories increased significantly the risk for a relatively severe malformation or for a cardiovascular defect.
- Neither did the combined use of SSRI and other sedative/hypnotics.

Strengths and limitations

- 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 a 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.

INTRODUCTION

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MATERIAL AND METHODS

Data source:

Data from the Swedish Medical Birth Register was used.[3] Women giving birth between July 1, 1995 and December 31, 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; 2,014 the use of benzodiazepines; 1,503 the use of hypnotic benzodiazepine receptor agonists (HBRA); and 1,003 the use of other

sedatives/hypnotics, the largest group of which was made up of 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 to 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 outcome was below 10, a risk ratio (RR) was calculated as the observed number divided with 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 seem to smoke more often than women only using SSRI. Women using SSRI in combination with benzodiazepines seem not to be of parity 1 or be 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 summarizes data on the occurrence of any relatively severe malformation and of any cardiovascular defect according to maternal use of these drugs. The odds ratio for any relatively severe malformation varied between 0.76 and 1.35. For cardiovascular defects, 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 0.61-8.68).

Women using SSRI drug also use many non-CNS active drugs in excess, some of which may have teratogenic effects: insulin (as an indicator of preexisting 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 5 cases and the RR was 1.09 (95% CI 0.36-2.55).

DISCUSSION

The present study was based on drug use as recorded in early pregnancy among more than 1 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 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 stigmatizing 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 will have revealed the presence of severe congenital malformations and an induced abortion has 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 (e.g., 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 little role in the analysis of cardiac defects, notably mild such 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. 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 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. The observation reported by Oberlander et al. could thus not be replicated.[2] In our study, 406 exposed infants were included, in the Oberlander et al. study 359. In our study there were 16 infants with relatively severe malformations, in the Oberlander et al. study there were 20 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), Oberlander et al. found six. In both studies, 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. material 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. material it was lorazepam followed by clonazepam. This is a possible explanation to the discrepancy in results; another

possibility is that 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 numbers of infants exposed to specific drug combinations were low and an existing synergism may have gone undetected.

Data sharing: No additional data available.

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Authorship: The two authors jointly planned the study, data collection and analysis was made by BK who also drafted the article. MR revised the text critically and both authors approved the final text.

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Competing interests: All authors declare that the answer to the questions on your competing interest for bmj.com/cgi/content/full/317/7154/291/DCI are all No and therefore have nothing to declare.

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

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.

Ethics: 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.

Table 1: Some characteristics of women using SSRI and/or sedatives/hypnotics during early pregnancy. For each variable, adjustments were made for all other studied variables. Odds ratios (OR) with 95% confidence intervals within brackets comparing exposed women with all other women in the population (n=1,290,672).

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

HBRA = hypnotic benzodiazepine receptor agonist, SSRI = selective serotonin reuptake inhibitor.

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

Table 2: Risk 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 respective drug groups, in the population. Odds ratios (OR) or risk ratios (RR) with 95% confidence intervals (95% CI) after adjustment for year of birth, maternal age, parity, smoking, and BMI.

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

HBRA = hypnotic benzodiazepine receptor agonist, SSRI = selective serotonin reuptake inhibitor.

#Relative risk (RR) as observed over expected numbers with 95% CI from Poisson distributions.

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