PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Combined use of selective serotonin reuptake inhibitor and sedatives/hypnotics during pregnancy: Risk of relatively severe congenital malformations or cardiac defects. A register study
AUTHORS	Reis, Margareta; Källén, Bengt

VERSION 1 - REVIEW

REVIEWER	Marie Pardon School of Biomedical Sciences University of Nottingham NG7 2QA United Kingdom
REVIEW RETURNED	02-Nov-2012

GENERAL COMMENTS	The manuscript is well written and the conclusion well supported by the data. Might be worth mentioning more precisely how each of the possible confounding variable affects adverse effects on its own

REVIEWER	Helle Kieler MD, PhD, Head of Centre for Pharmacoepidemiology Karolinska Institutet Stockholm Sweden
REVIEW RETURNED	03-Nov-2012

GENERAL COMMENTS	Reis and Källén report findings from a study on use of SSRIs, hypnotics and sedatives in pregnancy and risks of congenital anomalies using information from the Swedish Medical Birth Register. The study addresses an important question as little is known about how combinations of drugs might affect embryonic and fetal development. Major comments: The study is impressive by its size and included more than 1.2 million women giving birth and their neonates between 1995 and 2008. However, despite its large size the study population might not have been large enough to assess associations between the rare exposures and rare outcomes, which was the aim of the study. A total of 12 195 had used an SSRI, which is equivalent to 1% of the total study population and only 822 (0.06% of the study population) were classified as users of both SSRI and hypnotics/sedatives.

	Considering the rare outcomes (3.3% had any congenital malformation) it seems unlikely that the study had sufficient statistical power to answer the research questions. Accordingly and in contrast to the views of the authors I do not believe that the strength of the study is its large size and I would have liked to know whether any power calculations were made before starting the study and the results of these. Information on drug exposure was obtained from the Medical Birth Register and this information is based on the interview with the pregnant woman at her first antenatal visit. The pregnant woman is asked whether she has used any drug after she became pregnant and as the mean gestational length for the first visit is approximately 12 gestational weeks, mostly first trimester exposure was evaluated (Stephansson et al. Drug use during pregnancy in Sweden - assessed by the Prescribed Drug Register and the Medical Birth Register. Clin Epidemiol. 2011 Feb 1;3:43-50). The teratogenic period for most congenital malformations would be covered by this time window, but for some cardiovascular defects the critical period is in early second trimester and information on exposure during this time of gestation was not evaluated for all women included in the study (Czeizel et al, Use of specified critical periods of different congenital abnormalities instead of the first trimester concept. Birth defects Res A Clin Mol Teratol 2008;82(3):139-146). Another limitation of the study, which should have been addressed, is the information on combined use of drugs that might not be sufficiently detailed in the Medical Birth Register to assess a synergistic effect. Though SSRIs and hypnotics/sedatives might have been reported as being used in early pregnancy, they may not have been used concomitantly at all or during the critical window. Cardiovascular defects were one of the major outcomes, however, which specific malformations that were included in this entity were not described, which they should have been. In addition it should have been mentioned that the Medical Birth Register covers only malformations detected in the neonatal period, which means that malformations detected later in life would not have been included in this study. This limitation should have been commented on in the discussion. A first report concerning associations between rare exposures and outcomes might be useful, even if no firm conclusions can be drawn due to insufficient statistical power. However, when the aim is to reevaluate a reported finding the study should have sufficient power to assess the association, which might not have been the case for the present study. Also considering the opportunities for collaborate studies combining information from several data sources I believe that the time has passed for studying associations between groups of drugs and malformations in general, which merely have been done for power reasons. Drugs belonging to the same group of drugs by ATC-code, such as SSRIs might not necessarily have the same teratogenic potential and should therefore preferably be

	analyzed by substance. Also the information that a drug or a group of drugs is associated/not associated with increased risks of malformations in general is of limited value considering the different pathophysiology for the various types of malformations. As mentioned in the discussion and conclusion further and larger studies are needed to address the question of an association and larger studies than the present one is probably only possible through collaborations between databases. For outcomes, with an expected number of less than ten, risks were calculated using information on the expected number of events in the general population instead of using the numbers in the unexposed cohort. As this low number was the case for most of the assessed associations with a cardiovascular defect as outcome the results are mainly based on calculations using expected numbers instead of actual numbers. This should have been mentioned already in the abstract and also clearly expressed as a limitation in the discussion. In the declaration of competing interests it is stated that “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.” This statement does not seem to be in agreement with what is stated in the paragraph concerning independency of funders. If the work was done without an ethical approval by or for the National Board of Health and Welfare it should be explicitly stated that the paper reports data on behalf of the National Board of Health and Welfare and the sentence concerning independency of the funders should be deleted. Half of the 10 references were authored or co-authored by the authors and these five references mainly describe findings from other drug exposures than the ones evaluated in this study. Considering the recent large studies on SSRIs and congenital malformations/cardiovascular defects, I do not find the references to be quite up to date. Minor comments: The fact that not only the combined use of SSRIs and hypnotics or sedatives were assessed but also risks of single use of the drugs should have been apparent from the title and written explicitly in the introduction. In the first sentence in the introduction it is mentioned that “the combined use of selective serotonin receptor inhibitors (SSRI) and sedatives/hypnotics, including benzodiazepines, during early pregnancy is not uncommon”, with no reference to support this. This statement does not seem to be in accordance with the present data with only 0.06% classified as combined users and I suggest rephrasing the sentence.

	Tables: I suggest presenting the descriptive information in Table 1 the traditional way by numbers and proportions as columns and including information on the comparison group(s). A complete table should include numbers and proportions for exposed and unexposed and I suggest changing Table 2 accordingly.

VERSION 1 – AUTHOR RESPONSE

Reviewer Marie Pardon

Might be worth mentioning more precisely how each of the possible confounding variables effects on its own.
We have added under “Statistical analysis”, line 3: --and body mass index (BMI). These variables affect malformation rates in different ways according to the malformation studied.

Reviewer Helle Kieler

We have tried to summarize and number the points raised by this reviewer.

1) Size of the study.

We do not quite understand the way the reviewer argues. Obviously this is a large study which is necessary to identify a reasonable number of relatively rare exposures (SSRI+sedatives/hypnotics) and relatively rare outcomes (various malformations). The end result of the exposed outcomes will be 30 with a relatively severe malformation and 8 with a cardiac defect. The confidence intervals in Table 2 will give the likely upper and lower risk estimates given these numbers. It will tell that the effect is unlikely to be larger than 1.57 for any malformation and 1.82 for a cardiac defect.

We present as far as we know the first follow-up study of the Oberlander et al. observation and the data are of about the same size as in that study. Obviously it had been nice to have a still larger study but this is what we had when this study was made. A power analysis before the start of the study would be difficult to make because there was no information available on exposure rate at that time. When we had exposure time we, at the same time, had the outcome with confidence intervals that show the precision of the estimates.
Throughout the article we have changed the word “verified” (with regards to the Oberlander et al. findings) to “replicated” which may be better.

2) The reviewer is concerned about the “sensitive period” of the various malformations studied and notably cardiovascular defects.

She refers to Czeizel’s paper which is actually a critique of the use of the first trimester as the exposure window and he suggests using months II-III and does not recommend studies into the 2nd trimester. Cardiac development starts very early in development (3rd week after conception) and cardiac morphogenesis is basically finished at the end of the 9th week, that is well within the first trimester. The exact time when a specific cardiac defect originates is difficult or impossible to fix (in spite of what can be thought from various embryology textbooks).

3) The reviewer points out that we do not know that the women had used the SSRI drug and the sedative/hypnotic simultaneously.

This is right and we have added a sentence in the Discussion, line 10, first paragraph: Further, it is not certain that the women who reported the use of SSRI and a sedative/hypnotic had used both drug categories simultaneously.

4) The inclusion criteria for cardiovascular defects were not given.

Actually we instead gave exclusion criteria: exclusion of patent ductus at preterm birth and single umbilical artery (second last line under Data source).

5) Data on malformations were restricted to information from the Medical Birth Register.

This is wrong; the sources are given on second paragraph under Data source: Congenital malformations in the infants were identified from three registers etc. These include data from hospitalizations also years after birth (length of observation depends on birth cohort). The sources are described in detail in ref. 4.

6) The reviewer suggests collaborative studies in order to increase power.

This is an obvious possibility – but such data should be obtained using unbiased sources. Very few possibilities exist to get such information. Most studies are made retrospectively with a serious risk for recall or interviewer bias. Other studies used prescription registers. The weaknesses of this approach for studies of first trimester exposures have been demonstrated (Kallen et al., Eur J Clin Pharmacol 2011; 67: 839-845) and we do not know about any other large scale studies which are based on early pregnancy interviews. The closest are the Danish and Norwegian prospective studies, both of limited size and hardly large enough to study unusual exposures similar to the combination of SSRI and sedatives/hypnotics.

7) The reviewer points out that different SSRIs may have different teratogenic effects (which incidentally is suggested for paroxetine and possibly fluoxetine and cardiac defects) and also that different sedatives/hypnotics could have different effects.

This was the reason we presented details in Table 3 of which drugs were involved and also which other drugs were reported. We also discussed the possibility that the difference in results between the Oberlander et al. study and our study was due to the fact that different drugs were involved.

8) The reviewer thinks that studies of larger groups of malformations are not useful because the malformations have different pathophysiology

We suppose she means that they have different pathogenesis. Actually there are drugs (like valproic acid and some other anticonvulsants) which have very broad teratogenic effects and causing malformations of very different types (e.g., spina bifida, hypospadias, poludactyly, cardiac defects) and other drugs which have very specific effects. This is the old problem of splitting or lumping and we think it is a good policy first to lump, then to split.

9) The reviewer thinks that the expected number in the RR calculations should be estimated from unexposed children, not from the total population.

This can be debated. Considering (as the reviewer herself pointed out) that only 0.06% of the population is exposed, perhaps this would not be necessary: the change of the estimate would hardly

be noticeable! What the sentence “the results are mainly based on calculations using expected numbers instead of actual numbers” means is unclear for us. RR is calculated as the quotient between observed number and expected number.

10). The reviewer mixes two things: the fact that the study was part of the surveillance of drug use and delivery outcome performed at the National Board of Health and Welfare and the funding of the present study.

There is an ongoing analysis of data on drug use during pregnancy collected by the National Board of Health and performed by BK and collaborators and annually discussed in meetings with the National Board of Health and the Medical Drug Agency. Such analyses sometimes give as a result findings which are thought to be of general interest and are then published. The cost of the analyses, however, was funded by two other sources as stated in the manuscript and these sources were not involved in the study or had any influence on the results.

11) The reviewer is concerned that half of the ten references given refer to publications from our group and that no reference is given to the “recent large studies on SSRIs and congenital malformations/cardiovascular defects”.

We have given references which support statements in the text and have had no intention to review the large literature on SSRI and pregnancy outcome. As far as we know there is no other study but that by Oberlander et al. on the specific research question we discuss.

12) The reviewer suggests that the title should contain information that also the effect of SSRI alone and sedative/hypnotics alone.

We disagree – these results are just background information and the study concerns the combination of the drugs.

13) The reviewer dislikes the statement that a combination of SSRI and sedatives/hypnotics is not uncommon.

Actually, 7% of all women reporting the use of SSRI during pregnancy also reported the use of sedatives/hypnotics, a figure which is more relevant than the 0.06% of the population which the reviewer uses. We have changed the first sentence in the Introduction and included a reference: The combined use of selective serotonin receptor inhibitors (SSRI) and sedatives/hypnotics, including benzodiazepines in the first trimester of pregnancy is not uncommon.[2]

14) Contents of Tables 1-2.

Table 1 intends to demonstrate similarities and differences between women characteristics according to the different drug combinations and gives the absolute numbers and the estimated ORs. We can see no reason to go into details with actual numbers (and percentages) of women <25 years, for instance. The important thing is to see that for instance women who used the drug combinations were more often smoking than women who used only SSRI. We wanted to keep the tabular material as small as possible and only to give relevant information.

A few (minor) mistakes were found in the original manuscript and are now corrected by the authors:

•Abstract page 2 line 8/9, primarily benzodiazepines, were inserted.

•Introduction page 4, line 18; Inserted: (or venlafaxine) which more correctly refers to the Oberlander et al. study.

•Introduction page 4 line 23; Inserted: did, notably, increased the risk..

•Discussion: page 9 line 50: deleted: (venlafaxine was also included among SSRI).

•Table 2. Deleted: RRs are not presented when three or less observed cases.

VERSION 2 – REVIEW

REVIEWER	Helle Kieler Karolinska Institutet
REVIEW RETURNED	18-Dec-2012

THE STUDY	The authors replied to all the questions I rose, but regrettably only very minor changes were made in the manuscript. I comment the author's reply by using the same numbering as they did. 1) I believe that it would have been fully possible to perform a power analysis beforehand by using the numbers from the Oberland study (ref 1) and if needed take into consideration possible differences in use of SSRIs and hypnotics/sedatives during pregnancy between Canada and Sweden. This type of studies would benefit from such an approach. 2) Czeizel tested effects on risk estimates for different exposure periods, including first trimester and the "critical period" and presented for several malformations risks estimates of varying size based on these exposure periods. A statement that evaluation of drug exposure in the first trimester might not cover the teratogenic period for all the evaluated malformations would have been appropriate. 3) OK 4) As I understand from the text, it was only in the subanalyses that PD and single umbilical artery were excluded. 5) I dare say that the methods section is not enough detailed for readers not acquainted with the Swedish registers to understand how and what type of data that was gathered. Neither is it said that information on malformations was obtained to a certain age of the child, which, by the way, differed by year of birth according to the reply. Ref 4 does not clarify this. 6) OK 7) Yes, but only for SSRI+benzodiazepine, not for the other combinations. 8) If the information is not meaningful, then I doubt that it is wise to lump. 9) I believe the authors need to explain from where the "expected number" is derived (source, period of time and if any adjustments were made). 10) I leave to the editors to decide whether independency of funders only imply financial relations. 11) I believe that citing some of the key references from the relevant literature on SSRIs and benzodiazepines during pregnancy would have been appropriate. 12) OK 13) I can't see that ref 2 (The Swedish Medical Birth Register – a summary of content and quality, 2003) supports that use of SSRIs and sedatives hypnotics is not uncommon. 14) The information in tables 1 and 2 is presented in such a way that

	it is not possible for the reader to follow the numbers between the tables. All the numbers behind the risk estimates in table 2 should have been presented.

VERSION 2 – AUTHOR RESPONSE

Response:

The reviewer comments that only minor changes have been made in the manuscript. The reviewer comments gave no reasons for other changes.

Our responses to the new comments of the reviewer:

1. In order to make a power analysis one must know exposure rate and outcome rate in the population. Outcome rate was known. Exposure rate (women using SSRI and sedatives but not other CNS-active drugs) was not known. The reviewer thinks that one should use data from the Oberlander et al. study – such data are not available in the Canadian material and even if they were, they could not be applied to a Swedish material. Even the total rate of SSRI use during pregnancy varies between populations.

2. The reviewer thinks that exposures during the first trimester would not cover the sensitive periods of all malformations studied – notably cardiac malformations. We pointed out in our previous response that the period of cardiogenesis is from about week 3 to week 9 after conception so it is relatively well covered by our exposure window. What Czeizel probably means with his study is that exposures between LMP and two weeks after conception are not relevant which in principle is correct (although some animal experiments show that also during this window, teratogenic effects can be obtained). It is true that our exposure data are imprecise but refer to the period when the woman detects her pregnancy until the first antenatal care visit which will roughly cover the period of cardiac organogenesis.

4. That patent ductus and single umbilical artery were excluded also at the analysis of “relatively severe malformations” is clear from the Material and Methods section.

5. The information is given in the manuscript and a reference is also given to a detailed description of the sources used. The previous comment of the reviewer stated that malformations were only ascertained via the Medical Birth Register which was a mistake which she apparently now tries to hide.

7. The details were given for SSRI + benzodiazepines because that was the combination which Oberlander et al. described and is the central problem in the study.

8. The new statement of the reviewer that information on total malformation rate is not meaningful is a misunderstanding. We tried to explain that in certain situations a broad teratogenic effect is seen and should always be explored, then it is useful to select large enough groups of malformations with a similar pathogenesis (in this situation cardiovascular defects) and finally to describe individual cases, when this is possible, in order to identify unusual malformations or combinations of malformations. This is a common method in epidemiological studies of congenital malformations, well known for everybody with experience in the field.

9. The reviewer now changes her approach from a discussion if expected numbers should be calculated from population data or from unexposed data to a request to learn how expected numbers were calculated. This information was given at the end of the Methods section where it was stated that the expected number was adjusted in the same way as in the OR calculations, for year of birth, maternal age, parity, smoking habits, BMI.

10. Now the reviewer asks if “independency of funders only imply financial relations”. The exact meaning of this sentence is unclear. We have stated that we have got financial support from two different sources and that the work was performed without any influence from these funders. The previous concern of the reviewer was that the National Board of Health and Welfare does not need

approval from external ethical committees to analyse their data.

11. We disagree. The paper does not deal with the problems of the published literature on the effect of SSRI or on benzodiazepines but on the possibility that the combined use is teratogenic. We know of no other reference than that given on this problem.

13. Sorry, there was a mistake in the reference numbering. What was called reference “2“ should have been number “6”. As this reference appears as the first one quoted, a correction/renumbering of the reference list is now made.

14. We do not understand what the reviewer means that the reader cannot follow the numbers between the tables. The two tables describe two different data sets. The first one describes maternal characteristics at various exposure situations. Here are given number of women with each combination of drugs and (in the head) the total number of women. We could have added numbers of women <25 etc. which would give a very large table without adding much useful information. Table 2 gives number of infants (which is higher than number of women because the presence of multiple births) and among them numbers with relatively severe malformations or with cardiovascular defects. These are the numbers behind the risk estimates – or does the reviewer mean that we should give numbers for each year of birth, each maternal age class, each parity class, each smoking habit group, each BMI class? This would hardly be realistic.