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Systematic review

Selective serotonin reuptake inhibitor (SSRI) use during pregnancy and risk of preterm birth: a systematic review and meta-analysis

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Background Depression is a prevalent condition in pregnancy affecting about 10% of women. Maternal depression has been associated with an increase in preterm births (PTB), low birthweight and fetal growth restriction, and postnatal complications. Available treatments for depressive disorders are psychotherapeutic interventions and antidepressant medications including selective serotonin inhibitors (SSRIs). SSRI use during pregnancy has been associated with several fetal and neonatal complications; so far, however, the risk of PTB in women using SSRIs during pregnancy is still a subject of debate.

Objective To evaluate the risk of preterm birth (PTB) in cases of exposure to SSRIs during pregnancy.

Search strategy Electronic databases (MEDLINE, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE and the Cochrane Central Register of Controlled Trials) were searched from their inception until May 2015 with the use of a combination of the following text words 'depression', 'pregnancy', 'exposure', 'antidepressant', 'SSRI', 'selective serotonin reuptake inhibitor', 'preterm birth', 'small for gestational age' and 'prematurity'.

Selection criteria We included studies evaluating the effect of SSRIs exposure *in utero* and pregnancy outcomes. All cohort and case-control studies were eligible to be included if they reported the incidence of PTB after any exposure to SSRIs and had a comparison group of unexposed pregnant women. Studies without a control group were excluded.

Data collection and analysis The primary outcome was the incidence of PTB <37 weeks. Subgroup analysis of studies in which controls were defined as women with depression but without SSRI exposure during pregnancy were planned.

Main results Eight studies (1 237 669 women) were included: 93 982 in the exposure group and 1 143 687 in the control group. After adjusting for confounders, the incidence of PTB was significantly higher in the group of women treated with SSRIs compared with controls (i.e. both women with depression but without SSRI exposure and women without depression) (adjusted OR (aOR) 1.24, 95% CI 1.09–1.41). In the subgroup analysis of studies in which controls were defined as women with depression but without SSRI exposure during pregnancy, an increased risk of PTB (6.8 versus 5.8%; OR 1.17, 95% CI 1.10–1.25) in the SSRI group was found compared with controls (i.e. depressed women treated with psychotherapy alone).

Conclusions Women who received SSRIs during pregnancy had a significantly higher risk of developing PTB compared with controls. This higher risk remained significant even when comparing depressed women on SSRI with women not on SSRI.

Keywords Depression, drug, malformation, prematurity, preterm birth.

Tweetable abstract Selective serotonin reuptake inhibitors may be associated with preterm birth.

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Introduction

Depression is a prevalent condition in pregnancy affecting about 10% of women.[1] Untreated antenatal depression is associated with poor self-care during pregnancy, risk of postpartum depression as well as risk of impaired maternal–infant bonding when it persists into the postpartum period.[2] Maternal depression has also been associated with

an increase in preterm births (PTB), low birthweight, fetal growth restriction, and postnatal complications.[2] Several explanations for the concept that maternal depression may contribute to PTB have been postulated: higher circulating levels of inflammatory markers such as C-reactive protein and the pro-inflammatory cytokines interleukin (IL)-1b, IL-6 and tumour necrosis factor (TNF)-α; higher level of placental CRH due to the increase of maternal pituitary-adrenal stress hormones (e.g. ACTH, cortisol); higher risk of bacterial vaginosis in women with maternal psychosocial stress.[3]

Available treatments for depressive disorders are psychotherapeutic interventions and antidepressant medications including selective serotonin inhibitors (SSRIs). SSRI use during pregnancy has been associated with several fetal and neonatal complications such as pulmonary hypertension,[4,5] cardiac malformations and spontaneous abortion.[6,7] However, so far the risk of PTB in women using SSRIs during pregnancy is still a subject of debate.

The aim of this meta-analysis is to evaluate the risk of PTB in cases of *in utero* exposure to SSRIs.

Methods

Eligibility criteria

This review was performed according to a protocol designed *a priori* and recommended for systematic reviews and meta-analyses.[8] Two authors (A.E., G.S.) identified studies by searching independently the electronic databases MEDLINE, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE and the Cochrane Central Register of Controlled Trials with the use of a combination of the following text words: 'depression', 'pregnancy', 'exposure', 'antidepressant', 'SSRI', 'selective serotonin reuptake inhibitor', 'preterm birth', 'small for gestational age' and 'prematurity' from inception of each databases until May 2015. No restrictions as to language or geographic location were applied.

Study selection

We included studies evaluating the effect of SSRIs exposure *in utero* and pregnancy outcomes. All cohort and case-control studies were eligible to be included if they reported the incidence of PTB after any exposure to SSRIs and had a comparison group of unexposed pregnant women. We included both studies in which controls were defined as 'all women', i.e. without depression and without SSRI exposure, as well as studies in which controls were defined as women with depression but no SSRI exposure during pregnancy. Studies were excluded if they lacked the outcome of interest (i.e. incidence of PTB). Studies without a control group were also excluded.

Risk of bias

The risk of bias of the included studies was assessed via the Methodological Index for Non-Randomized Studies (MINORS).[9] Seven domains related to risk of bias were assessed in each study: (1) aim (i.e. clearly stated aim), (2) rate (i.e. inclusion of consecutive patients and response rate), (3) data (i.e. prospective collection of data), (4) bias (i.e. unbiased assessment of study end points), (5) time (i.e. follow-up time appropriate), (6) loss (i.e. loss to follow-up), (7) size (i.e. calculation of the study size).[9] Review authors' judgments were categorised as 'low risk', 'high risk' or 'unclear risk of bias'.

Data abstraction

Two review authors (A.E., G.S.) independently assessed inclusion criteria, risk of bias and data extraction. Discrepancies were resolved by discussion with a third reviewer (V.B.). Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. Data not presented in the original publications were requested from the principal investigators.

Primary and secondary outcomes were defined before data extraction. The primary outcome was the incidence of PTB (i.e. PTB <37 weeks). Secondary outcome included birthweight and the incidence of respiratory distress syndrome (RDS). We planned to assess the primary outcome in sensitivity analyses according to type of study, type of SSRIs used and gestational age at antidepressant exposure. We also planned to assess the incidence of PTB in an *a priori* subgroup analysis of studies in which controls were defined as women with depression but without SSRI exposure during pregnancy.

Data analysis

The data analysis was completed independently by two authors (A.E., G.S.) using REVIEW MANAGER 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014),[8] and STATA command metandi (Stata Corp. College Station, TX, USA: 2013). The completed analyses were then compared and any difference was resolved with review of the entire data and independent analysis. Statistical heterogeneity between studies was assessed using the Higgins I^2 statistic.[8] In case of statistically significant heterogeneity ($I^2 \geq 50\%$) the random effect model of DerSimonian and Laird was used to obtain the pooled risk estimate, otherwise a fixed effect model was planned.[8] The summary measures were reported as odds ratio (OR) or as mean difference (MD) with 95% confidence interval (CI). A P-value <0.05 was considered statistically significant. Potential publication biases were assessed graphically using the funnel plot, and statistically using Begg's and Egger's tests.

For studies which reported both unadjusted and adjusted risk for confounders statistically proven, we performed an aggregate data meta-analysis using generic inverse variance method in order to obtain the adjusted OR for the primary outcome and for the secondary outcomes in the main analysis.[8,10]

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement.[11] Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration No.: CRD42015027379) following the PRISMA guidelines for protocols (PRISMA-P).[12]

Results

Study selection and study characteristics

The flow of study identification is shown in Figure S1. Table 1 shows the characteristics of the included studies. Eight studies including 1 237 669 women, were analysed.[13–20] Of the 1 237 669 women included, 93 982 used SSRIs as antidepressant during pregnancy, and 1 143 687 formed the non-exposed group (control group). Three studies came from USA,[17,18,20] two from Canada,[15,16] and the other three from Northern Europe.[13,14,19] Five studies used women with no depression or SSRI exposure as controls.[13–15,17,18] In the other three studies, controls were defined as women with depression but without SSRI exposure during pregnancy;[16,19,20] these 97 303 controls were prescribed no drugs and were treated with psychotherapy alone.[16,19,20] The quality of the studies included in our meta-analysis was assessed by the MINORS tool for assessing the risk of bias (Figure S2). Most of the included studies had low risk of bias in 'aim', 'rate', and 'size'. Three of them were prospective cohort studies,[15,18,19] two retrospective,[14,20] while the other three were large, high-quality population-based cohort studies.[13,16,17] Regarding the type the controls, all studies were judged as low risk of bias regarding 'contemporary groups' and 'baseline equivalence group'.[9] Two studies included only women who received fluoxetine as SSRI,[18,20] two only paroxetine,[15,19] and the others included women who received other SSRIs. Five studies included women who received SSRIs only in the first trimester,[13,14,16,19,20] one only in the third trimester.[15] Chambers et al.[18] stratified data for gestational age, reporting data both for the first and the third trimester. Hayes et al.[17] did not report gestational age at antidepressant treatment. The majority had PTB as primary outcome. In all of the included studies, there was a high risk for bias due to confounding by indication.

Risk of publication bias was assessed by visual inspection of funnel plot, and the symmetric plot suggested no publication bias (Figure S3). Publication bias, assessed using Begg's and Egger's tests, showed no significant bias ($P = 0.17$ and $P = 0.14$, respectively).

Synthesis of results

The meta-analysis showed that the incidence of PTB was significantly higher in the group of women treated with SSRI than in controls (11.6 versus 5.2%; OR 1.45, 95% CI 1.24–1.68, Figure 1), even after adjusting for statistically proven confounders, including maternal age, smoking, parity, prepregnancy counselling, race and education (aOR 1.24, 95% CI 1.09–1.41, Figure 2). Neonates from women who received SSRIs during pregnancy had a significantly higher risk of RDS (3.7 versus 1.4%; OR 1.33, 95% CI 1.14–1.56, Figure 3; aOR 1.22, 95% CI 1.19–1.58) and significantly lower birthweight (MD −117.12 g, 95% CI −125.99 to −108.24, Figure S4).

We found an increased risk of PTB in sensitivity analysis of prospective cohort studies (OR 1.83, 95% CI 1.30–2.59);[15,18,19] of retrospective cohort studies (OR 1.51, 95% CI 1.31–1.75);[14,20] of population-based cohort studies (OR 1.14, 95% CI 1.11–1.17);[13,16,17] of women who received SSRIs in the first trimester (OR 1.67, 95% CI 1.25–2.23);[13,14,16,18–20] of women who received SSRIs in the third trimester (OR 1.86, 95% CI 1.13–3.61);[15,18] of studies in which fluoxetine was used (OR 1.91, 95% CI 1.07–3.41);[18,20] and in studies in which paroxetine was used (OR 2.07, 95% CI 1.42–3.02).[15,19] Women who received paroxetine had a similar risk of PTB to those who received fluoxetine (OR 1.42, 95% CI 0.88–2.31). Women who received SSRIs in the third trimester had a significantly higher risk of PTB compared with those who received SSRIs only in the first trimester (OR 4.17, 95% CI 2.75–6.30).

In subgroup analysis of studies in which controls were defined as women with depression but without SSRI exposure during pregnancy,[16,19,20] we found an increased risk of PTB in the exposed group (6.8 versus 5.8%; OR 1.17, 95% CI 1.10–1.25; $I^2 = 0\%$) compared with controls (i.e. depressed women treated with psychotherapy alone).

Discussion

Main findings

This meta-analysis showed that women who received SSRIs during pregnancy had a significantly higher risk of developing PTB. This remained significant even when comparing depressed women on SSRI versus depressed women not on SSRI. This is important, as depression itself is associated with preterm delivery.[3] Neonates from women who received SSRIs during pregnancy had a significantly higher risk of RDS and significantly lower birthweight compared with controls. The risk of PTB seems to be higher if the SSRIs were given in the third trimester compared with an earlier exposure.

Table 1. Descriptive data of included studies

	Study location	Type of study	Number of included women	SSRI used	GA at exposure	Confounders adjusted	Control group	Definition of depression	Primary outcome
Chambers 1996[18]	USA	Prospective cohort	228 vs 254	Fluoxetine	First and third trimester	None	No depression, no SSRIs	Prescription of SSRI during the first or third trimester	PTB
Costei 2002[15]	Canada	Prospective cohort	55 vs 54	Paroxetine	Third trimester	None	No depression, no SSRIs	Prescription of SSRI during the third trimester	PTB and RDS
Simon 2002[20]	USA	Retrospective cohort	209 vs 209	Fluoxetine	First trimester	None	Women with depression but no SSRIs exposure	Not reported	PTB
Kallen 2004[13]	Sweden	Population-based cohort	28 634 vs 535 022	Various type*	First trimester	Maternal age, smoking, parity	No depression, no SSRIs	Prescription of SSRI during the first trimester	GA at delivery
Oberlander 2006[16]	Canada	Population-based cohort	15 685 vs 92 192	Various type*	First trimester	Pre-pregnancy counselling, maternal age, smoking	Women with depression but no SSRIs exposure	One 3- or 4-digit ICD-9 code	PTB
Lund 2009[19]	Denmark	Prospective cohort	329 vs 4902	Paroxetine	First trimester	None	Women with depression but no SSRIs exposure	Self-administered questionnaire	PTB
Kallen 2012[14]	Sweden	Retrospective cohort	15 045 vs 315 975	Various type*	First trimester	None	No depression, no SSRIs	ICD-10 code	PTB
Hayes 2012[17]	USA	Population-based cohort	33 797 vs 195 079	Various type*	N/R	Maternal age, race, smoking, education, parity	No depression, no SSRIs	ICD-9 code of 296.2, 296.3, 300.4, or 311	GA at delivery, PTB

Data are presented as number of exposed versus number of non-exposed. GA, gestational age; ICD, International Classification of Diseases; N/R, not reported; PTB, preterm birth; RDS, respiratory distress syndrome; SSRI, selective serotonin reuptake inhibitor.
*Various type of SSRIs, including citalopram, paroxetine, fluoxetine or sertraline.

Comparison with existing literature

To date, most meta-analyses have found that exposure to SSRI during pregnancy may be associated with several pregnancy complications including neonatal pulmonary hypertension and cardiac defects.[4–7] These meta-analyses did not analyse the correlation between SSRI and PTB. To our knowledge, this is the first systematic review evaluating this possible association. Other meta-analyses have reported an association between antidepressants and PTB.[21,22] Huybrechts et al. pooled data from 14 studies and found an increased risk of preterm delivery in women taking antidepressants, including tricyclic and noradrenergic antidepressant, during the second and third trimester of pregnancy.[22]

Strengths and limitations

The most important strength of our work rests on the attention to potential confounding factors. Generic inverse variance method was used to obtain the aOR for studies which adjusted for statistically proven confounders. No prior meta-analysis on this issue is as large, up-to-date or comprehensive. The number of the included women is very high. Most of the included studies had low risk of bias. Subgroup analyses and sensitivity analyses were performed to reduce the clinical heterogeneity within the studies. Primary outcome was assessed in subgroup analysis of studies in which controls were defined as women with depression but without SSRI exposure during pregnancy, which was the most clinical meaningful analysis.

Although meta-analytical techniques pool all available data, limitations include those of the original articles. All the included studies were cohort studies; no randomised controlled trials were included in this systematic review and this is a major shortcoming of this study. None of the included studies stratified data for PTB aetiology, so data regarding this outcome referred to both spontaneous and indicated. This limitation places the biologic plausibility of a drug–preterm delivery association in question, as the two types of PTB have distinct aetiologies and pathogeneses. There were different control groups and this point raises the question of selection of the overall control group. Only three studies adjusted for confounders and these may not have been sufficient to control for a study of risk factors for PTB.[13,16,17] Even within the subgroup analysis, there remained confounding by severity of depression that had the potential to bias results significantly. Confounding factors that influence birth outcomes were variably controlled; these potential confounders, such as poor prenatal care and drug, nicotine and alcohol use, occur at a higher rate in

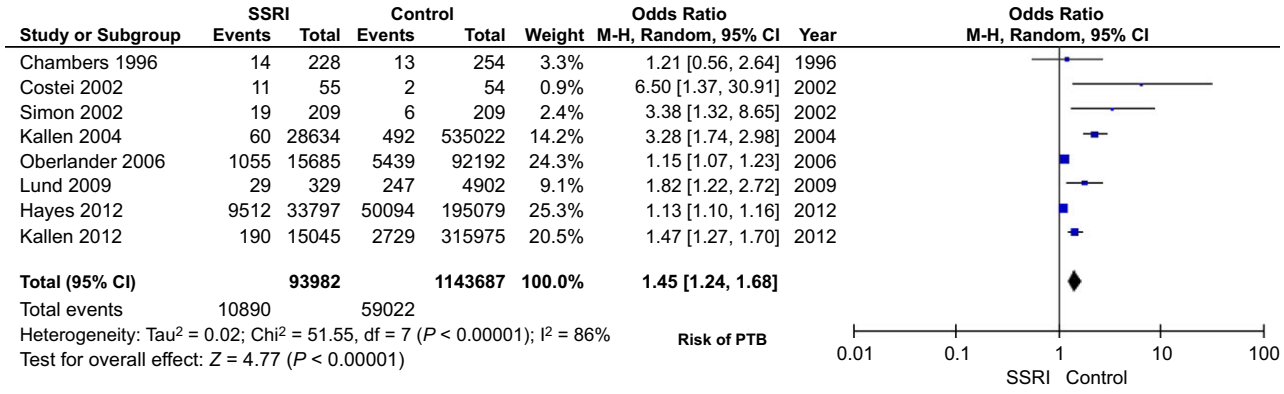

Figure 1. Unadjusted estimates Forest plot for the risk of preterm birth in women treated with selective serotonin reuptake inhibitor. CI, confidence interval; M-H, Mantel-Haenszel test; PTB, preterm birth; SSRI, selective serotonin reuptake inhibitor.

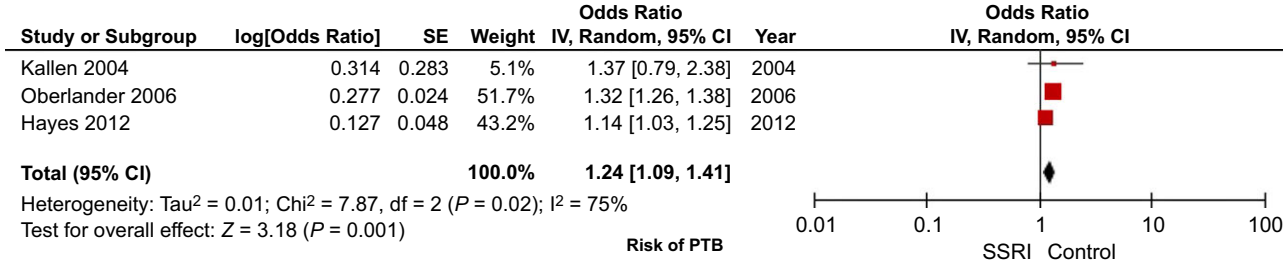

Figure 2. Adjusted estimates forest plot for the risk of preterm birth in women treated with selective serotonin reuptake inhibitor. CI, confidence interval; IV, independent variable; PTB, preterm birth; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

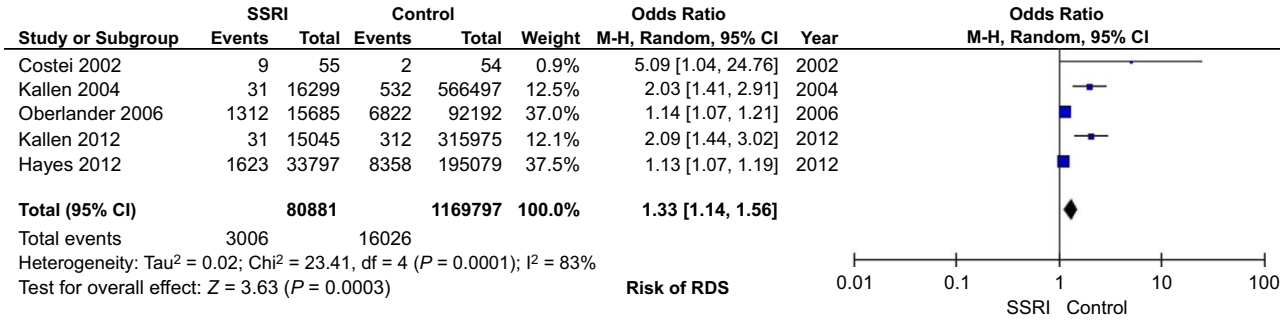

Figure 3. Forest plot for the risk of respiratory distress syndrome in women treated with selective serotonin reuptake inhibitor. CI, confidence interval; M-H, Mantel-Haenszel test; RDS, respiratory distress syndrome; SSRI, selective serotonin reuptake inhibitor.

depressed than non-depressed women.[23,24] Because SSRI use occurs in the context of maternal depression, we were not able to study the effects of SSRI exposure independent of exposure to depression alone. This bias cannot be reliably eliminated with a multivariable analysis. To avoid this limitation we performed subgroup analysis of studies in which controls were defined as women with depression but without SSRI exposure during pregnancy. This subgroup analysis concurs with the main analysis. However, only three studies (113 526 women) were included; moreover, restricting unexposed controls to depressed patients without SSRI exposure does not remove the possibility of confounding by indication, as treatment groups were not randomised. For example, it is possible that women in the SSRI treatment group had more severe disease compared with those who were not given medication, simply because their physicians selected them for SSRI treatment. Based on the characteristics of the included studies and the summary statistics for heterogeneity there was a large amount of both statistical and clinical heterogeneity. The studies vary markedly by overall study design, analysis (e.g. some not controlling for confounders), drug exposure timing, drug type(s), and study population, especially with regard to controls. This may impact the validity of the pooled results. The statistical heterogeneity within the studies for the primary outcome was high (I^2 = 86%). For this reason, random effects models were used in most of the analyses performed. Another major issue is the small OR (1.45 for the primary outcome). The OR seems to be smaller in the largest and best-designed studies (Figure 1).

Interpretation

There are many methods to treat depression during pregnancy.[24] Many patients with mild-to-moderate depression can be treated by psychosocial approaches such as individual and group psychotherapy instead of medication. Interpersonal and cognitive behavioural psychotherapy have been shown to be effective for depression in pregnant women,[25] and are recommended by The American College of Obstetricians and Gynecologists (ACOG) and The American Psychiatric Association (APA).[24] Regarding antidepressant treatment during pregnancy, SSRIs are the most frequently prescribed drugs;[26] physicians rarely use monoamine oxidase inhibitors or tricyclic antidepressants.[26,27] However, there are no randomised controlled trials of antidepressant drug efficacy in depressed pregnant women.

The biological plausibility of our findings is not completely clear. With respect to prematurity, some studies have suggested that maternal stress may increase the risk of preterm delivery.[28] Women who received SSRIs during pregnancy in whom the rate of PTB was increased, may have had more severe depression or anxiety and therefore been at higher risk for PTB (i.e. bias due to illness severity). In this case, if the antidepressant treatment lessened the effect of maternal depression, then in the absence of treatment, the outcome of these pregnancies may have been even worse. Alternatively, SSRIs could have affected the outcome of PTB separately from the effect of depression. Regarding birthweight, the findings of decreased birthweight are consistent with the results of a study in which pregnant rats treated with fluoxetine delivered smaller pups.[29] Sometimes, the use of SSRIs during pregnancy is inevitable. Untreated antenatal depression has been associated with suicidal tendencies, including death. Studies have shown that stopping SSRI treatment in pregnant women with a previous history of depression leads to relapse in the majority of women. Untreated depression during pregnancy has also been shown to be a strong risk factor for subsequent postpartum depression. Hence, in situations where it may be necessary to use SSRIs in pregnancy (prior history of severe antepartum or postpartum depression, current history of suicidal tendencies in the setting of depression in pregnancy, or in depressed patients dependent on high doses of antidepressants in pregnancy), the decision to use SSRIs during pregnancy must be weighed against the risks

of untreated depression and this risk/benefit ratio, including the risk of preterm birth. This must be carefully discussed with the patient, and should ideally be done in collaboration with the patient's psychiatrist.

Conclusion

This meta-analysis showed that women who received SSRIs during pregnancy had a significantly higher risk of developing PTB compared with controls. This higher risk remained significant (17% increase in PTB) even when comparing depressed women on SSRI versus depressed women not on SSRI, which is the most clinical meaningful analysis.

In summary, these data warrant caution in the use of SSRIs during pregnancy. Women should be informed about possible risks of antidepressant medication during pregnancy. However, as other confounding cannot be excluded, these data warrant further research on possible effects of SSRI on PTB.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

All authors contributed equally to this work.

Details of ethics approval

None required.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow diagram of studies identified in the systematic review.

Figure S2. Assessment of risk of bias.

Figure S3. Funnel plot for assessing publication bias. OR, odds ratio; SE, standard error.

Figure S4. Forest plot for birthweight in women treated with selective serotonin reuptake inhibitor.

Video S1. Author Insights. ■

References

1 Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. *Obstet Gynecol* 2005;106:1071–83.

2 Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birthweight, and intrauterine growth restriction. *Arch Gen Psychiatry* 2010;67:1012–24.

3 Wadhwa PD, Entringer S, Buss C, Lu MC. The contribution of maternal stress to preterm birth: issues and considerations. *Clin Perinatol* 2011;38:351–84.

4 Ornoy A, Koren G. Selective serotonin reuptake inhibitors in human pregnancy: on the way to resolving the controversy. *Semin Fetal Neonatal Med* 2014;19:188–94.

5 Huybrechts KF, Bateman BT, Palmsten K, Desai RJ, Patorno E, Gopalakrishnan C, et al. Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. *JAMA* 2015;213:2142–51.

6 Myles N, Newall H, Ward H, Large M. Systematic meta-analysis of individual selective serotonin reuptake inhibitor medications and congenital malformations. *Aust N Z J Psychiatry* 2013; 47:1002–12.

7 Nifkar S, Rahimi R, Hendoiee N, Abdollahi M. Increasing the risk of spontaneous abortion and major malformations in newborns following use of serotonin reuptake inhibitors during pregnancy: a systematic review and updated meta-analysis. *Daru* 2012;20:75.

8 Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (update March 2011). The Cochrane Collaboration, 2011. [www.cochrane-handbook.org] Accessed 21 October 2015.

9 Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (MINORS). Development and validation of a new instrument. *ANZ J Surg* 2003;73:712–6.

10 Peters J, Mengersen K. Selective reporting of adjusted estimates in observational epidemiology studies: reasons and implications for meta-analyses. *Eval Health Prof* 2008;31:370–89.

11 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006–12.

12 Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.

13 Kallen B. Neonate characteristics after maternal use of antidepressants in late pregnancy. *Arch Pediatr Adolesc Med* 2004; 158:312–6.

14 Kallen B, Reis M. Neonatal complications after maternal concomitant use of SSRI and other central nervous system active drugs during the second or third trimester of pregnancy. *J Clin Psychopharmacol* 2012;32:608–14.

15 Costei AM, Kozer E, Ho T, Ito S, Koren G. Perinatal outcome following third trimester exposure to paroxetine. *Arch Pediatr Adolesc Med* 2002;156:1129–32.

16 Oberlander TF, Warburton W, Misri S, Aghajanian J, Hertzman C. Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. *Arch Gen Psychiatry* 2006;63:898–906.

17 Hayes RM, Wu P, Shelton RC, Cooper WO, Dupont WD, Mitchel E, et al. Maternal antidepressant use and adverse outcomes: a cohort study of 228,876 pregnancies. *Am J Obstet Gynecol* 2012;207:49.e1–9.

18 Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Birth outcomes in pregnant women taking fluoxetine. *N Engl J Med* 1996;335:1010–5.

19 Lund N, Pedersen LH, Henriksen TB. Selective serotonin reuptake inhibitor exposure in utero and pregnancy outcomes. *Arch Pediatr Adolesc Med* 2009;163:949–54.

20 Simon GE, Cunningham ML, Davis RL. Outcomes of prenatal antidepressant exposure. *Am J Psychiatry* 2002;159:2055–61.

21 Huang H, Coleman S, Bridge JA, Yonkers K, Katon W. A meta-analysis of the relationship between antidepressant use in pregnancy and the risk of preterm birth and low birthweight. *Gen Hosp Psychiatry* 2014;36:13–8.

22 Huybrechts KF, Sanghani RS, Avorn J, Urato AC. Preterm birth and antidepressant medication use during pregnancy: a systematic review and meta-analysis. *PLoS ONE* 2014;26:e92778.

23 Kitamura T, Shima S, Sugarawa M, Toda MA. Psychological and social correlates of the onset of affective disorders among pregnant women. *Psychol Med* 1993;23:967–75.

24 Yonkers KA, Wisner KL, Stewart DE, Oberlander TF, Dell DL, Stotland N, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Gen Hosp Psychiatry* 2009;31:403–13.

25 Spinelli M, Endicott J. Controlled clinical trial of interpersonal psychotherapy versus parenting education program for depressed pregnant women. *Am J Psychiatry* 2003;160:555–62.

26 Headley J, Northstone K, Simmons H, Golding J; ALSPAC Study team. Medication use during pregnancy: data from the Avon Logitudinal Study of Parents and Children. *Eur J Clin Pharmacol* 2004;60:355–661.

27 Cooper WO, Pont ME, Ray WA. Increasing use of antidepressants in pregnancy. *Am J Obstet Gynecol* 2007;196:544e1.

28 Berkowitz GS, Papiernik E. Epidemiology of preterm birth. *Epidemiol Rev* 1993;15:414–43.

29 Vorhees CV, Acuff-Smith KD, Schilling MA, Fisher JE, Moran MS, Buelke-Sam J. A developmental neurotoxicity evaluation of the effects of prenatal exposure to fluoxetine in rats. *Fundam Appl Toxicol* 1994;23:194–205.

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Is fetomaternal haemorrhage still a major obstetric complication despite new technologies management?

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Fetomaternal haemorrhage (FMH) due to bleeding of fetal blood into the maternal circulation can be responsible for unexplained stillbirths and neonatal mortality. Severe FMH can lead to fetal anaemia, cardiovascular failure, fetal hydrops and subsequently to intrauterine death but this is a rare condition with a prevalence of 0.3% (Maier et al. *Arch Gynecol Obstet* 2015;292:595–602). Before fetal monitoring and ultrasound imaging to estimate fetal anaemia, FMH diagnosis was based on Kleihauer, Braun and Betke stain, measuring the acidity resistance of fetal haemoglobin, and was possibly affected by abnormal haemoglobin carrier status (Pilkingston et al. *J Obstet Gynaecol Br Cwlth* 1966;73:909–16). In this study, blood trafficking from fetus to the mother was found in normal pregnancy blood samples, especially during labour and after delivery (Figure 1). It was increased in pre-eclampsia, artificial rupture of the membranes, forceps delivery and manual removal of the placenta.

Fetomaternal haemorrhage has been known since the 1940s and even a small amount of transplacental blood transfer can be responsible for haemolytic disease of the fetus and the newborn (HDFN) whose mechanisms have been reported previously (Hubinont. *BMJ* 1949;10:574–5). As maternal rhesus D antibodies are responsible for the majority of HDFN, clinical guidelines recommend prevention by systematic administration of anti-D immunoglobulin in RhD-negative pregnant women at 28 weeks of gestation but also in all situations at risk of FMH, such as miscarriage, termination of pregnancy, invasive procedures and external version. Anti-D is also given postnatally to prevent RhD immunisation in subsequent pregnancies. A Dutch case–control study has evaluated the risk factors for immunisation despite an adequate anti-D prophylactic policy. They found that assisted vaginal delivery or caesarean section, post maturity, maternal red blood cell transfusion and age were more frequently associated with prophylaxis failure. Overall, they found that 50% of the RhD immunisation cases were due to either a massive FMH or to insufficient anti-D administration (Koelewijn et al. *BJOG* 2009;116:1307–14).

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TABLE III

ABO-Incompatibility and Foetal-Maternal Transfusion

	Mean Numbers of Foetal Cells per 50 High Power Fields		
	Antenatal Cases	During Labour	After Delivery of Placenta
ABO-Incompatible .. (24 cases)	0·11	0·62	1·08
ABO-Compatible .. (76 cases)	0·43	0·34	0·49

Figure 1. Quantification of fetal red cells in maternal blood in ABO compatible and incompatible women during pregnancy, labour and after placental delivery. Reproduced from Pilkington, R. et al (1966), Foetal-maternal transfusion and rheus sensitization. *BJOG* 1966;73:909–916. doi:10.1111/j.1471-0528.1966.tb06113.x.

The Kleihauer, Braun and Betke stain test is still used for diagnosis even if flow cytometry is the reference standard for FMH quantification. Management using ultrasound and invasive fetal procedures improved FMH prognosis over the last 40 years. Fetal anaemia can be detected by Doppler peak systolic velocity measurement of the middle cerebral artery with an excellent sensitivity and specificity (Mari et al. *N Engl J Med* 2000;342:9–14). Management of fetal anaemia by intrauterine fetal intravascular blood transfusion was first described in 1981 (Rodeck et al. *Lancet* 1981;1:625–7) and is associated with a high perinatal survival rate reaching 90%. However, despite this management, massive FMH responsible for stillbirth still occurs. In conclusion, FMH is a rare condition possibly associated with fetal anaemia. HDFN could be prevented in Rhesus-negative patients with anti-D prophylaxis. Fetal intrauterine transfusion improved FMH prognosis but did not suppress its mortality rate in severe cases.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information. ■