Prenatal exposure to antidepressants and persistent pulmonary hypertension of the newborn: systematic review and meta-analysis


CRD summary
This well-conducted review concluded that exposure to selective serotonin reuptake inhibitors in late pregnancy seemed to be associated with an increased risk of newborn persistent pulmonary hypertension, but did not find an association in early pregnancy. The authors’ conclusions appear reliable and reflect the limitations of the varied studies. No conclusions could be made about other classes of antidepressants.

Authors’ objectives
To examine the risk for persistent pulmonary hypertension of the newborn associated with prenatal exposure to antidepressants.

Searching
MEDLINE, PsycINFO, EMBASE, CINAHL, and Scopus were searched from inception up to 30 December 2012. Some of the search terms were reported; a full list of keywords was available from the authors on request. Reference lists of reviews and meta-analyses were checked.

Study selection
Eligible studies were cohort and case-control studies that compared persistent pulmonary hypertension of the newborn after any exposure to antidepressants versus newborn who were not exposed to the antidepressant under analysis. Studies that did not report an effect size were included if they reported sufficient data to allow the calculation of an effect size. Studies had to be published in English.

All included studies reported on exposure to selective serotonin reuptake inhibitors (SSRIs). Outcomes were reported for SSRI exposure in early pregnancy (three studies), at any time or point in pregnancy (two studies), during most or all of pregnancy (two studies), and in late pregnancy (five studies). Methods for assessing antidepressant exposure varied across the studies and included self report, record or database review, and blood tests. Included studies used a range of lower gestational age thresholds as exclusion criteria for preterm birth: under 36 weeks (one study), 34 weeks or under (two studies), under 34 weeks (two studies), and under 33 weeks (one study). Studies were conducted in the USA (three), Canada (one), USA and Canada (one), Sweden (one), and in several European countries (one).

Two reviewers independently selected studies for inclusion. It was not explicitly stated but it was likely that any differences were resolved by consensus.

Assessment of study quality
The Systematic Assessment of Quality in Observational Research (SAQOR) tool, developed by the authors specifically for assessing research in psychiatry, and a modification of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool were used to assign a final rating of high, moderate, low or very low to each study.

Study quality was assessed by two reviewers independently and any differences were resolved by consensus.

Data extraction
Adjusted risk estimates for persistent pulmonary hypertension (as defined by the study authors), with their variances, were extracted. If these were not available data to compute crude odds ratios and sample variances were extracted.

Data were extracted by two reviewers independently and any differences were resolved by consensus.

Methods of synthesis
Adjusted or unadjusted odds ratios, odds ratios calculated by the review authors from raw data, prevalence, or relative risks were included in analyses. The DerSimonian and Laird random-effects model was used to pool odds ratios. When
pooling odds ratios from only two studies, a fixed-effect model was used. Heterogeneity was assessed using Cochran’s Q and I².

Planned subgroup analyses included study quality, study design, preterm birth, maternal obesity, caesarean section, and whether the study controlled for congenital malformations or meconium aspiration.

**Results of the review**

Five cohort studies and two case-control studies were included in the review (approximately 2.8 million participants). Four studies reported data for women exposed to any type of antidepressant. Comparable data were not sufficient to allow the pooling of at least three studies, so the analysis was restricted to data for women exposed to selective serotonin reuptake inhibitors (SSRIs) only.

All of the included studies were at least low quality. Studies did not consistently control for the severity of persistent pulmonary hypertension, or for confounding variables such as preterm birth, maternal obesity, caesarean section, congenital malformations, and meconium aspiration. Studies differed in their definitions of early and late pregnancy, and in some studies antidepressant exposure may not have been accurately measured.

Exposure to SSRIs in late pregnancy was significantly associated with persistent pulmonary hypertension in the newborn (OR 2.50, 95% CI 1.32 to 4.73; five studies; I²=52%), as was exposure to SSRIs during most or all of pregnancy (OR 3.33, 95% CI 1.58 to 7.02; two studies; I²=0%). Exposure to SSRIs in early pregnancy (OR 1.23, 95% CI 0.58 to 2.60; three studies; I²=78%) or at any time during pregnancy (OR 1.55, 95% CI 0.79 to 3.04; two studies; I²=0%) was not associated with persistent pulmonary hypertension in the newborn. The number needed to harm (NNH) in late pregnancy ranged from 286 to 351 women with a SSRI to see one additional case of persistent pulmonary hypertension in their newborn; the number needed to harm in early pregnancy was 2,288 women.

Evidence of possible publication bias was found.

**Authors’ conclusions**

There seemed to be a statistical association between selective serotonin reuptake inhibitors (SSRI) exposure in late pregnancy and the risk of persistent pulmonary hypertension in the newborn, but clinically the absolute risk was low. A statistical association between SSRI exposure in early pregnancy and the risk of persistent pulmonary hypertension was not evident.

**CRD commentary**

The review question and inclusion criteria were clear. The authors searched several databases. The restriction to studies published in English and full publications (rather than abstracts) may have excluded some relevant data. Methods to minimise error and bias in the review process were adequate.

Results of the quality assessment for individual studies were not clearly reported. The review was restricted by the limitations of the included studies, such as the variation in controlling for confounding factors. There was significant heterogeneity in the analysis of early and late pregnancy exposure to SSRIs. There may have been overlap in the study samples of two studies that contributed the most weight to the meta-analysis of late pregnancy SSRI exposure.

This was a well-conducted review; the authors’ relatively cautious conclusions appear reliable and reflect the limitations of the evidence.

**Implications of the review for practice and research**

**Practice:** The authors stated that pregnant women using or considering using SSRIs and that their families should be educated about persistent pulmonary hypertension of the newborn, and neonatologists must be made aware of any exposure to SSRIs.

**Research:** The authors stated that future research should determine if other classes of antidepressants show a similar association with persistent pulmonary hypertension as SSRIs and more research controlling for confounding variables was required.

**Funding**
Canadian Institutes of Health Research; Ontario Ministry of Health and Long-Term Care through Drug Innovation Fund, Canada.

**Bibliographic details**

**DOI**
10.1136/bmj.f6932

**Original Paper URL**
http://www.bmj.com/content/348/bmj.f6932

**Additional Data URL**
http://www.bmj.com/content/348/bmj.f6932?tab=related#webextra

**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Antidepressive Agents, Second-Generation; Humans; Female; Infant, Newborn; Pregnancy; Risk Factors; Serotonin Uptake Inhibitors; Persistent Fetal Circulation Syndrome

**AccessionNumber**
12014005116

**Date bibliographic record published**
15/01/2014

**Date abstract record published**
20/01/2014

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.