Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications
Moses-Kolko E L, Bogen D, Perel J, Bregar A, Uhl K, Levin B, Wisner K L

CRD summary
This review assessed the adverse effects on infants of in utero exposure to serotonin re-uptake inhibitors (SRIs) during the last trimester of pregnancy. The authors concluded that SRI exposure may result in a mild, self-limited neonatal behavioural syndrome. The conclusions are reasonable, although there were some methodological weaknesses in the conduct of the review.

Authors' objectives
To review the evidence relating to serotonin re-uptake inhibitor (SRI) neonatal syndrome and to help clinicians guide their patients in a risk-benefit decision-making process.

Searching
MEDLINE (from 1966 to February 2005) and PsycINFO (from 1974 to February 2005) were searched; the search terms were reported. In addition, reference lists were checked for further articles. There were no language restrictions.

Study selection
Study designs of evaluations included in the review
Study designs were not specified as part of the inclusion criteria. The review included case reports, case series and cohort studies.

Specific interventions included in the review
The inclusion criteria specified that studies should have a clearly identified maternal exposure to an SRI. The included studies evaluated exposure to the following SRIs at various doses (where reported): paroxetine (5 to 120 mg/day), fluoxetine (10 to 80 mg/day), sertraline (25 to 200 mg/day), citalopram (20 to 40 mg/day) and venlafaxine (one case report with a dose of 75 mg/day). The length of SRI exposure varied from during the third trimester only to throughout pregnancy. Some studies also included a control group that was not exposed to an SRI or was exposed only during the first 6 months of pregnancy.

Participants included in the review
Eligible participants were neonates whose mothers had been exposed to an SRI for a minimum of the final trimester of pregnancy through to delivery. One case report of an infant with a gestational age of 27 weeks was excluded because extreme prematurity could confound the presence of neonatal signs attributable to an SRI.

Outcomes assessed in the review
The inclusion criteria specified that neonatal outcomes should be assessed. The outcomes assessed by the included studies varied and included: special care nursery admission, respiratory difficulties, poor neonatal adaption (defined as jitteriness, tachypnoea, hypoglycaemia, hypothermia, poor tone, respiratory distress, weak or absent cry, or desaturation during feeding), low birth weight, hypoglycaemia, prematurity, and congenital anomalies.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

If not reported in the article, the relative risks and corresponding 95% confidence intervals (CIs) were calculated using exact methods.

Methods of synthesis
How were the studies combined?
The results of the cohort studies were combined by calculating pooled risk ratios (and corresponding 95% CIs) using the Mantel-Haenszel fixed-effect method. The results of the case reports, case series and cohort studies were also presented as a narrative synthesis, with different study designs grouped separately.

How were differences between studies investigated?
Differences between the studies were not assessed using statistical methods. The authors discussed the limitations of the included cohort studies and potential variability due to differences in study designs, treatments and outcome definitions. The results of the individual studies were described in a narrative synthesis, and the outcomes were pooled if sufficient data were available.

Results of the review
The review includes 9 cohort studies, of which eight had a control group that was either not exposed or had early exposure (before 26 weeks of pregnancy) to an SRI (exposed n=992, controls n=4,462,180). An additional 18 case reports (reported by 13 papers) and 2 case series were included.

Five of the 9 cohort studies (4 prospective and 1 retrospective) defined a neonatal behavioural syndrome which included signs of poor neonatal adaption (such as jitteriness, problems with breathing or feeding, and hypothermia). In the pooled analysis of these studies, there was an increased risk of an SRI-related neonatal behavioural syndrome for late SRI exposure compared with no or early exposure, with a relative risk (RR) of 3.0 (95% CI: 2.0, 4.4). Most reports of a behavioural syndrome in the case reports and cohort studies were related to exposure to paroxetine and fluoxetine.

There were also increased risks of admission to a special care nursery (RR 2.6, 95% CI: 1.4, 4.7) and respiratory difficulties (RR 2.3, 95% CI: 1.6, 3.2) for infants with late SRI exposure compared with no or early exposure. There were no occurrences of a 'severe' syndrome (seizures, dehydration, excessive weight loss and hyperpyrexia) in 313 full-term infants where sufficient details were reported for this to be assessed. No neonatal deaths attributable to late pregnancy SRI exposure were reported.

Authors' conclusions
The neonatal behavioural syndrome associated with in utero exposure to SRIs during the last trimester of pregnancy is usually mild, self-limited, similar to familiar syndromes such as infantile colic, and can be managed with supportive care.

CRD commentary
This review had broad inclusion criteria, specifying eligible participants and outcomes, but not eligible study designs. Two relevant databases were searched with no language restrictions but, since no efforts were made to locate unpublished data, some research might have been missed. The authors did not state how papers were selected for the review or how relevant data were extracted, so it was not possible to assess whether steps were taken to minimise bias during the review process. The limitations of case reports and cohort studies as sources of evidence were discussed. However, the quality of the cohort studies and differences between them were not assessed.

Owing to differences in the study designs, outcome definitions and length of SRI exposure between comparator groups in the individual studies, the pooling of individual study results might not have been appropriate and, therefore, should
be treated with some caution. The authors’ conclusions and recommendations for practice and further research seem reasonable given the evidence presented in the review.

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

Practice: The authors stated that the risks and benefits of discontinuing an SRI during pregnancy need to be carefully balanced on an individual patient basis.

Research: The authors stated that further research should develop a definition and instrument for the diagnosis of neonatal behavioural syndrome. In addition, the incidence, severity spectrum, and preventive and therapeutic interventions for this syndrome need to be established.

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