Psychotropic medications in pregnant women: treatment dilemmas

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Authors' objectives
To review the evidence from all studies of adverse effects on infant outcome of psychotropic medications taken during pregnancy.

Searching
MEDLINE and EMBASE were searched from January 1976 to February 1998 using the following exploded medical subject headings: follow-up studies; psychotropic drugs; pre-natal exposure; adverse effects; anticonvulsants; pregnancy; depressive disorder; antidepressants; infant; and child development. Studies were restricted to the English language.

Study selection
Study designs of evaluations included in the review
Prospective controlled studies, retrospective studies and case studies that focused on adverse effects associated with drugs during pregnancy were included.

Specific interventions included in the review
The following psychotropic medications were included:

- antidepressants including selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, tricyclic antidepressants (TCAs) and newer antidepressants such as moclobemide, venlafaxine, nefazodone, mianserin, mono amine oxidase inhibitors (MAOIs);
- benzodiazepines including diazepam and alprazolam;
- mood stabilisers including lithium and anticonvulsants such as carbamazepine and sodium valproate;
- antipsychotics including chlorpromazine, trifluoperazine and haloperidol; and
- atypical newer antipsychotics such as clozapine, risperidone, olanzapine and zuclopenthixol.

Participants included in the review
The infants of women who had been exposed to psychotropic medications during pregnancy were included. The mothers of these infants were being treated for medical conditions including depression and epilepsy.

Outcomes assessed in the review
Three types of adverse infant outcome were assessed: major and minor congenital anomalies; perinatal complications including poor obstetric outcome and neonatal withdrawal or toxicity in first few days after birth; and neurobehavioural sequelae (developmental delay, learning difficulties, and deficits resulting from exposure).

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

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

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative review.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Twenty-three studies, including 9 prospective non-randomised studies, were included. The number of participants was not stated.

The studies were reported as being heterogeneous in outcome indicators. Some studies controlled for maternal age, past obstetric history, alcohol and smoking but none controlled for other drugs.

Fluoxetine (2 prospective controlled non-randomised studies, 2 non-controlled prospective studies, one cohort study with a control group): one prospective study that controlled for maternal age and past obstetric history reported no increase in rates of major anomalies and obstetric complications in women taking fluoxetine compared to two control groups (women with depression on TCA and non-exposed, not depressed women). Groups with depression had increased rates of miscarriage and neonatal complications and a number of minor physical anomalies. The other prospective study found no increase in miscarriage or major anomalies but found a significant increase among those exposed in infants with three or more anomalies. The two non-controlled studies reported conflicting results. One study reported no increase in neurodevelopmental deficits or developmental delays compared with non-exposed children at aged four years.

Tricyclics (one review that pooled results from 338 women, 2 prospective studies, one other study, and 2 case reports): The review reported no increased risk of major structural anomalies with first-trimester exposure. "Findings from the 2 prospective studies were identical to those reported for fluoxetine”. Case reports mentioned neonatal TCA withdrawals syndromes and anticholinergic effects. One study reported no increase in neurodevelopmental deficits or developmental delays compared with non-exposed children.

Other antidepressants: MAOIs (one study): higher rate of congenital anomalies in exposed infants. Mianserin (one cohort of 48 infants): one case of congenital anomaly. No studies on moclobemide, venlafaxine, or nefazodone were identified.

Benzodiazepines (2 reviews and 2 prospective studies were conflicting): Results were conflicting. One review based on birth registry data of several hundred women found the relative risk for cleft palate and lip to be approximately 2 to 3 fold with diazepam and 7-fold with alprazolam. One prospective study (137 women) found no increase in congenital anomalies after first trimester exposure to benzodiazepines (drug not specified) but an approximately two fold increase in miscarriage. One prospective study (17 infants) reported developmental delays at 18 months. One review (550 infants followed up for a maximum of four years): found no increase in neurobehavioural sequelae.

Lithium (2 reports of pooled data, one prospective controlled trial, one cohort, and one cohort with matched control): Conflicting results. The two studies with pooled data and one prospective study reported significantly increased rates of cardiovascular malformations. One cohort study (60 children) found no significant difference in congenital anomalies compared with non-exposed siblings and the other cohort found no difference in developmental milestones compared to a matched control group.

Carbamazepine (one observational study, one prospective study with 36 exposed infants): Conflicting results. The observational study found an incidence of spina bifida in 0.5% to 1% of infants exposed in the first trimester. The prospective study found no developmental delays or cognitive impairment in exposed infants.
Sodium valproate (one observational study, one small case series): The observational study found an incidence of spina bifida in 1% to 5% of exposed infants. The case series mentioned withdrawal seizures in exposed infants.

Chlorpromazine (one review, one five-year follow-up study, case reports and one case series): Inconsistent results. The review found that low dose in first trimester may increase congenital anomalies by 0.4%. The follow-up study found no increase in abnormalities in exposed infants. Case reports of chlorpromazine and other typical antipsychotics in the third trimester mentioned neonatal restlessness, tremor, poor suckling, abnormal movements, jaundice and functional bowel obstruction.

Trifluoperazine (one review): no increase in congenital anomalies.

Haloperidol (two small retrospective studies): no increase in congenital anomalies.

Authors' conclusions
While some psychotropic drugs are associated with congenital anomalies and perinatal complications, mental illness per se may also be associated with an adverse outcome in the infant. Clearly the risks to both mother and infant need to be weighed carefully and discussed with the parents.

CRD commentary
The aims were stated. The inclusion criteria were broad. Details were given of the search strategy. Given the diversity of outcomes, a narrative review was appropriate. Limiting included studies to those in the English language may have omitted some relevant studies. No attempt was made to locate unpublished studies thus raising the possibility of publication bias. No details were given of methods used to select primary studies or extract data (such as number of reviewers involved). Validity was not assessed. Results from reviews were mentioned without any critical appraisal. Sample size of primary studies was not mentioned. Drugs included in some primary studies were not specified. Significance levels of comparative studies were not reported making interpretation difficult. More comprehensive information is required on the primary studies before an assessment of the evidence can be made. Adequate control of potential confounding factors is required before an association between depression per se and infant outcomes may be evaluated. Insufficient evidence was reported to support the authors' conclusion.

Implications of the review for practice and research
Practice: Before a decision concerning the use of psychotropic management medication in pregnant women can be made, the risk-benefit ratio must be determined and discussed with the patient.

Research: The authors did not state any implications for further research.

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