Mood stabilizers in pregnancy: a systematic review
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CRD summary
This review concluded that exposure to commonly used mood stabilisers in pregnancy may be teratogenic and was associated with increased rates of perinatal complications. These findings must be balanced with the risks of untreated maternal bipolar disorder. The review had some methodological limitations and it was unclear to what extent the results apply to women with bipolar disorder.

Authors' objectives
To assess the effects of exposure to mood stabilising drugs in pregnancy on teratogenicity and on pregnancy and neonatal complications.

Searching
MEDLINE, EMBASE, PsycINFO, The Cochrane Library and DARE were searched for articles published between 1950 and June 2009. Search terms were indicated. Bibliographies of relevant reference books and review articles and reference lists of included studies were checked for further studies. Only English-language studies were included.

Study selection
Studies were eligible if they were controlled cohort studies, uncontrolled cohort studies or case series/case studies of use of lithium or the anti-epileptic mood stabilisers (AED) sodium valproate, carbamazepine and lamotrigine in pregnancy. Studies needed to evaluate malformation rates, perinatal outcomes (pregnancy and neonatal) or child neurodevelopmental outcomes.

Developmental outcomes for AEDs were reported from 2004 onwards only as a relevant Cochrane review that reported developmental outcomes following AED administration during pregnancy was identified and covered studies published between 1966 and December 2003. Case series were excluded from the evaluation of malformations following AED administration, as prospective controlled cohort studies were available.

Most of the studies of AEDs were carried out in pregnant women with epilepsy. Malformations reported in the included studies of AEDs included neural tube defects for both sodium valproate and carbamazepine; craniofacial, cardiac and limb defects and a range of minor malformations were also identified.

The authors did not state how many reviewers performed study selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how data were extracted for the review.

Methods of synthesis
Data were summarised narratively using tables and text.

Results of the review
The review included 51 studies. Participant numbers ranged from one to 2.5 million; the total number included was unclear as some studies cited only selected populations. Of the AED studies, 22 cohort studies reported on malformations and 16 studies (n=10,309 participants) quoted malformation rates for comparison between drugs. Ten cohort studies reported on pregnancy and neonatal outcomes. Thirteen studies (one case series and 12 cohort studies, published from 2004 onwards) reported on neurodevelopmental outcomes. Twelve studies (one case report, four case series and seven cohort studies) reported on outcomes with lithium carbonate. Most studies of AEDs were cohort studies. Studies on lithium carbonate included one case report, four case series and seven cohort studies (six were
mentioned in the text, but the table showed seven). More than half of the studies were prospective cohort studies with a control group.

In studies that allowed comparison between drugs, there was a consistent finding of higher malformation rates with sodium valproate (4.2% to 20.3%, 12 studies) than with carbamazepine (zero to 8.2%, 11 studies) and lamotrigine (1% to 3.2%, four studies). In four studies, risk of malformation with sodium valproate was further increased with doses higher than 1,000mg.

Consistent findings for perinatal outcomes included reduced head circumference with carbamazepine (four studies) as well as reduced birth weight and length (two studies). A significant association between sodium valproate and neonatal hypoglycaemia was found in one study.

Eleven studies examined the effect of sodium valproate on child development and all found an association with poorer developmental outcomes (such as global reduction in IQ, lower verbal IQ, autism, memory and attention). In studies of dose effects, doses of sodium valproate greater than 1,000mg and polytherapy were associated with poorer neurodevelopmental outcomes (two studies). No association was seen between carbamazepine or lamotrigine and developmental outcomes.

Evidence on effects of lithium exposure in pregnancy was more limited. There was a trend of increase in cardiovascular malformations with lithium, specifically with an increase in Epstein's anomaly (seven studies). Data from the table also suggest a high rate of stillbirths (two studies). Lithium exposure was associated with prematurity (one study) and increased birth weight (two studies). Information on developmental outcomes was limited.

Authors’ conclusions
Exposure in pregnancy to the mood stabilisers sodium valproate, carbamazepine, lamotrigine and lithium carbonate may be teratogenic and was associated with increased rates of pregnancy and neonatal complications. Sodium valproate may be associated with poorer longer term child developmental outcomes. These findings must be balanced with the risk of relapse and poor pregnancy and child outcomes with untreated maternal bipolar disorder.

CRD commentary
This systematic review addressed a clearly stated research question. Appropriate inclusion criteria were defined. There were some weaknesses in review methodology. The literature search included a range of relevant databases and supplementary searches were carried out. Only studies in English were included, so relevant studies may have been missed. Methodological quality of the included studies was not assessed and methods of data extraction were not described. Information on the included studies was limited. Studies of AEDs included large controlled cohort studies, but for lithium exposure only a few controlled cohort studies were identified and these generally had a small sample size. The authors stated that studies of AEDs were generally in women with epilepsy. The extent to which epilepsy contributed to poorer outcomes was unclear (some evidence was cited of adverse effects of the drugs over and above those of the epilepsy).

The extent to which the authors’ conclusions followed from the data presented was unclear, as there was no quality assessment, some studies had quality limitations, there was a risk of publication bias and the extent to which AED results can be transferred to women with bipolar disorder was unclear.

Implications of the review for practice and research
Practice: The authors stated that early monitoring for the different malformations and developmental problems cited was indicated. The balance of risks and benefits of different treatments should be carefully discussed with women and their partners or other support people to devise a management plan for pregnancy and postpartum. Risks of the medications should be discussed with women of child-bearing age as part of standard care.

Research: The authors stated that studies of women who took AEDs as mood stabilisers (rather than anti-epileptic agents) were required.
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