Preconception counselling for women with epilepsy to reduce adverse pregnancy outcome (Review)

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Preconception counselling for women with epilepsy to reduce adverse pregnancy outcome (Review)

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Preconception counselling for women with epilepsy to reduce adverse pregnancy outcome

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ABSTRACT

Background

The provision of preconception counselling to women with epilepsy (WWE) has become established as recommended practice and includes a review of drug treatment and the provision of information and advice on both seizure and treatment-related risks to both mother and child. In this review we assess the evidence regarding the effectiveness of preconception counselling for WWE.

Objectives

To determine the effectiveness of preconception counselling for WWE, measured by a reduction in adverse pregnancy outcome in both mother and child; increased knowledge of preconception issues in WWE and increasing intention to plan pregnancy.

Search strategy

We searched the Epilepsy Group’s Specialized Register (30/01/2008), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2007, Issue 4), and electronic databases: MEDLINE (OVID) (1950-February 2008); SCOPUS (1966-March 2008); CINAHL (1982-March 2008); PsyclNFO (1806-March 2008); ASSIA (1987-March 2008).

Selection criteria

Randomised control trials; including cluster and quasi-randomised trials, prospective cohorts, controlled before and after studies, and interrupted time series that compared the outcomes in mothers with epilepsy and infants of mothers with epilepsy who received preconception counselling, to the outcomes of mothers with epilepsy and their infants who received standard care or no intervention.

Data collection and analysis

The methodological quality of potentially relevant studies were assessed to determine appropriate inclusion. Where necessary, study authors were contacted for additional information. No studies met the review inclusion criteria.

Main results

The search strategy identified 11 studies for consideration of inclusion. However, none met the required criteria for inclusion.

Authors’ conclusions

Preconception counselling for women with epilepsy to reduce adverse pregnancy outcome (Review)
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There is no evidence to inform the content, methods of delivery or effectiveness of preconception counselling to improve pregnancy outcomes for WWE and their offspring. The value of counselling delivered to WWE prior to conception, with the intention of reducing the risks of adverse outcome in mother and child, requires evaluation in well-designed studies, appropriately powered to detect changes in both maternal and infant outcome.

**PLAIN LANGUAGE SUMMARY**

**Preconception counselling for women with epilepsy to reduce adverse pregnancy outcome**

No evidence to support preconception counselling for women with epilepsy.

The majority of women with epilepsy will experience a normal pregnancy and delivery; however, this requires informed decisions by women, balancing the risk to the fetus against the need to maintain seizure control during their reproductive years. The review did not find any evaluations of preconception counselling and educational interventions that were of sufficient quality to be included in the systematic review. There was not enough evidence to reach a conclusion about the effect of counselling and educational interventions to improve pregnancy outcome for women with epilepsy preparing for pregnancy.
**BACKGROUND**

Epilepsy is the most common serious neurological disorder, with a worldwide incidence varying between 40 and 80 per 100,000 people (Wallace 1998), and a lifetime prevalence of developing an active epilepsy in the UK of 4/1000 population (MacDonald 2002). The incidence of a treated epilepsy in the UK, calculated by the UK General Practice Research Database (GPRD), was estimated at 80.8 per 100,000 people (Wallace 1998), and an age-specific prevalence rate in treated women with epilepsy aged 16-44 years of between 6.9 and 7.8 per 1000 (Purcell 2002).

Women with epilepsy (WWE) during their child-bearing years face specific gender-based challenges relating to their experience of epilepsy and its treatment: namely, the potential for changes in menstrual function and fertility, interaction with hormonal contraception and the potential risk for adverse pregnancy outcome as a result of the teratogenic effects of antiepileptic drugs (AEDs) upon the developing fetus (Morrell 1998; Stokes 2004).

The outcome of pregnancy for most WWE is normal; however, there are additional risk factors for the mother and child including: potential teratogenic effects of AEDs; potential effect of maternal seizures on the developing fetus, and genetic risks, all of which contribute to a two- to three-fold increased risk of adverse outcome (Barrett 2003). The potential risk of adverse pregnancy outcome includes the risk for maternal mortality and morbidity, and the risk of fetal major congenital malformation (MCM) and long-term developmental delay. Although not all women would require ongoing treatment, recent estimates suggest around 95% of WWE remain on treatment in the US, resulting in approximately 22,800 children born each year following in-utero AED exposure (Meador 2004). Potential adverse pregnancy outcome due to AED exposure resulting in birth defect and delayed development has been recognised in several large prospective cohort studies and registries; however, methodological shortcomings, including insufficient sample size, have led to uncertainties about the precise risks (Adab 2004a), especially for the newer antiepileptic drugs (Adab 2001; Adab 2004; Kini 2006; Morrow 2006; Vinter 2004). The UK Epilepsy and Pregnancy Register confirmed that the risk for MCM was significantly higher for infants exposed to multiple, rather than single, antiepileptic drug regimens. The crude rate for MCM with any polytherapy exposure was 6.0% (adjusted odds ratio (OR) 1.76; 95% confidence interval (CI) 0.80 to 3.86), compared to 3.7% (adjusted OR 1.03; 95% CI 0.49 to 2.17) for pregnancies exposed to a single antiepileptic drug; with 95% CI calculated using no AED exposure as comparator, adjusting for age at delivery, parity, family history of MCM, periconceptional folic acid exposure and sex of infant (Morrow 2006). Increasing evidence of a drug-specific risk of adverse pregnancy outcome has been demonstrated from several recent studies, with Valproate posing the highest risk to the fetus (Meador 2006; Vajda 2006; Wyszynski 2005). While caution is required in interpreting the findings of these observational studies, the potential drug-specific risk has directed clinical practice guidelines recommending avoidance or reduction of the dosage of sodium valproate ahead of conception where possible (Tomson 2007).

The potential risks from AED treatment must be balanced against the potential risk from seizures during pregnancy; with concern for the impact of maternal tonic-clonic seizures during pregnancy upon fetal development (Adab 2004). Reports from a community-based Finnish study and the EURAP study group have suggested that there maybe a relatively low risk of change in seizure frequency during pregnancy, with 56% of women reporting no change in seizure frequency and 58.3% remaining seizure free throughout their pregnancies (EURAP 2006; Viinikainen 2006). Measures of seizure frequency from observational studies need to account for the potential influence of confounding factors and the ability of the findings to represent the population of WWE, supported by the less encouraging report within the same publication that status epilepticus occurred in 1.8% of pregnancies (EURAP 2006). The UK Confidential Enquiry into Maternal Deaths identified WWE as an indirect risk of mortality, reporting 11 epilepsy-related deaths from 2003 to 2005, six meeting the criteria for sudden unexpected death in epilepsy (SUDEP), and a further two late deaths meeting the criteria for SUDEP (late deaths defined as occurring between 42 days and one year after abortion, miscarriage, or delivery that are due to direct or indirect maternal cause) (CEMACH 2007). A consistent recommendation throughout all recent CEMACH reports has been the need to establish epilepsy review mechanisms that promote increased awareness and knowledge both about epilepsy management prior to and during pregnancy, while promoting the need for WWE, their partners and family to engage with epilepsy review services. The report draws attention to the uncertainty of association between SUDEP and pregnancy, concluding that pregnancy is an indirect risk factor for SUDEP as many women stop treatment through reluctance when pregnant or breastfeeding for fear of harming the baby (CEMACH 2007). Promoting increased awareness of the importance of seizure control in WWE and the role AEDs play in maintaining seizure control is seen as a component of preconception counselling (Kalviainen 2006).

Preconception counselling is a complex intervention; built up from a number of components, including behavioural parameters and organisational issues of timing and delivery, all contributing to difficulties in defining the ‘active ingredients’ of the intervention (MRC 2000). It has been defined as the process of planning and preparation for pregnancy, through which physical, mental and emotional health is optimised ahead of conception (Chamberlain 1986). As a complex intervention, it brings together an intervention process involving assessment, planning, treatment, education, decision support and counselling, resulting in a wide range of potential health outcomes before, during and after pregnancy for both the woman and her future offspring.

The components of preconception counselling for WWE incor-
An essential component of preconception counselling relies on the provision of information to enable women to make informed decisions. This must take account that concern for both epilepsy and AED therapy can influence decisions made by women regarding pregnancy; with WWE reported as more likely than their health-care providers to initiate conversations about pregnancy issues (Vazquez 2007). However, WWE appear to experience difficulty recalling the provision of information about preconception issues (Bell 2002; Crawford 2003; Wallace 1999); only 38% of women in a UK prospective population-based study of the care of women with epilepsy recalled receipt of preconception counselling (Fairgrieve 2000); and a quarter of surveyed female members of the British Epilepsy Association did not discuss pregnancy with anyone (Crawford 1999a).

The need to take account of a failure to access healthcare systems by WWE, either when planning pregnancy or on discovery of an unplanned pregnancy, was emphasized by the Quality Standards Subcommittee of the American Academy of Neurology; suggesting the need for a coordinated approach to the care of WWE, with interdisciplinary communication from primary care physicians, obstetricians, geneticists and neurologists (AAN QSS 1998).

The National Institute of Clinical Excellence Clinical Practice Guideline in the UK (Stokes 2004) recommends that the content of preconception counselling include review of diagnosis and treatment with the aim of optimising seizure control and promoting fertility, through offering advice on drug substitution or AED withdrawal. Folic acid supplementation is recommended, commencing during the preparatory phase (dosing advice and guideline recommendations varying both within and between countries, with doses between 0.4 mgs and 4 mgs recommended in the US, while 5 mgs is recommended in the UK) (Kjaer 2007). The informational content of preconception counselling should include information on teratogenic effect of AEDs, effects of pregnancy on seizure control, effects of epilepsy on the foetus, and the risk of inheritance (Stokes 2004). Earlier guidelines included topics such as contraception, birth and the neonatal period, breastfeeding and care of the infant (ILAE 1993).

Measures of the effectiveness of preconception counselling would be improvements in patient knowledge, and positive changes to health promoting behaviours such as engagement with services to improve seizure control, review of antiepileptic medication ahead of conception, and commencement of folic acid, all with the goal of reducing adverse pregnancy outcomes for mother and child. This review will address these important issues affecting women with epilepsy and their children.

**OBJECTIVES**

The primary objective of this review is to determine the effectiveness of preconception counselling aimed at:

- reducing adverse pregnancy outcome in both mother and child;
- increasing the knowledge of women with epilepsy;
- increasing intention to plan pregnancy.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

1. Randomised control trials; including quasi-randomised and cluster randomised trials where the unit of randomisation is the epilepsy clinic population (e.g. adolescent clinic).
2. Prospective cohort studies.
3. Controlled before and after studies.
4. Interrupted time series.

**Types of participants**

The review includes studies of women of childbearing potential (12 to 50 years) with a confirmed diagnosis of epilepsy (in the UK, the diagnosis of epilepsy in adults should be established by a specialist medical practitioner with training and expertise in epilepsy) (Stokes 2004). Women with epilepsy (WWE) for the purpose of the review, includes any women diagnosed with epilepsy continuing to take antiepileptic medication into childbearing age, and any women with active epilepsy (one or more seizures in the last two years) on or off treatment.

**Types of interventions**

Preconception counselling, defined as educational and counselling interventions targeted at WWE prior to conception, with the intention of reducing adverse pregnancy outcomes. The range and content of the interventions were based on the following sources; National Collaborating Centre for Primary Care and National Institute of Clinical Excellence (NICE 2004; Stokes 2004), Scottish Intercollegiate Guideline Network (SIGN...
The intervention should include any activity (health education or counselling activity) with the aim of reducing adverse pregnancy outcome in WWE of child-bearing age. Interventions might include, for example, any combination of the following listed items.

- Review of epilepsy diagnosis.
- Discussion of the importance of planned pregnancy.
- Discussion of the potential interaction of AEDs and hormonal contraception.
- Commencement of folic acid prior to conception.
- Discussion of the risk of malformation (major, minor anomalies and dysmorphic features) in exposed infant.
- Discussion of the risk of cognitive delay in exposed infant.
- Discussion of drug-specific pregnancy risk.
- Discussion of the importance of good seizure control and medication compliance.
- Discussion of seizure risk (maternal and fetal).
- Review of AEDs (adjustment of number of AEDs, switch from polytherapy to monotherapy, switch of AEDs).
- Review of AED withdrawal in woman with epilepsy in remission for > 2 years.
- Discussion of the potential benefits and limitations of prenatal diagnostic testing achieved by booking early into antenatal (perinatal) care.
- Discussion of safe child care, including advice on breastfeeding.
- Registration of the pregnancy with an appropriate register.

The comparison group should be WWE of childbearing age managed with usual care, defined as no targeted educational or counselling preconception intervention.

Types of outcome measures

**Primary outcomes**

- Increased knowledge of pregnancy and treatment risk (increase in knowledge measured by validated epilepsy knowledge/quality of life scale. There are a number of knowledge/quality of life scales that might be used; it is recognised that the nature of increased knowledge will be defined by the scale employed).

**Maternal outcomes**

- Reduced incidence of all major and minor congenital malformation/anomaly, including reduced incidence of developmental delay (as defined by trial authors).

**Secondary Outcomes**

**Maternal outcomes**

- Mortality (defined as death of a woman while pregnant or up to 12 months after delivery as a result of pre-existing epilepsy or onset of epilepsy during pregnancy, and not due to direct obstetric causes). Indirect maternal death related to epilepsy includes death classified as SUDEP.
- Morbidity (increased seizure frequency or severity (measured by seizure severity index or scale), treatment side effects, serious adverse events, postnatal depression).
- Reduction in number of unplanned pregnancies.
- Commencement of folic acid 5 mg daily.
- Increased concordance with epilepsy treatment-management plan.
- Increased uptake of breastfeeding.
- Increased satisfaction with care.
- Adherence to intervention.

**Fetal outcomes**

- Reduced infant mortality.
- Reduced morbidity (reduced admission into Special Care Baby Unit/Neonatal intensive care).
- Preterm birth (defined as the delivery of a baby before 37 completed weeks’ gestation).
- Small-for-gestational age (based on birthweight, defined as birthweight below the 10th percentile for gestational age).

**Timing of outcome assessment**

- Measurement of change following intervention.

**Economic data**

- Cost-effectiveness analysis.
- Cost-utility analysis.
- Direct and indirect costs, both immediate and long-term.

**Search methods for identification of studies**

We searched the Epilepsy Group’s Specialized Register (30 January 2008). This register contains reports of trials identified from regular searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and of MEDLINE. Relevant reports are also identified by hand searching selected journals and conference proceedings. A more detailed description of this activity can be seen by clicking on the link above.

In addition, we searched the following electronic databases up to March 2008:
(1) The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 4, 2007).
We did not impose language restrictions.
We used the following search strategies:

**Electronic databases**

MEDLINE (OVID)
1. epilep$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2. exp EPILEPSY/
3. seizure$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4. exp SEIZURES/
5. 1 or 2 or 3 or 4
6. exp Preconception Care/
7. (prepregnancy or pre-pregnancy or "pre pregnancy").mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8. (plan$ adj3 pregnan$).ti,ab.
9. (plan$ adj3 conceive).ti,ab.
10. (plan$ adj3 conception).ti,ab.
11. (preconception$ or pre-conception$ or "pre conception").mp. [mp=title, original title, abstract, name of substance word, subject heading word]
12. reproductive health.mp.
13. exp FAMILY-PLANNING
14. (family planning or planned parenthood).ti,ab.
15. exp FOLIC ACID/
16. exp Counseling/
17. (counsel$ or educat$ or inform$ or advice or advise).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
18. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
19. 16 or 17
20. 18 and 19
21. 20 or 6
22. 5 and 21
We also searched the following databases using the modified version of the above strategy:

- SCOPUS (1966-March 2008)
- CINAHL (1982-March 2008)
- PsyclINFO (1806-March 2008)

**References from published studies**

Other sources included:
- We reviewed reference lists of all retrieved studies and relevant reviews to search for additional reports of relevant studies.
- We contacted authors of relevant papers and experts in the field were contacted to identify any additional trials, or unpublished work.
- We searched the Database of Abstracts of Reviews of Effectiveness (DARE) was searched for related reviews (June 2007).

**Data collection and analysis**

**Selection of studies**

JW carried out the searches, and read all the abstracts found to identify publications that appeared to meet the inclusion criteria. Each of the other review authors (AJ, RS & GB) independently checked the search results and identified studies. All four review authors independently read the identified studies, and classified them as either:

1. relevant (meeting all of the pre-specified inclusion criteria);
2. possible (meeting some, but not all, inclusion criteria); and,
3. rejected (not relevant to the review, failing to meet any of the inclusion criteria).

All review authors examined full-text versions of all studies classified in categories (1) and (2). The final results were reached by consensus amongst the review authors, with disagreements resolved by discussion. We contacted the authors of the leading pregnancy registers, and asked whether they were involved in or aware of any additional studies assessing pre-pregnancy interventions (*EURAP 2006*; *Holmes 2004*; *Morrow 2006*). We contacted trial authors for missing information and data.

**Data extraction and management**

We planned to use data extraction forms to gather data on study location, methods, and participant characteristics at baseline, details of the intervention and control group management and outcome. It was agreed that two review authors would independently undertake data abstraction, entering data into Review Manager Software (*RevMan 2003*). Disagreements would be resolved through discussion by the two review authors. We would seek missing and unclear data from the authors as necessary to perform the planned analysis.

We planned to perform double-data entry.

**Assessment of methodological quality of included studies**

We planned to assess the quality of included studies according to the following characteristics:

1. allocation bias;
2. performance bias;
3. detection bias;
4. report bias;
5. attrition bias;
Randomised control trials and cluster randomised control trials
We planned to describe the methods used to generate the randomisation sequence for randomised control trials to consider issues of bias as follows:

(1) Selection bias (allocation concealment)
Assign a quality score for each trial, using the following criteria:
(a) adequate concealment of allocation: such as telephone randomisation, consecutively numbered sealed opaque envelopes;
(b) unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes or study does not report any concealment approach;
(c) inadequate concealment of allocation: such as open list of random number tables, use of case record numbers, dates of birth or days of the week.

(2) Attrition bias (loss of participants, e.g. withdrawals, dropouts, protocol deviations)
Assess completeness to follow up using the following criteria:
(a) less than 5% loss of participants;
(b) 5% to 9.9% loss of participants;
(c) 10% to 19.9% loss of participants;
(d) more than 20% loss of participants.

(3) Performance bias (blinding of participants, researchers and outcome assessment)
Assess blinding using the following criteria:
(a) blinding of participants (yes/no/unclear);
(b) blinding of caregiver (yes/no/unclear);
(c) blinding of outcome assessment (yes/no/unclear).

Measures of treatment effect
We planned to carry out statistical analysis using the Review Manager software (RevMan 2003), and to use fixed-effect meta-analysis to combine data in the absence of significant heterogeneity if trials had been sufficiently similar. We planned to deal with heterogeneity if found, using sensitivity analysis followed by random-effects analysis if required.

Dichotomous data
For dichotomous data, we planned to present the results as summary relative risk with 95% confidence intervals.

Continuous data
For continuous data, we planned to use the weighted mean difference if outcomes were measured in the same way between trials. We planned to use the standardised mean difference to combine trials that measured the same outcome, but used different methods. We also planned to report evidence of skewness.

Unit of analysis issues
Cluster-randomised trials
We planned to include cluster-randomised trials in the analyses, along with individually randomised trials. We planned to adjust their sample sizes using methods described by Gates 2005, using estimates of the intra-cluster correlation co-efficient (ICC) derived from the trial (where possible), or from other sources. If ICCs from other sources were used, we would report this, and conduct sensitivity analyses to investigate the effect of variation in the ICC. Where both cluster-randomised trials and individually randomised trials were identified, we planned to synthesise the relevant information and combine the results from both, if there was little heterogeneity between study designs and interactions between the effect of the intervention and the choice of randomisation unit were considered unlikely.

We planned to acknowledge heterogeneity in the randomisation unit and perform a separate meta-analysis.

Dealing with missing data
We planned to analyse data on all participants with available data in the group to which they were allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants were not analysed in the group to which they were randomised, whilst sufficient information was in the trial report, attempts would be made to restore them to the correct group.

Assessment of heterogeneity
We planned to apply tests of heterogeneity between trials (chi-squared test), if appropriate, quantifying inconsistency across studies using the I-squared (I²) statistic (Higgins 2005). If high levels of heterogeneity were identified among the trials, (exceeding 50%), we planned to explore them using a priori subgroup analysis and sensitivity analysis. A random-effects meta-analysis was planned as an overall summary if considered appropriate.

Dealing with multiple outcome data
For the purpose of statistical analysis of multiple comparisons between study groups/outcomes we planned to apply the Bonferroni technique. This technique is appropriate to reduce error rate and adjust for multiple dependent variables.

Subgroup analyses
We planned to conducted subgroup analyses as data permitted; classifying whole trials by interaction tests as described by Deeks 2001; and, subgroup analyses of the primary outcomes:

- parity-primigravid versus parous women;
- number of counselling sessions - one session versus more than one;
- different types of counselling/communication delivery styles;
- timing of intervention - as continual process of planned preconception intervention, at timed intervals up to conception (i.e. one year prior, six months prior)

Sensitivity analyses
We planned to evaluate sensitivity analysis exploring the effect of trial quality assessed by concealment of allocation, and excluding
studies with clearly inadequate allocation of concealment (rated C).

**Prospective cohort**
We planned to use the Newcastle-Ottawa Scale to assess quality, reporting on selection, comparability and outcome. In addition, we planned to consider the following criteria adapted from Khan 2001.

1. Were the groups comparable on all important confounding factors?
2. Was there adequate adjustment for the effects of these confounding variables?
3. Was the intervention reliably ascertained?
4. Was outcome assessment blind to intervention status?
5. Was follow up long enough for the outcomes to occur?
6. What proportion of the cohort/study group were followed up?
7. Were drop-out rates and reasons for drop-out similar across intervention and non-intervention group?

**Controlled before and after studies (CBA)**
We planned to apply the seven standard criteria developed by the Cochrane EPOC Group to assess methodological quality.

1. Baseline measurement:
   - done, if patient or performance outcomes measured prior to the intervention, and no substantial differences were present across study groups (e.g. where multiple pre-intervention measures describe similar trends in intervention and control group(s)).

2. Characteristics of studies using second site as control:
   - done, if characteristics of study and control providers are reported and similar.

3. Blinded assessment of primary outcome(s) with protection against detection bias:
   - done, if the authors state explicitly that the primary outcome variables were assessed blindly OR the outcome variables are objective (e.g. assessed by standardised test).

4. Protection against contamination in studies using a second site as control:
   - done, if allocation was by community, institution, or practice and was unlikely the control group received the intervention.

5. Reliable primary outcome measure(s):
   - done, if two or more raters with at least 90% agreement or kappa greater than or equal to 0.8 OR the outcome were obtained from some automated system (e.g. assessed by standardised test).

6. Follow-up of professionals (protection against exclusion bias)
   - done, if outcome measures obtained 80-100% subjects allocated to groups.

7. Follow up of patients:
   - done, if outcome measures obtained 80-100% of patients allocated to groups or for patients who entered the study.

**Interrupted time series (ITS)**
We planned to use criteria developed by the Cochrane EPOC Group to assess methodological quality.

1. Clearly defined point in time when the intervention occurred.
2. At least three data points before and three after the intervention.

We planned to apply the following quality criteria for ITS design.

1. Protection against secular changes:
   - the intervention is dependent of other change.

2. Data analysed appropriately:
   - done, if Auto Regression Integrated Moving Average models used OR times series regression models used to analyse the data and serial correlation adjusted/tested for;
   - if there are sufficient data points to enable reliable statistical inference;
   - done, if at least 20 data points recorded before the intervention AND the authors had done traditional time series analysis Model, OR at least three data points recorded pre- and post-intervention AND the authors had done a repeated measure analysis OR if at least three data points recorded pre and post intervention AND the authors had used ANOVA or multiple t-tests AND there were at least 30 observations per data point;
   - formal test for trend, judged complete if authors used ANOVA modelling.

3. Reason for the number of points pre- and post-intervention given:
   - done, if rationale for the number of points stated (e.g. monthly data for 12 months post-intervention used because anticipated effect expected to decay) OR sample size calculation performed.

4. Shape of the intervention effect specified:
   - done, if rationale explanation for the shape of intervention effect given by authors.

5. Protection against detection bias:
   - intervention unlikely to affect data collection;
   - blinded assessment of primary outcome(s).

6. Completeness of data set:
• done, if data set covers 80-100% of total number of participants.

(7) Reliable primary outcome measure(s):
• done, if two or more raters with at least 90% agreement or Kappa greater than or equal to 0.8 OR the outcome is obtained from some automated system assessed by a standardised test.

RESULTS

Description of studies

See: Characteristics of excluded studies; Characteristics of ongoing studies.

The search strategy generated 225 citations, of which two were from the Cochrane Epilepsy Group Specialized Register. From the initial search results, we discounted 211 papers as not relevant, of which, 65 were guideline documents and narrative review articles, including two systematic reviews of the effectiveness of preconception counselling in a non-epilepsy population. Of note; from those discounted, four surveyed the information needs of WWE, six assessed the information needs of professionals/organisations. Following retrieval for assessment, we discounted four articles as not including WWE in their study population, and another eight as non-interventional. We contacted 17 authors for additional information/data to enable appropriate assessment of eligibility. We considered 11 studies (14 published papers) potentially relevant and retrieved them for further assessment; from these, we excluded five studies as they did not meet the inclusion criteria for preconception intervention (Candito 2006; Candito 2007; Czeizel 1999; Kampman 2005; Martin 1993). From this group, the descriptions of intervention were variable: describing a single intervention; pre-/peri-conception folic acid or multivitamin supplementation (Candito 2006; Candito 2007; Czeizel 1999) and AED drug change policy (Martin 1993). The Hungarian randomised controlled trial by Czeizel 1999 measured the effect of folic acid supplementation on pregnancy outcome, with long-term outcomes assessed in a case-control trial.

Of the remaining six studies judged potentially relevant, the study design included one before and after study (Oguni 1992) and five retrospective case note reviews (Betts 1999; Cox 1992; Richmond 2004; Sablock 2002; Scale 1998). The review group discussed each paper initially considered potentially relevant, reviewing the merits of each. After much deliberation and discussion, we made a final decision based on their relevance, using the predetermined inclusion criteria, with no disagreements. No study met the inclusion criteria; the rationales for exclusions are shown in the ‘Characteristics of excluded studies’ table.

Contact with two authors identified an ongoing preconception intervention study in Croatia (Miskov) and a reanalysis of data from a cohort of preconception counselled women identified by poor outcome in an earlier pregnancy (Mawer); these are displayed in the ‘Characteristics of ongoing studies’ table.

We considered three studies potentially eligible. For two studies (Beffa Negrini 1998; Shafer 1996) we have contacted their authors to verify relevant information; both remain listed as ‘Studies awaiting assessment’ (Beffa Negrini 1998 awaiting translation; Shafer 1996, awaiting author reply). For the third study (Nguyen 2007) we are awaiting translation.

Risk of bias in included studies

No studies met the eligibility criteria for inclusion in the review.

Effects of interventions

No studies met the eligibility criteria for inclusion in the review.

DISCUSSION

We found no high-quality studies that addressed the effectiveness of preconception counselling to optimise pregnancy outcome in WWE. We located and appraised several studies that attempted to show evidence of the positive effect of counselling intervention. Although each of these studies reported on the outcome of preconception intervention, we can draw no firm conclusions or implications for practice because of the methodological weakness of the studies.

Learning from the work conducted in this field of research demonstrates the potential opportunities for conducting studies in this population. The majority of studies identified as potentially relevant were retrospective in design, making comparison of counselled WWE to non-matched un-counselled pregnant WWE; counselled women with other chronic diseases; or no comparison group. Although we excluded these studies as not meeting the review inclusion criteria, due to the risk of introducing bias, they suggest positive benefit from preconception counselling interventions. These examples demonstrate the methodological challenges in trial design and the dependence on clearly defined interventions. The complexity of the preconception intervention requires further investigation to identify the components of the intervention that are likely to be ‘active’ to support their reproducibility within a trial. This could be achieved by applying a framework, such as that developed by the MRC, to develop and evaluate complex interventions. The framework is based on developing a theoretical underpinning by gaining insights into the interconnectedness of the constituent parts of the intervention process, and acknowledging the multifaceted nature of the interventional components that may act both independently and interdependently within a social context (MRC 2000).
Preconception care is based in the desire to improve child health, adopted by the Department of Health in the concept “healthy mothers produce healthy babies who become healthy children and adults” (DH 2004). This concept is also espoused in the United States, with the goal of improving preconception and reproductive health outcomes, with the potential for reducing societal costs (MMWR 2006). The general concept of improving women’s health during their childbearing years has been transformed into preconception health promotion activity for all women, promoting the use of folic acid; reduction of smoking, alcohol and illicit drug use prior to conception; and for women with chronic disease, the need for additional disease/treatment specific care prior to conception.

We identified studies evaluating the delivery of preconception counselling to the wider community of women with chronic diseases during the review search strategy, and while not relevant to this review, the potential to measure the effectiveness preconception counselling for women with diabetes has been studied extensively. The meta-analysis by Ray 2001 demonstrates a reduction in major anomalies in pooled data from 14 cohorts, showing lower anomalies in preconception care recipients than non-participants (RR 0.36, 95%CI 0.22 to 0.59); and lowering of the risk of major and minor anomalies in women who received preconception care (RR 0.32, 95%CI 0.17 to 0.59). Of interest in relation to the components of preconception care, they located only one study that evaluated the addition of preconception folic acid to stabilising glycaemic control prior to conception, concluding that studies must include a range of interventions associated with improving pregnancy outcome, such as smoking cessation and folic acid use, while drawing caution to generalising from their results (Ray 2001).

Comparison of effectiveness of preconception counselling drawn from the study of counselling women with conditions including diabetes mellitus, phenylketonuria, blood disorders, asthma and hypothyroidism (to name but a few) may offer some support for the timing and delivery of optimal preconception care, but it is unclear whether direct comparisons can be made for WWE. Further evaluation in the general population of women at risk of poor pregnancy outcome has had variable success, with the RCT targeting women at risk of low birth weight babies in Australia drawing caution to the potential for detecting negative outcomes, an outcome not envisaged at the trial design stage (Lumley 2006).

Following from this systematic review of preconception care for WWE, it is evident further work is required to build theory and model for major confounders and identify underlying mechanisms to develop well-designed randomised controlled trials and cluster randomised trials to address the safety and efficacy of preconception counselling to reduce adverse pregnancy outcome in WWE. Prospective cohort studies, interrupted time series and before and after studies along with qualitative studies, are required to explore and describe the components of preconception counselling and the optimal delivery methods.

There remains a need to evaluate the cost-effectiveness of promoting the general concept of preconception counselling in women’s health care. By drawing on social marketing theories, a business case can be proposed, pointing to the need for evidence of effectiveness, defining the optimum methods of interventional delivery, and establishing how costs and benefits might be distributed among the healthcare organisation (Grosse 2006). Future service developments must take into account that less than half the target population of WWE of childbearing potential plan pregnancy; emphasizing the need to both promote and create a demand for preconception care amongst WWE and their healthcare providers (Prue 2006).

The review has demonstrated that whilst there is widespread support for pre-conception counselling interventions for WWE, there is insufficient evidence to evaluate their effectiveness in this group, thus preventing estimates of the likely benefit, harms or costs to reduce adverse pregnancy outcome. The need remains for robust evidence to support the provision of services for WWE during their childbearing years. While there is uncertainty of effectiveness, the component parts of the preconception intervention must be evaluated to avoid the risk of increasing adverse outcome.

**Authors’ Conclusions**

**Implications for practice**

There is no information available from appropriately designed studies to support the role of preconception counselling for WWE, or identify which elements of counselling or mode of delivery might be most effective.

**Implications for research**

We require well-designed, appropriately powered, randomised controlled trials, prospective cohorts, controlled before and after trials, and interrupted time series to evaluate the effectiveness of preconception counselling. While we judge randomised controlled trials as offering the best evidence of interventional effectiveness, we recognise that other study designs may be required to define, identify and test the active components of the intervention as suggested within the MRC framework. The following topics require further investigation:

- What clinical and behavioural interventions provided before pregnancy will improve pregnancy outcome for WWE and their offspring?
- What is the effectiveness of the various components of preconception counselling to reduce adverse pregnancy outcome?
- How effective are different models of preconception counselling delivery (including comparison of the role
of healthcare professionals, settings and timings of delivery)?

• How would preconception counselling, delivered at different stages of a WWE’s reproductive life stages, influence pregnancy planning behaviour?

• What impact would preconception counselling have upon quality of life and satisfaction of care?

• What impact would differing seizure severity have on the outcome of preconception care and costs?

• What are the costs and benefits to the WWE and the healthcare organisation?

In addition, qualitative research enquiry is needed to answer:

• How do WWE plan pregnancies?

• What do WWE want from preconception care?

We make the following suggestions for design and conduct of future trials.

• Prospective evaluation of the outcome of preconception counselling.

• Trials should be appropriately powered to rule out important differences in maternal and fetal outcome.

• Trials must look at clinically relevant outcomes, including health outcomes for both WWE and infants of mothers with epilepsy, satisfaction, resource utilisation and costs should be measured using standardised methods.

• Trials need clearly specified inclusion criteria, including definition of seizure frequency/control, AEDs efficacy using validated scale.

• The provision of the intervention must be clearly specified, including: clearly defined role of the health professional and WWE; the context of intervention delivery, including comparison of the effectiveness of non-specialist intervention, primary care intervention, and interventions offered opportunistically in family planning clinics.

• Data on economic outcomes including economic analysis, to calculate costs, sensitive to the different resources involved in preconception counselling used over the duration of the episode(s) of care.

• Blinding of outcome assessment. While it might be difficult to blind WWE and clinicians to the intervention, cluster randomised trials might overcome this obstacle. It is necessary to blind outcome assessors to the intervention group.

• Studies should be appropriately powered to enable the long-term followup and outcome measurement.

• Consumer involvement at all stages of the trial, most significant in the planning stage in order to identify outcomes deemed of most relevance and importance.

• Trial protocols should be publicly available to allow comparison of reported outcomes and pre-specified outcomes; and, allow reporting bias to be kept to a minimum.

**Acknowledgements**

Thanks go to members of the Cochrane Epilepsy Review Team for support and comments on the protocol and draft reports: Tony Marson (University of Liverpool), Rachael Jowett (Cochrane), Alison Beamond (Cochrane). Special thanks for additional information and clarification provided by: Timothy Betts, Mirande Candito, Andrew Czeizel, Brenda Liggan, Steve Lindow, Judith Lumley, Brian Jack, Margaret Jackson, Françoise Nguyen, George Mawer, Snjezana Miskov, Merry-K Moos and Fidelma O’Mahony.
REFERENCES

References to studies excluded from this review

Betts 1999 *(published and unpublished data)*

Candito 2006 *(published data only)*

Candito 2007 *(published data only)*

Cox 1992 *(published data only)*

Czeizel 1999 *(published and unpublished data)*


Kampman 2005 *(published data only)*

Martin 1993 *(published data only)*

Oguni 1992 *(published data only)*

Richmond 2004 *(published data only)*

Sablock 2002 *(published and unpublished data)*

Scale 1998 *(published data only)*
Scale CG, Morrell MJ. Nelson L. Druzin ML. Analysis of prenatal and gestational care given to women with epilepsy.. *Neurology* 1998 (Oct);51(4):1039–45.

References to studies awaiting assessment

Beffa Negrini 1998 *(published data only)*

Nguyen 2007 *(published data only)*

Shafer 1996 *(published data only)*

References to ongoing studies

Mawer *(unpublished data only)*
Ongoing study Starting date of trial not provided. Contact author for more information.

Miskov *(unpublished data only)*
Surveillance of Croatian pregnant women with epilepsy - neurodevelopmental and teratogenetic effects of antiepileptic drug exposure.. Ongoing study 2003.

Additional references

AAN QSS 1998

Adab 2001

Adab 2004

Adab 2004a

Barrett 2003
Preconception counselling for women with epilepsy to reduce adverse pregnancy outcome (Review)

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Bell 2002

CEMACH 2007

Chamberlain 1986

Cochrane EPOC Group
www.epoc.cochrane.org.

Crawford 1999

Crawford 1999a

Crawford 2003

Crawford 2005

Deeks 2001

Delgado-Escueta 1992

DH 2004

EURAP 2006

Fairgrieve 2000

Gates 2005

Grosse 2006

Higgins 2005

Holmes 2004

ILAE 1993

Janz 1989

Kalviainen 2006

Khan 2001

Kjaer 2007

Kramer 2006

Lumley 2006

MacDonald 2002
MacDonald BK, Cockerell OC, Sander JW, Sharff KS. The incidence and lifetime prevalence of neurological disorders in a prospec-
Preconception counselling for women with epilepsy to reduce adverse pregnancy outcome (Review)

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Meador 2004

Meador 2006

MMWR 2006

Morrell 1998

Morrow 2006

MRC 2000

NICE 2004

Prue 2006

Purcell 2002

Ray 2001

RevMan 2003

SIGN 2003

Stokes 2004

Tomson 2007

Vajda 2006

Vazquez 2007

Viinikainen 2006

Vinten 2004

Wallace 1998

Wallace 1999

Wyszynski 2005

* Indicates the major publication for the study
### Characteristics of excluded studies  

#### Betts 1999
- **Study design:** Retrospective case note review (Audit)
- **Participant:** WWE referred for preconception counselling ($n = 85$). Pregnant WWE (control) no preconception counselling ($n = 59$).
- **Intervention:** Preconception investigation schedule, question and action point checklist, and preconception counselling checklist.
- **Main findings:** No cases of MCM in counselled WWE, 11 cases in the control group (18%), with 3 terminations. Malformations reported included spina bifida, congenital heart defect, hypospadias, microcephaly associated with developmental delay, and skeletal deformity. Obstetric complications reported in 2 cases in counselled group (early miscarriage; premature birth) and 3 cases in the control group (premature birth). All cases of MCM were linked to not taking folic acid. Cases of malformation were associated with 45% of pregnant WWE taking two AEDs, whilst sodium valproate, either alone or in combination, was associated with 64% of all malformations including those terminated.
- **Reason for exclusion:** Retrospective study design. Additional data provided by author.

#### Candito 2006
- **Study design:** Case report.
- **Participant:** WWE receiving Lamotrigine during triplet pregnancy ($n = 1$). Controls: normal triplet pregnancy ($n = 1$), normal pregnant women with normal pregnancy ($n = 58$).
- **Intervention:** Pregnancy use of folic acid.
- **Main findings:** The results indicate a decrease in vitamin B12 and B6 values and polymorphism A66G in the patient.
- **Reasons for exclusion:** Case report design.

#### Candito 2007
- **Study design:** Case report.
- **Participants:** Cases: Pregnant WWE treated with Sodium Valproate (1500mgs total daily dose) and folic acid 5mg/day ($n = 4$), Valproate controls: Pregnant WWE treated with the same dose of Sodium Valproate with normal pregnancies ($n = 2$). Controls without therapy: pregnant healthy women ($n = 40$).
- **Intervention:** Periconceptional 5mg/day folic acid supplementation
- **Main findings:** Potential for dysfunction in folate metabolism.
Reasons for exclusion:
Case report design.
Additional data provided by author, awaiting response from second author.

Cox 1992

Study design:
Retrospective cohort.
Participants:
WWE and their partners preparing for pregnancy (n = 19).
Intervention:
Initial protocol assessment, detailed history, review of the partner, investigations, referral to a specialist were necessary to plan care for future pregnancy.
Main findings:
Outcomes for WWE were grouped with a wide range of chronic medical disorders (19/240); including, hypertension, diabetes mellitus, heart disease, renal disease, thyroid disease and asthma. This group all received counselling and 63/240 attempted further pregnancy with 51(81%) having a live birth of a normal infant when compared to their previous live birth rate 42% (95% CI difference 28.5-54.9%; χ² test: P<0.001).
Reasons for exclusion:
Retrospective study design. No reply from author.

Czeizel 1999

Study design:
Randomised double blind placebo-controlled trial.
Participants:
Non-pregnant WWE (n = 60).
Healthy non-pregnant controls (n = 12 011).
Intervention:
1. Reproductive health check-up, detection of specific pregnancy risks.
2. 3 month preparation for pregnancy visit - risk assessment and management; intervention to reduce residual risk, AND entry into RCT comparing supplementation with 0.8mg folic acid or no folic acid.
3. 'Benefit of periconceptional care' visit, reinforcing benefits of folic acid & health promotion to 'protect early pregnancy'.
4. Farewell visit at 10-12 wk gestation, referral to antenatal clinic.
Main findings:
The subset (‘diabetes mellitus, cardiovascular diseases, epilepsy etc’) identified at first visit for specialist review, 8% continued to treatment in pregnancy.
MCM = 1/60 in WWE not taking AEDs (cleft lip and palate).
No cases of ‘epilepsy-related’ side effects in WWE.
One still birth in WWE (1/60) (taking CBZ 200mg daily and Clonazepam 3mg daily & preconception folic acid 0.8mg), experienced skin rash at 18wks gestation, seizures & status epilepticus secondary to additional vitamin supplementation including 1mg folic acid.
Additional data on the outcome of WWE (n = 60) provided by author. No infant mortality or serious morbidity until first birth year; rate of preterm birth (less than 37 week) in epilepsy group was 10% compared to 7.5% in healthy controls (n = 8648); and rate of low birth weight (less than 2500g) was 15% in epilepsy group compared to 4.4% in healthy controls.
Reasons for exclusion: The RCT compared supplementation with folic acid and preconceptual care was provided to all study participants preventing assessment of effect in WWE.
### Kampman 2005

**Study design:**
Before and after study.

**Participants:**
215 electronic medical records of WWE.
28/215 pregnant WWE.

**Intervention:**
Passive guideline dissemination = publication of practice guidelines.
Active guideline dissemination = Interactive educational sessions for health professionals; patient educational handouts; presentation of audit findings.

**Main findings:**
No MCM in active dissemination group; two infants were born with MCM (meningomyelocele, diagnosed prenatally; biliary atresia, diagnosed postnatally) during the passive phase of guideline dissemination.
Fewer women took folic acid 0.4mg > 4 weeks before conception during active guideline dissemination (7/11 active compared to 15/17 passive), with no difference in higher dose folic acid 4mg use, recommended dose for women taking Carbamazepine and Sodium Valproate > 4 weeks before conception (6/11 active compared to 10/17 passive). More women during the active guideline dissemination took the recommended dose of folic acid during the first trimester (9/11 active compared to 9/17 passive).

**Reasons for exclusion:**
Intervention of interest not included.

### Martin 1993

**Study design:**
Retrospective comparative cohort.

**Participants:**

**Intervention:**
Changes in AED prescribing prior to second cohort.

**Main findings:**
MCM: 1st cohort 5/92(2.9%) (2.7% control); 2nd cohort 7/115 (4.8%)(4.1% control).
Perinatal deaths: 1st cohort 8/92 (4.7%)(1.4% control), 2nd cohort 3/115 (2.1%)(0.9% control).

**Reasons for exclusion:**
Retrospective study design, not including intervention of interest.
Attempts to contact authors were unsuccessful.

### Oguni 1992

**Study design:**
Before and after study.

**Participants:**
Two cohorts of pregnant WWE.
Cohort 2 (1982-1989) (n = 103 reporting on 115 pregnancies).

**Intervention:**
Study aimed to detect changes in pregnancy outcome following the introduction of changes in prescribing practice.

**Main findings:**
Significant reduction in frequency of MCM (25.5% cohort 1 and 11.1% cohort 2, <0.01), attributed to changes in prescribing. 68% of pregnancies exposed to monotherapy, compared to 40% prior to changes in practice. Increase folic acid supplementation following changes in practice.
Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design:</th>
<th>Participants:</th>
<th>Intervention:</th>
<th>Main findings:</th>
<th>Reasons for exclusion:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richmond 2004</td>
<td>Retrospective case note review.</td>
<td>WWE delivered between 1978-2000 (n = 414).</td>
<td>Preconception counselling delivered as routine care to all study population.</td>
<td>Outcome of MCM: WWE 26/414 (6.28%, p = 0.76) compared to non-epilepsy population (4.47%).</td>
<td>The study was excluded as retrospective comparison group with no pre-intervention data. Attempts to contact author unsuccessful.</td>
</tr>
<tr>
<td>Sablock 2002</td>
<td>Retrospective case note review.</td>
<td>Non-pregnant women with long-term medical disorders including 4/60 WWE.</td>
<td>Preconception counselling, review/withdrawal/changes of AEDs, secondary referral, commencement of folic acid.</td>
<td>The study authors concluded that few WWE were referred into the service in contrast with diabetes, suggesting a lack of emphasis placed on preconception care by physicians who manage the care of WWE.</td>
<td>Contact with author confirmed retrospective study design.</td>
</tr>
<tr>
<td>Seale 1998</td>
<td>Retrospective chart review.</td>
<td>Pregnant WWE delivered between 1988-1995 (n = 131; pregnancies, n = 161).</td>
<td>Preconception care provided as part of routine review with folic acid following practice guidelines. Preconception care was provided by the obstetrician in 5%, and neurologist in 15% of pregnancies.</td>
<td>135 live births (84%), 26 cases of fetal loss before delivery, 6 fetal deaths and 5 neonatal deaths. Six infants experienced intrauterine growth retardation; 3 resulting in death. MCM = 6. Folic acid supplementation increased during the study period, with usage by AED treated women (n = 124) increasing from 68% (1988-1991), up to 78% (1992-1995).</td>
<td>Retrospective study design.</td>
</tr>
</tbody>
</table>

WWE: Women with epilepsy  
AED: Antiepileptic drug(s)  
VPS: Sodium Valproate  
CBZ: Carbamazepine  
MCM: Major Congenital Malformation  
SE: Standard error
### Characteristics of ongoing studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial name or title</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Starting date</th>
<th>Contact information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mawer</td>
<td>WWE recruited after poor outcome of earlier pregnancy.</td>
<td>Education and counselling. AED switch or dose reduction.</td>
<td></td>
<td>Measure change in frequency of MCM.</td>
<td></td>
<td></td>
<td>George Mawer</td>
</tr>
<tr>
<td>Miskov</td>
<td>Surveillance of Croatian pregnant women with epilepsy - neurodevelopmental and teratogenetic effects of antiepileptic drug exposure.</td>
<td>Prospective trial.</td>
<td>(1) WWE recruited before pregnancy. (2) Pregnant WWE. 3) Healthy controls.</td>
<td>Intervention Group periconceptional folic acid; modification of AEDs (monotherapy instead of polytherapy, switch of AED, monitoring of drug concentrations and changes of dosage). Group 2&amp;3- no preconception intervention.</td>
<td>Measure: Planned versus unplanned pregnancy. Variables - proportion of stillbirths, abortions, mode of delivery, preterm delivery, presence of MCM or neurological delay &amp; psychological status of child.</td>
<td>2003</td>
<td>Snježana Miškov MD PhD Department of Neurology University Hospital “Sisters of Mercy” Vinogradska cesta 29, 10 000, Zegreb, Croatia</td>
</tr>
</tbody>
</table>

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*Preconception counselling for women with epilepsy to reduce adverse pregnancy outcome (Review)*

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Notes

FU all children - neurological exam yearly until school age.
DATA AND ANALYSES

This review has no analyses.

WHAT’S NEW

Last assessed as up-to-date: 30 January 2008.

9 May 2008 Amended Converted to new review format.

HISTORY


CONTRIBUTIONS OF AUTHORS

J Winterbottom completed the bibliographic search, assessed methodological quality of all included studies, extracted data and wrote the draft review. R Smyth, A Jacoby, G Baker reviewed search results, commented on study selection, assessed methodological quality and commented on the review manuscripts.

DECLARATIONS OF INTEREST

G Baker is the principal investigator for a study of the outcomes of pregnancy in WWE, which is partially funded by an educational grant from Sanofi-Synthelabo.

SOURCES OF SUPPORT

Internal sources

• No sources of support supplied

External sources

• FO608 Epilepsy Research Foundation, UK.
  During the time of preparing this review Janine Winterbottom was the recipient of a fellowship grant from Epilepsy Research UK (ID: FO608).
INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [adverse effects]; *Counseling; Epilepsy [*drug therapy]; *Preconception Care; Pregnancy Outcome

MeSH check words

Female; Humans; Pregnancy