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Effects of monitoring strategies on seizures in pregnant women on lamotrigine: a meta-analysis

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ABSTRACT

Objectives: Pregnant women with epilepsy have a significantly increased risk of mortality and morbidity compared to non-pregnant women. At least one in 250 pregnancies is exposed to anti-epileptic drugs (AED). Seizure deterioration occurs in up to a third of pregnant women. AED levels fall in most pregnant women, although it is uncertain that this is responsible for seizure deterioration rather than a hormonal effect. Current practice of AED monitoring is either therapeutic drug monitoring (TDM) or clinical features monitoring (CFM) to adjust the AED dose. We have systematically reviewed the effectiveness of the two monitoring regimens for AEDs, especially lamotrigine, the most commonly used AED in pregnancy on maternal and fetal outcomes.

Study design: We searched MEDLINE (1966–2012), EMBASE (1980–2012) and Cochrane, for relevant citations on the effectiveness of different monitoring strategies on seizure deterioration in pregnant women with epilepsy on lamotrigine. Study selection, quality assessment and data extraction were carried out by two independent reviewers. We calculated the rates of deterioration in seizures with the two strategies and pooled the estimates with random effects meta-analysis.

Results: Six observational studies (n = 132) evaluated the effectiveness of the two monitoring strategies on pregnant women with epilepsy on lamotrigine. There were no randomised controlled trials. The rate of seizure deterioration was 0.30 (95% CI 0.21–0.41) in women monitored by therapeutic drug monitoring (TDM) compared to 0.73 (95% CI 0.56–0.86) in those receiving clinical feature monitoring (CFM) alone.

Conclusion: Evidence based on observational data suggests that monitoring of AED levels in pregnancy reduces seizure deterioration, although the included studies have numerous sources of bias. There is paucity of evidence to make firm recommendations on optimal monitoring of AED drugs in pregnancy. Further research is needed to advise on the best clinical practice in managing AED in pregnancy.

1. Introduction

In pregnant women with epilepsy, the odds of dying are increased tenfold compared with the general population. This greatly exceeds the two to three-fold increase in standardised mortality rate observed throughout life in people with epilepsy [1]. Furthermore, the triennial Confidential Enquiries into Maternal Deaths in the UK reported concerns about the responses to seizure deterioration in pregnancy, with substandard care in all 14 maternal deaths [2]. Seizure deterioration has an enormous impact on quality of life. It can lead to falls, electrocution, drowning, scalding, depression, loss of driving licence, loss of job, and SUDEP (sudden unexpected death in epilepsy). Dose escalation of anti-epileptic drugs (AEDs) in pregnancy can lead to toxic side effects (such as depression, paranoia, tiredness, impaired memory and concentration), teratogenic harm to the baby and impaired neuro-cognitive development. Generalised seizures carry risks of harm to the baby including miscarriage, fetal hypoxia, acidosis and fetal loss [3–5]. They have been independently associated with low

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child verbal IQ [6] as has the use of some AEDs. There is a consensus that the risks of uncontrolled seizures in the mother probably outweigh the teratogenic risk of the medication. Preventing seizure deterioration in pregnancy is therefore vital to improve quality of life in women with epilepsy.

Most women with active epilepsy are advised to conceive on the lowest dose of the most appropriate single AED for their particular epilepsy syndrome or seizure type, and continue with this medication during pregnancy [7]. Up to one third of women experience seizure deterioration in pregnancy and this may be due to direct effects of pregnancy hormones on neurons, or it may be related to decreased concentrations of AED due to haemodilution and increased excretion. However, most women have falling drug levels in pregnancy yet do not have seizure deterioration, and the hypoalbuminaemia of pregnancy may actually decrease drug binding and increase the therapeutic and toxic availability of AEDs. The management of mothers with epilepsy on AEDs involves a dilemma between minimising drug exposure and avoiding seizures.

Lamotrigine (LTG) is currently the most commonly used AED in pregnancy, but there is controversy over whether therapeutic drug monitoring (TDM) with a view to dose escalation is beneficial or harmful. In the UK, the Scottish Intercollegiate Guidelines Network (SIGN) and the National Institute of Clinical Excellence (NICE) guidelines do not recommend regular AED monitoring in pregnancy due to paucity of evidence [9], but instead recommend waiting for evidence of deterioration, i.e. clinical features monitoring (CFM). In contrast, TDM of serum LTG levels in each trimester and after delivery has been recommended by the American Academy of Neurology based on consensus as a good practice due to the risk of increase in seizures associated with fall in serum AED levels in pregnancy [8].

We undertook a systematic review to evaluate the current evidence on the effect of the therapeutic drug monitoring and clinical features monitoring methods on seizures in pregnant women with epilepsy on LTG.

2. Methods

2.1. Literature search and study selection

We searched MEDLINE (1966–2012), EMBASE (1980–2012) and Cochrane (2012) for relevant citations without language restrictions. A combination of Medical Subject Headings (MeSH) and text words were used to generate subsets of citations, one indexing Lamotrigine ('Lamotrigine' and 'Lamictal') another indexing pregnancy ('pregnancy'); the third indexing epilepsy ('epilepsy') and the final indexing dose response relationship ('dose increase', 'increase dose', 'decrease dose' and 'dose decrease'). These subsets were combined using 'AND' to generate a subset of citations relevant to our research question. The reference lists of all known primary and review articles were examined to identify cited articles not captured by electronic searches. Articles frequently cited were used in the Science Citation Index to identify additional citations.

Studies which met the predefined and explicit criteria regarding population, intervention, outcomes and study design (Fig. 1) were

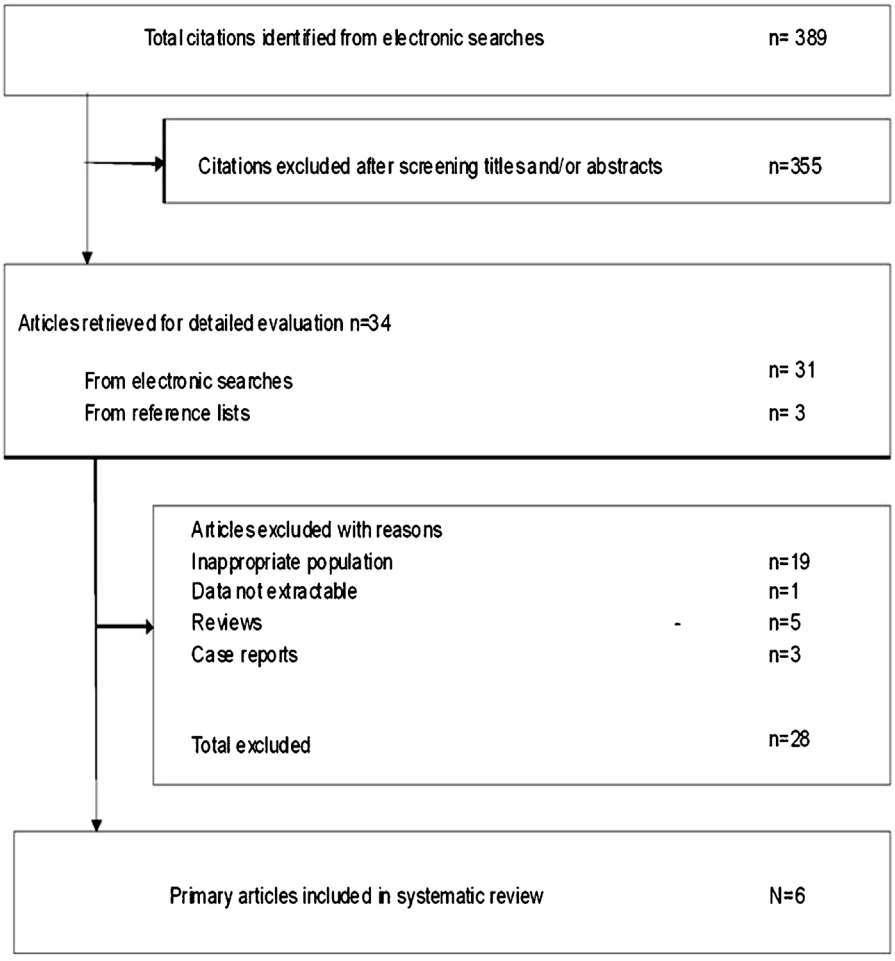

Fig. 1. Study selection process for systematic review of effectiveness of therapeutic drug monitoring vs clinical features monitoring in the management of pregnant women with epilepsy on lamotrigine.