AntiEpileptic drug Monitoring in PREgnancy (EMPiRE): a double-blind randomised trial on effectiveness and acceptability of monitoring strategies

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Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

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Scientific summary

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Scientific summary

Background

Management of women with epilepsy on antiepileptic drugs (AEDs) is aimed at achieving seizure control on the lowest possible dose and number of AEDs. A reduction in serum AED levels in pregnancy is believed to be associated with seizure deterioration. A strategy of therapeutic drug monitoring of AED in pregnancy is considered to have the potential to minimise seizures.

Objectives

Primary

To determine, in pregnant women with epilepsy on AEDs who experience a 25% decrease in serum AED levels, if additional therapeutic drug monitoring reduces the risk of seizure deterioration in comparison to clinical features monitoring alone.

Secondary

- To determine if there is a relationship between the level of reduction in serum AED levels and seizures.
- To evaluate the effects of the two strategies on pregnancy complications.
- To determine the effect of two monitoring strategies on quality of life.
- To assess if there is a difference in the total AED exposure between the two randomised groups.
- To assess the adverse effects of AED in all women exposed to the drugs.
- To obtain women's views by a qualitative study.

Methods

Design

A double-blind, randomised trial nested within a cohort study was conducted and a qualitative study of acceptability of the two strategies was undertaken.

Setting

Fifty obstetric and/or epilepsy clinics in the UK between November 2011 and May 2015.

Participants

Inclusion criteria

- Pregnant women on AED with a viable pregnancy (< 24 weeks' gestation).
- Confirmed diagnosis of epilepsy.
- Women on AED monotherapy (lamotrigine, carbamazepine, phenytoin or carbamazepine) or polytherapy (lamotrigine with either carbamazepine, phenytoin or levetiracetam).
- Capable of understanding English.

Exclusion criteria

- Women aged < 16 years.
- A diagnosis of status epilepticus or non-epileptic seizures.

- On non-lamotrigine polytherapy, sodium valproate monotherapy or polytherapy.
- Significant learning disability.
- Alcohol or substance abuse.
- Unable to complete seizure diaries or take AED in pregnancy.
- Participation in a blinded, placebo-controlled trial of an investigational medicinal product in pregnancy.

Outcome measures

Primary

Seizure deterioration defined as timing of all seizures after randomisation until 6 weeks after delivery.

Secondary

- Maternal: neurological, obstetric and quality of life.
- Fetal and neonatal: mortality and morbidity, birthweight, head circumference and cord blood serum AED levels.

Study conduct

Women with epilepsy on AED recruited in the study cohort were randomised to either therapeutic drug monitoring or clinical features monitoring if there was a $\geq 25\%$ decrease in serum AED levels at any time in pregnancy, compared with baseline or pre-pregnancy levels. Women and clinicians in the clinical features monitoring arm and non-randomised cohort were blinded to the serum AED levels. The seizure status was elicited from seizure diaries and complications from hospital records.

Sample size

We estimated that 660 randomised women are required to demonstrate a 25% seizure hazard decrease [hazard ratio (HR) $\approx$0.75] with therapeutic drug monitoring, providing 80% power (at a *p*-value of 0.05) and assuming an outcome-free survival rate of 60% in the clinical features monitoring group and 10% loss to follow-up.

Analysis

All analyses were on an intention-to-treat basis, and estimates of effect size (e.g. hazard or risk ratio) were presented as point estimates, with corresponding 95% confidence intervals (CIs). A multivariate failure time analysis of time to first seizure, and subsequent seizures, was performed using a generalisation of Cox proportional hazard model, taking into account the correlation of observations within each subject by incorporating robust standard errors for parameter estimates with the Andersen–Gill model.

Results

We recruited 560 mothers from 50 hospitals, randomised 267 women to either the therapeutic drug monitoring or clinical features monitoring group and included data from 257 women for primary analysis. There were no significant differences between the two groups for the time to first seizure (HR 0.82, 95% CI 0.55 to 1.2) or time to multiple seizures (HR 1.34, 95% CI 0.70 to 2.6). There were no differences between the arms in maternal and fetal complications, breastfeeding, birthweight, cord pH and quality of life. Cord blood levels of lamotrigine and levetiracetam were higher in the therapeutic drug monitoring group than in the clinical features monitoring group with adjusted mean differences (MDs) of 0.55 mg/l (95% CI 0.11 to 1.0 mg/l) and 7.8 mg/l (95% CI 0.86 to 14.8 mg/l), respectively, with similar levels of carbamazepine in both groups.

In comparison with the non-randomised group with stable serum AED levels, there were no significant increases in seizures in the clinical features monitoring (odds ratio 0.93, 95% CI 0.56 to 1.5) or therapeutic drug monitoring group (odds ratio 0.93, 95% CI 0.56 to 1.5). Increase in exposure to AED dose in women on monotherapy and polytherapy had no significant effect on maternal and neonatal outcomes, except for an increase in cord blood levels of lamotrigine (MD 0.55 mg/l, 95% CI 0.11 to 1.0 mg/l) and levetiracetam (MD 7.8 mg/l, 95% CI 0.86 to 14.8 mg/l) in the therapeutic drug monitoring group than in the clinical features monitoring group. There were no differences for cord blood levels of carbamazepine (MD –0.47 mg/l, 95% CI –1.5 to 0.6 mg/l) between the two groups.

Mothers with epilepsy on medication felt that they should weigh up their increased vulnerability to seizures during pregnancy against teratogenic effects of AEDs. We identified possible tension between health professionals' focus on drug adherence and the women's desire for their babies to be born without any health problems.

Conclusions

There is no evidence to support the theory that regular monitoring of AED drug levels in pregnancy offers additional benefit in seizure control than management based on only clinical features. Although there are no increases in short-term maternal or fetal complications with the drug monitoring strategy compared with a clinical-based strategy, the long-term neurodevelopment of babies exposed to higher serum AED levels in this group needs further evaluation.

Trial registration

This trial is registered as ISRCTN01253916.

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