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Antiepileptic drug monitoring In pregnancy

Submission date
02/06/2011

Recruitment status
No longer recruiting

Registration date
07/06/2011

Overall study status
Completed

Last Edited
09/05/2018

Condition category
Nervous System Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Many mothers require long-term treatment with drugs to manage epilepsy, called antiepileptic drugs (AEDs). The levels of these drugs in the blood usually fall in pregnancy. This may increase the risk of seizures. Currently, some doctors carry out regular blood tests to check the level of the drugs in the blood in pregnancy. They offer to increase the dose if the levels fall compared to the last level. This is called therapeutic drug monitoring (TDM). Other doctors do not carry out regular blood tests in pregnancy. They only increase the dose if seizures worsen or if they occur for the first time in pregnancy. This is called clinical features monitoring (CFM). This study aims to find the AED monitoring method that is best and safest for seizure control in pregnancy. Currently, there is not enough evidence to strongly recommend one method of monitoring over the other in pregnancy.

Who can participate?
Pregnant women who are known to have epilepsy and are currently on one or more of the following drugs: carbamazepine, lamotrigine, levetiracetam or phenytoin.

What does the study involve?
Participants are seen as usual in a hospital antenatal clinic, every 4 weeks up until 6 weeks after they given birth. They are asked to:
1. Have regular blood tests every 4 weeks to check the drug (AED) levels in their blood until labour or delivery. The blood samples are stored for the lifetime of the trial and for 3 years after the completion of the trial. After this period, the samples are destroyed.
2. Complete a seizure diary throughout their pregnancy and up to 6 weeks after birth to document the type and frequency of any seizures they may experience, including any side effects.
3. Complete questionnaires about general well being (quality of life) at each clinic visit.
4. Provide a sample of blood from the umbilical cord after it has been cut. This will give us information on the level of AED in the babys blood at birth. When the baby is 6 weeks old, at a routine 6-week postnatal appointment, we will assess clinical information about the participant and her baby. Participants and their babies may be requested to attend a long-term follow-up appointment about five years after delivery. Participants can choose whether or not to participate in this visit.
5. Complete a questionnaire about any out of pocket expenses (e.g. transport costs, time lost from work or child care costs) they may have incurred when attending the clinics. This will help

us find out about the wider cost implications of the two monitoring methods on the health service.

What are the possible benefits and risks of participating?
As we do not know the best method to monitor drugs in pregnancy, we cannot say if there will be any direct benefit to the participant and/or her baby. However, taking part in this study will help inform decisions about management of pregnant women with epilepsy in the future. Participants may have side effects related to the type and dose of AED. It is expected that they will continue to take their usual AEDs, as it is less likely for these to be changed during pregnancy. If it is necessary to increase/decrease the dose of AEDs or change them, then the reasons for this will be discussed with the participant and their clinician/nurse in the usual way, giving them the opportunity to discuss concerns about the process.

Where is the study run from?
The study takes place at various joint neurology obstetric antenatal clinics or high-risk clinics at hospitals throughout the United Kingdom, with a total of 41 centres expressing interest or participating.

When is the study starting and how long is it expected to run for?
Patients will be enrolled in the study between November 2011 and October 2013. Follow-up examinations will continue until April 2014.

Who is funding the study?
NIHR Health Technology Assessment Programme (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Protocol serial number
HTA 09/55/38

Study information

Scientific Title
AntiEpileptic drug Monitoring in PREgnancy: an evaluation of effectiveness, costeffectiveness and acceptability of monitoring strategies

Acronym
EMPiRE

Study objectives
Does therapeutic drug monitoring (TDM), among pregnant women with epilepsy on antiepileptic drugs (AEDs), reduce the risk of seizure deterioration compared to clinical features monitoring (CFM) alone?
1. What is the effect of TDM Vs CFM on quality life in pregnant women on anti epileptic drugs?
2. Is there a difference in the total AED exposure between TDM and CFM monitoring strategies?
3. What, if any, is the relationship between level of fall in serum AED levels and seizures?
4. What are the adverse effects of AED exposure on mother and foetus?
5. What are the views and experiences of pregnant women with epilepsy?
6. What is the most cost-effective method of monitoring for the health service?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Coventry & Warwickshire REC approval pending as of 03/06/2011

Study design
Multicentre randomised controlled trial within a cohort study and a qualitative study of patient acceptability

Primary study design
Interventional

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Epilepsy in pregnancy

Interventions
Relevant neurological and obstetric history will be obtained from pregnant women with epilepsy at booking / antenatal visit. Baseline data will be collected on age, ethnicity, age at first seizure (excluding febrile seizures), seizure frequency over the previous 6 months, seizure types, epilepsy syndrome, aetiology of epilepsy, duration of epilepsy, current AED and dose, baseline AED level, learning difficulty, any neurological signs, school leaving age, educational

performance, current employment, previous AED pregnancy exposure, previous pregnancy complications, perinatal outcome, number of children, health of child and educational status of child at the first visit.

There are 3 groups - The treatment groups will be clinical features monitoring alone versus therapeutic drug monitoring (for some centres around the UK clinical features monitoring is usual practice whereas in other therapeutic drug monitoring is usual practice). The third group will be participants whose blood AED levels remain stable.

Women will be followed up in the usual way every 4 weeks. Serum AED levels will be obtained but results will be kept blinded. Details of seizures, responses to QoL questionnaire and obstetric assessments will be recorded 4 weekly. A seizure diary specially developed for collecting trial data will be obtained but results will be kept blinded. It will provide details of type of seizure, frequency of seizure in the last 4 weeks and any side effects from the medication. The daily dose of AED and any increase will be recorded.

The foetus will be evaluated by detailed ultrasound scan at 20 weeks for congenital abnormalities and serial growth scans if fetal growth restriction is suspected. Foetal outcomes will be collected antenatal, at delivery and 6 weeks after delivery. An online data entry system, with appropriate security, will allow physicians, and specialist nurses to enter data directly.

Intervention Type
Other

Phase
Not Applicable

Primary outcome(s)
Time from randomisation to first seizure and time to first tonic clonic seizure throughout pregnancy up to and including six weeks post-delivery. Statistical analysis will take into account the time to each event per woman over the whole period of monitoring. Participants will be asked to document the occurrence of each seizure by frequency and type in a trial specific seizure diary.

Key secondary outcome(s))
Maternal:
1.Neurological
1.1. Percentage of women experiencing seizures who were seizure free in three month prior to consent. Number of seizures per week and number of seizure free days per week throughout pregnancy and up to and including six weeks post delivery
1.2. Serum levels of AED in each trimester, daily dose exposure by trimester, cumulative dose exposure for pregnancy, adverse events as measured by the Liverpool Adverse Events Profile
2. Obstetric
Maternal death, mode of delivery, preterm labour, induction of labour, pre eclampsia, antepartum and postpartum haemorrhage, admission to high dependency/ intensive care unit, breast feeding, infection, gestational diabetes mellitus
3. Quality of Life: Epilepsy specific QoL as measured by QOLIE-31, generic QoL as measured by EQ-5D

Foetal and neonatal:
Major and minor congenital malformation: major congenital malformations defined as structural

abnormalities with surgical, medical or cosmetic importance at antenatal or post natal diagnosis. Apgar score at 1 and 5 minutes, admission to neonatal unit, birth weight, head circumference, foetal growth, stillbirths, neonatal deaths, Bayley Scales of Infant Development (BSID).

Completion date
31/05/2015

Eligibility

Key inclusion criteria
1. Have signed a consent form before undergoing any trial-related activities
2. Have a confirmed viable pregnancy of less than 16 weeks gestation at booking
3. Have a confirmed diagnosis of epilepsy (any syndrome: primary, localised or unclassified)
4. Currently prescribed lamotrigine monotherapy or polytherapy (with carbamazepine, phenytoin or levetiracetam), carbamazepine monotherapy, phenytoin monotherapy or levetiracetam monotherapy
5. Be capable of understanding the information provided, with use of an interpreter if required

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
Female

Key exclusion criteria
1. Be beyond 16 weeks gestation at booking
2. Documented non-epileptic seizures in the last 2 years
3. Documented of status epilepticus in the last 12 months
4. A history of alcohol or substance abuse or dependence in the last 2 years
5. Sodium valproate (VPA) monotherapy or polytherapy
6. Non lamotrigine polytherapy
7. A history of poor AED adherence
8. Unable to complete a seizure diary or recall frequency of seizures accurately
9. Have a significant learning disability
10. Participation in any blinded, placebo-controlled trials of investigational medicinal products in pregnancy

Date of first enrolment
01/07/2011

Date of final enrolment
31/08/2014

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

Study participating centre
Barts and The London School of Medicine and Dentistry
Women's Health Research Unit
Centre for Primary Care and Public Health
Blizard Institute
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Yvonne Carter Building
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Morriston Hospital
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SA6 6NL

Study participating centre
University Hospital of Wales, Cardiff & Vale
Longcross Street
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Newcastle upon Tyne
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NE1 4LP

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DH1 5TW

Study participating centre
Jessops Wing
Tree Root Walk, S10 2
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Study participating centre
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LS1 3EX

Study participating centre
Warrington Hospital
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BB2 3HH

Study participating centre
Burnley General Hospital
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Study participating centre

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Sponsor information

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ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/05/2018		Yes	No