ISRCTN01253916 https://doi.org/10.1186/ISRCTN01253916

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?
Prof. Khalid Khan
k.s.khan@qmul.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Khalid Khan

Contact details
Women’s Health Research Unit
Centre for Primary Care and Public Health
Blizard Institute
Barts and The London School of Medicine and Dentistry
Yvonne Carter Building
58 Turner Street
London
United Kingdom
E1 2AB
-
k.s.khan@qmul.ac.uk

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
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

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
Not available in web format, please use contact details to request a patient information sheet

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 measure
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.

Secondary outcome measures

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).

Overall study start date
01/07/2011

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

Age group
Adult

Sex
Female

Target number of participants
Target sample=1000, Recruited sample 540

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
England

Northern Ireland

Scotland

United Kingdom

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
Barts and The London School of Medicine and Dentistry
Yvonne Carter Building
58 Turner Street
London
United Kingdom
E1 2AB

Study participating centre
Royal Jubilee Maternity Hospital
274 Grosvenor Road
Belfast

United Kingdom
BT12 6BA

Study participating centre
Queen Elizabeth Maternity Unit
1345 Govan Road
Glasgow
United Kingdom
G51 4TF

Study participating centre
Royal Infirmary of Edinburgh
51 Little France Cres
Edinburgh
United Kingdom
EH16 4SA

Study participating centre
Royal Gwent Hospital
Cardiff Road
Newport
United Kingdom
NP20 2UB

Study participating centre
Nevill Hall Hospital
Brecon Road
Abergavenny
Monmouthshire
United Kingdom
NP7 7EG

Study participating centre
Glan Clwyd Hospital
Rhuddlan Road
Rhyl
United Kingdom
LL18 5UJ

Study participating centre
Morriston Hospital
Heol Maes Eglwys
Morriston
Swansea
United Kingdom
SA6 6NL

Study participating centre
University Hospital of Wales, Cardiff & Vale
Longcross Street
Cardiff
South Glamorgan
United Kingdom
CF24 0SZ

Study participating centre
Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
United Kingdom
NE1 4LP

Study participating centre
Sunderland Royal Hospital
Kayll Road
Sunderland
United Kingdom
SR4 7TP

Study participating centre
University Hospital of North Durham
North Road
Durham
United Kingdom
DH1 5TW

Study participating centre
Jessops Wing
Tree Root Walk, S10 2
Sheffield

United Kingdom
S10 2

Study participating centre
Leeds General Infirmary
Great George Street
Leeds
United Kingdom
LS1 3EX

Study participating centre
Warrington Hospital
Lovely Ln
Warrington
Cheshire
United Kingdom
WA5 1QG

Study participating centre
Liverpool Women's Hospital
Liverpool
United Kingdom
L8 7SS

Study participating centre
Royal Blackburn Hospital
Haslingden Rd
Blackburn
United Kingdom
BB2 3HH

Study participating centre
Burnley General Hospital
Burnley General Hospital
Casterton Avenue
Burnley, Lancashire
United Kingdom
BB10 2PQ

Study participating centre
St Marys Hospital, Central Manchester University Hospitals
Manchester
United Kingdom
M13 9WL

Study participating centre
The Royal Derby Hospital
Uttoxeter Rd
Derby
United Kingdom
DE22 3NE

Study participating centre
Stafford Hospital
Weston Rd
Stafford
United Kingdom
ST16 3SA

Study participating centre
University Hospital of North Staffordshire, Maternity UHNS
Stoke-on-Trent
United Kingdom
ST4 6QG

Study participating centre
Royal Shrewsbury Hospital
Mytton Oak Rd
Shrewsbury
Shropshire
United Kingdom
SY3 8XQ

Study participating centre
Birmingham Women's Hospital
Mindelsohn Way
Birmingham
United Kingdom
B15 2TG

Study participating centre
Birmingham City Hospital
Dudley Rd
Birmingham
United Kingdom
B18 7QH

Study participating centre
Northampton General Hospital
Cliftonville
Northampton
United Kingdom
NN1 5BD

Study participating centre
University Hospitals of Leicester, Women's Hospital
Leicester
United Kingdom
-

Study participating centre
University Hospitals of Coventry & Warwickshire
Clifford Bridge Rd
Coventry
West Midlands
United Kingdom
CV2 2DX

Study participating centre
Worcestershire Royal Hospital
Charles Hastings Way
Worcester
United Kingdom
WR5 1DD

Study participating centre
John Radcliffe Hospital
Headley Way
Oxford

United Kingdom
OX3 9DU

Study participating centre
Queen's Hospital, Barking, Haveridge & Redbridge University Hospitals
Rom Valley Way
Romford
Essex
United Kingdom
RM7 0AG

Study participating centre
Whipps Cross Hospital
Whipps Cross Road
London
United Kingdom
E11 1NR

Study participating centre
Newham University Hospital
Glen Rd
London
United Kingdom
E13 8SL

Study participating centre
The Royal London
Whitechapel Rd
London
United Kingdom
E1 1BB

Study participating centre
St Thomas' Hospital
Westminster Bridge Rd
London
United Kingdom
SE1 7EH

Study participating centre
Chelsea & Westminster Hospital
369 Fulham Rd
London
United Kingdom
SW10 9NH

Study participating centre
St Georges Hospital
Blackshaw Rd
London
United Kingdom
SW17 0QT

Study participating centre
St Richard's Hospital
Spitalfield Lane
Chichester
United Kingdom
PO19 6SE

Study participating centre
Worthing Hospital
Lyndhurst Rd
Worthing
West Sussex
United Kingdom
BN11 2DH

Study participating centre
Frimley Park Hospital
Portsmouth Road
Frimley
Surrey
United Kingdom
GU16 7UJ

Study participating centre
Royal Sussex County Hospital
Eastern Rd
Brighton

United Kingdom
BN2 5BE

Study participating centre
Southend Hospital
Prittlewell Chase
Westcliff-on-Sea
United Kingdom
SS0 0RY

Study participating centre
Colchester General Hospital
Turner Rd
Colchester
United Kingdom
CO4 5JL

Study participating centre
Royal Hampshire County Hospital
Romsey Rd
Winchester
SO22 5DG

Study participating centre
Basingstoke and North Hampshire Hospital
Aldermaston Rd
Basingstoke
Hampshire
RG24 9NA

Study participating centre
Queen Alexandra Hospital
Southwick Hill Rd
Portsmouth
United Kingdom
PO6 3LY

Study participating centre

Princess Anne Hospital
Coxford Rd
Southampton
Hampshire
United Kingdom
SO16 5YA

Study participating centre
Gloucester Royal Hospital
Great Western Rd
Gloucester
United Kingdom
GL1 3NN

Study participating centre
Royal Cornwall Hospital
2 Penventinnie Ln
Treliske
Truro, Cornwall
United Kingdom
TR1 3LQ

Study participating centre
North Middlesex Hospital
Sterling Way
London
United Kingdom
N18 1QX

Study participating centre
Bradford Royal Infirmary
Duckworth Ln
Bradford
Yorkshire
United Kingdom
BD9 6RJ

Sponsor information

Organisation

Queen Mary, University of London

Sponsor details
Queen Mary Innovation Centre
5 Walden Street
Whitechapel
London
England
United Kingdom
E1 2EF
-
sponsorsrep@bartshealth.nhs.uk

Sponsor type
University/education

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

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

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal in August 2017.

Intention to publish date

31/08/2017

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