Antiepileptic drug monitoring In pregnancy

Submission date	Recruitment status No longer recruiting	[X] Prospectively registered		
02/06/2011		☐ Protocol		
Registration date	Overall study status Completed	Statistical analysis plan		
07/06/2011		[X] Results		
Last Edited	Condition category	[] Individual participant data		
09/05/2018	Nervous System Diseases			

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

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k.s.khan@qmul.ac.uk

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
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

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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 SSO ORY

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

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 adde	d Peer reviewed	? Patient-facing?
Results article	results	01/05/2018	Yes	No
Participant information sheet	Participant information sheet	11/11/2025 11/11/202	.5 No	Yes