Epilepsy and Pregnancy: For Healthy Pregnancies and Happy Outcomes

John Paul Leach on behalf of the Multispecialty UK Epilepsy Mortality Group

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Abstract

Between 2009 and 2012 there were 26 epilepsy-related deaths of women in the UK who were pregnant or in the first post-partum year. The number of pregnancy-related deaths in women with epilepsy (WWE) has been increasing. Expert assessment suggests that most epilepsy-related deaths in pregnancy were preventable and attributable to poor seizure control. While prevention of seizures during pregnancy is clearly important, a balance must be struck between seizure control and the teratogenic potential of antiepileptic drugs (AEDs). A range of professional guidance on the management of epilepsy in pregnancy has previously been issued, ~~but little~~but little attention has been paid to how optimal care can be delivered to WWE by a range of healthcare professionals. We summarise the findings of a multidisciplinary meeting with representation from a wide group of professional bodies. This focussed on the implementation of optimal pregnancy epilepsy care aiming to reduce mortality of epilepsy in mothers and reduce morbidity in babies exposed to AEDs in utero.

We ~~identify in~~ particularly address the following questions:

- **What** stage to intervene at - Golden Moments of opportunities for improving outcomes
- **Wh~~o~~ich** – which Key Groups have a role in making change
- **When** - 2020 vision of what these improvements aim to achieve.
- **How** to monitor the success in this field

While pregnancy care of WWE with epilepsy will pose somewhat different challenges in other healthcare systems w~~W~~e believe that ~~t~~our ~~hc~~ multidisciplinary approach and the service improvement ideas developed for the UK may provide a template for similar initiatives in other countries.

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Background

Epilepsy is the most common life-threatening neurological disorder, affecting an estimated 50 million people around the world. About 30% of people with epilepsy will continue to experience seizures even with optimal medical management (Nelligan 2011, Brodie and Kwan 2000). Uncontrolled convulsive seizures are a significant risk factor for epilepsy-related mortality, and, if occurring in pregnancy, pose a risk to the fetus. The risk of mortality due to epilepsy ranges from 0.1-1.0% per annum depending on a number of factors, most especially the frequency of generalised tonic clonic seizures (Shorvon and Tomson 2011). Uncontrolled convulsive seizures not only are a significant risk factor for epilepsy-related mortality, but also pose a risk to the fetus if occurring in pregnancy.

For women with epilepsy who are free of seizures, pregnancy is a time when full control of seizures should be maintained if at all possible while rationalising and minimising exposure to those antiepileptic drugs (AEDs). Where pregnant women continue to have seizures, the aim to minimise potentially harmful AED exposure (Weston 2016, Bromley 2014) must be balanced with the need to minimise seizure frequency and severity.

Maternal Mortality – Latest UK Findings

In the United Kingdom (UK), maternal deaths have been regularly audited since the 1950s, most recently under the auspices of MBRRACE-UK (Mothers and Babies: Reducing Risks through Audits and Confidential Enquiries across the UK). The latest iteration collected data on all maternal deaths in the UK from 2009-2012, demonstrating that neurological disorders comprise the second most frequent cause of maternal mortality during pregnancy. Epilepsy contributes to deaths in pregnancy and, uniquely among contributing neurological disorders, is associated with increased risk of maternal death both during and after pregnancy (Kelso and Wills 2014).

There are over 800,000 pregnancies per annum across the UK each year (total population 65 million, Office of National Statistics data 2015). Over the latest 3-year audit period, there were 14 deaths during pregnancy in women with epilepsy. Closer analysis of these deaths (Kelso and Wills 2015) suggested that pre-partum deaths were preventable in 10/14 cases. It is thought that sleep deprivation, reduced medication adherence, high risk behaviours and suboptimal AED regimes may contribute to this increased mortality rate, all of which may be reduced with better care, in particular with shared decision making and patient education (Kelso and Wills 2015).

There is evidence that the mortality rate during pregnancy and in the twelve months thereafter is higher than in women with epilepsy who do not get pregnant (Kapoor et al 2014). Action at this time is justified and appropriate (Leach 2015) since pregnancy related deaths bring about an additional social cost, and there will be multiple contacts with health services presenting opportunities to pass on information and reinforce lifestyle changes that may reduce mortality and risk to both mother and child during and after pregnancy. What is more, poor quality healthcare provision offered to women with epilepsy (as measured by maternal deaths) is likely to reflect poor quality of healthcare services in general, and epilepsy services in particular.

Other reasons for improving maternal epilepsy care

The potential for reducing maternal mortality is not the only reason to focus attention on the improvement of the pregnancy-related epilepsy care. It is recognised that some AEDs (particularly sodium valproate), whether used alone or in combination, carry an increased risk of major congenital malformations and neurocognitive difficulties following in utero exposure (Weston 2016, Bromley et al 2014). Such effects have been monitored in pregnancy registers such as the UK and Ireland Pregnancy Register for almost 20 years (Campbell 2014). Registration is voluntary, and while the information is of enormous value, it only takes into account an estimated 25% of all UK and Ireland pregnancies in women with epilepsy. Higher registration rates would help support efforts to track the effects of all AEDs on major congenital malformations (Campbell et al 2014). Further work with an enhanced registration rate could more effectively monitor and quantify AED-associated neurocognitive sequelae, marked by significant reductions in IQ and increased rate of autism with prenatal VPA use (Meador et al 2013). So while mortality data should be a call to action in improving epilepsy care, it is not the only one.

Proposed way forward

While guidelines are already in place promoting best practice in women of reproductive age, (SIGN Guideline No143 2015, NICE 2014, RCOG) there appears to be little coherence in efforts to embed identified 'best practice' into routine care, and so improve actual standards of care before and during pregnancy. Professional guidelines are well-meaning and evidence-based, but tend to focus on single specialty groups, with little suggestion on how 'best practice' may be achieved across the range of different specialities and health professionals.

In order to facilitate and effect change in UK practice, a meeting was called for 17/12/2015 with ~~representation from~~representation from a range of professional organisations (see appendix1) and in consultation with some voluntary sector organisations. Our aim was to review optimal ways of improving care and monitoring improvement.

This document sets out the immediate and long-term aims of the group, with some practical suggestions on how these may be achieved. It will focus on four~~three~~ areas:

- **What** stage to intervene at - Golden Moments of opportunities for improving outcomes
- **Who** – which Key Groups have a role in making change
- **When** - 2020 vision of what these improvements aim to achieve.
- **How** to monitor the success in this field

~~When to intervene - Golden Moments - Opportunities for Change~~

What stage to ~~en to~~ intervene at - Golden Moments of– o~~O~~pportunities for c~~C~~hange

Pregnancy-related healthcare encounters provide a series of opportunities for medical and nursing intervention. We recognise that prenatal advice should be prominent in epilepsy care from its earliest stages of diagnosis and treatment. Additionally, planning of pregnancy, diagnosis of pregnancy, antenatal care, delivery planning, and

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post-partum care all provide opportunities to consolidate this advice, to reinforce information provision, and empower patients to share in decision-making. We have named these the Golden Moments:

Preconception

All guidelines recognise the need for clear information on effects of epilepsy and AEDs on fetal and maternal health to be given at the time of diagnosis, since approximately half of pregnancies in women with epilepsy are unplanned (Pennell 2004, Davis 2008) and patients with well controlled epilepsy (though still on medication) may lose touch with specialist services. Unfortunately, patients may see the provision of such information as irrelevant and it is therefore easily forgotten or unheeded in the lead up to pregnancies that may occur a decade or more later.

While early (and repeated) iteration of up-to-date evidence is important in a clinical setting (Epilepsy Specialist Nurses are particularly adept at this) the group postulated that there may be other modes of communication (including upskilling of nurses in general practice and family planning clinics as well as pharmacists) that will reinforce the messages about the importance of avoiding severe or potentially harmful seizures and the more risk-inducing AEDs. This should build upon the toolkit recently produced in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA). This specifically highlights the risks associated with taking AEDs including valproate (VPA) during pregnancy and encourages women of childbearing age and healthcare professionals to carefully consider alternative medications.

In women on monotherapy with lamotrigine (Pennell 2008), or where AEDs have been titrated to minimum levels with retained control (Tomson et al 2013) there may be a case for measuring baseline serum AED levels, as this may help inform future dose increases during pregnancy (Battino 2013). Patients having previous AED-related problems in offspring might benefit from review by a geneticist.

Diagnosis of pregnancy

The definitive diagnosis of pregnancy will usually lead to direct contact with general practice or obstetric services. Management of possible complications of early pregnancy such as vomiting (which may reduce AED blood levels) can be important in preventing exacerbation of epilepsy. In view of the recognised rate of self-initiated AED cessation when patients discover that they are pregnant, advice is needed for WWE not to stop AEDs precipitously or without prior expert advice. In any event, discovery of co-existent epilepsy and pregnancy should prompt rapid specialist review to ensure optimisation of epilepsy control, protection from exacerbation of seizures, and appropriate dosing and utilisation of AEDs. Such specialist input at an early stage would help in enhancing adherence and empowering patients to take control of their own treatment and disease monitoring. The presence of any risk factors for seizure control worsening in pregnancy should be taken into account in planning any dosage changes (Battino 2013).

That many patients will not book with a midwife before 12 weeks gestation is a separate but related issue outwith the remit of these guidance notes, but it reinforces the need for a robust pre-conception clinical relationship. Despite delayed diagnosis or registration of pregnancy, every effort must be made to expedite the neurological review once a patient has been referred, not least ~~because serum~~because serum levels of some AEDs may fall early in pregnancy and reactive dosage adjustments may be appropriate (See table 1) (Tomson 2013).

Later in pregnancy

Patients who are seizure free pre-pregnancy are likely to remain well controlled in pregnancy (Battino 2013). As pregnancy progresses, some argue that AED dosage adjustments (in particular in the case of lamotrigine) may be required to help clinicians compensate for falling AED serum levels (Pennel 2008) although the evidence for improvement in outcomes with therapeutic drug level monitoring is as yet lacking. Such AED levels are not always available, especially in a short enough time to justify frequent testing. AED dose adjustment may be indicated where there is a perceived high risk of deterioration in seizure control, or where seizure control worsens (Battino 2013).

An agreed and comprehensive birth plan is essential, with input from both antenatal and epilepsy specialists. For patients whose AED doses were increased during pregnancy to maintain pre-pregnancy serum levels or in response to seizures, arrangements may need to be made to reinstate pre-pregnancy doses early in the post-natal period. Breastfeeding should be specifically discussed.

Post –partum

Sleep deprivation and a change in lifestyle may combine to reduce adherence to medication and reduce seizure thresholds, with a subsequent risk of increasing seizure frequency and severity. Proper planning with specific individualised information should be given by heath providers to ensure optimal AED treatment and minimisation of seizure triggers. Putting safeguards in place before or very shortly after delivery would make most sense to prevent breakthrough seizures, and ensure that babies of mothers with epilepsy are not exposed to physical risks from seizures. At all stages, planning of breast feeding, opportunistic planning of future contraception and pregnancies will be important, but these are most relevant at this stage. Discussion about future parenting and the effect of epilepsy on safety in coming years could also take place around this time.

Who – which Key Groups have a role in making change?

~~**Whose Business is Improving Epilepsy Care in pregnancy?**~~

Women with epilepsy and their children should be at the heart of all care and information provision for epilepsy in pregnancy. Professional input will be of little value if the patient and / or carers are not signed up to a process of enhancing quality and safety of epilepsy treatment. This ensures a major role for patient organisations and voluntary sector organisations in reinforcing key messages about optimal epilepsy management in and around pregnancy. Evidence-based information will come to naught if patients do not see the value for themselves.

Joint effort by professionals and voluntary sector organisations

Efforts to improve pregnancy outcomes in women with epilepsy are not only the responsibility of neurologists, health professionals involved in obstetric and emergency care or epilepsy organisations: it is important to recognise that women with mental illness, alcohol and substance misuse, learning difficulties, in social deprivation, or who are homeless may not engage effectively with traditional models of medical and social services. Those charged with providing support to these patients may have to help them engage with obstetric and neurological services or help mediate between patients and such services. Neurological and obstetric service providers on the other hand must make particular efforts to reach out to women with these additional problems as they are likely to be at particular risk of seizures and refractory epilepsy (Leach 2012) which would suggest a higher risk of other pregnancy complications and SUDEP.

As a minimum, efforts to optimise pregnancy outcomes in women with epilepsy must involve Primary Care physicians and nurses, obstetricians / midwives, neurologists, epilepsy specialist nurses, pharmacists, health visitors, emergency department physicians~~,~~ and psychiatrists.

Roles of different contributors to healthcare for pregnant women with epilepsy

These professionals need to collaborate to ensure coverage of the four ‘Golden Moments’. Each professional group may vary in the extent or focus of information provided, but we foresee a need for

- Signposting and access to information about seizure control, safety and risk, and efficacy of AEDs
- Signposting and access to information about the utility of vitamin supplements such as folate
- Signposting specialist services needed at times of deterioration in seizure control
- Signposting and access to information about particular obstetric needs in patients with epilepsy

Health service commissioners should support the professionals delivering care and information by ensuring that responsive and joined up services are available for their patients.

Table 2 provides more information about the responsibilities of the key professionals as well as patients themselves.

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Table 2: Responsibilities for each group

i) What patients could do

(When planning pregnancy, thinking they might be pregnant, becoming pregnant, booking into the obstetric services, planning delivery or preparing for the first year after delivery)

- Be aware what effect their AEDs will have on contraception, fertility, and conception.
- Be aware what extra vitamins might help their baby to be fit and well.
- Plan for pregnancy (we realise this is not always possible).
- Be active in ensuring availability of shared care pregnancy notes.
- Request rapid access to specialist epilepsy services.
- Register online on the epilepsy in pregnancy register or ask their healthcare professional to register their pregnancy.

ii) What obstetricians and midwives should do

- Ensure that all pregnant women with epilepsy are directed towards specialist epilepsy services at the first opportunity.
- Ensure that a plan is in place for action if seizures occur during delivery
- Where patients are seizure free – epilepsy expert advice should be sought to establish which dosing regime is most appropriate.
- Where seizures continue – epilepsy expert advice should be sought to discuss treatment change and action should be considered to improve epilepsy control (Nashef 2014).
- When discharge is planned after delivery, ensure that follow up is arranged in the next month with telephone or clinic contact. Discussion should include reinforcement of the benefits of breastfeeding.

iii) What neurologists, epilepsy nurses, and epileptologists should do:

- Ensure that all females are provided with information about epilepsy and reproduction from the earliest stages of their diagnosis.
- Ensure that rapid access is available for epilepsy review for anyone planning pregnancy, at any stage in pregnancy, and in the immediate post-partum period.
- Provide individualised assessment of risk of drug continuation and drug withdrawal in pregnancy.
- Communicate using patient-held pregnancy notes.
- At each encounter with a woman of reproductive age taking AEDs, there are major questions to address
    1. Is the diagnosis of epilepsy secure?
    2. Is current treatment effective?
    3. Is it possible to reduce dose or number of AEDs?
    4. If sodium valproate (VPA) is being used, is it possible to withdraw VPA or reduce daily dose?

iv) What pharmacists can do

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- Ensure that any woman of reproductive age prescribed VPA is counselled ,about the associated risks in pregnancy, and how to access advice regarding alternative treatments. The application of MHRA's policy on VPA would be appropriate.
- Advise adherence with current regime pending specialist review.

iv) What Emergency Physicians Should Do

- Ensure that any woman of reproductive age receiving VPA is directed towards epilepsy specialist services to allow assessment of appropriateness of use +/or dose.
- Ensure WWE or first seizures are directed or referred to specialist services for urgent review if pregnant.
- Communicate using patient-held pregnancy notes

v) What Primary Care Physicians Should Do

- Ensure that any woman of reproductive age receiving VPA is directed towards epilepsy specialist services to allow assessment of appropriateness of use +/or dose.
- Ensure WWE or first seizures are directed or referred to specialist services for urgent review if pregnant.
- Ensure that rapid access is requested for epilepsy review for anyone planning pregnancy, at any stage in pregnancy, and in the immediate post-partum period.

vi) **What those Commissioning Services Should do**

- Ensure that epilepsy services are commissioned to include rapid access available (<2 weeks) for high risk groups.
- Ensure that Obstetric services are commissioned to deliver effective multi-disciplinary epilepsy care for WWE.
- Ensure that robust and monitored referral pathways are in place facilitating timely access to specialist services for WWE.
- Ensure that the needs of WWE are met by collecting and monitoring patient engagement feedback.

When - 2020 vision of what these improvements aim to achieve.

~~2020 Vision – What should we aim to achieve?~~

At present there are a number of barriers to achieving optimal pregnancy outcomes for women with epilepsy in the UK: the rate of unplanned pregnancies means that it is difficult to carry out pre-pregnancy medication reviews and ensure folate supplementation. A lack of confidence in dealing with epilepsy in the obstetric community (including midwives) means that women with epilepsy (WWE) may not be referred to specialist epilepsy services. Limited access to neurology / epilepsy services may make it difficult for patients (and obstetric services) to obtain timely advice. There is currently no structured approach to information provision about epilepsy, AEDs and pregnancy by pharmacists. WWE may not be aware of pregnancy registers and health professionals may not prioritise patients' registration sufficiently.

While complete cessation of maternal epilepsy related deaths and fetal harm would be ideal, these challenges are clearly complex, and it is important to focus on achievable and measurable targets. The targets identified and the methods of measurement are summarised in Table 3.

The authors realise that the key targets identified and the methods of measurement are specific to the United Kingdom. While the optimal management of epilepsy in pregnancy is a universal concern for those involved in care provision for patients with seizures, other health services will have slightly different problems and will need to identify different measures. However, we hope that our multidisciplinary approach and this summary of our discussion will inspire others to set similar targets for improvement in their countries.

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Table 3: 2020 targets and measures

Target	Measurement
Reduce epilepsy-related maternal deaths by two thirds as measured by 2020	MBRRACE
Increase registration rates with national registry to capture data on outcomes in 90% of pregnancies to WWE by 2020 (including miscarriages)	UK and Ireland Pregnancy Register
Ensure minimisation of unnecessary use of valproate in Pregnancy	i) Monitor rates of VPA use in pregnancies registered with the UK and I pregnancy Register ii) Monitor Rate of provision of Epilepsy toolkit to women prior to booking with obstetric se rvices
Ensure VPA doses are kept as low as possible	Measured by analysis of UK and NI pregnancy data
Quantify the numbers of pregnancies lost in WWE	Measured by numbers of miscarriages in those registered with the UK and Ireland Pregnancy Register
Increase the availability of resources	

List of Attendees

ILAE UK Chapter - UK Chapter of the International League Against Epilepsy (ILAE UK)

ABN - the Association of British Neurologists

RCP - Royal College of Physicians (London)

RCPSG - Royal College of Physicians and Surgeons of Glasgow,

RCPE - Royal College of Physicians of Edinburgh

RCGP - Royal College of General Practitioners

RCOG - Royal College of Obstetricians and Gynaecologists

ESNA - Epilepsy Nurse Association

After the first draft, further input was sought from a range of voluntary sector organisations. Responses were received from Epilepsy Action

Table 1
Effect of pregnancy on serum levels and clinical effectiveness of AEDs

Drug	Pregnancy Effect on serum levels	Timing	Clinically Significant?
Carbamazepine	Reduced levels	Late pregnancy	Variable - uncertain
Gabapentin	No change		
Levetiracetam	Variably Reduced	1st -3rd trimester	Potentially
Oxcarbazepine	Reduced levels		
Lamotrigine	Variably Reduced	Progressive from 1st trimester	Potentially
Phenytoin	Variably Reduced		Unlikely
Phenobarbital	Variably reduced		Unlikely
Topiramate	Variably reduced	3rd Trimester	Uncertain
Valproate	Variably reduced	3rd Trimester	Unlikely
Zonisamide	Uncertain		
Others: Felbamate, pregabalin, perampanel, retigabine, vigabatrin, lacosamide, eslicarbazepine	Unknown		

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