BJOG An International Journal of Obstetrics and Gynaecology

DOI: 10.1111/1471-0528.14430
www.bjog.org

Maternal medicine

Development of a core outcome set for epilepsy in pregnancy (E-CORE): a national multi-stakeholder modified Delphi consensus study

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Accepted 23 September 2016. Published Online 16 November 2016.

This article includes Author Insights, a video abstract available at https://vimeo.com/rcog/authorinsights14430.

Objective To develop a set of core outcomes for studies on pregnant women with epilepsy.

Design Delphi consensus study.

Population Healthcare professionals, and patient representatives with lived experience of epilepsy in the UK.

Methods We used a modified Delphi method and a consultation meeting to achieve consensus. Potential outcomes were identified by systematic review, and were scored using a Likert scale anchored between 1 (least important) and 5 (most important). We included outcomes that scored ≥4 by >70% of participants, and outcomes that scored ≤2 by <15% of participants.

Main outcome measures Outcomes in studies on epilepsy in pregnancy.

Results Seventy-five healthcare professionals completed the first round, 48 (64%) completed the second round, and 37 (49%) completed the third round of the survey. Twenty-four patient representatives participated. The final core outcome set included 31 outcomes in three domains: neurological, offspring, and obstetric. Outcomes in the neurological domain were seizure control in pregnancy and postpartum, status epilepticus, maternal mortality, drowning, sudden unexpected death in epilepsy, postnatal depression, and quality of life. Offspring domain included congenital abnormalities (major and minor), fetal anticonvulsant syndrome, neurodevelopment, autism disorder, neonatal clinical complications, admission to a neonatal intensive care unit, and anthropometric measurements. The obstetric domain included live birth, stillbirth, miscarriage, ectopic, termination of pregnancy, admission to a high dependency or intensive care unit, breastfeeding, mode of delivery, preterm birth, pre-eclampsia, and eclampsia. Outcomes specific for studies on anti-epileptic drugs (AEDs) included maternal AED toxicity, AED compliance, neonatal withdrawal symptoms, and neonatal haemorrhagic disease.

Conclusion Embedding this core set in future clinical trials will promote the standardisation of reporting to inform clinical practice.

Keywords Core outcomes, CROWN, Delphi, epilepsy, pregnancy.

Tweetable abstract A Delphi method identifying core outcomes for epilepsy in pregnancy. Final core set includes 31 outcomes.

Linked article This article is commented on by G Mawer, p. 668 in this issue. To view this mini commentary visit http://dx.doi.org/10.1111/1471-0528.14432.

Please cite this paper as: Al Wattar BH, Tamilselvan K, Khan R, Kelso A, Sinha A, Pirie AM, McCorry D, Khan KS, Thangaratinam S for the Antiepileptic Drug Management in Pregnancy (EMPIRE) Collaborative Network. Development of a core outcome set for epilepsy in pregnancy (E-CORE): a national multi-stakeholder modified Delphi consensus study. BJOG 2017;124:661–667.

Introduction

Epilepsy, one of the most common neurological conditions in pregnancy, is associated with maternal and offspring mortality and morbidity.[1] Women with epilepsy are at an increased risk of neurological and obstetric complications such as uncontrolled seizures and preterm birth.[2] Their offspring are at risk of congenital abnormalities, growth restriction, and long-term neurodevelopmental delay.[3] Currently, clinical studies on epilepsy in pregnancy vary widely in the nature and quality of the outcomes,[4] which is undesirable. There is no consensus on the main outcomes to be reported in studies on women with epilepsy.

The outcomes evaluated in studies should be important to stakeholders such as healthcare professionals, policy makers, and mothers for it to be relevant in evidence-based practice. Many of the outcomes reported are chosen by healthcare professionals, such as neurological events in pregnancy.[4] There is little focus on the outcomes of concern to women, such as breastfeeding and quality of life. The current variation observed in reported outcomes hinders the synthesis of evidence, and limits the precision and applicability of findings in clinical guidelines.[4,5]

There is a need to generate a set of core outcomes to be reported in studies on pregnant women with epilepsy. To achieve this, consensus should be reached among different stakeholders involved in the care of women with epilepsy, as well as patient representatives.[6] We undertook a UK-wide multistakeholder modified Delphi method to develop consensus on a set of core outcomes for reporting in clinical studies on pregnant women with epilepsy.

Methods

We conducted an electronic modified Delphi method including various stakeholders involved in the care of pregnant women with epilepsy. Patient representatives were included in the process, in line with recommended methods.[7] A prospective study protocol was registered in the Core Outcome Measures in Effectiveness Trials (COMET) database.[8] A dedicated core management group was responsible for the overall conduct of the study (BHA, KT, KSK, and ST). Members of the core group took part in the survey anonymously. We reported the study following the COMET recommendations (Appendix S1).[9]

Identification of outcomes

We undertook a systematic review of all studies on pregnant women with epilepsy to create a long list of clinically relevant outcomes.[4] We searched the major electronic databases of MEDLINE, Embase, CINAHL, AMED, and the Cochrane Library (1999–January 2015) for studies on women with epilepsy. We included all primary studies reporting on outcomes for pregnant women with epilepsy of all study designs. Outcomes were extracted by two independent reviewers into an electronic standardised data collection tool. The study core management group categorised the outcomes into three main domains: maternal neurological, offspring, and obstetric outcomes. Any disagreement in categorising the identified outcomes was resolved by consensus between the group members, through face-to-face discussions. We combined outcomes that were clinically and pathophysiologically similar, to improve the ease of response to the Delphi method. For example, placenta praevia and placenta accreta were grouped under placental abnormalities. Similarly, venous thrombotic events were also combined as one outcome. The core outcome list was sent to the participants to rate the outcomes for their clinical importance in the evaluation of pregnant women with epilepsy. Additionally, we asked participants to report any other relevant outcomes that were not included in the initial list. All outcomes were included in all rounds of the modified Delphi method. Lay definitions of outcomes were generated for the patient representative survey using the University of Michigan Simplification Guide to Medical Terms.[10]

Survey participants

We included participants from the following stakeholder groups: obstetricians and midwives; neurologists and epilepsy nurses; neonatologists; and patient representatives. We identified healthcare professionals from the National Collaborators group of the Antiepileptic Drug Monitoring in Pregnancy (EMPIRE) study.[11] Participants were identified via direct email invitations using the EMPIRE investigators' email database. Participants were either principal investigators with experience in clinical trials on pregnant women with epilepsy or clinical experts in this field. We identified patient representatives with the help of the UK national epilepsy charity, Epilepsy Action, via an electronic advert on the charity website, as well as sending an invitation in the charity newsletter.[12] Patient representatives were identified as women who had lived the experience of epilepsy in pregnancy, their family members, such as partners, or individuals with significant experience in caring for women with epilepsy, such as campaign coordinators from the Epilepsy Action charity.

Modified Delphi method

We sent invitations to all participants by email. Initially we sent them questionnaires using Survey Monkey software (surveymonkey.com). In subsequent rounds we used direct email questionnaires based on feedback from participants. We predefined non-responders as those participants who did not complete the survey despite three email reminders. We did not include non-responders in subsequent rounds, but they were invited to the final consultation meeting.

We asked participants to use a five-point Likert scale to rank each outcome for its clinical importance (anchored

between 1 as least important and 5 as most important). A score of 1 was considered to be least important; a score of 5 was considered to be most important or critical. The scores of the individual participants were kept anonymous throughout the survey. At the end of each round, we provided the mean scores and standard deviations for each outcome to all participants, to enable reflection before completion of the subsequent round. Additionally, at the end of the second round we provided the scores by each stakeholder group. Results were then fed back to participants using numerical tables. All three rounds were moderated by the same researcher (BHA). Patient representatives completed only one survey round. Their responses were included in the final analysis.

We pre-specified the criteria for inclusion of outcomes into the core set: score of ≥4 by more than 70% of participants and a score of ≤2 by less than 15% of participants. Outcomes were excluded if they received a score of ≥4 by less than 15% of participants and a score of ≤2 by more than 70% of participants. Outcomes that did not fulfil either of the two criteria were considered equivocal, and were taken forwards for discussion in a consultation meeting.

Consultation meeting

We held a consultation meeting at the end of the survey to finalise the core outcome set. The consultation meeting discussed outcomes that were equivocal in the modified Delphi method. All participants in the modified Delphi method, from all stakeholder groups, were invited to attend the consultation meeting. We used a mobile phone-based electronic voting system to assess consensus between the participants at the meeting.[13] The meeting included two rounds. The first round screened the list of equivocal outcomes and identified those needing detailed discussion, and the second round selected the outcomes for inclusion in the final core outcome set. We used the same criteria as those for the modified Delphi method to determine consensus in the consultation meeting.

Data analysis

We entered participants' scores into an electronic EXCEL sheet at the end of each round. We calculated the mean and standard deviation of the scores for each outcome. All statistical analyses were conducted using Microsoft Excel 2007 (Microsoft Corp., Redmond, WA, USA) and SPSS 19 (IBM Inc., New York, NY, USA).

Results

Seventy-five participants completed the first round (47 obstetricians and midwives, 14 neurologists and epilepsy nurses, and 14 neonatologists). In the second round, two-thirds (48/75, 64%) completed the survey (25 obstetricians and midwives, ten neurologists and epilepsy nurses, and 13 neonatologists). And half of all participants (37/75, 49.3%) completed the third round of the survey (20 obstetricians and midwives, six neurologists and epilepsy nurses, and 11 neonatologists). Twenty-four patient representatives completed their round of the survey. The final consultation group comprised obstetricians, midwives, neurologists, epilepsy specialist nurses, neonatologists, patient representatives, and researchers (Table 1). The characteristics of the study participants are reported in Appendix S2.

Prioritisation of outcomes

Our systematic review identified 70 different outcomes, which were reported in 232 primary studies on epilepsy in pregnancy.[4] After grouping the initial list included 48 outcomes; 30 outcomes reached consensus in the first round for their clinical importance (30/48, 62.5%), and a third (18/48, 37.5%) were considered to be of equivocal importance. In the second round, consensus was reached for 25 outcomes (25/48, 52.0%), and about half (23/48, 47.9%) were equivocal. In the final round, 21 outcomes (21/48, 43.7%) were identified as important by consensus, and over half (27/48, 56.2%) were equivocal. Patient representatives considered 40 outcomes (40/48, 83.3%) to be important, and the rest of the outcomes as equivocal (8/48, 16.6%).

At the end of the modified Delphi method, 24 outcomes were considered to be important for inclusion in the core outcome set, and 24 outcomes were seen as equivocal (Table S1). These included nine maternal neurological outcomes: seven were relevant to all women with epilepsy, such as seizure control, status epilepticus, sudden unexpected death in epilepsy (SUDEP), maternal death, postnatal depression, quality of life, and drowning; two were only applicable for studies on women exposed to AEDs, such as maternal toxicity from AED and compliance with AED intake. The eight important offspring outcomes included six general outcomes such as major and minor congenital

Table 1. Number of participants included in the Delphi survey for the development of a set of core outcomes for reporting in clinical studies on pregnant women with epilepsy

Participant group	Round 1	Round 2 (%)	Round 3 (%)	Consultation meeting
Obstetricians and research midwives	47	25/47 (53)	20/47 (43)	7
Neurologists and epilepsy nurses	14	10/14 (71)	6/14 (43)	3
Neonatologists	14	13/14 (93)	11/14 (79)	3
Patient representatives	24	–	–	2
Trial coordinator	–	–	–	1

abnormalities, stillbirth, admission to a neonatal intensive care unit (NICU), neurodevelopment of the offspring including autism spectrum disorder, and postnatal clinical complications in the newborn (acute respiratory distress syndrome, anaemia, hypoglycaemia, hyperglycaemia, hypocalcaemia, hypotonia, feeding problems, sedation syndrome, icterus/convulsions, cephalhaematoma, and Apgar scores), and two AED-specific outcomes of fetal anticonvulsant syndrome and neonatal withdrawal symptoms. The six important obstetric outcomes included general outcomes such as live birth, miscarriage, ectopic pregnancy, eclampsia, maternal admission to high dependency or intensive care unit, and those specific to AED exposure, such as breastfeeding.

Consultation meeting

In the first round, the panel discussed the equivocal outcomes. After the first round of voting, four outcomes were chosen for further detailed discussion. These were anthropometric measurements, including birthweight, preterm birth, pre-eclampsia, and mode of delivery. Termination of pregnancy was included in the pregnancy viability outcomes, as it was judged to be important by the panel. A further two additional outcomes, postpartum seizure control and neonatal haemorrhagic disease, were recommended for further evaluation. In the second voting round, all seven outcomes reached consensus and were included in the core outcome set.

The final core set included 31 outcomes: ten maternal neurological, ten offspring, and 11 obstetric outcomes. Of these, four were specific for studies on pregnant women taking anti-epileptic medications, and one was specific for studies with long-term follow-up. Table 2 provides the list of the individual outcomes in various domains.

Discussion

Main findings

Our study is the first to identify a set of core outcomes for reporting in studies on pregnant women with epilepsy. The final set of outcomes has incorporated all reported epilepsy-related outcomes in neurology, obstetrics, and neonatology by involving the relevant stakeholders, including patient representatives. The patient representatives led to the inclusion of outcomes important to pregnant women, such as quality of life, postnatal depression, and drowning, which were not well reported in current studies.

Strengths and limitations

We used a robust methodology to capture the whole range of outcomes to reach consensus. We used predefined criteria for the inclusion of outcomes into the core set. The modified Delphi method allowed us to maintain the anonymity of participants, and thereby avoid the overt influence of particular individuals or stakeholder groups on the final score.[14] The Delphi technique has been widely used to develop core outcome sets and to generate consensus between stakeholders.[7] Participation was voluntary, and all participants were informed that they could withdraw from the survey at any stage. A sizable proportion of patient representatives were involved in the survey, and in the consultation process. The

Table 2. Core outcome set for studies on pregnant women with epilepsy

Maternal neurological outcomes	Offspring outcomes	Obstetric outcomes
Seizure control in pregnancy	Major congenital abnormalities	Live birth
Postpartum seizure control	Minor congenital abnormalities	Stillbirth
Status epilepticus	Fetal anticonvulsant syndrome	Miscarriage
Maternal mortality	Neurodevelopment***	Ectopic pregnancy
Drowning	Autism spectrum disorder***	Termination of pregnancy
Sudden unexpected death in epilepsy	Neonatal clinical complications**	Maternal admission to high dependency or intensive care unit
Postnatal depression	Admission to neonatal intensive care unit	Breastfeeding
Maternal quality of life	Anthropometric measurements, including birthweight	Mode of delivery
		Preterm birth
		Pre-eclampsia
		Eclampsia
Women with epilepsy on anti-epileptic drugs		
Maternal anti-epileptic drug toxicity*	Neonatal withdrawal symptoms*	
Compliance with anti-epileptic drug intake*	Neonatal haemorrhagic disease*	

*Outcomes applicable only in studies on pregnant women on anti-epileptic drugs.
**Acute respiratory distress syndrome, anaemia, hypoglycaemia, hyperglycaemia, hypocalcaemia, hypotonia, feeding problems, sedation syndrome, icterus/convulsions, cephalhaematoma, and Apgar scores.
***Relevant for studies with long-term follow-up.

final consultation meeting provided an interactive forum for stakeholders to agree on equivocal outcomes, and to discuss any previously missed outcomes.

Our results were limited by the progressive attrition in the modified Delphi method. The attrition was greatest after the first round, and was lower in the second round. This is not unexpected with the use of multiple survey rounds.[15] The high attrition rate in patient representatives limited their inclusion to one round only. We intended to involve patient representatives in all three rounds of the survey; however, this was not possible within the study timeline. In view of the increased emphasis on including patients' views in the development of core outcomes,[16] we resolved to include their input in the final consultation meeting. The convergence of scores for the outcomes was a slow process as the survey progressed, indicating the difficulty experienced by the participants in assessing the importance of each outcome. Our systematic review highlighted a large number of outcomes on neonatal clinical complications with varied outcome measures: for example, jaundice can be reported using biochemical measures or clinical severity.[4] Including each of these outcomes independently into our Delphi survey was outside the scope of this project. We resolved to group them all together under one outcome domain in the Delphi survey. Further consensus work is needed to standardise outcome reporting, and the individual ranking of outcome measures in this field may have identified fewer components. Some of the core outcomes identified are only applicable to studies on pregnant women on AEDs, such as maternal toxicity and fetal anticonvulsant syndrome. It is possible that the generalisability of our findings is limited to settings in developed countries, as our survey just targeted stakeholders from the UK.

Interpretation

Maternal neurological outcomes

The maternal neurological outcomes identified reflect the findings of the recent Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries acroos the UK (MBRRACE-UK) report on confidential enquiries into maternal deaths (2009–2012), which emphasised the need to prioritise both the antenatal and the postnatal care of women with epilepsy.[17] In addition to the outcomes prioritised by the survey, such as seizure deterioration in pregnancy, the consensus panel additionally prioritised postpartum seizure control. Postnatal seizures are often exacerbated by many factors, such as sleep deprivation or non-compliance with AED intake because of concerns for the safety of the baby in breastfeeding mothers.[18] Additionally, we identified quality of life and postnatal depression as important outcomes, which were rated as critically important by most patient representatives as well as healthcare professionals.

Offspring outcomes

We identified traditionally well-reported outcomes such as congenital malformation in the fetus. Additionally, clinical complications in the newborn and specific outcomes, including neonatal haemorrhagic disease, were included. The panel acknowledged the paucity of evidence on the association of AED exposure *in utero* and the risk of neonatal bleeding caused by decreased levels of vitamin K,[19] leading to the inclusion of this important additional outcome. Some core outcomes such as neurodevelopment of the offspring and autism spectrum disorder require long-term follow-up. The inclusion of all relevant outcomes will ensure that the health of both mother and baby is given equal importance, thus minimising research wastage. We acknowledge that including such long-term outcomes may not be feasible for all future studies; however, researchers are prompted to consider and reflect on the proposed core outcome set covering this issue in the discussion section of their papers. They may use the power inherent in multi-stakeholder consensus to justify the need for funding in order to persuade grant-giving bodies.

Obstetric outcomes

The stakeholders felt that five separate outcomes for fetal viability (live births, stillbirth, miscarriage, ectopic pregnancy, and termination of pregnancy) should be reported. Termination of pregnancy was judged by the panel to be a surrogate for major or minor abnormalities, and also reflective of maternal concerns as a result of epilepsy and AED exposure.[2] Preterm birth, caesarean section, and pre-eclampsia are significantly associated with epilepsy,[1] and have been included in the core outcome set. Eclampsia, a condition with seizures in pregnancy, is one of the main differential diagnoses of epilepsy, and was also included in the core set. The safety of breastfeeding while taking AEDs is understandingly a major worry for mothers, and our knowledge on the potential risks to their offspring is still limited.[20] Our participants have identified this as an important outcome.

Implications for research and clinical practice

The standardised reporting of core outcomes identified across all studies will help in improving the quality of evidence synthesis, and will enable researchers to combine and compare results from different studies. Further research is needed on the development of validated assessment tools in pregnancy for women with epilepsy, particularly for outcomes such as quality of life in pregnancy and postnatal depression. We acknowledge that including all identified core outcomes might not be feasible for all future studies because of funding limitation or high attrition rate. We encourage researchers to consider all of the outcomes

identified in this core set and to provide a critical account on all excluded outcomes at the study design stage.

Conclusion

Embedding this core set in future clinical trials will promote the standardisation of reporting to inform clinical practice.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

ST conceived the idea for the paper, and provided input to all stages of the article. BHA wrote the first manuscript and moderated the survey. KT, RK, AK, AS, AMP, DM, and KSK provided critical input to the manuscript.

Details of ethics approval

Not needed.

Funding

We received funding from the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) (no. 09/55/38) to identify clinically important outcomes to be reported in clinical studies on epilepsy in pregnancy. This work was undertaken as part of the continuing EMPIRE trial. The funders did not play a role in the planning and execution of this work, or in drafting the manuscript.

Acknowledgements

The authors thank the following participants for taking part in the Delphi survey: Abby Rand, Alastair Campbell, Alexander Pirie, Andrew Ewer, Angela Rooney, Ann Robbins, Carole Ashworth, Catharina Schram, Cathrine Armour, Christine Lorraine Goldschmidt, Clair Cobbold, Dawn Kelly, Debbie Bullen, Denise Hughes, Elaine Rooney, Ellen Knox, Ellie Jenkins, Elmo Thambapillai, Emily Beach, Emma Barclay, Emma Dooks, Faye Chambers, Fiona Fairlie, Gary Dennis, Helen Bryant, Helen Probert, Hollie Cresswell, Ismail Hassan, Jacqueline Tay, Jane Norman, Jean Dent, Jennifer Ruth Packer, Jill Riches, Jill Smith, Joanne Hutchinson, John Philip O'Dwyer, John Paul Leach, Jon Dorling, karen Henderson, Karen Louise Armstrong, Karen Lowe, Kathryn Hewardine, Katie Lewis, Katie Peck, Kayleigh Hickinbotham, Keri John, Lauren Knight, Lisa Starrs, Liz Quinlan-Jones, Louisa Forrest, Louise Kennedy, Lucy Mackillop, Lyn Greenhill, Maire Home, Maitrayee Thoppay Kumarasamy, Marian O'Donnell, Marion Kay Cumbers, Martin J Brodie, Matthew Hogg, May Ching Soh, Melissa Logan, Michele breton, Michelle Fowkes, Molly Lappin, Nagawi Moss, Nicola Jane Bennett, Nicole Crosby-McKenna, Pam Inniss, Parthasaradhi Rachakonda, paula trinham, Phil Tittensor, Philippa Chisholm, Philippa Marsden, Rajith de Silva, Rajiv Mohanraj, Rebecca Elizabeth Bevan, Rebecca Jane Wedderburn, Samantha Lawrie, Sangeetha Pradeep, Sally Higgins, Sarah Davis, Sarah Ladd, Sharon Jones, Sheila Lewis, Sian Diana Colburn, Sian Newton, Siobahn Quenby, Sophia Stone, Srinivasagam Muthumeenal, Sriparna Kar, Sujith Pereira, Teresa Kelly, Theresa holder, Therese McSorley, Vardwhi Cahill, Viswa Vani Penumala, Vivienne Cannons, Zoe Lancet, and Zandele Maseko.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Checklist for developing core outcome sets for clinical trials.

Appendix S2. Basic characteristics of Delphi participants.

Table S1. Proportion of Delphi survey participants in each round who scored outcomes as important for inclusion in the core outcome set for studies on pregnant women with epilepsy.

Video S1. Author Insights. ■

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