Effective Health Care

Management of Neurologic Disorders in Pregnancy

Results of Topic Selection Process & Next Steps

The nominator, The American College of Ob GYN (ACOG) is interested in a new evidence review on Management of Neurologic Disorders in Pregnancy to develop new guidelines.

There are six overlapping systematic reviews on harms (KQ2), and several protocols in progress, and only a single review on effectiveness for treatment of multiple sclerosis. The nominator felt that information about of the available systematic reviews would be sufficient for their needs, and a formal feasibility assessment was not done.

No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Number and Name: #0818, Management of Neurologic Disorders in Pregnancy

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Background

The three conditions of interest for this topic nomination are seizures and epilepsy, multiple sclerosis, and myasthenia gravis.

Seizures and Epilepsy

- A seizure is the result of sudden, uncontrolled electrical activity in the brain, and car result from many causes.
- The International League Against Epilepsy (ILAE) defined epilepsy as a disease of the brain characterized by an enduring predisposition to generate epileptic seizures. This definition is usually practically applied as having two unprovoked seizures >24 h apart, but there are special circumstances. [1] However, it is recognized that epilepsy is not a single condition, but a group of disorders, and many patients and providers still debate whether it should be labelled as a disease, disorder or condition.
- In 2015, 1.2% of the US population had active epilepsy (95% CI* = 1.1-1.4). This is about 3.4 million people with epilepsy nationwide. https://www.cdc.gov/epilepsy/data/index.html. It is estimated to affect up to 0.8% of pregnant women. [2]
- Women with epilepsy are at increased risk for several complications, such as preeclampsia, preterm birth and bleeding in pregnancy. Their infants are at higher risk for congenital anomalies and cognitive delay. In addition, the clinician must balance the risk of maternal disease and seizures with the risk to the fetus of exposure to anti-epileptics. [2, 3]

Multiple Sclerosis

- MS is a chronic, typically progressive disease involving damage to the sheaths of nerve cells in the brain and spinal cord, whose symptoms may include numbness, impairment of speech and of muscular coordination, blurred vision, and severe fatigue.
- In 2012, the overall MS prevalence was 149 per 100,000 individuals, or about 400,000 persons in the US. Prevalence was higher in females, (224 per 100,000 individuals), in those aged 45–49 years, and in the East Census region. [4]. A review of a single state database estimated 1100 cases over 10 years, for a prevalence of 2 cases per 10,000 pregnancies. [5].
- Relapses of MS may decrease during pregnancy. Some observational studies report no increased incidence of poor maternal outcomes [5]; whereas others report increases in problems like premature labor, infection and congenital malformations.[6] However, some disease-modifying treatments (DMTs) are contraindicated in pregnancy and lactation.[7]

Myasthenia Gravis (MG)

- MG is an autoimmune neuromuscular disorder that is characterized by fatigue and exhaustion of muscles. MG is caused by an immune response to the nicotinic acetylcholine receptors, which are found in junctions between muscles and the nervous system.
- The prevalence of myasthenia gravis in the United States is estimated at 14 to 20 per 100,000 population, approximately 36,000 to 60,000 cases in the United States. However, myasthenia gravis remains underdiagnosed and the prevalence may be higher.
- Problems in pregnancy. Women with MG require an anesthesia consult due to the disease process as well as their medications. They are at increased risk for respiratory depression and prolonged intubation. They are resistant to succinylcholine, a depolarizing neuromuscular blocking agent (NMBA), and are unpredictably sensitive to nondepolarizing NMBAs.

At present, ACOG does not have any clinical guidance for any of the neurologic conditions that they propose to address.

The 2017 AAP/ACOG Guidelines for Perinatal care contains only a three references to neurologic syndromes: [8]

- Women of reproductive age should be screened for epilepsy and "counseled on the effects on future pregnancies".
- Women with epilepsy (on medication) should have consultation with an Obstetrician Gynecologist early in prenatal care.
- Women with myasthenia gravis should have an anesthesia consult.

A group from the UK developed consensus based guidelines for epilepsy care in pregnancy. Their goals are to reduce epilepsy- related maternal deaths and to reduce fetal exposure to valproic acid.[9]

Nominator and Stakeholder Engagement

The nomination as written was broad. After consultation, ACOG agreed to limit the scope to three common and serious conditions (Epilepsy, Multiple sclerosis, and Myasthenia gravis).

Key Questions and PICOTs

The proposed key questions for this nomination are:

1. What is the effectiveness, and comparative **effectiveness** of ***pharmacotherapy*** for neurologic diseases in pregnancy?
   (By neurologic condition)
   a) Epilepsy/Seizures
   b) Multiple Sclerosis
   c) Myasthenia Gravis

2. What are the maternal and fetal harms, and comparative **harms** of ***pharmacotherapy*** for neurologic diseases in pregnancy?
   (By neurologic condition)
   a) Epilepsy/Seizures
   b) Multiple Sclerosis
   c) Myasthenia Gravis
3. Compared to usual care, does **additional antenatal monitoring** improve maternal and fetal outcomes among pregnant women with neurologic diseases?
   (By neurologic condition)
   a) Epilepsy/Seizures
   b) Multiple Sclerosis
   c) Myasthenia Gravis

4. Compared to usual care, does **altering labor management plans** improve maternal and fetal outcomes among pregnant women with neurologic diseases?
   (By neurologic condition)
   a) Epilepsy/Seizures
   b) Multiple Sclerosis
   c) Myasthenia Gravis

A contextual question was proposed by the ACOG content expert: How should drug dosages be adjusted during pregnancy?

To define the inclusion criteria for the key questions, we specify the population, interventions, comparators, outcomes, timing, setting (PICOTS) of interest (Table 1).

Table 1. Key Questions and PICOTS

Key Questions	KQ1: effectiveness of medication	KQ2: harms of medication	KQ3: antenatal monitoring	KQ4: labor management
Population	Pregnant women with neurologic diseases: 1. Multiple Sclerosis 2. Epilepsy/Seizures 3. Myasthenia Gravis	Pregnant women with neurologic diseases: 1. Multiple Sclerosis 2. Epilepsy/Seizures 3. Myasthenia Gravis	Pregnant women with neurologic diseases: 1. Multiple Sclerosis 2. Epilepsy/Seizures 3. Myasthenia Gravis	Pregnant women with neurologic diseases: 1. Multiple Sclerosis 2. Epilepsy/Seizures 3. Myasthenia Gravis
Interventions	Any pharmacotherapy	Any pharmacotherapy	Alternatives to usual care, drug monitoring, etc.	Alternatives to usual care, drug monitoring, etc.
Comparators	Other pharmacotherapy, Placebo, No intervention	Other pharmacotherapy, Placebo, No intervention	Usual care	Usual care
Outcomes	Maternal Symptom severity, Resolution	<u>Maternal harms:</u> Adverse drug effects Quality of life Death <u>Fetal/neonatal harms</u>: Neuro-developmental outcomes	<u>Maternal benefits:</u> Full term delivery Antenatal complications <u>Fetal/ neonatal benefits:</u> Live birth Birthweight Fetal distress Neonatal resuscitation	<u>Maternal benefits:</u> Route of delivery (vaginal) <u>Fetal/ neonatal benefits:</u> Live birth Fetal distress Neonatal resuscitation
Timing/Setting	Any	Any		

Methods

We assessed nomination #0818, Management of Neurologic Disorders in Pregnancy for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix A for detailed description of the criteria.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years on the key questions of the nomination. See Appendix B for sources searched.

Results

See Appendix A for detailed assessments of all EPC selection criteria.

Appropriateness and Importance

This is an appropriate and important topic. Epilepsy is fairly common, and women with epilepsy are at increased risk for several complications, such as preeclampsia, preterm birth and bleeding in pregnancy. Their infants are at higher risk for congenital anomalies and cognitive delay. MS is less common, however, some disease-modifying treatments are contraindicated in pregnancy and lactation.

Desirability of New Review/Duplication

A new evidence review would be partially duplicative of existing evidence reviews. There are six overlapping reviews on harms, and one on MS treatment. See Table 2, Duplication column.

We describe results by condition and Key Question

A. Epilepsy/Seizures

KQ1: (effectiveness): We found no systematic reviews of effectiveness or comparative effectiveness of medications for epilepsy that included pregnant women.

We found two in-process systematic reviews:

Binny Thomas, Pallivalapilla Abdul Rouf, Moza Al HaIL, Wessam El Kassem, Doua Al Saad. ***Safety and efficacy of levetiracetam monotherapy during pregnancy and lactation: a systematic review***. PROSPERO 2016 CRD42016034096 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016034096

Chooi Shawn Loh, Laura A Magee, Peter von Dadelszen, Radin Farizuan Radin Baidrul Ikram, Shakila Thangaratinam, Hannah Cock, Trudy Williams, Judith Scammel. ***Epilepsy in pregnancy: a systematic review of recent international clinical practice guidelines***. PROSPERO 2017 CRD42017057434 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017057434

KQ2: (harms)
We found four recent SRs, one out of date SR (2015) and one in-process SR that evaluated the effect of epilepsy medications on maternal or fetal harms. These were consistent in recognizing that epilepsy itself confers risks regardless of treatment. Among treatments, lamotrigine appeared to be associated with fewer poor outcomes, and valproic acid with the most congenital anomalies.

- Veroniki et al performed a high quality systematic review (2017), in which they compared the safety of antiepileptic drugs (AEDs) on **neurodevelopment** of infants/children exposed in utero or during breast feeding. The review assessed monotherapy and polytherapy with AEDs including first-generation (carbamazepine, clobazam, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, valproate) and newer-generation (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, vigabatrin) AEDs. Epileptic women who did not receive AEDs during pregnancy or breast feeding served as the control group. Search updated 04/2017.

- Westin et al published a high quality Cochrane review on the effect of monotherapy epilepsy treatment in pregnancy on **congenital malformations.** Search ended September 2015. [11]

- Chen et al reported a 2016 SR of uncertain quality (original article unavailable).[12] They examined the effect of epilepsy in pregnancy (with and without treatment) on **fetal growth restriction.** Their search ended January 2016.

- A fair quality systematic review by Pariente et al (2017) examined the effect of lamotrigine (for any disease) on **maternal** and **neonatal** outcomes. Search date ended July 2016. [13]

- A good quality, but slightly older review by Viale, L., et al. (2015) examined the effect of epilepsy in pregnancy (with and without treatment) on **reproductive outcomes**. The search date ended Jan 2015. They assessed the odds of maternal and fetal complications (excluding congenital malformations) by comparing pregnant women with and without epilepsy and undertook subgroup analysis based on antiepileptic drug exposure in women with epilepsy.

In addition, we found an in-process systematic review:

- Binny Thomas, Pallivalapilla Abdul Rouf, Moza Al HaIL, Wessam El Kassem, Doua Al Saad. Safety and efficacy of levetiracetam monotherapy during pregnancy and lactation: a systematic review. PROSPERO 2016 CRD42016034096 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016034096

KQ3-KQ4: We found no reviews and no protocols on altering antenatal or intrapartum care for pregnant women with epilepsy.

B. Multiple Sclerosis

KQ1: (effectiveness): We found one complete and one in-process systematic review of effectiveness of medications for multiple sclerosis that included pregnant women.

- Rosa et al (2018) published a good quality systematic review SR on the effect of post-natal IVIG to reduce the number of postpartum relapses. Search dates were 1990-2010. [14]
- *Intravenous immunoglobulin to prevent relapses during pregnancy and postpartum in multiple sclerosis*. Fernandez Liguori, Nora. Rojas, Ignacio Juan. Klajn, Diana S. Ciapponi, Agustin. Cochrane Database of Systematic Reviews. 9, 2018. AN: 00075320-100000000-09008 **[PROTOCOL]**

KQ2: (harms)

We found one complete and one in-process systematic review.

- Butler et al from the EHC program published a high quality systematic review of treatment discontinuation for MS. The search date ended Aug 2014, and included 11 studies..[7]
- Safi Alqatari, Grainne Murphy, Sinead Harney, Louise Kenny, Ali Khashan, Sinead O'Neill. ***The use of biologics in pregnant women with chronic conditions and adverse maternal outcome: a systematic review and meta-analysis***. PROSPERO 2017 CRD42017070720 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017070720

KQ3-KQ4: We found on in-process systematic review on altering antenatal or intrapartum care for pregnant women with MS.

- Kristen Krysko, Alice Rutatangwa, Jennifer Graves, Evans Whitaker, Ann Lazar, Kristine Yaffe, Emmanuelle Waubant. ***Effect of breastfeeding on postpartum multiple sclerosis relapses: a systematic review and meta-analysis***. PROSPERO 2018 CRD42018105853 Available

from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018105853

C. Myasthenia Gravis

KQ1-KQ4: We found no systematic reviews addressing any key question for pregnant women with MG.

Table 2. Key Questions and Results for Duplication

Key Question	Duplication (12/2015-12/2018)
KQ 1: effectiveness of therapy	Total number of identified systematic reviews: 1 A. Epilepsy: 0 B. Multiple Sclerosis:1[14] • Other: 1[14] C. Myasthenia: 0
KQ 2: harms of therapy	Total number of identified systematic reviews: 6 A. Epilepsy: 5 [10-13, 15] • Cochrane: 1 [11] • Other [10, 12-13, 15] B. Multiple Sclerosis:1[7] • AHRQ EPC-1 C. Myasthenia: 0
KQ 3: additional antenatal monitoring	Total number of identified systematic reviews: 0
KQ 4: alterations to labor monitoring	Total number of identified systematic reviews: 0

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review would be duplicative of existing products. There are six overlapping reviews on harms, and a single limited review of effectiveness. We identified no reviews addressing KQ 3 and 4; and none addressing women with myasthenia gravis.

The nominator felt that information about of the available systematic reviews would be sufficient for their needs, and a formal feasibility assessment was not done.

References

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13. Pariente G, Leibson T, Shulman T, et al. Pregnancy Outcomes Following In Utero Exposure to Lamotrigine: A Systematic Review and Meta-Analysis. CNS Drugs. 2017 Jun;31(6):439-50. doi: 10.1007/s40263-017-0433-0. PMID: 28434134.
14. Rosa GR, O'Brien AT, Nogueira EAG, et al. There is no benefit in the use of postnatal intravenous immunoglobulin for the prevention of relapses of multiple sclerosis: findings from a systematic review and meta-analysis. Arq Neuropsiquiatr. 2018 Jun;76(6):361-6. doi: 10.1590/0004-282x20180041. PMID: 29972417.
15. Viale L, Allotey J, Cheong-See F, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. Lancet. 2015 Nov 7;386(10006):1845-52. doi: 10.1016/S0140-6736(15)00045-8. PMID: 26318519.

Appendix A. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes
1b. Is the nomination a request for a systematic review?	Yes, it would be at least 3 separate SRs
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Epilepsy is estimated to affect up to 0.8% of pregnant women. Women with epilepsy are at increased risk for several complications, such as preeclampsia, preterm birth and bleeding in pregnancy. Their infants are at higher risk for congenital anomalies and cognitive delay. In 2012, the overall MS prevalence was 149 per 100,000 individuals, or about 400,000 persons in the US. Prevalence was higher in females, (224 per 100,000 individuals). Relapses of MS may decrease during pregnancy. Some observational studies report no increased incidence of poor maternal outcomes whereas others report increases in problems like premature labor, infection and congenital malformations However, some disease-modifying treatments (DMTs) are contraindicated in pregnancy and lactation. The prevalence of myasthenia gravis in the United States is estimated at 14 to 20 per 100,000 population Women with MG require an anesthesia consult due to the disease process as well as their medications. They are at increased risk for respiratory depression and prolonged intubation. They are resistant to succinylcholine, a depolarizing neuromuscular blocking agent (NMBA), and are unpredictably sensitive to nondepolarizing NMBAs.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes
2c. Represents important uncertainty for decision makers	Yes. The clinician must balance the risk of maternal benefits vs. fetal harms of treatment
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes, especially the balance of maternal vs. fetal harms
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Somewhat.
3. Desirability of a New Evidence Review/Duplication	

Selection Criteria	Assessment
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	There are six overlapping reviews on harms. Although we found no reviews on effectiveness, the nominator was satisfied with the search results.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question

Appendix B. Search for Evidence Reviews (Duplication)

Listed below are the sources searched, hierarchically

Primary Search
AHRQ: Evidence reports and technology assessments https://effectivehealthcare.ahrq.gov/; https://www.ahrq.gov/research/findings/ta/index.html; https://www.ahrq.gov/research/findings/evidence-based-reports/search.html
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program https://www.hsrd.research.va.gov/publications/esp/
Cochrane Systematic Reviews http://www.cochranelibrary.com/
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/
Secondary Search
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
Tertiary Search
PubMed https://www.ncbi.nlm.nih.gov/pubmed/