Results of Topic Selection Process & Next Steps

The nominator, American College of Chest Physicians, is interested in a new evidence review on Prevention and Treatment of Venous Thromboembolism (VTE) in Pregnancy to inform an update of their 2012 clinical practice guideline.

Because limited original research addresses the nomination, a new review is not feasible at this time. No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Name: Prevention and Treatment of VTE and Pregnancy

Nomination Date: 12/26/2017

Topic Brief Date: 1/19/2018

Authors

Christine Chang

Conflict of Interest: No affiliations or financial involvement that conflict with the material in this report

Acknowledgements: We acknowledge the input from Jill Huppert on this brief.

Summary

- This nomination met the selection criteria of appropriateness, importance, and impact.
- Available reviews are partly duplicative of the nomination scope. We identified reviews on mechanical heart valves in pregnant women and the use of vena cava filters in pregnant women. However the review on vena cava filters was not useful to the nominator.
- We identified 14 primary studies. This evidence base is small and appears to be mainly comprised of case series and case reports.
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Background

- Physiologic changes increases women’s risk of venous thromboembolism (VTE) during pregnancy especially in the third trimester.
- In a recent systematic review the pooled overall incidence of pregnancy-related VTE was 1.2 per 1000 deliveries. 
- 9.2% of pregnancy deaths from 2011-2013 in the US were related to pulmonary embolism (PE). 
- There are challenges around timing of anticoagulation drugs because of potential harms, risk of bleeding, risk of hemorrhage or anesthesia-related complications during delivery, and effect on breastfeeding.
- The American College of Chest Physicians (ACCP or CHEST) plans to use an AHRQ systematic review to inform an update to their 2012 guideline on the use of anticoagulation in pregnant women.
- This is a topic of interest to multiple specialties. A pregnant woman with VTE could be managed by multiple specialties including obstetrics, maternal-fetal medicine, pulmonology, hematology, anesthesiology, interventional radiology, and cardiology.

Nominator and Stakeholder Engagement: The initial nomination was broad and included questions about use of anticoagulants for VTE prophylaxis and treatment, and for improving pregnancy outcomes. We identified an in-process guideline from the American Society of Hematology (ASH) on VTE prophylaxis and treatment. The McMaster GRADE Group is developing the systematic reviews to inform this guideline. After consultation with the nominator, we excluded questions on anticoagulation for improving pregnancy outcomes and areas covered by the in-process ASH guideline.

The key questions assessed for this nomination are:

Key Question 1: What is the effectiveness of antithrombotic drugs to prevent VTE in pregnant women with a mechanical heart valve?

Key Question 2: What is the optimal duration for treatment with antithrombotic drugs in pregnant women with VTE?

Key Question 3: What is the effectiveness of vena cava filters to prevent PE in pregnant women with VTE?

Key Question 4: In pregnant women with VTE who do not have a scheduled delivery, what is the effectiveness of antithrombotic drugs around the time of delivery?

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

Table 1. Key Questions and PICO

<table>
<thead>
<tr>
<th>Key Questions</th>
<th>Mechanical heart valves</th>
<th>Duration of treatment</th>
<th>Vena cava filter</th>
<th>Anticoagulation management around delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Pregnant women with a mechanical heart valve</td>
<td>Pregnant women with acute VTE</td>
<td>Pregnant women with acute VTE and contraindications to antithrombotic therapy</td>
<td>Pregnant women with acute VTE, around the time of delivery</td>
</tr>
<tr>
<td>Key Questions</td>
<td>Mechanical heart valves</td>
<td>Duration of treatment</td>
<td>Vena cava filter</td>
<td>Anticoagulation management around delivery</td>
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| Interventions | • VKA throughout pregnancy  
• UFH throughout pregnancy  
• LMWH throughout pregnancy  
• Sequential treatment with VKA: UFH during first trimester beginning at or before 6 weeks, then VKA during second and third trimester  
• Sequential treatment with VKA: LMWH during first trimester beginning at or before 6 weeks, then VKA during second and third trimester  
• Sequential treatment with VKA: UFH during first trimester after 6 weeks, then VKA during second and third trimester  
• Sequential treatment with VKA: LMWH during first trimester after 6 weeks, then VKA during second and third trimester  
• Antithrombotic with aspirin throughout pregnancy | • Throughout pregnancy  
• Throughout pregnancy and 6 week postpartum (at least 3 month)  
• Throughout pregnancy and 6 week postpartum (at least 6 month)  
• Throughout pregnancy and indefinite postpartum | Vena cava filter | • UFH without scheduled delivery  
• Prophylactic dose of antithrombotic agent without scheduled delivery |
| Comparators | • No antithrombotic therapy  
• Other antithrombotic strategy | Other duration | No vena cava filter | Other intervention |
| Outcomes | • Maternal thromboembolism  
• Major bleeding  
• Maternal death  
• Congenital malformations  
• Fetal/neonatal hemorrhage  
• Pregnancy loss | • Symptomatic recurrent DVT or pulmonary embolism  
• Fatal pulmonary embolism  
• Major bleeding | • Symptomatic recurrent DVT or pulmonary embolism  
• Fatal pulmonary embolism  
• Major bleeding  
• Postthrombotic syndrome | • Symptomatic recurrent DVT or pulmonary embolism  
• Major bleeding  
• Epidural hematoma  
• Postthrombotic syndrome |

Abbreviations: DVT=deep vein thrombosis; LMWH=low molecular weight heparin; UFH=unfractionated heparin; VKA=vitamin K antagonist; VTE=venous thromboembolism

**Methods**

We assessed nomination Prevention and Treatment VTE and Pregnancy, for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria (Appendix A). Assessment of each criteria determined the need for evaluation of the next one.

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.

Impact of a New Evidence Review
The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review
We conducted a literature search in PubMed from June 2009 to present, to overlap with the search dates for the 2012 CHEST guideline. We reviewed all identified titles and abstracts for inclusion and classified identified studies by study design, to assess the size and scope of a potential evidence review. We included case studies and case series because these were included in the 2012 CHEST guideline.

See Appendix C for the PubMed search strategy.

Compilation of Findings
We constructed a table with the selection criteria and our assessments (Appendix A).

Results

Appropriateness and Importance
This is an appropriate and important topic. In a recent systematic review the pooled overall incidence of pregnancy-related VTE was 1.2 per 1000 deliveries. 1 9.2% of pregnancy deaths from 2011-2013 in the US were related to pulmonary embolism. There were 1.99 hospitalizations for VTE per 1000 births in 2006-2009. 25

Desirability of New Review/Duplication
A new evidence review would be partly duplicative of an existing product.
- KQ 1: We identified two relevant systematic reviews.5,6 Though these did not analyze studies by the timing of substitution of unfractionated heparin (UFH) or low molecular weight heparin (LMWH) during the first trimester in sequential treatment intervention arms, the nominator indicated that these reviews would meet their needs.
- KQ 3: We identified one systematic review that covered the scope of this question.7 However the nominator indicated that the review did not meet their needs because of its quality.
- KQ 4: We identified three related systematic reviews that did not fully meet the PICO and are not considered duplicative, but warrant mention. One focused on the impact of peripartum prophylaxis dosing of UFH and LMWH in pregnant women on epidural hematoma. However it did not indicate whether or not the women had a VTE.8 Another focused on thromboprophylaxis dosed anticoagulants in pregnant women on outcomes,
including major bleeding during delivery.\textsuperscript{9} They did not focus specifically on pregnant women with VTE. The last review examined intermediate dosing of anticoagulation for pregnant women with VTE, rather than prophylactic dosing of anticoagulants.\textsuperscript{10}

See Table 2, Duplication column.

**Impact of a New Evidence Review**
A new systematic review may have moderate impact. Guidelines across different specialties vary duration of treatment (3 or 6 months), and choice and timing of anticoagulation around delivery. There may be practice variation due to differences across guidelines. Guidelines appear consistent about the role of vena cava filters and transitioning to unfractionated heparin before spontaneous labor.\textsuperscript{26} Guidance appears to mainly supported by case series, case reports, and expert opinion.

**Feasibility of a New Evidence Review**
A new evidence review is not feasible. See Table 2, Feasibility column.

### Table 2. Key Questions and Results for Duplication and Feasibility

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>KQ 1: Mechanical heart valve</td>
<td>Total number of identified systematic reviews: 2</td>
<td>Size/scope of review</td>
</tr>
<tr>
<td></td>
<td>Systematic review: 2 \textsuperscript{5,6}</td>
<td>Relevant Studies Identified: 0</td>
</tr>
<tr>
<td>KQ 2: Duration of VTE treatment</td>
<td>Total number of identified systematic reviews: 0</td>
<td>Size/scope of review</td>
</tr>
<tr>
<td></td>
<td>Literature review: 0</td>
<td>Relevant Studies Identified: 0</td>
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<tr>
<td>KQ 3: Vena cava filter for VTE</td>
<td>Total number of identified systematic reviews: 1</td>
<td>Size/scope of review</td>
</tr>
<tr>
<td></td>
<td>Literature review: 1</td>
<td>Relevant Studies Identified: 13</td>
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<tr>
<td>KQ 4: Anticoagulation management around delivery</td>
<td>Total number of identified systematic reviews: 0</td>
<td>Size/scope of review</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relevant Studies Identified: 1</td>
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</table>

*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 partly duplicative of an existing product. Existing systematic reviews cover the scope of KQ 1 (prophylaxis in women with mechanical heart valves).
- **Impact:** A new systematic review has the potential for moderate impact. Available guidance is inconsistent for two of the three key questions, and supported mainly by expert opinion, case reports, and case series.
- **Feasibility:** A new review is not feasible. The evidence base is likely small and mainly comprised of case reports and case series.

**References**


<table>
<thead>
<tr>
<th>Selection Criteria</th>
<th>Assessment</th>
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<tbody>
<tr>
<td>1. Appropriateness</td>
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<tr>
<td>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.?</td>
<td>Yes</td>
</tr>
<tr>
<td>1b. Is the nomination a request for a systematic review?</td>
<td>Yes</td>
</tr>
<tr>
<td>1c. Is the focus on effectiveness or comparative effectiveness?</td>
<td>Yes</td>
</tr>
<tr>
<td>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?</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Importance</td>
<td>In a recent systematic review the pooled overall incidence of pregnancy-related VTE was 1.2 per 1000 deliveries. 1 9.2% of pregnancy deaths from 2011-2013 in the US were related to pulmonary embolism 2</td>
</tr>
<tr>
<td>2a. Represents a significant disease burden; large proportion of the population</td>
<td>Yes this affects healthcare decisionmaking around choice of treatment for pregnant women in the US.</td>
</tr>
<tr>
<td>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</td>
<td>Yes</td>
</tr>
<tr>
<td>2c. Represents important uncertainty for decision makers</td>
<td>Yes</td>
</tr>
<tr>
<td>2d. Incorporates issues around both clinical benefits and potential clinical harms</td>
<td>Yes</td>
</tr>
<tr>
<td>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</td>
<td>Yes. There were 1.99 hospitalizations for VTE per 1000 births in 2006-2009. 25</td>
</tr>
<tr>
<td>3. Desirability of a New Evidence Review/Duplication</td>
<td>A new review would be partly duplicative. We identified two reviews on anticoagulation in pregnant women with mechanical heart valves (KQ 1) which met the need of the nominator. A literature review on vena cava filters in pregnancy (KQ3) was identified but was not useful for the nominator. Several reviews were related to anticoagulation management around delivery (KQ 4) but did not completely fit the PICO. They are included as related references that might be useful for the nominator.</td>
</tr>
<tr>
<td>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)</td>
<td></td>
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<tr>
<td>4. Impact of a New Evidence Review</td>
<td>Guidelines across different specialties vary duration of treatment (3 or 6 months), and choice and timing of anticoagulation around delivery. Guidelines appear consistent about the role of vena cava filters and transitioning to unfractionated heparin before spontaneous labor. 26</td>
</tr>
<tr>
<td>4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?</td>
<td>Guidance appears to mainly supported by case series, case reports, and expert opinion.</td>
</tr>
<tr>
<td>Selection Criteria</td>
<td>Assessment</td>
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<tr>
<td>4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?</td>
<td>Likely practice variation because of the differences in some details of guidelines</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>5. Primary Research</th>
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<tr>
<td>5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)</td>
<td>We identified 14 studies across three KQ. This review is likely small and were mainly case reports and case series. Based on the number and type of studies, it is likely not feasible for a full systematic review to support a guideline.</td>
</tr>
</tbody>
</table>

*Abbreviations: ACCP=American College of Chest Physicians; AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question; PICO=population, intervention, comparator, outcome; SR=systematic review; VTE=venous thromboembolism*
Appendix B. Search for Evidence Reviews (Duplication)
Listed are the sources searched.

AHRQ: Evidence reports and technology assessments, USPSTF recommendations
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program
Cochrane Systematic Reviews and Protocols http://www.cochranelibrary.com/
PubMed
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/
PROSPERO Database (international prospective register of systematic reviews and protocols)
http://www.crd.york.ac.uk/prospero/
CADTH (Canadian Agency for Drugs and Technologies in Health) https://www.cadth.ca/
Systematic Reviews (Journal) : protocols and reviews
http://systematicreviewsjournal.biomedcentral.com/
Appendix C. Search Strategy & Results (Feasibility)

KQ 3
June 1, 2009 to present. Search (((pregn*) OR antepartum) OR peripartum) AND vena cava filter

KQ 2, 4