Cohort Study Potential PURL Review Form
PURL Jam Version

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

A. Citiation: 1: Righini M, Robert-Ebadi H, Elias A, Sanchez O, Le Moigne E, Schmidt J, Le Gall C, Cornuz J, Aujesky D, Roy PM, Chauleur C, Rutschmann OT, Poletti PA, Le Gal G; CT-PE-Pregnancy Group. Diagnosis of Pulmonary Embolism During Pregnancy: A Multicenter Prospective Management Outcome Study. Ann Intern Med. 2018 Dec 4;169(11):766-773. doi: 10.7326/M18-1670. Epub 2018 Oct 23. PubMed PMID: 30357273.
B. Link to PubMed Abstract: https://www.ncbi.nlm.nih.gov/pubmed/30357273
C. First date published study available to readers: October 23, 2018
D. PubMed ID: 30357273
E. Nominated By: Stephen Wilson
F. Institutional Affiliation of Nominator: UPMC
G. Date Nominated: 10/25/2018
H. Identified Through: Annals of Internal Medicine
I. PURLs Editor Reviewing Nominated Potential PURL: Dean Seehusen
J. Nomination Decision Date: 11/6/18
K. Potential PURL Review Form (PPRF) Type: Cohort Study
L. Assigned Potential PURL Reviewer: Pam Hughes
M. Reviewer Affiliation: NV - Nellis
A. Abstract: **BACKGROUND:**
DATA ON THE OPTIMAL DIAGNOSTIC MANAGEMENT OF PREGNANT WOMEN WITH SUSPECTED PULMONARY EMBOLISM (PE) ARE LIMITED, AND GUIDELINES PROVIDE INCONSISTENT RECOMMENDATIONS ON USE OF DIAGNOSTIC TESTS.

OBJECTIVE:
TO PROSPECTIVELY VALIDATE A DIAGNOSTIC STRATEGY IN PREGNANT WOMEN WITH SUSPECTED PE.

DESIGN:
MULTICENTER, MULTINATIONAL, PROSPECTIVE DIAGNOSTIC MANAGEMENT OUTCOME STUDY INVOLVING PRETEST CLINICAL PROBABILITY ASSESSMENT, HIGH-SENSITIVITY D-DIMER TESTING, BILATERAL LOWER LIMB COMPRESSION ULTRASONOGRAPHY (CUS), AND COMPUTED TOMOGRAPHY PULMONARY ANGIOGRAPHY (CTPA). (CLINICALTRIALS.GOV: NCT00740454).

SETTING:
11 CENTERS IN FRANCE AND SWITZERLAND BETWEEN AUGUST 2008 AND JULY 2016.

PATIENTS:
PREGNANT WOMEN WITH CLINICALLY SUSPECTED PE IN EMERGENCY DEPARTMENTS.

INTERVENTION:

PULMONARY EMBOLISM WAS EXCLUDED IN PATIENTS WITH A LOW OR INTERMEDIATE PRETEST CLINICAL PROBABILITY AND A NEGATIVE D-DIMER RESULT. ALL OTHERS UNDERWENT LOWER LIMB CUS AND, IF RESULTS WERE NEGATIVE, CTPA. A VENTILATION- PERFUSION (V/Q) SCAN WAS DONE IF CTPA RESULTS WERE INCONCLUSIVE. PULMONARY EMBOLISM WAS EXCLUDED IF RESULTS OF THE DIAGNOSTIC WORK-UP WERE NEGATIVE, AND UNTREATED PREGNANT WOMEN HAD CLINICAL FOLLOW-UP AT 3 MONTHS.

MEASUREMENTS:
THE PRIMARY OUTCOME WAS THE RATE OF ADJUDICATED VENOUS THROMBOEMBOLIC EVENTS DURING THE 3-MONTH FOLLOW-UP.

RESULTS:
441 WOMEN WERE ASSESSED FOR ELIGIBILITY, AND 395 WERE INCLUDED IN THE STUDY. AMONG THESE, PE WAS DIAGNOSED IN 28 (7.1%) (PROXIMAL DEEP VENOUS THROMBOSIS FOUND ON ULTRASONOGRAPHY [N = 7], POSITIVE CTPA RESULT [N = 19], AND HIGH-PROBABILITY V/Q SCAN [N = 2]) AND EXCLUDED IN 367 (CLINICAL PROBABILITY AND NEGATIVE D-DIMER RESULT [N = 46], NEGATIVE CTPA RESULT [N = 290], NORMAL OR LOW- PROBABILITY V/Q SCAN [N = 17], AND OTHER REASON [N = 14]). TWENTY-TWO WOMEN RECEIVED EXTENDED ANTICOAGULATION DURING FOLLOW-UP, MAINLY FOR PREVIOUS VENOUS THROMBOEMBOLIC DISEASE. THE RATE OF SYMPTOMATIC VENOUS THROMBOEMBOLIC EVENTS WAS 0.0% (95% CI, 0.0% TO 1.0%) AMONG UNTREATED WOMEN AFTER EXCLUSION OF PE ON THE BASIS OF NEGATIVE RESULTS ON THE DIAGNOSTIC WORK- UP.

LIMITATION:
THERE WERE SEVERAL PROTOCOL DEVIATIONS, REFLECTING THE DIFFICULTY OF PERFORMING STUDIES IN PREGNANT WOMEN WITH SUSPECTED PE.

CONCLUSION:
A DIAGNOSTIC STRATEGY BASED ON ASSESSMENT OF CLINICAL PROBABILITY, D-DIMER MEASUREMENT, CUS, AND CTPA CAN SAFELY RULE OUT PE IN PREGNANT WOMEN.

B. Pending PURL Review Date**:** 8/1/2019

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]

A. The study address an appropriate and clearly focused question. Well covered
Comments:

B. The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation. Not Applicable
Comments: Participants were not separated into groups, but rather all participants were treated using a pre-determined algorithm.

C. The study indicates how many of the people asked to take part in it in each of the groups being studied. Not Applicable
Comments: Participants not separated into groups in this study.

D. The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis. Adequately addressed
Comments: Patient's that were given anticoagulation for other reasons were included in the results w/ a sensitivity analysis to estimate the risk that they may have developed a PE

E. What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed? No patient's dropped out prior to the completion of the study and no patients were lost to follow up.

F. Comparison is made between full participants and those lost to follow up, by exposure status. Not Applicable
Comments:

G. The outcomes are clearly defined. Well covered
Comments: The outcomes were the development of VTE in patient's after being ruled out with a pre-determined treatment algorithm.

H. The assessment of outcome is made blind to exposure status. Adequately Addressed
Comments: 3 member independent adjudication committee reviewed the suspected VTE events and were blinded to the initial workup that the patient underwent.

I. Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome. Not Applicable
Comments:

J. What are the key findings of the study? Following a prescribed diagnostic strategy utilizing clinical probability, d-dimer, CUS and CTPA could rule out PE in pregnant patients.

K. How was the study funded? Any conflicts of interest? Any reason to believe that the results may be influenced by other interests? The study was funded by Swiss National Foundation for Scientific Research, Groupe d'Etude de la Thrombose de Bretagne Occidentale and INternation Society on Throbosis and Haemostasis. No conflicts of interest identified.

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions: For up-to-date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS on editor & current year as publication year.

Example: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert date modified if given.} Accesses February 12, 2009. [whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:
Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert date modified if given.} Accessed June 5, 2009. {search date}

A. DynaMed excerpts

DynaMed citation/ Title. Author. In: DynaMed [database online]. Available at: access date www.DynamicMedical.com Last Updated:Accessed

B. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)

C. UpToDate excerpts

D. UpToDate citation

Malhotra A, Weinberger S. Pulmonary embolism in pregnancy: Epidemiology, pathogenesis and diagnosis. In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2019. Available at: http://www.uptodate.com. Last updated: Mar 25, 2019. Accessed Aug 13, 2019.

E. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

In the absence of DVT symptoms, chest x-ray should be performed as the initial diagnostic study of choice. If CXR is neg, recommend to proceed to V/Q scan as next diagnostic test. If chest x-ray abnormal or V/Q scan non-diagnostic a CTPA is then recommended.

F. Other excerpts (USPSTF; other guidelines; etc.)

-American Thoracic Society

G. Citations for other excerpts

Leung AN, Bull TM, Jaeschke R, et al. An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy. American journal of respiratory and critical care medicine. 2011 Nov 15; 184(10):1200-8.

H. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

- In patient's without signs of DVT, CXR is the initial recommended test for PE. If CXR is normal a V/Q scan is recommended for the diagnosis of PE, if abnormal at CTPA is recommended. Recommend against the use of D-dimer in pregnancy.

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

A. **Validity**: Are the findings scientifically valid? 1 (extremely well)

B. If **A** was coded "Other, explain or No", please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

C. **Relevance**: Is the topic relevant to the practice of family medicine and primary care practice, including outpatient, inpatient, obstetrics, emergency and long-term care? Are the patients being studied sufficiently similar to patients cared for in family medicine and primary care in

the US such that results can be generalized?
1 (extremely well)

D. If **C** was coded "Other, explain or No", please provide an explanation.

E. **Practice changing potential**: If the findings of the study are both valid and relevant, are they not a currently widely accepted recommendation among family physicians and primary care clinicians for whom the recommendation is relevant to their patient care? Or are the findings likely to be a meaningful variation regarding awareness and acceptance of the recommendation?
Yes

F. If **E** was coded as "Yes", please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.
-D-dimer is not currently routinely obtained in pregnant patients as a means to rule out VTE due to the fact d-dimer increases as pregnancy increases. Based on the results of this study, providers could obtain a d-dimer in those patient's with low or intermediate pre-test probability. If the d-dimer is negative a PE may be confidently ruled out in low or intermediate risk patients.

G. **Applicability to a Family Medical Care Setting**:
Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention? 1 (definitely could be done in a medical care setting)

H. Please explain your answer to **G**.
-Providers working in both clinic and hospital settings are able to order these diagnostic tests for the diagnosis of PE as described in the algorithm.

I. **Immediacy of Implementation**:
Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug, or other essentials available on the market? 1 (definitely could be immediately applied)

J. If **I** was coded "Other, explain or No", please explain why.

K. **Clinically meaningful outcomes or patient oriented outcomes**:
Do the expected benefits outweigh the expected harms? Are the outcomes patient oriented (as opposed to disease oriented)? Are the measured outcomes, if true, clinically meaningful from a patient perspective?
1 (definitely clinically meaningful or patient oriented)

L. If **K** was coded "Other, explain or No", please explain why.

M. In your opinion, is this a pending PURL? 1 (definitely a pending PURL)

1. Valid: Strong internal scientific validity; the findings appear to be true.

2. Relevant: Relevant to the practice of family medicine.

3. Practice Changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.

4. Applicability in medical setting.

5. Immediacy of implementation

N. Comments on your response for question M.
-The diagnostic algorithm used in the study uses CUS early in the diagnostic workup of pregnant patients. Other evidence suggests that CUS should not be used in the workup unless patients are presenting with signs or symptoms of DVT. Providers could change to using d-dimer more regularly in pregnant patients with low or intermediate risk to help rule out PE without performing further diagnostic testing. This is a low cost and low risk change that could be made, and in this study ruled out PE in 11% of the low/intermediate risk patients.