Critical Review Form
Prognosis

Resident: JD Landon **Date: 5/20/2019**

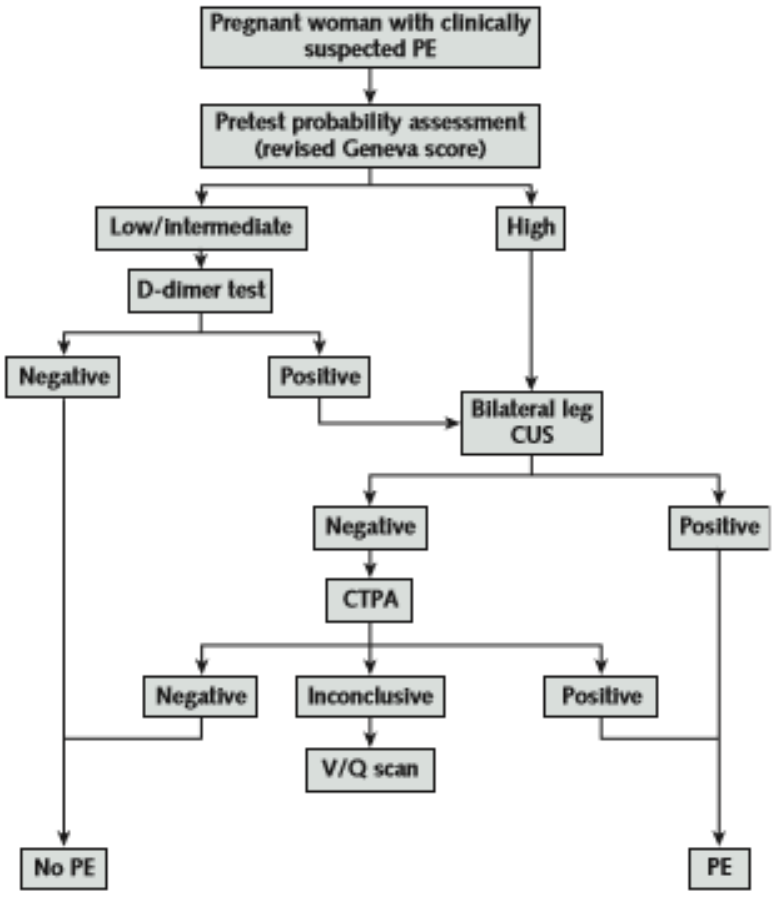
Citation: Righini M. Diagnosis of PE during pregnancy: A multi-center prospective management outcome study. Ann Intern Med. 2018 Dec 4;169(11):766-773.

Objectives: To prospectively validate a diagnostic strategy in pregnant women with suspected PE.

Why?

1. Typical PE tools only validated in non-pregnant populations
2. D-dimer levels, SOB, heart rate all increase during pregnancy at baseline leading to unnecessary further testing
3. Retrospective studies suggest rate of inconclusive CTA chest higher during pregnancy
4. Concerns that DVT ultrasound w/o DVT symptoms has limited benefit and DVT U/S possibly lower accuracy during pregnancy.

Figure 1. Diagnostic algorithm used in the study.



CTPA = computed tomography pulmonary angiography; CUS = compression ultrasonography; PE = pulmonary embolism; V/Q = ventilation-perfusion.

Methods:
11 centers
2 countries (France/Switzerland)
Inclusion
- Pregnant
- Clinically suspected PE (acute onset of new/worsening SOB/CP w/o obvious cause

Exclusion
- Age <18yo
- Contrast allergy
- Creatinine clearance <30 ml/min
- Diagnosis already present
- On full dose anti-coagulation
- Inaccessibility for followup

Guide		Comments
I.	**Are the results valid?**	
A.	**Was the sample of patients representative?** *In other words, how were subjects selected and did they pass through some sort of "filtering" system which could bias your results based on a non-representative sample. Also, were objective criteria used to diagnose the patients with the disorder?*	The authors did not describe their enrollment process such as how patients were identified, whether or not it was a convenience sample which could lead to selection bias. Mean BMI was 25.9, I suspect this is likely a smaller BMI compared to our SNGH population. A CDC report from 2016 shows that Virginia has more than 50% of our population as overweight or obese. Additionally, they did not report on comorbid conditions (HTN, DM, HLD, etc). However, given that we have so little other data for evaluation of PE in pregnant patients, this appears to be the best worst option. It is possible that in our population we may underestimating the presence of VTE.
B.	**Were the patients sufficiently homogeneous with respect to prognostic risk?** *In other words, did all patients share a similar risk from during the study period or was one group expected to begin with a higher morbidity or mortality risk?*	Uncertain. First trimester (21%) were probably under-represented. They did not identify other demographic data that could represent a high-risk population. No group comparisons were made specifically between the negative and positive PE groups. Other important disease states not discussed - SCD - APLS - Nulliparity vs multiparity - Lupus - Hypercoagulable state continues 6 wks postpartum, unclear how many pts 3 month

		follow-up included the post-partum period.
C.	**Was follow-up sufficiently complete?** *In other words, were the investigators able to follow-up on subjects as planned or were a significant number lost to follow-up?*	Yes. 3-month follow-up. No patients lost to follow-up. This is a strength.
D.	**Were objective and unbiased outcome criteria used?** Investigators should clearly specify and define their target outcomes before the study and whenever possible they should base their criteria on objective measures.	Yes. The primary outcome was focused on assessing risk. The question was "how many people would have adjudicated VTE events during the 3-month follow-up among the group who didn't receive AC because of a negative diagnostic algorithm. Also of note, they utilized a CI of 95% with the estimate that VTE risk at 3 months should not be more than 3%.
II.	**What are the results?**	No untreated pts with negative diagnostic workup developed symptomatic VTE's in the f/u period. 0.0% (95% CI, 0.0% to 1.0%). In a per protocol analysis that excluded women with protocol deviations The 3-month risk for VTE in women not receiving anticoagulant therapy was 0.0% (CI, 0.0% to 1.2%) Pretest probability was low in 192 women (48.6%), intermediate in 200 (50.6%), and high in 3 (0.8%). Among the 392 women who did not have high pretest probability, 46 (11.7%) had a negative D-dimer result,341 (87%) had a positive result, and 5 (1.3%) had no D-dimer testing. Negative D-dimer results decreased with increasing gestational age (21 of 83 [25.3%] during the first trimester, 19 of 170 [11.1%] during the second trimester, and 6 of 142 [4.2%] during the third trimester) Of the 349 women with a positive D-dimer result, no D-dimer test, or high pretest probability, 321 (92%) had negative results on CUS, 7 (2.0%) had positive results. Overall, PE was diagnosed in 28 (7.1%) women.

		During follow-up, of the 367 women in whom PE was ruled out, - In total 22 received AC during followup period - 20 pts received ppx AC, 17 in setting of prior VTE event, 2 for preE, 1 for ovarian hyperstim syndrome - 2 received therapeutic AC for DVT During followup, 4 women were evaluated for suspected VTE. PE(3), DVT(1) – all of these patients had negative diagnostic tests.
A.	**How likely are the outcomes over time?**	
B.	**How precise are the estimates of likelihood?** *In other words, what are the confidence intervals for the given outcome likelihoods?*	As above. CI was 95%, (0%-1%)
III.	**How can I apply the results to patient care?**	This model is a reasonable approach to the pregnant patient with clinical suspicion for PE. Ideally, a screening tool more specific to the pregnant patient could be utilized in determining initial risk as shortness of breath and chest pain are common among this population.
A.	**Were the study patients and their management similar to those in my practice?**	I suspect the patients enrolled are likely healthier than the typical SNGH pregnant patient. Unclear what percentage of these patients were ED patients. They described study sites as "centers"
B.	**Was the follow-up sufficiently long?**	Follow-up was 3 months however there is no description of the distribution of weeks pregnant at the time of follow-up. I imagine a better design would have been to follow for 6 weeks postpartum for all patients.
C.	**Can I use the results in the management of patients in my practice?**	Yes. Overall, I feel that given the very few prospective studies available to evaluate pregnant patients, this gives a good framework for the evaluation of pregnant pts in whom I am concerned about PE.

Limitations:

1) Use of modified Geneva test score, not validated in pregnant patients. Several components don't even apply to pregnant patients typically (age over 67, active cancer, etc)

2) No data about other comorbid conditions including APLS, SCD, parity, lupus, etc. Pt selection into high risk, intermediate risk and low risk could significantly change the results.

3) This diagnostic management study is heavily dependent on progression of pregnancy as both d-dimer levels change with gestational age as well as cardiac output which was discussed as a cause for increased number of inconclusive CTPAs. Unclear why authors did not report on average d-dimer levels encountered by weeks pregnant. This could have helped to inform adjusted D-dimer levels by week or trimester of pregnancy. There is very little discussion on the various outcomes of pts based on trimester. Additionally, 3-month follow-up for a 1st trimester does not reveal data pertaining to the period of time surrounding labor/delivery or post-partum where risks continue. Similarly, there is less benefit to 3-month follow-up if pt enrolled merely 1 week before delivery.

4) Protocol deviations of 10%, however in the per protocol analysis they had similar results.

5) Yield of CUS was extremely low and its uncertain that it adds much to the work-up and clearly adds to length of stay and costs.

6) Selection criteria and enrollment process unclear and may predispose to bias.

Bottom Line:

1) If low/intermediate risk + negative D-dimer…probably don't need to worry about PE. (Unfortunately, likelihood of neg d-dimer significantly decreases further along in pregnancy) This resulted in a decrease of CT by 11.6%
2) If bilateral leg CUS is negative, this does NOT rule out PE as 6% of the patients with negative BCUS were positive for PE on CTA or VQ