SOMANZ

SOCIETY OF OBSTETRIC MEDICINE OF AUSTRALIA AND NEW ZEALAND

The SOMANZ Position Statement on Pulmonary Embolism in Pregnancy and Post-Partum

2021

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Pulmonary embolism (PE) is an uncommon but important condition that occurs more frequently in pregnancy and the post-partum period. In Australia maternal deaths from venous thromboembolism (VTE) have reduced slightly since the 1970s, but remain the third most common overall cause of maternal death in the 2012-2014 triennium and the most common direct cause of maternal death (1). In New Zealand, between 2006-2016, VTE was the third most common cause of direct death with a rate of $0.86/10^5$ compared to the Australian rate of $0.6/10^5$ (2). The most recent UK data (2016-2018) demonstrated a mortality rate of $1.48/10^5$ with thromboembolism remaining the most common cause of direct maternal death in the last 5 triennial reports (3). In addition, a review of a sample of survivors of pulmonary embolism identified the potential to improve care amongst 73%, and in 29% it was it thought that such improvements may have made a difference to outcome (3).

A large range of specialties may be involved in the care of women with suspected or proven PE in pregnancy and post-partum including obstetricians, midwives, general practitioners, emergency physicians, haematologists respiratory physicians, intensivists, radiologists and nuclear physicians.

The Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) is a specialist society bringing together a range of experts in medical disorders of pregnancy with extensive experience and knowledge in the investigation and management of women with PE. From our collective experience, there are numerous challenges involved including:

- Distinguishing normal physiological changes of pregnancy from the symptoms and signs of PE
- Non-pregnant prediction tools are unreliable and the use of D-dimer measurement can be problematic
- Appropriate and safe selection of pulmonary imaging during pregnancy
- Treatment options are more limited
- Management of therapeutic anticoagulation around the time of birth including neuraxial analgesia/ anaesthesia and bleeding risks
- Prevention is controversial: who, when, what

From these and other recognised challenges, a series of questions relating to the investigation and management of pulmonary embolism in pregnancy and post-partum were developed. Evidence was sought from MEDLINE, EMBASE and PUBMED searches and based on an extensive review of this literature, a fully referenced position statement was written. The quality of evidence was evaluated and the recommendations made according to NHMRC principles and described below (4). Where there was insufficient evidence, the expert opinion of the author group was sought and agreement reached by majority opinion.

RECOMMENDATION	DESCRIPTION
Evidence based (EBR)	Where sufficient evidence was available
Consensus based recommendations (CBR)	Where there was insufficient evidence, the expert development group made clinical consensus recommendations
Clinical practice points (CPP)	Important implementation and other issues (such as safety, side effects or risks) arose from discussion of evidence based or clinical consensus recommendations

The recommendation terms include the terms “should” or “must” (where benefits of the recommendation exceed the harms), “consider” (where the quality of evidence was limited or the available studies demonstrated little clear advantage of one approach over another, or the balance of benefits to harm was unclear) and “should not” or “do not” or “avoid” (where there is either a lack of appropriate evidence, or the harms outweigh the benefits).

The authors were selected by the Council of the Society of the Obstetric Medicine Group of Australia and New Zealand and represent a diverse group of physicians, obstetricians with expertise in these conditions.

These are presented as the SOMANZ Position Statement on Pulmonary Embolism in Pregnancy and Post-partum.

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Recommendations	Evidence Grade
1. Perform a careful history and examination including consideration of • additional risk factors for VTE • physiological changes of pregnancy: a heart rate of >105 (up to 12 weeks' gestation) or >115 bpm (after 12 weeks' gestation) may be considered abnormal • concurrent pregnancy/fetal concerns • symptoms or signs of a more likely alternate diagnosis	 EBR EBR CPP CPP
2. No symptoms or signs are adequately predictive to exclude or diagnose PE in pregnancy or post-partum	EBR
3. Perform relevant investigations as indicated including FBC, UEC, LFTs, ferritin, ECG, troponin and/or CXR to assess for alternate diagnoses	CPP
4. Do not perform thrombophilia testing as part of the **acute** assessment/ management of PE	CBR
5. Non-pregnant clinical prediction rules have limited utility in determining which women will require pulmonary imaging for possible PE in pregnancy	EBR
6. The SOMANZ "Diagnostic Management Algorithm for Suspected PE in Pregnancy" should be used to guide assessment	CBR
7. Therapeutic LMWH should only be administered prior to pulmonary imaging in hemodynamically unstable women or if pulmonary imaging is not immediately available	CBR
8. Only perform limb compression ultrasonography if there are symptoms or signs of DVT • Ensure whole limb imaging • If DVT is confirmed, consider the need for pulmonary imaging if PE is suspected clinically	EBR
9. Based on currently available data, the addition of D-Dimer testing will reduce the incidence of pulmonary imaging but at the cost of missing up to 40% of women with pulmonary emboli	EBR
10. Identify haemodynamically unstable patients for urgent assessment and management including pulmonary imaging if PE is the most likely diagnosis • A cut-off of ≤90 mmHg systolic blood pressure represents hypotension in the context of PE. Where a bedside cardiac echocardiogram is readily available, it should be performed urgently in a haemodynamically unstable patient with likely PE. The absence of echocardiographic signs of RV overload or dysfunction effectively excludes PE as the cause of haemodynamic instability and other causes of hypotension should then be considered.	CPP CBR
11. If pulmonary imaging is indicated: • Counsel and consent using appropriate data regarding the fetal and maternal risks and the benefits of the procedure • Ventilation/perfusion (V/Q) scanning and Computerised Tomography Pulmonary Angiography (CTPA) are both safe and appropriate pulmonary imaging techniques in pregnancy and the choice of modality may be based on local availability and experience • V/Q scanning, if available, may be preferred in hemodynamically stable women with a normal CXR because of a lower rate of non-diagnostic studies, particularly in the third trimester	 CPP EBR CBR

Recommendations	Evidence Grade
• CTPA is the preferred imaging modality in hemodynamically unstable women or if other pulmonary pathology is suspected. • A cardiac echo may be done first, if clinically appropriate, and readily available. • The choice of CTPA versus V/Q in breastfeeding women requires counselling regarding a very low but possible increased risk of breast cancer with the higher breast doses associated with CTPA versus the requirement to pump and store breast milk for 12 hours after administration of Technitium (99mTc)-Macroaggregated Albumin (MAA) for V/Q scanning. • Modifications of standard imaging compared with non-pregnant practise e.g. low dose perfusion only scanning or modified CTPA are not necessary as the fetal and maternal radiation doses from standard imaging are already very low • Decisions regarding management and repeat imaging for indeterminate results should be made in consultation with a senior, experienced clinician • If multiple investigations are performed, a cumulative fetal and maternal breast radiation dose should be calculated • Consider non-gadolinium Magnetic Resonance Angiography (MRA) if radiation or contrast are contraindicated	CBR CBR CBR EBR CPP EBR EBR
12. Assessment and management for PE in pregnancy should be undertaken by clinicians with suitable experience. This should include a Haematologist, Respiratory Physician, Obstetric Physician or General Physician. The ongoing management of the pregnancy or post-partum period in a woman with confirmed PE must include a Consultant Obstetrician Additional advice may be required from an Obstetric Anaesthetist • In women with massive PE or haemodynamic instability, urgent consultation with an Intensivist, Interventional radiologist or Cardiothoracic Surgeon may be required	CPP CBR
13. All pregnant women with proven PE should be admitted to hospital for initial management including regular clinical and haemodynamic monitoring, symptom management and anticoagulation • Post-partum, women should ideally be cared for in a setting that allows ongoing contact with her baby and suitable support for breast feeding if this is appropriate	EBR CPP
14. If PE is confirmed, commence weight-adjusted therapeutic dose of LMWH • Twice daily dosing has been considered the standard in pregnant women. Once daily versus twice daily dosing has not been compared directly but has not demonstrated any increase in the risk of recurrence • Monitoring of anti-Xa levels is not required except in the case of renal dysfunction, extremes of weight or Antithrombin deficiency • Vitamin K antagonists should not be used for management of PE in pregnancy but may be used post-partum even when breast feeding • Direct oral anticoagulants are contraindicated in pregnancy and breastfeeding. • Optimal duration of anticoagulant therapy for treatment of pregnancy-related PE has not been determined. A treatment duration of 3-6 months would be considered appropriate, continuing until at least 6 weeks post-partum	EBR CPP EBR EBR EBR CBR
15. Thrombolysis and thrombectomy are feasible at almost all stages of pregnancy and should be considered for the same indications and (given in the same doses) as non-pregnant subjects • Thrombolysis post-partum can result in uncontrolled bleeding.	EBR CPP
16. Indications for inferior vena cava (IVC) filters are similar to those for non-pregnant patients e.g. acute PE and contraindications to anticoagulant therapy e.g. imminent birth, surgery or recurrent PE despite therapeutic anticoagulation	CBR

Recommendations	Evidence Grade
17. The type and frequency of fetal monitoring will be determined both by the gestation and severity of maternal illness • In the absence of hemodynamic instability or maternal hypoxia, no additional monitoring or investigation beyond routine antenatal care is required for women diagnosed with PE in pregnancy. If the mother has been unstable, additional fetal growth monitoring would be considered prudent.	CPP CBR
18. Pulmonary embolism per se is not necessarily an indication for immediate birth, however, in women with life threatening pulmonary embolism, birth may be considered essential to improve the maternal resuscitation efforts.	CPP
19. The mode of birth in stable women with PE should be determined on standard obstetric grounds and caesarean section should not be recommended simply on the basis of the presence of a pulmonary embolism	CBR
20. Management of birth in women on therapeutic anticoagulation requires careful planning by a multidisciplinary team including an Obstetrician, Physician and Anaesthetists • The woman and her partner should also be active participants in this decision making with the aim to optimise her birth experience in the safest manner possible • Management of women on therapeutic or intermediate dose anticoagulation will usually require planned delivery to allow cessation/management of anticoagulation. It is recognised that some women will labour spontaneously or require urgent Caesarean section prior to the planned birth time and appropriate management plans must be documented for both possibilities • The planning and documentation for both planned versus spontaneous onset of labour/urgent Caesarean section should be made well in advance i.e. prior to 36 weeks gestation. A written multidisciplinary plan should be made after appropriate counselling by a senior consultant obstetrician, physician (Obstetric/ Haematologist/General), anaesthetist and midwife (see Peri-partum Therapeutic Anticoagulation Management Plan) • All women will require a consultation with an Anaesthetist at or before 36 weeks gestation including discussion of alternate options to neuraxial analgesia/ anaesthesia • Indwelling neuraxial catheters removal should occur a minimum of 12 hours after the last prophylactic dose of LMWH or 24 hours after the last therapeutic dose. Subsequent dosing should occur a minimum of 4 hours after catheter removal • The first dose of intermediate/therapeutic LMWH should be given no sooner than 12-24 hours post-partum, providing there is full neurological recovery and no evidence of active bleeding or coagulopathy and after review by a Senior Obstetrician. A prophylactic dose of LMWH or adjusted dose intravenous UFH may be given in the interim. The risk of bleeding is greater with intermediate and therapeutic than lower dose LMWH	EBR CPP CPP CPP EBR EBR EBR
21. Women diagnosed with PE in pregnancy or post-partum should be offered appropriate contraception advice taking into account the risks, efficacy and reversibility of the various options available • Appropriate contraception should be advised for any woman receiving warfarin or a direct oral anticoagulants for secondary prevention of VTE	CPP EBR
22. Women with a past history of PE in pregnancy should undergo pre-pregnancy counselling so that they are aware of the need to commence LMWH prophylaxis as soon as a viable pregnancy is confirmed (usually 6-8 weeks amennorrhoea) • Specific instructions must be given to women taking Vitamin K antagonists or DOACs • Women who need to undergo assisted reproductive treatment (ART) to conceive, and have a history of pregnancy related PE, should receive LMWH prophylaxis commenced in conjunction with controlled ovarian stimulation. Intermediate or therapeutic dose LMWH should be considered if moderate-severe ovarian hypertstimulation occurs	CBR EBR CPP

Abbreviations

ABG	Arterial blood gas
w	Activated partial thromboplastin time
ART	Assisted reproductive technology
ASH	American Society of Hematology
ASTH	American Society of Thrombosis and Hematology
ATS	American Thoracic Society
BNP	Brain natriuretic peptide
BP	Blood pressure
BPM	Beats per minute
CBR	Consensus based recommendation
CI	95% confidence intervals [ ]
COC	Combined oral contraceptive pill
CPP	Clinical practise points
CTPA	Chest tomography pulmonary angiogram
CUS	Compression ultrasonography (Doppler)
CXR	Chest X-ray
DiPEP	Diagnosis of pulmonary embolism in pregnancy
DOAC	Direct oral anticoagulant
DVT	Deep venous thrombosis
EANM	European Association of Nuclear Medicine
EBR	Evidence based recommendation
ECG	electrocardiograph
ECMO	Extracorporeal membrane oxygenation
ESC	European Society of Cardiology
FBC	Full blood count
FT4/FT3	Free thyroxine/tri-iodothyronine
H-FABP	Heart-type fatty acid-binding protein
HR	Heart Rate
HsTn	High sensitivity troponin
IUD	Intra-uterine device

Abbreviations

IV	Intravenous
IVC	Inferior vena cava
LFT	Liver function tests
LNG	Levonorgestrel-releasing
LNT	Linear no threshold
LMWH	Low molecular weight heparin
^{99m}Tc MAA	Technitium-Macroaggregated Albumin
MDPA	Depot medroxyprogesterone
MRA/MRI	Magnetic resonance angiogram/imaging
NHMRC	National Health and Medical research Council
OR	Odds ratio
PE	Pulmonary embolus/emboli
POP	Progesterone only pill
PP	Post-partum
PPH	Post-partum haemorrhage
PTP	Pretest probability
RCOG	Royal College of Obstetrics and Gynaecology
RIETE	Registro Informatizado de Enfermedad TromboEmbólica: Computerized Registry of Patients with Venous Thromboembolism
RR	Respiratory rate
SOMANZ	Society of Obstetric Medicine of Australia and New Zealand
SPECT	Single photon emission computed tomography
SpO2	Pulse oximetry oxygen saturation
SSPE	small sub-segmental pulmonary embolism
TSH	Thyroid stimulating hormone
UEC	Urea, electrolytes, creatinine
UFH	Unfractionated heparin
UKOSS	United Kingdom Obstetric Surveillance System
V/Q	Ventilation/perfusion nuclear lung scan
VTE	Venous thromboembolism

Introduction

Although the risk of VTE in pregnancy and post-partum is increased 5-10 fold, the incidence of PE is still very low at 0.07 per 1000 deliveries antenatally and 0.08 per 1000 deliveries in the puerperium.(5) A surveillance study in the United Kingdom calculated the risk of antenatal PE at 1.3 per 10,000 deliveries between 2005-6 (6). The risk of VTE increases from early pregnancy and is highest in the third trimester and peri-partum (7-12). A number of additional risk factors will alter the likelihood of PE during pregnancy and the risk remains elevated for at least several weeks post-partum reflecting the gradual return to a non-pregnant physiology (13-15).

There are a large number of existing guidelines both locally and internationally that recommend certain pathways for the assessment and management of pregnant or post-partum women with suspected pulmonary emboli (PE) (16-19). These present a variety of strategies that attempt to consolidate the existing evidence regarding the validity, safety and reliability of clinical prediction /scoring tools, bloods tests and indirect (assessment for DVT) and direct imaging (V/Q scans and CTPA/MRA).

The management of the pregnant or post-partum woman with PE remains challenging even after the establishment of the diagnosis. It includes management of symptoms and hemodynamic instability, prescription and monitoring of anticoagulation, antenatal monitoring as well as planning and management of birth and the peri-partum period with particular consideration of breast feeding. In addition, the management should include longer term issues such as contraception and management in future pregnancies. These aspects require multidisciplinary care by experienced teams and should remain focused on the expectations and preferences of the woman and her family.

Pregnant women with symptoms suggestive of PE may have a range of alternative diagnoses. It is imperative to consider the range of more common conditions which may cause the symptoms of PE including the physiological effects of pregnancy. Particularly in the woman without additional risk factors (see below), alternate diagnoses should be considered prior to pursuing specific testing for PE and/or after PE has been excluded. Avoiding PE over-diagnosis in pregnancy is as important as not missing a PE diagnosis. The incorrect diagnosis of PE may have significant, lifelong implications for a woman, including the risk of anticoagulation treatment in the short term as well as the withholding of oestrogen contraception, hormone replacement therapy and the requirement for thromboprophylaxis during future pregnancies.

The purpose of this position statement is to provide guidance for the overall management of women with suspected or proven PE in pregnancy and post-partum, based on the best available evidence. In many cases, robust evidence to guide management does not exist, hence pragmatic recommendations are presented by a working group of clinicians with expertise in managing PE during pregnancy and the post-partum period.

Scope

This SOMANZ Position Statement addresses a series of questions to guide the diagnosis and management of women with suspected or proven PE in pregnancy and post-partum.

ASSESSMENT AND DIAGNOSIS

How do we assess clinical signs and symptoms to predict PE in pregnancy and post-partum?
Which alternative diagnoses should be considered in a woman with symptoms and signs of PE in pregnancy and post-partum?
What signs and symptoms predict PE in pregnancy?
What investigations should be performed in women with symptoms suspicious for PE?
What clinical prediction tools are validated for women where PE is the most likely diagnosis?
What is the best modality for Pulmonary Artery Imaging for suspected PE in pregnancy?
Recommendations for diagnostic work up for PE in pregnancy and post-partum.

MANAGEMENT

Can non-pregnant risk stratification algorithms be used for pregnant/post-partum women with PE?
Who should care for women with confirmed PE in pregnancy and post-partum?
Where should management of women with confirmed PE take place?
What is the appropriate therapy for PE in pregnancy and post-partum?
What is the recommended duration of anticoagulation for confirmed PE?
What additional obstetric/fetal monitoring is required for women with PE?
What are the management options for labour and birth for women with confirmed PE in pregnancy?
How should you plan for and manage neuraxial anaesthesia/analgesia in women on treatment for PE in pregnancy?
How should women with PE be managed after birth?
What are options for contraception for women with previous PE in pregnancy or post-partum?
What preconceptual advice should women receive following a diagnosis of PE in pregnancy?
What audit tools should be considered for quality review of the investigation and management of PE in pregnancy?
What are future research considerations in this field?

Appendix 1

Peri-partum management plan for women with PE in pregnancy receiving therapeutic anticoagulation

ASSESSMENT AND DIAGNOSIS

HOW DO WE ASSESS CLINICAL SIGNS AND SYMPTOMS TO PREDICT PE IN PREGNANCY AND POST-PARTUM?

What are important aspects of clinical assessment?

A thorough history and examination should be performed including an accurate history of the pregnancy and potential additional risk factors for VTE (Textbox 1). This may lead to consideration of alternate diagnoses including those specific to pregnancy e.g. preeclampsia causing atypical chest pain, peri-partum cardiomyopathy causing dyspnoea (Table 1).

In addition to the usual clinical assessment outside of pregnancy, the following information may assist with diagnosis and management.

- history of recurrent miscarriage suggestive of antiphospholipid syndrome
- additional risk factors for VTE (Textbox)
- concurrent or recent complications such as preeclampsia, fetal growth restriction, preterm labour, placental abruption, bleeding during pregnancy
- any ongoing pregnancy/fetal concerns
- history of recent vaginal birth/Caesarean section
- history or symptoms of alternate diagnoses such as infection, underlying lung or heart disease

Risk factors to consider when assessing women with symptoms suspicious for PE in pregnancy or post-partum (19)

Pre-pregnancy risk factors
Immediate family history
Previous VTE
Thrombophilia
Ovarian hyperstimulation syndrome
Smoking

Antenatal risk factors:
Age > 35years old
Parity ≥3
Assisted reproductive technology
Preterm birth
Hypertensive illness especially with high range proteinuria (>3g/day)
Antepartum Haemorrhage
Gross varicose veins
Immobility
Hyperemesis
Sepsis

Additional Postnatal risk factors:
Stillbirth/Fetal death
Caesarean section
Post-partum haemorrhage > 1L

What are the physiological changes of normal pregnancy?

Normal physiological changes in pregnancy can often mimic the signs and symptoms thought to be predictive of PE. In a recent prospective observational study, the median heart rate (HR [95% Confidence Intervals]) was lowest at 12 weeks of gestation; 82 [63-105]beat per minute (bpm) rising to 91 [68-115] bpm at 34 weeks and decreasing slightly towards 40 weeks (89 [65-114] bpm)(20). The median respiratory rate at 12 weeks of gestation was 15 breaths per minute which did not change with gestation and a respiratory rate of more than 22 occurred in fewer than 3% of observations in normal pregnancy. Temperature and oxygen saturation decreased marginally as pregnancy progressed.

Despite these very small physiological changes a sense of tachycardia and palpitations are common and 50% of women will experience ectopic beats (21, 22) .Dyspnoea is reported in 60-70% of pregnant women whilst syncope and near-syncope has been reported in 6% of pregnant patients secondary to physiological vasodilatation (23) . Vasodilation and venous stasis frequently cause bilateral lower limb oedema however unilateral oedema is likely to be significant. Chan et al. found that women with calf circumference difference of at least 2 cm were 18 times more likely to receive a diagnosis of DVT in the symptomatic leg (24).

For practical purposes, a cut-off of ≤90 mmHg systolic blood pressure represents hypotension in the context of sepsis and may be considered an appropriate cut-off in the context of PE in pregnancy (25). Similarly a heart rate of >105-115 bpm may be considered abnormal (20).

Chest pain is much less common but may be due to musculoskeletal causes or other more serious pathology including PE or myocardial ischaemia.

Pulse oximetry (SpO_2) measures peripheral capillary oxygen saturation as a surrogate marker for tissue oxygenation. A SpO_2 value of ≥90% will usually lie within 2-3% of the true arterial saturation and measurement of it is not affected by pregnancy. In a multicentre study of non-pregnant subjects, a pulse oximetry cut off of 94.5% room air oxygen saturation at sea level effectively differentiated patients with PE into high-risk (mortality 20% [CI 12-29%)) and low-risk (mortality 2% [CI 0-6%]) groups (26).

Which alternative diagnoses should be considered in a woman with symptoms and signs of PE in pregnancy and post-partum?

The woman with symptoms suggestive of PE may have a range of alternative diagnoses. All the recognised clinical prediction rules (discussed below) require PE to be the most likely diagnosis. There are a range of much more common conditions which may cause these symptoms. Particularly in the woman without additional risk factors (Textbox), the following alternate diagnoses should be considered prior to pursuing specific testing for PE or after PE has been excluded (Table 1).

Table 1: Common symptoms in women presenting with suspected PE in pregnancy and post-partum.
T:Trimester, PP:post-partum, Y:yes, N:No, ECG: Electrocardiograph, CXR: Chest X-ray, CT: Computerised tomography, TSH: Thyroid stimulating hormone, FT4: free thyroxine, FT3: Free triiodothyronine

SYMPTOM	Dyspnoea/ Tachypnoea	Tachycardia	Chest pain	Collapse/ Syncope	Haemoptysis	Gestation (or PP) when most common	Additional investigations
CONDITION							
Anaemia/ Iron deficiency	Y	Y	N	Presyncope	N	T2-3	Iron studies
Gastroesophageal reflux	N-occasional overnight choking, wheeze	N	Y	N	N- but may rarely cause haematemesis	T3	Nil
Musculoskeletal pain: back or ribs	N	N	Y	N	N	T3	Nil
Anxiety/ hyperventilation	Y	Y	Y	Presyncope	N	Any	Nil
Arrhythmia	Intermittent	Intermittent	Rarely	Rarely	No	Any	ECG, Holtor monitor
Cardiac failure- orthopnoea valvular heart disease, cardiomyopathy	Y-predominant	Y	N	Rarely	Rarely	T3	CXR, Cardiac Echo
Pleurisy/pericarditis	Sometimes	No	Yes	N	No	Any	CXR, Cardiac Echo
Asthma	Episodic	No- may increase transiently after salbutamol	N	N	N	Any	Spirometry
Pneumonia	Y	Y	Sometimes		Rarely	Any	CXR,
Pneumothorax/ pneumomediastinum	Y	Y	Y	N	N	Any or PP	CXR
Myocardial ischemia	Y	Y	Y	Sometimes	N	Any	ECG, Troponin, Cardiac Echo
Aortic dissection	Y	Y	Y +++	Sometimes	Sometimes	Late T3	CXR, Chest/Abdo CT Transesophageal Echo
Thyrotoxicosis	N	Y	N	N	N	Early pregnancy	TSH T3 T4
Phaeochromocytoma metanephrines	Y	Y	N	Rarely	N	Any	Fasting plasma

What signs and symptoms predict PE in pregnancy?

Goodacre et al. recently published findings from the Diagnosis of PE in Pregnancy: DiPEP study(27). Through a combination of prospective cohort and retrospective case finding, they compared clinical history data and basic biometry in 181 women with positive imaging and 259 women where PE was ruled out (254 by negative imaging, 5 with equivocal imaging and 42 with no imaging). They confirmed the known association between risk of PE and age, parity, recent surgery, previous thrombosis, family history of thrombosis and interestingly the absence of long-haul travel or varicose veins. A higher proportion of women given thromboprophylaxis had subsequent PE (OR 2.56 CI 1.72-3.82; p<0.001). By both univariate and multivariate analysis, higher temperature and lower systolic blood pressure and oxygen saturation were statistically significant between the groups but the differences were very small and not biophysically relevant.

The more common presenting symptoms of women with and without proven PE from the DiPEP study are presented in Table 2 (28) and compared with two other cohorts. The DiPEP study did not report the data for combinations of presenting symptoms but determined that none of these symptoms had a statistically significant value to distinguish women with and without PE. The rates of these symptoms were similar in the Artemis study (29) and in the pregnant women with pulmonary embolism collected by the RIETE Registry (n=158), a European database of subjects with pulmonary embolism. Of note, there seem to be a lower threshold of symptoms suspicious for PE in pregnancy than in non-pregnant subjects, even though as described above, apart from haemoptysis, these symptoms are common in normal pregnancy and appear to be non-discriminatory for likely PE. They were unable to determine any specific symptoms and signs that helped differentiate pathological symptoms from normal physiological symptoms of PE in pregnancy.

Table 2. Frequency (%) of symptoms in subjects with and without proven PE: from the DiPEP study (28) and Artemis study (29) (personal communication) and RIETE registry*no control group available (30).

FREQUENCY	DiPEP with proven PE*(%)	DiPEP without PE (%)	Artemis with proven PE*(%)	Artemis without PE (%)	Reite with proven PE*(%)
Chest pain • pleuritic • non-pleuritic • any	 53 18 -	 52 21 -	 - - 88	 - - 69	 - - 59
Dyspnoea: • at rest • on exertion • any	 61 48 -	 54 52 -	 - - 71	 - - 76	 - - 85
Syncope	3	5	6	5	8
Haemoptysis	4	7.2	5	3.8	4
Cough	9	9	6	26	-
Palpitations	12	13	13	18	-

What investigations should be performed in women with symptoms suspicious for PE?

A number of basic investigations should be considered in women with symptoms suspicious for PE depending on the clinical presentation. They may be useful to confirm an alternate diagnosis or assist with diagnosing or excluding PE.

1. Electrocardiograph (ECG)

The ECG has limited usefulness in the diagnosis of PE because of its low sensitivity and specificity. The main role of an ECG is to rule out other diagnoses e.g. myocardial ischemia or pericarditis.

In pregnancy, normal variations of the ECG include(31)

- deviation of QRS axis towards left as pregnancy advances
- increased incidence of prominent Q waves in lead II, III and avF
- T-wave abnormalities e.g. flat and inverted T-waves in lead III, V1 - V3

In the DiPEP study, an undefined abnormality of the ECG was not statistically significantly associated with the diagnosis of PE (OR 0.71, CI 0.19-2.29) (28).

2. Chest X-Ray (CXR)

A CXR is often performed in the evaluation of possible PE but is most helpful when clinical signs and symptoms suggest an alternate diagnosis e.g. pneumonia, cardiomyopathy, pleural effusion or pneumothorax. An abnormal CXR may alter the choice of direct imaging with a preference for CTPA to assess for these alternative diagnoses as well as PE. A CXR is associated with a trivial radiation dose to both mother and fetus and should not be withheld if indicated.

Both PE-related and unrelated CXR abnormalities were significantly associated with an increased risk of PE in the Di-Pep cohort (28).

3. Full blood count (FBC), Urea, electrolytes, creatinine (UEC), liver function tests (LFT), ferritin.

Iron deficiency is common in pregnancy and presents with dyspnoea, tachycardia and if severe, even chest pain. It may cause symptoms even in the absence of significant anaemia. Other routine blood investigations may reveal alternate diagnoses e.g. infection, acidosis.

4. Arterial blood gases (ABG)

Methods of measuring oxygen status (more commonly by SpO_2) in patients with suspected PE have been used as both diagnostic criteria and to predict adverse outcome from proven PE. Unexplained hypoxemia, oxygen saturation of < 94%, increases the likelihood of PE in a pregnant woman (OR 4.37, CI 2.12 to 9.71 < 0.001), although the absence of hypoxemia is an insensitive marker (28) .

An arterial blood gas will directly measure arterial oxygen saturation but is less often performed because of discomfort and potential risks to both patient and collector. In pregnancy, the A-a gradient appears to be a poor test for PE with one study of 102 pregnant/post-partum women with a total of 13 positive for PE demonstrating negative and positive predictive values for A-a gradients of 80.0%, and 11.5%, respectively (32). As with a CXR and ECG, a normal arterial blood gas does not exclude a PE.

5. D-Dimer

a) What are the normal changes in D-Dimer measurements in pregnancy?

In pregnancy D-dimer levels are elevated and overlap the values normally associated with pulmonary embolism (Figure 1) (29). In a systematic review, the percentage of normal pregnant women with a D-Dimer below the cut-off threshold (i.e. the D-dimer level used for predictive algorithms in non-pregnant subjects with suspected PE) varied from 50-100% in the first trimester to 0-76% in the third trimester (26). Numerous attempts have been made to define "pregnancy-adjusted normal ranges" for D-Dimer but identifying a normal range by statistical methods is very different to determining a threshold for excluding the diagnosis of PE (29). In a mixture of longitudinal and cross-sectional studies, suggested upper limits for D-Dimer were 0.27-0.95 mg/L in the first trimester, 0.46-2.79 mg/L in the second trimester and 0.64-3.12 mg/L in the third trimester. D dimer levels drop off rapidly in the first 3 days following birth (33). By day 30 post-partum, 79% of women have a D dimer below the non-pregnant threshold of 500ng/ml and this increases to 93% by Day 45 post-partum (33).

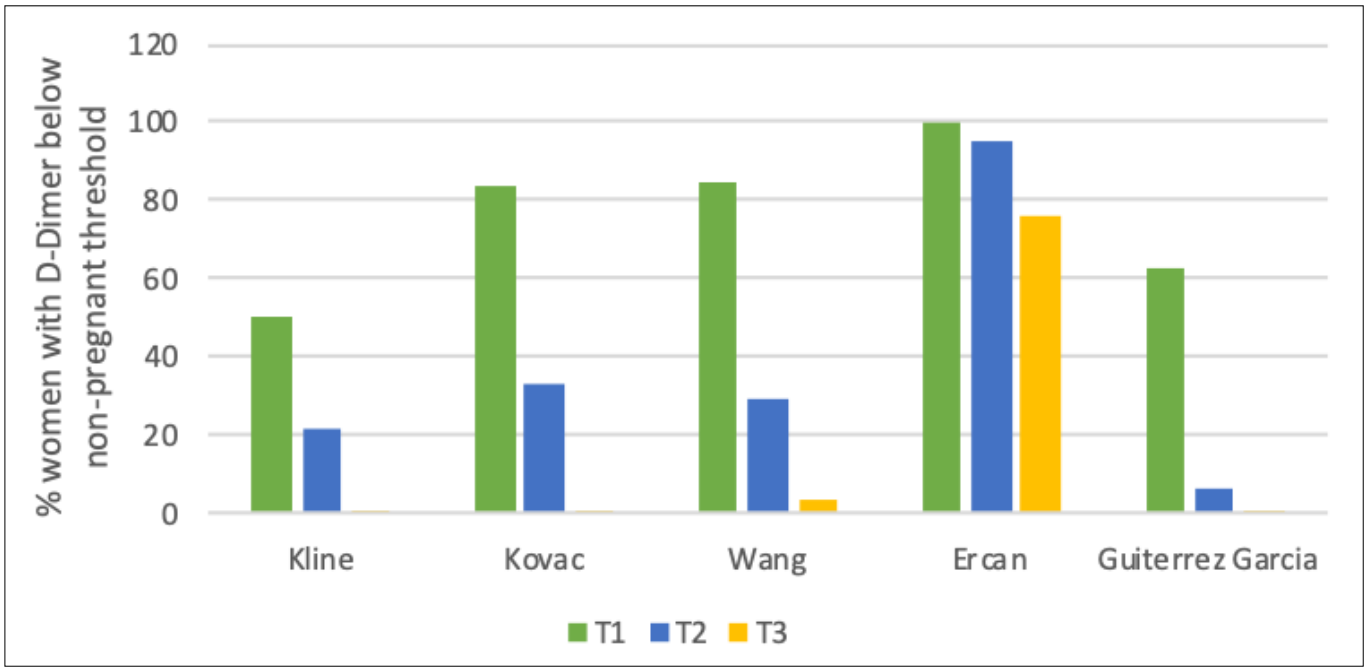


Figure 1: D dimer levels in normal pregnancy per trimester: Clinical threshold for d-dimer (type of study) in each study: Kline: <0.5mg/L, (longitudinal), Kovac: <0.23 mg/L (cross-sectional), Wang: <0.5mg/L, (longitudinal), Ercan <0.5mg/L, (cross-sectional), Gutierrez Garcia: <0.5mg/L (longitudinal) (34-38).

In non-pregnant patients D-dimers are useful to aid in the exclusion of diagnosis of PE as they have a high sensitivity and high negative predictive value. In pregnant women, even using pregnancy derived thresholds for D-dimer has not been found discriminatory with sensitivity 69.4% (51.9-83.7%) and specificity 37.8% (27.8 -48.6%) for the diagnosis of PE (29).

The D-dimer may be less useful in pregnancy. There are numerous reports of pulmonary emboli occurring in pregnancy associated with negative D-dimer testing (39). In the DiPep study, most women had received heparin prior to D-Dimer testing according to local guidelines, which may have resulted in false negative results (40). Previous studies in non-pregnant subjects have demonstrated that 24 hours after starting therapeutic heparin, D-dimer levels have decreased by

25% in patients with acute VTE (41), while a more recent small study reported a mean decrease of 16% , twelve hours after a single dose of therapeutic LMWH (42). In two studies of the effect of prophylactic LMWH (either enoxaparin or dalteparin) , there were mixed results with one study finding a non-significant decrease in D-Dimer (p.0.08) (43) whilst the other study showed an increased D-Dimer at all stages of pregnancy (p<0.0001) (44). In a cross-sectional study of post-partum women, D-dimer levels were not statistically different in women on (1.13 mg/L) or off (1.27mg/L) LMWH thromboprophylaxis (33).

Guidelines from the European Society of Cardiology recommend measuring D-dimer levels in women with suspected PE, stating that normal D-dimer levels do exclude PE in pregnancy (Class IIb, level C recommendation) whilst guidelines from the American Thoracic Society (45) and the RCOG (19) recommend that D-dimer should not be used to exclude PE in pregnancy. Variable D-Dimer thresholds (<0.5mg/l or <1.0 mg/L) based on the presence or absence of additional risk factors were used in the Artemis study (discussed below) but this is the only large study to have adequately validated their use of D-dimers in a pregnant population (29, 46).

6. Biomarkers

In non-pregnant patients with PE, several studies have examined the role of biomarkers such as troponin, brain natriuretic peptides (BNP) or N-terminal pro BNP and heart-type fatty acid-binding protein (H-FABP) to diagnose or prognosticate for PE.

In pregnancy, the Di-pep study examined the area under the curve for a range of biomarkers including B-type natriuretic peptide, C-reactive protein, Clauss fibrinogen, D-Dimer, pro-atrial natriuretic peptide, prothrombin fragment, plasmin-antiplasmin complexes, prothombin time, thrombin generation lag time, thrombin generation endogenous potential, thrombin generation peak and time to peak, soluble tissue factor, and serum troponin. No diagnostically useful threshold for diagnosing or ruling out VTE was identified (47).

7. Thrombophilia testing

Thrombophilia testing is not recommended as part of the work up for a pregnant woman with symptoms suspicious for PE or even following a confirmed diagnosis of PE. The acute management of newly diagnosed PE is the same regardless of the presence or absence of a recognised inherited thrombophilia (Table 3), but their presence may impact on the risk of recurrence and recommendations regarding duration of anticoagulation (16). Outside of pregnancy, the presence of various thrombophilic factors is related to a variable increase in the risk of VTE.

Table 3: Prevalence and risk of VTE associated with inherited thrombophilias in a non-pregnant Caucasian population and an Australian antenatal population (48, 49).

Thrombophilia	Caucasian	Australian	Risk of initial VTE
Factor V Leiden heterozygous	1 in 20	1 in 20	3-4x
Factor V Homozygous	1 in 400	1 in 200	11x
Prothrombin G2021GA heterozygous	1 in 50	1 in 50	3-4x
Prothrombin G2021GA homozygous	1 in 2500	-	7x
Protein C deficiency	1 in 200-500	N/A	7-30x
Protein S deficiency	Uncertain	N/A	5-30x
Antithrombin deficiency	1 in 600-5000		15-30x

Women with proven thromboembolic disease in pregnancy have a high incidence of inherited thrombophilia. In one study, 40% of women with pregnancy related thromboembolism were heterozygote for the factor V Leiden mutation and 17% had a prothrombin gene G20210A mutation (50). However, the probability of an individual with the common genetic mutations having a thrombosis in pregnancy is very low, with 0.34% for the factor V Leiden and 0.37% for the prothrombin gene G20210A mutation. The probability of thrombosis for an individual with both the factor V Leiden and prothrombin gene mutation is 5.2%. However, these are relatively common genetic mutations in the general population and many women presenting with a PE will not have an identified thrombophilia.

Current VTE guidelines advise limited use of thrombophilia testing. It rarely changes the individual's management, does not alter outcome and can lead to increased anxiety in both patients and clinicians. The recent SCOG guideline recommends against thrombophilia screening with a first episode of VTE in pregnancy although it suggests there may be an exception if there is a family history of Protein S, Protein C or Antithrombin deficiencies or if thrombosis occurs in an unusual site (17). The measurement of thrombophilias with functional assays (especially Protein S deficiency) should be deferred until after pregnancy as the level falls physiologically in all women. An argument may be made for screening for the presence of antiphospholipid antibodies and Antithrombin levels during pregnancy as their presence may alter management e.g. addition of aspirin in early pregnancy or more intensive fetal monitoring.

8. Lower (rarely upper) limb venous compression ultrasonography

Some guidelines recommend bilateral lower limb compression ultrasonography be performed in all pregnant women presenting with suspected PE (51, 52). The rationale for this is that confirmation of a DVT leads to the same management with therapeutic anticoagulation without exposing the mother or fetus to radiation. However, the diagnostic yield in women with no symptoms of DVT is extremely low and there is the potential for over diagnosis because the rate of a false positive test is increased when the pre-test probability is low.

In a range of studies in pregnancy, the rate of positive CUS was between 1.8%-10.5% (53). In the study by Cooper et al of 158 pregnant women who had bilateral leg Doppler ultrasounds performed because of suspected PE, no DVT were diagnosed in any asymptomatic women (54).

Performing bilateral venous compression ultrasonography in women with no signs or symptoms of DVT is not clinically useful and is likely to delay definitive imaging and treatment of women with suspected PE. Whole limb CUS is the investigation of choice for the diagnostic workup of symptomatic lower (rarely upper) limb deep venous thrombosis. Investigation for pelvic vein thrombosis in pregnancy and post-partum is technically difficult and particularly post-partum, will be positive in a large number (up to 30% of low-risk women following vaginal birth (55) with uncertain clinical significance. If pelvic vein thrombosis is considered clinically likely, Magnetic Resonance Venography has greater sensitivity than ultrasound (56)

If PE is considered confirmed based on the presence of DVT without pulmonary imaging, this has a number of potential important implications including difficulties in the management of ongoing or recurrent symptoms of PE and decisions regarding the duration of anticoagulation.

9. Echocardiography

Echocardiography is not recommended routinely for the assessment of acute PE, but may be helpful in patients with haemodynamic compromise (57). It can be used to assess right ventricular dysfunction and can aid in the assessment of high risk PE where thrombolytic therapy is being considered (58). Echocardiography is also of value if other diagnoses are being considered such as cardiomyopathy, valvular heart disease, pulmonary hypertension or aortic dissection.

In suspected acute PE, multiple echocardiographic signs are highly specific: right-heart thrombus, McConnell's sign (depressed contractility of the RV free wall compared with the RV apex), paradoxical septal movement and RV free wall hypokinesis (57). These clinical signs retain high specificity even in point-of-care examinations performed by non-cardiologists. Patients with haemodynamic instability or cardiac arrest might also benefit from focused echocardiography when acute PE is suspected and direct pulmonary imaging is not immediately feasible. Conversely, in suspected high-risk PE, the absence of echocardiographic signs of RV overload or dysfunction practically excludes PE as the cause of haemodynamic instability and other cause of hypotension should be considered (59).

The use of echocardiography in non-pregnant, haemodynamically stable patients with acute PE does not have adequate negative predictive value and is associated with increased costs and resource utilization without showing any benefit in patient mortality (60).

Echocardiography should be performed in pregnant and post-partum women with suspected PE who have haemodynamic compromise to aid in diagnosis, risk stratification and to assess for alternate causes of haemodynamic instability. It does not replace direct pulmonary imaging and is not mandatory for the diagnostic work-up in stable pregnant women with suspected PE.

What clinical prediction tools are validated for women where PE is the most likely diagnosis?

The poor performance of existing clinical prediction tools is not necessarily a flaw in the tools but likely indicates the very low threshold that clinicians have to consider PE as a potential diagnosis. This is almost certainly related to the perception that PE is "common" in pregnancy but in fact it is an uncommon diagnosis. At the same time, missing a diagnosis of PE can be life threatening.

Outside of pregnancy, many strategies have been used to help in the "diagnosis" of pulmonary embolism using a combination of clinical features and diagnostic tests. In the non-pregnant population pre-test probability (PTP) assessment tools combined with a positive D-dimer gives excellent sensitivity and specificity (61). In reality, these are not true diagnostic strategies but tools which may be used to minimise harm/interventions without increasing adverse outcomes. This is a practical approach particularly in pregnancy where there is a large cohort of women with symptoms "suspicious" for PE but a very low incidence overall.

In the pregnant population, 4 studies have retrospectively reviewed the diagnostic accuracy of clinical decision-making tools in women that underwent diagnostic imaging for PE using either VQ scanning and/or CTPA (62-65). Three of these studies concluded that clinical prediction scores may be usefully applied to pregnant women with a possible diagnosis of PE and prospective studies should be considered, one did not.

Subsequent to these smaller studies, two large studies have attempted to devise modified pregnancy specific PTP (46,53).

In the Artemis trial from the Netherlands, suspected PE was defined by new onset or worsening chest pain, dyspnoea, haemoptysis or tachycardia and a total of 498 women were included in this study (46). The aims of the study were to reduce the use of pulmonary imaging by means of a simple clinical prediction tool; the pregnancy-adapted YEARS algorithm. This included only 3 criteria for stratification (% of study population who had this feature):

1. Clinical signs of deep-vein thrombosis (19%)
2. Haemoptysis (7.7%)
3. Pulmonary embolism as the most likely diagnosis (89%)

Two hundred and fifty-two of the 498 women had no YEARS criteria i.e. in 51% i.e. an alternate diagnosis was considered more likely. In this study, 4 women (0.8%) avoided imaging because they had a proven lower limb DVT (3/43 with signs of DVT and 1/79 without). The remaining 494 women were managed as per the planned algorithm. In the intention to diagnose analysis, 195 women avoided pulmonary imaging (39%), predominantly in the first trimester (48/74=65%). The equivalent rates were 46% in second trimester and 32% in the third trimester. Of those 195 women who did not have pulmonary imaging, only one VTE was diagnosed during the 3 months follow up period; a lower limb DVT at Day 90. Of the 299 women who underwent pulmonary imaging (all with CTPA), 5.4% had a PE. Of note, the clinical prediction of deep venous thrombosis was also relatively poor with only 3 DVTs diagnosed amongst 43 studies (7%) with compression ultrasonography. With such a low prevalence, it was not unexpected that the YEARS algorithm met the pre-test hypothesis that suspected PE could be safely managed using a clinical predictive tool modified for pregnancy.

In 2018, Righini et al published the results of an 8 year multicentre European study of pregnant women with suspected PE using the revised Geneva score and a high sensitivity D Dimer test as well as bilateral lower limb compression ultrasonography (CUS) (53). PE was "excluded" in patients with a low or intermediate pre-test 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. Three hundred and ninety-five women were included with a total of 28 PE diagnosed.

Four hundred and forty-one 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 in 7, positive CTPA result in 19 and high-probability V/Q scan in 2. It was excluded in 367:clinical probability and negative D-dimer result 46, negative CTPA 290, normal or low-probability V/Q scan 17 and other reason 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.

A *post hoc* analysis of the Righini cohort using the pregnancy-adapted YEARS algorithm also demonstrated a zero [0-3.9%] risk of "missed cases of PE" during follow up with a total of 21% of women potentially avoiding pulmonary imaging (66).

When assessed for accuracy of diagnosis, the various non-pregnant scoring systems although helpful outside of pregnancy, show both poor sensitivity and specificity when applied to pregnant and post-partum populations. The Di-PEP investigators assessed 3 clinical decision rules designed for pregnancy (by Delphi consensus) as well as 4 existing prediction tools and found areas under the receiver-operator curves (AUROC) ranging from 0.577 to 0.732 (27) . No clinically useful threshold for decision-making was identified for any of these rules. In this study, the Wells criteria had modest diagnostic value only if the a priori assumption ("that an alternative diagnosis is less likely than PE") was applied strictly [AUROC 0.732 (0.682-0.782)] with sensitivity of 38% and specificity 90%.

In an attempt to test the sensitivity and specificity of the YEARS and modified Geneva algorithms, the DiPEP study group did a secondary analysis of their data including only the prospective cohort of 219 pregnant women who had a D-dimer measured. However, as noted previously, most women in the DiPEP study received anticoagulation prior to blood sampling according to local guidelines, which may have affected D-Dimer results (40). If sensitivity is prioritised, both techniques were poor discriminators with the YEARS algorithm missing 5 of the 12 positives and the Geneva missing 3 (Table 4). Four out of the 5 "missed cases" had received LMWH prior to d-dimer testing and all cases were solitary/small or "likely" PE rather than multiple PE. They concluded that PTP rules could not be used to select women with suspected PE for diagnostic imaging. However, as the DiPEP authors themselves point out, "both the Righini and Van der Pol studies are management studies that estimate the risk of adverse outcome in women who have PE ruled out without imaging" rather than tests of the diagnostic accuracy of these tools.

Table 4: Sensitivity and specificity of PTP rules (the YEARS and modified Geneva algorithms) in the DiPEP population (40).

	Sensitivity% [95% CI]	Specificity % [95% CI]
Modified Years	58.3 [28.6-83.5]	44.0 [37.1-51.0]
Geneva/ D dimer	75% [42.8-93.3]	20.8% [15.6-27.1]

The 2019 ESC Guidelines for the diagnosis and management of acute PE and a clinical guide from Thrombosis Canada have endorsed the use of D-Dimer measurement and the modified YEARS clinical prediction rule to reduce the use of pulmonary imaging in women with low probability of PE (18, 67). In women with intermediate - high probability of PE, pulmonary imaging is still recommended, even with a negative D-Dimer.

Based on currently available data, the addition of D-Dimer testing will reduce the incidence of pulmonary imaging but may miss up to 40% of women with pulmonary emboli (40). Further studies are required to elucidate if D-dimer, performed prior to the administration of LMWH, may be used to assist in the diagnosis/exclusion of PE in pregnancy.

What is the best modality for Pulmonary Artery imaging for suspected PE in pregnancy?

The vast majority of pregnant or postpartum women who have chest imaging for suspected pulmonary emboli have negative studies with only 0.0 to 8.7% having a positive diagnosis in a range of studies (68). In a systematic review of patients presenting to the emergency department and thought to have PE, the rate of positive imaging for subjects with symptoms of PE was 4.1% [CI 2.6-6%] in pregnant women compared with 12.4 % [CI 9-16.3%] outside of pregnancy (69). In other words, most women who are even considered to have PE in pregnancy or post-partum have an alternate explanation for their symptoms.

In view of the discussion above regarding the difficulties of clinical assessment and prediction of PE in pregnancy, it is not surprising that in a review by Van Mens of 11 studies of imaging to diagnose PE, the overall rate of positive imaging was only 3.3% (range 0.0% to 8.7%) (68). In a more recent survey of 24 sites in the United Kingdom reflecting a period of 12 months from October 2014 to September 2015, 991 women were imaged, with only 48 positive scans (4.8%) (70). Sixty-three per cent of positive scans were in the third trimester although most inadequate/indeterminate scans were also in the third trimester. This is even less than the 2.1% rate of positive testing in young women, both pregnant and non-pregnant presenting with symptoms of PE to an Emergency Department (71). In a 2020 retrospective review of CTPAs performed for suspected PE in 1224 women aged 18-40 years, 105 women were pregnant and 134 were post-partum (72). The rate of CTPA positive for PE was less among pregnant patients compared to early post-partum and non-pregnant women of similar age: 2.9% vs 11.5% and 10.3%, respectively. The increased availability of imaging tests, mainly CTPA has led to a tendency to suspect PE much more frequently which is illustrated by historical rates of positive imaging of ~ 50% reported in the early 1980s. With this current low level of positive testing, the importance of minimising harm to both mother and fetus is paramount.

The decisions regarding specific imaging for PE in pregnancy are therefore complex and should be made by a consultant (Emergency, Physician, Obstetrician or Radiologist) who is experienced in the assessment of PE in pregnancy.

The choice of imaging is based on:

- maternal and fetal risks associated with the test (radiation and contrast agents)
- diagnostic value: sensitivity, specificity, rate of inconclusive results
- availability and cost.

A 2019 systematic review of pulmonary imaging for PE in pregnancy considered the relative merits of CTPA versus V/Q scanning based on diagnostic accuracy, rate of non-diagnostic tests and radiation risks (Table 5) (73). Due to the age and range of studies, direct comparisons with current techniques were difficult to predict but overall, neither technique was distinctly favourable. In Australia, V/Q_{SPECT} is more commonly used than V/Q Planar (46% compared with 15%), whilst the opposite is the case in New Zealand (74). The European Association of Nuclear Medicine (EANM) recommend V/Q_{SPECT} for the diagnosis of PE outside of pregnancy because of its superior sensitivity and specificity (75). In these systematic reviews, results of V/Q_{PLANAR} and V/Q_{SPECT} are reported together.

Table 5. Results of a systematic review of CTPA and V/Q imaging for PE in pregnancy (73).

	CTPA n=837	V/Q n=1270
Pooled negative predictive value	100%	100%
Rate of subsequent positive study	3	0
Pooled rate of non-diagnostic studies	12%	14%
Requirement for additional imaging after non-diagnostic first study	14-100%	0-62%

Subsequent to this systematic review (73), Sun et al described a 27.6% rate of suboptimal or inadequate contrast opacification of the pulmonary arteries by CTPA in their pregnant subjects compared with 33.6% in post-partum women and 15% in non-pregnant women of similar age ($p<0.001$) (72). There were also higher rates of motion artefact (19% pregnancy 10% post-partum and 11% non-pregnant, $p<0.05$). Overall, 2-3% of studies were considered non-diagnostic, similar between the 3 groups. These differences were not statistically significant.

The recent MBRRACE review identified a reluctance to ensure an appropriate response to non-diagnostic pulmonary imaging in women with suspected PE and one of their key recommendations for 2020 was to develop guidance regarding the need for a definitive radiological diagnosis in women who have an inconclusive imaging (3).

Low-dose perfusion-only scanning (LDQ) as a diagnostic procedure was studied by Sheen and colleagues in a retrospective cohort study of 322 pregnant women who underwent imaging for PE with LDQ (n-22) or CTPA (n=97) (76). They described a negative predictive value (based on VTE diagnosis within 90 days) of 100% for LDQ and 97.5% for CTPA. In this study, the

non-diagnostic rates were 9.3% for both modalities. Overall, there was a low rate of PE, 2.7% in the LDQ group and 4.1% in the CTPA group. The EANM suggest using a Q_{SPECT} only scan in the first trimester but standard V/Q_{SPECT} protocols after that (75).

In a quality comparison study of CTPA in early pregnancy versus late pregnancy, all arteries showed a significantly higher attenuation in early pregnancy and in the non-pregnant group compared to later in pregnancy ($p < 0.05$). Fewer suboptimal opacified arteries were found in early pregnancy (11.1%) and controls (5.7%) compared to later in pregnancy (33.3%),($p < 0.01$) (77). In a more recent UK survey, most inadequate/indeterminate scans were in the third trimester (6).

A recent retrospective cohort study compared Single-Energy CTPA (SE-CTPA) with Dual-Energy CT (DE-CTPA) in pregnant, post-partum and control women and demonstrated a reduced incidence of suboptimal studies with DE-CTPA (10 v 37% p=0.02), with the sub-optimal studies for DE-CTPA both being women weighing more than 190kg (78). The maternal radiation dose was equal with the 2 techniques. Again, the yield of positive studies was low at 3.4%.

Tester et al have commented that the variability between studies in rates of non-diagnostic imaging may be due to a number of factors including gestational age and different definitions of non-diagnosis (79).

A clinically important measure of diagnostic performance is the radiation dose per correct diagnosis, which takes into account the need for repeat or additional imaging studies. In a non-pregnant study comparing overall radiation burden, V/Q_{SPECT} (single photon emission computed tomography) was the most effective with a dose of 2.12 mSv per correct diagnosis compared with 3.46 mSv for V/Q_{PLANAR} and 4.96 mSv for CTPA (80). Data is not available for pregnant women but is likely to be similar.

Outside of pregnancy, there are concerns regarding over-diagnosis of PE, particularly following the introduction of CTPA which was associated with changes consistent with over-diagnosis: a 30% higher rate of positive scans than with V/Q, a rising incidence but minimal change in mortality, and lower case fatality (81). In particular, there was a doubling in the incidence of small, sub-segmental PE (SSPE) (82). With CTPA, a recent systematic review demonstrated a pooled prevalence of SSPE of 4.6% [1.8%–8.5%] (81). In those with only SSPE, there was no difference in VTE recurrence or death for patients who were not anticoagulated, however, the authors acknowledged this inference "is limited by small numbers, imprecision, and the lack of a controlled clinical trial". There is a total absence of data regarding management of SSPE in pregnancy and post-partum and the conservative approach would be to treat.

In non-pregnant subjects MRA has demonstrated good negative predictive value but a high level of inconclusive results (84). Newer techniques not requiring gadolinium are showing promise with low incidence of inadequate studies, and sensitivity of 90-93% with 100% specificity and this may be very suitable for pregnant women (85).

A comparison of the various imaging modalities and their efficacy and radiation dosage is presented in Table 6.

Table 6. Performance of various imaging modalities for the exclusion of PE in pregnancy (68,86,87,88).

Median [range]	Negative predictive value	Sensitivity	Frequency of inconclusive results (median)	Estimated fetal radiation absorbed dose (mGy)	Estimated maternal breast exposure dose (mSv)
CTPA	100% [96-100%]	83% [0-100%]	5.9% [0.9-36%]	0.01-0.1	10-70
V/Q	100% [99-100%]	100% [0-100%]	4.0% [0-23%]	0.01-1.6	<1.5
CXR and Q only (non-P)	83% [71-90%] 96.6% [95.5%–97.4%]	60% [41-76%] 80.4% [75.9–84.3%]	21-49% 0%	CXR .002-.43 + Q 0.35-0.55 =0.75-0.98	CXR 0.07-0.017+Q 0.6 =0.67
V/Q SPECT	*N/A*	*N/A*	0	0.08 (0.03–0.15)	0.56 (0.24–1.3)
MRA-only non-pregnant data available	95-99%	77-100% -poorer sensitivity for distal PE	30%	0	0
Pulmonary angiography				2.2-3.7	

[ ]: 95% Confidence Interval Non-P: Non-pregnant data, CTPA Computerised Tomography pulmonary angiography, V/Q Ventilation Perfusion nuclear scan, SPECT Single-photon emission computed tomography, MRA Magnetic Resonance Angiography, N/A Not available, Q perfusion only scan

Maternal and Fetal Risk

Apart from ultrasound assessment for DVT or Echocardiography for cardiac assessment, all imaging for PE involves radiation exposure. The only non-radiation option for pulmonary artery imaging is MRI/MRA which may rarely have a role.

Although risks such as extravasation or anaphylaxis are possible with direct imaging for PE, it is the risk associated with radiation that is considered the major issue (89). Table 7 summarises the fetal and maternal breast doses associated with the various imaging modalities. Improved radiographic and nuclear medicine techniques have led to a reduction in both maternal and fetal radiation doses in the last 10 years (90). Breast radiation exposure from CTPA may be reduced by approximately 50% with the use of thin bismuth radioprotective shielding to breasts (91).

Technical advance in CT technology have dramatically reduced radiation exposure without reducing image quality e.g. reducing the CTPA contrast-monitoring component which particularly reduces breast dosage (92). Breast doses as low as 3-4mGy may be achieved (18) and a recent local study in Australia has calculated absorbed breast doses as low as 0.23 mSv (personal communication). The OPTICA study (Optimised Computed Tomography Pulmonary Angiography in Pregnancy Quality and Safety study) will assess an optimised low-dose CTPA protocol for use in pregnancy but is yet to report (93).

Table 7. Estimated absorbed dose for maternal breast and fetus from CT and nuclear imaging for PE (90).

Target organ dose (mGy)	CTPA non-contrast	CTPA contrast enhanced	Perfusion SPECT scan only	V/Q SPECT
Estimated maternal breast dose	12	22	0.25	0.50
Estimated fetal absorbed dose by gestation				
Early	0.16	0.21	0.14	0.18
3 months gestation	0.20	0.28	0.20	0.25
6 months gestation	0.43	0.73	0.25	0.31
9 months	0.42	0.57	0.20	0.25

Fetal Risk

Fetal radiation doses from most correctly performed diagnostic procedures for investigation of pulmonary embolus are below 1mSv and present no measurably increased risk of miscarriage, genetic damage, developmental damage, congenital malformation (94). If the procedure or cumulative procedures lead to a potential fetal dose greater than 10mGy, conservative estimates indicate an increased risk of childhood cancer from 20 per 10000 to 21 per 10000. Put another way, for every 1667 exposures of 10mGy there may be 1 additional case of childhood leukemia increasing to 1 in 834 at fetal total dose exposure of 20mGy. More recent research has suggested that the extrapolation from higher dose radiation risks down to these very low dose radiation exposures; the Linear No Threshold (LNT) Hypothesis is not supported by current biological and epidemiological data (95). Critics of the LNT hypothesis use convincing biological and epidemiological data to demonstrate the absence of risk in the low and very low dose range where the shape of the dose-response curve is uncertain. Despite this relatively convincing data, most National authorities recommend health risks from radiation even at low doses be determined based on the LNT hypothesis as a prudent approach to radiation protection for patients and workers (96) .

In summary, both CTPA and V/Q scans impart very low fetal radiation risks. This could be considered negligible compared with the risks of PE in pregnancy.

Maternal Risk

Previous assessments have estimated the lifetime risk of breast cancer from a dose of 20 mGy to the breast is approximately 1/1200 at age 20, 1/2000 at age 30, and 1/3500 at age 40. The lifetime additional risk from CTPA with a breast dose of 20 mSv dose in a 30-year-old woman is estimated as 1/2000 compared with a V/Q scan dose of 1.0 mSv that increases risk by 1/40,000. This figure is not very high, but studies have suggested that this rate is 7 times higher in the pregnant woman (and potentially the lactating woman) and hence should be considered in the diagnostic algorithm (86, 97). With modern techniques as discussed above, the risk, if any, with breast doses of 3-4mGy is substantially lower than these estimates.

Recent data regarding tissue weighting have estimated breast radiation doses to be 20–60 mGy for a CT examination performed for PE (90, 98). A retrospective database linkage study from Ontario assessed the one-year risk of breast cancer in women exposed to low dose chest radiation during pregnancy or up to 6 weeks post-partum (99). A total of 5859 pregnancies were exposed to thoracic CT, 4075 to VQ scan and more than 1 million to neither. The median duration of follow-up was 5.9, 7.3 and 11.1 years in the three groups respectively and there was no statistically significant increased risk for breast cancer in either exposed group with this relatively short follow-up.

Contrast agents

CTPA requires the administration of iodinated contrast to both mother and fetus as the contrast crosses the placenta and recirculates in the amniotic fluid (100). The use of non-ionic contrast agents has significantly reduced the risk of adverse maternal reactions which vary from mild (3% of patients) to severe (0.04%) with fatal reactions being extremely rare (1 in 1:170,000) (89). A theoretical risk of hypothyroidism exists for the fetus and neonate exposed to iodinated contrast media in utero, although no adverse neonatal outcomes have been demonstrated (101-103).

The European Society of Urological Radiologists and American Society of Radiology both recommend continuing breastfeeding after the administration of iodinated contrast media although the data on which this is based is very limited (104). In breastfeeding women: only tiny amounts of iodinated contrast medium (<0.01%) given to a lactating mother reach the milk, and only a minute proportion enters the baby's gut.

No significant risk has been demonstrated with the radiopharmaceuticals involved in V/Q scans. Women should be informed that radiopharmaceuticals used for V/Q scanning contain albumin ^{99m}Tc-MAA, a blood product.

After V/Q scanning, there is considerable variability in milk radioactivity, and close contact with an infant may result in additional exposure. A conservative recommendation suggest expressing and storing breast milk for at least 12 hours after which it may be used safely (105).

In the case of MRA using gadolinium, a minimal amount (0.04%) of the intravenous dose reaches human milk, and, of that, less than 1% to 2% is absorbed by the infant. Therefore, breastfeeding can be continued without interruption after the use of iodinated contrast or gadolinium (106).

Current recommendations regarding pulmonary imaging for PE in pregnancy and post-partum

Currently the major international organisations representing nuclear physicians recommends a perfusion-only study using a reduced administered activity of 18.5–37 MBq (0.5–1mCi) of Tc99m-MAA for pregnant women with likely PE and normal or mildly abnormal chest radiograph, and even with a severely abnormal chest radiograph consider perfusion only (107). This is in contrast to a range of international guidelines which have recommended V/Q as the preferred imaging modality for suspected PE in pregnancy despite low quality evidence: American College of Obstetrics and Gynecology (106), American Thoracic Society (45) , American Society of Thrombosis and Hemostasis (16), Society of Obstetricians and Gynaecologists of Canada (108) whilst others recommend either V/Q or CTPA: Royal College of Obstetrics and Gynaecology (19), European Society of Cardiology (18) European Association of Nuclear Medicine (75).

Counselling and obtaining informed consent for pulmonary imaging

The requesting clinician or suitable specialist needs to communicate the potential risks and benefits of pulmonary imaging and ensure informed written consent prior to referral to the radiologist or nuclear physician. This should include a realistic estimate of the potential radiation dose to herself and her fetus (Table 7), the maternal and fetal risks of this estimated dose and the benefits of the imaging procedure. They must clearly respond and document any questions or concerns. As all pulmonary imaging involves doses below 1mGy to the fetus, clinically indicated investigations should not be withheld during pregnancy. All allied staff must also be well informed to ensure the patient receives a consistent message about the risks and benefits of the proposed test.

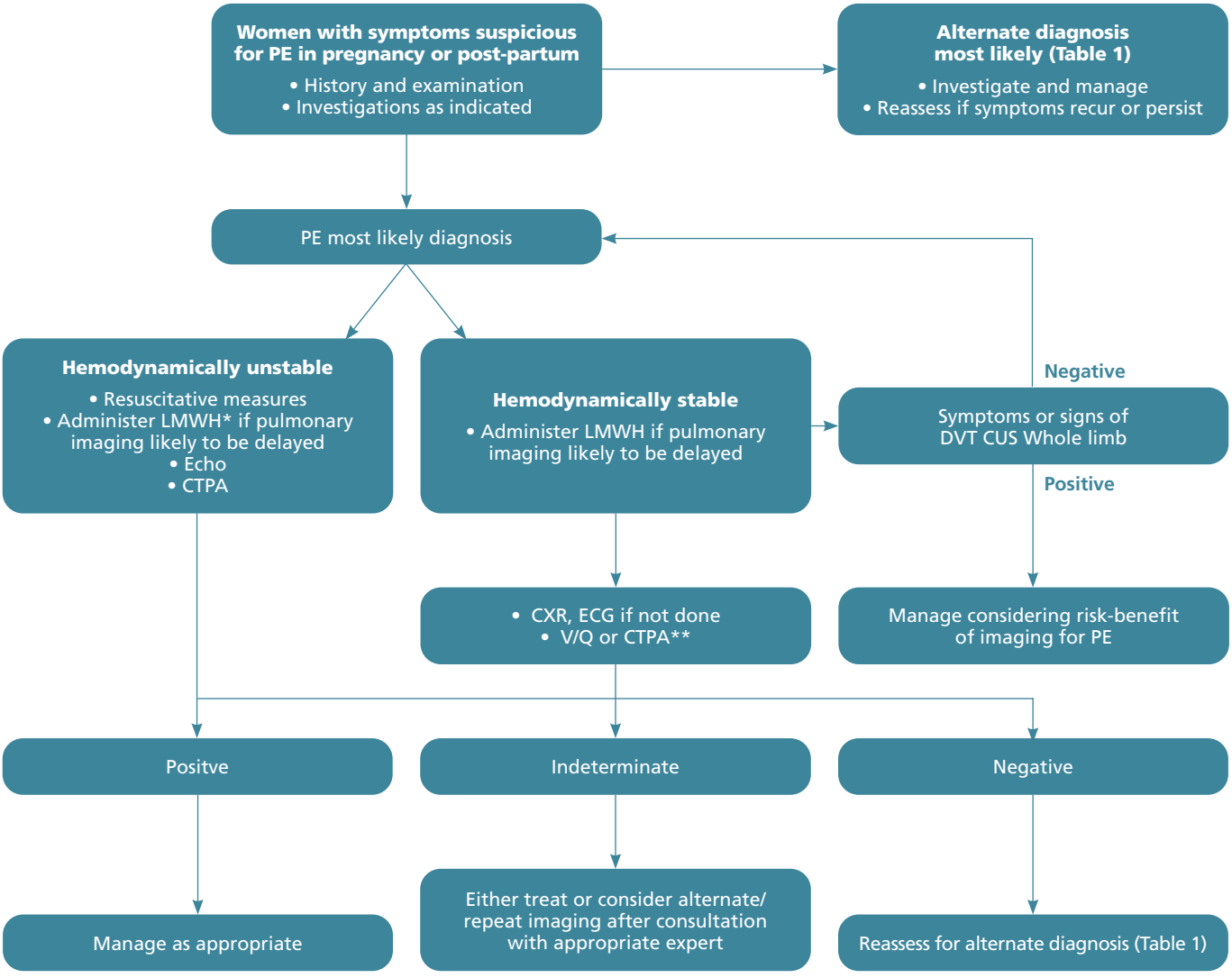
RECOMMENDATIONS

Based on the preceding data, we have devised an assessment algorithm (Figure 2) that is practical and applicable in most resource settings. However, we recognise this model has not been validated.

- The finding of a more likely alternate diagnosis than PE will substantially reduce the number of women having pulmonary imaging but should not prevent further investigation if symptoms/signs persist or recur. Similarly, after negative pulmonary imaging, an alternate explanation should be sought for the woman's symptoms/signs.
- Assessment for DVT in women with symptoms/signs of peripheral VTE should be performed prior to pulmonary imaging in haemodynamically stable subjects
- Although the fetal and maternal risks of pulmonary imaging are very low, its use should be restricted to women where the diagnosis of PE is considered most likely.
- As the most likely positive criteria in the Artemis study was "PE as the most likely diagnosis" (89%), this has been used as the main criteria in this algorithm to stratify the need for pulmonary imaging.
- The addition of D-dimer testing after determination that "PE is the most likely diagnosis" is not recommended at this time.
- Therapeutic LMWH should only be administered prior to pulmonary imaging in hemodynamically unstable women or if pulmonary imaging is not immediately available.

- V/Q and CTPA are both safe and appropriate pulmonary imaging techniques and the choice of modality may be based on local availability and experience.
- V/Q scanning, if available, may be preferred in hemodynamically stable women with a normal CXR because of a lower rate of non-diagnostic studies, particularly in the third trimester as well as a lower maternal breast dose.
- CTPA is the preferred imaging modality in hemodynamically unstable women or if other pulmonary pathology is suspected.
- A cardiac echo may be done first in haemodynamically unstable women if clinically appropriate and readily available.
- The choice of CTPA versus V/Q in breastfeeding women requires counselling regarding a very low but possible increased risk of breast cancer with the higher breast doses associated with CTPA versus the requirement to pump and store breast milk for 12 hours after administration of Tc99m-MAA for V/Q scanning.
- Modifications of standard imaging compared with non-pregnant practise e.g. low dose perfusion only scanning or modified CTPA are not necessary as the fetal and maternal radiation doses from standard imaging are already very low.
- Decisions regarding management and repeat imaging for indeterminate results should be made in consultation with a senior, experienced clinician
- If multiple investigations are performed, a cumulative fetal and maternal breast radiation dose should be calculated.
- Consider non-gadolinium MRA if radiation or contrast are contraindicated

Figure 2: Diagnostic workup and management of women with suspected PE during pregnancy and post-partum (pp). * single dose of therapeutic LMWH may be administered if pulmonary imaging is indicated but not immediately available ** V/Q preferred over CTPA if CXR normal and procedure equally available.



MANAGEMENT

Can non-pregnant risk stratification algorithms be used for pregnant/post-partum women with PE?

The intention of risk stratification of women with PE in pregnancy and post-partum is to ensure the most appropriate level of monitoring and the availability of specialised services e.g. intensive care, interventional radiology, ECMO, in order to reduce adverse outcomes for both mother and baby.

The most basic clinical risk stratification uses blood pressure to stratify women with PE into normotensive and hypotensive cohorts. In pregnancy, the diagnosis of hypotension must be modified to recognise the physiological fall in blood pressure that occurs from early pregnancy. Median (3rd–97th centile) heart rate is lowest at 12 weeks' gestation: 82 (63–105) bpm, rising progressively to a maximum of 91 (68–115) bpm at 34 weeks (Table 8) (20).

Table 8. Normal upper limits for HR, RR, BP in pregnancy (20).

Median [3rd-97th centile]	12 weeks	19 weeks	34 weeks	40 weeks
Sys BP	114 [95-138]	113 [95-136]	-	121 [102-144]
Dias BP	70 [56-87]	69 [55-86]	-	78 [62-95]
Heart rate	82 [63-105]	-	91 [68-115]	-

For pragmatic reasons, a cut-off of ≤90 mmHg systolic blood pressure represents hypotension in the context of sepsis and may be considered an appropriate cut-off in the context of PE in pregnancy (25). Similarly, a heart rate of >105bpm (<12 weeks' gestation) and >115 bpm (>12 weeks' gestation) may be considered abnormal in the context of proven PE in pregnancy, depending on gestation.

A number of prognostic tools are commonly used to classify non-pregnant patients with PE into high-, medium- or low-risk categories. In a recent publication, the prognostic value of 7 available tools was applied to a subgroup of subjects under the age of 50 years from the RIETE database of PE subjects from 2001 to 2017 (109). This included 297 women identified as pregnant or post-partum from the total of 5822. Overall, the majority were deemed low risk (between 48.6-95.9% depending on the tool) and the 30-day mortality rate was low (1.43%). This compared with a case fatality rate of 3.5% [95% CI 1.1–8.0%] found in the 2008 UKOSS survey of pregnant women with PE (6).

High sensitivity troponin (hsTn) and pro-BNP or NT pro-BNP are promising markers of adverse outcome, conferring a 10% risk of early death and 23% risk of adverse clinical outcome in unselected non-pregnant populations with PE (111). Levels of both hsTn and BNP are unchanged in normal pregnancy. In a meta-analysis investigating 1680 patients with PE, H-FABP concentrations ≥6 ng/mL were associated with an adverse short-term outcome (OR 17.7 [6.0-51.9]) and all-cause mortality (OR 32.9 [8.8-123.2] (112). None of these biomarkers have been validated for their prognostic value in a pregnant cohort.

In summary, clinical risk stratification of women with PE in pregnancy must take into consideration the altered physiological normal ranges of pregnancy. A systolic blood pressure ≤ 90mm Hg and/or heart rate >110 bpm and/or hypoxemia should warrant closer monitoring. None of the current commonly used risk stratification scoring tools have been validated for use in pregnancy. Cardiac biomarkers may have a role in the future and warrant further research.

Who should care for women with confirmed PE in pregnancy and post-partum?

Women with symptoms suspicious for PE may present to a range of clinicians including Maternity Caregivers, General Practitioners or Emergency Physicians. Assessment and management should be undertaken by clinicians with suitable experience of the investigation and management of PE. This may include a Haematologist, Respiratory Physician, Obstetric Physician or General Physician. The ongoing management of the pregnancy or post-partum period in a woman with confirmed PE must include a Consultant Obstetrician. Additional advice may be required from an Obstetric Anaesthetist.

The primary Maternity Caregiver i.e. Obstetrician, Midwife or General Practitioner should also be involved with ongoing management where suitable.

In women with massive PE or haemodynamic instability, urgent consultation an Intensivist, Interventional radiologist or Cardiothoracic Surgeon may be required. In some centres this will be managed by a multidisciplinary Pulmonary Embolism Response Team.

Where should management of women with confirmed PE take place?

All pregnant women with proven PE should be admitted to hospital for initial management including regular clinical and haemodynamic monitoring, symptom management and anticoagulation (109, 113).

The duration of admission will be dependent on:

- the response to initial treatment
- control of symptoms
- the ability of the woman to self-administer therapy
- any obstetric concerns

The appropriate setting i.e. general ward, maternity ward, high dependency or intensive care should be based on local resources and the availability of haemodynamic monitoring for both mother and baby and the likelihood of more intensive interventions. Where fetal monitoring is required, the availability of staff to interpret and act on this if required is imperative.

Post-partum, women should ideally be cared for in a setting that allows ongoing contact with her baby and suitable support for breast feeding if this is appropriate.

What is the appropriate therapy for PE in pregnancy and post-partum?

The treatment of PE in pregnancy is based on heparin anticoagulation because heparin does not cross the placenta. Low molecular weight heparins are preferred due to their more predictable pharmacokinetics and risk profile although in some situations e.g. around the time of birth, unfractionated heparin may be used.

The management of symptoms of PE may require modification in pregnancy. Pleuritic chest pain may be difficult to manage in pregnancy. Nonsteroidal anti-inflammatories are often used outside of pregnancy but should be avoided during pregnancy due to the fetal risks associated with premature closure of the ductus arteriosus (114). They may be given post-partum. For pregnant women, alternate analgesia, including opioids, may be required for days or even weeks.

If PE is confirmed

- Commence weight-adjusted therapeutic dose of LMWH (see Table 9)
  - Check FBC, UEC, coagulation prior to commencing treatment
  - Pharmacokinetic changes of pregnancy result in a reduced anti Xa activity (115).
  - The choice of pre-pregnancy versus current weight can lead to a significant variation in dosing. Whilst the RCOG recommend early pregnancy based weight dosing (19), the SCOG use current weight (17). No data is available to support either recommendation. In view of the pharmacokinetic changes resulting in lower anti-Xa activity in pregnancy and because weight at onset of therapy is easily obtained, this is the recommendation of SOMANZ.
  - Twice daily dosing has been considered the standard in pregnant women. Once daily versus twice daily dosing with enoxaparin, nadroparin or dalteparin has not been compared directly but observational studies in pregnant women with acute PE have not demonstrated any increase in the risk of recurrence with a once-daily regimen compared with twice-daily schedules (116). Once-daily therapy may simplify administration and enhance compliance in women up to 80kg body weight.
  - Following initial treatment for 3-6 months depending on severity, both the Society of Obstetrics and Gynecology of Canada and a previous Australian guideline have suggested that anticoagulation intensity may be decreased to intermediate or prophylactic for the remainder of the pregnancy and for at least 6 weeks postpartum (17, 117), although this is based on non-pregnant evidence only (118). No evidence for or against using this strategy in pregnancy is available but particularly around the time of birth, management will be potentially impacted by full versus reduced intensity anticoagulation.

Table 9. Anticoagulation dosage for PE

Drug/Dose#	Initial treatment-at least 3 months	Intermediate	Prophylactic
	Therapeutic dosage	Consider dose reduction after 3-6 months	
Enoxaparin	1mg/kg every 12 hours or 1.5mg/kg daily (max 120mg)	0.75mg/kg 12 hourly or 1mg/kg daily	40mg daily
Dalteparin	100U/kg every 12 hours or 200U/kg daily	75 U/kg bd or 150 U/kg daily	5000U/daily
Nadroparin	86U/kg every 12 hours or 171U/kg daily	65U/kg bd or 121U/kg daily	2850U/daily

based on weight at time of commencement of therapy
All therapy given as subcutaneous injection

- Monitoring of anti-Xa levels is not required except in the case of renal dysfunction, extremes of weight e.g. >90kg or <50kg or Antithrombin deficiency (16, 119) . There are no trials of the optimal "therapeutic anti-Xa LMWH range" in pregnancy and dose-adjustments have not been demonstrated to increase the safety or efficacy of LMWH therapy.
- The risk of heparin induced thrombocytopenia in pregnant women treated with LMWH alone is low (less than 0.1 %) (120), Monitoring of platelet counts in pregnant women on LMWH is not required.
- Fondaparinux may be considered if there is an allergy or adverse response to LMWH, although minor transplacental passage has been demonstrated (121). The ASH recommends danaparoid as an alternative agent (15).
- Vitamin K antagonists should not be used for management of PE in pregnancy but may be used post-partum even when breast feeding. Women prescribed warfarin must receive appropriate education regarding drug interactions and monitoring, prior to discharge from the hospital

- **Direct oral anticoagulants are contraindicated in pregnancy and whilst breastfeeding.**

Haemodynamically unstable patients

- Unfractionated heparin (UFH) may be considered for initial treatment in specific scenarios e.g. in unstable patients with PE or when the risk of bleeding is high (109, 122). In non-pregnant studies, LMWH was associated with a reduced incidence of recurrent thrombotic complications and major haemorrhage during initial treatment compared with adjusted dose UFH (123).
- Pharmacokinetic properties of UFH are altered in pregnancy such that pregnant women require higher daily doses of UFH than non-pregnant women. Heparin or anti-Xa levels (targeted range 0.35-0.67 U/mL) may provide more accurate dosing but are not readily available (124). Most units will have protocols for administration of therapeutic UFH based on APTT levels (targeted range 60-85 seconds) and these may be used with the exception of women with an abnormal APTT prior to therapy e.g. in women positive for lupus anticoagulant.

- Thrombolysis and thrombectomy are feasible at almost all stages of pregnancy and should be considered for the same indications as non-pregnant subjects (see below)
  - Pregnant women have been excluded from clinical trials with thrombolytics, and all data available in this population are published as case reports or case series. A recent systematic review included 127 cases of severe PE during pregnancy (and until 6 weeks post-partum) treated with thrombolysis, thrombectomy, and/or ECMO (125) Twenty three per cent of these cases experienced cardiac arrest. The survival rates were 94% following thrombolysis and 86% after surgical thrombectomy. Major bleeding occurred in 18 and 58% of cases during pregnancy and in the post-partum period, respectively. Fetal deaths occurred in 12% of the cases following thrombolysis and 20% following thrombectomy respectively.
  - The use of thrombolysis for PE in pregnancy has been limited to high-risk or life-threatening PE. Catheter-directed thrombolysis offers several advantages over systemic thrombolysis, the most significant of which is a reduced risk of bleeding, but no data suggest it should be preferred over systemic therapy (18). All current International guidelines recommend thrombolysis be used for life threatening or massive PE only. Recombinant tissue plasminogen activator and streptokinase have minimal transplacental passage whilst urokinase is a small molecule which does cross the placenta. Alteplase appears to be the best option for systemic thrombolysis in pregnancy due to its availability, properties, and pharmacokinetic profile (126).
  - Thrombolysis post-partum can result in uncontrolled bleeding and should be reserved for life-threatening events.
- Indications for inferior vena cava (IVC) filters are similar to those for non-pregnant patients e.g. acute PE and contraindications to anticoagulant therapy e.g. imminent birth, surgery or recurrent PE despite therapeutic anticoagulation
  - Retrievable (IVC) filters have a role in the prevention of lethal pulmonary emboli when anticoagulation is contraindicated or has failed. A literature review of the use of IVC filters in pregnancy identified a total of 43 cases (127). There were no instances of pulmonary embolus after placement of the IVC filter and complications were uncommon including thrombosis of the filter (2.3%) and perforation of the IVC (7.0%). Failure to retrieve the filter occurred more commonly in pregnancy than in non-pregnant historical controls (26% vs. 11%, p = 0.006) and carries additional risks including long term anticoagulation.

What is the recommended duration of anticoagulation for confirmed PE?

There have been no studies assessing optimal duration of anticoagulant therapy for treatment of pregnancy-related PE. In non-pregnant subjects with PE, particularly with a provoking event which would include pregnancy, a treatment duration of 3 months would be considered appropriate. A more prolonged period of treatment may be considered if additional risk factors are present (see above). Given the increased risk of VTE in pregnant women and following birth, all current guidelines suggest that treatment should be continued until at least 6 weeks post-partum.

A recent systematic review described 4 four studies in which pregnant women with symptomatic VTE were transitioned to intermediate-dose LMWH (less than 75 % of a full treatment dose but greater than prophylactic dose) within 6 weeks of VTE diagnosis. They reported a low risk of VTE recurrence (1/ 152) but the studies included only 4 women with PE. The Canadian guideline also suggests an option to reduce further to prophylactic dosage after a period of therapeutic anticoagulation (Evidence Grade III) (109).

No high-level evidence is available to guide dose reduction but it may be considered particularly if the PE has occurred early in pregnancy and 3 months therapy has been completed.

What additional obstetric/fetal monitoring is required for women with PE?

- The type and frequency of fetal monitoring will be determined both by the gestation and severity of maternal illness.
- In the acute setting of pulmonary embolism associated with maternal hypoxia, efforts to restore maternal oxygen status will benefit the fetus (128). Whilst abnormalities in the cardiotocograph may be detected during an episode of acute maternal hypoxia, efforts to improve the maternal status should be regarded as a priority rather than expediting birth on fetal grounds in an unwell mother.(128, 129)

- In the absence of hemodynamic instability or hypoxia, no additional monitoring or investigation beyond routine antenatal care is required for women diagnosed with PE in pregnancy. If the mother has been unstable, additional fetal growth monitoring would be considered prudent.

What are the management options for birth for women with confirmed PE in pregnancy?

Birth in the setting of life-threatening PE

Pulmonary embolism per se is not necessarily an indication for immediate birth, however, in women with life threatening pulmonary embolism, expediting birth may be considered essential to improve the maternal resuscitation efforts. In the case of massive pulmonary embolism with cardiac arrest, a perimortem caesarean section should be performed within five minutes if resuscitation is unsuccessful in a woman in whom the gestation is considered to be above 22-24 weeks or the uterus is palpable 3cm above the umbilicus (130). While at very early gestations, neonatal survival may not be expected, evacuation of the uterus may improve venous return to the heart and has been associated with return of spontaneous circulation (131).

Non-urgent birth: timing and mode

The mode of birth in stable women with PE should be determined on standard obstetric grounds and caesarean section should not be recommended simply on the basis of the presence of a pulmonary embolism. Where caesarean birth is required, careful tissue handling and meticulous attention to intraoperative haemostasis is essential to minimise the risk of subsequent haematoma formation when anticoagulants are recommenced post-partum (92).

Management of birth in women on therapeutic anticoagulation requires careful planning by a multidisciplinary team including an Obstetrician, Physician and Anaesthetists.

The woman and her partner should also be active participants in this decision making with the aim to optimise her birth experience in the safest manner possible.

Planning requires an individual risk assessment of

- The likely mode and timing of birth including the risk of spontaneous labour particularly preterm
- The risks of bleeding both antenatal and post-partum versus the risks of further/recurrent thrombosis or emboli during any period off anticoagulation.
- In a systemic review including 2777 pregnant women using prophylactic and therapeutic dose of LMWH, 0-3.0% had any maternal bleeding either antenatal or postpartum (120). In the much larger group of women on prophylactic LMWH, the rate of maternal bleeding was 0-16%. In another systematic review (132) including 18 studies with a total of 981 pregnancies, the weighted mean incidence (WMI) of major bleeding was 1.41% [0.60–2.41%] antenatally and 1.90% [0.80–3.60%] during the first 24 h after birth. In this same review, the estimated WMI of recurrent VTE during pregnancy was 1.97% [0.88–3.49%], of which 7 of the 16 cases occurred during the acute phase of treatment. In a retrospective cohort study, the incidence of post-partum haemorrhage (PPH) >500 ml was 18% in women using LMWH users and 22% in those who did not use LMWH [RR 0.8; 95% CI 0.5–1.4] (133). A more recent meta-analysis of the efficacy and safety of anticoagulant drugs for treatment of VTE in pregnancy (134) included 9 studies with a total of 834 cases and 3424 controls. There were no significant differences in the incidence of prenatal haemorrhage (OR 1.08 [0.84–1.40] or VTE (OR 1.30 [0.72–2.33] between the case group and the control group. The incidence of pulmonary embolism was significantly higher in the case group than in the control group (OR 3.90, 95% CI 1.23–12.34). The rates of PPH were not reported.
- The likelihood of Caesarean birth or other interventions during labour
- The relative or absolute requirement for neuraxial analgesia/anaesthesia
- The relative location of the woman and appropriate services e.g. access to 24-hour blood banks, high level obstetric and anaesthetic care
- Appropriate consultation with an anaesthetist prior to birth
- Access and support from Pathology services i.e. ability to measure anti-Xa levels urgently, blood bank facilities, management plan for haemorrhage.

Management of women on therapeutic or intermediate dose anticoagulation will usually require planned birth to allow cessation/management of anticoagulation. It is recognised that some women will labour spontaneously or require urgent Caesarean section prior to the planned birth time and appropriate management plans must be documented for both possibilities.

- Planned induction/Caesarean section before onset of spontaneous labour allows appropriate cessation of therapeutic LMWH, the option of conversion to unfractionated heparin in high risk women i.e. PE within last 14 days (135), minimises bleeding risk and allows neuraxial analgesia/anaesthesia if desired/required (see Table 11). The disadvantages of this approach are that onset of labour is not predictable and induction may result in a prolonged period off anticoagulation with a potential increased risk of recurrent VTE.

- The occurrence of spontaneous onset of labour or urgent Caesarean section may reduce the period of time off anticoagulation but may mean that appropriate staffing and resources may be inadequate out of hours and the timing may not allow appropriate cessation of LMWH which may increase bleeding risk and may prevent the use of neuraxial analgesia/anaesthesia with increased risk of general anaesthesia. Alternate analgesia/anaesthesia must be considered for these situations.
- The planning and documentation for both planned versus spontaneous onset of labour/urgent Caesarean section should be made well in advance i.e. from at least 36 weeks gestation.
- A written multidisciplinary plan should be made after appropriate counselling by a senior consultant obstetrician and physician (Obstetric/Haematologist/General) and anaesthetist and midwife (see Appendix 1).
- All women will require a consultation with an Anaesthetist at or before 36 weeks gestation including discussion of alternate options to neuraxial analgesia/anaesthesia
- Protamine sulfate can result in full reversal of UFH but only partial reversal of LMWH. (136). Advice should be sought from a Haematologist if rapid reversal is required.

Previous studies have highlighted that many patients receiving UFH or LMWH were off treatment for significantly more than the recommended 24 hours prior to neuraxial analgesia placement potentially increasing their risk of thrombosis (137). In a retrospective cohort study of women on LMWH thromboprophylaxis, 26/100 women went into spontaneous labour before planned induction at 38-39 weeks (138). Only 3 were unable to have a neuraxial anaesthesia when respecting the 12 hour delay between the last injection of LMWH and the need for anaesthesia (138). In a larger more recent retrospective study, there were 138 women on LMWH (81 prophylaxis/intermediate dose and 57 therapeutic dose) and 51 who switched from LMWH to UFH prior to birth (42 prophylaxis/intermediate, 9 therapeutic) (139). There was no difference in the 2 groups in terms of rates of neuraxial anaesthesia type 82.4% versus 79.7%. Only 2% of women in each group required a general anaesthetic because of recent administration of either LMWH (3/138) or UFH (1/51). In addition, there was no difference in rates of bleeding complications (6% versus 10%), re-laparotomy due to haemoperitoneum (2% in both groups) and the complications were similar in the two groups regardless of time of last injection. The rates of preterm birth (17.6% versus 24.6%) were the same in the 2 groups and similar to their control population. Preliminary results on 587 women who participated in the Highlow study showed that in only 2.4% of women the time interval was too short to receive neuraxial anaesthesia in patients using prophylactic-dose LMWH and in 6.0% of patients using intermediate-dose LMWH (140).

Management of birth in women on therapeutic anticoagulation requiring urgent/unexpected delivery

- Perform all standard pregnancy assessments
- Consult specialist obstetrician and obstetric anaesthetist urgently
- Cease anticoagulation
- Measure antiXa (LMWH) or APTT (UFH) urgently if available
- Determine if labour or Caesarean section can safely be suppressed/delayed to allow time for anticoagulant effect to reduce with time
- Ensure appropriate IV access, Group and Hold/ Crossmatch depending on risk of bleeding
- Consult haematologist/physician urgently regarding management of
  - reversal of anticoagulation if indicated
  - timing of recommencement of anticoagulation after delivery if not previously determined
- Monitor closely for bleeding during and after labour/surgery.
- Post birth care should be in a high acuity setting

How should you plan for and manage neuraxial anaesthesia/analgesia in women on treatment for PE in pregnancy?

One of the most critical issues for women receiving treatment for PE in pregnancy is analgesia/anaesthesia for labour and birth. As described above, in 2 previous studies the rate of neuraxial anaesthesia were ≥80% including a significant group of therapeutic anticoagulation prior to birth and only 2 of women required a general anaesthetic because of the recent administration of either LMWH or UFH (138, 139).

The Society for Obstetric Anaesthesia and Perinatology (SOAP) has published "Consensus Guidelines on the Anaesthetic Management of Pregnant and Post-partum Women Receiving Thromboprophylaxis or Higher Dose Anticoagulants" (141) . This has considered the numerous existing International guidelines as well as the altered pharmacokinetics of UFH and LMWH in pregnancy (Table 10).

The equivalent Australian guideline is not prescriptive but recommends "Clinical assessment of the patient's coagulation status and anticoagulant medications is required in all circumstances as many regional analgesic techniques may have serious complications in the presence of a coagulopathy, for example, epidural hematoma, and retroperitoneal haematoma from lumbar plexus blocks. Laboratory investigations should be undertaken where appropriate"(141)

- If neuraxial blockade is not appropriate/safe, alternative analgesia should be available e.g. opioid based intravenous patient-controlled analgesia with appropriate local protocols for their use.

Table 10. Recommended timing of cessation and recommencement of anticoagulation in pregnancy (141). *Recommend assessment of coagulation in high risk women eg renal insufficiency

ANTICOAGULANT - DOSE	Last dose recommendation-hours before neuraxial block (hours)	Emergency/Urgent and less than recommend hold period		Check coagulation status* prior to neuraxial block	Removal of epidural catheters	
					From last dose (hours)	Before recommencement (hours)
LMWH – prophylactic dose	12	Consider not proceeding with neuraxial-balance potential risk of spinal/epidural hematoma with risk of GA		Consider	12	4
LMWH – intermediate	12-24	Insufficient data to guide therapy		Yes	24	4
LMWH - therapeutic	24	Consider not proceeding with neuraxial-balance potential risk of spinal/epidural hematoma with risk of GA		Yes	24	4
UFH - intravenous	4-6			Yes		1
UFH - -prophylactic dose	4-6	Check APTT		Consider	4-6	1
		Normal-proceed with neuraxial block	Raised-balance potential risk of spinal/ epidural hematoma with risk of GA			
UFH - intermediate	24	Check APTT		Consider	4-6	1
		Normal-balance potential risk of spinal/ epidural hematoma with risk of GA	Raised - consider not proceeding with neuraxial block			
UFH - therapeutic dose	24	Check APTT-minimal data to guide decision - consider not proceeding with neuraxial block		Yes	4-6	1

How should women with PE be managed after birth?

Immediate post-partum:

- The requirement for removal of an epidural catheter as well as the risks of post-partum vaginal or wound haemorrhage/ hematoma will influence the timing and dosage of anticoagulation post-partum (see Table 10)
- Prophylactic dose LMWH can be restarted at 6-12 hours after birth, providing there is full neurological recovery and no evidence of active bleeding or coagulopathy (104)
- The decision to recommence therapeutic or intermediate dose anticoagulation should be made by a senior obstetrician. The risk of bleeding is greater with intermediate and therapeutic than lower dose LMWH
- Therapeutic intravenous adjusted dose UFH (without a bolus) may be considered as an option in women at high risk of recurrent VTE or bleeding. This may be restarted within 4-6 hours but only after review by a senior obstetrician
- The first dose of intermediate/therapeutic LMWH should be given no sooner than 12-24 hours post-partum. A prophylactic dose may be given in the interim
- Indwelling neuraxial catheters removal should occur a minimum of 12 hours after the last prophylactic dose of LMWH or 24 hours after the last therapeutic dose. Subsequent dosing should occur a minimum of 4 hours after catheter removal.
- As an alternative for women requiring more urgent therapeutic anticoagulation, e.g. after recent PE or recurrent PE on prophylactic dosage, adjusted dose intravenous UFH may be commenced after 1-hour post-partum, without a bolus, according to local protocol including monitoring APTT regularly

Women diagnosed with PE during pregnancy need to continue their treatment for a minimum of 6 weeks post-partum. The risk of VTE remains elevated after birth and fatal VTEs have been documented out to week 6 post-partum but not after that (19). They must also complete a total minimum of 3 months of treatment as described above.

After 24-48 hours; the main options for the choice of anticoagulants in a breastfeeding woman are low molecular weight heparin (LMWH) or warfarin. Warfarin is not found in breast milk hence is safe in breastfeeding, and while LMWH is found in breast milk in small amounts, it has a poor oral bioavailability and is therefore considered safe in breastfeeding (114). The use of warfarin will require ongoing, regular monitoring with blood tests to ensure a therapeutic range is achieved.

Women need to complete at least their 3-6 months therapeutic LMWH, depending on severity, but after that, may be reduced to a prophylactic dose until 6 weeks post-partum. Women on warfarin are recommended to maintain an INR of 2-3.

- Oral direct thrombin (e.g., dabigatran) and factor Xa inhibitors (e.g., rivaroxaban, apixaban) are found in significant quantities in breast milk and are orally bioavailable to the infant. They are generally not recommended for breastfeeding women but may be used if a woman chooses or is unable to breastfeed (16). On the basis of a small number of case reports indicating low breast milk concentrations of rivaroxaban, Lactmed have updated their advice such that "if rivaroxaban is required by the mother, it is not a reason to discontinue breastfeeding. However, until more data become available, an alternate drug may be preferred" (143).

What are options for contraception for women with previous PE in pregnancy or post-partum?

The aims of contraception advice for women with a history of PE are to ensure safe, effective contraception with minimal side effects and reversibility if desired; whilst not increasing her risk of further thromboembolic events. This requires the clinician to have expert knowledge of the potential effects of different contraceptive options on the risk of recurrent VTE. Relevant co-morbidities such as obesity, sexual health risks, patient preference, potential adverse effects and availability of medications and procedures may influence contraceptive options. Although some contraceptives carry no additional risk of VTE, the risk associated with pregnancy due to contraceptive failure may outweigh any perceived benefit.

The risks of VTE with non-hormonal contraception e.g. male or female barrier methods, fertility awareness, sponges, spermicides and sterilisation are assumed to be equal to non-users. Combined oral contraceptive use has been associated with a two to sixfold increased risk of VTE in a number of studies. (144-148), with a higher risk of DVT than PE. Despite their convenience, this increased risk means the COC is unsuitable for women who have already experienced PE (148). The estrogen containing vaginal ring is similarly contra-indicated. The World Health Organisation has classified all estrogen containing contraceptives including COCs and even vaginal rings as Category 4 i.e. not to be used whilst all other methods are acceptable.

The World Health Organization and the Center for Disease Control and Prevention advocate the use of all progestin-only contraceptives in women at risk of VTE despite several studies raising concerns regarding an increased risk of VTE with depot medroxyprogesterone (MDPA) or injectable preparations and their use in high risk population merits further investigation (149).

Table 11 summarises the important information to guide contraceptive choice for women with previous PE. Those in green are recommended, in red contra-indicated and in orange may be considered if better options not acceptable/available.

Table 11. Contraceptive information to consider for women with previous PE (149, 150).Green recommended, orange consider, red contraindicated.

TYPE OF CONTRACEPTIVE	Reversible	Breast feeding compatible	Efficacy with real world "common" use	Women on long term anti-coagulation
Levonorgestrel intra-uterine device	Yes	Yes	99.80%	
Progestin only implant	Yes	Yes	99.90%	May reduce menstrual blood loss
Progestin only oral (POP)	Yes	Yes	91-93%	
Copper IUD	Yes	Yes	99.20%	Menorrhagia
Depot medroxyprogesterone (DMPA)	Yes	Yes	96%	May reduce menstrual blood loss
Combined oral contraceptive (COC)	Yes	No	93%	
Oestrogen containing vaginal ring	Yes	No	93%	
Barrier methods (male and female)	Yes	Yes	87% male 79% female	
Male or female Sterilisation	No	Yes	99.9% (Male) 99.5%(Female)	
Post coital Emergency contraception	N/A	Yes	98-100%	

Although there may be differences in VTE risk between products with different progestogens, the absolute risks are very small(147). The contraceptive efficacy of progestin contraceptives however do vary by the type of preparation, with unintended pregnancy rates of 9% with oral POP and 0.2% with LNG-IUDs (150).

- Previous PE is not a contraindication for post-coital emergency contraception.(151) including oral progestin and copper IUDs

Based on these data, SOMANZ recommends the following contraceptive advice for women with a history of PE during or outside of pregnancy:

For women desiring reversible contraception

- LNG-IUD is the most efficacious option for women with a risk of VTE and is an appropriate first line choice for multiparous women and selected nulliparous women.
- Alternative progestin only contraceptives including progestin only oral contraceptives, progestin-only implants, depot medroxyprogesterone acetate intramuscularly may be considered based on patient preference
- Other contraceptive options, including barrier methods and fertility awareness, do not increase risk of VTE but generally have lower efficacy.

For women not desiring further pregnancies

- In addition to the above options, female or male sterilization may be a suitable choice.

For women on long term anticoagulation:

- Women on therapeutic anticoagulants are at increased risk of menorrhagia and its consequences.(152, 153) In theory the increased risk of a recurrent VTE while taking COCs should be decreased with therapeutic doses of anticoagulants, however no direct evidence is available to support this.(154) All the above options may be considered but the LNG-IUD had the potential benefit of reducing menstrual blood loss by 79–96% (152, 155)
- Expert counselling may be indicated for women at increased risk of contraceptive failure e.g. obesity, previous bariatric surgery or women with additional thrombotic or bleeding risk factors.

What preconceptual advice should women receive following a diagnosis of PE in pregnancy?

Women who have experienced a previous VTE in pregnancy have a high rate of recurrence (4.5%) antenatally and post-partum. Thromboprophylaxis with LMWH has been estimated to reduce this risk by 75%. Women with a past history of PE in pregnancy or at any time in the past, should undergo pre-pregnancy counselling so that they are aware of the need to commence LMWH as soon as a viable pregnancy is confirmed (usually 6-8 weeks amennorrhoea). They will need ongoing review once pregnant.

A subgroup of women with previous PE in pregnancy or recurrent VTE will be taking longterm anticoagulation e.g previous VTE on thromboprophylaxis or antiphospholipid syndrome. Appropriate contraception should be advised for any woman receiving warfarin or a DOAC for prevention of VTE (see above). Both warfarin and the direct oral anticoagulants are not recommended in pregnancy due to risk of embryopathy/fetopathy (114). Elective pregnancy termination for fear of DOAC embryotoxicity is not recommended as evidence for a specific teratogenic effect is limited (156). Appropriate counselling and pregnancy surveillance is recommended for women who fall pregnant while on warfarin or a DOAC.

If these women are planning a further pregnancy, they should be advised to cease oral anticoagulant therapy either

1. immediately after a missed period and confirmation of pregnancy and/or within 6 weeks amennorrhoea (19) or
2. perform regular pregnancy tests and cease after confirmation of pregnancy (113).

These women will require either therapeutic or intermediate dose LMWH commencing 1-3 days after cessation of oral therapy. The decision regarding LMWH dosing should be made by a suitable clinician eg haematologist, obstetric physician or general physician; preferably pior to pregnancy. Seeking haematological expertise to help generate this plan is recommended.

All plans for VTE prophylaxis with LMWH in pregnancy should include advice regarding management of anticoagulation in the event of vaginal or other bleeding in early pregnancy.

Women who need to undergo assisted reproductive treatment (ART) to conceive, and have a history of pregnancy related PE, will be at have an increased risk of VTE during ART and any subsequent pregnancy (157). Additional risk factors during ART include aggressive stimulation, elevated oestradiol levels, hCG as a trigger, ovarian hyperstimulation, occurrence of pregnancy, multiple pregnancy, and use of exogenous estrogen. These women should receive LMWH prophylaxis commenced in conjunction with controlled ovarian stimulation. Intermediate or therapeutic dose LMWH should be considered if moderate-severe ovarian hypertstimulation occurs. A recommended schedule has been suggested by Nelson (158).

What audit tools should be considered for quality review of the investigation and management of PE in pregnancy?

1. Documentation of risk factors in women presenting with symptoms suspicious for PE in pregnancy
2. Management of therapeutic anticoagulation peripartum in women with PE in pregnancy:
   - Evidence of multidisciplinary team plan including anaesthetic consultation
   - Documentation of peripartum plan before 36 weeks
   - Audit of appropriate cessation, recommencement of anticoagulation as per plan to restart treatment dose anticoagulation
3. Rates of post-partum haemorrhage/haematoma/thrombosis in women on anticoagulation for PE in pregnancy anticoagulation
4. Evidence of contraception counselling prior to discharge.

What are future research considerations in this field?

1. Does the addition of D-Dimer testing have a role in ruling out PE in pregnancy and post-partum?
2. How should therapeutic anticoagulation be managed in the peripartum period?
3. What is the appropriate duration of anticoagulation therapy for PE in pregnancy and post-partum? Is dose reduction after 3 months therapy safe?
4. What is the risk/benefit with once daily versus twice daily dosing of therapeutic LMWH in the treatment of PE in pregnancy? Is there a role for biomarkers to risk-stratify PE in pregnancy e.g. troponin, BNP?
5. Does the use of the SOMANZ algorithm reduce the use of pulmonary imaging and does this impact on subsequent diagnosis/incidence of VTE?
6. Do DOACS have a role in the management of PE in pregnancy or in breastfeeding women?
7. What are the normal physiological changes in coagulation following birth and when do they return to normal?

APPENDIX 1

Peripartum management plan for women with pulmonary embolism in pregnancy receiving therapeutic anticoagulation

An individualised peripartum management plan should be developed and represents the communication and consultation record of the discussion between all relevant members of the treating team and the woman. The plan should be in place at least 4 weeks prior to the expected date of delivery. It should include the following information and be recorded in the patient medical record and a copy given to the woman. The plan should be reviewed regularly and updated if required.

Baseline information

- Estimated date of confinement (EDC)
- Gravidity and parity status and previous birth outcomes or complications
- Obstetrician / Multidisciplinary Team members
- Emergency out of hours/on call contact
- Planned mode of birth and gestation (date and time)
- Current obstetric/other medical/psychosocial concerns
- Current anticoagulation (type and dose) and indication (including date of commencement, planned duration)

Peripartum management plans: must cover both

  - Planned birth – vaginal or caesarean
  - In the event of preterm spontaneous labour / premature rupture of membranes/other indication for urgent delivery

The plan must include the following advice/information:

Intrapartum

- Intended mode and timing of birth
- Specify who must be informed at time of planned/unplanned birth e.g. specialist obstetrician, obstetric anaesthetist
- In the event of preterm spontaneous labour / premature rupture of membranes/other indication for urgent delivery: advice if labour or Caesarean section can safely be suppressed/delayed to allow time for anticoagulant effect to reduce with time
- Ensure appropriate IV access, Group and Hold/ Crossmatch depending on risk of bleeding
- Planned cessation of anticoagulation-date, time, laboratory assessment ie antiXa, APTT
- In event of preterm spontaneous labour / premature rupture of membranes/other indication for urgent delivery:
- Consult haematologist/physician urgently regarding
  - temporary management of anticoagulation
  - reversal of anticoagulation if indicated
  - timing/dosing of recommencement of anticoagulation
- Planned analgesia/anaesthesia-alternate plan if neuraxial not an option, specify recommended timing of insertion and removal of neuraxial catheters relative to anticoagulation doses
- Specify any additional monitoring -maternal and fetal

Postpartum

- Requirement for higher acuity observation post-delivery

Planned anticoagulation after delivery: -drug, dose, timing, monitoring, duration

  - initial 24 hours
  - after 24 hours

- Monitor closely for bleeding during and after labour/surgery.
- Contraception plan
- Plans for follow up and preconception planning

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