

Workshop

Antenatal medical management
and diagnosis.

Aims of workshop

- Improvement in the assessment and management of medical disorders occurring in pregnant women.
- Improvement in knowledge of potential teratogenic medications commonly taken by women of child bearing age.

Hypertension in early pregnancy

- Case One
- 35 year old – G1P0
- Missed period by 6 days, +ve Bhcg
- Chronic hypertension
 - Previous investigations normal
 - On Cilazapril 5mg daily
 - Booking BP 150/92

Questions

- What would you advise this woman about pregnancy risks?
- Would you continue her antihypertensive medication. If so – what would you use.
- Would you advise any other additional medication?
- What level of antenatal care would you advise?

Antihypertensives

Increasing incidence of hypertension in women
childbearing age

- Obesity
- Increasing maternal age (15-50!!!)
- Assess need to treat – aim $< 150/95$ unless underlying renal disease/diabetes.
 - 2nd trimester BP drop allows stopping of medication.
- Four main groups used
 - Methyldopa
 - B blockers (Labetolol or Metoprolol)
 - Ca channel blocker (Nifedipine, Diltiazem)
 - Alpha blockade (Prazosin)



Chronic hypertension risks

- Increased rates of placental insufficiency and its complications (10-30%)
 - Preeclampsia
 - IUGR
 - Preterm delivery
 - Highest risk in severe hypertension, underlying renal or autoimmune disease.

ACE inhibitors/receptor blockers

- Clear evidence of 2nd and 3rd trimester effects – interfere with fetal renal function
 - Fetal renal failure
 - Oligohydramnios
 - Lung hypoplasia/limb contractures
- 1st trimester – 2.7x risk of fetal malformations (7.1% vs 2.6%)
 - Mainly CNS and cardiac

Table 2. Risk of Major Congenital Malformations among Study Infants According to Fetal Exposure to Antihypertensive Medications during the First Trimester Alone.*

Variable	ACE Inhibitor (N = 209)	Other Antihypertensive Medication (N = 202)	No Antihypertensive Medication (N = 29,096)†
Any congenital malformation			
No. of infants	18	4	834
Percentage of births	7.12	1.73	2.63
Risk ratio	2.71	0.66	1
95% confidence interval	1.72–4.27	0.25–1.75	Reference
Cardiovascular malformation			
No. of infants	9	2	294
Percentage of births	2.90	0.70	0.78
Risk ratio	3.72	0.89	1
95% confidence interval	1.89–7.30	0.22–3.59	Reference
Central nervous system malformation			
No. of infants	3	0	80
Percentage of births	1.46	0	0.33
Risk ratio	4.39	—	1
95% confidence interval	1.37–14.02	—	Reference
Other malformations			
No. of infants	6	2	469
Percentage of births	2.71	0.95	1.55
Risk ratio	1.75	0.62	1
95% confidence interval	0.79–3.89	0.15–2.45	Reference

* Infants could have both cardiovascular and central nervous system malformations and be included in these groups; the other malformations group included only infants without cardiovascular or central nervous system malformations. The proportions and risk ratios are adjusted for potential confounders. Models include maternal age, race, presence or absence of a chronic illness, rural or urban residence, and income quartile and the year of the child's birth. The estimation accounts for clustering due to a woman with either multiple pregnancies during the study period or a multiple-gestation pregnancy.

† Infants in this group had no fetal exposure to antihypertensive medications.

Recommendation

- Avoid ACE inhibitors/receptor blockers in women of child bearing age unless there is no other alternative.
- If overwhelming indication to prescribe then need
 - Clear advice to detect pregnancy and plan to stop/swap medication immediately.
 - Adequate contraception.

Prevention of complications

- Preeclampsia/iugr cannot be accurately predicted or prevented
 - Aspirin (low dose) – risk reduction 15%
 - Calcium – risk reduction especially if they have a low calcium diet
 - Low dose pregnancy multivitamins.
- Specialist level care/supervision advised.

Case 2

- 26 year old woman
- Wants to get pregnant in the next year.
- History of generalised epilepsy.
- Seizure free for 3 years on Epilim 1200mg daily.
- Previous normal EEG and MRI scans.

Questions

- What are the risks of her medication in pregnancy?
- How could you reduce this risk?



Sodium Valproate

- Large registries recently reported – UK, USA, Australia.
- Confirm much higher rate of teratogenicity than other older AEDs.
- 10-17% with monotherapy – including all malformations. 1-2% neural tube defects
 - Tegretol monotherapy 2-4%

Vajda, F. J. E. & Eadie, M. J.
Maternal valproate dosage and foetal malformations.
Acta Neurologica Scandinavica **112** (3), 137-143.

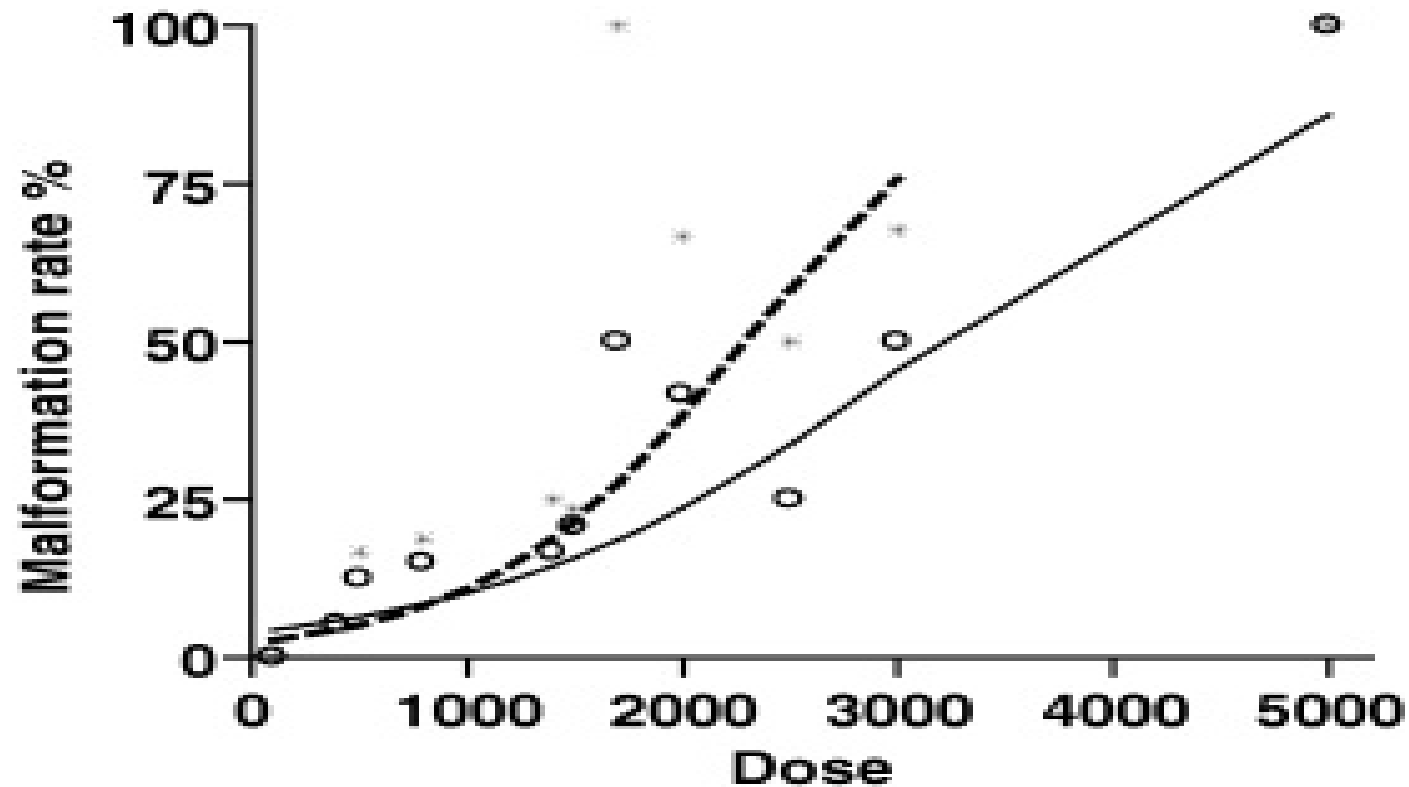


Table 2 The more common foetal malformations encountered

Malformation	Comparisons		P (Fisher's exact test)
	Valproate (<i>n</i> = 165)	Other AEDs & no AEDs (<i>n</i> = 337)	
Spina bifida & sacral clefts	6	0	0.0012
Hypospadias	6	1	0.0060
Heart abnormalities	8	1	0.0008
Cleft palate	3	0	0.0360
	Valproate <1401 mg/day (<i>n</i> = 110)	Valproate >1400 mg/day (<i>n</i> = 55)	
Spina bifida & sacral clefts	0	6	0.0011
Hypospadias	0	6	0.0011
Heart abnormalities	1	7	0.0021
Cleft palate	2	1	1.00
	Valproate <1401 mg/day (<i>n</i> = 110)	Other AEDs & no AEDs (<i>n</i> = 337)	
Spina bifida & sacral clefts	0	0	—
Hypospadias	0	1	0.754
Heart abnormalities	1	1	0.432
Cleft palate	2	0	0.061

Advice to women with epilepsy - prepregnancy

- Review medications before conception.
 - Major seizure control is vital
 - Continuous folic acid 5mg.
- If possible
 - Monotherapy or trial off therapy
 - Avoid valproate especially in combination
 - Adequate contraception
- Unplanned pregnancy – early referral by phone – early anatomy scans.

So in this woman....

- Consider several options
 - Trial off therapy – recurrence rate of seizures around 40% over two years – driving advice.
 - Switch to Tegretol – slow transition and driving advice.
 - Conceive on Epilim but try to reduce dose.
 - Don't conceive!!!

Case 3

- 34 year old mother of two.
- Presents at 8/40 gestation in unplanned pregnancy.
- On Paroxetine 40mg for severe anxiety disorder with depressive features.
 - Read on the internet that her baby will have major abnormalities.

Questions

- What is the actual risk of congenital abnormalities in this pregnancy?
- Should she stop her medication acutely?
- What addition to antenatal care might be advisable?

Consequences of poor diagnosis and treatment

- Maternal effects
 - poor antenatal care attendance
 - illicit drug use
 - poor nutrition, sleep, self-care
 - increased post-partum depression
 - risk of psychosis
 - suicide risk

Adverse effects of depression on offspring

- Impaired maternal-infant bonding
- Anxiety effects on fetal development
- Genetic predisposition to mood disorder
 - 1.5 to 3 times higher rate

Management

- Psychotherapy
- Family therapy
- Social support
- Pharmacotherapy
- Risks weighed against risk of untreated disorder

General rules

- Use single agents at lowest doses where possible - reduce doses very slowly
- Avoid newly released medication unless risk of change or discontinuation is high
- Do not stop psychoactive drugs abruptly
 - withdrawal effects common (30%)
 - relapse higher

Composite SSRI data

- USA Birth Defects Prevention Study (1997-2001)
 - increased rates of omphalocele (OR 3.0) and craniosynsotosis (OR 1.8).
- Swedish Medical Birth Registry
 - 4,291 exposed in 1st trimester - no difference in malformation rates
- Danish data
 - increased abnormalities esp cardiac malformations (OR 1.6)

Paroxetine specific data

- Retrospective data on 3581 women exposed to antidepressants in 1st trimester
- Paroxetine cf others
 - all malformations increased by OR 2.2
 - cardiovascular malformations doubled with 10/14 having VSD. AR is 1.5%
- Swedish National Registry data
- 2 fold increase for cardiac abnormalities. Overall rate 2% vs 1%.
- Majority ASD and VSD.

Paroxetine label warning

- Clear warning re use in first trimester
- Data from both retrospective databases presented.
- “The prescribing physician will need to weigh the option of alternative treatments in women who are pregnant or planning to become pregnant”

What other options are there?

- Citalopram - total of over 1000 early pregnancy exposures
 - no increased risk of congenital malformations
- Sertraline
 - limited data available (about 150 cases) but “clean” so far
- Venlafaxine (bicyclic)
 - 125 first trimester exposures only
- Trazodone and Nefazodone
 - 121 live births
- Bupropion
 - 266 first trimester exposures on registry

Neonatal behavioural syndrome

- 18 case reports of abnormal neonatal behaviour with maternal 3rd trimester exposure
 - Paroxetine exposure in 11/18
 - Tremors, jitteriness, shivering, increased tone, feeding disturbance, agitation, respiratory distress.
- FDA/WHO reports a further 284 possible cases

Neonatal behavioural syndrome

- Controlled cohort studies
- Five studies - late SSRI exposure carried an overall neonatal behavioural syndrome risk ratio of 3.0. One study suggested a 13% incidence.
- SCBU admissions increased.
- No severe cases but possible increased seizure rate

Prevention

- Consider tapering of drug dose in last trimester
- Preferably two weeks prior to delivery
- Resume medication at usual dose immediately postpartum.
- BUT optimal treatment of maternal depression must remain the primary concern.

Treatment of affected neonates

- Recognise risk of syndrome
 - Advise paediatricians
 - Educate parents re shortlived minor symptoms
 - Encourage maternal/neonatal close contact
 - Low light, quiet environment with frequent feeds
- Severe cases rare - may need anticonvulsants, fluids, respiratory support.

Recommendations

- If possible, avoid paroxetine exposure in first trimester
- Use of fluoxetine or citalopram is, as yet, not associated with increased abnormality rates
- Consider careful reduction/withdrawal of SSRI in third trimester - restart in immediate post-partum.

Breastfeeding

- Shorter acting SSRIs have not been shown to cause concerns in breastfeeding mother/infant pairs.
 - ?potential to reduce any withdrawal effect in offspring
- Fluoxetine and metabolites may have more significant effects on serotonin levels in offspring, due to longer half life
 - Not clear yet what this means in long term.

Case 4

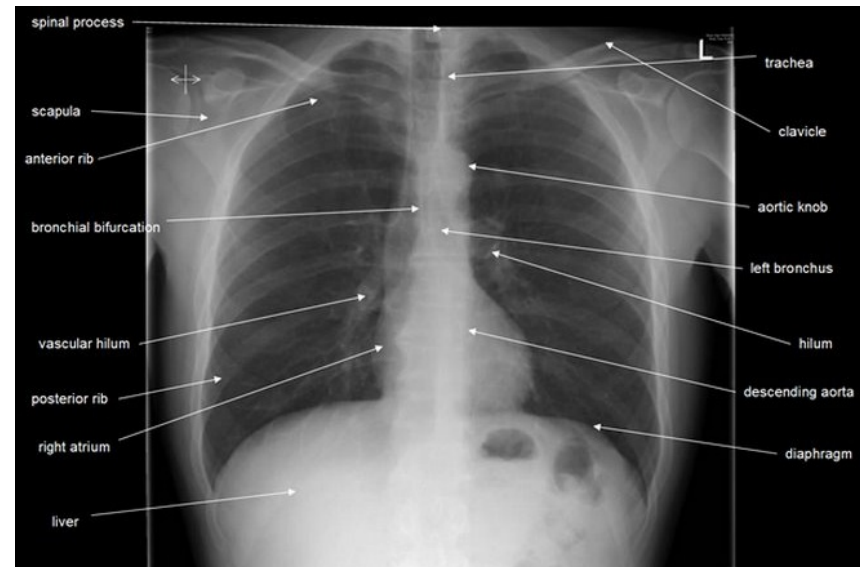
- 35 year old primigravida
- 32 weeks gestation, weight 110kg.
- Presents with acute SOB and pleuritic chest pain.
 - Tachycardic 90/min, RR 16/min
 - Chest clinically clear, legs normal.
- Refer to hospital - ?PE
 - Phone call – “they want to scan my chest!!”

To x-ray or not

- Always concern to limit radiation exposure in pregnancy to a minimum

BUT

- Can lead to lack of diagnostic certainty and subsequent maternal morbidity.



Two examples

- 22 yr old polynesian primip. SOB/wheeze at 17/40, admitted.
 - ECG abnormal
 - No CXR performed – diagnosis “bronchitis”
 - Worsened over pregnancy, despite increased asthma treatment.
 - Readmitted with uncontrolled AF
 - ECHO – severe rheumatic heart disease.

Second example

- 32 year old non-smoking multip
- Cough, increasing SOB over pregnancy from 6/40 gestation.
- Reviewed by three specialist physicians
 - No CXR performed
- At 28/40 developed worsening stridor
- CXR – obstructing lung tumour.

Radiation Exposure in pregnancy

- The fetal radiation risk is proportional to the stage of gestation and absorbed dose
 - Teratogenicity threshold $>100\text{mSv}$
 - Fetal dose $>1000\text{mSv}$: mental retardation/microcephaly
 - Oncogenesis: 40% increase over the normal incidence of malignancy with doses $>10\text{mSv}$
 - No increased IUD/stillbirths
- Aim for levels less than 1mSv

Radiation Exposure in Pregnancy

	Fetus (mSv)	Mother (mSv)
Mobile Phone Microwave Computer screen	0	0
Short-haul flight		0.001-0.003mSv/hr
Long-haul flight		0.005mSv/hr
Perfusion scintigraphy 99mTc-MAA	0.2-0.6	1.0
Ventilation scintigraphy 99mTc-aerosol	0.3-1.2	0.5
CTPA Single section	0.03-0.06	1.6-4.0
CTPA Multi-section	0.01-0.02	4.0-6.0
Chest Xray	<0.01	<0.01
Conventional pulmonary angiography	>0.5	5-30

Pulmonary Embolism in Pregnancy

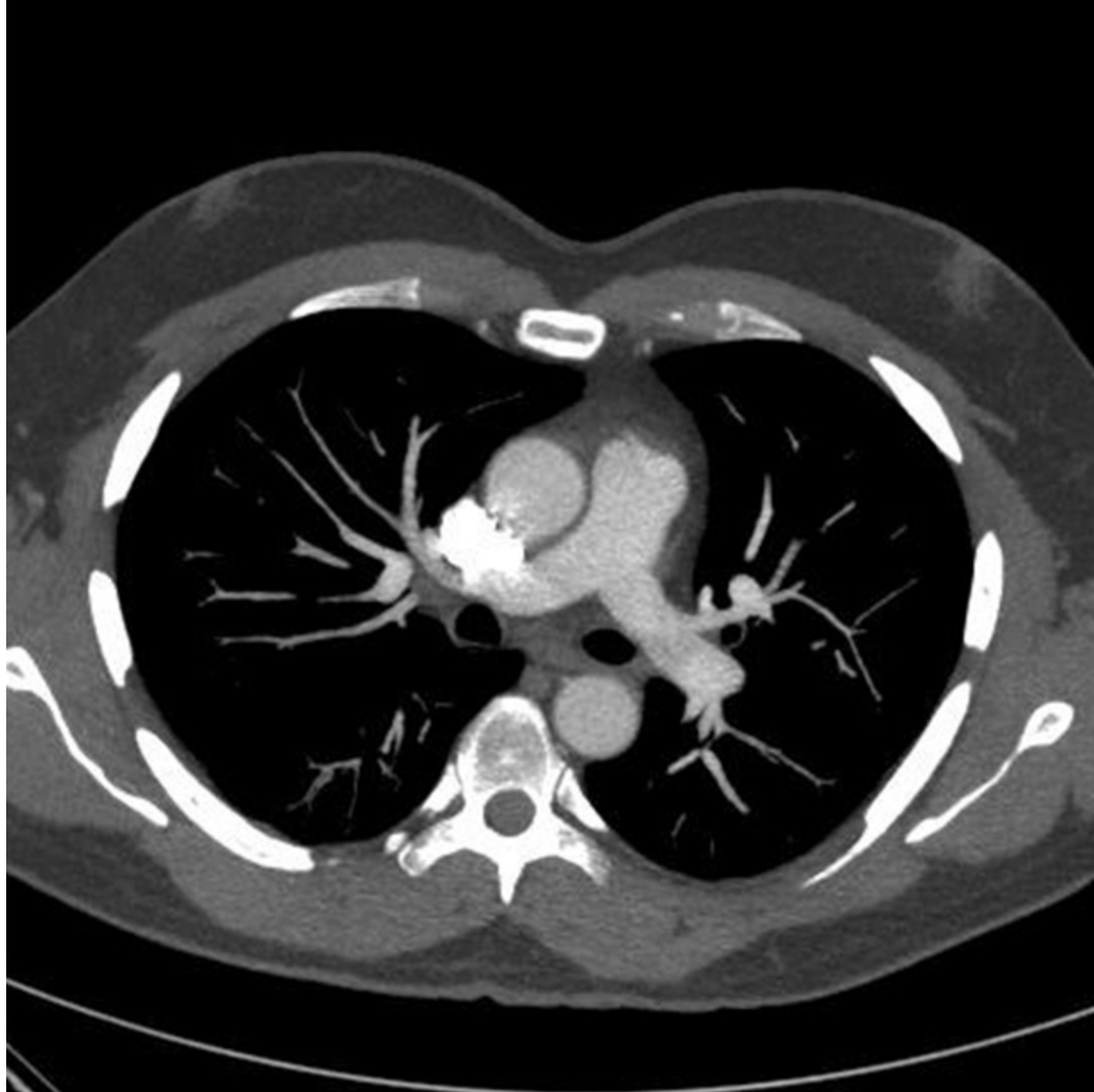
- The risk of VTE in pregnancy is increased 2-4 fold
- It remains a leading cause of maternal mortality
- Reported incidence 1:5,882

The clinical diagnosis of PE in pregnancy

- Non-thrombotic leg or respiratory symptoms are very common in pregnancy
- Routine lab studies, chest Xray, ECG and ABG lack sensitivity and specificity
- Many tests extensively studied in the non-pregnant population but not appropriately validated in pregnancy

D-Dimer testing in pregnancy

- D-Dimer assays have a high negative predictive value in non-pregnant patients with suspected VTE
- Limited value in pregnancy as the D-Dimer level gradually increases during normal pregnancy
- D-Dimer levels go beyond the normal threshold after 16/40, and return to normal four weeks postpartum



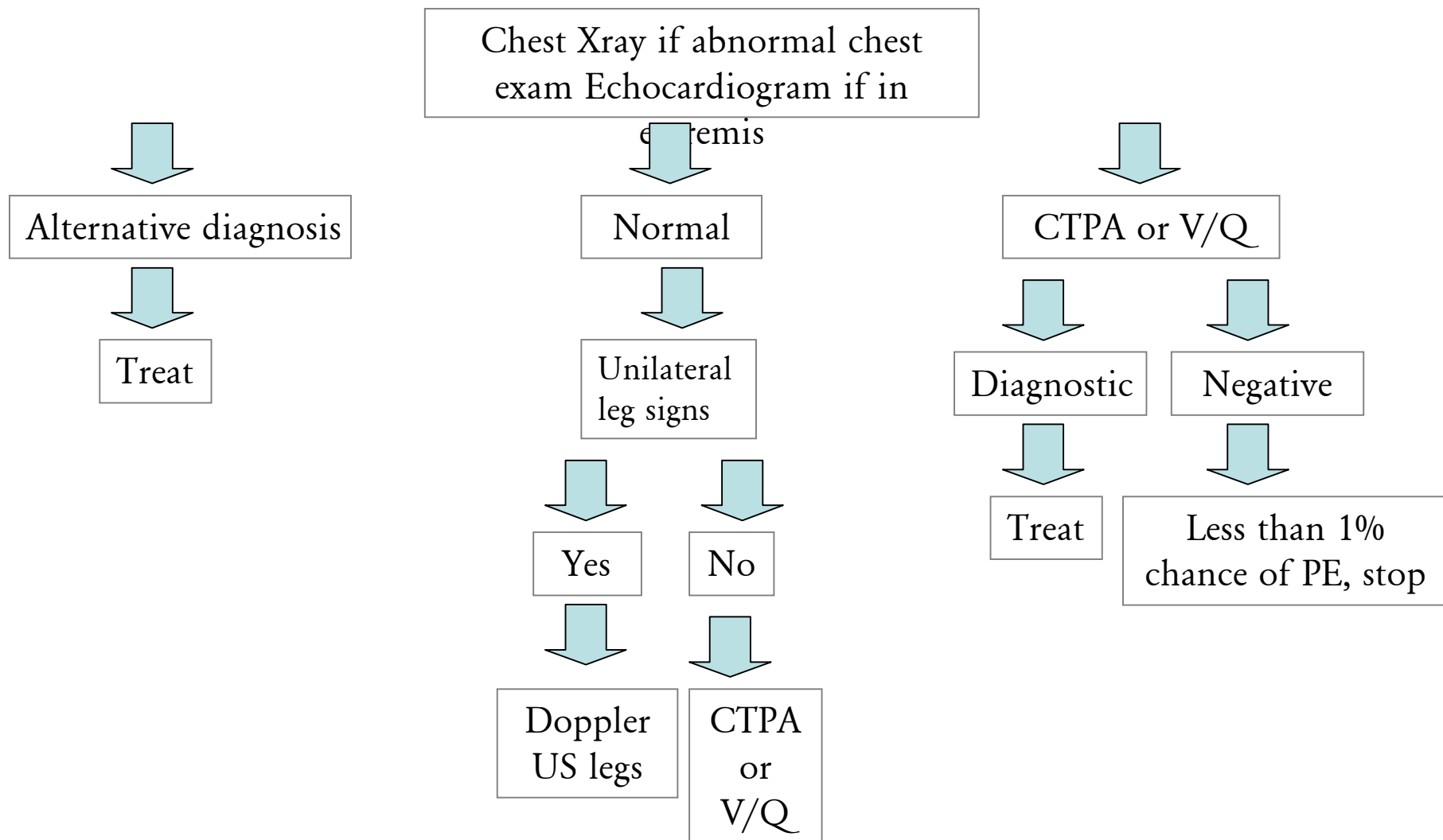
CT Pulmonary angiography

- Direct visualisation of emboli and well as the detection of parenchymal abnormalities as an alternative diagnosis
 - Sensitivity 75-100%, specificity 78-100%
- No reports on the efficacy of CTPA in diagnosing PE in the pregnant patient
- Is there a higher proportion of non-diagnostic scans in pregnant women.
 - NON-DIAGNOSTIC SCANS INCREASED 5-10%
 - HYPERDYNAMIC CIRCULATION/INCREASED PLASMA VOLUME
 - SUBOPTIMAL CONTRAST OPACIFICATION
 - MOTION ARTEFACT
 - TECHNICAL FACTORS
- Important that radiologist experienced in performing scans on pregnant women – do in daytime hours if possible.

CTPA imaging and cancer risk

- Breast tissue is particularly radiosensitive in the latter stages of pregnancy, and there may be an increased risk of cancer induction after radiation exposure during CTPA
 - Organ specific doses during CTPA: 5.5-13.1mSv per breast
 - An exposure of 10mSv to the breast in women more than 35 years of age increases the rate of breast cancer by 14%
- No clear registry studies yet to confirm risk

Investigating PE in pregnant women: an alternative algorithm



Take home messages

- All women of childbearing age, commencing new medication, should have advice regarding pregnancy risks.
- If you would usually perform a radiological procedure on a patient in a particular clinical setting, then you should probably still do that when they are pregnant – but speak to the radiologist first!!