CHALLENGES IN MEDICAL MANAGEMENT IN PREGNANCY

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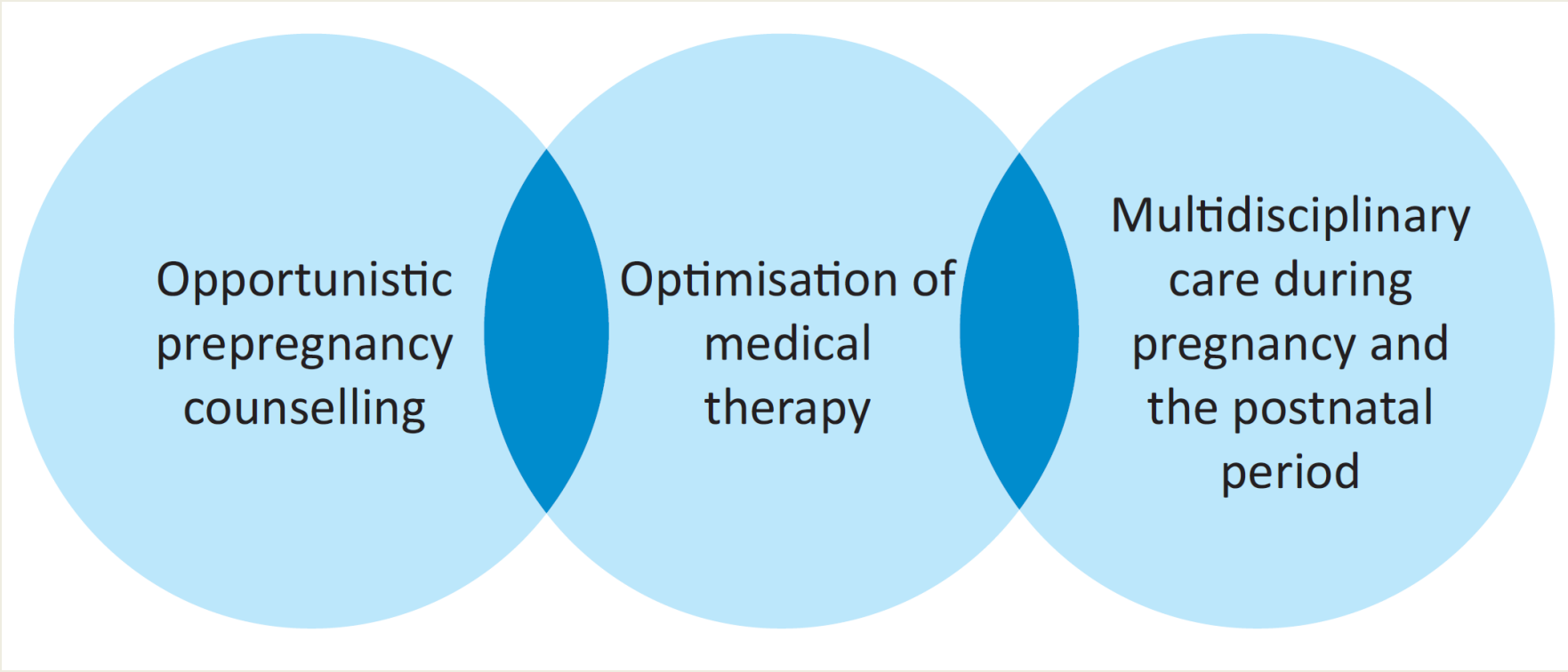
INTRODUCTION

- The interactions between disease and the physiology of pregnancy poses significant challenges for physicians
- All too frequently, a pregnant woman with a preexisting illness receives substandard medical care
- Maternal mortality and morbidity resulting from treatable medical conditions have not decreased in recent years
- It is vital that all physicians acquire a basic knowledge and understanding of medical problems in pregnancy.

OBJECTIVES

- At the end of this talk, we will be able to
  - Act on evidence-based recommendations for evaluation and management of common medical problems in pregnancy.
  - Confidently prescribe needed medications in pregnancy.

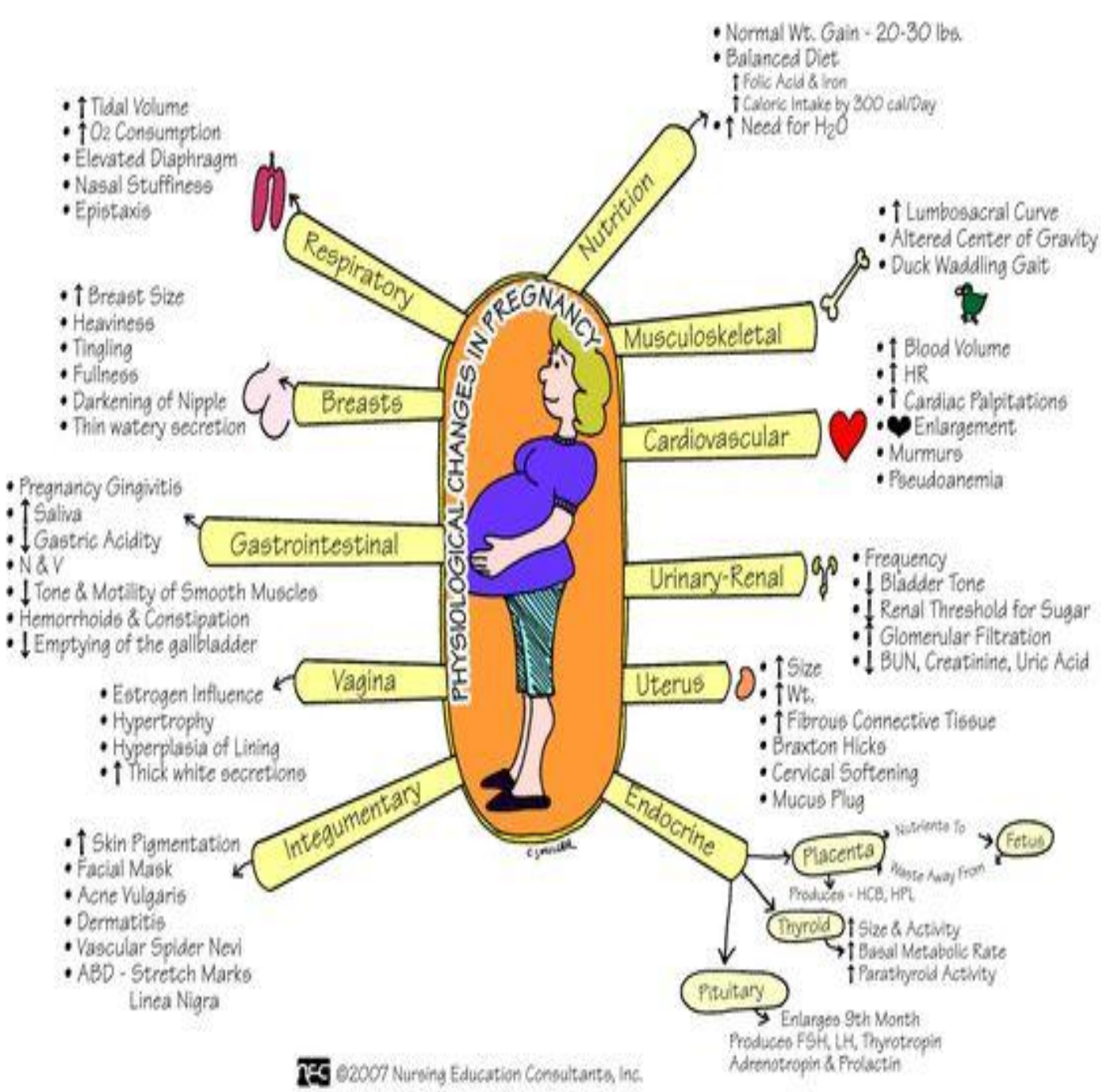
Three aspects of management



Approach: The Tools We Need

- An understanding of the physiologic changes of pregnancy and how they affect disease
- A basic knowledge of pregnancy specific illnesses
- A strategy for evaluating drug safety in pregnancy

Physiologic Changes in Pregnancy



CHANGES IN PREGNANCY

Haematology
↑ Plasma volume (by 50%)
↓ Haemoglobin
↓ Platelets
↑ Fibrinogen (by 50%)
↑ Clotting factors VIII, IX, X
Venous stasis (L >R)

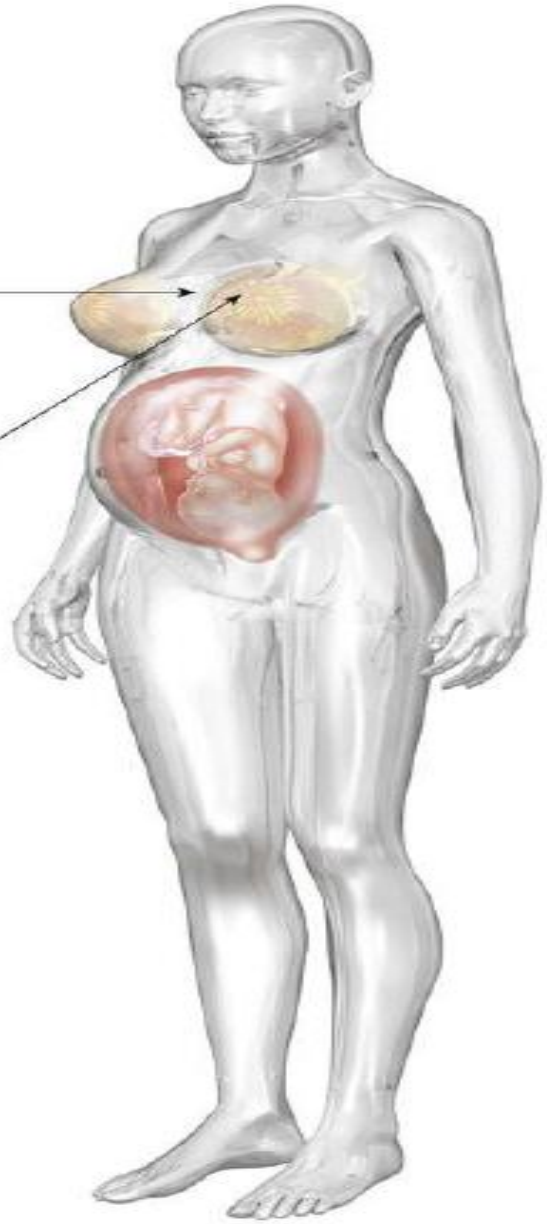
Respiratory
↑ Oxygen consumption (by 20%)
↑ Minute ventilation (by 40–50%)
↑ pO_2
↓ pCO_2
↓ FVC (3rd trimester)

Cardiac
↑ Cardiac output (by 40%)
↑ Stroke volume
↑ Heart rate (by 10–20 bpm)
↓ Blood pressure (↓ in 1st and 2nd trimesters)
↓ Systemic vascular resistance (by 25–30%)
↓ Serum colloid osmotic pressure (by 10–15%)

Renal
↑ Renal plasma flow (by 60–80%)
↑ Glomerular filtration rate (by 55%)
↑ Protein excretion (up to 300 mg / 24 hours)
↓ Serum creatinine (max = 75 µmol/l)
Glycosuria
Physiological hydronephrosis (R>L)

Gastroenterology
↓ Motility
↑ Alkaline phosphatase
↓ Albumin (by 20–40%)

Endocrine
Impaired glucose tolerance
Insulin resistance
↑ Prolactin (10 fold)
↑ Cortisol
↑ Renin, angiotensin, aldosterone



General
Fatigue
Weight gain
Nausea/Vomiting
Constipation
Breathlessness
Palpitations
Ankle oedema

Skin
Palmar erythema
Dry skin
Telangiectasia
Pruritus (in 20%)

PREGNANCY AND CHRONIC DISEASE

- Pregnancy is likely to unmask occult chronic disease
  - Glucose intolerance
  - Renal dysfunction
  - Hypercoaguable states
  - Valvular heart disease
  - Cerebral aneurysm
- Pregnancy as a “stress test for life”

Kaaja and Greer, JAMA 2006

POSTPARTUM EFFECTS

- Increased rates of postpartum chronic disease
  - Women with GDM have up to 50% likelihood of developing Type II DM in subsequent ten years
  - Women with preeclampsia more likely to develop CAD and stroke later in life
- Higher rates of hypertension, insulin resistance, dyslipidemia and inflammatory markers
- Primary prevention could play an important role

O'Sullivan, J, Diabetes 1991; JAMA 1982; Kaaja, JAMA 2005

IMPLICATIONS

- **Adverse effect on mother**
- **Adverse effect on fetus**

-Disease

-Drugs

-Prematurity

Common Medical Disorders in Pregnancy

- Asthma
- Cystic fibrosis
- Hypertension/PIH/PET
- Arrthymias
- Valvular disease
- Cardiomyopathy
- Cyanotic heart disease
- VSD/ASD
- Pulmonary hypertension
- Epilepsy
- Multiple sclerosis
- Intracranial hypertension
- Benign cranial tumours eg pit adenomas
- Obstetric Cholestasis
- Acute Fatty Liver of Pregnancy
- IBS
- Crohns/Ulceative colitis
- Thrombophilias
- VTE
- Antiphospholipid syndrome
- SLE
- Rheumatoid arthritis
- Sickle cell disease/thalassaemias
- Anaemia
- Diabetes
- Hypo/hyperthyroidism
- Adrenal disease
- Cancer

All cannot be addressed a few are chosen

- Asthma
- Diabetes
- Hypertension
- Cardiomyopathy
- Seizure/Epilepsy
- Thromboembolism

ASTHMA

- Commonest chronic medical illness to complicate pregnancy
- Up to 3-8% of women of childbearing age
- Often undiagnosed or undertreated

– A significant increase in complications of pregnancy in asthmatic women.

– The largest study to date shows a 15 to 20 percent increased risk of perinatal mortality, preeclampsia, preterm delivery, or low birth weight infants compared to non-asthmatic women

– Patients with more severe asthma have a 30 to 100 percent increased risk#

Kwon HL, et al. Ann Epidemiol. 2003;13(5):317 # Kallen, B, et al. Eur J Epidem 2000; 16:167.

I am wheezing more often

- A 23-year-old non-smoking woman (gravida 1, para 0) referred to you at 11 weeks' gestation with an 8-year history of asthma, which has worsened over the past year.
- She reports symptoms requiring sulbutamol two or three times per day and interfering with sleep every night.
- Her forced expiratory volume in 1 second is 65% of the predicted value; it increases to 88% after administration of salbutamol. How should her case be managed?

ANSWER?

- (A) Continue the current regimen
- (B) Add Budesonide √
- (C) Add theophylline
- (D) Add salmeterol √
- (E) Add inhaled cromolyn

Background: Respiratory Changes in Pregnancy

- 20% increase in O_2 consumption
- Tidal volume increases
- Minute ventilation increase 40-50%
- Inspiratory capacity increases
- Residual volume decreases
- Expiratory reserve decreases
- Marked reduction in functional residual capacity.
- FEV1 and PEFR are unchanged

Managing the Challenge

- Emphasis on prevention rather than treatment
- Optimise control prior to pregnancy
- Achieve control asap in acute attacks
- Treatment in pregnancy is no different to non-pregnant women

ACUTE ASTHMA ATTACK

- Manage as non-pregnant
  - IV rehydration
  - O2
  - B2 agonists as O2 nebulizer (may be repeated)
  - CXR if suspicion pneuthorax/pneumonia or failure to improve
  - Give steroids **JUST AS IF** pt was not pregnant! (often inappropriately withheld)
  - If not improving, may need IV steroids or inhaled B2 agonists +/- Magnesium sulfate

MEDICATION ISSUES

- B2 agonists
  - Safe in pregnancy
  - Serevent experience growing and ALSO appears safe
- No adverse fetal effects reported with the use of the following inhaled drugs
  - Disodium chromoglycate
  - Nedocromil
  - Anticholinergics (ipratropium)
  - Inhaled cortocosteroids

MEDICATION ISSUES

- Steroids
  - Inhaled:
    - minimal absorption
    - No evidence fetal malformations or adverse fetal effects
  - Oral
    - Should not be withheld in acute attacks
    - No strong evidence of fetal malformations, miscarriage, stillbirth or neonatal death
    - Will worsen glycaemic control in diabetics or may increase risks GDM with long-term use
    - Long-term high dose steroids ↑risk premature ROM

Wendel PJ et al; Am J Obstet Gynecol. 1996 Jul;175(1):150-4.

I HAVE SEIZURES AND WANT TO GET PREGNANT

- A 25-year-old woman with epilepsy comes to the office seeking advice about pregnancy.
- She first developed seizures after sustaining a head injury in a motor vehicle collision at age 16 years.
- MRIs obtained since then have shown an area of encephalomalacia in the right temporal lobe. Her seizures were initially refractory to carbamazepine and valproic acid monotherapy. Carbamazepine was stopped, and lamotrigine was added to the valproic acid 1 year ago. She has not had any seizures since that time.

ANSWER?

- Which of the following is the most appropriate management?

A. Advise the patient not to become pregnant

B. Continue the valproic acid and lamotrigine

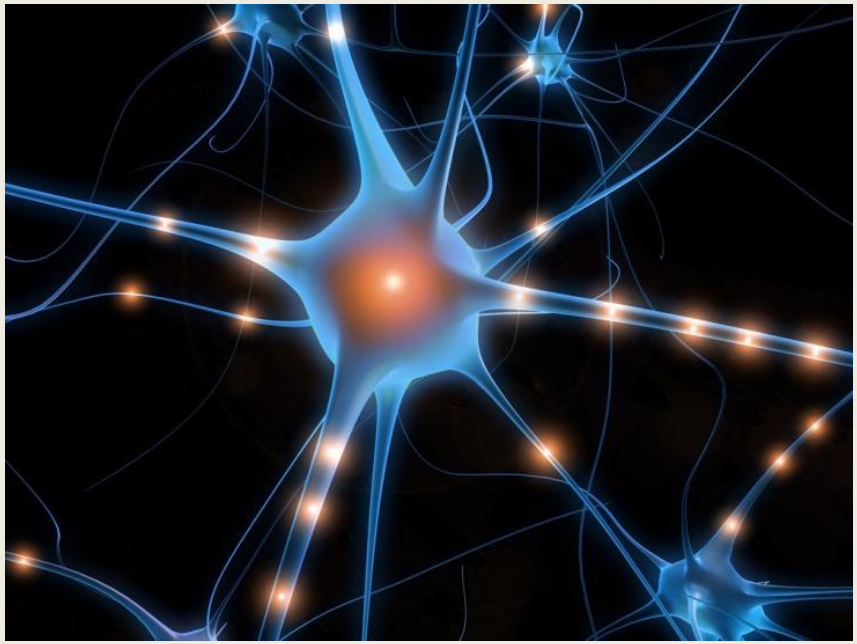
C. Discontinue the valproic acid and continue the lamotrigine

D. Discontinue the valproic acid and lamotrigine

E. Substitute phenobarbital for her current medications

EPILEPSY

- About 0.5% women of childbearing age
- Most diagnosed (known) prior to pregnancy
- All seizure types may be affected by pregnancy
- Associated with risks of maternal death due to aspiration and SUDEP



EFFECT OF PREGNANCY ON EPILEPSY

- 54% no change
- 25-30% ↑seizure frequency
- If seizure free unlikely to have seizures UNLESS stops medications
- Poorly-controlled (>1/month) likely to deteriorate in pregnancy
- Risk of seizures highest in peripartum period

REASONS FOR DETERIORATION OF CONTROL

- Poor compliance (Fears of teratogenesis)
- Decreased drug levels due to nausea and vomiting
- Decreased drug levels due to ↑volume of distribution and ↑drug clearance
- Lack of sleep towards term and during labour
- Lack of absorption of drugs during labour
- Hyperventilation during labour

EFFECTS OF EPILEPSY ON PREGNANCY

- No evidence adverse effects
- No increased risks of miscarriage or obstetric complications (IUGR, PTL, PET etc)
- Status Epilepticus occurs in <1% pregnancies BUT dangerous for mum and baby-TREAT VIGOROUSLY!
- Major risk is teratogenicity of drugs

RISK OF CHILD DEVELOPING EPILEPSY

- 5% if either parent has epilepsy
- 15-20% if both
- 9-12% if parent has idiopathic generalized
- only 3% if partial seizures

TERATOGENIC RISKS OF ANTICONVULSANTS

- **ALL are teratogenic**-newer drugs thought to be safe but now shown to have risks associated with use
- Major malformations are:
  - Neural tube defects
  - Orofacial clefts
  - Cardiac defects

TERATOGENIC RISKS OF ANTICONVULSANTS

- Little difference in risk levels between drugs
- Risk for any one drug is 6-7%
- Risk increases with number of drugs (polypharmacy)- taking 2 or more: risk 15%
- If take phenytion, valproate AND carbamazepine, risk to fetus is up to 50%
- Risk with newer AED: Lamotrigine, Levetiracetam are lower
- Benzodiazepines are not teratogenic

MANAGEMENT IN PREGNANCY

- **Preconceptually:**
  - Take folic acid 5mg/day from at least 12 weeks prior to conception
- **Pregnancy**
  - Continue **folic acid throughout as risks of folic deficiency anaemia**
  - Continue current drugs if well controlled

MANAGEMENT IN PREGNANCY

- Detailed fetal scan at 18-20 weeks with detailed fetal cardiac scan at 22 weeks
- Vit K 10-20mg orally from 34-36 weeks if on enzyme inducers due to risks of fetal Vit K deficiency and Haemorrhagic Disease Newborn

DIABETES IN PREGNANCY

- Pre-existing diabetes
- Gestational diabetes

MATERNAL EFFECT OF DIABETES

- -Increase in insulin requirements
- -Hypoglycaemia
- -Deterioration of diabetic nephropathy and retinopathy
- -Infections- UTI, Vaginal candidiasis, wound infection
- -Diabetic ketoacidosis is rare- but is a risk in the presence of hyperemesis, infection and corticosteroid therapy

FETAL EFFECTS OF DIABETIS

- Miscarriage
- Congenital anomalies- anencephaly, spina bifida, sacral agenesis. Cleft lip/palate, GI atresias, heart and renal defects
- Large for gestational age/macrosomia
- Birth injury:clavicle fracture, Erb's palsy.
- Hypoglycemia
- Hypocalcemia
- Respiratory distress syndrome

GDM

- GDM diagnosis-
  - 75-g OGTT, with glucose values determined after 8 hours of fasting and at 1 and 2 hours
  - Diagnosis is made if at least one value is more than: Fasting value 92 mg/dL; 1-hour value 180 mg/dL; 2-hour value 144 mg/dL
- Screening: 24-28 wks for all. Early for high risk mothers

MANAGEMENT OF GDM

- **Initial management:** Nutritional counseling, exercise, blood glucose surveillance
- **Insulin is 1st line:** Usual starting threshold fasting > 95 mg/dL; 1-hour levels ≥140 mg/dL; 2-hour levels ≥120 mg/dL; starting dose: 0.7-1.0 units/kg daily in divided doses
- **Metformin:** Most commonly used in women with PCOS or pregestational diabetes, and continued in pregnancy, with the addition of insulin

"I had a headache and found the BP high"

- A 21-year-old pregnant woman, gravida 2 para 1, presented with hypertension and proteinuria at 20 weeks of gestation without any prior history of raised BP.
- Diagnosis?
  - Eclampsia
  - Pre-eclampsia √
  - Gestational hypertension
  - Chronic hypertension

Classification of Pregnancy Induced Hypertension

Preeclampsia/Eclampsia	Hypertension and proteinuria of ≥ 300 mg/24 hours after 20 weeks gestation. Eclampsia (the convulsive form of preeclampsia) affects 0.1% of all pregnancies.
Gestational hypertension	Hypertension occurring for the first time after 20 weeks of pregnancy in the absence of proteinuria.
Chronic hypertension	Blood pressure greater than or equal to 140/90 mm Hg prior to pregnancy, or before the 20th week of gestation.
Preeclampsia superimposed on chronic hypertension	Up to 30% of women with chronic hypertension develop preeclampsia, heralded by proteinuria

THE PATHOPHYSIOLOGY

- Cardiac output increases by almost 40%
- Mostly due to an increase in stroke volume
- Cardiac output peaks at around 18 to 24 weeks
- The initiating event in PIH appears to be reduced uteroplacental perfusion as a result of abnormal cytotrophoblast invasion of spiral arterioles
- Placental ischemia is thought to lead to widespread activation/dysfunction of the maternal vascular endothelium
- That results in enhanced formation of endothelin and thromboxane, increased vascular sensitivity to angiotensin II, and decreased formation of vasodilators such as nitric oxide and prostacyclin

MATERNAL COMPLICATIONS

- Eclampsia
- Cerebral Haemorrhage
- Placental abruption
- Renal failure
- Pulmonary oedema
- ARDS
- Disseminated Intravascular coagulopathy
- HELLP syndrome, liver haemorrhage and rupture
- Thromboembolism
- Cortical blindness

FETAL EFFECTS

- Intrauterine growth restriction
- Intrauterine death
- Iatrogenic preterm delivery

HYPERTENSION IN PREECLAMPTIC PATIENTS

- sFlt-1/PlGF ratio is a novel immunassay recommended by NICE to rule out Pre-Eclampsia, following clinical assessment

MANAGING THE CHALLENGE

- Aim for target blood pressure lower than 150/100 mmHg
  - 2010 National Institute for Health and Care Excellence guidelines
- Theoretical concerns that lower targets might compromise uteroplacental circulation is abolished by recent evidence
- The aim should now be tight control, with a target diastolic blood pressure of 80–85 mmHg
- First-line drugs: labetalol or modified-release nifedipine
- Second-line options: Methyldopa and amlodipine
- Contraindicated: angiotensin-converting enzyme inhibitors,angiotensin II receptor blockers and spironolactone

"I get tired more easily; my feet are swollen"

- A 35-year-old woman is evaluated for progressive dyspnea 3 weeks after delivery of her first child. Other than hypertension during pregnancy, the pregnancy and delivery were uncomplicated. She has no history of cardiovascular disease.
- On physical examination:
  - Pedal edema is present; Blood pressure: 110/70 mm Hg
  - HR: 105/min and regular and RR is 28/min
  - The apical impulse is displaced and diffuse with a grade 2/6 holosystolic murmur noted. 3rd and 4th HS are also noted
  - Percussion note dull at the posterior lung bases bilaterally, and there are crackles extending up half of the lung fields..
  - ECG: sinus tachycardia; no ST-T-wave changes
  - CXR: bilateral pleural effusions and interstitial infiltrates

DIAGNOSIS?

A. Acute myocardial infarction (AMI)
B. Aortic dissection
C. Coarctation of the aorta
D. Acute pulmonary embolism (PE)
E. Peripartum cardiomyopathy(PPCM) √

PERIPARTUM CARDIOMYOPATHY

- Defined as heart failure with LVEF < 45%;
- – diagnosed from 3 months before upto 6 months PP in the absence of an identifiable cause.
- Usually diagnosed in month 1 postpartum.
- Risk factors :Age (>30 years at the time of the pregnancy), race (black, African, Haitian), and the presence of gestational hypertension.

PERIPARTUM CARDIOMYOPATHY

- Maternal mortality rate ~10%,
- Improvement in LV function in ~ 50% of women within 6 months after delivery.
- Intravenous immune globulin and pentoxifylline have been shown to improve outcomes in some studies.
- Anticoagulation is recommended for thromboembolic prophylaxis when LVEF < 35%.

PREDICTORS OF POOR OUTCOME IN WOMEN WITH HEART DISEASE

- New York Heart Association Class III or IV

  Symptoms with less than ordinary physical activity or at rest
- History of prior cardiac event or arrhythmia
- Left sided obstruction in mitral or aortic valve
- Ejection fraction less than 40%

Siu, SC, Circulation 2001

Managing the challenge

- A major challenge is to distinguish the peripartum discomforts in healthy women (fatigue, shortness of breath, and oedema) from the pathological symptoms
- Urgent confirmation of global ventricular systolic dysfunction by TTE; and treatment with standard heart failure therapy are critical
- Beta-blocker, thiazide diuretics, or furosemide treatment can be necessary in some patients with PPCM before delivery. All at lowest possible dose
- After delivery, standard therapy for heart failure is recommended including beta-blockers, ACE-inhibitors/AT1-blockers, mineralocorticoid receptor antagonists (MRA), and diuretics.

39 YO, G4P2 WITH RESPIRATORY DISTRESS AND HISTORY OF PE

- You want to order a chest x-ray for initial evaluation
- She is concerned about the effects on the fetus
- What would you say?

Challenges of Diagnostic Imaging in Pregnancy

- Greater risk of harm by **not** getting a needed study than getting one
- Little evidence that radiation exposures <5 rads have significant fetal effects
- Almost all imaging studies involve radiation well below this level
  - CXR <0.001 rad
  - Chest CT PE protocol 0.001-0.002 rads
  - CT abdomen/pelvis 0.64 rads

IV CONTRAST

- Theoretical concern for effects on fetal thyroid
- Case reports of women receiving high dose iodine in pregnancy-->no adverse outcomes
- General advice: avoid if possible, but use contrast when clinically necessary

MRI

- Few studies
  - –Animal evidence shows little risk
- NIH consensus statement

  Recommends MRI to be reserved for 2nd and 3rd trimester if possible, but can be performed in pregnancy
- Gadolinium –Little data—use if clinically warranted

Prescribing Challenges in Pregnancy

- Do not start medication unless clearly indicated
- Do not discontinue medicines that successfully maintain the maternal condition stable unless there are clear indications to do so
- Have a pregnancy medication reference
- Favor medicines with longer record of use
- Educate and negotiate with your patient
  - Pregnant women more likely to stop needed medication
- Report adverse outcomes

FDA DRUG RATINGS IN PREGNANCY

Category	Interpretation
A	Controlled human studies show no risk
B	No evidence of risk in studies
C	Risk cannot be ruled out
D	Positive evidence of risk
X	Contraindicated in pregnancy

CLEARLY CONTRAINDICATED

- **ACE inhibitors**: renal dysgenesis
- **Tetracycline**: abnormalities of bone and teeth
- **Fluoroquinolones**: abnl cartilage development
- **Systemic retinoids**: CNS, craniofacial, CV defects
- **Warfarin**: skeletal and CNS defects
- **Valproic acid**: neural tube defects
- **NSAIDS**: bleeding, premature closure of the ductus arteriosis
- **Live vaccines (MMR, oral polio, varicella, yellow fever)**: may cross placenta

TAKE HOME MASSAGE

- Maternal mortality and morbidity resulting from treatable medical conditions have not decreased in recent years
- Part of the solution is to improve the training of physicians in the management of pregnant patients, including pre-conception counseling.
- Prompt recognition of acute illness and optimal treatment of chronic conditions is of clear benefit, and
- Most drugs and many radiological investigations can be used in pregnancy.

THANK YOU