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CCP Guidelines

Maternal Medicine

Ceylon College of Physicians

IN COLLABORATION WITH SLCOG & FHB

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1.Thyroid disease in pregnancy

1.1 Introduction

- Thyroid dysfunction in pregnancy includes hyperthyroidism and hypothyroidism.
- Hypothyroidism is commoner than hyperthyroidism and is known to affect around 2.5-3% of pregnancies.
- Prevalence of hyperthyroidism in pregnancy is around 0.1-1%.
- Important changes in thyroid physiology during pregnancy include:
    - 10% increase in size of the thyroid gland in iodine replete women
    - Lowering of thyroid stimulating hormone (TSH) in the first trimester due to effect of serum hCG, with gradual increase thereafter with advancing pregnancy, but still below the non-pregnant reference range
    - Serum TSH > 4 μIU/mL by the third trimester in nearly one fifth of women with autoimmune thyroid dysfunction
    - Development of postpartum thyroid dysfunction in 33-50% of women with thyroid autoimmunity
- Testing for thyroid functions
    - Total binding globulin (TBG) increases by around 50 % by 6-8 weeks of pregnancy and remains high until delivery. Therefore, the free fraction of thyroxine (FT4) should be assessed, in addition to serum TSH level.
    - Free T3 assay is not reliable and therefore should not be routinely performed unless the patient is clinically thyrotoxic with a low TSH and normal FT4.
    - The optimal method to assess serum FT4 during pregnancy is measurement of T4 in the dialysate or ultrafiltrate of serum samples employing on-line extraction/liquid chromatography/tandem mass spectrometry (LC/MS/MS). This method is not routinely available and immunoassay methods are employed for assessment of thyroid function in Sri Lanka.

Box 1.1 Normal reference range for thyroid hormones in pregnancy

Trimester	*SerumTSH (µIU/mL)*	*FT4 (pg/ml)*
First	0.1-2.5	0.83-1.27
Second	0.2-3.0	0.71-1.05
Third	0.3-3.0	0.72-1.06

1.2 Hypothyroidism in pregnancy

Overt hypothyroidism

Definition:

- TSH above 2.5 µIU/mL with free T4 below the trimester specific reference range or
- TSH >10 µIU/mL, irrespective of the free T4 level

Adverse effects of overt hypothyroidism include:

Maternal complications

- Gestational hypertension
- Placental abruption
- Postpartum haemorrhage

Foetal complications

- Foetal loss
- Premature birth
- Low birth weight
- Neonatal respiratory distress
- Impaired neurocognitive development in the offspring

Subclinical hypothyroidism (SCH)

Definition:

- TSH between 2.5-10 µIU/mL with normal FT4 level

SCH is known to be associated with infertility, foetal loss, preterm delivery and neonatal respiratory distress. SCH needs to be treated in pregnancy.

Isolated hypothyroxinaemia

Definition:

- Normal TSH with FT4 below the trimester specific reference range.

There is no conclusive evidence of benefit of treating with levothyroxine during pregnancy.

1.2.1 Management of hypothyroidism in pregnancy

Preconception care

- Pregnancy should be planned, with TSH levels maintained below 2.5 µIU/ml.
- If pregnancy is unplanned, the dose of thyroxine should be increased by 25-50% of the preconception dose as early as possible in pregnancy, while awaiting the TSH result.

Antenatal management

- The aim of treatment should be maintenance of TSH within the trimester specific reference range.
- TSH should be assessed every 4-6 weeks to ensure that the woman is euthyroid.
- If the TSH fails to normalise while the patient is compliant with medication, refer her to the endocrinologist/physician for further management.
- Levothyroxine is the treatment of choice for overt and subclinical hypothyroidism.
- Advise on general measures that enhance the absorption of thyroxine.
    - To take thyroxine on an empty stomach upon waking in the morning with a lapse of at least half an hour until the first drink or meal
    - To take iron and calcium supplements at separate times of day

Hypothyroidism diagnosed for the first time in pregnancy

- TSH should be normalised as rapidly as possible with the aim of achieving the trimester specific reference range.
- The usual starting dose of thyroxine is 2µg/Kg/d (maximum of 2.5 µg /Kg/d).
- The dose should be titrated according to the thyroid status of the woman assessed by serum TSH.

Women with pre-existing hypothyroidism

- A TSH should be performed as soon as possible.
  - If the TSH is within the trimester specific reference range,
    - Continue the same dose of thyroxine and arrange for review at 4-6 weeks with a TSH value.
  - If the TSH is above the trimester specific reference range,
    - Modify the thyroxine dose as follows

Box 1.2- Dose increment based on serum TSH level

TSH level (µIU/mL)	Dose increment (as a percentage of thyroxine dose)
2.5-10	25-50%
10-20	50-75%
>20	75-100%

Postpartum management

- Thyroxine is safe during breast feeding.
- Most women could be changed over to the pre-pregnancy dose of thyroxine.
- A follow up TSH at 6 weeks postpartum is recommended.
- Neonatal TSH should be tested by one week.

1.2.2 Screening for hypothyroidism in pregnancy

- There is no evidence on benefit of routine screening for thyroid dysfunction in pregnancy.
- All pregnant women should be clinically evaluated at the booking visit for any of the features listed below.

  - A family history of autoimmune thyroid disease or hypothyroidism
  - Presence of a goitre
  - Presence of thyroid antibodies, primarily thyroid peroxidase antibodies
  - Symptoms or clinical signs suggestive of hypothyroidism
  - Women with type 1 diabetes mellitus, or other autoimmune disorders
  - Women with infertility
  - Women with a prior history of miscarriage or preterm delivery
  - Women with prior therapeutic head or neck irradiation or prior thyroid surgery
  - Women currently receiving levothyroxine replacement
  - Women living in a region presumed to be iodine deficient

- A serum TSH level should be performed in women with any of the risk factors mentioned above and managed accordingly.

1.3 Hyperthyroidism in pregnancy

Overt hyperthyroidism

Definition:

- Low serum TSH with an elevated free FT4 level (according to the trimester specific reference range).

Adverse effects of maternal hyperthyroidism include:

Maternal complications

- Miscarriage
- gestational hypertension
- thyroid storm
- maternal congestive heart failure

Foetal complications

- Prematurity
- low birth weight
- foetal growth restriction
- stillbirth
- neonatal goitre

- *Subclinical hyperthyroidism (Low TSH with normal FT4) and isolated hypothyroxinaemia does not require treatment in pregnancy.*

➢ Causes of hyperthyroidism in pregnancy include:

o Gestational thyrotoxicosis

- Commonest cause of hyperthyroidism; Affects 1-3% of pregnancies
- Transient hyperthyroidism due to marked elevation in serum hCG; Seen in the first/early second trimester
- This should be suspected when symptomatic. Ex: tremulousness, heat intolerance, palpitations
- Associated with hyperemesis gravidarum. More common with multiple pregnancies and hydatidiform mole
- Treatment – Supportive therapy; Hydration and antiemetics. Beta blockers may provide symptomatic benefit. Antithyroid medication is not needed

o Graves' disease

- Usually pre-existing but may present for the first time in pregnancy
- Is associated with thyroid eye signs
- Characterised by presence of thyroid receptor antibody (TRAb)

o Toxic multinodular goitre

o Toxic adenoma

1.3.1 Management of overt hyperthyroidism in pregnancy

Preconception care

- Pregnancy should be planned with women rendered euthyroid (TSH between 0.3-2.5 µIU/mL) before attempting pregnancy.
- If ^{131}I is used to achieve euthyroidism, conception should be delayed for a minimum of 6 months (ideally 12 months).
    - These women require a reliable method of contraception preferably IUD.

Antenatal management

- First line therapy for hyperthyroidism is antithyroid drugs (ATD).
    - Propylthiouracil (PTU) should be used in the first trimester of pregnancy
    - Carbimazole should be started from the second trimester onwards
    - The initial dose of ATDs depends on the severity of the symptoms and the degree of hyperthyroxeamia
    - In general, initial doses of ATDs are as follows:
        - Carbimazole, 10–15 mg daily in divided doses
        - PTU, 50–300 mg daily in divided doses
    - Use the smallest possible dose of ATD to maintain euthyroidism and keep FT4 in the upper normal range
- For symptomatic relief, beta blockers could be used.
    - Ex. Propranolol 20–40 mg every 6–8 hours
        - The dose should be reduced as early as possible in view of risk of foetal growth restriction, foetal bradycardia and neonatal hypoglycaemia
        - In the vast majority of cases, beta blockers can be discontinued in 2–6 weeks
- Thyroidectomy in pregnancy is rarely indicated to control hyperthyroidism.
    - If required, the optimal time for thyroidectomy is the second trimester

- Radioactive iodine treatment is contraindicated during pregnancy.

Monitoring

- Treatment is monitored with FT4 and TSH every 4–6 weeks.
    - Aim to maintain serum FT4 at the upper reference range.
- Foetal monitoring is performed for early detection of complications and management.

Graves' disease

- During the first trimester of pregnancy exacerbation of symptoms may occur.
- As pregnancy advances, a gradual improvement in disease activity is seen.
    - This will result in a need to decrease the dose of ATDs
    - Discontinuation of all ATD therapy is feasible in 20%–30% of patients in the last trimester of gestation
    - The exception are women with high levels of thyroid receptor stimulating antibodies (TRAb), in which case ATD therapy should generally be continued until delivery
- Indications for ordering a TRAb test in a woman with Graves' disease include,
    - Active maternal hyperthyroidism
    - History of treatment with radioiodine
    - History of delivering an infant with hyperthyroidism
    - History of thyroidectomy for treatment of Graves' disease
        - Serum TRAb levels should be determined at 24–28 weeks gestation in these women
    - A value over three times the upper limit of normal is an indication for close follow up of the foetus
    - Foetal monitoring includes serial ultrasound scan for assessment of foetal growth, foetal heart rate, amniotic fluid volume and goitre
    - The neonate should be reviewed by a paediatrician at birth.

(TRAb assay is not available in the state sector. Patients suspected with Graves' disease maybe managed without this test considering its cost.)

Delivery

- No special precautions are needed during delivery.
- Women with poorly controlled hyperthyroidism should be closely monitored due to risk of exacerbation of thyrotoxic symptoms and risk of thyroid storm.

Box 1.3 Management of thyroid storm

1. Propylthiouracil 500-1000mg followed by 250mg 4 hourly
   or
   Carbimazole 60-80 mg 4 hourly

2. Oral Propranolol 60-80mg 4-6 hourly
3. Lugols iodine 5 drops oral 6 hourly
   –Start 1 hour after commencement of antithyroid drugs
4. Hydrocortisone 200 mg bolus; 100mg 6 hourly
5. Intravenous hydration
6. Antipyretics

Postpartum care

- Breast feeding
  - Breastfeeding is safe in mothers on ATDs at moderate doses
  - Mothers should be advised to take their ATDs in divided doses immediately following the feed
- Due to risk of flares postpartum in women with Graves' disease, a review should be arranged at 6 weeks or before in women with poorly controlled disease.
- Any form of contraceptive is acceptable.

1.4 Postpartum thyroid dysfunction (PPTD)

Definition:

- Occurrence of thyrotoxicosis or hypothyroidism within the first postpartum year, in a woman without clinically evident thyroid disease before pregnancy
    - This usually occurs in thyroid antibody (TPO Ab and antithyroglobulin Ab) positive women
    - The prevalence is around 7% and is seen more often in women with other autoimmune conditions. Ex. Type 1 diabetes mellitus.
    - The classical course is hyperthyroidism followed by hypothyroidism and finally euthyroidism.
        - However, the majority will not show this pattern and may present with hyperthyroidism or hypothyroidism alone.

Hyperthyroid phase

- Thyrotoxic symptoms occur around 3 months postpartum.
- Graves' disease is the main differential diagnosis.
    - Physical stigmata of Graves' disease, TRAb levels and USS of the thyroid will help differentiate between hyperthyroidism associated with Graves' disease and PPTD.
        - TRAb positivity and high radio iodine uptake by the thyroid gland suggest Graves' disease

Hypothyroid phase

- This occurs around 6 months postpartum and lasts for 4-6 months.
- More than 50% will be asymptomatic.
- This stage may be preceded by a thyrotoxic phase.

Euthyroid phase

- The majority of women with PPTD become euthyroid by 1 year postpartum.

- However, 30% of women who develop PPTD will remain hypothyroid at 1 year with risk of permanent hypothyroidism

Figure 1.1 Management of postpartum thyroid dysfunction

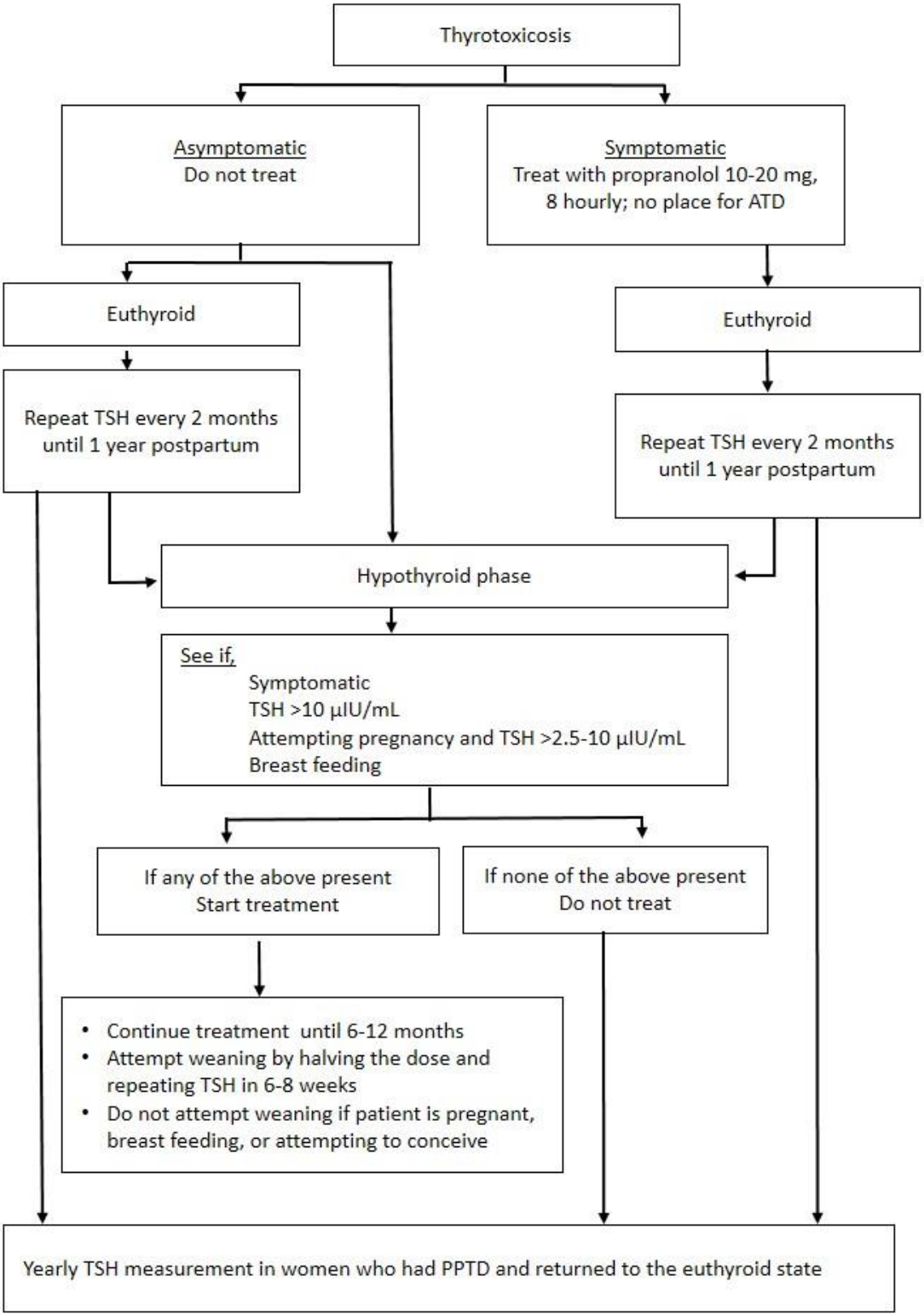
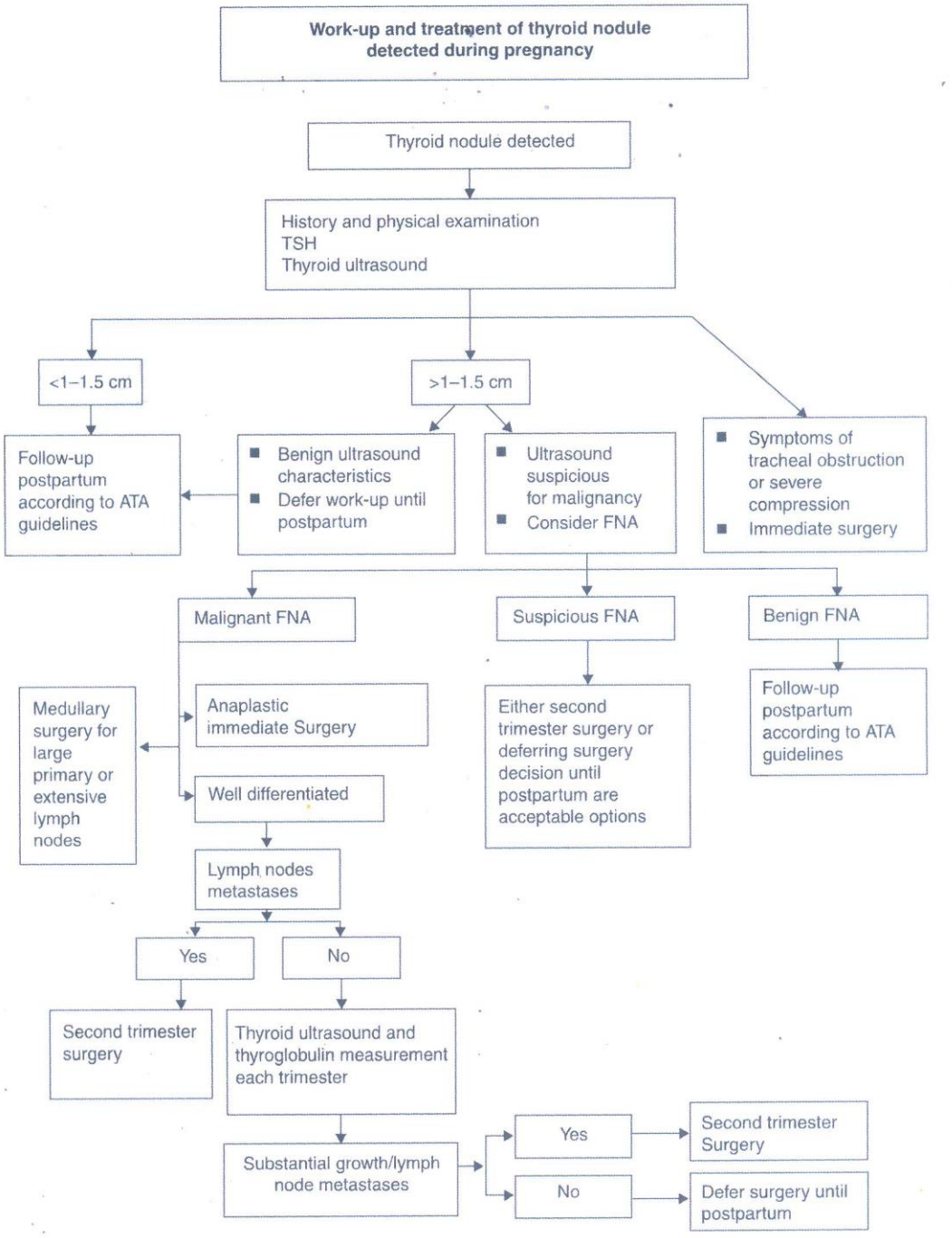


Figure 1.2 Management of thyroid nodule in pregnancy



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2.Bronchial asthma in pregnancy

2.1 Introduction

- The majority of women with bronchial asthma (BA) have an uncomplicated pregnancy.
- Poorly controlled BA is associated with maternal and perinatal morbidity and mortality, including,
    - Spontaneous abortion
    - Foetal growth restriction
    - Preterm delivery
    - Low birth weight babies

Women with pre-existing bronchial asthma

- Optimise control of bronchial asthma in those with poorly controlled disease.
    - This should be done in the preconception period or at least in early pregnancy
- Women who are on prophylactic medication for BA should continue it during pregnancy.
- The course of BA is pregnancy is variable.
    - One third of women experience improvement in symptoms, one third worsening and one third remain unchanged
    - Women with poorly controlled asthma, are more likely to experience worsening of symptoms during pregnancy
    - Worsening of symptoms is most likely in the second and third trimesters
    - In the last month of pregnancy and the peripartum period, patients are least likely to have an asthma attack

When to suspect bronchial asthma in a previously healthy woman

- BA is a clinical diagnosis based on the recognition of characteristic pattern of symptoms and signs in the absence of an alternative explanation.


2.2 Diagnosis of bronchial asthma
likely
unlikely
Clinical features that increase the probability of asthma
• Wheeze, cough, difficulty breathing, chest tightness and audible wheeze on auscultation, particularly if these symptoms:
-- are frequent and recurrent
-- are worse at night and in the early morning
-- occur in response to, or are worse after, exercise or other triggers such as exposure to pets, cold or damp air or with emotions or laughter .
Especially in the presence of,
• a personal history of atopic disorder
• unexplained pulmonary eosinophilia
• family history of atopic disorder and/or asthma
• history of improvement in symptoms in response to adequate therapy
Clinical features that lower the probability of asthma
• Isolated cough in the absence of wheeze or difficulty breathing
• Repeatedly normal physical examination of chest when symptomatic
• Normal peak expiratory flow rate (PEFR) or spirometry when symptomatic
• No response to a trial of asthma therapy
• Clinical features suggestive of an alternative diagnosis

➢ When the diagnosis of BA is doubtful, objective assessment should be carried out.

Box 2.2 Objective assessment of bronchial asthma

Bronchial asthma is confirmed by demonstrating reversibility of airflow obstruction by spirometry or peak expiratory flowmetry during the symptomatic stage.

- A FEV1/FVC ratio <0.7 on spirometry, suggests an obstructive element and probable asthma

- Reversibility testing - An increase in FEV1 of > 400ml or peak expiratory flow rate (PEFR) of >15% of baseline PEFR after inhalation of

  a. Salbutamol 400 µg (100 µg *4) via a spacer device

  OR

  b. Inhaled corticosteroids (Beclomethasone 200µg BD) for 6-8 weeks or oral steroids 30mg OD for 14 days

    - confirms a diagnosis of bronchial asthma.

- It is important to assess the PEFR and document the highest/best reading for an individual patient for monitoring of disease.

- PEFR should be recorded as the best of three forced expiratory blows from total lung capacity with a maximum pause of two seconds before blowing.

2.3 When to consider a diagnosis other than bronchial asthma– Red flag symptoms/ signs

- Constitutional symptoms /inadequate weight gain in pregnancy /loss of appetite
- Haemoptysis
- Excessive sputum production
- Pleuritic chest pain
- Elevated JVP/significant murmurs
- Crackles on auscultation of the lungs

- Cardiac disease in particular should be excluded, when symptoms are atypical and not responding to conventional antiasthma medications.

2.4 Management of bronchial asthma in pregnancy

Pharmacological management

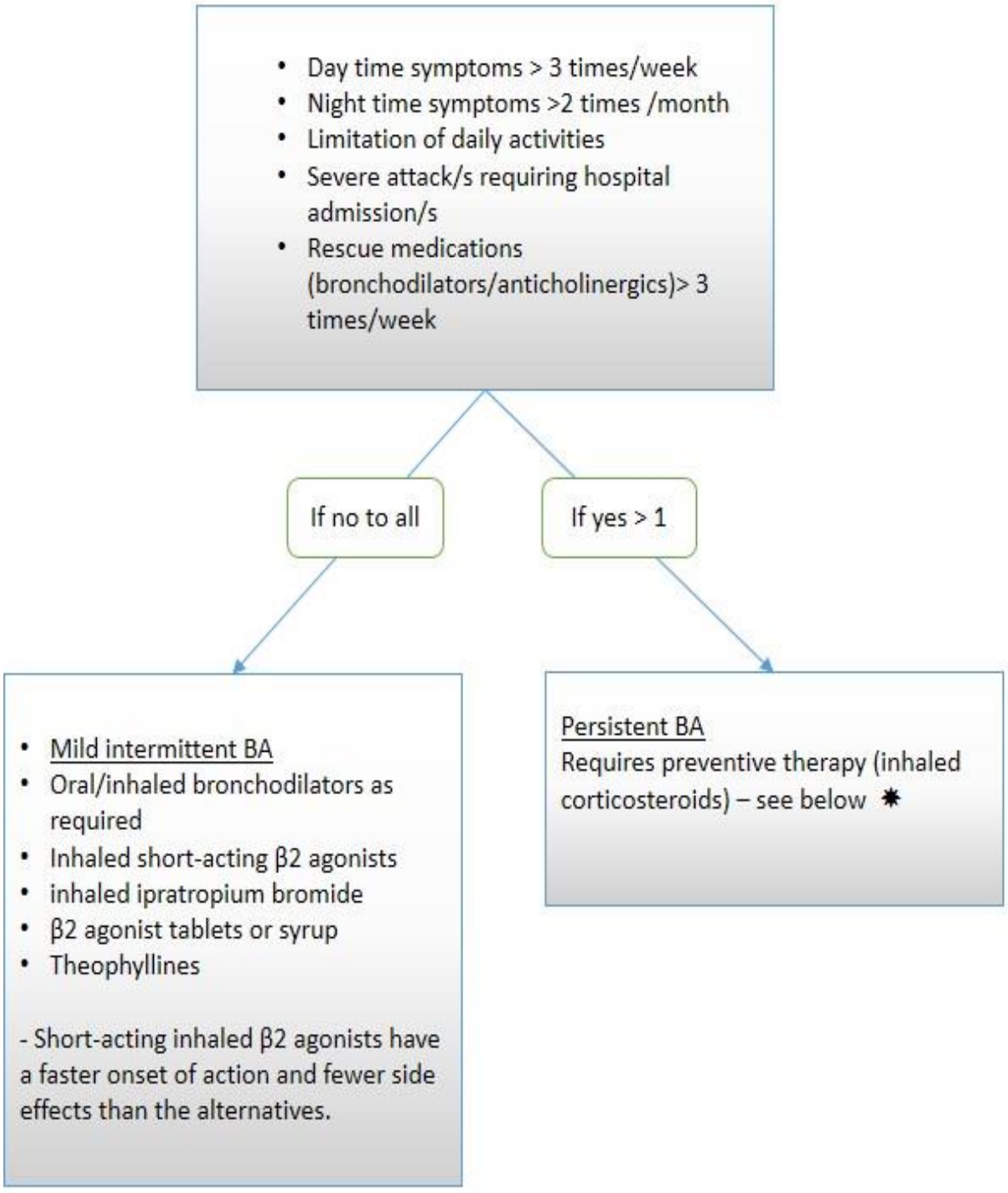
- Medications used in the non-pregnant population have been shown to be safe in pregnancy in treatment doses.

- Harm to the fetus from severe or chronically undertreated asthma outweighs any small risk from the medications used to control asthma.

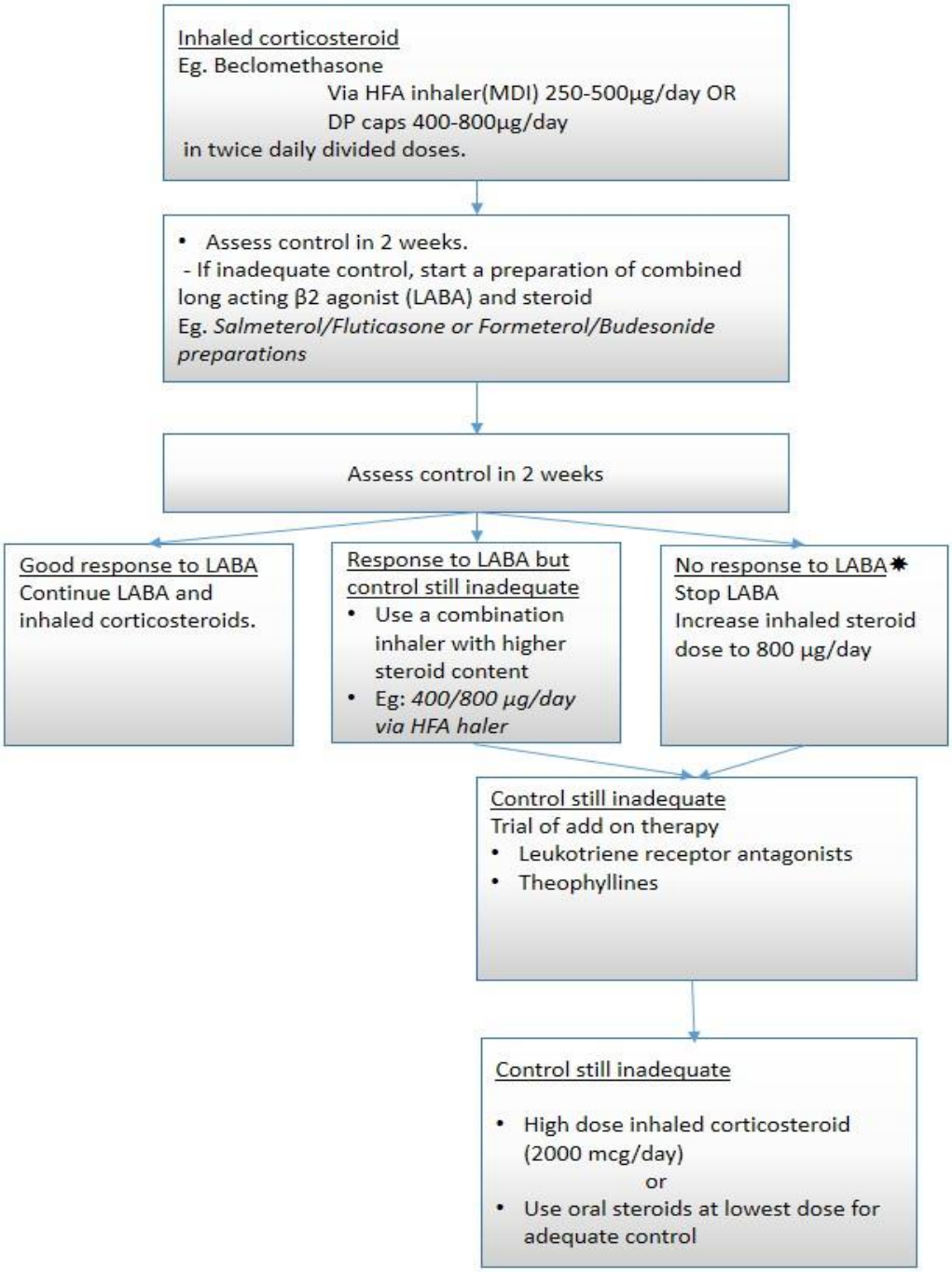
- Women should be informed of the importance of continuing their asthma medications during pregnancy to ensure good asthma control.

- Management is similar to that outside pregnancy.

Stepwise approach to pharmacological management of pre-existing or newly diagnosed bronchial asthma



- Titrate the dose of inhaled corticosteroid to the lowest dose at which effective control of asthma is achieved.
  - Before initiating a new medication, practitioners should recheck adherence to inhaler technique and help eliminate trigger factors.



Box 2.4 Medication summary

Relievers (For quick relief)

- Short acting bronchodilators (SABA)

- Inhaled salbutamol (HFA -100 µg per puff, DP capsules- 200 µg, 400 µg) or oral salbutamol
- Ipratropium inhalers (DP capsules -20 µg, HFA - 40 µg per puff)
- Oral theophylline – Theophylline 125 mg bd or modified release formulations for short periods only (Since serum level monitoring is not available and protein binding could change in pregnancy)

  - *Metered dose inhalers should preferably be used with a spacer device, especially in the third trimester*.

Preventers (Long term control medications)

- Inhaled corticosteroids (ICS)

- ICS are more effective when taken twice rather than once daily.
- There is little evidence of benefit for dosage frequency more than twice daily.
- Titrate the dose of inhaled corticosteroid to the lowest dose at which effective control of asthma is maintained.

- Long acting beta 2 agonists (LABA)

- These should always be given in combination with ICS.
- Combined inhaler preparations are available.

  Ex: Salmeterol/Fluticasone
  Formoterol/ Budesonide

- Leukotriene receptor antagonists

  Ex: Montelukast 10mg once daily, usually at night

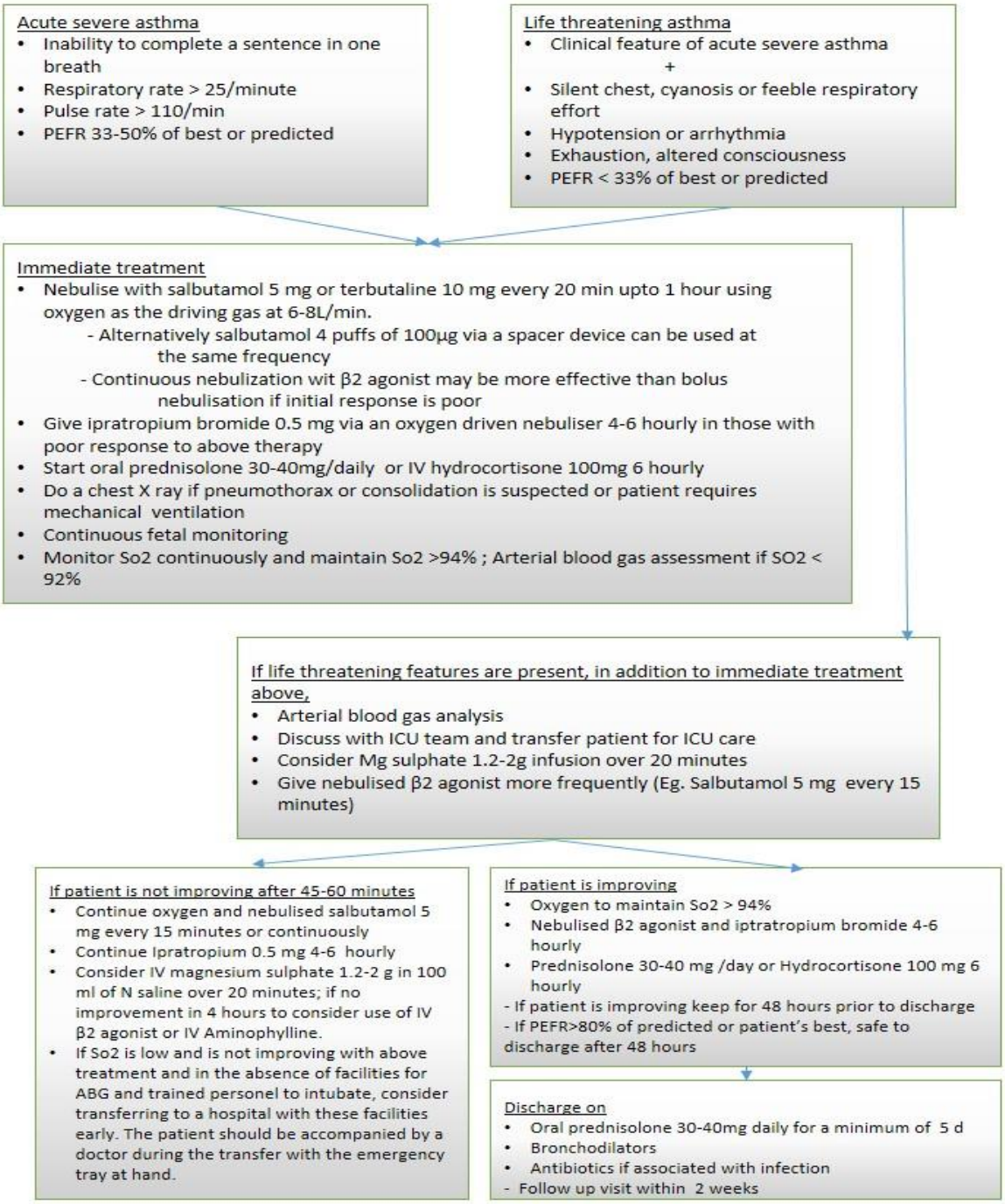
2.5 Adjuvant therapy for bronchial asthma

- Women with recurrent exacerbations related to gastro oesophageal reflux disease or allergic rhinosinusitis, need control of these with appropriate medication and lifestyle measures.
    - Antihistamines - No teratogenicity reported
        - Sedating antihistamines used towards the latter part of pregnancy may adversely affect the neonate
    - Intranasal steroids- Beclomethasone, Budesonide and Fluticasone are safe
    - Antacids
        - Omeprazole and H2 receptor blockers are safe
- Active and passive smoking and indoor air pollution to be avoided

Prevention of acute deterioration

- A register of patients at risk may help primary care health professionals to identify patients who are at high risk of deterioration.

Management of acute exacerbation of BA



2.6 Indications for transfer to the intensive care unit (ICU)

- Deteriorating PEFR despite appropriate treatment
- Persisting or worsening hypoxia
- Hypercapnia or inappropriate eucapnia (see box below)
- Arterial blood gas analysis showing a fall in pH or rising H + concentration
- Exhaustion, feeble respiration
- Drowsiness, confusion, altered conscious state
- Respiratory arrest

Box 2.6 Interpretation of arterial blood gas in pregnancy

- Due to progesterone driven increase in minute ventilation the following changes are expected in healthy pregnant women
  - High Pao2
  - Hypocapnia
  - Respiratory alkalosis

Oxygen saturation remains unaltered

2.7 Antenatal care

- If patient's disease is under control, the patient does not require any additional monitoring or interventions.
- However, if the patient is on preventive therapy and disease not adequately controlled, refer to a physician for optimising management and formulating a plan for the rest of pregnancy.
- In the event of uncontrolled/severe BA, regular growth monitoring of the fetus should be performed.

2.8 Delivery

- Worsening disease is generally not a problem at this time due to endogenous steroid production at time of labour.
- Women should continue their routine asthma medications during labour.
- In the absence of acute severe asthma, caesarean section is performed only for obstetric indications.
- If anaesthesia is required, regional anaesthesia is preferred over general anaesthesia.
- Women who have received a dose of prednisolone > 7.5 mg/day for more than two weeks prior to delivery, should be commenced on hydrocortisone 100mg 6 hourly during labour.
- Prostaglandin E2 could be safely used for induction of labour.
- Prostaglandin F2α (Carboprost/Hemobate) used to treat postpartum haemorrhage due to uterine atony may cause bronchospasm.
- Ergometrine may cause bronchospasm, though Syntometrine does not.

2.9 Postpartum care

- All medications used in control and treatment of asthma is safe to be used during breastfeeding.
    - Maternal dose of up to 20 mg of prednisolone daily is considered safe.
    - Women on higher doses of prednisolone should be advised to breastfeed after a lapse of 3-4 hours of taking the steroid.

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3. Rheumatoid arthritis

3.1 Introduction

- Disease activity in women with rheumatoid arthritis (RA) usually improves or remains the same during pregnancy although flares could occur postpartum.

- Women with poorly controlled disease have a greater risk of flares in the postpartum period.

3.2 Preconception care

Aims of preconception care:

- To assess suitability for pregnancy

    - Contraindications to pregnancy include moderate /severe pulmonary hypertension, advanced rheumatoid lung disease and advanced renal impairment (serum creatinine > 2.8 mg/dL)
    - Specialist assessment is needed for all women with active disease
    - Disease remission should be maintained for at least one year prior to conception.
        - Disease activity should be assessed by using one of the accepted composite disease activity scores. e.g. Disease Activity Score (DAS) - DAS 28 or clinical disease activity index- CDAI

- To screen for target organ damage

    - Cardiac, pulmonary and renal assessment (blood pressure, serum creatinine, echocardiography and lung function tests) should be performed depending on organ involvement

- To screen for concomitant autoimmune conditions, especially autoimmune thyroid dysfunction.

- To advice contraception until disease activity is controlled

    - Intrauterine Device (IUD) /Oral contraceptive Pill (OCP)/Depot Medroxy Progesterone Acetate (DMPA)/Implants are acceptable
    - Emergency contraception in the event of unprotected sexual intercourse.

- Periconceptional folate supplementation- Folic acid at a dose of 5 mg daily should be commenced.

- For review of medication and appropriate adjustment prior to pregnancy (*Box 3.3*).

Box 3.3 Safety of medications used for rheumatoid arthritis in pregnancy

Pregnancy category X

Methotrexate

Stop for at least 3 months prior to attempting conception.

Leflunomide

Conception should be avoided for minimum of 2 years since discontinuing Leflunomide. If cholestyramine washout is carried out for a special indication, pregnancy must be deferred for 3 menstrual cycles after the wash out period.

Pregnancy category D

Non-steroidal anti-inflammatory drugs (NSAIDS)

NSAIDs, including COX-2 inhibitors, are contraindicated in the third trimester. Could be used with caution prior to 24 weeks of gestation, with intermittent use of those with a short half-life. Risk of miscarriage in the first trimester.

Pregnancy category C

Hydroxychloroquine

Lowest possible dose (200mg) should be used.

Steroids

Prednisolone and hydrocortisone are preferred. Lowest possible dose should be used.

Pregnancy category B

Sulphasalazine (Category D if used for prolonged periods or near term)

Lowest possible dose (500mg -1g/day) if absolutely indicated.
Folate supplementation is encouraged during its use during preconception and pregnancy.

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3.3 Antenatal care

- Frequency of monitoring should vary depending on the patient's disease activity and systemic involvement.
    - All patients should be reviewed by the rheumatologist/physician at least every trimester.
    - Women with unstable disease needs more frequent monitoring.
- Review of medications (Refer details in *Box 3.1* above).

3.4 Delivery

- No special measures are needed during delivery. Women with hip deformities or valgus knee deformities should be considered for caesarean section.

3.5 Postpartum care

- Review drugs for suitability for breast feeding.

Box 3.5- Safety of medications during breast feeding

Safe to continue during lactation

NSAIDs
Corticosteroids
Hydroxychloroquine
Sulfasalazine*1*

Inadequate data regarding lactation –Avoid

TNFα inhibitors
Anakinra
Abatacept
Rituximab
Tocilizumab
Tofacitinib

Contraindicated during lactation

Methotrexate
Leflunomide
Azathioprine *2*

1 Use with caution in settings of prematurity, hyperbilirubinemia and glucose-6-phosphate dehydrogenase deficiency.
2 Avoidance is recommended by the manufacturer, primarily based on theoretical risk.

- Advice to take medication immediately after breast feeding and preferably postpone the next feed for four hours after taking the medication.

- Women should be monitored more frequently, due to risk of disease flares.
    - Review at six weeks postpartum, with those with active disease reviewed earlier and more frequently.

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4 Systemic Lupus Erythematosus

4.1 Introduction

- Disease activity of systemic lupus erythematosus (SLE) varies in pregnancy.
    - Disease activity in the preconception stage is the most important predictor of flares during pregnancy
    - Disease flares commonly involve the skin and musculoskeletal system
    - Identifying a disease flare is challenging as physiological changes of pregnancy mimic a disease flare

- Factors associated with an adverse pregnancy outcome include,
    - Active disease in the preconception stage
    - Lupus nephritis with increased baseline serum creatinine (S creatinine >1.4mg/dL).
    - Presence of antiphospholipid syndrome (APS)

- SLE could present for the first time in pregnancy.
- Maternal and foetal complications of active disease include,

<u>Maternal complications</u>

- Hypertensive disorders including preeclampsia, HELLP syndrome
- Gestational diabetes mellitus (GDM)
- Premature rupture of Membranes (PROM)
- Arterial and venous thrombosis especially in the presence of APS
- Catastrophic APS
- Immune thrombocytopaenia
- Infections
- Autoimmune hepatitis

<u>Foetal complications</u>

- Miscarriage (more common in the presence of APS)
- Foetal growth restriction
- Stillbirth
- Prematurity
- Neonatal lupus.

(*Presence of active disease and lupus nephritis substantially increase the risk of foetal loss and prematurity)*

4.2 Preconception care

Aims of preconception care:

- Assess suitability for pregnancy
  - Pregnancy should be avoided in the presence of moderate/ severe pulmonary hypertension, severe restrictive lung disease (forced vital capacity <1L) or advanced renal disease (serum creatinine level >2.8 mg/dl)

  - Pregnancy should be deferred if disease remission has not been achieved for at least six months.
    - Disease activity score could be assessed using the European Consensus Lupus Activity Measurement (ECLAM) modified version validated for use in pregnancy

    - Levels of serum complements (C3 and C4) and dsDNA may be used for monitoring of disease activity

- Assessment for other autoantibodies
  - Anti - Ro and anti - La antibodies should preferably be assessed to identify risk of complete heart block (CHB) in the foetus

  - Anticardiolipin antibodies, lupus anticoagulant and anti-β2 glycoprotein should be assessed to detect the presence of antiphospholipid syndrome

- Review of medications
  - Antihypertensives
    - Withhold angiotensin converting enzyme inhibitors (ACEI) and Angiotensin receptor blockers (ARB) in pregnancy
    - Give alternative antihypertensives (etc. Calcium channel blockers, Methyldopa)

  - Most immunosuppressive drugs (Cyclophosphamide, Methotrexate, Mycophenolic acid, Leflunomide) are contraindicated during pregnancy. (*Refer Box 3.1 –Rheumatoid arthritis*)

    - They should be discontinued at least 3 months before conception

    - Leflunomide has a long half-life; Pregnancy should either be deferred for 2 years after discontinuation of the drug or a washout procedure should be employed

- Contraception
  - A contraceptive method should be used until it is safe to conceive.

Hormonal contraception

- Low dose combined hormonal contraceptive may be used in patients with inactive or mild disease activity. In moderate to severe disease and with prolonged use, they may be associated with lupus flares and thromboembolic risk especially in the presence of APS

- Progesterone containing oral, injectable or implantable contraceptives may be recommended as contraceptives in SLE for shorter periods, but use over 2 years could increase the risk of osteoporosis

Intrauterine contraceptive device

- May be suitable for patients on minimal immunosuppressive for long term use.

4.3 Antenatal care

- Women with major organ involvement or poorly controlled disease are best managed in a tertiary care centre with involvement of a multidisciplinary team.

- Folic acid 5 mg daily should be continued throughout the first trimester.

- Aspirin 75mg daily should be commenced at 10- 12 weeks and continued until 36 weeks of pregnancy.

- Women on steroids or heparin should receive supplemental calcium and vitamin D
  - Elemental calcium 1200 U (minimum 800 U) daily.
  - Vitamin D 800-1000 U daily.

(*Vitamin A and D preparations should be avoided as a method of supplementing vitamin D due to teratogenic potential of vitamin A).*

- Regular review by the rheumatologist/specialist physician should be undertaken for assessment of disease activity and control.

  - Those with active disease - at least fortnightly
  - Those in disease remission - monthly

- Close monitoring of blood pressure, blood sugar levels and maternal weight gain in women on steroids.

- Review of medications
    - Hydroxychloroquine could be continued during pregnancy
    - Azathioprine is safe, provided the dose does not exceed 2 mg/ kg day
    - Calcineurin inhibitors, Tacrolimus and Cyclosporine could be considered in persistent disease activity
    - Most immunosuppressive drugs (Cyclophosphamide, Methotrexate, Mycophenolic acid, Leflunomide) are contraindicated during pregnancy

- Foetal monitoring
    - Monitoring of growth and doppler uterine artery blood flow for detection of fetal growth restriction.
    - Foetal echocardiography if indicated.

4.4 Delivery

- Women who have been on steroids >7.5mg/day for ≥ 2 weeks preceding delivery, should be given IV Hydrocortisone 100mg followed by 50 mg 6 hourly for 24 hours from the time of active labour.

4.5 Postpartum care

- The risk of disease flare is high.
    - Review all women at 6 weeks and those with active disease at 2 weeks postpartum.

- In women with APS, heparin should be continued postpartum. (*Refer section on APS for duration of anticoagulation).*

- Women on lifelong anticoagulation should be converted to warfarin prior to discharge.

- Breast feeding- Refer the section on Box 3.5 *Safety of medications during breast feeding* Rheumatoid arthritis for advice on medication during breast feeding.

4.6 Contraception

- Refer section on contraception - preconception care in SLE.

4.7 Neonatal lupus syndrome

- Neonatal lupus syndrome represents foetal manifestations of passively acquired autoimmunity.
- NLS may manifest as rash, haematologic/hepatic abnormalities or cardiac complications.
- These manifestations generally resolve by 6 to 8 months after birth.
- All babies born to mothers with SLE need to be reviewed by a paediatrician.

4.8 Treatment of lupus nephritis (LN) in pregnancy

- Risk of renal flare is high in pregnancy and requires differentiation from pre-eclampsia.

Box 4.8- Differentiating features of pre-eclampsia and lupus nephritis.

Clinical and laboratory features	**Pre-eclampsia**	**Lupus nephritis**
Hypertension	Onset usually after 20 weeks	Onset could be any time
Urinary sediment	Inactive	Active
DNA antibody levels	Normal	Rising
Complement levels- C3, C4	Normal	More than 25% decline

- If active nephritis is present, glucocorticoids could be prescribed to control disease activity, and if necessary, Azathioprine can be added. (The dose of Azathioprine should not exceed 2 mg/kg in a pregnant woman).
- For patients with persistently active nephritis with documented or suspected class III or IV lupus nephritis with crescents, consider early delivery.

5 Other autoimmune connective tissue disease

5.1 Systemic Sclerosis

- Contraindications to pregnancy include moderate/ severe pulmonary hypertension, severe pulmonary fibrosis and advanced renal disease (S. Creatinine > 2.8mg/dL).

- Risk of premature rupture of membranes (PROM) is high.

- Nifedipine given for Reynaud's disease may interfere with uterine contractions in the latter part of pregnancy.

- In women with gastrointestinal involvement,
  - nutritional problems and constipation require specialist attention and care
  - anaesthetic review is required due to anticipated problems during intubation

Women with **undifferentiated autoimmune connective tissue disease (CTD), dermatomyositis, mixed CTD and overlap syndrome** should be referred for specialist assessment for gauging of disease activity and organ involvement prior to pregnancy.

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6 Immune thrombocytopaenia purpura

6.1 Introduction

- Thrombocytopaenia in pregnancy is defined as a platelet count <150x 10^9/L.
- It is the second commonest haematological disorder in pregnancy after anaemia, and affects around 7–10% of pregnancies.
- Immune thrombocytopenic purpura (ITP) is just one of several causes in pregnancy and is a diagnosis following exclusion of more sinister causes of thrombocytopaenia.
- In the absence of an initiating/ underlying cause for isolated thrombocytopaenia AND absent lymphadenopathy and hepatosplenomegaly, a diagnosis of ITP can be made.

Box 6.1 Causes of thrombocytopaenia in pregnancy in order of frequency

Condition	Incidence (%)	Diagnostic features	Clinical presentation	Laboratory findings
Gestational thrombocytopenia	5-9%	▪ Commonest cause of thrombocytopaenia in pregnancy (70-80%) ▪ Is a diagnosis of exclusion ▪ Onset in late second or third trimester ▪ Platelet count normal outside pregnancy ▪ No neonatal thrombocytopenia ▪ Thrombocytopenia resolves postpartum	▪ Asymptomatic	▪ Platelets usually >70 x 10^9/L
Pre-eclampsia	5-8%	▪ Onset in late second or third trimester	▪ Headache, blurred vision, epigastric pain, oedema ▪ Systolic BP≥ 140mmHg and/or diastolic BP ≥ 90mmHg	▪ > 0.3g urine protein / 24hrs ▪ Elevated liver transaminases, renal impairment and coagulopathy in severe cases
Viral infections		▪ Seen in any trimester	▪ Fever, associated with headache, myalgia and arthralgia	▪ White blood cell count is low or in the lower normal range ▪ Elevated transaminases may occur

ITP	<1%	▪ Seen in any trimester ▪ Thrombocytopenia outside of pregnancy is seen ▪ May be associated with foetal thrombocytopaenia	▪ May have signs of bleeding - bruising, petechiae	▪ Platelet <100 x 10^9/L +/- large platelets on peripheral blood smear
HELLP syndrome	<1%	▪ Variant of pre-eclampsia ▪ 70% onset in late second or third trimester ▪ In 30% onset postpartum	▪ Majority will have preeclampsia	▪ Microangiopathic haemolytic anaemia; Elevated LDH ▪ Elevated liver transaminases
Acute fatty liver of pregnancy (AFLP)	<0.01%	▪ Onset in third trimester	▪ Right hypochondrial pain ▪ Jaundice ▪ Nausea/vomiting ▪ Hepatic encephalopathy	▪ Moderate or severe thrombocytopaenia ▪ Elevated LFTs, creatinine, WBC, uric acid, ammonia ▪ Prolonged PT/APTT ▪ Hypoglycaemia (Liver dysfunction more significant than in HELLP/pre-eclampsia)
Thrombotic thrombocytopaenic purpura (TTP)/ Haemolytic uraemic syndrome (HUS)	<0.01%	▪ Onset in any trimester, but common during third trimester or postpartum	▪ Fever ▪ Visual changes ▪ Altered mental status ▪ Thrombotic episodes ▪ Renal	▪ Microangiopathic haemolytic anaemia ▪ Elevated creatinine ▪ Normal coagulation screen

			impairment	▪ Elevated LDH
Disseminated intravascular coagulation (DIC)		▪ Secondary to pregnancy related complications such as severe pre-eclampsia, amniotic fluid embolism, IUD, placental abruption	▪ Clinical features of the underlying condition with evidence of coagulopathy	▪ Prolonged INR and APTT ▪ Haemolysis ▪ Multiorgan failure may occur

6.2 Preconception care

- Disease remission for at least 6 months prior to conception should have been achieved.

6.3 Antenatal care

- The mother needs to be followed up in collaboration with a haematologist for specialised care.
- Aim to keep the platelet count > 30 x 10^9/L throughout pregnancy.

Box 6.4.1 First line treatment for ITP in pregnancy

Steroids

Oral prednisolone 0.25-0.5 mg/Kg (15-30mg/day) taken as a single dose in the morning +/- proton pump inhibitors.

- In pregnancy, prednisolone is preferred to dexamethasone, as the latter crosses the placenta more readily.
- The patient should be reviewed in one week to assess the platelet count.
    - 70-80% responds initially
    - Approximate time to response vary from several days to several weeks
    - The steroid dose should be tapered to maintain a safe platelet count
        - Regular monitoring for steroid induced diabetes should be performed

Box 6.4.2 Second line treatment (In order of priority)

1. IV immunoglobulins
- This is considered in the absence/inadequate response to prednisolone
- Dose: 1g/kg/day for 1-2 days
- Up to 80% responds initially; Usually a rapid response, typically in 2-4 days

2. Splenectomy
- Is safe to perform in the second trimester
- Response rate is 80%

3. Azathioprine
- Dose is 1-2mg/kg/day; Maximum dose is 150mg/day
- Response rate is 40%; Usually a slow response; May need to continue for several months
- Can be used as a steroid sparing agent

Contraindicated in pregnancy

Cyclophosphamide, Mycophenolate, Vincristine, Danazol

Transfusion of platelets *has no place in the management of ITP, except in the following circumstances:*

- *Platelet count <10 x 10^9 /L with bleeding*
- *Need for emergency delivery, surgery or invasive procedures with suboptimal platelet count*
- *Life threatening bleed*

Box 6.4.3 Management of a life-threatening bleed

- In the event of a life-threatening bleed (E.g. intracranial hemorrhage) associated with a low platelet count the following should be administered.
  - Platelet transfusion, IV immunoglobulin (1g/kg/day for 1-2 days) and IV Methyl prednisolone (0.5-1.0 g/d for 3 days)

- Monitoring during pregnancy should be individualised according to the platelet count, the trimester and the trend of platelet rise.
  - Monthly monitoring of platelet count is recommended in 1st and 2nd trimesters
  - In the third trimester more frequent monitoring is recommended
- Avoid IM injections and NSAID use when the platelet count is < 50 x 10^9/L.
- Weigh the risk and benefits in women with a platelet count < 50x 10^9/L, who require aspirin for obstetric indications.

6.5 Indications for admission

- If the platelet count is less than < 10 x 10^9 /L (repeated and confirmed)
- When spontaneous bleeding occurs (irrespective of the platelet count)

6.6 Delivery

- The platelet count should be monitored every week from 36 weeks onwards. If delivery is planned earlier, weekly monitoring from 34 weeks onwards is advised.
- ITP is not an indication for caesarean section. Mode of delivery should be based on obstetric indications.

Box 6.6- Safe platelet count for delivery

- **Vaginal delivery >50 x 10^9/L**
- **Caesarean section >50 x 10^9/L**
- **Epidural anesthesia> 80 x 10^9/L**

- If a safe platelet count is not achieved with steroid treatment and the patient is close to delivery (>37 weeks of gestation) consider,
  - IV immunoglobulin 1g/Kg /day-for 2 consecutive days. The response lasts for 2-3 weeks.
  - If IV immunoglobulin is not available, a course of i.v. methylprednisolone (1g daily for 3 days) can be given.

- If maternal platelet count remains low (<50x 10^9/L**)** around the time of delivery in spite of all above measures, platelets should be available on standby.

- If the platelet count is < 10x 10^9/L or if haemorrhage occurs with a platelet count < 50 x 10^9/L at delivery, 6-10 units of platelet packs should be given

.

- Paediatric team to be informed at time of delivery.

6.7 Postpartum care

- Risk of disease flare is increased.
- Plan to review with a platelet count at one month postpartum and if normal at six weeks postpartum.
- Arrange for long term care after the 6-week review.

6.8 Neonate of a mother with ITP

- Check the full blood count on a cord blood sample; Maternal platelet count is a poor predictor of the neonatal platelet count.
  - The platelet count should be reassessed the following day, if the initial count is low.
  - Neonates with low platelet count should be monitored as the platelet count falls to a nadir between 2-5 days.
- If the neonatal platelet count is < 50 x 10^9/L at any time, perform a cranial US scan.
- If the platelet count is < 20 x 10^9/L with evidence of haemorrhage, a single dose of IV immunoglobulin (1g/Kg) could be administered and repeated as necessary.
- Platelets should be transfused for life threatening bleeds.
- Intramuscular vitamin K should be avoided until the platelet count is known; Consider giving it orally if the platelet count is <50 x 10^9 /L.

6.9 Thrombotic thrombocytopaenic purpura (TTP)

- This is a prothrombotic state caused by ultra large Von Willebrand factor (Vwf) molecules leading to aggregation and adhesion of platelets within the microvasculature.
- Pregnancy is known to precipitate TTP. It is also associated with autoimmune conditions.
- Without appropriate treatment the mortality is high as 90%.
- This can recur in future pregnancies.

6.9.1 Diagnostic criteria

- Fever
- Acute Renal impairment
- Central nervous system involvement
- Thrombocytopaenia
- Microangiopathic haemolytic anaemia

- Blood picture is helpful in suspected TTP and with very high LDH levels helps confirm.
- The pentad need not be fulfilled for diagnosis.
- A normal coagulation profile is seen.

6.9.2 Management

- If TTP is suspected, plasma exchange should be instituted **as early as possible**. These patients should be transferred to a tertiary care unit urgently where facilities for plasma exchange and specialist care is available.
  - If facilities for plasma exchange are not available, cryo-poor plasma should be infused without delay.
  - If cryo-poor plasma is not available FFP can be given.
- Platelet transfusion is <u>contraindicated</u> in this situation
- Once platelet count rises to >50,000 consider LMWH for thromboprophylaxis as DVT risk is very high.

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7. Antiphospholipid syndrome

7.1 Introduction

- Antiphospholipid syndrome (APS) is an acquired thrombophilic state caused by autoantibodies.
- APS is diagnosed when 1 clinical and 1 laboratory criteria (confirmed on two occasions 12 weeks apart) is positive.

Box 7.1 Revised diagnostic criteria for APS

Clinical criteria

1. Vascular thrombosis
   - One or more clinical episodes of arterial, venous or small vessel thrombosis in any tissue or organ
2. Pregnancy related morbidity
   - One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation OR
   - One or more premature births of a morphologically normal neonate before 34 weeks of gestation, due to eclampsia, severe preeclampsia or recognised features of placental insufficiency OR
   - Three or more unexplained consecutive spontaneous miscarriages before 10th week gestation with maternal, anatomical, hormonal abnormalities and parental chromosomal causes excluded

Laboratory criteria (A positive test should be repeated after a minimum interval of 12 weeks)

1. Positive lupus anticoagulant in plasma
2. Anticardiolipin antibody of IgG/IgM present in medium/high titres measured by a standardized ELISA test
3. Anti β2 glycoprotein 1 of IgG and/or IgM in titre > 99th percentile measured by a standardized ELISA test

- Time lapse between the clinical event and laboratory testing should not be less than 12 weeks or more than 5 years.
- Lupus anticoagulant (LA),
  - is a coagulation-based test.
  - should not be tested during pregnancy and until 6 weeks postpartum

- testing should not be performed while on anticoagulants

- Anticardiolipin (aCL) antibody and anti-β2 glycoprotein 1 inhibitor (Anti- β2 GP1),
  - are immune mediated tests.
  - could be evaluated during pregnancy and while on anticoagulation.

Management of APS during pregnancy

7.2 Preconception

- A history of pulmonary embolism needs assessment for pulmonary hypertension, which is a contraindication for pregnancy.

- Secondary APS (APS associated with autoimmune connective tissue disease, commonly SLE) should be excluded in view of adverse implications in pregnancy.

7.3 Antenatal care

- Women already on anticoagulation should withhold warfarin on confirmation of pregnancy and be reviewed by a haematologist/specialist physician for advice on suitable anticoagulation during pregnancy. (The different anticoagulation regimens are given in Box 7.3 below)

  - Baseline full blood count and coagulation assays should be performed prior to commencement of heparin.

  - Low molecular weight heparin (LMWH), throughout pregnancy is the preferred. Use of heparin in the first trimester with warfarin substituted in the second trimester until 36 weeks of gestation, is an alternative when there are constraints in accessing LMWH.

  - LMWH and Aspirin should be commenced in early pregnancy once an intrauterine viable foetus is confirmed by ultrasound scan.

- Graduated compression leg stockings are recommended for those at risk of deep vein thrombosis in pregnancy and up to 2 weeks postpartum

Box 7.3 Preferred treatment in pregnancy in women with antiphospholipid syndrome

Clinical situations	Suggested treatment
aPL positive women with no history of thrombosis or pregnancy loss	Although there is no evidence of benefit, low dose Aspirin is recommended during the antenatal period; Consider 7 days of thromboprophylaxis with Heparin postpartum.
APS and previous recurrent first trimester miscarriage, second/third trimester loss, severe pre-eclampsia, fetal growth restriction or placental abruption	Start low dose Aspirin and fixed dose of Heparin (e.g. Enoxaparin 40 mg daily) early in pregnancy once a viable fetus is seen and continue until 7 days postpartum.
APS and previous venous thrombosis	Aspirin and fixed dose heparin, which is doubled at 16 – 20 weeks and continued until 6 weeks postpartum.

- Assessment of Anti Xa levels is not routinely recommended in pregnancy. It is indicated only in the following situations.
  - In women at extremes of body weight (less than 50 Kg or more than 90 Kg) on therapeutic dose of LMWH
  - Renal impairment
  - History of recurrent VTE while on anticoagulation
- Assessment of anti Xa levels is currently not available in Sri Lanka.

7.4 Delivery

- Women on warfarin should be changed over to LMWH at 36 weeks.

- Vaginal delivery is the preferred mode; Caesarean section should be performed only for obstetric indications.

- Delivery should be planned.
  - Prophylactic LMWH should be withheld 12 hours prior to delivery
  - Therapeutic LMWH should be withheld 24 hrs prior to delivery

7.5 Postpartum

- Therapeutic dose of LMWH should be continued for 6 weeks postpartum in the event of an acute thrombosis in pregnancy and in women who have a history of arterial or venous thrombosis outside pregnancy.

- In women with obstetric manifestations of APS, 7 days of prophylactic LMWH is adequate.

- Early mobilisation, adequate hydration and wearing of compression stockings until 2 weeks postpartum should be advised.

7.6 Contraception

- Oestrogen containing contraceptives and Depot-povera are contraindicated.
    - Copper IUD is acceptable.

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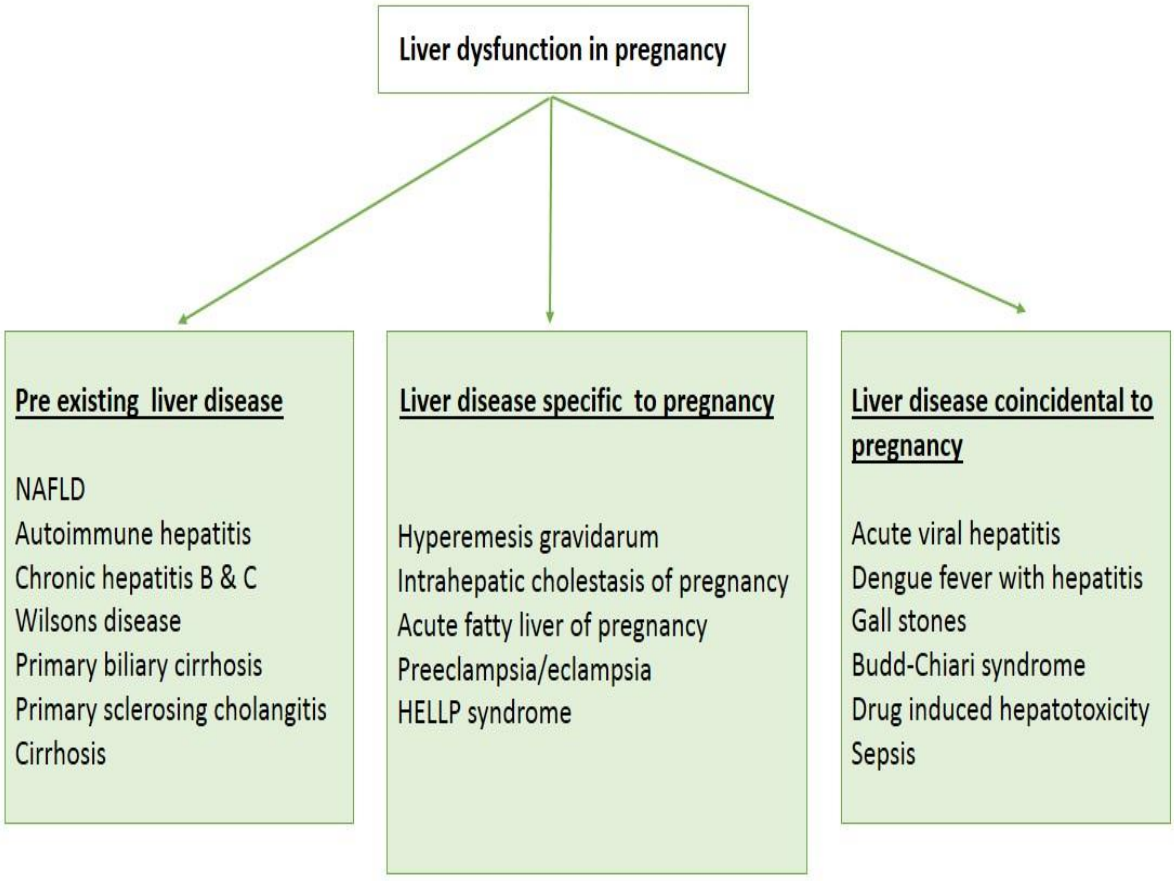
8. Liver disease in pregnancy

8.1 Introduction

- Liver dysfunction is known to affect up to 3% percent of pregnancies and is a leading cause of maternal mortality and morbidity in Sri Lanka.



8.2 Pre-existing liver disease

Pre conception care

- Risks of complications in the mother and fetus depends on the underlying condition and severity.
- The woman should be assessed by a specialist physician prior to pregnancy for advice on suitability for pregnancy, review and optimizing medication and target organ screening.

Chronic viral hepatitis

- Women should be reviewed by a hepatologist early in pregnancy for plan of management during pregnancy; Refer for hepatology opinion if the maternal viral load is high in the third trimester.
- Vertical transmission of hepatitis B during pregnancy is thought to be mainly transplacental even though transmission through secretions are also documented. However, studies to date have not shown any conclusive evidence of benefit of caesarean section over vaginal delivery. Mode of delivery should be based on obstetric indications.
- Mother to baby transmission is proportional to the maternal viral DNA and e antigen level.
- All babies born to hepatitis B surface antigen positive mothers should receive hepatitis B immunoglobulin and the first dose of the hepatitis B vaccine within 12 hours of birth.
- Patients with chronic viral hepatitis C are monitored closely, but there is no place for treatment during pregnancy. Mother to baby transmission rate of Hepatitis C has been shown to be higher with prolonged rupture of membranes.

Cirrhosis

- All patients with cirrhosis should be managed in a tertiary care center with facilities for endoscopy and variceal ligation.
- Women with suspected portal hypertension should have an upper endoscopy ideally in the preconception stage or at least in the second trimester to look for esophageal varices.
    - Management of esophageal varices:

- Prophylactic banding especially if the risk of bleeding is high, such as 'red signs' on varices or in patents with decompensated cirrhosis
- Avoidance of vaginal delivery due to risk of rupture of varices during the second stage of labor.
- Continuations of beta blockers (E.g.: Propranolol) throughout pregnancy with close maternal and fetal monitoring

- Management of upper GI bleeding:

  - Endoscopic banding is the treatment of choice
  - Broad spectrum antibiotics (preferably a 3rd generation cephalosporin such as IV Ceftriaxone) is recommended
  - Vasopressin is contraindicated; Terlipressin has not been studied in pregnancy
  - There is inadequate evidence for Octreotide, though if endoscopy and banding are delayed due to unavoidable circumstances, this may be considered. However, this should not be considered an alternative to timely endoscopy.

- Patients with cirrhosis should be screened with ultrasound specifically looking for the presence of a splenic artery aneurysm and if present referred to a tertiary care center for management

<u>Autoimmune hepatitis</u>

- Steroids and Azathioprine could be continued during pregnancy.
- Flares are infrequent during pregnancy though postpartum flares are expected.
  - Close surveillance postpartum with review at 6 weeks is recommended.

<u>Wilsons disease</u>

- Lowering the dose of D-penicillamine during the first trimester is recommended with maintenance on the lowest dosage during all trimesters.

- Reduce D-penicillamine to a minimal dose of 300–600 mg/day in the last trimester in order to avoid copper deficiency in the fetus and insufficient wound healing after caesarean section or episiotomy.

    - If caesarean section is planned, the dose of Penicillamine should be limited to 250 mg/day for 6 weeks before delivery and postoperatively until wound healing is complete

- Breast feeding under chelation therapy is not recommended.

8.3 Liver disease specific to pregnancy

When to suspect liver disease

Symptoms:

Pruritus, right hypochondrial pain, dark coloured urine or yellow discoloration of eyes, vomiting and swelling of feet (sudden onset in latter part of pregnancy), drowsiness and flu like symptoms.

Signs:

Icterus, peripheral oedema out of proportion to the gestational period/rapid onset or associated with hypertension, right hypochondrial tenderness, splenomegaly, reduced level of consciousness and liver flaps.

Box 8.4- First line Investigations in a pregnant woman suspected with liver disease

Investigation	**Finding**	**Comments**
SGOT (AST) SGPT(ALT)	Any rise warrants evaluation	Mild elevation Dengue infection (SGOT>SGPT) Preeclampsia/HELLP syndrome (SGOT>SGPT) Intrahepatic cholestasis of pregnancy (ICP) Hyperemesis gravidarum Acute fatty liver of pregnancy (AFLP) Marked elevation (Serum level >1000 U/L) Acute viral hepatits Drug induced liver disease including Paracetamol overdose Hypoxic hepatic injury Mild elevation in otherwise asymptomatic individual Preexisting fatty liver disease Cirrhosis
Serum bilirubin	Any rise warrants evaluation	Mild elevation Hyperemesis gravidarum (HG) Acute fatty liver of pregnancy (AFLP) –early stage Haemolysis, elevated liver enzymes and low platelets (HELLP) Sepsis Marked elevation Cholestatic viral hepatitis Late stage of AFLP Any cause of obstructive jaundice
FBC	Thrombocytopaenia	Cirrhosis with portal hypertension Severe pre-eclampsia HELLP syndrome Liver failure
PT/INR	Any rise needs further evaluation	Prolongation suggests liver failure
Gamma GT	Any rise needs further evaluation	Prolonged in cholestatic and drug induced liver disease
Alkaline phosphatase	Isolated elevation is normal in pregnancy	

8.5 Further evaluation of a woman with suspected liver disease

Details are specified under individual liver disease below.

8.5.1 Hyperemesis gravidarum

- Patients present with persistent vomiting, weight loss, dehydration +/- ketosis usually from 4^{th} to 20^{th} week of pregnancy.
- Affects 1-1.5% of pregnancies.
- Is more common with molar pregnancy, preexisting diabetes, and multiple pregnancies.
- Usually has no effect on fetal outcome, unless prolonged and associated with nutritional deficiencies.
- Liver dysfunction includes:
    - Increased transaminases in 50% (in the lower hundreds)
    - An increase in bilirubin being less common with jaundice found only occasionally
    - Severity of liver disease correlates with vomiting
- Management includes:
    - Hydration, with monitoring of fluid balance and electrolytes.
    - Endoscopic insertion of a NJ tube should be considered in very severe cases when adequate nutrition and hydration cannot be maintained by other means.
    - Antiemetics.

8.5.2 Intrahepatic cholestasis of pregnancy

- Prevalence is around 2/1000 of pregnancies.
- Typically presents with pruritus at around 25 to 32 weeks of gestation.
    - Pruritus is severe at night and affects palms and soles
- No maternal complications except for pruritus, which could be distressing.
- Fetal complications include premature labor and sudden fetal death.
- Pruritus and liver dysfunction resolve after delivery.
- High risk of recurrence in a subsequent pregnancy.
- Liver dysfunction includes:
    - Elevated aminotransferase levels (10 to 20-fold)
    - Jaundice in 10%-25% of patients, 2-4 weeks after pruritus; Bilirubin is usually less than 5mg/dL
    - Rise in alkaline phosphatase levels up to fourfold with a normal or mildly elevated GGT
    - Elevated fasting serum bile acid levels (>10 μmol/L) which is the most specific and sensitive marker of ICP; This could rise up to 100-fold
    - Deficiency of Vit K if liver functions are severely deranged
- Management includes:
    - Symptomatic therapy
        - Ursodeoxycholic acid (UDCA) 10 to 15 mg/kg body weight per day
        - Fat soluble vitamin supplementation in severe steatorrhoea
    - Close monitoring and early delivery of the fetus.

8.5.3 Preeclampsia

- Preeclampsia is the occurrence of hypertension, proteinuria +/- oedema after 20 weeks of pregnancy.
- It affects around 3% of pregnancies; Is the commonest cause of hepatic tenderness in pregnancy
- Liver involvement, indicates severe preeclampsia.
- Liver dysfunction includes:
    - Increase in serum aminotransferase levels which is usually mild. SGOT is usually more than SGPT.
    - Jaundice which is not common and usually associated with serum bilirubin level less than 5 mg/dL
    - Subcapsular haematoma which could occur with severe liver derangement
- Management includes:
    - Close monitoring of maternal and fetal well being
    - Delivery is the definitive therapy
        - No specific therapy is needed for hepatic involvement of preeclampsia; It's significance is as an indicator of severe disease.

8.5.4 HELLP Syndrome

- Severe preeclampsia is complicated in 2%-12% of cases by hemolysis (H), elevated liver enzymes (EL), and low platelet count (LP).
- Diagnosis requires the presence of all 3 laboratory criteria.

Box 8.5.4- Diagnostic Criteria for HELLP Syndrome

Haemolysis

- Fragmented red blood cells /LDH >600 U/L/ Elevated indirect bilirubin

Elevated liver enzymes

- AST>70U/L

Low platelets

- Plt ct< 150×10^9

- Most patients present in the 3rd trimester, but 25% present in the postpartum period.

- Most patients present with upper abdominal pain and tenderness, nausea, vomiting, malaise, headache, oedema, hypertension and proteinuria.

- The diagnosis of HELLP syndrome must be quickly established because of the necessity for immediate delivery considering the maternal and fetal risk.

- Liver dysfunction includes:
    - Raised aminotransferase levels from mild to 10-20-fold
    - Mildly elevated serum bilirubin; Jaundice is uncommon

- Management includes:
    - Delivery as the definitive therapy

8.5.5 Acute Fatty Liver of Pregnancy (AFLP)

- This almost exclusively occurs in the third trimester; Rarely in late second trimester.

- Common presentations are anorexia, nausea, vomiting and right upper quadrant pain.

- Patient may have jaundice, hypertension, peripheral oedema, ascites and hepatic encephalopathy.

- Patient may present with hepatic failure; Therefore, is associated with significant maternal and perinatal morbidity and mortality.

- About 50% of patients with AFLP have preeclampsia, and there is overlap with HELLP syndrome.

- Women with AFLP have an increased risk of recurrence in a future pregnancy.

- The main differential diagnoses for acute liver failure in the third trimester are AFLP, HELLP, and fulminant viral hepatitis.

- In comparison with HELLP syndrome, patients with AFLP are more likely to develop coagulopathy, hypoglycemia, encephalopathy, DIC, and renal failure

➢ Liver dysfunction include**:**

- Mild to severe elevation of aminotransferases (usually up to 300 to 500U/L)
- Mild elevation of serum bilirubin which is usually less than 5mg/dL but higher in severe or complicated disease

Box 8.5.5- Swansea diagnostic criteria for diagnosis of acute fatty liver of pregnancy

Six or more of the following features in the absence of another explanation suggests a diagnosis of AFLP

- Vomiting
- Abdominal pain
- Polydipsia/polyuria
- Encephalopathy
- High bilirubin (>14 µmol/L)
- Hypoglycaemia (<4 mmol/L)
- High uric acid (>340 µmol/L)
- Leucocytosis (>11×106/L)

➢ Other typical abnormalities are:

- Normochromic, normocytic anaemia
- Thrombocytopaenia

➢ Management

- Early referral to a specialist care center on suspicion of AFLP
- Consider immediate delivery to avoid adverse maternal and fetal outcome
- Intensive care to manage complications of liver failure

- Most patients improve in 1 to 4 weeks postpartum, although a cholestatic phase with rising bilirubin and alkaline phosphatase may persist.

- Recovery can occur in days or be delayed for months but is complete with no signs of chronic liver disease.

- Liver transplantation has a very limited role because of the great potential for recovery with delivery, but ideally may have a place in patients whose clinical course continues to deteriorate with advancing fulminant hepatic failure.

8.6 Liver disease coincidental to pregnancy

8.6.1 Non-alcoholic fatty liver disease (NAFLD)

- Incidental detection of fatty liver on USS with isolated, mild elevation in liver transaminases suggest NAFLD.
- First diagnosis of NAFLD during pregnancy should be made only after excluding other causes of liver dysfunction.
- Patient should have a plan for follow up after delivery.

8.6.2 Dengue infection

- It is associated with fever, myalgia, arthralgia, headache and vomiting.
- High transaminases (SGOT>SGPT) and thrombocytopenia is seen.
- Dengue antigen (Ag) is positive on day 1-2 of fever while Dengue IgM/IgG is positive on day 5-7 of illness.

8.6.3 Acute viral hepatitis

- It usually follows the same disease course as the nonpregnant population.
    - Exceptions are hepatitis E and herpes simplex infection, which have significant mortality and morbidity in pregnancy
- High transaminase levels typically over 1000 U/L, +/- recent history of fever, vomiting and right hypochondrial pain suggest viral hepatitis though AFLP could present in a similar way. (Elevation of transaminases is usually <1000U/L, in AFLP).
- Hep A IgM/Hep B s Ag/HCV antibodies/Hep E Ab should be requested for confirmation of viral hepatitis.
- Breast feeding in patients with Viral Hepatitis
    - Hepatitis A and E –Breast feeding can be continued
    - Hepatitis B –Once the baby is immunized, the benefits outweighs risk of transmission Therefore breast feeding should not be delayed. However it should be avoided if the nipples are cracked

- Hepatitis C - Benefits outweighs risk of transmission; Therefore breast feeding should not be delayed. If nipples are cracked, expressed breast milk can be used

Hepatitis E infection

- Acute infection with Hep E virus may result in fulminant hepatitis with risk of liver failure.

Herpes simplex virus (HSV) hepatitis

- High transaminase levels may occur.
- HSV DNA is positive.
- Consider Acyclovir.

8.6.4 Gall stone disease

- Gallstones are more common in pregnancy, especially during the second and third trimester and should be considered, especially in the presence of characteristic abdominal pain.
- Patients with symptomatic gall stones should be managed in a tertiary care centre where facilities for ERCP and laparoscopic cholecystectomy are available.
- ERCP can be performed if it is absolutely necessary with adequate radiation protection.
- Pregnancy itself does not increase frequency or severity of ERCP related complications.
- Cholecystectomy is best performed in the second trimester.
    - Laparoscopic cholecystectomy is preferred over open surgery.

8.7 Sepsis

- This mimics liver disease in pregnancy.
- Biochemical abnormalities include:
  - High WBC
  - Elevated serum bilirubin
  - Mild -moderate elevation in liver transaminases
  - Coagulopathy and DIC- high INR and thrombocytopaenia.
- Blood culture should be obtained and IV antibiotics commenced early.

8.8 Acute liver failure

Definition:

The presence of coagulopathy (international normalized ratio [INR] >1.5) and any degree of encephalopathy occurring within 24 weeks of the first onset of symptoms of liver disease in patients without previous history of liver impairment.

Causes of acute liver failure include,

Acute viral hepatitis, AFLP, Paracetamol poisoning, autoimmune hepatitis, Budd-Chiari syndrome.

Management of acute liver failure

General measures:

- The patient should be managed in an intensive care unit under the care of the obstetrician and hepatologist/gastrointestinal physician.

1. Close monitoring of mean arterial pressure, serum electrolytes, fluid balance, renal functions and blood sugar values.
2. Elevate the head of the bed 30° and maintain the head in a neutral position.
3. Lactulose may be used to ensure regular bowel opening.
4. Although oral Metronidazole is beneficial in patients with chronic hepatic encephalopathy, the benefit of these drugs in acute liver failure is controversial as the pathogenesis of acute liver failure is related to cerebral edema as opposed to ammonia excess.
5. 3rd generation cephalosporin is the choice of prophylactic antibiotic.

6. Consider IV N- Acetyl cysteine (NAC) - 150mg/Kg over 1 hour, 50mg/Kg over 4 hours, 150mg/Kg over 24 hours. Last dose should be repeated for 3 days.

7. Monitor with daily liver function tests including INR and clinical assessment of level of consciousness including liver flaps.
8. If sepsis is suspected, treat with IV antibiotics.

Specific measures:

The patient should be referred to the hepatologist for investigation and treatment of the underlying cause for acute liver failure.

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9. Renal disease in pregnancy

9.1 Introduction

- Renal disease could be either pre-existing or diagnosed for the first time in pregnancy. Renal impairment is associated with significant maternal and fetal morbidity and mortality.

Physiological changes in renal system in pregnancy

1. Increase in proteinuria
   - Proteinuria increases up to 300mg/d by the third trimester of pregnancy.
     - 24 h urine collection for urinary protein excretion and measurement of creatinine clearance remains the gold standard for measurement of renal function in pregnancy

2. Decrease in serum creatinine levels
   - Serum creatinine falls by an average of 0.4 mg/dL to a pregnancy range of 0.4 to 0.8 mg/dL.
     - Hence, a serum creatinine of 1.0 mg/dL, although normal in a non-pregnant individual, reflects renal impairment in a pregnant woman

3. Dilatation of the renal tract with increased incidence of reflux nephropathy
   - The urinary collecting system (renal calyces, pelvis, and ureters) dilate. The dilated collecting systems can hold up to 300 mL of urine and hence serves as a reservoir for bacteria.
   - In the later stages of pregnancy, mechanical compression of the ureter against the pelvic brim may lead to hydroureter and hydronephrosis.
   - Hydronephrosis occurs on the right in 90% of cases due to dextrorotation of the uterus by the sigmoid colon.

Pregnancy and kidney disease

The main determinant of pregnancy outcome is the degree of renal impairment.

Effect of pregnancy on kidney disease:
Worsening proteinuria
Loss of kidney function- may be irreversible

Effect of kidney disease on pregnancy:
Preterm delivery
Fetal growth restriction (FGR)
Intrauterine death
Preeclampsia

9.2 Preexisting renal disease

Preconception care

- All women with renal disease should be seen by a nephrologist prior to becoming pregnant.
- Women should be counselled on the risk of pregnancy, depending on the underlying renal disease and baseline renal functions.
- An individualized care plan including cardiac assessment should be performed, in view of increased risk of coronary artery disease.

Fertility

- Fertility rates are thought to decline proportionately with declining renal function. Women with CKD stage ≥ 3 (GFR < 30ml/min/1.73m^2) are generally less fertile.

Contraception

- Use of contraceptives should be advocated until it is safe for the woman to become pregnant.

- Most contraceptives could be used in women with renal impairment.
  - Oestrogen containing contraceptives should be avoided in women with hypertension and those at increased risk of thrombosis (e.g.: nephrotic syndrome).

- Intra uterine device (IUD) could be used.

Diabetic nephropathy

- The presence of diabetic nephropathy is a risk factor for increased perinatal morbidity and mortality.

  - A favourable outcome is to be expected with
    - Serum creatinine <1.4 mg/dl (124 mmol/L)
    - Proteinuria <1 g/24 h
    - Normal blood pressure

  - Serum creatinine >2 mg/dL (176 mmol/L) is the best predictor of the risk of pregnancy induced decline in maternal kidney function leading to end stage renal disease (ESRD) during pregnancy or shortly afterwards.

Management

- Multidisciplinary care with involvement of the obstetrician and nephrologist.

- Attain normotension and euglycaemia in the preconception stage, with counselling on the risk of worsening proteinuria and its implications on pregnancy.

- Angiotensin receptor inhibitors (ACEI) and angiotensin receptor blockers (ARB) must be withheld in pregnancy.

- During pregnancy, 75mg of Aspirin should be commenced at 12 weeks of gestation and continued until delivery.

- Aim to maintain blood pressure < 135/85mHg throughout pregnancy with monthly assessment of renal functions (serum creatinine, electrolytes and proteinuria).

- Fetal growth monitoring after 28 weeks.

9.3 Adult onset polycystic kidney disease

- Normotensive women with normal renal function generally have uncomplicated pregnancies, though there is an increased risk of maternal complications such as hypertension and preeclampsia.

- Cerebral imaging for aneurysm should be performed before pregnancy, and if present, consider elective caesarean as mode of delivery.

- The patient and the spouse should be counselled regarding the risks of giving birth to an offspring who has a 50% chance of developing this condition later in life

9.4 Lupus nephritis

- Pregnancy is safe if,
  - in remission with ≤10 mg daily of prednisone for 6 months
  - Serum creatinine is < 1.4 mg/dL
  - Blood pressure is well controlled

- Women with class III or IV lupus nephritis are at increased risk of hypertension and renal flares.

- Complications of poorly controlled disease include,

  - spontaneous abortions
  - fetal growth restriction
  - premature delivery
    - Especially in the presence of antiphospholipid antibodies

- Azathioprine and Prednisolone are safe in pregnancy.

9.5 Other glomerulonephritides

- Assessment for suitability of pregnancy and optimization of disease should be undertaken in the preconception stage.
    - Aim for disease remission for at least six months before planning pregnancy

- Focal segmental glomerulosclerosis (FSGS) and membranocapillary glomerulonephritis (MCGN) are generally associated with poor prognosis with risk of worsening renal impairment in pregnancy.

- Minimal change and membranous glomerulonephritis usually have a good outcome.

- Women with significant proteinuria are at high risk of deep vein thrombosis; Need for thromboprophylaxis during pregnancy and the postpartum period should be discussed.

9.6 Renal disease occurring during pregnancy

9.6.1 Urinary tract infections (UTI)

Lower UTI

- Take a single urine sample for culture before empiric antibiotic is started.

- A seven-day course of treatment is normally sufficient.

- A urine culture should be performed two weeks after completion of antibiotic treatment as a test of cure. Monthly urine cultures should be checked thereafter until delivery.

Box 9.6.1 Empiric antibiotic therapy for lower UTI

- Nitrofurantoin 100 mg 6 hourly
    - Avoid in G6PD deficiency
    - Do not prescribe in the last 2 to 4 weeks of pregnancy

- Amoxicillin 500 mg 8 hourly
- Coamoxiclav 625 mg 12 hourly
- Cephalexin 500 mg 8 hourly

Upper UTI

- The incidence of pyelonephritis is higher in pregnancy due to the physiological changes of the urinary tract.
- The risk of renal impairment secondary to pyelonephritis is also higher in pregnancy compared to the non-pregnant population.

Box 9.6.2 Empiric antibiotic therapy for upper UTI

- Ceftriaxone 1-2 g IV or IM daily
- Aztreonam 1 g IV 8-12 hourly
- Piperacillin-tazobactam 3.375-4.5 g IV 6 hourly
- Cefepime 1 g IV 12 hourly
- Imipenem-cilastatin 500 mg IV 6 hourly
- Ampicillin 2 g IV 6 hourly
- Gentamicin 3-5 mg/kg/day IV in 3 divided doses

- After clinical improvement parenteral therapy can be switched to oral therapy for a total treatment duration of 7-10 days.
- Those with complicated disease may require a longer course of antibiotic.
- Monthly urine cultures must be checked till delivery.
- Ultrasound scan of KUB should be done to look for obstruction, calculi or anatomical abnormalities.

Asymptomatic bacteriuria (AB)

- Asymptomatic bacteriuria is diagnosed when two consecutive voided urine specimens grow $>10^5$cfu/mL of the same bacterial species or a single catheterized specimen grows $>10^5$cfu/mL of an uropathogen, in the absence of symptoms of urine infection.
- Treatment of asymptomatic bacteriuria in pregnancy reduces the risk of pyelonephritis, preterm delivery and low birth weight babies.

- Asymptomatic bacteriuria in pregnancy is usually treated with a short course (3-7 days) of antibiotics, similar to that used in treatment of low UTI.

- All pregnant women should be screened for bacteriuria during the first trimester.

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9.6.2 Pre-eclampsia

- Pre-eclampsia (BP ≥ 140/90 mmHg, proteinuria ≥ 300mg/day +/- peripheral oedema, occurring after 20 weeks of gestation) is the commonest medical complication in pregnancy and is more common in women with preexisting hypertension and chronic renal disease of any cause or severity.

- Renal impairment could accompany severe preeclampsia, which is usually reversible following delivery.

- Women with the following risk factors should be commenced on 75mg of Aspirin at 12 weeks of pregnancy and continued until delivery, in order to reduce the risk of preeclampsia.

    - Pre-existing types 1 or 2 diabetes mellitus
    - History of hypertensive disease in pregnancy
    - Women with systemic lupus erythematosus (SLE) or antiphospholipid syndrome
    - Women with preexisting hypertension, irrespective of the aetiology
    - Women with chronic renal impairment, irrespective of the aetiology

9.6.3 Acute fatty liver of pregnancy (AFLP)

- This condition, which usually occurs in the third trimester, is primarily a disease of the liver which causes acute kidney injury (AKI) in severe cases.

- Management of renal impairment is similar to that described under AKI below. (AFLP is dealt with in detail in the section on 'liver disease in pregnancy')

9.6.4 Haemolytic Uraemic Syndrome (HUS) / Thrombotic Thrombocytopaenic Purpura (TTP)

- These thrombotic microangiopathies belong to a spectrum of disease, though they are two different entities.

- It typically occurs within in the last trimester and up to 8-10 weeks postpartum.

- Acute kidney injury is a feature.
- Plasma exchange is the treatment of choice.

9.7 Acute kidney injury (AKI)

Definition (Acute Kidney Injury Network criteria)

AKI is defined as any one of the following:

- Increase in serum creatinine by ≥ 0.3 mg/dL (≥26.5 μmol/l) within 48 hours or,
- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days or
- Urine volume <0.5 ml/kg/hour for 6 hours, in an individual without pre-existing renal impairment.

Box 9.7.1 Causes of AKI in pregnancy

1. Massive PPH
2. Acute pyelonephritis
3. Preeclampsia
4. Diabetic nephropathy
5. Glomerulonephritides
6. Acute fatty liver of pregnancy
7. Thrombotic thrombocytopaenic purpura/Haemolytic uraemic syndrome

Management

- Management is similar to that outside pregnancy.
- Stabilise the patient and arrange transfer to a tertiary care center with facilities for dialysis/CVVH and for multidisciplinary care.

Management of hyperkalaemia associated with AKI

- Hyperkalaemia is defined as serum K concentration > 5.5 mmol/L.
- In an emergency, K+ measured from an arterial or venous blood sample using a blood gas analyzer is acceptable whilst awaiting the results from a formal laboratory measurement.
- ECG monitoring is recommended for all patients with serum K+ value ≥ 6.5 mmol/L.

Box 9.7.2 Pharmacological management of hyperkalaemia

- 10ml of 10% Calcium gluconate over 10 minutes into a peripheral vein if ECG shows features suggestive of hyperkalaemia. (Tall peaked T waves, small/absent P waves, wide QRS complex)
    - Repeat ECG in 10 minutes- If no improvement repeat same dosage; Could give 3 doses in total
- Insulin Actrapid (short acting insulin) 10 units in 50 mL of 50% glucose over 30 minutes (via intravenous infusion).
- Monitor blood glucose after 15mins, 30mins and then hourly for up to 6 hours as there is a risk of late hypoglycaemia.
- Nebulised salbutamol 10-20mg.
- Serum potassium should be assessed at least 1, 2, 4, 6 and 24 hours after identification and treatment of hyperkalaemia.
- Arrange transfer to a nephrology center in whom hyperkalaemia cannot be controlled using medical measures, particularly in the presence of advanced or oliguric renal failure (either AKI or CKD).
    - A medical person should accompany all such transfers

9.8 Chronic kidney disease

9.8.1 Preconception care

- The degree of renal insufficiency, rather than the underlying renal diagnosis, is the primary determinant of outcome, with the exception of scleroderma and polyarteritis nodosa, which generally have a poor prognosis.

- Factors generally associated with unfavourable pregnancy outcome include:
  - Estimated GFR of ≤40 ml/min/1.73m^2
  - Proteinuria ≥1 g/d
  - Serum creatinine ≥ 1.4g/dL

  - Complications in the presence of any of the above include, accelerated progression towards end stage renal disease (ESRD) and preterm delivery.

- Review by a nephrologist for advice on suitability for pregnancy and review and optimizations of medications is mandatory.

Anaemia

- Consider erythropoietin when the Hb < 9g/dL and the iron stores are replete.

Bone disease

- Phosphate binders and vitamin D analogues are currently used with no adverse effects. There is limited experience with Cinacalcet and Lanthanum carbonate.

9.8.2 Antenatal care

- Arrange for regular review by the nephrologist.

- Patient should be assessed in the antenatal clinic every 2 weeks until 32 weeks and weekly thereafter.

  - BP should be carefully monitored

  Aim to:

- Maintain blood pressure below 150/100 mmHg and diastolic BP above 80 mmHg in women with uncomplicated chronic hypertension

- Maintain blood pressure below 140/90 mmHg in those with target organ damage secondary to chronic hypertension (e.g.: renal impairment)

  - Serum creatinine and 24-hour protein excretion should be monitored monthly

  - Fetal growth should be closely monitored

- If renal impairment is progressive, with no evidence of a reversible cause, termination of pregnancy should be considered at the earliest.

  - If only proteinuria is increasing, with no evidence of fetal growth restriction, pregnancy can be continued under close monitoring by the nephrologist and obstetrician

- Dialysis is required when the GFR falls to less than 20ml/min/1.73m^2.

  - At least 20 hours of dialysis per week is required with the aim of maintaining blood urea below 60mg/dL

9.8.3 Renal transplantation

- Fertility rates increase dramatically after transplantation.

- Women with a renal transplant should be referred to a nephrologist for advise on suitability of pregnancy and optimisation of the underlying renal condition.

- Graft rejection rates are similar to the general population.

- In general, fetal outcome is good.

  - Risk of preterm birth and small for gestational age babies increase in the presence of maternal hypertension and impaired baseline renal graft function

- Calcineurin inhibitors, steroids, and Azathioprine are safe for use in pregnant transplant recipients.
  - Screening for gestational diabetes is important, with prolonged use of steroids.

9.8.4 Women on long term renal dialysis

- It is not advisable to become pregnant because pregnancy usually leads to volume overload, exacerbation of hypertension and preeclampsia.
- If patient wishes to continue pregnancy, then frequency and duration of dialysis should be increased to 20 hours per week and blood urea maintained below 60 mg/dL.

9.8.5 Indications for renal biopsy during pregnancy

- Rapidly progressive renal failure (RPRF) with no obvious cause
- Symptomatic nephrotic syndrome– not a universal indication

Renal biopsy is best avoided after 32 weeks of gestation, at which time the risks and benefits of biopsy versus delivery should be considered.

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