

NATIONAL GUIDELINE FOR MATERNAL CARE

VOLUME II

Management of Medical Disease Complicating Pregnancies

- 1 Bronchial Asthma
- 2 Tuberculosis
- 3 Influenza A & B Virus Infection Including H1N1
- 4 Liver Disease
- 5 Renal Disease
- 6 Thyroid Disease
- 7 Rheumatoid Arthritis
- 8 Systemic Lupus Erythematosus
- 9 Immune Thrombocytopaenic Purpura
- 10 Antiphospholipid Syndrome
- 11 HIV
- 12 Syphilis
- 13 Malaria

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Statement of Intent

The main Purpose of these guidelines are to improve the quality of clinical care provided by the health care providers at all levels. These parameters of practice should be considered as recommendations only. The ultimate judgement regarding a particular clinical procedure or a treatment plan must be made by the clinician in light of the clinical data gathered from the patient and the diagnosis and treatment options available.

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Preface

This national guideline on maternal care is very well-timed, as a greater emphasis is being given for improving the quality of maternal care services for further reduction of maternal and newborn mortality and morbidity in Sri Lanka. This set of guidelines has addressed the relatively rare but important disease entities which is matching with the epidemiological transition of causality of maternal deaths from direct causes to indirect causes. This is an attempt to improve the quality and uniformity of clinical care with efficiency, cost effectiveness and accountability.

I highly appreciate the contribution made by Ceylon College of Physicians, Sri Lanka College of Obstetricians and Gynaecologists and relevant public health programmes in developing these guidelines. Their experience and updated scientific knowledge is reflecting in the guidelines.

Further, these guidelines have been developed considering the policies, facilities, and resources available in the country. As such this set of guideline will be considered as national guidelines for the conditions described.

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Content page

	Page
Preface	iii
Guideline Development committee	vi
List of Abbreviations	x
Disclaimer	xi
Introduction	xii

1.	Bronchial Asthma in Pregnancy	3
1.1	Introduction	3
1.2	Women with pre-existing bronchial asthma	3
1.3	When to suspect bronchial asthma in a previously healthy woman	4
1.4	Management of bronchial asthma in pregnancy	6
1.4.1	Pharmacological management	6
1.4.2	Adjuvant therapy for bronchial asthma	9
1.5	Indications for transfer to intensive care unit (ICU)	10
1.6	Antenatal care	11
1.7	Delivery	11
1.8	Postpartum care	12
2.	Management of Tuberculosis during Pregnancy	15
2.1	How does tuberculosis spread?	15
2.2	Risk of infection	15
2.3.1	Who is a TB suspect?	15
2.3.2	Case of a 'Bacteriological confirmed TB'	15
2.3.3	Case of a 'clinically diagnosed TB'	15
2.4	Common symptoms of pulmonary tuberculosis	16
2.5	Investigations	16
2.6	TB treatment regimens	18
2.6.1	Intensive phase	18
2.6.2	Continuation phase	19
2.6.3	Standard code for TB treatment regimens	19
2.6.4	Monitoring of sputum smear- positive pulmonary TB	20
2.6.5	Treatment during pregnancy	20
2.6.6	Treatment during breast feeding	21

2.6.7	Management of a new born child of a mother with active TB	21
2.6.8	Directly Observed Treatment	22
2.6.9	Interruption of treatment (Lost to follow up)	22
2.6.9.1.	Measures to minimize treatment interruption	23
2.6.9.2	Management of patients who interrupt treatment	23
2.7	Notification	23
2.8	Contact screening	23
2.9	Preventive Treatment	24
3.	Management of Influenza A & B Virus Infection Including H1N1 in pregnancy	27
3.1	Introduction	27
3.2	Protection against infection	27
3.3	Case identification	28
3.4	Seeking medical care	28
3.5	Management in the hospital	29
3.6	Laboratory diagnosis	30
3.7	Antiviral therapy	31
3.8	Management of Labour	32
3.9	New born care	32
3.10	Discharged criteria	33
3.11	Notification	33
3.12	Safety of HealthCare workers	34
4.	Liver Disease in pregnancy	37
4.1.	Introduction	37
4.2	Pre-existing liver disease	38
4.2.1.	Chronic viral hepatitis	38
4.2.2.	Cirrhosis	39
4.2.3.	Autoimmune hepatitis	39
4.2.4.	Wilscons disease	40
4.3	Liver disease specific to pregnancy	40
4.3.1.	When to suspect liver disease	40
4.3.2.	Hyperemesis gravidarum	42
4.3.3.	Intrahepatic cholestasis of pregnancy	42
4.3.4.	Preeclampsia	43
4.3.5.	HELLP Syndrome	43

4.3.6.	Acute Fatty Liver of Pregnancy (AFLP)	44
4.4.	Liver disease coincidental to pregnancy	46
4.4.1.	Non alcoholic fatty liver disease (NAFLD)	46
4.4.2.	Dengue infection	46
4.4.3.	Acute viral hepatitis	47
4.4.4.	Gall stone disease	48
4.4.5.	Sepsis	48
4.5.	Acute liver failure	48
5.	Renal disease in pregnancy	53
5.1.	Introduction	53
5.2.	Pre-existing renal disease	54
5.2.1.	Diabetic nephropathy	55
5.2.2.	Adult onset polycystic kidney disease	55
5.2.3.	Lupus nephritis	56
5.2.4.	Other Glomerulonephritides	56
5.3.	Renal disease occurring during pregnancy	56
5.3.1.	Urinary tract infections (UTI)	56
5.3.1.1.	Lower UTI	56
5.3.1.2.	Upper UTI	57
5.3.1.3.	Asymptomatic bacteriuria (AB)	57
5.3.2.	Preeclampsia	58
5.3.3.	Acute fatty liver of pregnancy (AFLP)	58
5.3.4.	Haemolytic Uraemic Syndrome (HUS) / Thrombotic Thrombo cytopaenicPurpura (TTP)	58
5.4.	Acute kidney injury (AKI)	59
5.5.	Chronic kidney disease	60
5.5.1.	Preconception care	60
5.5.2.	Antenatal care	61
5.6.	Renal transplantation	61
5.7.	Women on long term renal dialysis	62
5.8.	Indications for renal biopsy during pregnancy	62
6.	Thyroid disease in pregnancy	65
6.1.	Introduction	65
6.2.	Hypothyroidism in pregnancy	66
6.2.1.	Definitions	66
6.2.2.	Management of hypothyroidism in pregnancy	67

6.3.	Hyperthyroidism in pregnancy	69
6.3.1.	Definitions	69
6.3.2.	Management of overt hyperthyroidism in pregnancy	70
6.4.	Postpartum thyroid dysfunction (PPTD)	73
7.	Rheumatoid arthritis	79
7.1.	Introduction	79
7.2.	Preconception care	79
7.3.	Antenatal care	81
7.4.	Delivery	81
7.5.	Postpartum care	81
8.	Systemic Lupus Erythematosus	85
8.1.	Introduction	85
8.2	Preconception care	85
8.3	Antenatal care	87
8.4	Delivery	88
8.5	Postpartum care	88
8.6	Contraception	88
8.7	Neonatal lupus syndrome	89
8.8	Treatment of lupus nephritis (LN) in pregnancy.	89
8.9	Other autoimmune connective tissue disease	89
9.	Immune thrombocytopaenic purpura	93
9.1.	Introduction	93
9.2	Management of ITP in pregnancy	96
9.3.	Neonate of a mother with ITP	99
9.4.	Thrombotic thrombocytopaenic purpura (TTP)	99
10.	Antiphospholipid syndrome	103
10.1.	Introduction	103
10.2.	Management of APS during pregnancy	104
11.	Prevention and management of HIV in pregnancy	109
11.1.	Primary prevention strategies	109
11.2.	Screening for HIV during pregnancy	109
11.2.	When the confirmatory test results is negative	110
11.3.	When the screening test is positive	110
11.4.	Support to the HIV positive woman	111
11.5.	Delivery care	112

11.6.	Post partum care	112
11.7.	Counsel HIV positive woman on family planning	112
11.8.	Infant feeding with HIV	113
12.	Prevention and management of Syphilis during pregnancy	117
12.1.	Introduction	117
12.2.	Screening for syphilis	117
12.3.	Diagnosis of syphilis	117
12.4.	Treatment of maternal syphilis	118
12.4.1.	Treatment of primary, secondary and early latent syphilis	118
12.4.2.	Late latent syphilis:	118
12.5.	Follow up	119
12.6.	Allergy to penicillin	119
12.7.	Treatment of partners	119
12.8.	Diagnosis of congenital syphilis	119
12.9.	Treatment of the baby	120
13.	Guidelines on malaria chemotherapy and management of patients with malaria during pregnancy	125
13.1	Introduction	125
13.2	Patients likely to have malaria	125
13.3	Notification of malaria patients	126
13.4.	Diagnosis of malaria	126
13.5.	Monitoring during treatment and follow up of patients	127
13.6	Treatment of patients with malaria	127
13.6.1.	Mono-infection with Plasmodium vivax	128
13.6.2.	Uncomplicated mono-infection with Plasmodium falciparum	128
13.6.3.	Uncomplicated mixed infections with P. falciparum and P.vivax	129
13.6.4.	Severe P. falciparum malaria	130
13.6.5.	Patients infected with other malaria parasites	131
13.7.	Chemoprophylaxis for malaria	131
Annex I.	Severe malaria	132
Annex II.	Countries where malaria transmission occurs	133
Annex III.	Telephone numbers related to Anti Malaria Campaign	134

List of Abbreviations

WHO	World Health Organization
UNICEF	United Nations Children's Fund
UNFPA	United Nations Population Fund
SLCOG	Sri Lanka College of Obstetricians and Gynaecologists
BA	Bronchial Asthma
PEFR	Peak Expiratory Flow Rate
JVP	Jugular Venous Pressure
LABA	Long Acting Beta 2 Agonist
SABA	Short Acting Beta 2 Agonist
AFB	Acid Fast Bacilli
PTB	Pulmonary Tuberculosis
DOT	Directly Observed Therapy
CNS	Central Nervous System
NSAIDs	Non Steroidal Anti Inflammatory Drugs
MOMCH	Medical Officer Maternal and Child Health
ALT	Alanine Amino Transferase
AFLP	Acute Fatty Liver of Pregnancy
NAFLD	Non Alcoholic Fatty Liver Disease
WBC	White Blood Cells
DIC	Disseminated Intravascular Coagulation
IUD	Intra Uterine Device
ACEI	Angiotensin receptor Inhibitor
UTI	Urinary Tract Infection
HUS	Haemolytic Uraemic Syndrome
TTP	Thrombotic Thrombocytopenic Purpura
AKI	Acute Kidney Injury
GFR	Glomerular Filtration rate
TSH	Thyroid Stimulating Hormone
HCG	Human Chorionic Gonadotropins
APS	Anti Phospholipid Syndrome
RDHS	Regional Director of Health Services
MO-STD	Medical Officer – Sexual Transmitted Diseases
MOH	Medical Officer of Health
VOG	Visiting Obstetrician and Gynaecologist
LSCS	Lower Segment cesarean Section

Disclaimer

This guidance is intended to provide general advice to streamline the management and maintain overall quality of patient care. It should never be relied on as a substitute for proper clinical assessment with respect to the particular circumstances and needs of each patient under your care. It is the responsibility of each Practitioner to have regard to the particular circumstances of each individual patient, and the application of this guidance.

This guidance has been prepared having regard to the information available at the time of its preparation. Medicine is a continually evolving science and the users must have regard to relevant information, research or material, which may have been published or become available subsequently.

Introduction

Clinical Guidelines are systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions based on the best scientific evidence at the time of development. Guidelines are not intended to limit the clinical freedom; however, clinicians are expected to follow these recommendations as the basis for their decisions. Availability of resources, the existing situations, and the expectations of individual client needs to be considered.

The guidelines are intended to guide all health care workers in all levels of institutions where maternity care is provided. Although these guidelines are mainly targeted for the government sector institutions, use in the private sector institutions where maternity care is provided, is also encouraged.

These guidelines are developed by expert group from the Ceylon College of Physicians and consensus were obtained from the guideline development group of the Sri Lanka College of Obstetricians and Gynaecologists in consultation with other relevant specialists such as anaesthesiologists, physicians, endocrinologists, and haematologists etc. The existing national and international guidelines, and WHO guidelines were perused and mixed with the local scenarios and expert opinion. The latest available scientific evidences were considered and included where ever necessary. Then, the draft guidelines were presented to the wider forum of experts and consensus were reached. After that the guidelines were handed over to the Ministry of Health and consensus were built with the participation of multi-disciplinary team including medical administrators, provincial health authorities, representatives from SLCOG and other relevant professional colleges, and national programme managers.

Bronchial Asthma

1. Bronchial asthma in pregnancy

1.1. Introduction

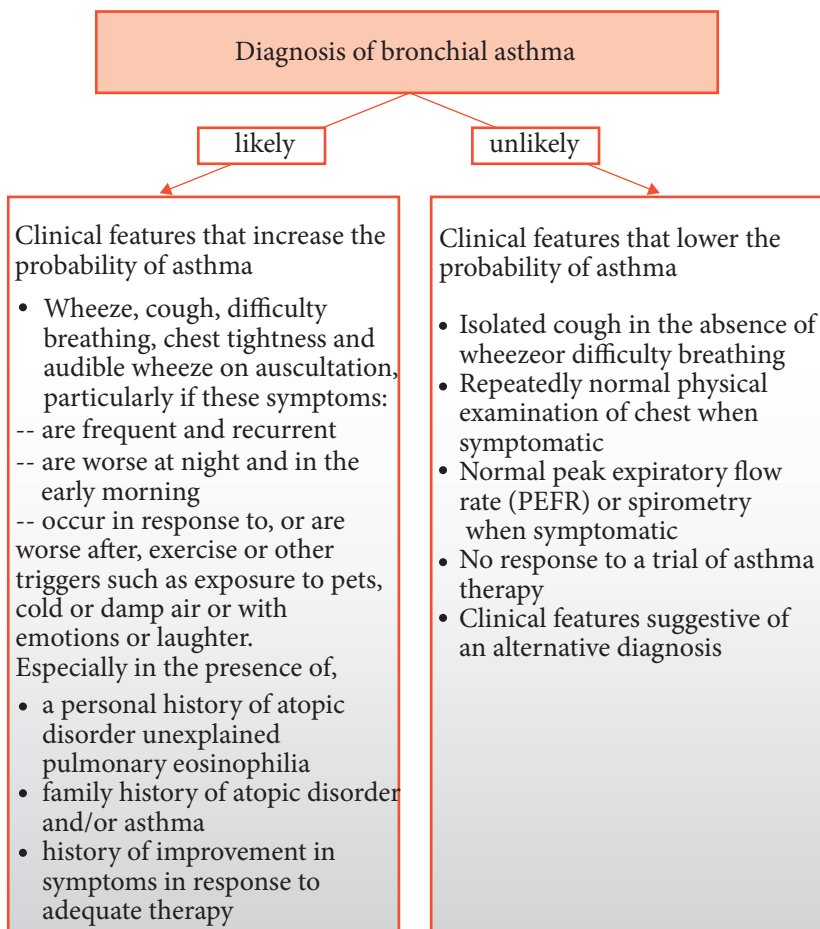
- The majority of women with bronchial asthma (BA) have an uncomplicated pregnancy.
- Poorly controlled BA is associated with maternal and perinatal morbidity and mortality, including,
 - o Spontaneous abortion
 - o Fetal growth restriction
 - o Preterm delivery
 - o Low birth weight babies

1.2. 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 in pregnancy is variable.
 - o One third of women experience improvement in symptoms, one third worsening and one third remain unchanged.
 - o Women with poorly controlled asthma, are more likely to experience worsening of symptoms during pregnancy.
 - o Worsening of symptoms is most likely in the second and third trimesters.
 - o In the last month of pregnancy and during the peripartum period, patients are least likely to have an asthma attack.

1.3. 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.



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

Box 1.1 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 $> 400\text{ml}$ or peak expiratory flow rate (PEFR) of $>15\%$ of baseline PEFR after inhalation of

a. Salbutamol $400\text{ }\mu\text{g}$ ($100\text{ }\mu\text{g} \times 4$) via a spacer device

OR

b. Inhaled corticosteroids (Beclomethasone $200\mu\text{g}$ 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.

➤ 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

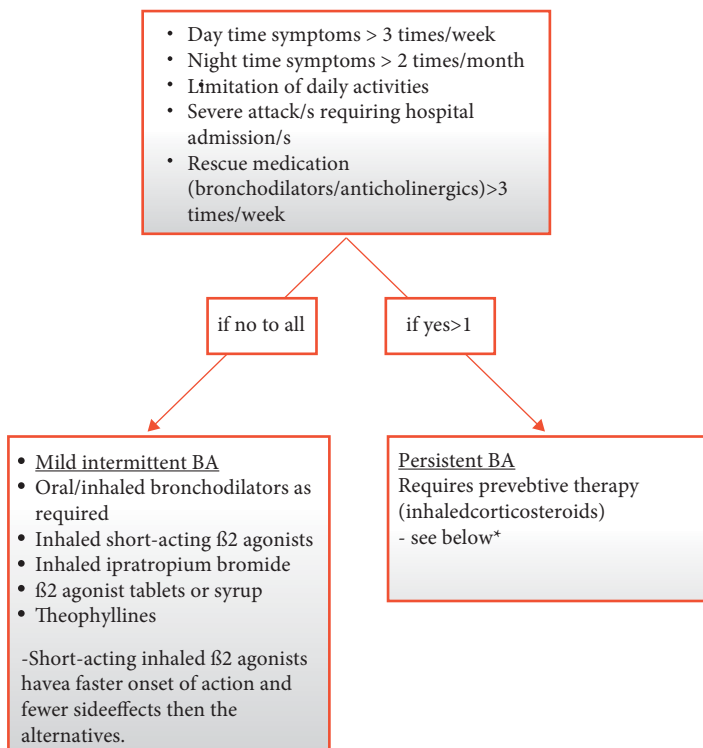
Cardiac disease in particular should be excluded, when symptoms are atypical and not responding to conventional antiasthma medications.

1.4. Management of bronchial asthma in pregnancy

1.4.1. Pharmacological management

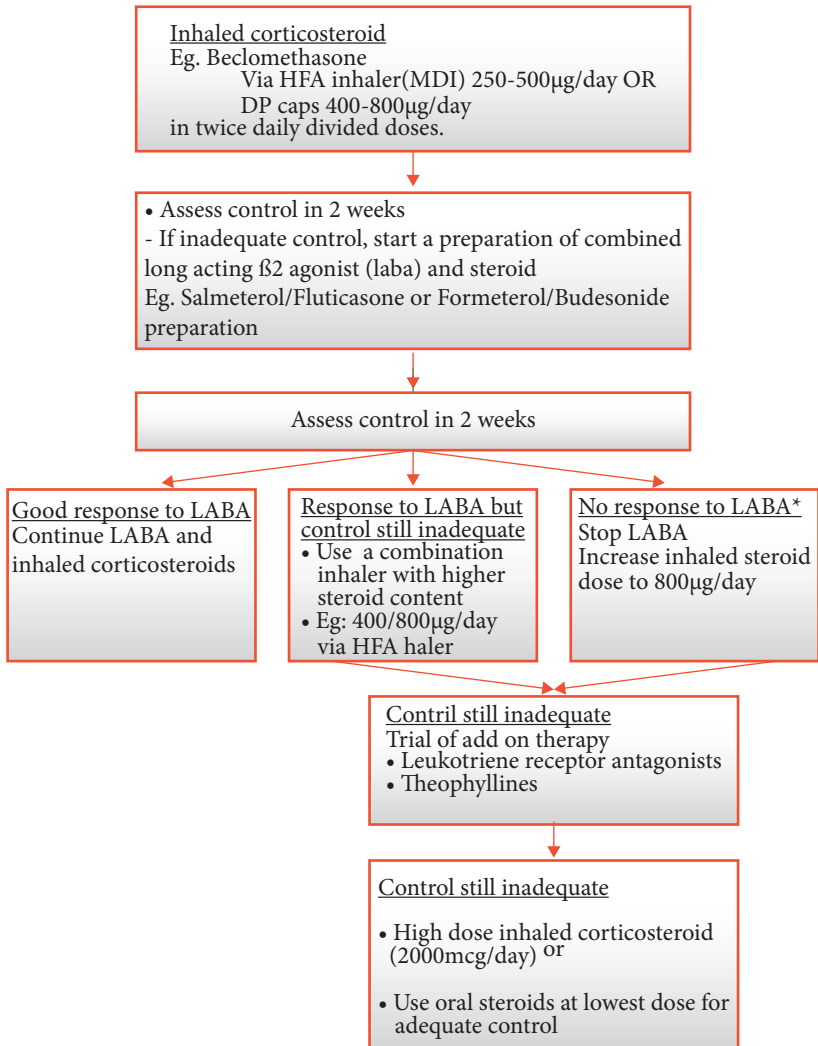
- Medications used in the non pregnant population have been shown to be safe in pregnancy in treatment doses.
- Harm to the fetus from severe or chronically undertreated asthma outweighs any small risk from the medications used to control asthma.
- Women should be informed of the importance of continuing 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



◆ Persistent BA

- Start patient at a dose of inhaled corticosteroids appropriate to the severity of disease.
- 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 1.2 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
 - Iprratropium inhalers (DP capsules -20 µg, HFA - 40 µg per puff)
 - Oral theophyllines – 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.
Eg: Salmeterol/Fluticasone
Formoterol/ Budesonide
- Leukotriene receptor antagonists
Eg: Montelukast 10mg once daily, usually at night

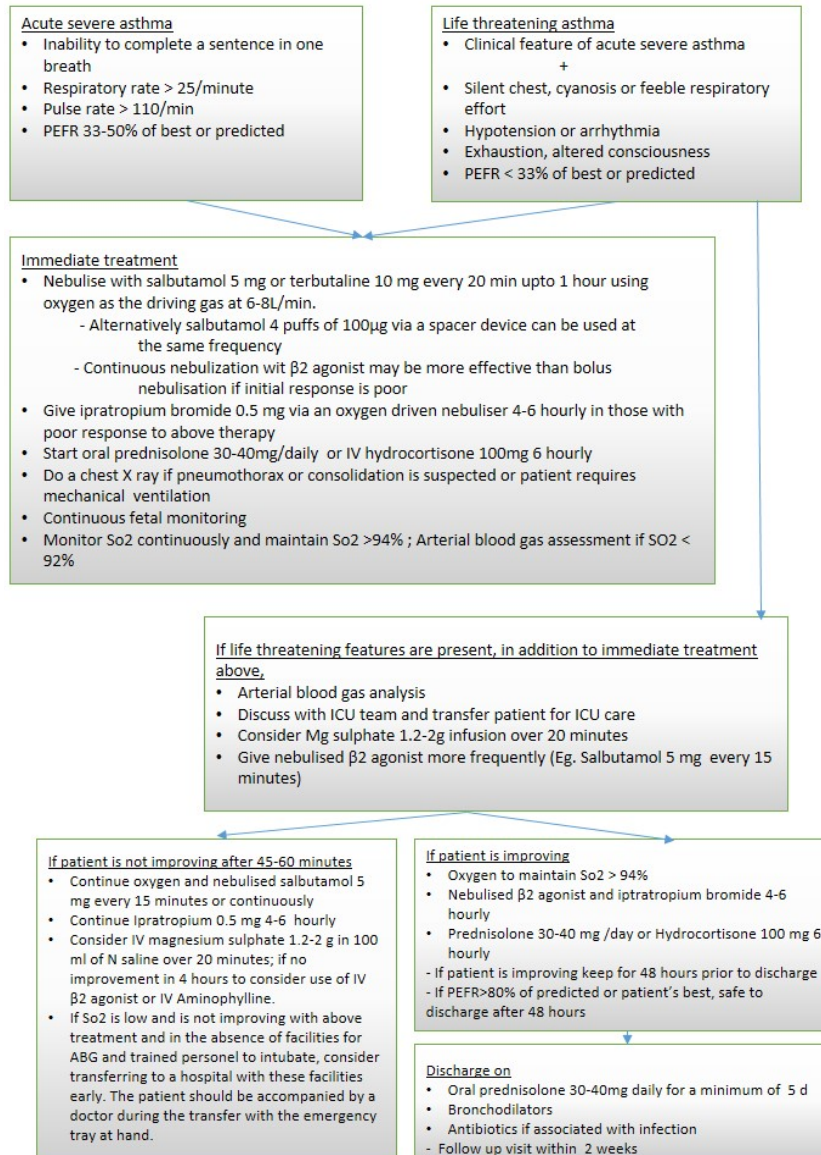
1.4.2. Adjuvant therapy for bronchial asthma

- Women with recurrent exacerbations related to gastro oesophageal reflux disease or allergic rhinosinusitis, need control of these with appropriate medication and lifestyle measures.
 - o Antihistamines - No teratogenicity reported
 - Sedating antihistamines used towards the latter part of pregnancy may adversely affect the neonate
 - o Intranasal steroids- Beclamethasone, Budesonide and Fluticasone are safe
 - o 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



1.5. Indications for transfer to the intensive care unit (ICU)

- Deteriorating PEFR despite appropriate treatment
- Persisting or worsening hypoxia

- Hypercapnia or inappropriate eucapnea (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 1.3 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

1.6. 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.

1.7. 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.

1.8. 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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Tuberculosis

2. Management of tuberculosis during pregnancy

Tuberculosis is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* and occasionally by *Mycobacterium bovis* and *Mycobacterium africanum*. Tuberculosis commonly affects the lungs, but it can affect any other organ in the body.

2.1. How does tuberculosis spread?

The bacteria that cause tuberculosis usually spread through air. When a patient with infectious pulmonary tuberculosis coughs, sneezes or laughs, bacilli are expelled into the air in the form of tiny droplets. These droplets dry up rapidly to form droplet nuclei and may remain suspended in the air for several hours. Adequate through and through ventilation removes and dilutes these droplet nuclei, and direct sunlight quickly kills the bacilli, but they can survive in the dark for several days. When a healthy person inhales these droplet nuclei containing the tubercle bacilli, he/she may become infected.

2.2. Risk of infection

An individual's risk of infection depends on the extent of exposure to an infectious source and susceptibility of the individual to infection. The risk of infection is therefore high in a person who has close, prolonged exposure to a person with sputum smear positive pulmonary TB. The risk of transmission of infection from sputum smear-negative pulmonary TB is low and with extrapulmonary TB, still lower.

2.3.1. Who is a TB suspect?

A TB suspect is a person who presents with symptoms or signs suggestive of TB, particularly cough of two weeks or more.

2.3.2. Case of a “Bacteriologically confirmed TB”

A patient whose biological specimen is positive by smear microscopy, culture or WRD (such as Xpert MTB/RIF).

2.3.3. A case of a “Clinically diagnosed TB”

One who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician who has decided to give the patient a full course of TB treatment. This definition includes cases

diagnosed on the basis of X-ray abnormalities or suggestive histology and extra pulmonary cases without laboratory confirmation.

Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

2.4. Common symptoms of pulmonary tuberculosis

The clinical presentation of tuberculosis in pregnant women is similar to that in non-pregnant patients.

Respiratory symptoms:

- Cough – usually more than two weeks
- Shortness of breath
- Chest pain
- Haemoptysis (blood stained sputum)

Constitutional Symptoms:

- Fever and night sweats
- Loss of appetite
- Loss of weight
- Tiredness (Fatigue)

However, prevalence surveys worldwide revealed that TB can be presented without cough also.

Symptoms of Extrapulmonary TB

The symptoms depend on the organ involved. Patients may present with constitutional features of the disease – fever, night sweats, loss of weight, and loss of appetite or local symptoms related to the site of the disease.

2.5. Investigations

Sputum Smear microscopy

Sputum smear microscopy is the most reliable and cost effective method of diagnosing infectious cases of pulmonary tuberculosis cases. Whenever tuberculosis is suspected in a patient who has had a cough of two weeks or more, three sputum samples should be collected and examined by microscopy for Acid-Fast Bacilli (AFB).

Collection of sputum samples

A PTB suspect should submit three sputum samples for microscopy. Three early morning samples are preferable. However due to practical reasons, sputum samples are taken in the following manner:

Patient should be advised to collect sputum after coughing following a deep inspiration and it should not be saliva.

First spot specimen - Supervised spot specimen at the first visit

Early morning specimen - Patient is given a sputum container to collect early morning specimen on the following day.

Second spot specimen - Second supervised spot specimen is collected when the patient returns with the early morning specimen, on the following day.

Chest X-ray

The chest X-ray has a limited role in confirming the diagnosis of pulmonary tuberculosis. Diagnosis of tuberculosis by means of X-ray alone is unreliable. Abnormalities seen on a chest X-ray may be mimicked by a variety of other conditions. However chest X-ray is helpful particularly to diagnose PTB in a suspect whose sputum smears are negative for AFB.

The decision to start on anti-TB treatment on patients should not be based solely on abnormal chest X-ray findings and all efforts should be made to perform sputum microscopy.

In pregnancy, chest X-rays should be avoided as far as possible, especially during the first trimester, because of the adverse effects of x-rays on the foetus.

Therefore, diagnosis will depend more on sputum examination when a pregnant mother presents with symptoms suggestive of tuberculosis. However, if an X-ray is absolutely necessary, this may be done with the abdomen covered with a lead apron.

Sputum Culture for AFB

Culture examination of sputum for AFB is more sensitive and specific than direct smear microscopy and may be useful in detecting cases where the number of organisms are fewer than can be detected by direct smear

microscopy. But this is more expensive and takes at least 6-8 weeks to get the results.

Under ideal circumstances pre-treatment sputum cultures for AFB should be performed on all PTB patients.

WHO recommended Rapid diagnostic tests

There are new rapid diagnostic methods available for detection of TB such as Xpert MTB/Rif and line probe assay.

Xpert MTB/Rif

Xpert MTB/Rif is an automated nucleic acid amplification test recommended by WHO for early detection of TB and resistance to rifampicin which is used as an indicator of multidrug resistance. The test takes around two hours, and requires minimal man power to perform. Xpert/Rif can detect TB bacteria at much lower concentrations.

Line probe assay

Line probe assay is a molecular method of diagnosing TB and the most common genetic mutations causing resistance to rifampicin and isoniazid. This technology can diagnose MDR-TB directly from smear positive sputum specimens and from culture isolates providing results in five hours. This test does not work well on smear negative specimens.

At present, these tests are offered for selected categories of patients (MDRTB suspects) due to limited availability.

2.6. TB treatment regimens

Treatment regimens consist of two phases:

1. Initial intensive phase
2. Continuation phase

2.6.1.Intensive phase

During the initial intensive phase, there is rapid killing of TB bacilli. Infectious patients quickly become non-infectious (within about two weeks) and symptoms improve. Most patients with sputum smear-positive pulmonary TB becomes smear negative within two months. Directly Observed Therapy (DOT) is essential in the initial phase to ensure that the patient takes every single dose. This prevents development of drug

resistance. The risk of development of drug resistance is higher during the early stages of anti-TB treatment, when there are more bacilli.

2.6.2.Continuation Phase

During the continuation phase, fewer drugs are necessary, but for a longer period. The sterilizing effect of the drugs eliminates the remaining bacilli, thus preventing subsequent relapses.

Patients who have taken anti-tuberculosis drugs previously are much more likely to develop drug resistance, which may have been acquired through inadequate prior chemotherapy. Such patients require a stronger regimen consisting of more drugs and for a longer period.

Therefore, before starting treatment, it is essential to question all patients closely and carefully to determine whether or not they have previously taken treatment for tuberculosis, so that they can be given the proper treatment regimen.

2.6.3.Standard code for TB treatment regimens

There is a standard code for TB treatment regimens and each anti-tuberculosis drug has an abbreviation.

H – Isoniazid
R - Rifampicin
Z - Pyrazinamide
E - Ethambutol
S – Streptomycin

A TB treatment regimen consists of two phases, the intensive phase and the continuation phase. The number before a phase is the duration of that phase in months. A subscript number (e.g. 3) after a letter indicates the number of doses of that drug per week. No subscript number after a letter indicates that the treatment is daily.

E.g.: 4 HR means 4 months of Isoniazid and Rifampicin daily.

5 H3 R3 E3 means 5 months of Isoniazid, Rifampicin and Ethambutol three times a week

Box 2.1 Case definitions, Treatment Categories and Recommended Regimens

Case Definition	Treatment Category	Treatment Regimen	
		Intensive Phase	Continuation Phase
New cases - PTB smear-positive - PTB smear-negative - Extrapulmonary TB	CAT I	2 HRZE	4 HR
Re-treatment cases - Relapses - Treatment after failure - Treatment after lost to follow up (smear-positive)	CAT II	2HRZES / 1 HRZE	5 HRE

2.6.4. Monitoring of sputum smear-positive pulmonary TB patients

Response to treatment should be monitored by sputum smear examination. For sputum smear positive PTB patients, sputum smear examinations should be performed at the end of the intensive phase of treatment (i.e., second month), during the fifth month and at the end of treatment. Negative sputum smears indicate good treatment progress.

For sputum smear negative patients also follow up sputum smear examinations should be performed at the end of two months, at the 5th month and at the end of the treatment period.

2.6.5. Treatment during Pregnancy

Anti-TB treatment should be started as soon as the diagnosis is made, and the full course of treatment given. The basic principles of treatment are the same in pregnancy. Most anti-TB drugs are safe for use during pregnancy except streptomycin.

Streptomycin should not be given because it can cause oto-toxicity in the foetus.

Pregnant mothers should be given pyridoxine 10mg daily along with INAH.

Vitamin K should be administered at birth to the infant of a mother taking rifampicin because of the risk of post-natal haemorrhage.

2.6.6. Treatment during breast-feeding

A patient who has TB and is breast-feeding should receive the full course of anti-TB treatment. Properly taken treatment is the best way of preventing transmission of TB to her baby. All anti-TB drugs are compatible with breast-feeding. A patient taking anti-TB treatment can continue to breastfeed her baby in the normal way.

Breastfeeding should be avoided only in cases where the mother has dual TB/HIV infection.

2.6.7. Management of a newborn child of a mother with active TB

- Do not separate the child from the mother unless she is acutely ill.
- If the mother is sputum smear negative, and if the infant has no evidence of congenital TB, BCG is given to the infant.

If the mother is sputum smear-positive at the time of delivery, infant should be carefully examined for evidence of active disease.

- If the infant is ill at birth and congenital TB is suspected, a full course of anti-TB treatment should be given.
- If the child is well, give prophylactic treatment with INAH 5mg/ kg body weight, daily for three months. BCG is withheld.
- The Mantoux skin test is done after three months.
 - If the Mantoux test is negative and the child is well, prophylactic treatment with INAH is stopped and child is given BCG.
 - If the Mantoux test is positive, careful examination of the child for active TB is done including a chest X-ray.
 - If active disease is diagnosed, a full course of anti-TB treatment should be commenced.
 - If the physical examination and the chest X-ray are normal, INAH chemoprophylaxis is continued up to six months and BCG is given.

2.6.8. Directly Observed Treatment

Directly Observed Treatment (DOT) is one of the important elements of the internationally recommended strategy for TB control. Directly Observed Treatment means that an observer watches the patient swallow their tablets. This ensures that a TB patient takes the right anti-tuberculosis drugs, in the right doses at the right intervals without interruption and ensures that the patient completes the full course of treatment. WHO recommendation is to provide DOTs throughout the whole treatment period.

DOT Providers –

The following categories will provide Direct Observation of Treatment.

- Health workers at state health care facilities
- Field health care workers
- General practitioners
- Trained volunteers
- Community leaders

Public health staff especially Public Health Nursing sisters and Public Health Midwives can play a significant role as DOT providers for antenatal and postnatal mothers in their areas who are on treatment.

Provision of drugs for the DOT Centres -

Drugs for each patient will be delivered to the DOT centres from the District Chest Clinic by the PHI or any other staff assigned by the DTCO.

2.6.9. Interruption of treatment (lost to follow up)

Directly Observed Treatment adapted to the needs of the patient is the best method of avoiding treatment interruption. However, even with directly observed treatment during the intensive period and during the continuation phase of treatment, which may be self-administered, there may be treatment interruption.

2.6.9.1.Measures to minimize treatment interruption

At the time of registration of a TB patient, the staff must educate the patient and the family regarding the duration of treatment and the importance of adherence to treatment.

It is vital to record the patient's address and other relevant addresses e.g. parents or work place etc. in order to help locate the patients who interrupt treatment. As far as possible, the address should be verified at the beginning of treatment.

Public Health Midwives in their field visits and at antenatal clinics should inquire about uninterrupted continuation of treatment from patients and should encourage them to continue treatment.

2.6.9.2. Management of patients who interrupt treatment

It is important to take action on defaulters immediately. Patients should be contacted the day after missing a dose during the intensive phase and as soon as possible during the continuation phase. It is important to find out the reason for the patient's absence in order to take appropriate action and continue treatment.

2.7. Notification

At the point of diagnosis, all tuberculosis patients should be notified using TB notification Form (H 816).

2.8. Contact screening

Household contacts of all TB patients (adults and children >5 years) should be screened for symptoms of TB. Those who have symptoms suggestive of TB should be investigated with sputum smears irrespective of the duration of the symptoms.

Children under the age of 5 years should be screened with chest X-ray and Mantoux test.

2.9. Preventive treatment

The aim of preventive treatment is to prevent progression of M. tuberculosis infection to disease.

Primary chemoprophylaxis

When a person is exposed to TB bacilli, but not yet infected eg. newborn breastfed baby of a sputum smear-positive mother

Secondary chemoprophylaxis

A person who is infected, but not yet developed clinical disease e.g. tuberculin positive close contacts of sputum smear-positive patients. In Sri Lanka, chemoprophylaxis is given for the following groups:

- Breast fed infants of sputum smear-positive mothers.
- Household contacts below 5 years of age of sputum smear-positive patients, who do not have evidence of active disease.
Prophylactic treatment in Sri Lanka is – INAH 5mg/ kg body weight for 6 months.

For further details refer ‘General Manual for Tuberculosis Control’ published by National Program for Tuberculosis Control and Chest Diseases.

Influenza A & B Virus Infection Including H1N1

3. Management of Influenza A & B Virus Infection Including H1N1 in Pregnancy

3.1. Introduction

With the presence of community transmission of influenza A/B (including H1N1) virus infection, it is important to note that pregnancy is considered as a high risk condition.

The disease may become more severe during pregnancy and there is a high risk of mortality due to complications especially in pregnant women with co morbidities such as diabetes, heart disease, bronchial asthma, cancer and anaemia. H1N1 infection is also associated with increased risk of adverse pregnancy outcomes such as spontaneous abortion, preterm birth and foetal distress.

The objective of this document is to provide all healthcare providers, both in preventive and curative sectors with specific guidelines to follow aiming to mitigate untoward consequences following H1N1 infection.

3.2. Protection against infection

- A. Pregnant women and women in reproductive age group should be educated on early clinical manifestations of influenza virus infection.

Clinical Manifestations

- Fever along with cough
- Sore throat
- Rhinorrhoea
- Headache
- Muscle pain
- Malaise

- B. They should avoid unnecessary travel, crowded public places and public transport as much as possible.
- C. They should be advised to stay at home and encourage to practice cough and sneeze etiquette (covering mouth and nose when coughing or sneezing) or wear a face mask (at least a home-made mask) if they have fever and flu-like symptoms.

- D. Pregnant women and new mothers should avoid providing care of persons with influenza like illnesses, except for their own newborns.
- E. All preventive measures to avoid transmission of infection should be taken by health care workers when attending to pregnant women.
- F. Anyone with respiratory symptoms should not provide care for the pregnant women, the mother and newborn baby.
- G. Care for symptomatic pregnant women (with fever and flu-like symptoms), should be organized in a separate area in the clinic or OPD whenever possible.

3.3. Case identification

Suspected Case:

An individual presenting with acute febrile respiratory illness (fever > 38 oC) with the spectrum of disease from influenza-like illness (cough, sore throat, shortness of breath) to pneumonia.

Probable case:

An individual tested positive for influenza A, but hasn't subtyped by reagents used to differentiate influenza virus strains.

Confirmed Case of H1N1 infection:

An individual tested positive for influenza A (H1N1) 2009 by real time RT-PCR

Note: A negative PCR result does not rule out that a person may be infected with influenza A (H1N1) 2009 virus. Results should be interpreted in conjunction with the available clinical and epidemiological information.

3.4. Seeking medical care

- A) Pregnant mothers should consult a qualified physicians (either in government or private sector) immediately if they have above symptoms (fever with cough, sore throat, rhinorrhea, headache, muscle pain, malaise).
- B) Suspected cases should be admitted to a hospital for specialized care, for management.

- C) If they present with features of complicated influenza or progressive disease such women may need ICU care.
- Manifestations of cardio-respiratory distress (e.g. shortness of breath either during physical activity or while resting / dyspnoea tachypnea, hypoxia, low blood pressure).
 - Radiological signs of lower respiratory tract disease (e.g. pneumonia)
 - Central nervous system (CNS) involvement (e.g. altered mental status, unconsciousness, drowsiness, recurring or persistent convulsions (seizures), confusion, severe weakness or paralysis)
 - Severe dehydration
- D) Medical Officers of Health and other healthcare workers involved in provision of care to pregnant mothers should highlight signs and symptoms of influenza illness in all health education activities, especially in routine antenatal clinics.
- E) Public Health Midwives and other field officials should refer any pregnant mother with fever and flu-like symptoms for proper medical care without delay.
- F) It is important to note that pregnant mothers and postpartum mothers can rapidly progress to severe form of the infection within a short period of time. Hence high degree of suspicion and vigilance is needed in treating influenza infection.

All pregnant mothers with influenza like illness should be admitted to a hospital with specialist care.

3.5. Management in the hospital

- A) Provide a disposable/surgical facemask to the patient.
- B) Ask to practice good hand hygiene and washing hands often using simple disinfectants such as soap. Discourage nose picking and limit touching the eyes, nose and mouth.
- C) Attending health care providers should wear face masks properly whenever in contact with infected/suspected mother.

- D) Isolation – care for symptomatic patients should be organized in a separate area in the antenatal ward (cohort isolation).
- E) Consultant or the clinician of the highest rank (Senior Registrar/ Registrar/ SHO) should be informed immediately on admission.
- F) Institutions managing pregnant women should request adequate stocks of oseltamivir
- G) Consider transferring patients only if required specialized care.
- H) Most of the infected pregnant women can be managed effectively if oseltamivir is started early. It is a must to start oseltamivir when influenza is suspected without waiting for laboratory confirmation.

3.6. Laboratory Diagnosis

- A) Upper respiratory samples are the most appropriate laboratory specimens. Samples should be taken from the deep nostrils (nasal swab), throat swab and nasopharynx (nasopharyngeal swab). Nasopharyngeal aspirate and bronchial aspirate gives the best diagnostic yield.
- B) Upper respiratory samples should be collected in to a special Viral Transport Medium (VTM) obtained from the Medical Research Institute (MRI).
- C) Health care workers should adhere to appropriate standard precautions when collecting specimens since this may expose to respiratory secretions from patients. Surgical mask and gloves are appropriate for obtaining upper respiratory tract samples and N95 mask, gown and gloves are recommended in aerosol generating procedures like aspirating respiratory secretions.
- D) Avoid collecting samples in open areas in the ward/clinic.
- E) These specimens should be sent to the MRI in ice packs without delay, using special request form developed by the MRI for this purpose.

- F) **A detailed clinical history** indicating the justification for the investigation should be included in the request.
- G) If there is a delay in transportation, place the sample temporally in the freezer compartment (4-8 Co) in the fridge for 24-48 hr. NEVER store the sample in deep freezer section in the fridge.

3.7. Antiviral therapy

Consultant or his delegate caring for the pregnant mother should start antiviral therapy immediately in suspected cases.

Dose: Oseltamivir 75 mg twice a day for 5 days.

In severe cases higher doses (150 mg) and longer duration of treatment may be considered.

Drug supply: Arrangements should be made to make 24hr availability of antiviral drugs in the hospital and /or obstetric and gynaecological wards.

The antiviral drug is safe for use even in the first trimester.

All pregnant mothers with severe/complicated disease or signs of progression of the disease (or even suspected cases) should be treated with oseltamivir.

Treatment should be initiated as soon as possible, without delay

Treatment with antiviral medications should begin without waiting for collecting specimen or results of diagnostic testing.

Chemoprophylaxis is NOT recommended in pregnancy

The patient should be provided with necessary supportive therapy (adequate nutrition and oral fluids) and medication (eg antipyretics, antibiotics where indicated, rehydration etc.).

Oxygen saturation should be monitored by pulse oximetry, whenever possible. Supplement oxygen should be provided to correct hypoxaemia. Severe cases may need care at an Intensive Care Unit. Therefore ensure the availability of such facilities beforehand.

Non-steroidal Anti Inflammatory Drugs. (NSAIDs) should be avoided.

Since there is high risk of foetal distress and preterm labour, consider administration of corticosteroids for promotion of fetal lung maturation where applicable.

3.8. Management of Labour

- A) Organize separate areas for labour and delivery for infected or suspected pregnant mothers
- B) Provided routine intrapartum and postpartum care.
- C) Provide appropriate interventions where indicated for specific complications related to childbirth, the postpartum/postnatal period or the newborn.
- D) Tocolytics can be used as for any other obstetric case.
- E) Since there is a higher risk of fetal distress, discuss with anaesthesiologist the risks and benefits of vaginal delivery and caesarean delivery. Consider the risks of anaesthesia in a severely ill woman.
- F) Reduce the length of stay in the postnatal ward to the minimum required by maternal and newborn condition.
- G) Anyone (including health care workers) with respiratory symptoms should not provide care for the pregnant woman or the mother and newborn baby.

3.9. Newborn Care

- A) Do not separate the baby from the mother even if the mother has influenza A pandemic (H1N1). Institute rooming –in.
- B) Mothers should wear a disposable/surgical facemask and practice good hand hygiene and hand washing with soap and water regularly before feeding or handing the baby.
- C) Support mothers to initiate breastfeeding within one hour of giving birth and to breastfeed frequently and exclusively on demand. If mother is ill, she should be helped to express her breast milk and feed it to the infant.

- D) **Antivirals not a contraindication for breastfeeding.**
- E) Newborns of infected mothers should be closely observed for possible development of infection.
- F) Newborn infants are unlikely to have typical influenza signs. Influenza or its complications in newborn infants may begin with less typical signs such as apnoea, fever, fast breathing, cyanosis, excessive sleeping, lethargy, feeding poorly and dehydration.
- G) Newborn infants with severe or deteriorating illness and those at risk of more severe or complicated illness should promptly be treated with antiviral drugs.

Oseltamivir dose for babies: 3mg/kg twice daily for 5 days

- H) Mothers who are breast feeding may continue breastfeeding while ill and receiving oseltamivir.

3.10. Discharged Criteria

Pregnant mothers could be discharged after completion of 4 days of treatment if she has clinically recovered. Decision on discharging those with severe disease should be taken by the treating clinicians based on their clinical judgment.

3.11. Notification:

All admitted cases should be notified using routine procedure to the relevant Medical Officer of Health by the treating clinicians.

Medical Officer – Maternal and Child Health (MO – MCH) should notify all suspected cases of H1N1 in pregnancy to Epidemiology Unit.

In the event of a maternal death, notification should be sent without delay to the Family Health Bureau. It should be emphasized that a post mortem is mandatory in all maternal deaths.

In addition to routine notification, all suspected or confirmed pregnant women/ newborns/children with H1N1 should be notified to family Health Bureau.

3.12. Safety of Health Care Workers

Please refer to the General Circular No: 01-37/2009 Interim Guidelines for Clinical Management and Laboratory Investigation of Patients with Pandemic Influenza A (H1N1) 2009. Virus Infection in a Setting with Sustained Transmission issued by Director General Services, Ministry of Health and Website of Epidemiology Unit www.epid.gov.lk

Care of pregnant HCW

Pregnant health care workers should be reassigned to non-contaminated or low risk areas eg. Orthopaedic units, dermatology Units.

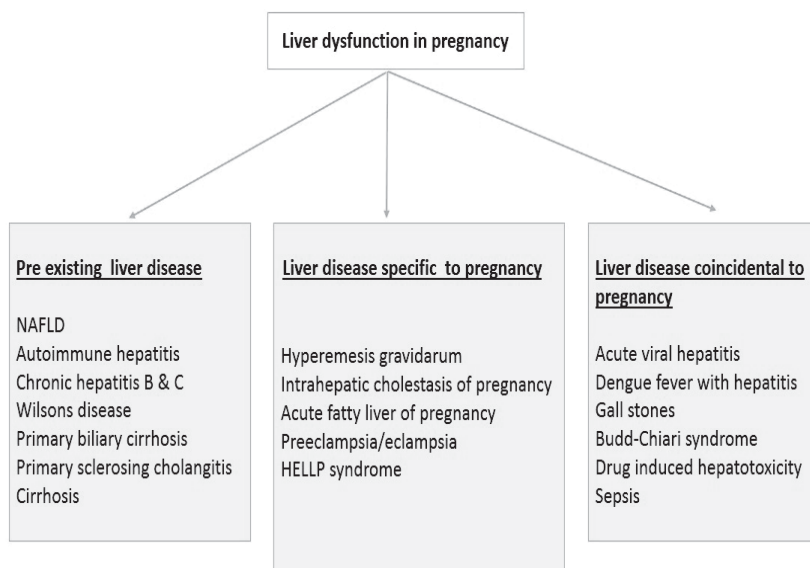
They should be given high priority to receive Personal Protection Equipments.

Liver Disease

4. Liver disease in pregnancy

4.1. 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.



Box 4.1: Normal biochemical changes during pregnancy

Total bilirubin	No change or slight decrease
AST/ALT	No change
Alkaline phosphatase	Increased by 200-400% (placenta and bone)
Gamma glutamyltransferase	No change or slight decrease
Albumin	Decreased
Prothrombin time/INR	No change
Platelets	No change/mild decrease
Total cholesterol and triglyceride	increased

- Therefore, any increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum bilirubin and INR in pregnancy warrants further evaluation.

4.2. 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.

4.2.1. 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.

4.2.2. 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 patients with decompensated cirrhosis
 - Avoidance of vaginal delivery due to risk of rupture of varices during the second stage of labour.
 - Continuations of beta blockers(Eg: 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
 - Vassopressin 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

4.2.3. Autoimmune hepatitis

- Steroids and Azathioprine could be continued during pregnancy.

- Flares are infrequent during pregnancy though postpartum flares are expected.
 - o Close surveillance postpartum with review at 6 weeks is recommended.

4.2.4. Wilsons disease

- 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.
 - o 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.

4.3. Liver disease specific to pregnancy

4.3.1. 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 4.2: 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 hepatitis 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	

Further evaluation of a woman with suspected liver disease

Details are specified under individual liver disease below.

4.3.2. Hyperemesis gravidarum

- Patients present with persistent vomiting, weight loss, dehydration +/- ketosis usually from 4th to 20th 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:
 - o Increased transaminases in 50% (in the lower hundreds)
 - o An increase in bilirubin being less common with jaundice found only occasionally
 - o Severity of liver disease correlates with vomiting
- Management includes:
 - o Hydration, with monitoring of fluid balance and electrolytes.
 - o Endoscopic insertion of a NJ tube should be considered in very severe cases when adequate nutrition and hydration cannot be maintained by other means.
 - o Antiemetics

4.3.3. Intrahepatic cholestasis of pregnancy

- Prevalence is around 2/1000 of pregnancies.
- Typically presents with pruritus at around 25 to 32 weeks of gestation.
 - o 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:
 - o Elevated aminotransferase levels (10 to 20 fold)
 - o Jaundice in 10%-25% of patients, 2-4 weeks after pruritus; Bilirubin is usually less than 5mg/d
 - o Rise in alkaline phosphatase levels up to fourfold with a normal or mildly elevated GGT
 - o Elevated fasting serum bile acid levels ($>10 \mu\text{mol/L}$)

- o which is the most specific and sensitive marker of ICP; This could rise upto 100 fold
 - o Deficiency of Vit K if liver functions are severely deranged
- Management includes:
 - o Symptomatic therapy
 - Ursodeoxycholic acid (UDCA) 10 to 15 mg/kg body weight per day
 - Fat soluble vitamin supplementation in severe steatorrhoea
 - o Close monitoring and early delivery of the fetus.

4.3.4. Pre eclampsia

- 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:
 - o Increase in serum aminotransferase levels which is usually mild. SGOT is usually more than SGPT.
 - o Jaundice which is not common and usually associated with serum bilirubin level less than 5 mg/dL
 - o Subcapsular haematoma which could occur with severe liver derangement
- Management includes:
 - o Close monitoring of maternal and fetal well being
 - o 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.

4.3.5. 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.
- Most patients present in the 3rd trimester, but 25% present in the postpartum period.

Box 4.3- Diagnostic Criteria for HELLP Syndrome

Haemolysis

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

Elevated liver enzymes

- AST >70 U/L

Low platelets

- Plt ct < 150 × 10⁹

- 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:
 - o Raised aminotransferase levels from mild to 10-20 fold
 - o Mildly elevated serum bilirubin; Jaundice is uncommon
- Management includes:
 - o Delivery as the definitive therapy

4.3.6. 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:
 - o Mild to severe elevation of aminotransferases (usually upto 300 to 500U/L)
 - o Mild elevation of serum bilirubin which is usually less than 5mg/dL but higher in severe or complicated disease

Box 4.4- 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 ($>14 \mu\text{mol/L}$)
- Hypoglycaemia ($<4 \text{ mmol/L}$)
- High uric acid ($>340 \mu\text{mol/L}$)
- Leucocytosis ($>11 \times 10^6/\text{L}$)

- 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.

4.4. Liver disease coincidental to pregnancy

4.4.1. 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.

4.4.2. 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.

4.4.3. Acute viral hepatitis

- It usually follows the same disease course as the non pregnant population.
 - o 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
 - o Hepatitis A and E –Breast feeding can be continued
 - o 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
 - o 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.

4.4.4. 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.
 - o Laparoscopic cholecystectomy is preferred over open surgery.

4.4.5. Sepsis

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

4.5.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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Renal Disease

5. Renal disease in pregnancy

5.1. 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
 - o Proteinuria increases upto 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
 - o 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
 - o 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.
 - o In the later stages of pregnancy, mechanical compression of the ureter against the pelvic brim may lead to hydroureter and hydronephrosis.
 - o 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

5.2. Pre-existing 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 ($\text{GFR} < 30 \text{ ml/min/1.73m}^2$) 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 (eg: nephrotic syndrome).
- Intra uterine device (IUD) could be used.

5.2.1. 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 < 135/85mmHg throughout pregnancy with monthly assessment of renal functions (serum creatinine, electrolytes and proteinuria).
- Fetal growth monitoring after 28 weeks.

5.2.2. 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

5.2.3. 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.

5.2.4. 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.

5.3. Renal disease occurring during pregnancy

5.3.1. Urinary tract infections (UTI)

5.3.1.1. 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 5.1: 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

5.3.1.2. 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 5.2: 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.

5.3.1.3. Asymptomatic bacteriuria (AB)

- Asymptomatic bacteriuria is diagnosed when two consecutive voided urine specimens grow >105cfu/mL of the same bacterial species or a single catheterised specimen grows >105cfu/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.

5.3.2. Preeclampsia

- Pre eclampsia (BP $\geq$ 140/90 mmHg, proteinuria $\geq$ 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.
 - o Pre-existing types 1 or 2 diabetes mellitus
 - o History of hypertensive disease in pregnancy
 - o Women with systemic lupus erythematosus (SLE) or antiphospholipid syndrome
 - o Women with preexisting hypertension, irrespective of the aetiology
 - o Women with chronic renal impairment, irrespective of the aetiology

5.3.3. 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')

5.3.4. Haemolytic Uraemic Syndrome (HUS) / Thrombotic Thrombocytopenic 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.

5.4. Acute kidney injury (AKI)

AKI is defined as any one of the following (Acute Kidney Injury Network criteria) :

- Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 μ mol/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 5.3: 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 thrombocytopenic 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 analyser 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 5.4: 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

5.5. Chronic kidney disease

5.5.1. 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:
 - o Estimated GFR of ≤ 40 ml/min/1.73m²
 - o Proteinuria ≥ 1 g/d
 - o Serum creatinine ≥ 1.4 g/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 advise 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.

5.5.2. 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.
 - o 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 (eg: renal impairment)
 - o Serum creatinine and 24 hour protein excretion should be monitored monthly
 - o 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.
 - o 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/1.73m².
 - o At least 20 hours of dialysis per week is required with the aim of maintaining blood urea below 60mg/dL

5.6. Renal transplantation

- Fertility rates increase dramatically after transplantation.
- Women with a renal transplant should be referred to a nephrologist for advice 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.
 - o 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.

5.7. 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.

5.8. 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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Thyroid Disease

6. Thyroid disease in pregnancy

6.1. 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:
 - o 10% increase in size of the thyroid gland in iodine replete women
 - o 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
 - o Serum TSH > 4 μ IU/mL by the third trimester in nearly one fifth of women with autoimmune thyroid dysfunction
 - o Development of postpartum thyroid dysfunction in 33-50% of women with thyroid autoimmunity
- Testing for thyroid functions
 - o 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.
 - o 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.
 - o 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 6.1: Normal reference range for thyroid hormones in pregnancy

Trimester	SerumTSH (μ IU/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

6.2. Hypothyroidism in pregnancy

6.2.1. Definitions

Overt hypothyroidism

Definition:

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

Adverse effects of overt hypothyroidism include:

Maternal complications

- Gestational hypertension
- Placental abruption
- Postpartum haemorrhage

Fetal complications

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

Subclinical hypothyroidism (SCH)

Definition:

- TSH between 2.5-10 μ IU/mL with normal FT4 level SCH is known to be associated with infertility, fetal 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.

6.2.2. Management of hypothyroidism in pregnancy

Preconception care

- Pregnancy should be planned, with TSH levels maintained below 2.5 $\mu\text{IU/mL}$.
- 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.
 - o 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
 - o 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 2 $\mu\text{g/Kg/d}$ (maximum of 2.5 $\mu\text{g/Kg/d}$).

- 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 6.2: Dose increment based on serum TSH level

TSH level (μ IU/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 prepregnancy dose of thyroxine.
- A follow up TSH at 6 weeks postpartum is recommended.
- Neonatal TSH should be tested by one week.

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

- o autoimmune disorders
 - o Women with infertility
 - o Women with a prior history of miscarriage or preterm delivery
 - o Women with prior therapeutic head or neck irradiation or prior thyroid surgery
 - o Women currently receiving levothyroxine replacement
 - o 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.

6.3. Hyperthyroidism in pregnancy

6.3.1. Definitions

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

Fetal complications

- Prematurity
 - low birth weight
 - fetal growth restriction
 - stillbirth
 - neonatal goitre
 - Subclinical hyperthyroidism (Low TSH with normal FT4) and isolated hyperthyroxinaemia 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. Eg: 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

6.3.2. Management of overt hyperthyroidism in pregnancy

Preconception care

- Pregnancy should be planned with women rendered euthyroid (TSH between 0.3-2.5 μ IU/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).
 - o These women require a reliable method of contraception preferably IUD.

Antenatal management

- First line therapy for hyperthyroidism is antithyroid drugs (ATD).
 - o Propylthiouracil (PTU) should be used in the first trimester of pregnancy
 - o Carbimazole should be started from the second trimester onwards
 - o The initial dose of ATDs depends on the severity of the symptoms and the degree of hyperthyroxinemia
 - o 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
- o 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.
 - o Eg. Propranolol 20–40 mg every 6–8 hours
 - The dose should be reduced as early as possible in view of risk of fetal growth restriction, fetal 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.
 - o 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.
 - o Aim to maintain serum FT4 at the upper reference range.
- Fetal 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.
 - o This will result in a need to decrease the dose of ATDs
 - o Discontinuation of all ATD therapy is feasible in 20%–30% of patients in the last trimester of gestation
 - o 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,

- o Active maternal hyperthyroidism
- o History of treatment with radioiodine
- o History of delivering an infant with hyperthyroidism
- o 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 fetus
- Fetal monitoring includes serial ultrasound scan for assessment of fetal growth, fetal 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 6.3: 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. Lugol's 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
 - o Breastfeeding is safe in mothers on ATDs at moderate doses
 - o 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.

6.4. 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. Eg. 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 6.1 Management of postpartum thyroid dysfunction

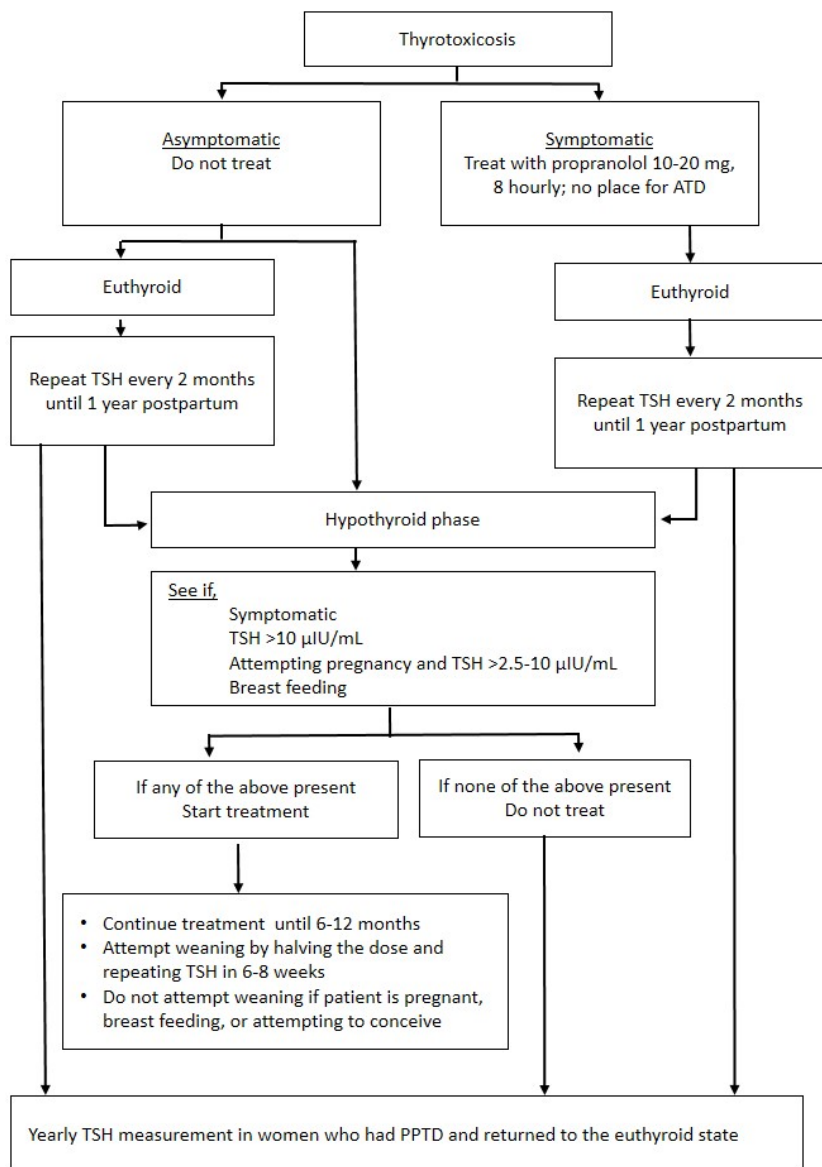
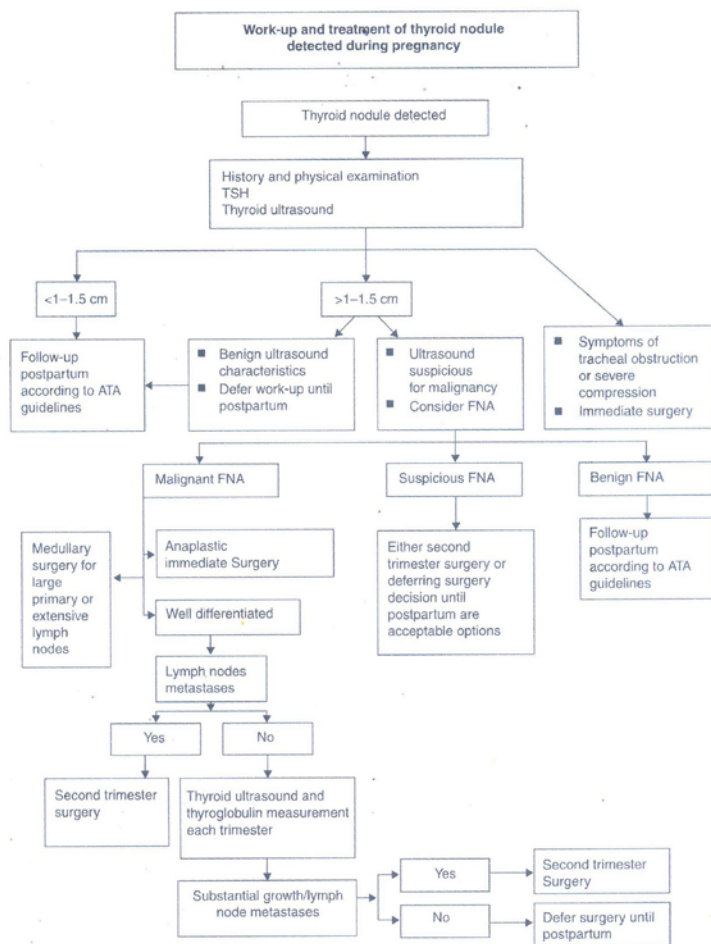


Figure 6.2 Management of thyroid nodule in pregnancy



Stagnaro Green et al **Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum** *Thyroid* 2011

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Rheumatoid arthritis

7. Rheumatoid arthritis

7.1. 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.

7.2. 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 2.1).

Box 7.1 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 an 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.

7.3. 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).

7.4. Delivery

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

7.5. Postpartum care

- Review drugs for suitability for breast feeding.

Box 7.2: Safety of medications during breast feeding

Safe to continue during lactation

NSAIDs
Corticosteroids
Hydroxychloroquine
Sulfasalazine¹

Inadequate data regarding lactation –Avoid

TNF α inhibitors
Anakinra
Abatacept
Rituximab
Tocilizumab
Tofacitinib

Contraindicated during lactation

Methotrexate
Leflunomide
Azathioprine²

- 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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Systemic Lupus Erythematosus

8. Systemic Lupus Erythematosus

8.1. 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 fetal complications of active disease include,

Maternal complications

- 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

Fetal complications

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

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

8.2. 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 fetus
 - Anticardiolipin antibodies, lupus anticoagulant and anti β 2 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 (eg. 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 immunosuppressives for long term use.

8.3. Antenatal care

- Women with major organ involvement or poorly controlled disease are best managed in a tertiary care center 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
 - o Elemental calcium 1200 U (minimum 800 U) daily.
 - o 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.
 - o Those with active disease - at least fortnightly
 - o 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
- Fetal monitoring
 - Monitoring of growth and doppler uterine artery blood flow for detection of fetal growth restriction.
 - Fetal echocardiography if indicated.

8.4. 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.

8.5. 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 Safety of medications during breast feeding Box 3.2 Rheumatoid arthritis for advice on medication during breast feeding.

8.6. Contraception

- Refer section on contraception - preconception care in SLE.

8.7. Neonatal lupus syndrome

- Neonatal lupus syndrome represent fetal 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.

8.8. Treatment of lupus nephritis (LN) in pregnancy

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

Box 8.1: 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.

8.9. Other autoimmune connective tissue disease

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 Raynauds disease may interfere with uterine contractions in the latter part of pregnancy.
- In women with gastrointestinal involvement,
 - o nutritional problems and constipations requires specialist attention and care
 - o 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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Immune Thrombocytopaenic Purpura

9. Immune thrombocytopaenic purpura

9.1. Introduction

- Thrombocytopaenia in pregnancy is defined as a platelet count $<150 \times 10^9/L$.
- It is the second commonest haematological disorder in pregnancy after anaemia, and affects around 7–10% of pregnancies.
- Immune thrombocytopaenic 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 9.1: 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 $>70 \times 109/L$
Pre eclampsia	5-8%	•Onset in late second or third trimester	•Headache, blurred vision, epigastric pain, oedema •Systolic BP $\geq 140\text{mmHg}$ and/or diastolic BP $\geq 90\text{mmHg}$	•$> 0.3\text{g}$ 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 fetal thrombocytopaenia	•May have signs of bleeding -bruising, petechiae	•Platelet $<100 \times 109/L$ +/- 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 preclampsia	•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 impairment	• Microangiopathic haemolytic anaemia • Elevated creatinine • Normal coagulation screen • 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

9.2. Management of ITP in pregnancy

Preconception care

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

Antenatal care

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

Box 9.2: 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.
 - o 70-80% responds initially
 - o Approximate time to response vary from several days to several weeks
 - o The steroid dose should be tapered to maintain a safe platelet count
- Regular monitoring for steroid induced diabetes should be performed

Box 9.3: 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 $<10 \times 10^9 /L$ with bleeding
- Need for emergency delivery, surgery or invasive procedures with suboptimal platelet count
- Life threatening bleed

Box 9.4: Management of a life threatening bleed

- In the event of a life threatening bleed (Eg. intracranial haemorrhage) 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 $< 50 \times 10^9/L$.
- Weigh the risk and benefits in women with a platelet count $< 50 \times 10^9/L$ who require aspirin for obstetric indications.

Indications for admission
- If the platelet count is less than $< 10 \times 10^9/L$ (repeated and confirmed)
- When spontaneous bleeding occurs (irrespective of the platelet count)

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 9.5: Safe platelet count for delivery

- Vaginal delivery $> 50 \times 10^9/L$
- Caesarean section $> 50 \times 10^9/L$
- Epidural anaesthesia $> 80 \times 10^9/L$

- 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 ($< 50 \times 10^9/L$) around the time of delivery in spite of all above measures, platelets should be available on standby.
 - If the platelet count is $< 10 \times 10^9/L$ or if haemorrhage occurs with a platelet count $< 50 \times 10^9/L$ at delivery, 6-10 units of platelet packs should be given

- Paediatric team to be informed at time of delivery.
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.

9.3. 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 $< 50 \times 10^9/L$ at any time, perform a cranial US scan.
- If the platelet count is $< 20 \times 10^9/L$ 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 $< 50 \times 10^9/L$.

9.4. Thrombotic thrombocytopenic purpura (TTP)

- This is a prothrombotic state caused by ultra large Von Willibrand 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.

Diagnostic criteria

- Fever
- Acute Renal impairment
- Central nervous system involvement
- Thrombocytopenia
- 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.

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 contraindicated in this situation
- Once platelet count rises to >50,000 consider LMWH for thromboprophylaxis as DVT risk is very high.

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Antiphospholipid Syndrome

10. Antiphospholipid syndrome

10.1. 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 10.1: 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 $\beta 2$ 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.

10.2. Management of APS during pregnancy

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.

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 Table 6.2 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 is constraints in accessing LMWH.
 - LMWH and Aspirin should be commenced in early pregnancy once an intrauterine viable fetus is confirmed by ultrasound scan.

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

Box 10.2: 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 (Eg. 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 X a 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 X a levels is currently not available in Sri Lanka.

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.

- o Prophylactic LMWH should be withheld 12 hours prior to delivery
- o Therapeutic LMWH should be withheld 24 hrs prior to delivery

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.

Contraception

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

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11. Prevention And Management Of HIV In Pregnancy

11.1. Primary prevention strategies

Raising awareness of antenatal mothers and their partners on HIV, AIDS and PMTCT

Information on sexually transmitted infections including HIV and syphilis should be included in the general information given to pregnant women along with information about other infections and antenatal tests. They should be informed:

- Perinatal transmission of HIV and adverse pregnancy outcomes.
- The potential benefits of knowing their HIV infection status by getting tested, both for their own health and to reduce the risk of perinatal transmission
- Mother to child transmission of HIV can be greatly reduced through antenatal and perinatal treatment with anti-retroviral drugs, safer delivery and safer infant feeding practices.
- Information on facilities for screening
- Information on safe and responsible sexual behaviour and practices

11.2. Screening for HIV during pregnancy

- HIV screening is included in the basic investigation services package during pregnancy. Blood samples are collected at the first antenatal clinic visit and send to the allocated STD clinic for testing. All mothers are to be screened before 12 weeks of gestation for syphilis and HIV (preferably at the first visit).
- Antenatal clinic services (MOH clinics and Hospital ANC clinics) have to arrange collection of 5cc of blood in a vacutainer tube and transport to the STD clinic for Syphilis and HIV testing. The mode of sample transport needs to be locally adopted, after discussions with RDHS, MOMCH, MO/STD and MOHs.

- The first blood test is called a screening test. All positive screening tests in Sri Lanka are tested with a confirmatory test. If the confirmatory test is positive, the woman is considered as infected with HIV.
- Assure the woman that her test result is confidential and will be shared only with her.
- STD clinics will carry out HIV screening tests on the blood samples received from ANC clinics and send reports to the relevant officers.
- The information on HIV positive reports will be informed to the MO, MOH or VOG and measures should be taken to strictly maintain the confidentiality of the information.
- The screening test positive pregnant women need to be referred to the STD clinic for further management.

Test result should be given only to the relevant person. Do not convey any HIV test result (positive or negative) to any other person or over the phone.

11.2. When the confirmatory test results is negative:

- Counsel on the importance of staying negative by safer sex including use of condoms.

11.3. When the screening test is positive:

- All pregnant women with HIV should be provided appropriate services including institutional care, without stigma and discrimination
- Refer them to the STD clinic and further **management will be done by the STD clinic.**
- MOH/MO has to briefly counsel her before sending to STD clinic.
- At the STD clinic she will be subjected to a detail one- to- one pre-test counselling session prior to the confirmatory test.
- Select a suitable place where the counselling session could be carried out maintaining privacy.
- Discuss the HIV screening test results when the woman is alone or with the person of her choice.
- State test results in a neutral tone and explain that this is only a screening test and now the confirmatory test has to be done.

- Explain to the woman that screening test can be positive due to reasons other than HIV (false positive results)
- Give the patient adequate time to express her emotions.
- Explain to her that only if the confirmatory test is positive, there is evidence that she is infected with HIV.
- For the confirmatory test, a second sample has to be taken and explain this to her. Then refer her to the closest STD clinic. Inform her that if she is positive, there are several interventions including medications, safe delivery and feeding practices which are able to minimize the risk of transmission of HIV to the baby.
- Inform her that support and counselling is available if needed. Identify what difficulties or problems the woman foresees and how to deal with them
- Encourage her to ask questions
- Ask if she has any concerns.

When the confirmatory test result is positive the woman will be counselled and managed at the STD clinic.

Maintain the confidentiality of HIV status

- Assure the woman that the test result is confidential and will be shared only with her.
- Ensure all records are confidential and kept locked away and only health care workers taking care of her have access to the records.
- **Do not enter** in the ANC record as HIV positive. Only the date, sample for HIV is taken and the date results informed are entered in the ANC record.

11.4. Support to the HIV positive woman

Pregnant women with HIV infection will receive HIV care services at the STD clinic. As the pregnant woman with HIV has to be managed at a tertiary care centre she will be referred to consultant obstetricians and other necessary specialists. You may get involved in the management when you are requested to do so by the MOH.

- Advise her to get admitted to the hospital as instructed.
- Tell her to take ART medicine as instructed.
- Discuss the infant feeding options
- Counsel her on post partum family planning.

11.5. Delivery care -

Avoid suctioning the infants mouth and pharynx, which may cause trauma to the mucus membranes thus promoting MTCT.

Clean the eyes of the baby with saline at delivery of the head.

Clamp the cord as soon as possible to minimise the maternal fetal micro-transfusions.

Cover the umbilical cord with a swab when cutting to prevent blood spurting.

Towel dry the baby.

Clean the baby's skin thoroughly before any infusions or injections.

11.6. Post partum care

- Be aware of signs of infection following delivery. Like uninfected women, HIV positive women are also vulnerable to infection following delivery and retained blood and placental tissues. Post partum uterine infection is a common and potentially life-threatening condition, and early detection and effective treatment are important measures to prevent complications.
- Monitor for secondary postpartum haemorrhage
- Manage infected tears or episiotomy
- Advise women to come back to the same institution if LSCS wound infection is observed
- When they are discharged from the healthcare facility women should be advised to return to the clinic or inform the PHM if they notice symptoms such as fever, lower abdominal pain, burning with urination, foul smelling discharge, abnormal bleeding, cough, shortness of breath, calf pain (increasing on walking), diarrhoea, unusual / abnormal behaviour
- Give information on care of the perineum and breasts.
- Instruct her about the safe disposal of lochia and blood-stained sanitary wear or other potential infectious materials.
- If contraception has not been discussed before delivery it should be done during the early postpartum period (see below).

11.7. Counsel HIV positive woman on family planning

Advice and counsel on family planning during antenatal period and post partum visits.

HIV positive women and men should be empowered to take informed choices relating to their reproductive lives, free of coercion.

The same contraceptive options which are available to uninfected couples are available to HIV infected couples. Most methods are considered to be safe and effective for HIV infected women. **However, as these women are on ART for lifetime, the decision on the suitable family planning method should be taken in consultation with the Venereologist.**

Protection against both unintended pregnancy and STI is referred to as “dual protection”. **Condoms are the mainstay of dual protection;** Condoms should be used in combination with another family planning method.

Contraceptive counselling may be done by the MOH in consultation with the STD clinic.

During counselling for a contraceptive plan;

- Encourage the woman to bring her husband for contraception counselling as it is best that they both decide on a suitable method.
- Discuss their thoughts about having more children.
- Listen carefully to the couples’ views. Correct any factual misunderstandings.
- If the husband is HIV negative emphasize the importance of using condoms to protect him from HIV infection.
- If the husband is HIV positive, explain that although they both have HIV they could become infected with another strain of HIV and so it is sensible to use condoms to prevent pregnancy and infection.
- Discuss where they could obtain condoms. Demonstrate how to use condoms correctly. Provide them with condoms and an information leaflet.
- If they have decided that they want no more children, discuss vasectomy and female sterilization.
- If they are uncertain about having more children in future, explain that waiting at least 2 years after the last birth to become pregnant again is healthiest for mother and child. Discuss the need of a planned pregnancy.
- Discuss other temporary methods of contraception.

11.8. Infant feeding with HIV

Counselling and support for safer infant feeding

The most appropriate infant feeding option for an HIV positive mother depends on her individual circumstances, including her health status and

the local situation, the health services availability and the counselling and support she is likely to receive.

The expectant mother should be counselled by a counsellor who has adequate knowledge on the safer feeding options that are currently recommended. The counsellor considers the risk of infants acquiring HIV through breast milk with the higher risk of death from causes other than HIV, in particular malnutrition and serious illness such as diarrhea among non-breastfed infants in identifying suitable options. Counselling is done by the Venereologist and Paediatrician to assist the mother in arriving at a decision.

Currently in Sri Lanka HIV positive pregnant mothers who decide on formula feeding are offered formula milk for the baby up to one year of age by an NGO.

12. Prevention And Management Of Syphilis During Pregnancy

12.1. Introduction

If a woman with untreated syphilis becomes pregnant, or a woman acquires syphilis during pregnancy, depending on the stage of syphilis, the infection can be transmitted to the foetus causing adverse pregnancy outcomes including congenital syphilis. Unlike many neonatal infections, congenital syphilis (CS) can be effectively prevented, either through prevention of maternal infection or by detecting the infection early in pregnancy and providing adequate treatment.

12.2. Screening for syphilis

- All mothers are to be screened before 12 weeks of gestation for Syphilis (preferably at the first visit).
- Antenatal clinic services (MOH clinics and Hospital ANC clinics) have to arrange collection of 5cc of blood in a vacutainer tube and transport to the STD clinic for Syphilis and HIV testing. The mode of sample transport needs to be locally adopted, after discussions with RDHS, MOMCH, MO/STD and MOHs.
- STD clinics have to carry out Syphilis screening tests on the blood samples received from ANC clinics and send reports to the relevant officers.

12.3. Diagnosis of syphilis

- All screening positive samples will be tested further using treponemal tests as confirmatory tests.

- The information of reactive treponemal reports need to be informed to the MO, MOH or VOG and measures should be taken to strictly maintain the confidentiality of the information.
- The screening test positive pregnant women need to be referred to the STD clinic for further management.
- All pregnant women with Syphilis should be provided appropriate services according to the national guidelines including institutional care, without stigma or discrimination.

12.4. Treatment of maternal syphilis

Treatment for syphilis should be provided early in gestation before significant fetal damage take place. Treating the mother with penicillin during the first and second trimester will prevent faetal wastage due to syphilis such as still birth, intrauterine death, abortion or birth of an infected child.

12.4.1. Treatment of primary, secondary and early latent syphilis

One or two doses of Benzathine benzyl penicillin 2.4 million units IM given depending on the stage after excluding allergy.

12.4.2. Late latent syphilis:

Benzathine benzyl penicillin 2.4 million units IM once a week for consecutive 3 weeks.

Adequate penicillin treatment will end infectivity within 24-48 hrs. Pregnant women who miss any dose must repeat the full course of therapy.

12.5. Follow up

Serological (VDRL) follow-up should be at months 1, 2, 3, 6 and 12, then 6 monthly until VDRL negative or for 2 years.

A sustained fourfold or greater increase in the VDRL titre suggests re-infection or treatment failure and needs to be retreated.

It is not necessary to retreat pregnant mothers who have positive treponemal test results and have documented evidence of adequate therapy for diagnosis of syphilis previously, so long as there is no evidence of serologic or clinical evidence of re-infection or relapse. Babies born to such mothers do not require prophylactic penicillin therapy.

If doubts exist about the adequacy of previous therapy, re-treatment should be commenced promptly.

12.6. Allergy to penicillin

Erythromycin 500mg four times per day for 14 days in early syphilis and for 28 days in late syphilis. (In pregnancy Doxycycline is contraindicated). When mother is treated with erythromycin baby should be considered as a presumptive case of congenital syphilis treat adequately for congenital syphilis.

12.7. Treatment of partners

Sexual partners should be referred to the STD clinic for assessment. They will be treated according to the stage of syphilis, if clinical evidence of syphilis is present or if serology is positive.

12.8. Diagnosis of congenital syphilis

All babies born to mothers with syphilis, should have

- Clinical evaluation: if lesions (bulbous skin rash, nasal discharge,) present carry out dark ground microscopy.

- Carry out serological tests

VDRL and TPPA in both mother and baby. Syphilis specific EIA IgM antibody test of baby (If available)

VDRL titre of the baby is more than fourfold that of the mother or positive syphilis specific IgM need to be managed as congenital syphilis. Until 18 months it's difficult to differentiate whether mother's antibodies or babies antibodies would give positive VDRL and TPPA results. Placental transfer of maternal IgG can give positive results in baby even in the absence of congenital syphilis. If clinical signs are present with positive serological tests a bone survey should be considered and baby should be treated for congenital syphilis

12.9. Treatment of the baby

If the mother had been adequately treated before 36 weeks of POA the risk of mother to child transmission (MTCT) is low. However, irrespective of mother's treatment all babies born to mothers with positive treponemal tests are given prophylactic penicillin.

Baby is given one dose of Benzathine penicillin 50,000IU/Kg of Body Weight, as prophylactic treatment.

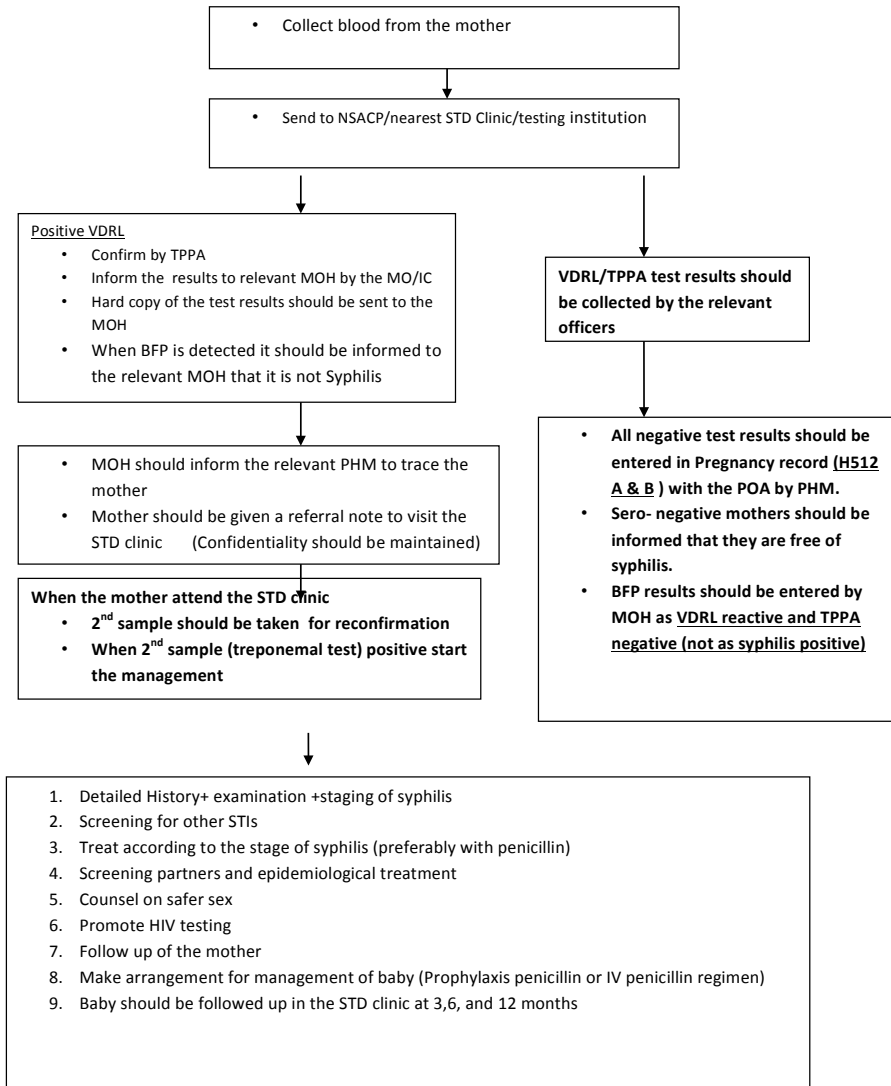
If congenital syphilis could not be excluded, baby need to be treated with crystalline penicillin 50,000IU/Kg/day twice day for 7 days and three times per day for further 3 days to complete the total of 10 days treatment

This should be given to:

1. All symptomatic babies
2. All asymptomatic babies
 - i. Whose VDRL titre is a 4 fold higher than that of the mother at delivery
 - ii. Rising non-treponemal titre (VDRL)

- iii. With a reactive syphilis specific IgM antibody test (If available)
- iv. Born to mothers who were treated with penicillin <4 weeks before delivery
- v. Born to mothers who did not complete the recommended course of penicillin during pregnancy
- vi. Born to mothers whose non treponemal high titre had not dropped four fold at the time of delivery
- vii. Born to mothers who were treated with non penicillin regimens (Erythromycin) during pregnancy
- viii. Born to mothers whose treatment status is unknown or undocumented

Protocol for antenatal testing for syphilis



Malaria

13. Guidelines on malaria chemotherapy and management of patients with malaria during pregnancy

13.1. Introduction

With no indigenous malaria cases being reported since October 2012, Sri Lanka is currently in the malaria elimination and prevention of re-introduction phase. With progressively increasing incidence of imported malaria cases in recent years, early diagnosis and treatment of such cases have become the highest priority for prevention of re-introduction. Most of these infections have been acquired in India, Pakistan, South East Asian and African countries.

Currently, a low level of clinical suspicion in the backdrop of a very low disease burden has led to a significant delay in diagnosis of malaria cases. As a result, there were several patients who presented to the health care institutions with uncomplicated fever progressing to develop severe malaria while being at the hospital.

13.2. Patients likely to have malaria

Malaria should be suspected in:

1. any febrile individual (including foreign nationals):
 - with unexplained fever and a history of recent travel (within 1 year) to a malaria endemic country (esp. India, Pakistan, Haiti and African countries). Refer Annex II for a list of countries where malaria transmission occurs).
 - belonging to high risk groups e.g. businessmen, pilgrims and seamen returning from malaria endemic countries, re-settled communities, skilled and unskilled foreign workers, illegal/irregular migrants, refugees, asylum seekers, security forces returning from peace keeping missions etc.
 - with a history of malaria infection within the past 3 years
 - with fever of unknown origin
2. any individual presenting with clinical features of severe malaria (refer Annex I for clinical features of severe malaria)
3. Patients with anaemia of unknown cause
4. Patients with hepatomegaly and/or splenomegaly

5. Recipients of blood or blood products who develop fever within 3 months of transfusion

Please note:

- Malaria can present with non-specific symptoms even if there is no fever.
- Thrombocytopaenia has been a frequent finding among patients with malaria reported in the recent years, yet a diagnosis of malaria has not been considered as a result of them being misdiagnosed as having dengue. This had led to a delayed malaria diagnosis resulting in adverse sequelae.

13.3. Notification of malaria patients

Any patient strongly suspected of having malaria should **immediately** be notified via telephone to the Regional Malaria Officer (RMO) and Anti Malaria Campaign Headquarters. In addition, it should be notified to the Medical Officer of Health (MOH) of the area where the patient resides following the standard notification procedure (Form H544).

The AMC will ensure:

- confirmation of diagnosis by species
- provision of appropriate anti-malarial drugs
- guidance on treatment
- initiation of rapid response to search for additional cases and prevent onward transmission of the disease
- follow up of the patient in the field in order to achieve radical cure.

The contact numbers of the AMC Headquarters and the RMOs are given in Annex III.

13.4. Diagnosis of malaria

- In every suspected case of malaria, laboratory confirmation by microscopic examination of blood smears and/or Rapid Diagnostic Test (RDT) is mandatory prior to initiation of anti-malarial treatment. Treating malaria based on clinical suspicion without laboratory confirmation should be avoided.
- If there is a strong clinical suspicion of malaria, and the blood smears/RDT are negative at the time of initial testing, a minimum of three consecutive blood smears/RDT should be done prior to concluding that the patient is negative for malaria.

- Blood should be collected for investigations prior to the administration of anti-malarials:
 - In all confirmed malaria patients
 - If anti-malarial treatment is required as a life saving measure based on clinical suspicion without laboratory confirmation of malaria
- Blood should be collected in the following manner:
 - 2ml of venous blood collected to an EDTA bottle and refrigerated until transported to the AMC headquarters.
 - Dried blood spots on filter paper: drop the blood (approx. 1.5 ml) in the syringe on the filter paper labelled with the patient's name; four blood spots with 3 drops per each spot. Air dry for one hour at room temperature. Place each filter paper in an individual envelope. Store at room temperature until transported to the AMC Headquarters.
 - (please contact AMC Headquarters for details).

13.5. Monitoring during treatment and follow up of patients

- To ensure an effective parasitological response to the anti-malarial drugs, a blood smear should be obtained daily and examined over the three day that the patient is admitted. If parasitaemia persists beyond 3 days blood smears should be taken daily until parasitaemia clears. In severe malaria cases, blood smears have to be taken at a higher frequency.
- Thereafter the patient will be followed up to one year (frequency and duration will depend on the species) by the AMC field staff.

13.6. Treatment of patients with malaria

Specific treatment and management of malaria will depend on the parasite species causing infection, severity of disease and the biological factors of the patient.

- Objectives of treatment:
 - Primary objective of treatment: to ensure rapid and complete elimination of the Plasmodium parasite from the patient's blood in order to prevent progression of uncomplicated malaria to severe disease or death.
 - From a public health perspective: to reduce transmission of the infection to others by reducing the infectious reservoir and to prevent the emergence and spread of resistance to anti-malarial medicines.
- All confirmed malaria patients should be admitted to a medical institution for a minimum of 3 days to be managed under supervision.
- If facilities are available, a test for G6PD deficiency should be carried out prior to administration of primaquine.

13.6.1. Mono-infection with *Plasmodium vivax*

- For radical cure of *P. vivax* malaria, the patient should be treated with chloroquine and primaquine.
- Chloroquine:** base at a total dose of 25 mg/kg body weight (bw) over three days. This dose should be divided as 10mg/kg on the first and second day followed by 5 mg/kg bw on the third day.
- Primaquine:** the adult dose is 15mg base (0.25mg/kg per day) for fourteen days unless it is contraindicated. The administration of primaquine is not recommended during pregnancy and lactation, infancy and in severe G6PD deficiency (<10% of residual enzyme activity).
- In patient with mild to moderate G6PD deficiency (10-60% of residual enzyme activity) primaquine can be administered in a dosage of 0.75 mg/kg weekly for 8 weeks under specialized supervision.

13.6.2. Uncomplicated mono-infection with *Plasmodium falciparum*

- For radical cure of *falciparum* malaria, the patient should be treated with ACT and primaquine.
- Artemisinin based combination Therapy (ACT):** Weight appropriate dose. Coartem® (containing 20mg of artemether and 120mg of lumefantrine) is the ACT used in Sri Lanka.
- Artemisinin and its derivatives should never be used as monotherapy.
- Coartem® tablets are packed in four colour coded blister packs. The recommended treatment is 6-dose regimen over a three day period according to the weight of the patient as indicated in table 1.

Table 13.1. Number of ACT (Coartem®) tablets administered based on weight of patient

Interval between doses	5 -14 kg (Yellow Pack)	15 -to 24 kg (Blue Pack)	25- 34 kg (Orange pack)	>35 kg (Green pack)
0 Hours	1	2	3	4
8 Hours	1	2	3	4
24 Hours	1	2	3	4
36 Hours	1	2	3	4
48 Hours	1	2	3	4
60 Hours	1	2	3	4
Total	6	12	18	24

ACT should be taken immediately after a meal or drink containing at least 1.2g of fat (e.g. a glass of milk) since its absorption is enhanced by co-administration with fat. As low blood levels of ACT with treatment failure could potentially result from inadequate fat intake, it is essential that patients or carers are informed of the need to take Coartem® with milk or fat containing food, particularly on the second or third day of treatment.

- **Primaquine:** A weight appropriate single dose of primaquine (0.75mg/kg bw) should be administered **unless contraindicated**, on day 3 of treatment or prior to discharge from hospital to destroy gametocytes.

Uncomplicated *P. falciparum* malaria in infants and young children

- ACT (Coartem®) is the first line treatment in infants and young children.
- Primaquine should be avoided in children less than 1 year of age.
- An acutely ill child requires careful clinical monitoring as she/he may deteriorate rapidly.
- Please contact Anti Malaria Campaign Headquarters for further guidance.

Uncomplicated *P. falciparum* malaria in Pregnancy

- 1st Trimester: Uncomplicated falciparum malaria is treated with oral quinine sulfate 10mg/kg body weight at 8 hourly intervals plus clindamycin 10 mg/kg bw twice a day for 7 days. If clindamycin is unavailable, quinine monotherapy may be given.
- 2nd and 3rd Trimester: Uncomplicated falciparum malaria is treated with Coartem®.
- Primaquine should not be administered during pregnancy.

Uncomplicated *P. falciparum* malaria during Lactation

- Lactating women can receive the recommended dose of Coartem®.
- Primaquine should not be given during lactation.

13.6.3. Uncomplicated mixed infections with *P. falciparum* and *P. vivax*

- Artemisinin based combination therapy: Coartem® is given at a weight appropriate dose.
- Primaquine base: at a dose of 0.25mg/kg bw per day for fourteen days unless it is contraindicated.

13.6.4. Severe *P. falciparum* malaria

Severe malaria is a medical emergency. After rapid clinical assessment and confirmation of the diagnosis, full doses of parenteral antimalarial treatment should be started without delay. Patients with severe malaria require intensive nursing care, preferably in an intensive care unit where possible. Clinical observations should be made as frequently as possible. These should include monitoring of vital signs, coma score, and urine output. Blood glucose should also be monitored every four hours, if possible, particularly in unconscious patients.

- **Intravenous artesunate**, 2.4mg/kg bw given on admission (time = 0), then at 12 hour and 24 hour, then once a day until the patient is able to take oral medication. If intra venous administration is not possible, it can also be given as an intramuscular injection.

If parenteral artesunate is NOT available:

- **Quinine dihydrochloride**, 20mg salt/kg bw (loading dose) on admission, then 10mg/kg every 8 hours. Each dose is given as a rate controlled intra venous infusion diluted in 10ml/kg bw of isotonic fluid over 2-4 hours at an infusion rate that should not exceed 5mg salt/kg body weight per hour.

The most important adverse effect is hyperinsulinaemic hypoglycaemia. Hypotension and cardiac arrest may result from rapid intravenous injection. Quinine causes prolongation of the electrocardiograph QT interval. Therefore; this administration should be accompanied by frequent blood glucose monitoring to prevent hypoglycaemia and cardiac monitoring.

Duration of parenteral treatment

Give parenteral antimalarials in the treatment of severe malaria for a minimum of 24 hours, even if the patient can tolerate oral medication. Follow up on oral treatment

Complete the treatment by giving a full course of Coartem® as soon as the patient is able to take oral medication, but not before a minimum of 24 hours of parenteral treatment. This should be followed by a single dose of primaquine.

Artesunate is dispensed as a powder of artesunic acid. This powder is dissolved in 1ml of 5% sodium bicarbonate to form sodium artesunate. The solution is then diluted with 5 ml of 5% dextrose and given immediately

by intravenous bolus ('push') injection or by intramuscular injection (to the anterior thigh). The solution should be prepared freshly for each administration and should not be stored.

Severe *P. falciparum* malaria in pregnancy

- 1st Trimester: should be treated with parenteral quinine until clinical improvement, followed by oral quinine therapy for a total of 7 days.
- 2nd and 3rd Trimester of pregnancy: parenteral artesunate/quinine can be administered as above. After clinical improvement, Coartem® should be administered in the weight appropriate dose.

Please note: Primaquine should not be administered during pregnancy. Severe *P. falciparum* and *P. vivax* mixed infections

- Parenteral administration of artesunate or quinine dihydrochloride followed by a full course of oral Coartem® (as described in management of severe *falciparum* malaria).
- These patients should be given a course of primaquine base at a dose of 0.25mg/kg per day for fourteen days unless it is contraindicated.

13.6.5. Patients infected with other malaria parasites

The recommended treatment for malaria caused by *P. ovale* is the same as that given to achieve radical cure in *P. vivax* malaria, i.e. with chloroquine and primaquine.

P. malariae should be treated with the standard regimen of chloroquine as for *P. vivax* malaria, but it does not require radical cure with primaquine.

13.7. Chemoprophylaxis for malaria

Chemoprophylaxis is not needed for visitors to Sri Lanka and anyone living within the country including pregnant women.

Chemoprophylaxis is recommended for travellers to malaria endemic countries (the list of countries where malaria transmission occurs is given in Annex II). Contact Anti Malaria Campaign to obtain chemoprophylactic drugs and for further details.

Annex I. Severe malaria

Definition of Severe malaria

Severe malaria is defined by clinical or laboratory evidence of vital organ dysfunction (WHO, 2012). In a patient with *P. falciparum* asexual parasitaemia and no other obvious cause of symptoms, the presence of one or more clinical or laboratory features classifies the patient as suffering from severe malaria.

Clinical features of severe malaria

- impaired consciousness (including unarousable coma);
- prostration, i.e. generalized weakness so that the patient is unable to walk sit up without assistance;
- multiple convulsions-more than two episodes in 24h;
- deep breathing, respiratory distress (acidotic breathing);
- acute pulmonary oedema and acute respiratory distress syndrome;
- circulatory collapse or shock, systolic blood pressure <80 mm Hg in adults and < 50 mm Hg in children;
- acute kidney injury;
- clinical jaundice plus evidence of vital organ dysfunction; and
- abnormal bleeding

Laboratory findings

- hyperparasitaemia
- hypoglycaemia (blood glucose <2.2 mmol/l or <40mg/dl);
- metabolic acidosis (plasma bicarbonate < 15 mmol/l);
- severe normocytic anaemia (In children: Hb <5g/dl, packed cell volume <15%. In adults: Hb<7g/dl, packed cell volume, PCV< 20%)
- haemoglobinuria;
- hyperlactataemia (lactate > 5 mmol/l);
- renal impairment (serum creatinine> 265 µmol/l);
- pulmonary oedema (radiological)

Reference:

WHO, 2012, Management of severe malaria, A practical handbook, 3rd Ed., World Health Organization

Annex II.

Countries where malaria transmission occurs

Afghanistan	Dominican Republic	Madagascar	Saudi Arabia
Angola	Ecuador	Malawi	Senegal
Bangladesh	Equatorial Guinea	Malaysia	Sierra Leone
Belize	Eritrea	Mali	Solomon Islands
Benin	Ethiopia	Mauritania	Somalia
Bhutan	French Guiana	Mayotte	South Africa
Bolivia	Gabon	Mozambique	Sudan
Botswana	Gambia	Myanmar	Swaziland
Brazil	Ghana	Mexico	Suriname
Burkina Faso	Guatemala	Namibia	Thailand
Burundi	Guinea	Niger	Timor Leste
Cambodia	Guinea-Bissau	Nigeria	Togo
Cameroon	Guyana	Nepal	Tajikistan
Central African Rep.	Haiti	Nicaragua	Turkey
Chad	Honduras	Pakistan	Uganda
China	India	Panama	Tanzania
Colombia	Indonesia	Papua New Guinea	Vanuatu
Comoros	Iran	Peru	Vietnam
Congo	Iraq	Philippines	Venezuela
Costa Rica	Kenya	Paraguay	Yemen Socotra Island
Cote d'Ivoire	Lao PDR	Rwanda	Zambia
Djibouti	Liberia	Sao Tome & Principe	Zimbabwe

Note: There are some other countries with very limited malaria risk. For more details please refer International Travel and Health-2012 at http://www.who.int/ith/chapters/ith2012en_countrylist.pdf

Annex III.

Telephone numbers related to Anti Malaria Campaign

Anti Malaria Campaign Headquarters:

Tele: (011) 2588408, (011) 2368173
(011) 2368174
(011) 7626626 (hotline)
e-mail : antimalariacampaignsl@gmail.com
Website : www.malariacampaign.gov.lk

Regional Malaria Offices

Ampara	(063) 2223464	Kandy	(081) 2210687	Monaragala	(055) 2276698
Anuradhapura	(025) 2221844	Kegalle	(035) 2222549	Mullaitivu	(024) 3248341
Badulla	(055) 2226018	Kilinochchi	(024) 3247236	Polonnaruwa	(027) 2226018
Batticaloa	(065) 2222931	Kurunegala	(037) 2222193	Puttalam	(032) 2265319
Hambanthota	(047) 2220135	Maho	(037) 2275254	Ratnapura	(047) 2230301
Jaffna	(021) 2227924	Mannar	(023) 2222326	Trincomalee	(026) 2222584
Kalmunai	(067) 2220206	Matale	(066) 2222295	Vavuniya	(024) 2222954