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MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA

GUIDELINES ON PRE PREGNANCY CARE IN MOH SPECIALIST HOSPITAL

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FOREWORD
DIRECTOR-GENERAL OF HEALTH MALAYSIA

Pre-pregnancy care has long been an established practice in Malaysia, with this service being readily available in all government-specialized hospitals. The principal aim of such care is to ensure optimal maternal health prior to conception, thereby reducing the likelihood of serious complications during pregnancy, delivery, and ultimately, the birth of healthy infants.

To accomplish Goal 3 of the Sustainable Development Goals for 2030, the Ministry of Health, Malaysia (MOH) is committed to providing consistent, evidence-based, and high-quality maternity care to women nationwide. As with all United Nations Member States, this will require the involvement of multidisciplinary teams to ensure that the needs of Malaysian women, their infants, and their families are met, regardless of any medical or obstetric complications.

The establishment of the Pre-Pregnancy Care at MOH Specialist Hospital Guideline demonstrates the MOH's unwavering dedication to improving the health of Malaysian women before conception and subsequently reducing adverse pregnancy and neonatal outcomes.

I want to express my gratitude to all those who played a direct or indirect role in developing this guideline, as their efforts will benefit all concerned parties. I am confident this guideline will promote greater consistency in pregnancy care and improve experiences and outcomes for all Malaysian women and their families.

TAN SRI DATO' SERI DR. NOOR HISHAM BIN ABDULLAH
Director-General of Health Malaysia

FOREWORD
DEPUTY DIRECTOR-GENERAL OF HEALTH (MEDICAL) MALAYSIA

Pregnancy, childbirth and the puerperium has been the number one cause of hospitalization in Ministry of Health (MOH) Hospitals for the past decade. Malaysia has succeeded in lowering the Maternal Mortality Rate since the 1960s as a result of ongoing efforts to improve the quality of services, including training for medical professionals and also practising evidence-based medicine.

The graph of the maternal mortality rate, however, has been plateauing since year 2000. The leading factor contributing to maternal mortality is medical condition, especially cardiac disease. Therefore, steps have already been taken to reduce high-risk pregnancies, including the establishment of a pre-pregnancy care in Malaysia. It is important to empower women especially those with chronic illnesses in reproductive age group by providing relevant advice, guidance, counselling, screening and treatment including access to available contraception methods. Our aim is to reduce the maternal morbidity and mortality by sharing responsibilities not only by O&G team, but involvement of expertise from other disciplines as well.

I would like to congratulate and acknowledge the effort of the writing committee especially Medical Development Division of MOH, Family Health Development Division of MOH, Jawatankuasa Pengurusan dan Perkembangan O&G KKM (JPPOBG) and members from all other disciplines for this great initiative in preparing this edition. Let's hope that these efforts for reducing high-risk pregnancies will be met, followed by the goal of reducing MMR in Malaysia.

DATO' DR. ASMAYANI BINTI KHALIB
Deputy Director-General of Health (Medical) Malaysia

1.0 Introduction

1.1. Pre-Pregnancy Care (PPC) is a set of healthcare and interventions given to women in their reproductive age before conception occur. Centre for Disease Control and Prevention in 2005 defined Pre-Pregnancy Care as '***A set of intervention that aim to identify and modify biomedical, behavioural and social risks to a woman's health or pregnancy outcome through prevention and management, emphasizing those factors that must be acted on before conception or early in pregnancy to have maximal impact (CDC 2006)'.***

1.2. Women in their reproductive age with identified obstetrics risks and those who have medical, surgical or psychological problems should receive pre-pregnancy care in order to achieve optimization of the health risk before conception at least 3 months prior to conception. **A planned pregnancy with optimisation of her condition will minimise the complications to the mother and fetus during the period of pregnancy. Therefore, multidisciplinary involvement in the care of her condition is vital to ensure a positive pregnancy outcome.**

1.3. The concept of PPC was first introduced in Malaysia in 2003. The planning toward implementation of the program was initiated around 2010 and PPC was formally implemented in Government Health Clinics and Hospitals in 2012. Currently, all government health premises (health clinics and hospitals) provide this Pre-Pregnancy Care service. Pre-pregnancy care services at health clinics are led by Family Medicine Specialists and at the hospital level by the Obstetrician & Gynaecologist.

1.4. It is the aspiration of Ministry of Health Malaysia to ensure the program is successful and all women are given the opportunity to optimize health issues prior to conception and reduce national Maternal and Perinatal morbidity and mortality in order to form a healthy nation.

2.0 Rationale

2.1 Pre-pregnancy care should be made available for reproductive age women with medical problems in order to optimize the medical conditions prior to conception. However, the number of referrals to the pre-pregnancy clinic from the specialist clinics within the hospitals is still low. This leads to high-risk pregnancies because of missed opportunities for effective family planning before optimising the medical conditions, hence inevitably maternal and perinatal morbidities and mortalities.

2.2 Among the issues identified contributing to this problem are:

a. In-coordinated pre-pregnancy care at the hospital level;
b. Lack of communication among the disciplines;
c. Lack of awareness of the effect of pregnancy on medical conditions and vice versa; and
d. Improper combined follow-up mechanism for high-risk patients post-delivery.

2.3 Because of these, a gap exists in the multi-disciplinary continuation of care of women in the high-risk group before their future pregnancies and many of them were only encountered again after conception.

2.4 The Pre-pregnancy Care Guideline for MOH Specialist Hospital is systematically developed to assist the health care professionals and providers at the MOH hospitals with specialists in managing women in the reproductive age group with underlying medical conditions.

3.0 Objectives

3.1 General objective

To develop a comprehensive manual and reference for secondary and tertiary care providers in optimizing and achieving a planned, safe, and successful pregnancy.

3.2 Specific objectives

a. To serve as a guide for healthcare providers to provide proper pre-pregnancy multidisciplinary care to reduce the adverse effect of pregnancy on both women and fetuses in high-risk patients.
b. To enable prospective parents and women in the reproductive age groups to plan for pregnancy through:
    i. Provision of appropriate and adequate information;
    ii. Health promotion and education; and
    iii. Counseling
c. To screen and counsel future mothers appropriately for early intervention and treatment, aimed to reduce maternal and perinatal morbidity and mortality.

4.0 Targets Groups and Entry Point

4.1 Target groups

Women in the reproductive age group (15-49 years old) with:

a. Medical disorders (refer to specific medical conditions in Chapter 8);
b. Familial genetic conditions;
c. Previous children affected by genetic disorders or structural congenital anomalies; and
d. Congenital anomalies.

4.2 Entry points

4.2.1 Specialised clinics:

a. Obstetrics and Gynaecology Clinic;
b. General Medicine Clinic;
c. Cardiology Clinic;
d. Nephrology Clinic;
e. Haematology Clinic;
f. Rheumatology Clinic;
g. Respiratory Clinic;
h. Neuromedical Clinic;
i. Psychiatry Clinic;
j. Surgical Clinic; or
k. Oncology Clinic.

4.2.2 Hospital Inpatient (All disciplines)

4.2.3 Ambulatory Care Centre

4.2.4 Others:

a. University Hospitals
b. Military Hospitals

5.0 Setting Up Pre-Pregnancy Care Service

5.1 Place of Pre-Pregnancy Care Services

5.1.1 Major specialist hospital with sub-specialty services

a. Pre-pregnancy care services are provided in the O&G clinic, led by Maternal Fetal Medicine (MFM) or O&G specialist.
b. Joined by the medical physician from the respective referring discipline.

5.1.2 Minor specialist hospital

a. Pre-pregnancy clinic is provided in the O&G clinic, led by visiting MFM or O&G specialist.
b. Joined by the visiting physician from the respective subspecialty unit/ general physician.

5.1.3 Respective medical specialised clinic

a. Pre-pregnancy care services are provided in the respective medical discipline led by the attending Physician.
b. Joined by MFM or O&G specialist.

5.1.4 Virtual Clinic

* *Combined pre-pregnancy clinic can be incorporated into the existing combined subspeciality clinic*.

5.2 Pre-Pregnancy Care Team

5.2.1 A designated team consist of:

a. MFM or O&G specialist;
b. Physician from each subspecialty unit; and
c. Medical officer/ staff nurse/ medical assistant from the primary team.

5.2.2 Equipped and prepared for multi-disciplinary discussion (MDT) when required.

5.2.3 Monitoring of cases involving undesired terminations of pregnancy due to unoptimized medical conditions.

5.2.4 In charge of continuous medical education (CME) to create and maintain awareness among medical practitioners and the public.

5.3 Timing of pre-pregnancy referral and counseling

5.3.1 As the health status and risk factors can change over time, pre-pregnancy counseling should occur several times during a woman's reproductive life span.

5.3.2 Patients should be seen at least 6 months to 1 year before a planned pregnancy to optimize the medical condition.

5.4 Schedule of Pre-pregnancy Clinic

5.4.1 Frequency – once a month (can be altered based on a load of patients).

5.4.2 Clinics can also be categorized based on the subspecialty services available in the hospitals.

5.5 Referral Pathway

5.5.1 Referrals should be discussed with the physician / MFM specialist in charge of the clinic.

5.5.2 Appointments are given based on the urgency of the referral.

5.5.3 Walk-in and impromptu appointments should be accommodated when required.

5.5.4 A designated team of specialist/ medical officer/staff nurse/medical assistant should be appointed to arrange the appointments.

5.6 Approach to Management in Pre-Pregnancy Clinic

5.6.1 Combined assessment by the attending physician and MFM or O&G specialist.

5.6.2 Disease assessment and staging.

5.6.3 Decision on the suitability of embarking on pregnancy.

5.6.4 If pregnancy is contraindicated:

a. Re-evaluation of therapeutic options.
b. Discussion on contraception.
c. Discussion on termination of pregnancy in the event of unplanned pregnancy.

5.6.5 If suitable for pregnancy, the patient should undergo:

a. Optimization via combined care until embarking on pregnancy.
b. Ancillary tests – e.g, biochemical tests (FBC, RP, urinalysis), antibodies for Systemic Lupus Erythematosus patients.
c. Re-evaluation of medical therapy.
d. Follow-up / care plan for the antenatal period.

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6.0 Flow Process

6.1 As the responsibility of identifying and providing pre-pregnancy care *does not solely* belong to obstetricians and gynecologists who involves in prenatal or reproductive health only[1], hence the flow process is crucial to ensure the identification of women during their visit with primary care clinicians. With that, the flow process in pre-pregnancy care with aim to ease the various steps involved from recruitment of the patient and referral to pre-pregnancy care.

6.2 The flow process for the guideline focuses on four (4) main aspects:

a. Pre-pregnancy care screening form;
b. Feedback form;
c. Flow chart for pre-pregnancy care clinic recruitment; and
d. Flow chart for pre-pregnancy care clinic assessment.

6.3 Pre-pregnancy care screening form, as shown in Figure 1, is to be completed by the primary team based on the criteria of the target groups.

6.3.1 This pre-pregnancy care screening form is a modified version of the Perinatal Care Manual, 4th Edition, 2020, in which the focus on women's conditions has been further specified into more complicated conditions that entitled them to be followed up under specialist care.

6.3.2 The pre-pregnancy care screening form will be made available in all subspecialty clinics or medical outpatient departments.

6.3.3 For inpatient referrals, the recruitment form will be available in the ward.

6.3.4 All pre-pregnancy screening forms must be filed in the patient's folder for future reference.

6.4 Feedback Form will be placed as continuation from the pre-pregnancy screening form, also shown in Figure 1.

FIGURE 1: PRE-PREGNANCY CARE SCREENING & FEEDBACK FORM

PRE-PREGNANCY CARE SCREENING FORM

(all **women** aged 15–49-year-old with complicated medical disorders)

Medical History

- DM with complication ☐
- HPT with complication ☐
- Cardiac disease ☐
- Renal disease ☐
- Connective Tissue Disease ☐
- Hematological Disorder ☐
- Epilepsy ☐
- Others, please specify; ☐

Psychological History

- Morbid Obesity *(BMI >40kg/m2)* ☐
- Substance abuse ☐
- High risk sexual behaviour ☐
- Social Risk *(Marginalised group, single mother, domestic violence)* ☐

List of Medication

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____

Contraception Use

- No ☐
- If yes, please specify
- Pills ☐
- Implanon ☐
- IM Depo Provera ☐
- IUCD ☐
- Condom ☐
- Calendar/Withdrawal method ☐
- Others, please specify ☐

Physical Examination:

BP : _____ / _____ mmHg

PR : _____ bpm

Weight : _____ kg

Height : _____ cm

BMI : _____ kg/m2

Pregnancy Intention : YES/NO (If YES, refer Pre-Pregnancy Clinic for assessment, if NO- refer for contraception (Health Clinic or hospital)

Suitability for Pregnancy : YES/NO (if NO, refer Pre-Pregnancy Clinic for counselling and contraception)

Care Plan & Follow-Up:

1. _____
2. _____
3. _____
4. _____

Prepared by :

Date :

FEEDBACK FROM PRE-PREGNANCY SCREENING ASSESSMENT

TO : _____ DEPARTMENT : _____

PATIENT'S NAME : _____ IC NO : _____

Outcome For Pre-Pregnancy Assessment:

1. Fit for pregnancy YES / NO If NO, answer next question	2. Contraception of choice: _____ Date contraception given: _____ Next contraception follow-up: Health Clinic/ Hospital	Next PPC follow up: YES / NO (Date: _____) Aim for next TCA:

Prepared by: Date:

6.5 Flow chart for Pre-Pregnancy Care Clinic Recruitment (refer Figure 2)

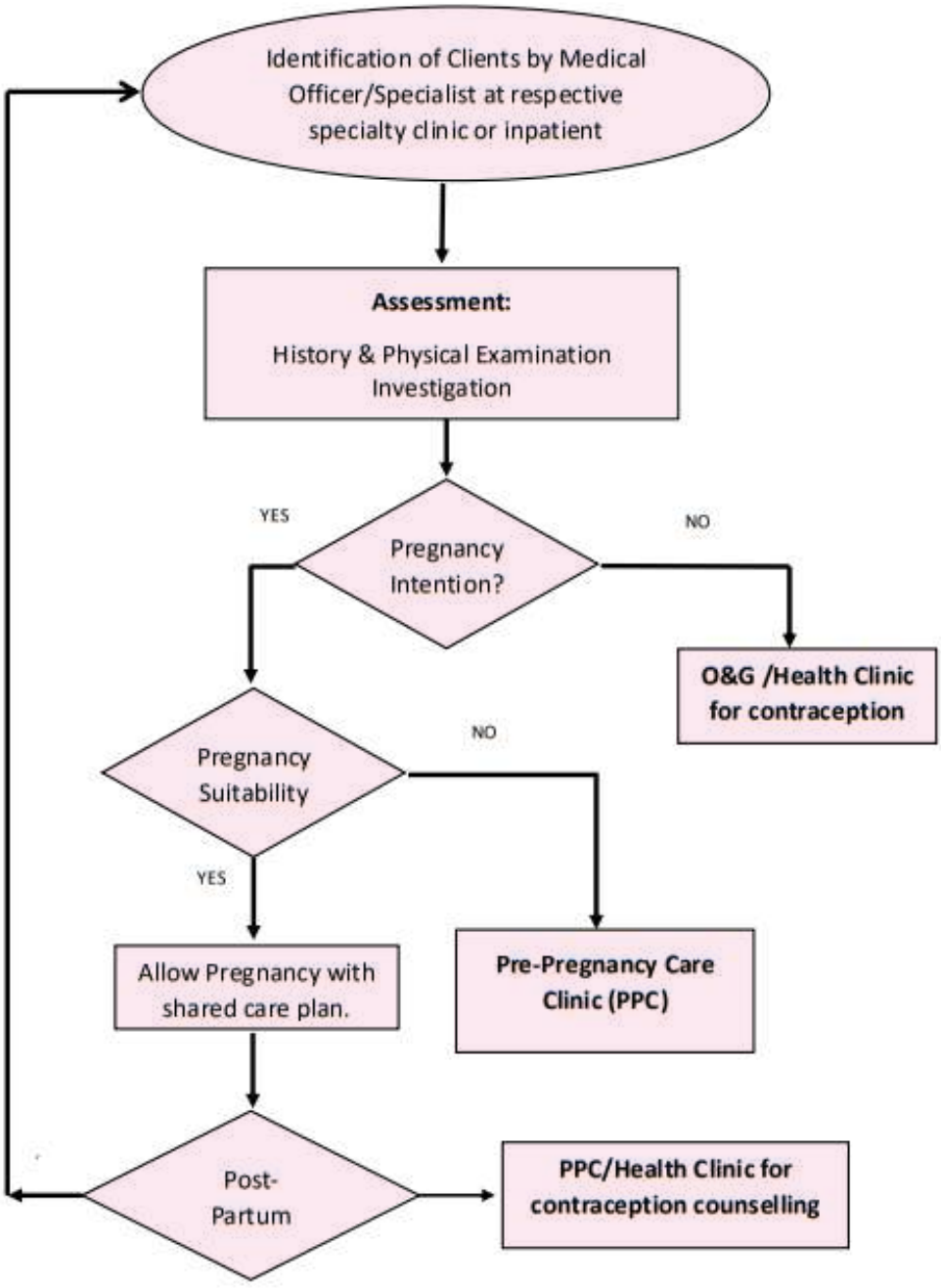
6.5.1 All women in reproductive age with comorbidities must be asked on the intention of starting the family/pregnancy during visit as a screening question for target groups[2].

6.5.2 This is the initial step to encourage primary health providers to provide routine counseling in women with targeted age group, which is termed as an opportunistic approach[3,4].

6.5.3 Any pregnancy intention in women with uncontrolled medical disorders should be referred to a pre-pregnancy care clinic for counseling.

6.5.4 Women who do not intend to become pregnant and who are not using contraception should be referred to O&G Clinic within the hospital or Family Medicine Specialist in the health clinic.

FIGURE 2: FLOW CHART FOR PRE-PREGNANCY CARE CLINIC RECRUITMENT



6.6 Flow chart on Pre-Pregnancy Care Clinic Assessment (refer Figure 3).

6.6.1 Assessment at the pre-pregnancy care clinic focus on the suitability of the patient to embark into pregnancy once the disease is stabilised/controlled.

6.6.2 Any risk factors identified that deemed the couple unfit for pregnancy will be discussed.

6.6.3 Outline of the management and intervention requirements to achieve disease or condition control with a specific target.

6.6.4 The outcome of the pre-pregnancy visit for women with the condition:

a. **Life-long unfit** for pregnancy AND couple agreed with suggested contraception; Patient may be discharged while continuing their contraception and receiving follow-up by the Family Medicine Specialist. If the patient/couple disagrees, a follow-up appointment will be given for re-counseling.

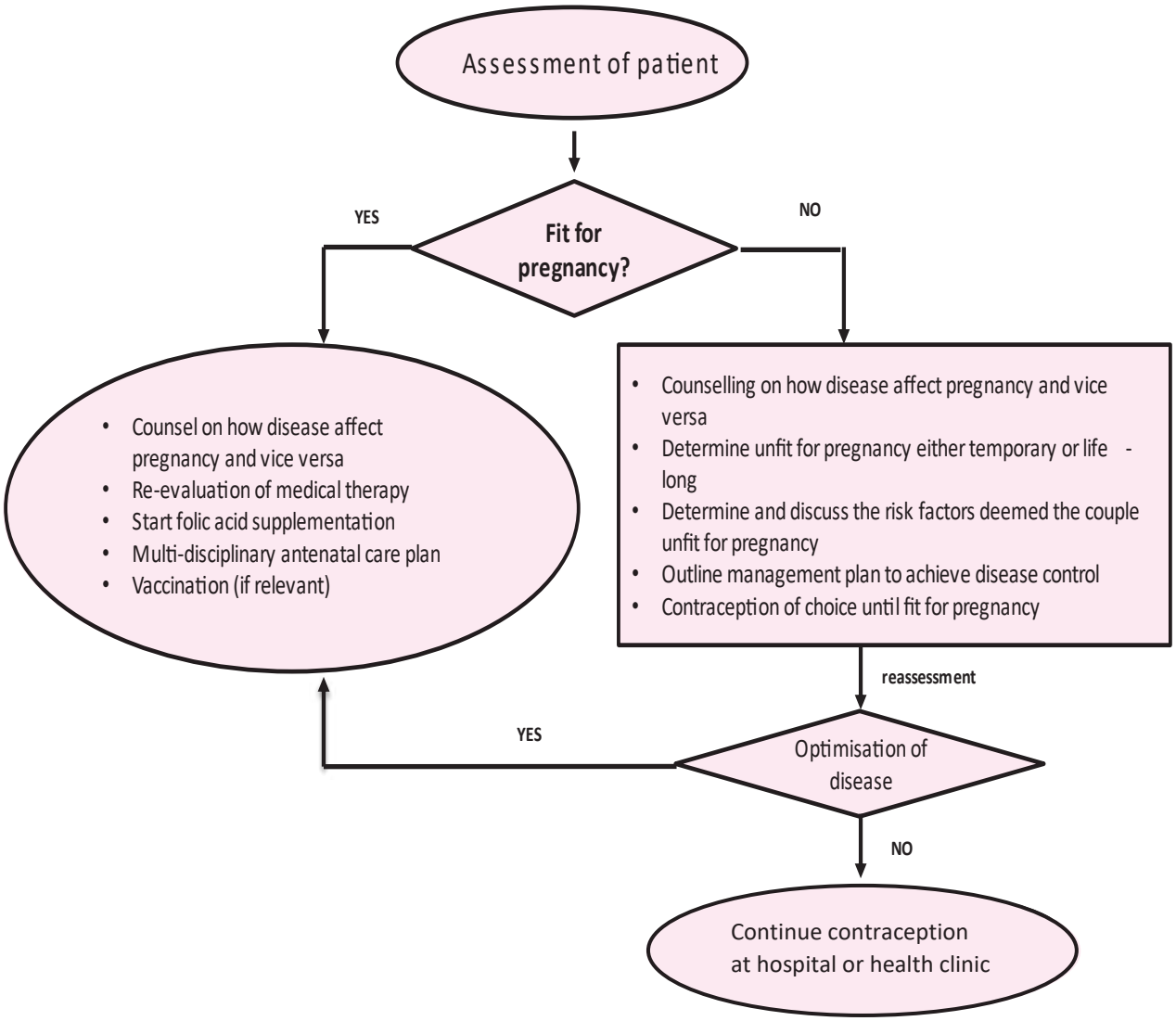
b. **Temporarily unfit** for pregnancy with risk factors modification identified; Agreeable for outline management to achieve the goal AND contraception of choice until the reassessment of the risk factors. If the couple disagrees, a follow-up appointment will be given for re-counseling.

6.7 Feedback Form from the pre-pregnancy care clinic to the primary treating team.

6.7.1 Feedback forms must be given to the primary treating team after the pre-pregnancy care assessment.

6.7.2 Another copy of the feedback form must be retained by the patient for reference by the health clinic.

FIGURE 3: FLOW CHART ON PRE-PREGNANCY CARE CLINIC ASSESSMENT



7.0 Main Activities During a Pre-pregnancy Care Visit

Activities involved during pre-pregnancy care visits as suggested below:

7.1	Assessment of the clients via history, physical examination, and laboratory results.
7.2	Identification of modifiable risk factors.
7.3	Explore the couple's wishes for pregnancy and family size desire.
7.4	Determine and discuss the risk factors that deemed the couple unfit for pregnancy.
7.5	Determine unfit for pregnancy, either temporary or life-long.
7.6	Outline appropriate management according to identifiable risk factors to achieve disease control.
7.7	Couple's counseling on how the disease affects pregnancy and vice versa.
7.8	Counseling on options of contraception suitable for the patient until fit for pregnancy or completed family.
7.9	Referral to the respective team, if necessary, i.e. dietician, dental, counsellor, Family Medicine Specialist (FMS) for a continuation of contraception.
7.10	Provide contraception i.e. Implanon, IUCD, IM Depo Provera.

8.0 Specific Medical Conditions

8.1 Cardiology

8.1.1 Introduction

All women of reproductive age with suspected or known cardiac disease should be referred for a proper cardiac and maternal cardiovascular risk assessment.[1] In the West, the risk of cardiovascular disease increased due to increasing maternal age at first pregnancy.[2.] Hypertension is most frequent, followed by congenital heart disease and rheumatic heart disease in non-western countries.[3]

In Malaysia, cardiovascular diseases lead to the non-obstetrics cause of maternal death (CEMD 2015-2019), with 49 cases reported maternal death from 2006-2008[4]. This figure increased to 33% in the following years from 2009-2011.[5] Rheumatic heart disease remains the leading cause of maternal death in Malaysia (29% of all deaths, 2009-2011), followed by peripartum cardiomyopathy.[6] Due to the masking of symptoms during pregnancy, identifying the high-risk patients, and managing these patients, recognizing cardiovascular disease in pregnancy remains challenging.

8.1.2 Physiology adaptation to pregnancy

Plasma volume and cardiac output (CO) reach a maximum 40-50% above baseline at 32 weeks of gestation, and 75% of this occurs by the end of the first trimester[1,2] Stroke volume (SV) increases in the first half of pregnancy followed by a gradual increment of heart rate (HR). While atrium and ventricular diameters increase, the ventricular function is preserved.[1,2]

Despite these physiological changes, systemic and pulmonary vascular resistance (SVR) decreases and remains constant until 32 weeks, subsequently increasing until it reaches pre-pregnancy normal values at term.[1,2]

8.1.3 Impact of cardiovascular disease on pregnancy

a. Pre-existing cardiovascular disease in pregnancy will compromise the maternal systemic circulation and maternal blood pressure as well as feta-maternal circulation. Thus, feta-maternal blood flow may also be affected, and complications such as intrauterine growth restriction, preterm birth and stillbirth can occur.
b. For pregnant women with congenital heart disease, the risk of their fetus having structural cardiac defects varies between 3% and 12%, compared with a background risk of 0.8% for the general population.[14]
c. Some essential medications prescribed in the treatment of cardiovascular disease are contraindicated in pregnancy. If discontinued, may affect the maternal outcome, and if continued, teratogenicity may result.

8.1.4 Impact of pregnancy in patients with pre-existing cardiovascular disease

a. Physiological changes in pregnant patients will have impact on patients with pre-existing cardiovascular disease.
b. Increased blood volume, heart rate and cardiac output will affect the stroke volume. This will further stress the heart contributing to reduced effort tolerance, fatigue, breathlessness and palpitation. It may lead to heart failure and worsen with the progression of pregnancy.
c. In addition to heart failure, the hypercoagulable state in these groups of patients may increase the occurrence of acute coronary syndrome.

TABLE 1: SUMMARY OF MODIFIED WHO (mWHO) CLASSIFICATION OF MATERNAL CARDIOVASCULAR RISK[6]

	mWHO I	mWHO II	mWHO II - III	mWHO III	mWHO IV
Diagnosis	Small or mild -Pulmonary stenosis -Patent ductus arteriosus -Mitral valve prolapse Successfully repaired simple lesions (atrial or ventricular septal defect, PDA, anomalous pulmonary venous drainage) Atrial or ventricular ectopic beats, isolated	Unoperated atrial or ventricular septal defect Repaired TOF Most arrhythmias (supraventricular) Turner syndrome without aortic dilatation	Mild left ventricular impairment (EF >45%) Native or tissue valve disease not considered WHO I or IV (mid mitral stenosis, moderate aortic stenosis) Marfan or other heritable thoracic syndrome without valve pathology Repaired coarctation Atrioventricular septal defect	Moderate left ventricular impairment (EF30-45%) Previous peripartum cardiomyopathy without any residual left ventricular impairment Mechanical valve Systemic right ventricle with good or mildly decreased ventricular function Fontan circulation Unrepaired cyanotic heart disease (if otherwise patient is well and the cardiac condition uncomplicated) Moderate mitral stenosis Severe asymptomatic aortic stenosis Moderate aortic dilated (40-45mm in Marfan syndrome or other HTAD; 45-50mm in bicuspid aortic valve, Turner syndrome ASI 20-25mm/m^2, TOF <50mm) Ventricular tachycardia	Pulmonary arterial hypertension Severe systemic ventricular dysfunction (EF <30% or NYHA class III-IV) Previous peripartum cardiomyopathy without any residual left ventricular impairment Severe mitral stenosis Severe symptomatic aortic stenosis Systemic right ventricle with moderate or severely decreased ventricular function Severe aortic dilatation (>45mm in Marfan syndrome or other HTAD >50mm in bicuspid aortic valve, Turner syndrome ASI >25mm^2, TOF > 50mm) Vascular Ehlers-Danlos Severe coarctation Fontan with any complication
Risk	No detectable increased risk of maternal mortality and no/mild increased risk in morbidity	Small increased risk of maternal mortality or moderate increase in morbidity	Intermediate risk of moderate to severe increase in morbidity	Significantly increased risk of maternal or severe morbidity	Extremely high risk of maternal mortality or severe morbidity
Maternal cardiac event rate	2.5-5%	5.7-10.5%	10-19%	19-27%	40-100%
Counseling	Yes	Yes	Yes	Yes: expert counseling required	Yes: pregnancy contraindicated; if pregnancy occurs, termination should be discussed
Care during pregnancy *	*Local hospital	*Local hospital	*Referral hospital	Expert centre for pregnancy and cardiac disease	Expert centre for pregnancy and cardiac disease
Minimal flow-up visits during pregnancy	Once or twice	Once per trimester	Bimonthly	Monthly or bimonthly	Monthly
Location of delivery	*Local hospital	*Local hospital	*Referral hospital	Expert centre for pregnancy and cardiac disease	Expert centre for pregnancy and cardiac disease

depends on the local setting of each state and availability of physicians and experts

8.1.5 Pre–pregnancy planning

i) Optimization of medical condition

a. For mWHO Class I-III patients, a detailed cardiac assessment, medical optimization and/or cardiac intervention is recommended prior to planned pregnancy. Patients who fall into mWHO class IV are contraindicated for pregnancy.[7,8]

b. The risk of genetic transmission to the fetus, such as in the following diseases, should be identified:
   - Congenital heart diseases (e.g., atrial septal defect, ventricular septal defect, atrial stenosis, coarctation of aorta, pulmonary stenosis, patent ductus arteriosus, Tetralogy of Fallot).
   - Autosomal dominant genetic disorder (Marfan syndrome), Long QT syndrome, Di George syndrome, and bicuspid aortic valve.
   - In timing-sensitive diseases, for example, Fontan circulation and systemic right ventricle.

c. Patients with mWHO class II-III, III and IV are advised to be referred to the pre-pregnancy clinic for optimization of maternal well-being.

d. Review and modification of current medication or therapy are recommended, particularly for patients on certain medications such as warfarin, antihypertensive drugs, heart failure therapy and antiplatelet therapy.

e. Patients with cardiac intervention before pregnancy, such as coronary angiogram and percutaneous coronary intervention, valve replacement, open heart surgery and radiofrequency ablation, will also need to be reviewed early prior to pregnancy.[7,8]

f. ACE inhibitors and Angiotensin Receptor Blockers (ARB) are not safe in pregnancy and not recommended in breastfeeding.

g. Beta-blockers (metoprolol, propranolol, atenolol), alpha-adrenergic agonists (methyldopa), calcium channel blockers and vasodilators such as hydralazine and nitro-glycerine are safe in pregnancy and during the lactation period.[7,9,10]

ii) Level of care

a. All patient needs pre-pregnancy counseling regardless of WHO classification.
b. However, those patients who fall into mWHO II-III, mWHO III, and mWHO class IV are advised to be referred to a tertiary hospital (with specialist care) and a hospital with a pregnancy and cardiology expert.
c. Other measures that need to be taken include:
    - Dental review – dental hygiene.
    - Prescription of folic acid for at least 3 – 6 months prior to conception.
    - Rubella vaccine at least 3 months prior to conception.
    - Antibiotic prophylaxis for secondary prevention of rheumatic fever.

8.1.6 Specific cardiovascular disease in pregnancy

i) Mitral Stenosis

a. Mitral Stenosis is a significant cause of maternal morbidity and mortality.[18] The most common cause of mitral stenosis is rheumatic fever.[18,19] It is often missed in pregnancy as clinical signs may be subtle.
b. Predictors of adverse outcome:
    - Mitral valve area < 1.0cm^2;
    - NYHA functional class III & IV;
    - Pulmonary hypertension; and
    - Development of atrial arrhythmias.
c. Maternal complications: [20,21]
    - Acute pulmonary edema.
    - Progressive heart failure.
    - Atrial fibrillation, which may lead to death.

d. Fetal complications: [20,21]

- Preterm delivery.
- Intrauterine growth restriction.
- Low birth weight.
- Fetal or neonatal death.

A likely explanation for these adverse events is uteroplacental insufficiency secondary to left ventricular inflow obstruction at the level of the mitral valve.[18,19,20,21].

ii) Peripartum Cardiomyopathy (PPCM)

a. Peripartum (post-partum) cardiomyopathy is the most common cardiomyopathy in pregnancy. PPCM is defined as cardiomyopathy that presents with heart failure secondary to left ventricular (LV) systolic dysfunction toward the end of pregnancy or in the months after delivery, in the absence of any other cause of heart failure (idiopathic).

b. PPCM is a diagnosis of exclusion.[22] Although many potential mechanisms for peripartum (post-partum) cardiomyopathy exist, its exact cause remains unknown but is likely to be multifactorial.[22,23,24]

c. Maternal complications[22,23,24] is:

- Progressive cardiac failure.
- Arrhythmias.
- Hypoxia.
- Thromboembolism.

d. Fetal complications:[22,23,24]

- Distress due to maternal hypoxia caused by pre-eclampsia.
- Distress due to placental hypoperfusion as a result of poor cardiac output, maternal hypovolemia due to excessive diuresis, or hypotension from aggressive afterload reduction, which leads to preterm delivery, intrauterine growth retardation and stillbirth.

iii) Congenital Heart Disease (CHD)

a. Patients with CHD can be grouped into:[14]
    - Acyanotic heart disease (e.g., atrial septal defect, ventricular septal defect, atrial stenosis, coarctation of aorta, patent ductus arteriosus, Tetralogy of Fallot);
    - Cyanotic heart disease (e.g., unrepaired TOF, pulmonary atresia, tricuspid atresia, transposition of great arteries, hypoplastic left heart syndrome); and
    - Surgically repaired/ palliative intervention (e.g., Fontan circulation, post Tetralogy of Fallot repair, Rastelli procedure, cyanotic heart disease with an aortopulmonary shunt).

b. Patients with acyanotic heart disease are generally well tolerated except in the presence of:[14]
    - Pulmonary hypertension;
    - Poor ventricular function; and/or
    - Obstructive valve lesions.

c. Patients with cyanotic heart disease have higher maternal and fetal morbidity.[14,15,16]

d. Maternal complications:[16,17]
    - Preterm labor.
    - Premature rupture of membrane.
    - Post-partum hemorrhage.
    - Pregnancy-induced hypertension and pre-eclampsia.

e. Fetal complications:[16,17]
    - Pre-maturity.
    - Fetal growth restriction.
    - Still-birth.
    - Miscarriage.
    - Fetal and perinatal mortality.
    - Risk of having congenital heart disease in the fetus.

APPENDIX

TABLE 2: DRUG AND SAFETY DATA

(Adapted from the 2018 ESC guidelines for the management of cardiovascular disease during pregnancy)

Drugs	Classification	FDA category	Placenta permeable	Transfer to breast milk (fetal dose)	Adverse effects
Abciximab	Monoclonal antibody with antithrombotic effects	C	Unknown	Unknown	Inadequate human studies; should be given only if the potential benefit outweighs the potential risk to the fetus.
Acenocoumarol	Vitamin K antagonist	D	Yes	Yes (no adverse effects reported)	Embryopathy (mainly first trimester), bleeding
Acetylsalicylic acid (low dose)	Antiplatelet drug	B	Yes	Well-tolerated	No teratogenic effects known (large datasets).
Adenosine	Antiarrhythmic	C	No	No	No fetal adverse effects reported (limited human data).
Aliskiren	Renin inhibitor	D	Unknown	Unknown	Unknown (limited experience).
Amiodarone	Antiarrhythmic (Class III)	D	Yes	Yes	Thyroid insufficiency (9%), hyperthyroidism, goitre, bradycardia, growth retardation, premature birth.
Ampicillin, amoxicillin, cephalosporins, erythromycin, mezlocillin, penicillin	Antibiotics	B	Yes	Yes	No fetal adverse effects reported.
Imipenem, rifampicin, teicoplanin, vancomycin	Antibiotics	C	Unknown	Unknown	Risk cannot be excluded (limited human data).
Aminoglycosides, quinolones tetracyclines	Antibiotics	D	Unknown	Unknown	Risk to the fetus exists (reserved for vital indications).
Atenolol	β-blocker (class II)	D	Yes	Yes	Hypospadias (first trimester); birth defects, low birth weight, bradycardia and hypoglycaemia in fetus (second and third trimester).
Benazepril	ACE inhibitor	D	Yes	Yes(maximum 1.6%)	Renal or tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death.
Bisoprolol	β-blocker (class II)	C	Yes	Yes	Bradycardia and hypoglycaemia in fetus.
Candesartan	Angiotensin II receptor blocker	D	Unknown	Unknown; not recommended	Renal or tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death.
Captopril	ACE inhibitor	D	Yes	Yes (maximum 1.6%)	Renal or tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death.
Clopidogrel	Antiplatelet drug	C	Unknown	Unknown	No information during pregnancy available.
Colestipol, cholestyramine	Lipid-lowering drugs	C	Unknown	Yes- lowering fat- soluble vitamins	May impair absorption of fat-soluble vitamins, e.g. vitamin K –> cerebral bleeding (neonatal).

Drugs	Classification	FDA category	Placenta permeable	Transfer to breast milk (fetal dose)	Adverse effects
Danaparoid	Anticoagulant	B	No	No	No side effects (limited human data).
Digoxin	Cardiac glycoside	C	Yes	Yes	Serum level unreliable, safe.
Diltiazem	Calcium channel blocker (class IV)	C	No	Yes	Possible teratogenic effects.
Disopyramide	Antiarrhythmic (class IA)	C	Yes	Yes	Uterus contraction.
Enalapril	ACE inhibitor	D	Yes	Yes (maximum 1.6%)	Renal or tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death.
Eplerenone	Aldosterone antagonist	-	Unknown	Unknown	Unknown (limited experience).
Fenofibrate	Lipid-lowering drug	C	Yes	Yes	No adequate human data.
Flecainide	Antiarrhythmic (class IC)	C	Yes	Yes	Unknown (limited experience).
Fondaparinux	Anticoagulant	-	Yes (maximum 10%)	No	New drug, (limited experience).
Furosemide	Diuretic	C	Yes	Well tolerated; milk production can be reduced	Oligohydramnios
Gemfibrozil	Lipid-lowering drug	C	Yes	Unknown	No adequate human data.
Glyceryl trinitrate	Nitrate	B	Unknown	Unknown	Bradycardia, tocolytic.
Heparin (low molecular weight)	Anticoagulant	B	No	No	Long-term application: seldom osteoporosis and markedly less thrombocytopenia than UF heparin.
Drugs	Classification	FDA category	Placenta permeable	Transfer to breast milk (fetal dose)	Adverse effects
Heparin (unfractionated)	Anticoagulant	B	No	No	Long-term application: osteoporosis and thrombocytopenia.
Hydralazine	Vasodilator	C	Yes	Yes (maximum 1%)	Maternal side effect: lupus-like symptoms; fetal tachyarrhythmias (maternal use).
Hydrochlorothiazide	Diuretic	B	Yes	Yes; milk production can be reduced	Oligohydramnion.
Irbesartan	Angiotensin II receptor blocker	D	Unknown	Unknown	Renal or tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death.
Isosorbide dinitrate	Nitrate	B	Unknown	Unknown	Bradycardia.
Isradipine	Calcium channel blocker	C	Yes	Unknown	Potential synergism with magnesium sulfate may induce hypotension.
Labetalol	α-β- blocker	C	Yes	Yes	Intrauterine growth retardation (second and third trimester), neonatal bradycardia and hypotension (used near term).
Lidocaine	Antiarrhythmic (class IB)	C	Yes	Yes	Fetal bradycardia, acidosis, central nervous system toxicity.

Drugs	Classification	FDA category	Placenta permeable	Transfer to breast milk (fetal dose)	Adverse effects
Methyldopa	Central α-agonist	B	Yes	Yes	Mild neonatal hypotension.
Metoprolol	β-blocker, class II	C	Yes	Yes	Bradycardia and hypoglycaemia in fetus.
Mexiletine	Antiarrhythmic (class IB)	C	Yes	Yes	Fetal bradycardia.
Nifedipine	Calcium channel blocker	C	Yes	Yes(maximum 1.8%)	Tocolytics, application and potential synergism with magnesium sulfate may induce hypotension (mother) and fetal hypoxia.
Phenprocoumon	Vitamin K antagonist	D	Yes	Yes (maximum 10%), well tolerated as inactive metabolite	Coumarin-embryopathy, bleeding (see further discussion in Section 5 for use during pregnancy).
Procainamide	Antiarrhythmic (class IA)	C	Yes	Yes	Unknown (limited experience).
Propafenone	Antiarrhythmic (class IC)	C	Yes	Unknown	Unknown (limited experience).
Propranolol	β-blocker (class II)	C	Yes	Yes	Bradycardia and hypoglycemia in fetus.
Quinidine	Antiarrhythmic (class IA)	C	Yes	Yes	Thrombopenia, premature birth,VIIIth nerve toxicity.
Ramipril	ACE inhibitor	D	Yes	Yes (maximum 1.6%)	Renal or tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death.
Sotalol	Antiarrhythmic (class III)	B	Yes	Yes	Bradycardia and hypoglycemia in fetus (limited experience).
Spironolactone	Aldosterone antagonist	D	Yes	Yes (maximum1.2%); milk production can be reduced	Antiandrogenic effects, oral clefts (first trimester).
Statin	Lipid-lowering drugs	X	Yes	Unknown	Congenital anomalies.
Ticlopidine	Antiplatelet	C	Unknown	Unknown	Unknown (limited experience)
Valsartan	Angiotensin II receptor blocker	D	Unknown	Unknown	Renal or tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death.
Verapamil oral	Calcium channel blocker (class IV)	C	Yes	Yes	Well tolerated (limited experience during pregnancy).
Verapamil i.v.	Calcium channel blocker (class IV)	C	Yes	Yes	Intravenously use is may be associated with a greater risk of hypotension and subsequent fetal hypoperfusion.
Vernakalant	Antiarrhythmic (class III)	-	Unknown	Unknown	No experience of use in pregnancy.
Warfarin	Vitamin K antagonist	D	Yes	Yes (maximum 10%), well tolerated as inactive metabolite	Coumarin-embryopathy, bleeding

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8.2 Nephrology

8.2.1 Introduction

Pregnancy is characterized by significant physiological alterations, which are critical for an optimal pregnancy outcome. Knowledge of these expected physiological changes is necessary to assist with the proper interpretation and identifying worsening kidney function. As such, kidney disease during pregnancy, even when mild, can considerably increase both maternal and fetal risks.[1,3,7-10]

8.2.2 Chronic Kidney Disease Non-Dialysis Dependent (CKD-ND)

CKD staging must be based on their estimated Glomerular Filtration Rate (eGFR) level prior to conception. However, the eGFR equations are inaccurate in assessing kidney function during pregnancy as they can under or overestimate the GFR.[1,3,7] Hence, timed urine clearance studies are preferred despite their inconvenience. Serum creatinine (Cr) remains the most practical way to assess kidney function during pregnancy.[1,3] The degree of kidney impairment in pregnancy has been arbitrarily defined as mild (Cr <125 umol/L), moderate (Cr 125 to 220 umol/L) and severe (Cr >220 umol/L).[7]

i) Impact of the disease on pregnancy

CKD has the following effects on pregnancy:[1,3,7-9]

a. Increased risk of adverse maternal outcomes such as gestational hypertension, pre-eclampsia, eclampsia and maternal death; and
b. Increased risk of fetal outcomes including premature birth, intrauterine growth restriction (IUGR), small-for-gestational-age (SGA), low birth weight, stillbirth, and neonatal mortality.

Their risks begin at CKD Stage 1 and continue to rise as the disease progresses. Baseline hypertension, baseline proteinuria (> 1 gm per day) and the presence of systemic disease are significant predictors of adverse maternal-fetal outcomes. The

risk of preterm delivery and IUGR correlate with maternal kidney function and level of proteinuria.[1,3,7-9]

ii) Impact of pregnancy on the disease

The rate of renal function deterioration and worsening of proteinuria during pregnancy correlates significantly with CKD stages:

a. Renal function deteriorates more in CKD Stage 3 – 4 compared with Stage 2 (60% vs 14.3%).[1]
b. Doubling of proteinuria as CKD stages progress is 20.5%, 86.5% and 70% in Stage 1, Stage 3 and Stage 4-5, respectively.[1]
c. Significant pregnancy-related loss of kidney function during pregnancy or within six weeks post-partum occurred in 43% of pregnancies, with 23% progressing to End Stage Kidney Disease by six months post-partum.[1]
d. Worsening of hypertension (25 % to 30%), and may require additional anti-hypertensives.[3,7]

iii) Pre-pregnancy planning

a. Pregnancy should be planned, taking into consideration the clinical status of the woman, with a pre-conception review of medication and early referral the combined specialist care.[1,3,7]
b. Patients with a serum creatinine > 124 umol/L, proteinuria of >1 gm/day, and uncontrolled hypertension or systemic disease should be counseled against pregnancy.[1,3,7]
c. ACE-I and ARB should be avoided in pregnancy.[1,3,7]
d. A higher dose of folic acid 5mg daily is recommended preconception to reduce the risks of malformation.[1,3,7]

iv) Pregnancy Care Plan

a. All pregnant women with CKD should be co-managed by a multidisciplinary team comprising of nephrologist/physician & obstetrician.[1,3,7]
b. The team should be focused on monitoring signs of deterioration of kidney function, pre-eclampsia, fetal growth restriction, and preterm labor.[1,3,7]
c. Prescribe low-dose aspirin if no contraindication to reduce the risk of pre-eclampsia.[1,3,7]

d. If the patient's kidney function deteriorates during the pregnancy, their management needs to be individualized based on the nephrologist's and the obstetrician's joint assessment and decision.

8.2.3 End Stage Kidney Disease (ESKD)

The incidence of pregnancy in women on hemodialysis ranges from 1 to 7%.[2,4] Documented pregnancy rates on peritoneal dialysis (PD) are even lower, occurring at approximately one-half of that reported for HD patients.[4,6] However, recent advances in care, including more intensive HD regimens, have made pregnancy a more viable option for young women during their reproductive years.[6] Currently, many programs no longer dissuade women who desire a pregnancy from conceiving while on dialysis if there is no forthcoming option for transplantation.[4-6]

i) Impact of the disease on pregnancy

a. Maternal-specific risks include exacerbation of hypertension, pre-eclampsia, and cervical incompetence.[4-6]
b. Fetal risks include intra-uterine growth restriction and pre-maturity. [4-6]

ii) Impact of pregnancy on the disease

a. Require intensification of dialysis. [2,3,4-7]
b. May require more blood transfusions and an increased dose of Erythropoietin.[2,3,4-7]
c. Electrolyte disturbances may occur with more frequent dialysis.[2,3,4-7]

iii) Pre-pregnancy planning

a. Patients should receive pre-pregnancy counseling, including the options of postponing pregnancy until transplantation (when feasible) and the need for long frequent dialysis prior to and during pregnancy.[2,3,7]
b. Careful counseling with respect to risk, optimization prior to pregnancy, which can take many months to years, close multidisciplinary follow-up for potential complications during pregnancy, and extensive post-partum support (both medical and emotional due to the complexity of raising children while managing chronic illness).[2,3,7]

c. Patients on peritoneal dialysis might need to convert to hemodialysis.[2,3,7]

iv) Pregnancy Care Plan

a. It should be managed by a nephrologist and an obstetrician familiar with the effects of renal disease in pregnancy.[2,3,7]

b. Intensify HD 24 to 48 hours per week targeting urea < 12.5 mmol/L, normal bicarbonate level, and normal blood pressure (but less can be prescribed if there is significant residual kidney function).[3,4,7]

c. Other supportive measures to increase the chance of successful live birth:

- Target Hb 10 to 11g/dl; [3,4,7]
- Careful uterine and fetal monitoring during HD, combined with measures to prevent dialysis-induced hypotension;[3,4,7]
- Attention to nutrition and proper weight gain, and careful examination to detect volume overload unrelated to the pregnancy;[3,4,7] and
- Avoid medications unsafe for pregnancy (e.g., non-calcium-based phosphate binders).[3,7]

8.2.4 Kidney Transplant Recipient (KTR)

A successful kidney transplant restores fertility with the resumption of normal menses at an average of five to seven months after transplantation.[3,7]

i) Impact of the disease on pregnancy

a. The first year after transplantation carries the highest risk of rejection. Therefore, higher usage of teratogenic medications is needed, which is associated with adverse pregnancy outcomes.[3,7]

b. Exposure to teratogenic medications such as mycophenolate mofetil in the first trimester of pregnancy can lead to abnormalities in the developing fetus.[3,7]

c. Risk of inferior perinatal outcome and maternal graft function similar to CKD-ND.[3,7]

d. Pre-eclampsia occurs in 25%–35% of pregnancies and IUGR or preterm birth in 30%–50% mainly due to fetal or maternal compromise.[3,7-9]

ii) Impact of pregnancy on the disease

a. Acute rejection during pregnancy and de-novo allosensitization post pregnancy < 6%. [3,7]

b. Stable and good allograft function has no long-term adverse impact on graft function or patient survival.[3,7]

iii) Pre-pregnancy planning

a. Contraception up to two years post-transplant.[3,7]

b. Allow patients to conceive if they fulfill the following criterias[3,7]:

- Stable allograft function;
- Creatinine < 124 umol/L;
- No recent episodes of acute graph rejection;
- Blood pressure ≤ 140/90 mmHg;
- No or minimal proteinuria ≤ 500 mg/24 hours;
- Prednisolone ≤ 15 mg/day;
- Azathioprine ≤ 2 mg/kg/day; and
- Stopping mycophenolate mofetil and sirolimus six (6) weeks prior to conception

iv) Pregnancy Care Plan

a. All pregnant KTRs should be co-managed by a multidisciplinary team comprising of nephrologist and obstetrician.[3,7]

b. Monitoring renal profile, trough calcineurin inhibitors (CNI) level, proteinuria, and blood pressure control.[3,7]

c. If the patient develops rejection or other transplant-related complications during the pregnancy, the management needs to be individualized based on the nephrologist's and obstetrician's joint assessment and decision.

8.2.5 Lupus Nephritis

i) Impact of the disease on pregnancy

a. Active nephritis or even previous nephritis predicts worse pregnancy outcomes with significantly higher documented rates of preterm delivery (30% of women with a history of nephritis delivering prior to 37 weeks compared to 11% of women without previous nephritis).[10]
b. Higher risks for maternal hypertension (16.3%), pre-eclampsia (7.6%), and eclampsia (0.8%).[10]
c. Higher risk for spontaneous abortions (16%), IUGR (12.7%), induced abortions (5.9%), stillbirth (3.6%), and neonatal death (2.5%).[10]

ii) Impact of pregnancy on the disease

Pregnancy has been demonstrated to increase the potential of a disease flare-up (25.6%) during any trimester or the early post-partum period.[10]

iii) Pre-pregnancy planning

a. Prognosis is favorable if in remission for > six months prior to conception with minimal immunosuppression.[3,7,10]
b. Risk of adverse maternal or fetal outcomes similar to CKD-ND.[3,7,10]
c. Avoid usage of medications contraindicated in pregnancy.[3,7,10]

iv) Pregnancy Care Plan

a. All pregnant patients with lupus nephritis should be co-managed by a multidisciplinary team comprising of nephrologist/physician and obstetrician.[1,3,7,10]
b. Monitor for disease activity during pregnancy.[3,7]
c. Monitoring of renal profile, proteinuria, and blood pressure control.[3,7]
d. Use of minimal immunosuppression to maintain disease remission (steroid, azathioprine, CNI).[3,7]
e. Maintain Hydroxychloroquine unless contraindicated to reduce relapse rate.[3,7]
f. The use of low molecular weight heparin follows the same indication for thromboembolic prophylaxis in patients with Systemic Lupus Erythematosus.[3,7]

g. If lupus nephritis relapses during pregnancy, the clinical management needs to be individualized based on Nephrologist's and the Obstetrician's joint assessment and decision.

8.2.6 Primary Glomerular Disease

i) Impact of the disease on pregnancy

Active glomerular disease increases the risk for adverse maternal and fetal outcomes.[3,7,8]

ii) Impact of pregnancy on the disease

a. Pregnancy increases the risk of relapse depending on the primary histological diagnosis.[3,7,8]
b. Worsening of hypertension, and may require additional anti-hypertensives.[3,7,8]

iii) Pre-pregnancy planning

a. Prognosis is favorable if remission for more than six months prior to conception with minimal immunosuppression.[3,7,8]
b. Risk of adverse maternal or fetal outcomes similar to CKD-ND.[3,7,8]
c. Avoid usage of medications contraindicated in pregnancy.[3,7]

iv) Pregnancy Care Plan

a. All pregnant patients with primary glomerular diseases should be co-managed by a multidisciplinary team comprising of Nephrologist and Obstetrician.[3,7]
b. Monitoring of renal profile, proteinuria, and blood pressure control.[3,7]
c. Use of minimal immunosuppression to maintain disease remission (steroid, azathioprine, CNI).[3,7]
d. If the primary glomerular disease relapses during pregnancy, the management needs to be individualized based on the nephrologist's and the obstetrician's joint assessment and decision.

8.2.7 Safety of medication during pregnancy

TABLE 3: SAFETY OF MEDICATION-RELATED TO NEPHROLOGY IN PREGNANCY [3,7]

DRUG NAME	FDA CLASS
Corticosteroids	C
Hydroxychloroquine	NOT ASSIGNED
Cyclosporin	C
Tacrolimus	C
Rituximab	C
IVIG	C
Azathioprine	D
Mycophenolate Mofetil	D
Cyclophosphamide	D
Methotrexate	X

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8.3 Rheumatology

8.3.1 Introduction

Rheumatic diseases often occur in women of reproductive age. The impact pregnancy has on rheumatic disease, or vice versa, often varies depending on the type and activity status of the disease. As rheumatic diseases often affect multiple organ systems, co-management with other sub-specialty teams is common. Disease activity of the affected organ system needs to be carefully assessed and adequately managed prior to conception, ideally by the attending rheumatologist or sub-specialty team (e.g., nephrology, hematology) during the initial pre-pregnancy discussion with the patient in their respective clinics.

Treatments with potential risks to pregnancy outcomes may be used if there are no suitable alternatives after a shared discussion between attending physicians and the patient. The principle of management is to prioritize the well-being of the patient over the fetus. This is applicable to all pregnancies in rheumatology patients.
In a patient with rheumatic disease, the aspects of pre-pregnancy planning include:

- optimization of disease control;
- counseling on the potential risks of pregnancy;
- determination of suitability and the appropriate timing of conception; and
- review and modification of therapeutic agents to pregnancy-compatible alternatives if available.

8.3.2 Risk Stratification

i) Pregnancy is at high risk if:

a. The disease is still active within the last six months (e.g., active lupus nephritis, active neuro-psychiatric Systemic Lupus Erythematosus);
b. Therapeutic agents used are not safe (with no effective alternative) in pregnancy; and/or

c. Presence of major organ involvement with significant residual functional impairment (e.g., moderate to severe Connective Tissue Disease (CTD)-related Pulmonary HPT, severe CTD-related interstitial lung disease (ILD).

Patients with the above conditions should be counseled strongly against pregnancy, and the practice of effective contraception should be emphasized.

ii) The main roles of Pre-Pregnancy Clinic (PPC) for Rheumatology patients are as follows:

a. For those with low-risk pregnancies and deemed safe to conceive:
   - To re-counsel and re-enforce the importance of treatment adherence; and
   - To review the therapy and ensure pregnancy-compatible medications (refer to Table 1).

b. For those with high-risk pregnancies and deemed unsafe to conceive:
   - To re-emphasize against conception;
   - To assist in the counseling and arrangement of effective and safe contraceptive methods; and
   - In the event of a pregnancy, the patient must inform the treating rheumatologist/physician as soon as possible.

8.3.3 Disease-related

Rheumatic diseases often encountered in pregnancy are Systemic Lupus Erythematosus (SLE), anti-phospholipid syndrome (APS) secondary to SLE, and inflammatory arthritis. Following is the list of general information with regard to the impact of disease on pregnancy and vice versa:

i) Systemic Lupus Erythematosus (SLE)

a. Impact of active or severe disease on pregnancy:
   - Adverse pregnancy outcome (e.g., fetal or neonatal death, birth before 36 weeks due to placental insufficiency, hypertension, or pre-eclampsia, and small-for-gestational-age (SGA) neonate).[2]

- Adverse effects of steroids (hypertension in pregnancy, gestational diabetes, premature rupture of membrane, and increased risk of infection).
- Immunosuppressive effects of treatment (increased risk of infection, teratogenicity).
- Intrinsic teratogenic effects of treatment.

b. Impact of pregnancy on disease:

- May precipitate flare or aggravate manifestations of the disease.
- Confounds laboratory test results (e.g., Hb, ESR, complement levels, UFEME), thus complicating the assessment of disease activity.

ii) Anti-phospholipid Syndrome (APS) secondary to SLE:

a. Impact of disease on pregnancy:

- Adverse pregnancy outcome (e.g., fetal or neonatal death, birth before 36 weeks due to placental insufficiency, hypertension, or pre-eclampsia; and small-for-gestational-age (SGA) neonate.[2]
- Increased risk of bleeding (due to the effect of anticoagulation).
- Patients with anti-phospholipid antibody positivity, in particular, triple positivity (i.e., positive tests for the presence of Lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti-β2 glycoprotein1(β2GP1) antibodies) without thrombosis or obstetric morbidity, should be on low-dose aspirin once pregnant.

b. Impact of pregnancy on disease:

- High risk for thrombosis.
- Patients with positive Lupus anticoagulant (LA) or triple positivity have higher rates of pregnancy complications/fetal loss and thrombosis than those with only obstetric-associated APS.[3,4]

iii) Inflammatory Arthritis (most common)

a. Impact of disease on pregnancy:

- Pregnancy outcomes in women with well-controlled inflammatory arthritis are comparable to those in the general population. However, overall risks of adverse pregnancy outcomes are increased, including hypertension, intrauterine growth restriction, and cesarean delivery, especially in patients with active disease.[5]
- In women with psoriatic arthritis, there may be a post-partum aggravation of disease activity. The possibility of a higher risk for pre-eclampsia, elective cesarean section, and preterm birth in psoriatic arthritic pregnancies cannot be ruled out.[6]
- Other risks include:
    - Adverse effects of steroids (hypertension in pregnancy, gestational diabetes, premature rupture of membrane, increased risk of infection).
    - Immunosuppressive effects of treatment (increased risk of infection, teratogenicity).
    - Intrinsic teratogenic effects of treatment.
    - Physical disabilities from damaged or deformed joints may cause difficulties during pregnancy and delivery.

b. Impact of pregnancy on disease:

- Disease control in approximately 50 to 70% of women with RA improves during pregnancy[7,8,9] but tends to flare-up during the post-partum period.
- Increased burden on joints (from weight gain in pregnancy) may cause more discomfort.
- Confounds laboratory test results (e.g., Hb, ESR), thus complicating the assessment of disease activity.

iv) For a woman with anti-Ro/SSa and/or anti-La/SSb positive

a. Patients must be counseled regarding the risk of fetal congenital heart block (CHB).
   - The incidence of CHB is 2% in cases of maternal anti-Ro/SSa antibody positivity and 3 % when both anti-Ro/SSA and anti-La-SSb are positive.[10]
   - Following the birth of one child with CHB, the risk of recurrence is nine times higher in subsequent pregnancies.[10]

b. Once pregnant, she needs to be followed up in a center with feta-maternal service.

c. She should be initiated on Hydroxychloroquine if there is no contraindication or reminded not to discontinue if already taken.

8.3.4 Pregnancy Care Plan

i) Antenatal and postnatal monitoring of disease should ideally be performed by the attending rheumatologist or subspeciality team (e.g., nephrology, hematology) primarily managing the disease in their respective clinics or a combined care setting. Alternative arrangements may be considered if agreed upon by the treating team and patient.

ii) In the event of an unforeseen complication of pregnancy, the principles of management are as follow:
   a. Obstetric-related care of patients with rheumatic disease shall follow the standard care of pregnancy provided by obstetric team;
   b. The rheumatologist or subspecialty team will co-manage the disease-related complications and provide optimal medical care for the pregnant woman; and
   c. Multi-disciplinary communication and combined management are vital.

TABLE 4: FDA PREGNANCY RISK CATEGORIES OF MEDICATIONS COMMONLY USED IN RHEUMATOLOGY[11]

Medication	FDA Pregnancy Risk Category
Hydroxychloroquine	C
Sulphasalazine	B
Azathioprine	D
Prednisolone	B
NSAIDs	C
Ciclosporin	C
Tumor necrosis factor inhibitors	B
Rituximab	N
Other biologics -=Interleukin-6 inhibitors	NA
Methotrexate	X
Leflunomide	X
Cyclophosphamide	X

Medication	FDA Pregnancy Risk Category
Mycophenolate mofetil & mycophenolic acid	D
Tofacitinib, Baricitinib	N
Warfarin	D

B: no proven human risk

C: risk cannot be ruled out

D: positive evidence of risk

X: contraindicated in pregnancy

N: not formally assigned to a category

NA: data in pregnancy use not available

Despite the FDA pregnancy risk categorization, women with SLE are strongly advised to continue Hydroxychloroquine (HCQ)/Azathioprine during pregnancy[12], in view of the maternal and/or pregnancy benefits of HCQ[13,14] and Azathioprine, and low risk of harm to the mother and foetus[15](refer Table 5). Any adjustment to the treatment regime should be discussed with the rheumatologist or subspecialty team primarily managing the patient.

TABLE 5: MATERNAL MEDICATION USE: OVERVIEW OF MEDICATION USE BEFORE AND DURING PREGNANCY, AND DURING BREASTFEEDING[12].

MEDICATION	PRE-CONCEPTION	DURING PREGNANCY	BREASTFEEDING
Conventional medications			
Hydroxychloroquine	++	++	++
Sulfasalazine	++	++	++
Colchicine	++	++	++
Azathioprine	++	++	+ Low transfer
Prednisolone	+ Keep at lowest effective dose & add pregnancy-compatible immunosuppressants	+ Keep at lowest effective dose & add pregnancy-compatible immunosuppressants	+ After a dose of >20 mg daily, delay breastfeeding for 4 hours
Ciclosporine, tacrolimus	+ Monitor blood pressure	+ Monitor blood pressure	+ Low transfer
NSAIDs (COX-2 inhibitors not preferred)	+ Discontinue if the woman is having difficulty conceiving	+ Continue in first and second trimesters; discontinue in third Trimester	+ Ibuprofen preferred
Medication	Pre-conception	During Pregnancy	Breastfeeding
Tumor necrosis factor inhibitors (tumor necrosis factor inhibitors are considered compatible with pregnancy)			
Infliximab, Etanercept, Adalimumab, Golimumab	+ Continue through conception	+ Continue in first and second trimesters; discontinue in third trimester several half-lives prior to delivery	++
Rituximab	+ Discontinue at conception	+ Life-/organ-threatening disease	++
Other biologics (limited safety data; limited transfer in early pregnancy but high transfer in second half of pregnancy)			

MEDICATION	PRE-CONCEPTION	DURING PREGNANCY	BREASTFEEDING
Belimumab, Tocilizumab, Secukinumab, Ustekinumab	+ Discontinue at conception	× Discontinue during pregnancy	+ Expect minimal transfer due to large molecular size, but no available data
Not compatible with pregnancy			
Methotrexate	×× Stop 1–3 months prior to conception	×× Stop and give folic acid 5 mg/day	× Limited data suggest low Transfer
Medication	Pre-conception	During Pregnancy	Breastfeeding
Leflunomide	×× Cholestyramine washout (if detectable levels)	×× Stop and give cholestyramine washout	××
Mycophenolate mofetil & mycophenolic acid	×× Stop >6 weeks prior to conception to assess disease stability	××	××
Cyclophosphamide	×× Stop 3 months prior to conception	+ Life-/organ threatening disease in second and third trimesters	××
Thalidomide	×× Stop 1–3 months prior to conception	××	××
Tofacitinib, Baricitinib	Unable to determine due to lack of data; small molecular size suggests transfer across the placenta and into breast milk		

Recommendation level:

	++	Strongly recommend
	+	Recommend
	+	Conditionally recommend
	×	Conditionally recommend against
	××	Strongly recommend against
		Unable to determine due to lack of data

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8.4 Endocrinology

8.4.1 Diabetes Mellitus

The term “pre-existing diabetes in pregnancy” refers to diabetes, either Type 1 (T1DM) or Type 2 (T2DM) diabetes mellitus, diagnosed before pregnancy. It is associated with risks to the woman and her developing fetus. The National Obstetric Registry involving 14 tertiary hospitals showed that the incidence of diabetes in pregnancy was 8.66% in 2011 and 8.83% in 2012. The cesarean section rates in this group of patients were around 13% in 2011 and 2012. In both years, approximately 16% of babies born to diabetic mothers weighed 4 kg and more.

i) Impact of the disease on the pregnancy

a. Hyperglycemia is teratogenic. Poor glycemic control in the first few weeks of conception increases the risk of congenital anomalies. A systematic review of 13 observational studies of women with T1DM and T2DM demonstrated that poor glycemic control resulted in a pooled odds ratio of 3.44 (95%CI 2.3-5.15) of a congenital anomaly, 3.23 (CI 1.64-6.36) of spontaneous loss, and 3.03 (1.87-4.92) of perinatal mortality compared to women with optimal glycemic control.
b. Periconception glycated hemoglobin (A1C) >6.6%, preconception retinopathy and lack of preconception folic acid supplementation were all independently associated with the risk of neonatal and infant death.
c. Women with diabetes should receive assistance in achieving optimal glycemic control preconception as this is associated with a reduction of congenital anomalies by 70%.
d. Pregnant women with pre-gestational diabetes mellitus are also at increased risk of macrosomia, pre-maturity, pre-eclampsia, operative delivery or increased rates of cesarean section.

ii) Impact of pregnancy on the disease

a. Pregnancy is a complex metabolic state that involves dramatic alterations in the hormones as well as changes in adipocytes and inflammatory cytokines. The first trimester is characterized by increased insulin sensitivity and pregnant women are at increased risk for hypoglycemia. The risk is higher in pregnant women with DM complicated by gastroparesis or hyperemesis gravidarum. Maternal hypoglycemia is common and often severe in women with type 1 diabetes mellitus and insulin requirements in the first trimester are likely to decrease by 10 to 20%.
b. By 18-20 weeks of gestation, peripheral insulin resistance increases resulting in increasing insulin requirements so that insulin regimes need to be intensified to multiple insulin injections. The insulin requirement is depending on baseline insulin resistance, carbohydrate intake and body mass index.
c. Diabetic ketoacidosis (DKA) may complicate pregnancy in women with diabetes with a relatively lower blood glucose level. It is due to increased propensity to ketosis in pregnant women and glomerular hyperfiltration in pregnancy which causes glycosuria at lower serum glucose. Identified precipitating factors for DKA include prolonged fasting, infection, hyperemesis, medications such as beta-mimetic tocolysis and steroids or non-compliant to insulin therapy.

iii) Pre-pregnancy planning

All women with pre-existing type 1 or type 2 diabetes should receive pre-conception care to optimize glycemic control, assess for complications, review medications and begin folic acid supplementation. Effective contraception should be provided until the woman is ready for pregnancy.

Care by a multidisciplinary team composed of a diabetes nurse educator, dietitian, obstetrician and endocrinologist/physician with expertise in diabetes, both prior to conception and during pregnancy, has been shown to minimize maternal and fetal risks in women with pre-existing type 1 and type 2 diabetes.

Women with type 1 or type 2 diabetes should discuss pregnancy plans with their diabetes healthcare team for:

a. Glycemic control.

- Women with pre-existing diabetes who plan for pregnancy to aim for A1C of less than 6.5%, if this is achievable without causing hypoglycemia. Any reduction in A1C levels towards the target is likely to reduce the risk of congenital malformation in the baby.
- Those with A1C of more than 10% (86 mmol/mol) are advised not to get pregnant because of the associated risks.
- Strategies to achieve optimal AIC level before pregnancy include medical nutritional therapy, regular physical exercise and pharmacological therapy.
- Obese women with pre-gestational diabetes need to reduce weight prior to pregnancy. A realistic target of weight loss is 5 to 10% of the original body weight over a period of 6 months.
- Medical nutritional therapy and physical exercise is continuously encouraged in women with pre-gestational diabetes plan for pregnancy.
- Optimization of pharmacological therapy may be achieved by the addition of insulin to oral diabetic medications.
- Self-monitoring blood glucose should be encouraged especially when insulin is used. Continuous Glucose Monitoring (CGMS) may help identify periods of hyper- or hypoglycemia and can confirm glycemic variability, especially in women with type 1 diabetes.

b. Folic acid supplementation.

- The main function of folate is to act as the co-enzyme in one-carbon transfer during the methylation cycle, an essential process for the synthesis of nucleic acids, which form part of deoxyribonucleic acid and neurotransmitters. Folate also plays an essential function in protein synthesis, metabolism and other processes associated with cell multiplication and tissue growth.

- Daily folic acid supplementation (alone or in combination with other vitamins and minerals) in women who become pregnant or are ≤12 weeks pregnant is effective in preventing neural tube defects (NTDs) compared with no intervention/placebo or vitamins and minerals without folic acid. It also has a protective effect for recurrence of NTDs.
- All women with diabetes should be counseled regarding intake of foods high in folic acid, folate-fortified foods and appropriate folic acid supplementation of 4 to 5 mg per day during the preconception period and in the first 12 weeks of gestation.

c. Screening for diabetic complications.
    - Women with pre-existing Diabetes Mellitus need to screen for diabetic complications, especially retinopathy and nephropathy.
    - The risk of progression of retinopathy is increased with poor glycemic control during pregnancy, and progression may occur for up to 1 year post-partum. Additional risk factors for retinopathy progression are chronic and pregnancy-induced hypertension, pre-eclampsia, severe pre-existing diabetic retinopathy and a greater decrease in A1C between the first and third trimesters of pregnancy. Closer retinal surveillance is recommended for women with more severe pre-existing retinopathy, those with poor glycemic control or women with greater reductions in A1C during pregnancy. Laser photocoagulation for severe non-proliferative or proliferative retinopathy prior to pregnancy reduces the risk of visual impairment in pregnancy.
    - Prior to conception, women should be screened for diabetic nephropathy. Albuminuria and overt nephropathy are associated with an increased risk of maternal and fetal complications. An estimated glomerular filtration rate (eGFR) should be used prior to pregnancy to determine risk of adverse outcomes. Proteinuria increases during pregnancy, but in women with a normal GFR, pregnancy has no adverse effects on long-term renal function as long as the blood pressure and blood glucose are well controlled.

iv) Review and modification of current medication/therapy

a. Anti-hyperglycemic agents.

Metformin and Glyburide/Glibenclamide are the only anti-hyperglycemic agents that have been used in gestational diabetes mellitus. Compared with insulin, metformin was associated with less maternal weight gain but a higher incidence of premature birth. Glibenclamide was associated with less maternal hypoglycemia but higher maternal weight gain compared to insulin. For neonatal outcomes, it was associated with higher incidence of macrosomia, neonatal birth weight and neonatal hypoglycemia. Women with type 2 diabetes who conceive on metformin or glyburide can continue these agents until insulin is initiated.

b. Insulin.

- Insulin should be initiated when Medical Nutrition Therapy (MNT) and oral diabetic medications therapy fail to achieve optimal glycemic control. Multiple insulin regimes are available to manage pre-gestational diabetes in women planning pregnancy. For women with Type 2 DM, the choice of insulin regimes will depend on their glycemic profile, meals pattern, risk of hypoglycemia and patient preference. Whereas for women with Type 1 DM, the recommended regime is Multiple Daily Injection (MDI) using 1-2 injections of basal insulin and short or rapid acting insulin at meals.
- The use of human insulin, both short acting and intermediate or long acting have been established in pregnancy. They are safe, effective and labelled as FDA pregnancy category B. Insulin analogues mimic natural insulin physiology. Both rapid- and long-acting (basal) insulin analogues are as efficacious as human insulin in pregnant women with pre-existing diabetes and gestational diabetes. Insulin analogues are associated with fewer incidences of hypoglycemia.
- There have been several studies showing insulin pump use is safe in pregnancy. In a large multicenter trial of women with T1DM during pregnancy, there was improved A1C both in the first trimester as well as

in the third trimester and no difference in rates of diabetic ketoacidosis (DKA) or severe hypoglycemia compared to women with T1DM treated with multiple daily injections during pregnancy.

c. Other medications.

- There is conflicting evidence on whether first-trimester exposure to angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) is associated with an increased risk of congenital malformations.
- Fetal exposure in the second and third trimesters is clearly associated with a fetal renin-angiotensin-aldosterone system (RAAS) blockade syndrome, which includes renal failure, oligohydramnios, hypotension, intrauterine growth restriction and death.
- The decision to discontinue an ACE inhibitor or ARB prior to pregnancy should be discussed with the woman and may depend on the indication for use and availability of effective alternative medication. However, once a woman is pregnant, ACE inhibitors and ARBs should be discontinued.
- Statins and/or fibrates should be discontinued prior to pregnancy as they are not recommended for use during pregnancy.

v) Pregnancy care plan

a. Women with pre-existing diabetes with an A1C of more than 10% should be referred to pre-pregnancy care clinic for counseling and contraception.
b. Women with pre-gestational diabetes with diabetic complications such as retinopathy and nephropathy should be referred to pre-pregnancy clinic for optimization of care.

8.4.2 Thyroid Disease in Pregnancy

Normal pregnancy is associated with increased in renal iodine excretion, thyroxine-binding proteins, thyroid hormone production, and increased thyroid stimulatory effects of human Chorionic Gonadotrophin (HCG).

The fetal thyroid gland starts synthesizing thyroid hormone after 12 weeks and is not fully functional until 18 to 20 weeks' gestation. Hence, for the first half of pregnancy, the fetus is dependent on the maternal supply of thyroxine. To ensure an adequate maternal and fetal supply, patients should understand that close monitoring of thyroid function and compliance with medication regimens is crucial in this time period.

The physiological changes in thyroid function in pregnancy necessitate population-based and trimester-specific reference ranges for serum TSH and free T4 (FT4). However, if these data are not available, the American Thyroid Association guidelines recommend that between week 7 and 12, the lower limit of TSH be reduced by 0.4 mU/L and the upper limit be reduced by 0.5 mU/L. For the average patient, this translates into an upper limit for TSH of 4.0 mU/L. In the 2nd and 3rd trimesters, non-pregnancy TSH reference ranges may be used.

8.4.2.1 Grave's Disease

In women of childbearing age, the most common cause of hyperthyroidism is Grave's Disease, as this etiology accounts for 85% of clinical hyperthyroidism in pregnancy. All women of childbearing age affected with Graves' hyperthyroidism should be strongly advised to seek contraception counseling, in order to avoid pregnancy while in a hyperthyroid state.

i) Impact of the disease on the pregnancy

a. Untreated hyperthyroidism carries a high risk of complications for the mother and child. The complications are related to the duration and adequate control of maternal hyperthyroidism.

b. In women with unrecognized maternal Grave's disease, the infants born with severe pre-maturity (mean gestational age of 30 weeks at delivery), associated with very low birth weight (<2 kg) and neonatal hyperthyroidism requiring treatment with anti-thyroid medication.

ii) Impact of pregnancy on the disease

a. Graves' hyperthyroidism usually tends to improve gradually during gestation, although exacerbations can be observed in the first weeks. The spontaneous improvement may be due to the partial immunosuppressive state of pregnancy and decrease in TSH receptor autoantibodies (TRAb) production, the rise in maternal serum Thyroid Binding Globulin levels and iodine losses in pregnancy.
b. The exacerbation of thyrotoxicosis in women with Grave's Disease during early pregnancy may be due in part to the stimulatory effect of high hCG levels.

iii) Pre-pregnancy planning

a. Discussing the different therapeutic choices for Grave's disease is important for those women planning a pregnancy. This includes Radioactive Iodine I-31 ablative therapy, thyroidectomy or medical therapy.
b. If Radioactive Iodine I-31 ablative therapy is chosen, a pregnancy test should be performed prior to treatment. The women are advised to delay the conception for about six months following the treatment to stabilize the thyroid status. They may develop hypothyroidism after the treatment and require thyroxine replacement and adjustment of the dose before pregnancy.
c. For women who have been on anti-thyroid (ATD) medications for more than two years, the possibilities of remission during pregnancy are very low. Continuation of ATD may be necessary for women with a high risk of developing thyrotoxicosis. Factors predicting high clinical risk include clinically remain hyperthyroid and require carbimazole dose more than 10 mg or PTU dose more 200 mg to maintain a euthyroid state.

d. Thyroidectomy may be indicated in women with Grave's disease who have not responded to prolonged antithyroid drug therapy, who develop toxic reactions to the drug, who are unsuitable for Radioactive Iodine I-31 ablative therapy, patients with huge goiter and causes obstruction and patients with thyroid nodules that raise a suspicion of carcinoma.

e. Measuring TRAb in pregnant women with Grave's disease may predict potential fetal and neonatal complications. TRAb can cross the placenta and place the fetus at risk of goiter.

f. Different modalities of treatment affect the reduction of TRAb titer. It is gradually disappeared following thyroidectomy and increases in titers which last for 12 months following Radioactive Iodine I-31 ablative therapy. Therefore, in patients with high TRAb titers, surgery appears to be the therapy of choice in women contemplating pregnancy.

iv) Review and modification of current medication/therapy

a. The anti-thyroid medications used in Grave's disease are propylthiouracil (PTU) and carbimazole (CMZ).

b. Patients who are well-controlled on CMZ and plan to conceive could switch to PTU before trying to conceive. The use of carbimazole in the first trimester has been associated with the teratogenic potential known as methimazole embryopathy, includes choanal atresia and/or esophageal atresia, minor dysmorphic features and development delay.

c. After the first trimester, no recommendation can be made on whether PTU should be continued or changed to CMZ.

v) Pregnancy Care Plan

a. Women taking ATD should be instructed to perform a pregnancy test as soon as possible, after a missed period. If the pregnancy test is positive, pregnant women should contact their caregiver immediately.

b. During early pregnancy, consider discontinuation of antithyroid drugs in a patient who is euthyroid on low dose of CMZ (≤10 mg daily) or PTU (≤100 mg daily), due to the potential teratogenic effects. Other factors to be considered before discontinuation of ATD include disease history, goiter size, duration of treatment, recent thyroid function tests results, TRAb measurement and other clinical factors.
c. The overall goal of therapy is to control maternal disease by maintaining the patient at a high euthyroid level, while minimizing the risk of fetal hyperthyroidism or hypothyroidism using the smallest possible dose of ATD. The lowest effective dose of ATD should be used during pregnancy, targeting fT4 at or just above the reference range.
d. If antithyroid medication is stopped, thyroid function testing and clinical examination should be performed monthly to ensure the pregnant woman remains clinically and biochemically euthyroid.

8.4.2.2 Primary Hypothyroidism

The prevalence of overt and subclinical hypothyroidism in pregnancy is estimated at 0.3-0.5% and 2-3% respectively. Subclinical hypothyroidism is a mild hypothyroid state detected biochemically when the Free T4 is normal but plasma TSH is elevated. The common cause of hypothyroidism seen in pregnant women is chronic autoimmune thyroiditis. Other causes include post-surgical, post-radioiodine ablation and hypothyroidism secondary to pituitary disease.

i) Impact of the disease on the pregnancy

a. Overt hypothyroidism in pregnancy may present classically but is often subtle and difficult to distinguish from the symptoms of normal pregnancy. The maternal complications associated with hypothyroidism include infertility, miscarriage, pre-term delivery, pre-eclampsia, abruptio placenta and post-partum hemorrhage.
b. Fetal complications are pre-maturity, intra-uterine growth restriction, intellectual disorder and death.

c. The associations between maternal subclinical hypothyroidism and adverse pregnancy outcomes have been less robust than maternal Overt Hypothyroidism. The adverse outcomes that were most consistently reported are pregnancy loss and preterm delivery and often exacerbated by the presence of thyroid peroxidase antibody (TPOAb).

ii) Impact of pregnancy on the disease

Several studies have indicated that thyroxine requirements increase during gestation. The increase is due to the rapid rise in TBG levels resulting from the physiological rise in estrogen concentrations, the increased distribution volume of thyroid hormones and the increased placental transport and metabolism of maternal Thyroxine.

iii) Pre-pregnancy planning

a. Women who are on thyroxine replacement should achieve normal serum TSH before contemplating pregnancy. The preconception thyroxine dose should be adjusted aiming to maintain serum TSH near the low-normal range and not more than 2.5 mIU/L.
b. Women should also be counseled those certain drugs may interfere with levothyroxine absorption or metabolism including iron sulfate, aluminum hydroxide antacids, calcium, phenytoin and carbamazepine.
c. Women with subclinical hypothyroidism planning for pregnancy are advised to start on thyroxine if the TSH level is more than 10mIu/L similar to non-pregnant patients.

iv) Pregnancy care plan

a. Women with hypothyroidism planning for pregnancy are advised to increase their daily dosage by 30-50% above preconception dosage once pregnancy is confirmed. The adjustment can be made without the availability of the TSH level at that time.

b. Once pregnancy is confirmed, women with subclinical hypothyroidism with positive TPOAb are recommended to start on thyroxine if plasma TSH is more than 4.0 mIu/L. If TPOAb is negative, treatment may be started if TSH is above 10 mIu/L.

c. Similar to pre-pregnancy management, thyroxine dose should be adjusted to achieve TSH not more than 2.5 mIu/L during pregnancy in patients with overt and subclinical hypothyroidism.

8.4.3 Safety of medication during pregnancy

TABLE 6: SAFETY OF MEDICATION-RELATED TO ENDOCRINOLOGY IN PREGNANCY

Drugs	FDA
Metformin	B
Glibenclamide	C
Human Insulin (short/intermediate acting)	B
Analogue insulin (rapid/ basal) (except Glargine and Glulisine) Glargine and Glulisine	B C
Carbimazole	C
Propylthiouracil	C
Thyroxine	B

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8.5 Psychiatry

8.5.1 Highly Prevalent Psychiatric Illnesses
- Major Depressive Disorders

High prevalence of depressive disorders in the perinatal period, 1 in 8-10 women (10-12%)[1]. High prevalence of depression in chronic medical illness (27%).[1]

i) Impact of disease on pregnancy

Risk of untreated depression: untreated depression is associated with miscarriage, premature delivery, low birth weight, poor antenatal self-care, interpersonal conflict, functional impairment, mother-baby bonding/attachment difficulties, low breastfeeding initiation, long-term behavioral problems in offspring, suicide and infanticide[1].

In patients with chronic medical illnesses: Adverse health risk behaviors and psychobiological changes in depression increase the risks of chronic medical illnesses. Additionally, biological changes and complications of chronic medical illnesses may contribute to depression[1].

ii) Impact of pregnancy on disease

Pregnancy as a major life event with significant biopsychosocial changes can be a stressor that leads to worsening of depressive symptoms in pre-existing illness, increased risk of relapse for those in remission or trigger for new onset of depression.

MBRRACE-UK (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK) reported that for many years suicide had been the leading cause of direct deaths in the year after pregnancy. Indeed, the latest report shows that mental ill-health is an increasing cause of maternal death and in 2020, women were 3x more likely to die by suicide during or up to six weeks after the end of pregnancy compared to 2017-2019.

iii) Contraindication for pregnancy

Depression is not an absolute contraindication for pregnancy.

a. Lower risk: Major depressive disorders in remission for 6-9 months after the first episode or in remission of more than two years for more episodes.
b. Higher risk: Severe depression with severe functional impairment or high suicidal risks.

iv) Pre-Pregnancy Planning

a. Re-evaluation of therapeutic options:
   The aim of treatment is to achieve remission of depressive symptoms and functional recovery. Treatment consists of medications and psychological interventions.

   The principles of treatment for depression must be based on:[1]

   - Risk-benefit of treatment – benefits of treating depression, risks of untreated depression and risks of stopping medications abruptly or changing medications for both mother and baby; and
   - Shared decision-making, taking into consideration the severity and risk of relapse or recurrence.

   Counsel on potential risks and benefits of treatment so that patients can make well-informed decisions on preferred treatment.[2]

   - There is no absolute contraindication for any antidepressants in pregnancy. Most antidepressants used are in Food and Drug Administration (FDA) Pregnancy Safety Category C or B[5]. (Refer to Appendix Table 6 on Psychotropic Medications According to FDA Pregnancy Safety Category).
   - Benefits of treatment include reducing symptoms, improving function and preventing detrimental complications to women, children and the family. The most devastating consequence of depression is a higher risk of suicide.

- However, we must acknowledge the uncertainties of risks as most data are not from clinical trials due to ethical conformity.
- When counseling the benefit and risks of treatment, use absolute risk values based on a common denominator (i.e., numbers out of 100 or 1000) to reflect risks more accurately to the woman[1]. (Refer to Appendix Table 7 on Absolute Risks of Adverse Outcomes Associated with Medications During Pregnancy).

b. Optimization of treatment

- Aim to optimize treatment of pre-existing depression while providing contraception. Ideally, the aims of optimization of treatment are:
  - to achieve remission; and
  - to achieve completion of maintenance therapy in remission, wherever possible (only for mild and moderate depression in remission with low risk of relapse).
- Maintenance treatment is 6-9 months after remission for the first episode of mild and moderate depression.
- Maintenance treatment is two years for those with two episodes of mild-moderate depression.

c. Review and modification of current medication/therapy.

- Switch medications that are contraindicated in pregnancy. Some patients with severe depression may be on mood stabilizers or antipsychotics for augmentation. Mood stabilizers such as Sodium Valproate and Carbamazepine are contraindicated in pregnancy, while Lithium is contraindicated in the first trimester.
- Start folic acid supplement.

- Patients with mild and moderate depression who are not on pharmacological treatment and patient with an indication for antidepressants but the patient refuses, arrange and expedite psychological intervention as below:
  (Options of the pathway for intervention by hierarchical orders, depending on availability)
  - Referral to psychiatric services for intensive psychological intervention or psychotherapy; or
  - Arrange for brief psychological interventions (e.g. brief cognitive behavioral therapy) by trained Family Medicine Specialists or trained persons in primary care; or
  - Arrange for counseling by counsellors; or
  - Provide adequate social support in primary care or O&G setting where the above services are unavailable.

v) Pregnancy Care Plan

a. Level of follow-up depends on the level of severity.
   - Mild to moderate depression – follow up at primary care.
   - Moderate to severe depression – follow up at tertiary care.

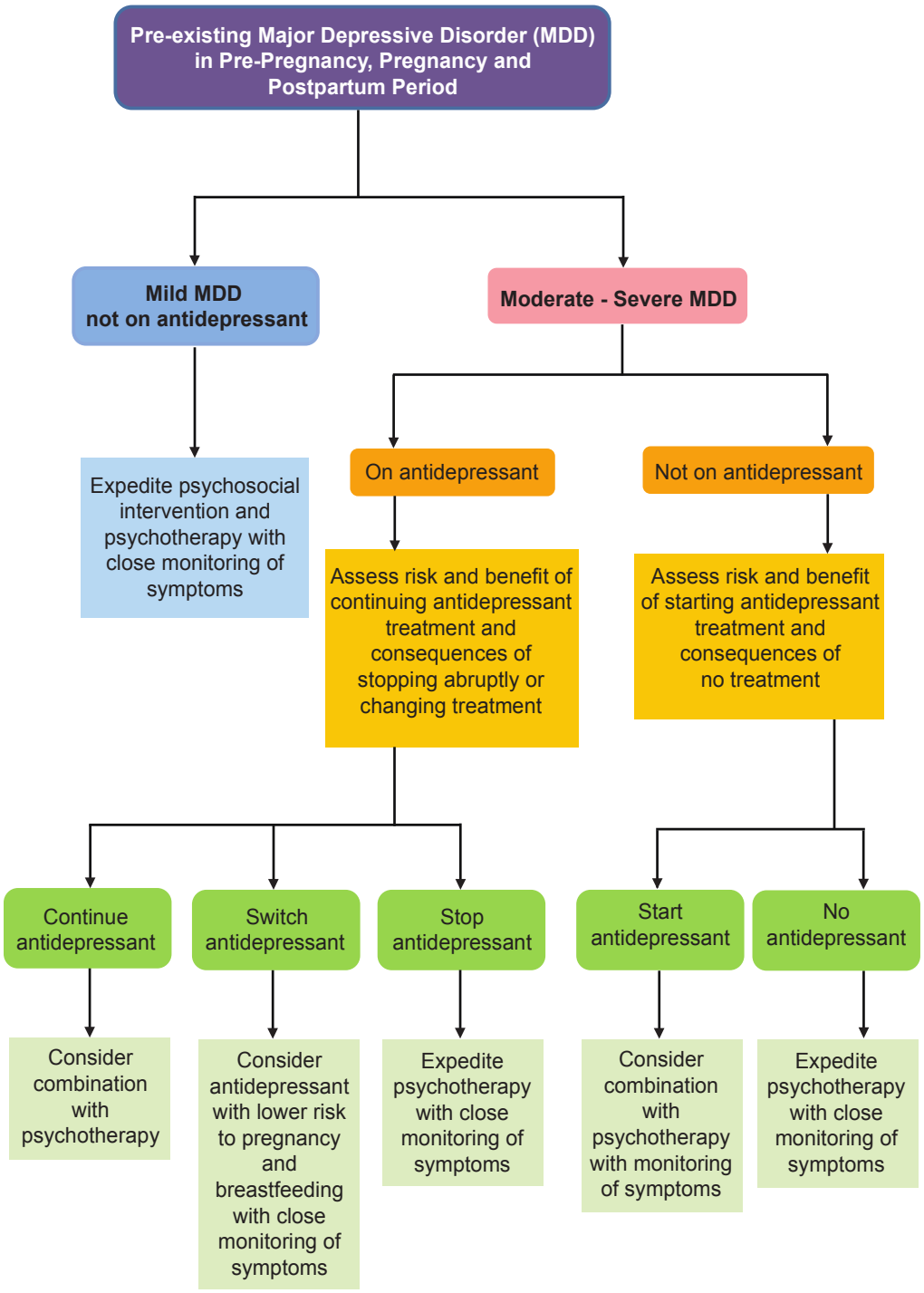
b. Frequency of follow-up.
   - Plan for early booking.
   - For patients in remission, antenatal follow-up is as usual.
   - For patients with modification of medications or switching from pharmacotherapy to psychological interventions, increase frequency for follow-up.

c. Monitoring of disease activity in pregnancy.
   - Monitor the severity of depressive symptoms.
   - Monitor risks of suicide.

d. Unforeseen management of the pregnancy.
   - Any unforeseen complications are to be managed by Consultation-Liaison Psychiatry services, if available, or general adult psychiatry services, and the multidisciplinary team involved.

FIGURE 4: FLOW CHART OF TREATMENT FOR PRE-EXISTING DEPRESSION IN PRE-PREGNANCY, ANTENATAL AND POST-PARTUM

(Source from Clinical Practice Guideline Management of Major Depressive Disorder Second Edition, 2019)



8.5.2 Severe Mental Illness (SMI)
- Schizophrenia and Bipolar Disorder

The prevalence of schizophrenia and bipolar in the general population is 1% each[2,3,4]. Although the prevalence is low, they usually require more intensive care during the perinatal period mostly due to the severity of the illness and the associated complex psychosocial situation.

i) Impact of the disease on the pregnancy

a. Mental capacity

The ability to have mental capacity in making decisions, giving consent on any treatment and pregnancy may be impaired by SMI.

b. Complicated pregnancy:

- There are increased risks of psychosocial problems including unplanned pregnancy, single parent, poor social support and poor socioeconomic background.[3,4]
- There was high prevalence of poor antenatal care in this group of patients. Cohort studies also have showed increased risk in pathological oral glucose tolerance test, anaemia, hypertension, premature contractions and delivery in women with SMI. Subsequently leads to increased risk in maternal-infant bonding, care and safety issues.[3,4]

ii) Impact of pregnancy on the disease

a. Increase risk of relapse.

Pregnancy has increased the risk of relapse in women with SMI especially during post-partum with an increased risk of admission when relapse.[3,4]

b. Contraindications for pregnancy:

- No absolute contraindication for pregnancy in women with SMI;
- Lower risk: good symptoms control and functional ability; and
- Higher risk: symptomatic with poor impairment in functioning.

iii) Revaluation of therapeutic options

In the management of schizophrenia, antipsychotics are the mainstay of treatment. While in the management of bipolar disorder, both mood stabilizers and antipsychotics either alone or in combination are being used.

As a general rule, treatment in which patient is stable, should be continued if the medications are not contra-indicated in pregnancy.[2,3,4] Majority of antipsychotics are safe in pregnancy including depot antipsychotics and clozapine.[2] However, most of the mood stabilizers are contraindicated during pregnancy except lamotrigine.[2]

a. Mood Stabilizers.

   Discontinuing mood stabilizers present high risks of recurrence among pregnant women diagnosed with bipolar disorder ranging from 40% to 73%4. Abrupt discontinuation of the medication carries a higher risk of recurrence compared to gradual discontinuation.

   - Lithium: Should not be used in the first trimester (*Category D)
   - Sodium Valproate: Should not be used in women who plan to conceive (*Category X)
   - Carbamazepine: Should not be used in women who plan to conceive (*Category X)
   - Lamotrigine: Safe in pregnancy (*Category C)

**Category refers to FDA Pregnancy Category[5]. (Refer to Appendix Table 8 on Psychotropic Medications According to FDA Pregnancy Safety Category).*

b. Antipsychotic.

   The majority of antipsychotics in pregnancy are safe, most are in category C while Clozapine is in category B according to the FDA pregnancy safety category.

c. Antidepressant.

   Refer 8.5.1.

iv) Pre-pregnancy Planning

a. All women with SMI in their reproductive age who plan to conceive should be offered pre-pregnancy care.[2,3,4]
b. Discussion with patients and their partners should cover the risk and benefit of pregnancy including the risk of relapse, the benefit of treatment of SMI during pregnancy as well as the option of contraception.[3,4]
c. Appropriate optimization of mental condition with intervention as necessary prior to pregnancy including biological, psychological and social intervention.[3,4]
d. Planned pregnancy should be encouraged.
e. Medication intervention[2]:
    - Continue medication if patient is stable and if medications are not contra-indicated in pregnancy.
    - Continue depot antipsychotic if patient is responding well and has a previous history of non-adherence with oral medication.
    - Continue Clozapine and refer to a psychiatrist for management.
    - Valproate and Carbamazepine should not be used in women who plan to conceive.
    - Lithium should not be used in the first trimester of pregnancy.
    - Switch contraindicated medications to antipsychotics or Lamotrigine.
    - Avoid benzodiazepine unless for short-term treatment of severe anxiety and agitation.
    - Choose the drug with the lowest risk profile for the woman, fetus and baby, taking into account previous response to medication.
    - Use the lowest effective dose, aiming for a single drug regime but taking into account response to medication.
    - Start the patient early on folate supplements.
f. May consider Cognitive Behavioral Therapy (CBT) and/or family intervention for women with SMI[3], who are at risk of relapse from stress-related to pregnancy and change of medication.
g. Close monitoring for relapse.
h. Assist in substance and smoking abstinence.
i. Advise on early booking.

j. Optimization of medical condition.
k. Documenting on the advance directive in case of severe relapse with impaired mental capacity when pregnant.

v) Pregnancy Care Plan

a. Level of follow-up.
    - Multidisciplinary team management involving psychiatrists, obstetricians and primary care physicians.
    - Treatment as usual for low-risk women with SMI with good symptoms controlled and functional ability: in primary care facilities.
    - High-risk groups who are symptomatic with poor impairment in functioning need to be seen with psychiatry services.

b. Frequency of follow-up.
    - Lower risk: Can be monthly or according to requirement / needs.
    - Higher risk: Can be of shorter interval.

c. Monitoring of disease activity in pregnancy.
    - Require multidisciplinary team management.
    - Monitoring for symptoms of SMI for relapse and pregnancy-related complications should be performed throughout the pregnancy.

d. Unforeseen management of the pregnancy.
    - Any unforeseen complications are to be managed by Consultation-Liaison Psychiatry services, if available, or general adult psychiatry services, and the multidisciplinary team involved.

8.5.3 Substance Use Disorders

i) Impact of disease on pregnancy

a. Substance use disorders during the perinatal period have been identified as critical to the health of mothers and babies

b. Illicit substance use affects pregnancy outcomes tremendously and is associated with multiple risks such as, not limited to miscarriage, intrauterine growth retardation, low birth weight, birth defects, stillbirth, placenta previa, placenta abruption, infant respiratory tract infection, sudden infant death syndrome, impaired fertility, fetal alcohol syndrome, central nervous system abnormalities, cognitive and behavioral problems.[2]

c. Substance use contributes to obstetrics, pediatrics and mental health complications such as:

- Unplanned pregnancy;
- Late or no antenatal booking;
- Low socio-economic background;
- Poor living conditions complicated with issues of estrangement from the family;
- Involvement with other high-risk behaviors; and/or
- High rate of mental health comorbidities and risks of self-neglect and self-harm.

ii) Impact of pregnancy on disease

Pregnancy as a major life event with significant biopsychosocial changes can be a stressor that complicates the underlying complex psychosocial issues faced by the patients.

iii) Contraindication for pregnancy

Ideally, patients with active substance use disorder are not advised to conceive.

iv) Pre-pregnancy planning

a. Re-evaluation of therapeutic options:

- Pregnancy may be seen as a golden opportunity for women, their partners and other people living with them to make a change in the patterns of their substance use.
- The key principle of treatment is ideally to aim for substance abstinence, using psychological intervention[2] (such as brief intervention i.e., a structured therapy of short duration offered with the aim of assisting an individual to cease or reduce the use of a psychoactive substance; counseling; motivational interviewing and brief cognitive behavioral therapy), wherever possible.
- Pharmacotherapy (also known as a replacement therapy) may be indicated when psychological intervention has failed or not suitable.[2] Replacement therapy is available for nicotine and opioid use.
- Pharmacotherapy is not recommended for routine treatment of dependence on amphetamine-type stimulants or cannabis.
- Health workers providing care for women with substance use disorders need to understand the complexity of the woman's social, mental and physical problems in order to provide appropriate advice and support.
- Contraception is important if they are not planning to conceive.
- Ensure safeguarding against discrimination and stigmatization.

b. Optimization of treatment:

- Aim of treatment is to reach substance abstinence before pregnancy.
- Inform patients on the availability of psychological intervention and pharmacological interventions.
- Arrange for psychological interventions, depending on types of substance, and availability of services:
  - Offer counseling and psychological support in primary care;
  - Arrange for brief psychological interventions by trained persons in primary care; and

- Referral to psychiatry services for intensive psychological intervention or psychotherapy.

- Counsel on continuing replacement therapy for opioid or nicotine use when psychological interventions are not suitable.
- Emphasize the importance of follow-up and adherence
- Close monitoring for relapse

c. Review and modification of current medication/therapy

- Counsel patients on starting replacement therapy for opioid or nicotine use, when psychological interventions are not suitable. Counsel patients on risk-benefits, types of replacement therapy and the possibility of relapse and effects on baby and breastfeeding.
- Replacement therapy:
    - Nicotine replacement therapy is safe during pregnancy under the supervision of a clinician. Combining cognitive behavioral therapy and counseling with nicotine replacement therapy is the most effective strategy to achieve smoking cessation during pregnancy.[2]
    - Methadone Replacement Therapy is safe during pregnancy and improves many of the adverse consequences of maternal and fetal outcomes associated with untreated opioid use. Infants exposed to methadone during pregnancy typically require treatment for withdrawal symptoms after delivery.[2]

v) Pregnancy Care Plan

a. Level of follow-up.
   Depends on psychiatric complications of substance use disorder or existing co-morbidity:
   - Substance use disorders with psychiatric complications or co-morbid psychiatric illness need to be seen with psychiatry services.
   - Other than the above can be seen in primary care.

b. Frequency of follow-up.
   - Plan for early booking.
   - For patients on replacement therapy or psychological intervention: frequency of follow-up according to the phase of therapy.

c. Monitoring of disease activity in pregnancy.
   - Monitor symptoms of withdrawal.
   - Monitor relapse.

d. Unforeseen management of the pregnancy.
   - Any unforeseen complications are to be managed by Addiction Psychiatry services, if available, or general adult psychiatry services, and the multidisciplinary team involved.

APPENDIX :

TABLE 7: ABSOLUTE RISKS OF ADVERSE OUTCOME ASSOCIATED WITH MEDICATIONS DURING PREGNANCY *

(Sourced from the Malaysian Clinical Practice Guideline Management of Major Depressive Disorder Second Edition, 2019)

Medications	Outcome	Absolute risk in pregnant women not taking medications per 1000	Absolute risk in pregnant women taking medications per 1000	Absolute risk difference per 1000	Possible association (Absolute risk difference per 1000)
Any antidepressant	Poor neonatal adaptation syndromes[2]	86	366	280	Paroxetine (107)
	Respiratory distress[2]	36	128	90	
	Tremors[2]	92	444	352	
SSRI	Congenital malformation[2]	34	46	12	Citalopram (35) Escitalopram (4) Fluoxetine (7) Paroxetine (7)
	Cardiac malformation[2]	11	13	2	Citalopram (2) Escitalopram(10) Fluoxetine (4) Paroxetine (3)
	Miscarriage[1]	81	109	28	
	Premature birth[1]	60	161	99	
	Neonatal convulsions[1]	3	4 - 15	1-12	
	Persistent pulmonary hypertension[1]	3	4	1	
	Respiratory distress[1]	32	45	13	
SNRI	Miscarriages[1]	81	138	57	

Medications	Outcome	Absolute risk in pregnant women not taking medications per 1000	Absolute risk in pregnant women taking medications per 1000	Absolute risk difference per 1000	Possible association (Absolute risk difference per 1000)
TCA	Miscarriages[1]	81	107	26	
	Premature birth[2]	53	100	47	
Long-acting Benzodiazepines (Repeated prescription around the time of birth)	Respiratory distress[1]	32	72	40	

* **To counsel together with benefits of treatment:** reducing symptoms, improving functions and preventing detrimental complications to women, children and the family from untreated depression such as obstetric complications (miscarriage, premature delivery, low birth weight, poor antenatal self-care), psychosocial issues (interpersonal conflict, functional impairment) as well as mother-baby bonding/attachment difficulties, low breastfeeding initiation, long term behavioral problems in off springs, suicide and infanticide.

TABLE 8: PSYCHOTROPIC MEDICATIONS ACCORDING TO FDA PREGNANCY SAFETY CATEGORY

NAME MEDICATIONS	PREGNANCY CATEGORY
FIRST GENERATION ANTIPSYCHOTICS	
Chlorpromazine	C
Haloperidol	C
Perphenazine	C
Sulpiride	NA
Trifluoperazine	C
SECOND GENERATION ANTIPSYCHOTICS	
Amisulpride	NA
Aripiprazole	C
Asenapine	C
Brexpiprazole	NA
Cariprazine	NA
Clozapine	B
Olanzapine	C
Paliperidone	C
Quetiapine	C
Risperidone	C
Ziprasidone	C
DEPOT INJECTIONS OF ANTIPSYCHOTICS	
Aripiprazole	C
Fluphenticol Decanoate	C
Fluphenazine Decanoate	NA
Paliperidone Palmitatae	NA
Risperidone Microsphere	C
Zuclophentixol Decanoate	NA
MOOD STABILIZER	
Lithium	D
Sodium Valproate	X
Carbamazepine	X
Lamotrigine	C

NAME MEDICATIONS	PREGNANCY CATEGORY
ANTIDEPRESSANTS	
Citalopram	C
Escitalopram	C
Fluoxetine	C
Fluvoxamine	C
Paroxetine	D
Sertraline	C
Duloxetine	C
Venlafaxine	C
Desvenlafaxine	C
Mirtazapine	C
Agomelatine	B
Vortioxetine	B
Bupropion	C
Amitriptyline	C
Clomipramine	C
Dothiepin	C
Imipramine	C
Mianserin	B
Nortriptyline	C
Phenelzine	B
Moclobemide	B

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4. Ministry of Health Malaysia. Clinical Practice Guideline Management of Bipolar Disorder Putrajaya: MoH; 2014.
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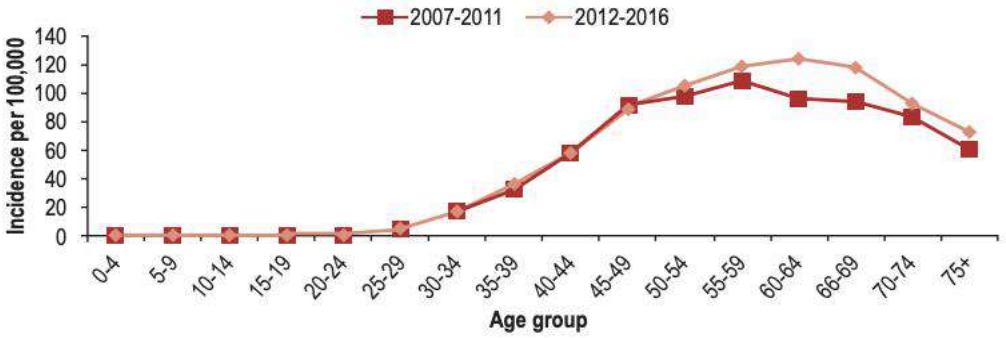
8.6 Breast Cancer

8.6.1 Introduction

Breast cancer is the most important cancer among women worldwide including in Malaysia. Regardless of gender, breast cancer contributed to 19.0% of all new cancer cases diagnosed in Malaysia in 2012 - 2016 compared with 17.7% in 2007 – 2011.[1] The incidence started to increase at the age of 25 and peaked at the age of 60 to 64 years.[1]

FIGURE 5: FEMALE BREAST CANCER: COMPARISON OF AGE-SPECIFIC INCIDENCE RATE BY YEAR IN MALAYSIA



Pregnancy-associated breast cancer is defined as the diagnosis of breast cancer during the gestational period, within 1 year after delivery or anytime during lactation.[3,4] It is the second most common malignancy occurring in pregnancy, after carcinoma of the cervix. The incidence of pregnancy-associated breast cancer is 1.3 to 3.7 per 10,000 deliveries.[2] The median age at diagnosis of breast cancer in pregnancy is 33 years.[2]

8.6.2 Definitions of Breast Cancer Survivorship

i) Acute survivorship: phase for diagnosis and treatment of cancer. Starts at the point of diagnosis until the end of the initial treatment.[5]
ii) Extended survivorship: Period following the completion of the treatments. Starts after initial treatment ends and can go up to 10 years.[5]
iii) Permanent survivorship: Phase where survivorship is roughly equivalent to cure, usually after 10 years or more since the treatment ended.[5]

8.6.3 Impact of Pregnancy on Breast Cancer

i) Diagnostic evaluation and staging are impaired during pregnancy. (e.g., Mammogram, MRI, CT scan, PET-scan)
ii) Treatment:
    a. Surgery;
    b. Systemic chemotherapy;
    c. Radiation therapy;
    d. Hormonal treatment; and
    e. Targeted therapy.
iii) The considerations and selection of optimal local therapy and systemic therapy are similar to that recommended in non–pregnancy-associated breast cancer. However, the selection and timing of chemotherapy, endocrine therapy, and radiotherapy is different in pregnant versus the non-pregnant patient.[4]
iv) Historically, mastectomy was considered the standard surgical procedure for the local management of pregnant patients with breast cancer.
v) Breast-conserving therapy may be appropriate if lumpectomy is performed in the third trimester and radiotherapy is given post-partum.[4]

8.6.4 Impact of Breast Cancer on Pregnancy

Approximately 50% of women with a history of breast cancer might wish for a subsequent pregnancy, but only 4 - 7% manage to become pregnant.[3] Breast cancer treatment can increase the risk of early menopause and result in reproductive difficulties. It exerts a negative impact on fertility mainly:

i) The toxic effects of chemotherapy on ovarian follicles reduce ovarian function and reserve.
ii) Once chemotherapy treatment is completed, women are advised to delay attempting conception for two years.
iii) When endocrine therapy is recommended for up to five years, ovarian function declines even further.

8.6.5 Criteria of breast cancer patients that should be referred for fertility preservation:

i) Interested in fertility preservation;
ii) Aged < 40 years old;
iii) Have a good prognosis;
iv) Able to undergo ovarian stimulation and egg collection; and
v) Have adequate time to undergo ovarian stimulation before the start of their cancer treatment.

8.6.6 Contraindications for Pregnancy

i) Acute phase of survivorship.
ii) Systemic chemotherapy is contraindicated in the first trimester because of a high rate of fetal abnormality but is safe from the second trimester onwards. [2,3]
iii) Hormonal treatment – Tamoxifen.[2,3]
iv) Trastuzumab – due to reported adverse fetal outcome.[2,3]

8.6.7 Pre-pregnancy planning

Women treated for breast cancer and wish to become pregnant should be counseled that pregnancy is possible and does not seem to be associated with a worse prognosis. However, they should be made aware that the evidence to support such advice is relatively poor. There is no evidence of an increased rate of congenital abnormalities in children conceived from the eggs of patients exposed to chemotherapy in the past.[3] Advice on the postponement of pregnancy should be individualized and based on treatment needs and prognosis over time.

i) Acute phase survivor
   a. Women with estrogen receptor-positive disease should be advised that the recommended duration of tamoxifen treatment is five years, therefore should not get pregnant.[2,3]

b. Those who are in high-risk recurrence received an extended 10 years of adjuvant hormonal treatment is recommended not to get pregnant. [2,3]
c. A conflict always remains for women with the ER-positive disease who are willing to interrupt their endocrine treatment to become pregnant. These women should be counseled that interruption of hormonal therapy could be detrimental to their breast cancer disease outcome. In women willing to consider the risk, interruption after 2–3 years of tamoxifen could be considered to allow for a pregnancy, with the resumption of tamoxifen after delivery.[2,3]

ii) Extended or permanent survivorship.
a. Generally, women are not recommended to get pregnant for at least four to six months after chemotherapy treatment.[3]
b. The rate of disease recurrence is highest in the first three years after diagnosis and then declines, although late relapses do occur up to 10 years and more from diagnosis.[3]

8.6.8 Pregnancy Care Plan

i) Acute phase survivorship.
a. Pregnancy following breast cancer should be jointly supervised by the obstetrician (Maternal-Fetal Medicine), oncologist and breast surgeon.
b. Regular and vigilant feto-maternal screening.

ii) Extended or permanent survivorship.
a. Similar to normal antenatal check-up. The available evidence does not reveal any negative effect of subsequent pregnancy on the prognosis of young women with breast cancer.[3]

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8.7 Hematology

Congenital Hematology Disorders

8.7.1 Thalassemia

Thalassemia is an inherited disorder of globin chain synthesis. Clinically, thalassemia can be classified into thalassemia major, intermedia or minor (carrier). Thalassemia majors are those who require regular transfusion since childhood while thalassemia intermedia are those who are non-transfusion dependent but may require some transfusion support during a certain period of stress and insult. Thalassemia carriers are asymptomatic and do not require transfusion. Thalassemia is inherited in a Mendelian recessive fashion. Women with thalassemia are advised to obtain specialist advice prior to conception.

i) Thalassemia major

a. Beta thalassemia majors constitute the vast majority of cases. Optimally treated thalassemia majors are fertile and are able to conceive.
b. Patients need to be assessed psychologically and medically.
c. Medical evaluation includes but is not limited to hematology, cardiac, liver, pulmonary and endocrine assessment. Compliance to iron chelation therapy and the presence of iron overload is of paramount importance prior to considering conception.
d. Iron chelation therapy is generally contraindicated during pregnancy and breastfeeding. Deferoxamine may be permitted in the 2nd & 3rd trimester.
e. Genetic counseling is important. Screening of the male partner is advocated to assess the risk of having a thalassemia major offspring. If the male partner is a beta thalassemia carrier, the chance of having a thalassemia major offspring is 50%.
f. Prenatal screening is recommended for women who conceived with a thalassemia carrier partner. Referral to a feta-maternal specialist should be offered. Chorionic villous sampling or amniocentesis can be performed during early conception to ascertain the status of the fetus.

g. Women who are advised not to conceive include those with:
   - Poor access to a multidisciplinary specialist center;
   - Poor compliance to transfusion and iron chelation;
   - Complications of severe iron overload; and/or
   - Evidence of severe extramedullary hematopoiesis

Important Clinical Points

All thalassemia majors who intend to conceive should be referred to the pre-pregnancy clinic for psychological and medical evaluation.

Genetic counseling and complete genetic assessment via Hb analysis and globin gene DNA analysis is mandatory.

Screening of partner and prenatal screening if partner is a carrier is strongly recommended.

Iron chelation therapy is generally contraindicated during pregnancy and breastfeeding.

Thromboprophylaxis may be considered.

ii) Thalassemia intermedia

a. Common thalassemia intermedia include E-beta thalassemia or HbH disease.
b. All-important clinical points under thalassemia major applies.

iii) Thalassemia minor (carrier)

a. A beta thalassemia carrier is asymptomatic and may only be detected via screening. However, if the partner is also a beta thalassemia carrier, the chances of having a beta thalassemia major offspring is 25%.
b. Co-existing alpha thalassemia may not be detected via Hb analysis.

Important Clinical Points

A full genetic assessment via Hb analysis and globin gene DNA analysis is strongly advocated.

Screening of partner is strongly recommended.

Prenatal screening is recommended if partner is also a carrier.

8.7.2 Hereditary Bleeding Disorders

i) Hemophilia

a. Hemophilia A and B are X-linked inherited coagulation disorders where there is a reduction of coagulation Factor 8 and 9 levels respectively. Clinically, hemophilia are categorized as severe, moderate or mild. Severe hemophilia is defined as factor level of < 1%.

b. As this is an X-linked disorder, a vast majority of hemophilia disease is suffered by males and the carriers are females. Thus, any women with a family history of hemophilia who intend to start a family are recommended to undergo hemophilia screening. Factor levels and genetic testing should be performed.

c. A female hemophilia carrier should be assessed on her bleeding history and factor levels. Genetic counseling should be offered to all carriers.

d. Hemophilia carriers who are advised not to conceive include those with;
   - Significant bleeding history.
   - Poor access to blood products and factor replacement.
   - Poor access to multidisciplinary specialist centers.

Important clinical points

All females with a family history of hemophilia who intend to conceive should be referred to the pre-pregnancy clinic for evaluation.

Bleeding risk must be assessed.

Factor levels and genetic testing is strongly advocated.

Genetic counseling must be offered.

ii) Congenital platelet disorders

a. Congenital platelet dysfunction syndromes such as Von-Willebrand Disease (vWD), Glanzmann Thrombasthenia (GT) and Bernard Soulier Syndrome (BSS) may result in a spectrum of bleeding tendency from mild to severe. Most cases of vWD are inherited in an autosomal dominant fashion while GT and BSS in an autosomal recessive manner.
b. Women with these disorders should be managed in specialist hospitals with appropriate multidisciplinary care.
c. Women who are advised not to conceive include those with;
    - Significant bleeding history.
    - Poor access to blood products and hemostatic agents.
    - Poor access to multidisciplinary specialist centers.

Important Clinical Points

All females with a family history of congenital platelet disorder who intends to conceive should be referred to the pre-pregnancy clinic for evaluation.

Bleeding risk must be assessed.

Genetic counseling must be offered.

8.7.3 Acquired Hematology Disorders

i) Chronic Myeloproliferative Neoplasm (MPN)

a. Myeloproliferative Neoplasm is a spectrum of chronic disorders which encompasses Essential Thrombocytosis (ET), Polycythemia Vera (PV) and Primary Myelofibrosis (PMF).
b. The risks of these disorders are mainly thrombosis, bleeding, infections and acute leukemic transformation. The risk of transformation is lowest in ET and highest in PMF.
c. The most important risk factor to consider is the history of thrombosis or bleeding.
d. Cytoreduction may be important in cases where optimization of counts is necessary. All oral medications used for cytoreduction in these conditions are not recommended during pregnancy and lactation. The risk and benefit of cytoreduction should be weighed individually. Alpha-interferon can be used in pregnancy and lactation; however, it is administered subcutaneously, has significant side effects and access is limited.
e. Antiplatelet or pharmacological thromboprophylaxis should be considered in high-risk cases. Generally, aspirin and low molecular weight heparin are safe during pregnancy.
f. Women who are advised not to conceive include those with;
    - Poorly controlled counts.
    - Poor access to multidisciplinary specialist centers.
    - History of pulmonary embolism, massive or unusual thrombosis.
    - Significant cytopenia and transfusion dependence.
    - Gross splenomegaly.
    - Acute leukemic transformation.

Important Clinical Points

Pre-pregnancy counseling is essential for women of reproductive age.

All oral cytoreductive therapies are contraindicated in pregnancy.

Risk and benefit of cytoreductive therapy should be discussed with patient.

Patients with history of thrombosis may be offered LMWH prophylaxis during pregnancy & post-partum.

Antiplatelet should be used as per MPN guideline.

ii) Chronic Myeloid Leukemia

a. Chronic Myeloid Leukemia (CML) is a clonal malignant disease which is characterized by the fusion of the BCR-ABL gene. Tyrosine Kinase Inhibitors (TKI) have revolutionized the treatment and altered the natural history of the disease. Women of reproductive age living with CML now commonly aspires for a normal life expectancy and hope to have a family.

b. CML is divided into 3 phases i.e., chronic, accelerated and blast phase. Treatment free remission can be attained by about 40% of patients in chronic phase who attained a deep molecular remission (DMR) consistently for at least two years.

c. TKI (e.g. Imatinib, Nilotinib, Dasatinib or Ponatinib) are all contraindicated in pregnancy. Alpha-interferon may be used, however, it is not an equivalent replacement for TKIs, carries significant side effects and access is limited.

d. For women aspiring to conceive, it is desirable for them to attain a treatment free remission prior to contemplating pregnancy.

e. Counseling is essential in all female CML patients of reproductive age. A hematologist's advice should be obtained prior to contemplating cessation of TKI therapy.

f. Women who are advised not to conceive include those;
   - In accelerated or blast phase of CML.
   - Not eligible for cessation of TKI therapy.
   - Unable to access molecular monitoring regularly (qPCR bcr-abl).

Important Clinical Points

Pre-pregnancy counseling is essential for women of reproductive age living with CML.

Tyrosine kinase inhibitors (TKI) are contraindicated in pregnancy.

A selected cohort of CML patients in chronic phase may attempt at cessation of TKI under expert supervision after achieving deep molecular remission consistently for more than two years.

Access to molecular monitoring is a pre-requisite for cessation of TKI.

iii) Immune Thrombocytopenic Purpura

a. Immune Thrombocytopenic Purpura (ITP) is characterized by an immune mediated peripheral destruction of platelets resulting in thrombocytopenia. ITP is a diagnosis of exclusion. Severity of ITP varies and ranges from mild to severe.
b. Generally, the risk of bleeding is low in ITP, however some features may harbor a higher risk such as mucosal bleeds. History of major bleeding is a significant risk factor.
c. Stable platelet count above 50,000/uL with no history of bleeding is generally considered safe for pregnancy and delivery.
d. Prednisolone, a common drug used in ITP is considered safe in pregnancy especially in lower doses.
e. Women who are advised not to conceive include those with;
    - Very low platelet counts < 20,000/μL.
    - History of intracranial bleed or other major bleeds.
    - Refractory, high steroid requirements or poor response to IVIG.

Important Clinical Points

Pre-pregnancy counseling is essential for women of reproductive age.

Platelet count of > 50,000/μL is considered safe for pregnancy and delivery.

History of major bleed is an important risk factor.

Consider patient's prior obstetric history.

Close monitoring is essential.

iv) Other malignant conditions; Acute Leukemias and Aggressive Lymphomas

a. All patients with a history of aggressive malignancy who wishes to conceive should be referred to the pre-pregnancy clinic for evaluation and counseling.

b. Generally, patients who wishes to conceive should be in remission for a reasonable length of time without any cytotoxic therapy and deemed low risk of relapse.
c. For patients with APML (Acute Promyelocytic Leukemia), there should be at least 6 months lapse from the last dose of all-trans-retinoic-acid (ATRA) before attempting pregnancy. ATRA is a known teratogen. Contraception is mandatory in patients on ATRA.
d. Patients who have active disease, not in remission or on cytotoxic therapy are advised not to conceive. Further specialist advice should be sought.

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8.8 Neurology

Introduction

Epilepsy is a heterogeneous group of diseases of the brain, the common symptoms of which are clinical seizures**.** The purpose of preconception care in women with epilepsy is to reduce the risk of fetal abnormalities and disorders of the subsequent development of the child through the optimization of pharmacological treatment and folate supplementation, as well as to control seizures in pregnancy.

8.8.1 Impact of Epilepsy on the Pregnancy

i) Seizures before pregnancy is a predictor for attacks during pregnancy. A first epileptic seizure may also have implications for the pregnancy, depending on the seizure etiology.

ii) Women with Epilepsy (WWE) are at increased risk for a range of perinatal complications ranging from mild to severe compared with the general population, including:

   a. Seizures affecting maternal awareness and responsiveness may have cardiac effects on the fetus and may impact the weight of the newborn;
   b. Slowing of the fetal heart rate;
   c. Fetal death;
   d. Decreased oxygen to the fetus;
   e. Preterm labor;
   f. Low birth weight / fetal growth restriction;
   g. Premature delivery;
   h. Trauma to the mother, such as a fall, that could lead to fetal injury, premature separation of the placenta from the uterus (placental abruption) or even fetal loss;
   i. Pre-eclampsia;
   j. Hemorrhage;
   k. Stillbirth;
   l. Increased risk of maternal mortality; and
   m. 3.5-5% of WWE will have a seizure during delivery.

iii) The magnitude of the increase in risk appears to be relatively small for most complications (between 1 and 1.7 times expected rates), with the exception of maternal mortality, which may be as much as 10-fold increased. However, this translates to a minimal increase in the absolute risk of less than 0.1%. There are several possible explanations for this finding, including:

a. Increase in medical comorbidities;
b. Increase in life-threatening complications of pregnancy; and
c. Increase in seizure-related complications, including sudden unexpected death in Epilepsy (SUDEP) due to uncontrolled tonic clonic seizures.

8.8.2 Impact of Pregnancy on Epilepsy

i) In pregnancy, there will be an increase in progesterone, which has anti-convulsive properties. Therefore, for the majority of women, seizure frequency declines or remains the same during pregnancy.

ii) Among WWE that experience seizure, 54 – 80% will have a static trend, 15-32% may increase frequency, and others might experience fewer attacks as estrogen and progesterone can alter neuronal excitability and affect the seizure threshold.Therefore, seizure control prior to pregnancy is one of the best predictors of seizure control during pregnancy.

iii) Women who have been seizure-free for 9 months to 1 year before pregnancy have 74%–92% chance of remaining seizure-free during pregnancy on their current regimen.

iv) Nausea and vomiting in pregnancy (which are common in the first trimester) might require adjustment of the timing of medication taken. However, it is important (as far as possible) to keep the interval between doses the same.

v) During pregnancy, WWE may require a higher dose of anti-seizure medication (ASM) to stop their seizure. This is especially true for ASM like Lamotrigine and Levetiracetam.

vi) Some ASMs can affect fetal growth and development in the womb, particularly in the first eight to 12 weeks of pregnancy when organogenesis occurs.

8.8.3 Contraindication for pregnancy

Epilepsy is not a contraindication to pregnancy. Over 90% of WWE will a have good outcome. Epilepsy alone does not have an effect on one's ability to get pregnant. Some drugs used to treat seizures might make it more difficult to become pregnant. Additionally, certain anti-seizure medications can reduce the efficacy of hormonal contraception.

Contraceptive failure is high in epilepsy patients on the combine oral contraceptive pills(COCP). When used properly the oral contraceptive failure rate is 1% in healthy women, but 3–6% in WWE. Non-oral contraceptives are preferred such as levonorgestrel/ etonogestrel, implants and depots as well as intrauterine devices like copper-based and progestin implants.

8.8.4 Pre – Pregnancy Planning

i) The purpose of preconception care in women with epilepsy is to reduce the risk of fetal abnormalities and disorders of the subsequent development of the child through the optimization of pharmacological treatment and folate supplementation, as well as to control seizures in pregnancy.

ii) It is important to explain the risks and impacts to the patient and partner, and emphasize that the potential teratogenic factor, i.e., an ASM, starts working in the first days after conception.

iii) The lowest effective dose of the most appropriate ASM should be used in order to reduce the risk of major birth defects, at least until the end of the first trimester of pregnancy.

iv) Withdrawal of ASMs for at least a year before the planned pregnancy can be considered in women after a three-year seizure-free period. On the other hand, pregnant women who have experienced seizures a year before conception require increased monitoring and treatment for epilepsy and changing ASMs during pregnancy risks precipitating seizures.

v) Pre-conceptional counseling should emphasize the importance of periconceptional folate supplementation, which has been shown to prevent neural tube defects. The American College of Obstetricians and Gynecologists recommends women with epilepsy take a daily multivitamin that includes 0.4 milligrams of folic acid.

vi) Review and modification of current medication/therapy:

a. 50% of patients will continue to have seizures after initiating their first ASM. This often leads to either switching to an alternative medication or the addition of an adjunctive ASM. These treatment challenges are especially problematic in WWE who are pregnant or are planning to become pregnant.

b. Ideally, prior to contraception, being seizure-free for at least 9–12 months is a relatively good predictor of freedom from seizure throughout the pregnancy. This predictor is dependent upon anti-seizure serum concentration staying within 35% of the preconception value throughout the pregnancy. This can be challenging due to the potential for significant pharmacokinetic changes during pregnancy, such as marked increases in clearance and volume of distribution.

c. Several ASMs have been documented to have increases in clearance that have led to decreased serum concentrations, which has resulted in increased seizure frequency.

TABLE 9: MEDICATION MANAGEMENT ISSUES - CHOOSING INITIAL THERAPY FOR WWE OF CHILDBEARING POTENTIAL WITH LOWER TERATOGENIC POTENTIAL, BASED ON EFFICACY AND EVIDENCE OF EFFECTIVENESS.

Seizure Types	ILAE (2013)1 (Level of efficacy and effectiveness evidence)	NICE (2020)[2]	
		1ST LINE	2ND LINE
Adults with partial-onset seizures	Level A: CBZ, PHT, LEV, ZNS Level B: VPA Level C: GBP, LTG, OXC, PB, TPM, VGB Level D: CZP, PRM	CBZ LTG LEV* OXC VPA	CBZ CLB GBP LEV† LTG OXC VPA TPM
Adults with GTC seizures	Level A: None Level B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA Level D: GBP, LEV, VGB		

Level A: ASM established as efficacious or effective as initial monotherapy

Level B: ASM probably efficacious or effective as initial monotherapy

Level C: ASM possibly efficacious or effective as initial monotherapy

Level D: ASM potentially efficacious or effective as initial monotherapy.

(CBZ: Carbamazepine, PHT: Phenytoin, LEV: Levetiracetam, ZNS: Zonisamide, VPA: Sodium valproate, GBP: Gabapentin, LTG: Lamotrigine, OXC: Oxcarbazepine, PB: Pregabalin, TPM: Topiramate, VGB: Vigabatrin, CZP: Clonazepam, PRM: Primidone)

8.8.5 Drug and teratogenicity

i) Drug teratogenicity risk should be routinely considered throughout pregnancy when treating a WWE. Pregnancy can be challenging for this population as a number of international registries have documented those children born to these women are at increased risk for major congenital malformations (MCM), lower intelligence quotient scores and neurodevelopmental disorders when the mother is managed on ASMs.

ii) By the time a pregnancy is confirmed, the risk of congenital malformations has already largely occurred. Changing ASM during pregnancy also entails the risk of precipitating seizures and putting both the mother and child at risk.

iii) More frequent monitoring of serum drug concentrations and patient education can be valuable tool when managing a pregnant WWE.

One important preconception goal is the utilization of medication monotherapy versus polytherapy. In general population, the risk of fetal malformations is 1–3%. However, if one AED is taken, the risk increases to 4–8%, and increases to 15% if more than one AED is taken.

The risk of fetal malformation is higher in polytherapy than in monotherapy (6% vs 3.7%), and the risk is even higher if the combination contains VPA.

Teratogenic effects of commonly used ASMs include cleft lip and palate and neural tube defects. Exposure to some AEDs may lead to long-term cognitive teratogenic effects, such as impaired verbal and non-verbal ability, executive function and memory. Monotherapy prior to and during pregnancy is preferred. Seizure control with the lowest effective dose of anti-seizure should be the goal.

iv) Polytherapy combinations with less teratogenic risk e.g., **levetiracetam and lamotrigine** should be considered prior to initiating valproate for idiopathic or genetic generalized epilepsy.

v) **Valproate** is the drug with the most evident for inducing major malformations and impairment and should be avoided during pregnancy, either as monotherapy or polytherapy. Malformation rates for valproate were about 10% vs. 2.8% for levetiracetam and 2.9% for lamotrigine in the EURAP study.

vi) **B**ehavioral teratogenesis of a seven to ten-point reduction in IQ was reported for valproate compared to other standard ASMs. These effects of valproate on cognition are also dose-dependent, but a dose as low as 800 mg/day has been shown to reduce verbal IQ and increase the need for special education. Fetal valproate exposure has been associated with an increased risk of autism (2.50%) and an autistic spectrum disorder (4.42%).

vii) **Lamotrigine** has the most evidence among newer ASM of safest use during pregnancy, but possibly has still more risks of malformations than the general population.

viii) **Topiramate** showed an intermediate risk of malformations with facial/palate cleft outcomes among the newer ASMs. When used in polytherapy, the malformation rate of **Topiramate** dramatically increases to 14.1% versus 2.4% when used as monotherapy. It's also associated with 2-4 fold increased risk of autistic spectrum disorder and intellectual disability, the risk increases with larger doses.

ix) **Valproate and Phenobarbital**, possess more risk of causing clinical malformations and cognitive impairment.

x) Dose-dependent teratogenicity risk within individual drugs and well documented with **Valproate and Topiramate.**

xi) Switching the brand to generic ASM is not recommended. Each individual ASM possesses its own associated teratogenicity risk when used as monotherapy and should be considered on an individual patient basis.

xii) ASMs that induce cytochrome P450 enzymes decrease folate levels. Folate requirements are 5-10 folds higher in pregnancy compared to nonpregnant women. Folic acid supplementation is recommended in WWE before conception and throughout pregnancy to prevent MCMs and neurodevelopmental disorders at a minimum dose of 0.4 mg/day (4 mg/day if family history of neural tube defect, or on valproic acid, carbamazepine, or gabapentin).

xiii) Amount of ASM an infant is exposed to depends on the maternal plasma concentration, the extent of transfer to breast milk, the amount of milk intake by the infant and their absorption, distribution, metabolism and elimination.

TABLE 10: LEVEL OF INFANT-MATERNAL PLASMA CONCENTRATION WITH ASM.

Low infant-maternal plasma concentration	Moderate infant-maternal plasma concentration	High infant-maternal plasma concentration
Carbamazepine (10-20%) Gabapentin (4-12%) Levetiracetam (<20%) Oxcarbazepine (7-12%) Topiramate (9-17%) Valproic acid (<5%)	Ethosuximide (40-60%) Lamotrigine (25-50%)	Phenobarbital (50-100%)

8.8.6 Pregnancy Care Plan

i) A care plan for patients with epilepsy should be like a 'road map' of their condition, and its treatment and management. Appropriate management of epilepsy during pregnancy may involve frequent monitoring of antiepileptic drug serum concentrations, potential preconception switching of antiepileptic medications, making dose adjustments, minimizing peak drug concentration with more frequent dosing, and avoiding potentially teratogenic.

ii) The care plan should also cover other issues such as education, work, driving, leisure activities and starting a family. This depends on their situation and their wishes and hopes for the future.

iii) Women with epilepsy should be informed that implementing a few safety guidelines can significantly reduce the risk of seizures and minimize anxiety about the effects of ASMs on the fetus.

iv) Risk factors for seizures, such as lack of sleep, stress, irregular intake of ASMs, as well as the type and frequency of seizures should be evaluated in WWE.

v) If women who are at a high risk of seizures have to be admitted to hospital before labor has begun, they should be placed in a location that allows the medical personnel or relatives to continuously monitor the patients.

vi) Symptoms such as an increase in the number of seizures, fatigue, dizziness, as well as the occurrence of potential risk factors for seizures such as lack of sleep and stress may require consultation with a neurologist, who may change the dose of medication, add new drugs or recommend hospitalization.

vii) WWE who has frequent seizures and whose seizures occurs during sleep or without witnesses are at high risk for SUDEP. These patients must not be left alone or unattended at night.

viii) Concentrations of lamotrigine, levetiracetam and oxcarbamazepine in pregnant women may fall by as much as 30% to 50%. Reduced concentrations of drugs can exacerbate seizures. Some doctors prophylactically increase the dose of drug during pregnancy, while others have concerns about the potential side effects of increased intake of drugs during pregnancy without clear preponderance of benefit over risk.

8.8.7 Level of follow up

An individualized approach delivered by a team of neurologists, obstetricians, primary care doctors, nurses, and clinical pharmacists with knowledge of various aspects of epilepsy in pregnancy is needed to improve outcomes in pregnant patients with epilepsy.

8.8.8 Frequency of follow up

i) WWE might need frequent blood tests to monitor ASM level serum concentrations of most ASM's may fluctuate in pregnancy due to changes in pharmacokinetics during absorption, metabolism, or excretion.

ii) It is therefore recommended:

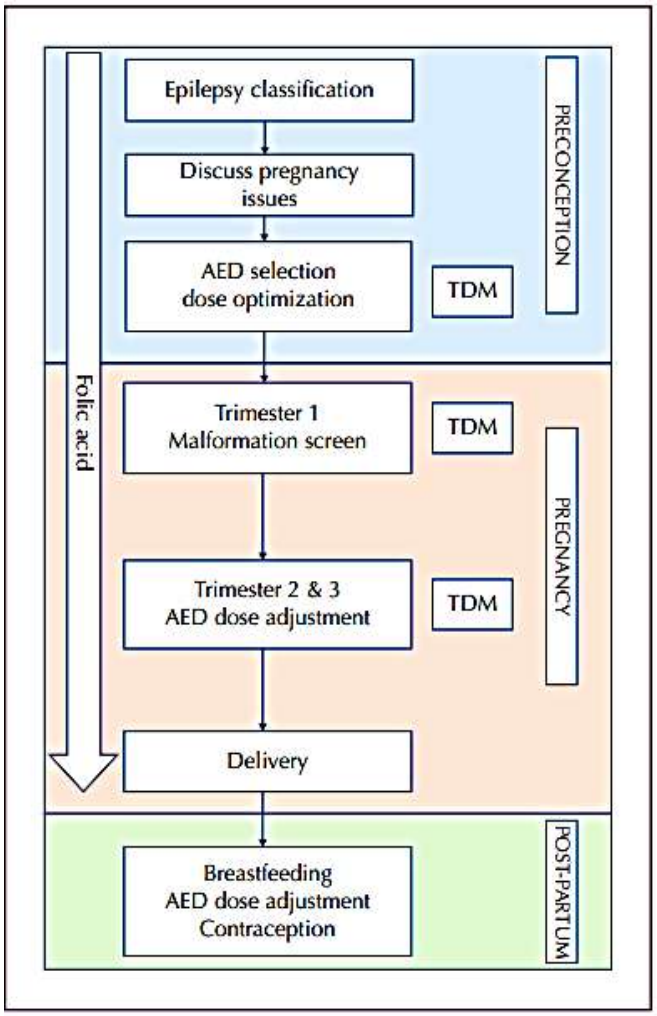
a. To monitor the serum levels of these drugs **before pregnancy** and at least **once during each trimester** of pregnancy and additionally in special situations such as lack of seizure control or the occurrence of adverse symptoms.

b. Common practice to recommend an ultrasound at 18–20 weeks gestational age for women taking ASM's during pregnancy. This is a detailed anatomic evaluation, which provides very high sensitivity for structural abnormalities affecting the fetus (95% for neural tube defects in most laboratories).

c. Blood screening for fetal congenital malformations can be offered.

d. Suggested flow chart for regular TDM and detail scan as in Figure 6.

FIGURE 6: SUGGESTED FLOWCHART FOR MANAGING WOMEN WITH EPILEPSY FROM THE PRECONCEPTION PERIOD THROUGH TO PREGNANCY DELIVERY AND THE POST-PARTUM PERIOD.



8.8.9 Monitoring of disease activity in pregnancy

An electroencephalogram (EEG) is used to examine seizure activity in patients diagnosed with epilepsy. However, it is not diagnostic of epilepsy and can be used as supportive evidence.

8.8.10 Unforeseen management of the pregnancy

i) Slightly higher risk of:
   a. Spontaneous miscarriage;
   b. Antenatal hemorrhage;
   c. Hypertension-related disorders (pre-eclampsia/eclampsia);
   d. Fetal stunting;
   e. Premature birth;
   f. Induction of labor;
   g. Cesarean section;
   h. Perinatal death and post-partum hemorrhage;
   i. Status epilepticus; and
   j. Sudden Unexpected Death In Preganancy (SUDEP).

ii) In unforeseen incidences patients must be referred appropriately to the respected team to manage the complications as quickly as possible to prevent any unwanted circumstances which can increase the maternal and fetal morbidity and mortality.

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Stroke

8.8.11 Introduction

i) Stroke is a leading cause of disability in adults.
ii) Stroke can happen in young women in of reproductive age.
iii) The impact on the mother, child, and families can be devastating when it occurs as a pregnancy complication.
iv) It is estimated stroke affects 30/100,000 pregnancies, roughly three times that seen in the general population of young adults, with the highest stroke risk occurring in the third trimester and post-partum.
v) The physiological changes of pregnancy, specifically venous stasis, edema, and hypercoagulability caused by activated protein C resistance, lower levels of protein S, and increased fibrinogen, combine to make pregnancy and the post-partum period a time of increased risk for stroke.
vi) Pregnancy-related hypertension is the leading cause of hemorrhagic and ischemic stroke in pregnant and post-partum women.

8.8.12 Impact of stroke on pregnancy

i) The long-term effects of stroke depend on which part of the brain was damaged and the extension of the infarct. Slightly more than one-third of patients with stroke have a disability that has affected their daily activities.
ii) The most common types of disability after stroke are impaired speech, restricted physical abilities due to weakness or poor coordination, cognitive impairment, mobility, and even stroke-related complications e.g., seizure.

8.8.13 Impact of pregnancy on stroke

i) Some patients might find that pregnancy causes worsening of the pre-existing physical disabilities as it contributes to extra stress to the body. However, many patients will still be able to undergo a successful pregnancy and delivery after the incident of stroke.

ii) Pregnancy also increases the risk of developing stroke particularly during the 3rd trimester and post-partum period. Common reason includes hypercoagulable states, pregnancy-induced hypertension, pre-eclampsia, eclampsia and gestational diabetes.

iii) Stroke in women of reproductive age, must be investigated extensively to eliminate or reduce the risk of developing another stroke especially during pregnancy. Careful evaluations are needed before getting pregnant.

8.8.14 Contraindication for pregnancy

Stroke is not a contraindication for pregnancy. Women with stroke who wish to get pregnant or are already pregnant need to be managed by a multidisciplinary team.

8.8.15 Revaluation of therapeutic options

i) Safety of medication during pregnancy

Medication	Level of safety during pregnancy
Aspirin	FDA Category C
Clopidogrel	FDA category B
Simvastatin	FDA Category X
Atorvastatin	FDA Category X
r-TPA	COR IIA-IIB
Warfarin	LOE C-LD
Novel anticoagulant	FDA Category D

TABLE 9: COMMON MEDICATION USED IN THE MANAGEMENT OF STROKE

Drugs	Transfer to breast milk	Adverse effects
Hypertension-β-blockers		No increased risk of major congenital abnormalities. Organ-specific malformations (cardiovascular defects, cleft palate/lip and neural tube defects) are more prevalent in the offspring of women treated with β-blockers. Labetalol is only licensed treatment for hypertension in pregnancy.
Labetalol	Yes	Commonly used in pregnancy. Association with mild fetal growth restriction (second and third trimester), neonatal bradycardia and hypotension (used near term) although this may reflect underlying maternal pathophysiology, i.e. pre-eclampsia/pregnancy-induced hypertension/chronic hypertension.
Bisoprolol	Yes	Reports of bradycardia and hypoglycaemia in the neonate. Commonly used for cardiac disease in pregnancy.
Atenolol	Yes	First-line postpartum. Associated with lower birth weight if used in antenatal period and fetal bradycardia and hypoglycaemia in fetus (second and third trimester).
Methyldopa	Yes	Second-line antihypertensive in pregnancy. Mild neonatal hypotension. Avoid postpartum because of the risk of postnatal depression.
Calcium channel blockers		Not associated with an increased incidence of congenital anomalies in humans.
Nifedipine	Yes	Safe at all gestations. Potential synergism with magnesium sulphate may induce hypotension (mother) and fetal hypoxia.
Nimodipine	Yes	Limited experience during pregnancy.
Platelet aggregation inhibitors		
Acetylsalicylic acid	Yes	Low-dose aspirin safe throughout pregnancy. No teratogenic effects known (large datasets).
Clopidogrel/dipyridamole	Unknown	Safe during pregnancy in animal studies, but experience in humans is limited. Benefit of use should outweigh risks. Discontinue clopidogrel one week prior to delivery to allow regional analgesia/anaesthesia.
Anticoagulants		
Warfarin	Yes	Risk of skeletal defects, abnormalities of the central nervous system and intracranial haemorrhage if used in the first trimester. Risk of fetal and maternal bleeding. Increased risk of miscarriage, intraventricular haemorrhage in fetus. Discontinue 1–2 weeks prior to delivery.
Heparin (low molecular weight)	No	Long-term application: seldom osteoporosis and markedly less thrombocytopenia than unfractionated heparin.
Direct oral anticoagulants	Uncertain	Limited data in pregnancy therefore use of alternative anticoagulants recommended.
Recombinant t-PA	Yes	Benefit of use outweighs risk of bleeding, particularly in context of moderate to severe stroke.
Drugs contraindicated in pregnancy		
ACE inhibitors and ARBs	No	Risk of neonatal renal failure and hypotension, renal tubular dysgenesis, intrauterine growth restriction, decreased skull ossification. Postnatally enalapril compatible with breast feeding.
Statins	Yes	Consensus view is to discontinue in pregnancy and breastfeeding due to limited data.

ii) Antithrombotic use in pregnancy (antiplatelets and anticoagulants) following ischemic stroke or transient ischemic attack (TIA):

a. Decision-making regarding antithrombotic use can be complex and a multidisciplinary review may be needed to assess maternal and fetal risk/benefit.

b. Antithrombotic management decisions can be tailored on an individual basis and may be informed by many issues, such as:

- Stroke etiology and accompanying stroke recurrence risk outside of pregnancy (e.g., prosthetic heart valve vs. cryptogenic stroke);
- Size and recency of the stroke (e.g., bleeding risk is higher with larger and more recent infarcts); and
- The stage of pregnancy (e.g., peripartum and post-partum stroke risk is higher than in the first and second trimesters).

c. If considering anticoagulation, consider a woman's medical and obstetrical history.

iii) In some women with a prior ischemic stroke whose underlying mechanism of stroke has resolved and residual risk is presumed to be comparable to the general population, it is reasonable to consider not starting antithrombotic prophylaxis during pregnancy.

iv) If antiplatelet agents such as clopidogrel, acetylsalicylic acid, combined acetylsalicylic acid, extended-release dipyridamole, or ticagrelor are indicated or started for stroke prevention, changing to a low-dose acetylsalicylic acid (100mg daily) is preferred prior to pregnancy or once a pregnancy is confirmed.

v) Warfarin is potentially teratogenic and should be avoided, particularly between six and 12 weeks of gestational age. When anticoagulation is considered, low molecular weight heparin (LMWH) is preferred throughout pregnancy. Collaboration with thrombosis experts may be required in certain rare situations with strong indications for warfarin such as women with a mechanical cardiac valve. In these situations, switching to an alternative to warfarin may be considered as soon as pregnancy is discovered, and could

consider restarting warfarin after the twelfth week of pregnancy until closer to delivery. Multidisciplinary management of these situations is preferred.

vi) There are insufficient data on the safety of direct oral anticoagulants (DOAC) (apixaban, dabigatran, edoxaban, rivaroxaban) in pregnancy. Switching to LMWH is encouraged as soon as a pregnancy is identified or if pregnancy is planned.

vii) In certain circumstances, therapeutic doses of LMWH can be considered a reasonable alternative to ASA or prophylactic doses could be considered with or without low-dose ASA. For example:
   a. Woman at high stroke/thrombotic risk (e.g., with multiple strokes).
   b. Woman with known hypercoagulability (e.g., anti-phospholipid antibody syndrome).

8.8.16 Pre–pregnancy planning

i) Optimization of the medical condition.

ii) Pre-pregnancy counseling for women with a history of stroke:

   a. Discussions of pregnancy and implications for stroke recurrence should be included as a routine part of post-stroke management for all female stroke survivors of reproductive age.
   b. Contraception should be addressed based on the patient's fertility and pregnancy plans as well as the stroke mechanism and type.
      - In cases of ischemic and thrombo-embolic stroke, systemic estrogen-containing contraceptives or hormone replacement therapy that can increase the risk of thrombosis should be carefully considered and, in most cases, should be avoided due to an increased risk of stroke.
      - Management alternatives can be considered, including progesterone-only oral contraceptives, progesterone-only or nonhormonal intrauterine devices, or barrier contraception.

c. During pre-conception consultation with all female stroke survivors of reproductive age, stroke risk factor assessment, and pharmacological management related to secondary stroke prevention in the context of pregnancy could be addressed. These include:
   - Counseling on a healthy diet, regular exercise, achievement of normal range body mass index, smoking cessation, alcohol use, and other lifestyle factors that may increase recurrent stroke risk during pregnancy.
   - A review of investigations to ensure stroke etiological work-up has been undertaken and appropriate secondary prevention strategies are in place.
   - A review of current medications to evaluate for potential teratogenicity. Where possible, consider preconception use of medications with reasonable safety data throughout pregnancy (from pre-conception to breastfeeding) to minimize the need for multiple medication switches throughout the pregnancy periods.
   - Communication between health professionals with stroke expertise and those with obstetrical expertise is encouraged in the pre-pregnancy counseling stages.
   - A discussion of the risk of recurrent stroke in a future pregnancy.

8.8.17 Antenatal and intrapartum risk factor screening for women with a history of stroke

i) Initial obstetrical work-up for pregnant women with a history of stroke should include screening for and assessment of vascular risk factors, and counseling for healthy lifestyle behaviors.

ii) An individualized stroke prevention management plan based on each woman's medical history, stage of pregnancy, type/etiology of stroke, stroke recurrence risk, and personal goals and preferences may be made at this time.

8.8.18 Post-partum stroke prevention management for women with a history of stroke

i) Stroke risk is highest peripartum and in the first six weeks post-partum. In this time frame, women may be educated about the signs of stroke (e.g., FAST) and to call 999 for sudden onset of new neurological symptoms, severe headaches or changes in mental status/consciousness.

ii) Women with high-risk conditions or conditions requiring regular assessment (e.g., diabetes, hypertension, pre-eclampsia) may require closer post-partum monitoring.

iii) Facilitating stroke prevention specialist assessment to review long-term stroke prevention management plan with consideration to breastfeeding:

a. A previous stroke is not a contraindication to breastfeeding.

b. Where available, allied health support (occupational therapy, breastfeeding specialists) can be beneficial to facilitate breastfeeding and support the mother in caring for the baby (e.g., in cases where women have residual cognitive or physical deficits from stroke, to address safety during feeding, transfers or bathing).

c. Stroke-prevention medications can be evaluated for compatibility with breastfeeding.

8.8.19 Pregnancy care plan

i) Blood pressure management for stroke prevention in pregnancy (ischemic and hemorrhagic):

a. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) – two common classes of medications used in stroke prevention carry an increased risk of fetal complications (kidney injury) and low amniotic fluid, especially if used after the first trimester. These medications should be discontinued prior to the conception of pregnancy or as soon as a pregnancy is recognized.

b. If they have been inadvertently taken, prompt referral to a feta-maternal specialist for detailed fetal structural ultrasound and counseling is encouraged.

c. Commonly used first-line oral medications for blood pressure control in pregnancy are labetalol, methyldopa, and long-acting nifedipine. Selection of specific antihypertensives should consider side-effect profiles for the woman, fetus or newborn baby.

d. All women who develop hypertension during pregnancy require prompt investigations and review by an expert in the management of hypertension in pregnancy. After 20 weeks of gestational age, the differential diagnosis should always include pre-eclampsia, which must be identified for appropriate obstetric and fetal management.

e. Women with previous strokes should have a blood pressure target of consistently lower than 140 mmHg systolic and consistently lower than 90 mmHg diastolic in pregnancy.

ii) Monitoring is warranted to ensure targets are achieved, to detect early rises in blood pressure or urinary protein suggestive of pre-eclampsia, and to avoid severe hypoperfusion.

iii) Considering statins for ischemic stroke prevention in pregnancy.

a. Interpretation of lipid levels is unreliable in pregnancy due to the normal physiologic changes of pregnancy and should not be used to guide decisions about therapy.

In addition, serum lipid levels should not be routinely measured during pregnancy. First-line management of dyslipidemia includes counseling for a healthy diet and exercise.

b. There is insufficient evidence regarding the safety of statins in pregnancy and lactation. It is reasonable to interrupt statin therapy preconception and throughout pregnancy temporarily.

The timing for restarting, or newly prescribing, statins for secondary stroke prevention after delivery should be individualized based on specific clinical circumstances (e.g., presence of high-risk conditions such as recent MI, compatibility with breastfeeding plans).

iv) Pre-existing diabetes and gestational diabetes for stroke prevention in pregnancy.

a. Women with diabetes in pregnancy (pre-existing type 1 or type 2 diabetes or gestational diabetes) require frequent, close follow-ups by an interdisciplinary team to monitor for maternal and fetal complications.
   Glycemic monitoring, monitoring for other vascular risk factors, and glucose management throughout pregnancy and post-partum should follow established Malaysian CPG.
b. For women with a history of stroke, glucose tolerance tests can be considered earlier in pregnancy (e.g., at 20 weeks instead of 24–28 weeks) if deemed at high risk of gestational diabetes.
c. It is reasonable to counsel women with a history of stroke and who have gestational diabetes to ensure long-term follow-up through primary care, with the goal of facilitating lifestyle interventions to reduce the future risk of developing diabetes and stroke.

In general, for women who experience gestational diabetes, the 10-year risk of diabetes and cardiovascular disease is elevated.

8.8.20 Unforeseen management of the pregnancy

Management considerations for specific ischemic stroke etiologies in pregnancy

i) Acute Ischemic Stroke.

a. Thrombolytic therapy.
   - Stroke thrombolysis improves the outcome of ischemic stroke in individuals presenting up to 4.5 hour after the onset of symptoms. Pregnancy was considered a relative contraindication for thrombolysis in ischemic stroke.

- The risks of maternal hemorrhage or abruption that could lead to preterm labor must be balanced against the risk of developing residual neurological deficits in 50 percent of stroke patients.
- Pregnancy and post-partum are NOT a contraindication to thrombolysis. Hence, thrombolysis should be considered if the benefit outweighs the risk following thorough discussion between neurologists/obstetricians with the patient/family members.

b. Thrombectomy.
   - Mechanical thrombectomy is licensed for use in selected patients that present within six hours of new onset of stroke symptoms and is of particular benefit to those who present with an arterial occlusion in the proximal anterior circulation. Some carefully selected patients may benefit up to 24 hours after onset of symptoms.
   - Pregnant lady with large vessel occlusion is NOT a contraindication for thrombectomy.

ii) Cardioembolic stroke.
   a. For syndromes that require anticoagulation outside of pregnancy (e.g., artificial cardiac valve, intracardiac thrombus), anticoagulation should be continued throughout pregnancy but may need to be adapted for safety.
   b. Patent foramen ovale (PFO) closure during pregnancy is not recommended. Low-dose oral ASA daily is considered as the first line of medical prevention.
   c. If a pregnant patient with a known PFO is at increased risk of venous thrombosis, prophylactic LMWH doses could be considered.

iii) Cerebral Venous Sinus Thrombosis (CVST).
   a. For acute CVST occurring during pregnancy, consider treatment with therapeutic doses of anticoagulation (LMWH) for the remainder of pregnancy and at least six weeks post-partum or until a post-partum switch to oral anticoagulation is feasible. The LMWH must be continued for a total minimum duration of therapy of six months.

b. A woman with a remote history of spontaneous CVST, not currently anticoagulated, can be considered for LMWH prophylaxis, during pregnancy and at least six weeks post-partum.

iv) Cervicocephalic artery dissection.

a. Antithrombotic therapy for stroke prevention is recommended for individuals diagnosed with extracranial carotid or vertebral artery dissection.

b. There is uncertainty about the comparative efficacy of antiplatelet therapy vs. anticoagulation even outside of pregnancy. Either treatment is considered reasonable, and decisions should be based on individual risk/benefit analysis.

c. If anticoagulation is chosen, LMWH is preferred.

d. There is a lack of evidence regarding the optimal duration of antithrombotic therapy and the role of repeat vascular imaging in decision-making. Decisions may be based on individual clinical factors.

e. In pregnancy, treatment options for cervicocephalic dissection include monitoring only (i.e., no treatment), low-dose ASA, or anticoagulation.

f. Low-dose ASA is often considered for women with recent dissections without thrombus, or chronic dissections with complex morphology (e.g., residual flap or pseudoaneurysms).

g. For women with a history of stroke caused by dissection and stopped ASA, restarting the prophylaxis during pregnancy and post-partum could be considered.

h. LMWH is a reasonable option in some cases for example in women with dissection in the highest thrombotic risk stages (peri-partum to six weeks post-partum), or women with intra-arterial thrombus.

i. Current evidence does not support routine cesarean delivery in women with prior cervical artery dissection. Cesarean delivery may still be considered for obstetrical indications, or if the dissection occurred during labor in a previous pregnancy. Individualized decision-making between the neurology and obstetrics teams is required.

v) Anti-phospholipid antibody syndrome.

Anti-phospholipid antibody syndrome in a woman with a history of stroke is often treated with therapeutic anticoagulation alone, or in combination with low-dose ASA. These treatment options are reasonable in pregnancy considering the stage of pregnancy and the presence or absence of obstetric complications.

vi) Cryptogenic stroke.

Antiplatelet agents are used for secondary stroke prevention after cryptogenic stroke.

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DRAFTING COMMITTEE GUIDELINES ON PRE-PREGNANCY CARE IN MOH SPECIALIST HOSPITAL

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