CHAPTER 6
OBSTETRICS

Note: For medical complications during pregnancy, refer to the relevant chapters. Only common conditions specific to pregnancy or requiring special management in pregnancy are included in this chapter.

6.1 ANAEMIA IN PREGNANCY

O99.0 + (D50.9/D64.9)

DESCRIPTION

Haemoglobin (Hb) <11 g/dL. Anaemia in pregnancy is most commonly due to iron deficiency. Hb levels in pregnancy should be checked routinely on-site at the first antenatal visit, and again at 30 weeks and 38 weeks. If Hb falls below 10 g/dL, commence treatment with iron and do a FBC.

LoE:IVb[i]

GENERAL MEASURES

A balanced diet to prevent nutritional deficiency.
Advise against eating soil, clay, charcoal, and excessive consumption of tea and coffee.

MEDICINE TREATMENT

Prophylaxis Z34.9 + (Z29.9)

- Ferrous sulfate compound BPC (dried), oral, 170 mg (± 55 mg elemental iron) twice daily.

OR

- Ferrous fumarate, oral, 200 mg (± 65 mg elemental iron) daily.

LoE:IVb[ii]

<u>If daily iron is poorly tolerated (e.g., epigastric pain, nausea, vomiting, and constipation), intermittent iron supplementation may be administered:</u>

- Ferrous sulfate compound BPC (dried), oral, 340 mg per week, (± 110 mg elemental iron), with meals.

LoE:IVb[iii]

OR

- Ferrous fumarate, oral, 400 mg per week (± 130 mg elemental iron).

(For folic acid supplementation guidance to prevent neural tube defects, Primary Health Care STGs and EML, Section 6.4.1: Antenatal supplements.)

Treatment: Iron deficiency (Hb <10 g/dL)

- Ferrous sulfate compound BPC, oral (dried), 170 mg (± 55 mg elemental iron) 12 hourly.

LoE:IIb[iv]

OR

- Ferrous fumarate, oral, 200 mg (± 65 mg elemental iron) 12 hourly.
  - Continue for 3-6 months after Hb reaches normal to replenish iron stores.
  - Hb is expected to rise by at least 1.5 g/dL in two weeks.
  - When using iron together with calcium supplementation, ensure that iron and calcium are taken at least 4 hours apart from one another.
  - If Hb has not increased after 4 weeks of therapy, do a FBC to confirm hypochromic microcytic anaemia.

LoE:IIIb[v]

Parenteral iron - See Section: 2.1.1 Anaemia, iron deficiency.
If there is no response to oral iron, and iron deficiency is confirmed, review adherence to oral iron, and consider:

- Iron, IV, e.g.:
- Iron sucrose, IV, 200 mg in 200 mL sodium chloride 0.9%, over 30 minutes, given on alternate days until the total dose has been given**.**
  - **Note:** Test dose is not required but administer only where personnel and therapies are readily available to manage anaphylactic-type reactions.
  - An initial total dose of 600 mg is usually adequate to raise the Hb to acceptable levels.
  - For markedly anaemic or very obese women, consult the package insert on the total dose of iron infusion.

LoE:IVb

REFERRAL/CONSULTATION

No response to management.

6.2 DIABETES MELLITUS IN PREGNANCY

O24.0-4/O24.9

This condition should ideally be managed in consultation with a specialist.

DESCRIPTION

Established diabetes: Diabetes (type 1 or 2) predating pregnancy.
Gestational diabetes mellitus (GDM): carbohydrate intolerance first recognised during pregnancy. It does not exclude the possibility that diabetes preceded the pregnancy.

Diagnostic criteria for GDM

Either a fasting plasma glucose ≥5.6 mmol/L **OR** a plasma glucose of ≥7.8 mmol/L two hours after a 75 g oral glucose tolerance test.

The following women should be screened for GDM, between 24 and 28 weeks of gestation:

» Women of Indian ethnic origin.
» BMI >35 kg/m^2.
» Age >40 years of age.
» GDM in previous pregnancy.

» Family history (first degree relative) of diabetes.
» Previous unexplained third trimester fetal death.
» Previous baby with birthweight >4.5 kg.
» Polyhydramnios in index pregnancy.
» Glycosuria (≥1+ glucose in urine on 2 or more occasions).
» A fetus that is large for gestational age. *LoE:IIIb*[vi]

GENERAL MEASURES

» Stop smoking.
» Moderate exercise.
» Dietary advice.

Elective delivery at about 38 weeks' gestation.

MEDICINE TREATMENT

If fasting glucose is <7 mmol/l at diagnosis, promote lifestyle changes (diet and moderate exercise).
Assess after 2 weeks. *LoE:IIIb*[vii]

Fasting glucose ≥7 mmol/l, or no response to lifestyle changes:

- Metformin, oral, 500 mg daily.
  - Increase dose to 500 mg 12 hourly after 7 days.
  - Titrate dose to a maximum of 850 mg 8 hourly according to glucose control.
  - Contra-indications to metformin: liver or renal impairment.
  - If not tolerated, change to insulin.

Do capillary (finger prick) glucose profiles, i.e. pre-prandial and 1-hour or 2-hour (2-hours more practical) post-prandial for breakfast, lunch and supper.
Aim for:

» Preprandial level <5.3 mmol/L and either:
  - 1-hour postprandial <7.8 mmol/L, or
  - 2-hour postprandial <6.4 mmol/L.

Abnormal profiles *LoE:IVb*[viii]

Women with diabetes treated with metformin but with poor glucose control should be admitted.
Add insulin.
Insulin requirements may increase with increasing gestation and later readmission may be necessary.

Preferred insulin regimen

- Insulin, short-acting with all 3 meals to maintain the 2-hour postprandial glucose levels <6.4 mmol/L.

AND

- Insulin, intermediate acting at bedtime (with a bedtime snack) to maintain the fasting (morning) preprandial glucose levels <5.3 mmol/L.

Insulin dosing (in addition to metformin):

- Total daily dose: SC, 0.1 units/kg/day.
- One third of the total dose: intermediate acting insulin at bedtime.
- The remaining two thirds divided into three equal doses: short-acting insulin given before each meal (breakfast, lunch and supper).
- Adjust insulin dosage daily according to blood glucose profiles, until control is adequate.

LoE:IIIb[ix]

Where the above recommended regimen is not feasible

Twice-daily regimen with biphasic insulin.

- Insulin, biphasic.
  - Daily dose: SC, 0.5 units/kg/day, two thirds, 30 minutes before breakfast and one third 30 minutes before supper.
  - Titrate to achieve target capillary (finger prick) glucose as above.

LoE:IIb[x]

Delivery

Plan induction of labour at 38 weeks' gestation, provided glucose control is adequate, or earlier with maternal co-morbid conditions, or if glycaemic control is poor. If the estimated fetal weight (EFW) on ultrasound is >4 kg, offer elective Caesarean delivery.

During labour:

Monitor glucose hourly.

Stop subcutaneous insulin.

Administer short-acting insulin to maintain physiological blood glucose levels.

- Insulin, short-acting, continuous IV infusion, 20 units plus 20 mmol potassium chloride in 1 L dextrose 5% at an infusion rate of 50 mL/hour, i.e. 1 unit of insulin/hour.
  - If blood glucose <4 mmol/L, discontinue insulin.
  - If >7 mmol/L, increase infusion rate to 100 mL/hour.

Postpartum insulin requirements decrease rapidly.

During the first 48 hours give insulin 4-hourly according to blood glucose levels.

Resume pre-pregnancy insulin or oral hypoglycaemic regimen once eating a full diet.

The newborn is at risk of:

- » hypoglycaemia
- » respiratory distress syndrome
- » hyperbilirubinaemia
- » congenital abnormalities

Postpartum management

Contraception Z30.0 + (O24.3-4/O24.9)

Tubal ligation should be considered.

Consider:

- Low-dose combined contraceptive in well-controlled cases.
- Progestin-only preparation **or** intra-uterine contraceptive device if planning to breastfeed.

See PHC Chapter 7: Family planning.

Need for ongoing anti-diabetic therapy
Offer women diagnosed with GDM during the index pregnancy an oral glucose tolerance test after 6 weeks postpartum to assess whether they have diabetes needing ongoing therapy.

REFERRAL/CONSULTATION
» Obese women (BMI > 40 kg/m^2)
» Excessive fetal growth despite adequate diabetes control.
» Poor glucose control despite adequate insulin.

6.3 HEART DISEASE IN PREGNANCY
O99.4 + (I51.9)

All women with heart disease require referral for specialist evaluation and risk assessment. The risk is particularly high in women with mechanical valves, Eisenmenger's syndrome or pulmonary hypertension. Termination of pregnancy (TOP) is an option for women with severe heart disease if recommended by a specialist.

GENERAL MEASURES
All pregnant women with haemodynamically significant heart disease require multidisciplinary management in consultation with both obstetrician and physician/cardiologist.
Consider thyrotoxicosis, anaemia, and infection, which may precipitate cardiac failure.
Spontaneous delivery is usually preferable to Caesarean delivery, unless there are obstetric reasons for surgery.
Women with prosthetic heart valves should be counselled about the risks of pregnancy to themselves and their fetus; and offered effective contraception.

During labour:
» Nurse in semi-Fowler's position.
» Avoid unnecessary intravenous fluids.
» Give adequate analgesia.
» Give antibiotic prophylaxis for infective endocarditis, guided by the nature of the heart lesion (for cardiac indications and antibiotic recommendations see Section 3.5: Endocarditis, Infective). Procedures for which endocarditis prophylaxis is indicated include:
  – Vaginal delivery in the presence of suspected infection.
  – Caesarean delivery.
  – Assisted vaginal delivery.
  – Prelabour rupture of membranes.
» Avoid a prolonged second stage of labour by means of assisted delivery with forceps (preferably) or ventouse.
» Avoid ergometrine after delivery of the newborn.

» Observe in a high care area for 24 hours post-delivery, as the risk of pulmonary oedema is highest in this period.

Contraception, including the option of tubal ligation should be discussed during the antenatal period and after delivery in all women with significant heart disease.
Women who had life-threatening complications during pregnancy should be advised not to become pregnant again.

Anticoagulation during pregnancy:
Indications for full anticoagulation during pregnancy (high risk):

» *Valvular disease with atrial fibrillation*: Women with valvular heart disease should be guided to consider completing their family early and then consider family planning including tubal ligation, before progressing to requiring mechanical valves.
» *Mechanical prosthetic heart valves:* Women with mechanical prosthetic heart valves should be offered contraception (preferably a LARC not containing estrogen); see PHC Chapter 7: Family planning. If they conceive, offer the option of TOP or refer to tertiary centre for anticoagulation management by a multi-disciplinary team.

MEDICINE TREATMENT

A. Thromboprophylaxis for pregnant women with valvular disease and atrial fibrillation:

1. First trimester

- Enoxaparin SC, 1 mg/kg 12 hourly.

OR

- Unfractionated heparin, IV, 5 000 units as a bolus.
  - Followed by 1 000–1 200 units/hour as an infusion.

OR

- Unfractionated heparin, SC, 15 000 units 12 hourly.
  - Adjust the dose to achieve a mid-target PTT at 2–3 x control.

Practise strict infection control if using multi-dose vials, with one vial per patient and use of needle-free adaptor.

2. Second trimester until 36 weeks

- Warfarin, oral, 5 mg daily.
  - Adjust dose to keep INR within the therapeutic range of 2–3.

3. After 36 weeks until delivery

- Enoxaparin SC, 1 mg/kg 12 hourly.

OR

- Unfractionated heparin, IV, 5 000 units as a bolus.
  - Followed by 1 000–1 200 units/hour as an infusion.

OR

- Unfractionated heparin, SC, 15 000 units 12 hourly.
  - Adjust dose to keep aPTT 2–3 x control.

4. Delivery

Stop heparin on the morning of elective Caesarean delivery (6 hours before scheduled surgery) or when in established labour, and re-start 6 hours after vaginal delivery or 12 hours after Caesarean delivery, as long as there is no concern that the patient is bleeding.

Secondary prophylaxis for venous thromboembolism - see Chapter 2: Blood and blood forming organs, Section 2.8.3: VTE during pregnancy and the puerperium.

B. Cardiac failure during pregnancy O99.4 + (I50.9)

See Section 3.4: Congestive Cardiac Failure (CCF).

Treatment is as for non-pregnant women, except that **ACE-inhibitors, ARBs and spironolactone are contra-indicated.** *LoE:IVb*[xi]

If a vasodilator is needed:

- Hydralazine, oral, 25 mg 8 hourly.
  - Maximum dose: 200 mg daily.

AND

- Isosorbide dinitrate, oral, 20 mg 12 hourly.
  - Maximum dose: 160 mg daily.

C. Delivery by a cardiac patient O99.4 + (I51.9)

Contraction and retraction of the uterus after delivery increases the total peripheral resistance and causes a relative increase in circulating volume. This may precipitate pulmonary oedema.

In women with NYHA grade II dyspnoea or more, consider the use of furosemide:

- Furosemide, IV, 40 mg with delivery of the baby.
  - Monitor for 48 hours thereafter for pulmonary oedema.

REFERRAL

» All pregnant women with mechanical prosthetic heart valves requiring anticoagulation.

Pregnant women with mechanical prosthetic valves should not receive LMWH unless antifactor Xa levels can be monitored reliably weekly. Therapeutic range is pre-dosing level 0.6 units/mL and a 4-hour peak level of 1–1.2 units/mL

6.4 HYPERTENSIVE DISORDERS IN PREGNANCY

O10.0/O11/O14.0-2/O14.9/O16

DESCRIPTION

Hypertensive disorders are one of the most common direct causes of maternal mortality and are responsible for significant perinatal and maternal morbidity. These disorders include chronic hypertension, pre-eclampsia, eclampsia and HELLP Syndrome. Early detection and timely intervention is essential to prevent maternal and perinatal complications.

GENERAL MEASURES

Bed rest, preferably in hospital.
Lifestyle adjustment and diet.
Monitor BP, urine output, renal and liver function tests, platelet count, proteinuria, and fetal condition.
Consider delivery when risks to mother outweigh risks of prematurity to baby.

MEDICINE TREATMENT

Treatment

Antihypertensives

Medicine treatment will be dictated by blood pressure response.
Monitor progress until a stable result is achieved.
In general, diuretics are contra-indicated for hypertension in pregnant women.
When needed, combine drugs using lower doses when BP >160/100 mmHg, before increasing single medication doses to a maximum.

- Methyldopa, oral, 250 mg 8 hourly as a starting dose. *LoE:IVb*[xii]
  - Increase to a maximum of 750 mg 8 hourly, according to response.

AND/OR

- Long-acting calcium channel blocker, e.g.:
- Amlodipine, oral, 5 mg daily.
  - Increase to 10 mg daily. *LoE:IIb*[xiii]

Preeclampsia

Preeclampsia is defined as hypertension with significant proteinuria developing for the first time after 20 weeks' gestation and can also be superimposed on chronic hypertension - evidenced by the new onset (after 20 weeks' gestation) of persistent proteinuria in a woman who had an initial diagnosis of chronic hypertension.

Pre-eclampsia without severe features:

A diastolic BP of 90-109 mmHg and/or systolic BP of 140-159 mmHg; but no symptoms or organ dysfunction.

Maternal features of severe disease:

» Acute severe hypertension (diastolic BP ≥ 110 mmHg and/or systolic ≥160 mmHg).

» Thrombocytopenia (platelet <100 000/µL).
» Impaired liver function (ALT or AST >40 IU/L).
» Severe persistent right upper quadrant or epigastric pain.
» HELLP syndrome (platelets <100 000 and AST >70 U/L and LDH >600 U/L).
» Serum creatinine ≥120 micromol/L.
» Pulmonary oedema.
» New-onset severe headache unresponsive to medication.
» Visual disturbances.

Hypertensive emergency O10.0/9
SBP ≥160 mmHg and/or DBP ≥110 mmHg. Admit to a high care setting for close monitoring.

- Nifedipine, oral, 10 mg.
  - Repeat after 30 minutes if needed, until systolic blood pressure <160 mmHg and diastolic blood pressure <110 mmHg.
  - Swallow whole. Do not chew, bite or give sublingually.

If unable to take oral or inadequate response:

LoE:IIIb[xiv]

- Labetalol, IV infusion, 2 mg/minute to a total of 1–2 mg/kg.
  - Reconstitute solution as follows:
    - Discard 40 mL of sodium chloride 0.9% from a 200 mL container.
    - Add 2 vials (2 x 100 mg) of labetalol (5 mg/mL) to the remaining 160 mL of sodium chloride 0.9% to create a solution of 1 mg/mL.
    - Start at 40mL/hour to a maximum of 160 mL/hour.
    - Titrate against BP – aim for BP of 140/100 mmHg.
  - Once hypertensive crisis has resolved, switch to an oral preparation.

Delivery

LoE:Ia[xv]

- Oxytocin, IM, 10 units as a single bolus after delivery of the baby.

LoE:IVb[xvi]

Ergot-containing medicines are contraindicated in hypertensive women, including pre-eclampsia, following delivery of the baby.
Pre-eclamptic and eclamptic women are often hypovolaemic, particularly when the haematocrit exceeds 40%, but are also susceptible to pulmonary oedema. Consequently, hypotension is a risk during anaesthesia. Careful infusion of IV fluids is important. Limit blood-loss at Caesarean section.

6.4.1 PREECLAMPSIA

O11/O14.0-2/O14.9

DESCRIPTION

Preeclampsia is defined as hypertension with significant proteinuria developing for the first time after 20 weeks' gestation and can also be superimposed on chronic hypertension - evidenced by the new onset (after 20 weeks' gestation) of persistent proteinuria in a woman who had an initial diagnosis of chronic hypertension.

Pre-eclampsia without severe features:
A diastolic BP of 90-109 mmHg and/or systolic BP of 140-159 mmHg; but no symptoms or organ dysfunction.

Maternal features of severe disease:
» Acute severe hypertension (diastolic BP ≥ 110 mmHg and/or systolic ≥160 mmHg).
» Thrombocytopenia (platelet <100 000/µL).
» Impaired liver function (ALT or AST >40 U/L).
» Severe persistent right upper quadrant or epigastric pain.
» HELLP syndrome (platelets <100 000 and AST >70 U/L and LDH >600 U/L).
» Serum creatinine ≥120 micromol/L.
» Pulmonary oedema.
» New-onset severe headache unresponsive to medication.
» Visual disturbances.

Prevention of pre-eclampsia Z29.2 + O10.0/O24.0-3/O99.1/O99.8 + (D68.6/M32.9)
For women at high risk of pre-eclampsia, e.g. pre-eclampsia in a previous pregnancy, chronic hypertension, diabetes, antiphospholipid syndrome, or SLE.

From 6 weeks' gestation onwards, preferably starting before 16 weeks' gestation:
- Aspirin, oral, 150 mg daily until 36 weeks. *LoE:Ia*[xvii]

At confirmation of pregnancy
- Calcium, oral.
  - For high-risk patients: Calcium (elemental), oral, 1 gram daily.
  - Although the benefit is greatest in high-risk women, consider use of this agent in all pregnant women.
  - When using iron together with calcium supplementation, ensure that iron and calcium are taken at least 4 hours apart from one another.

LoE:Ia[xviii]

Prevention of eclampsia
To prevent eclamptic seizures, magnesium sulfate is recommended for patients with severe features. In some cases, this allows for delivery to be delayed to improve neonatal outcome. When used for prevention of eclampsia, magnesium sulfate is administered for 24 hours and then stopped. The same dose regimens are used as for eclampsia. Women with severe features should be managed under specialist care.

6.4.2 ECLAMPSIA

O15.0-2/O15.9

DESCRIPTION

Generalised tonic-clonic seizures after 20 weeks of pregnancy or within 7 days after delivery associated with hypertension and proteinuria. Exclude any other obvious cause of the seizure before making the diagnosis. Management will include preventing further seizures, controlling the blood pressure, referral to a high-care unit, and delivery of the baby if not already post-delivery.

GENERAL MEASURES

Place patient in left-lateral position.
Clear airway. If necessary, insert oropharyngeal airway.
Abort seizures with magnesium sulfate.

MEDICINE TREATMENT

If necessary:

- Oxygen via nasal prongs or face mask to maintain a saturation of >90%.

Treatment

Where infusion pumps are not available:

- Magnesium sulfate, IV, 4 g in 200 mL sodium chloride 0.9% over 20 minutes.

Follow with:

- Magnesium sulfate, IM, 5 g every 4 hours administered at different sites, until 24 hours after delivery or following the last convulsion.

In high-care setting:

- Magnesium sulfate, IV, 4 g in 200 mL sodium chloride 0.9% over 20 minutes (loading dose).

Follow with:

- Magnesium sulfate, IV infusion, 1 g every hour, until 24 hours after delivery, or after the last convulsion (maintenance dose).

STOP MAGNESIUM SULFATE IF KNEE REFLEXES BECOME ABSENT OR IF URINE OUTPUT <100 ML/ 4 HOURS OR RESPIRATORY RATE <16 BREATHS/MINUTE.

IF RESPIRATORY DEPRESSION OCCURS:

- Calcium gluconate 10%, IV, 10 mL given slowly at a rate not exceeding 5 mL/minute.

Recurrent eclamptic seizure despite magnesium sulfate loading dose administration:

- Magnesium sulfate, IV, 2 g over 10 minutes.

For agitated and restless women with eclampsia:

- Lorazepam, IV/IM, 4 mg.
  - May be repeated after 10-15 minutes.

- Maximum dose: 8 mg.

OR

Clonazepam, IV, 2 mg.

- May be repeated after 5 minutes.
- Maximum dose: 4 mg.

OR

If above not available:

Diazepam, IV, 10–20 mg, not faster than 2 mg/minute.

Notify the person who will resuscitate the newborn that a benzodiazepine and/or magnesium has been given to the mother.

REFERRAL

Refer all eclampsia cases to a high or intensive care facility.

6.4.3 CHRONIC HYPERTENSION

O10.0-4/O10.9

GENERAL MEASURES

Lifestyle modification

» No alcohol should be taken.
» Regular moderate exercise, e.g. 30 minutes brisk walking at least 3 times a week.
» Smoking cessation.
» Aim to keep BP <140/90 mmHg.

Screen for end-organ damage.
Fetal surveillance by symphysis-fundus height (SFH) growth. Umbilical artery Doppler screening (where available) at 24-26 weeks.
Ask mother about fetal movements at each antenatal visit. *LoE:IIb*[xix]

Consider labour induction if:

» BP persistently ≥160/110 mmHg, or
» pregnancy of ≥38 weeks duration, or
» in the presence of maternal or fetal compromise, e.g., poor SFH growth and oligohydramnios, etc.

MEDICINE TREATMENT

See prevention and treatment of pre-eclampsia.

Switch ACE-inhibitors and diuretics to methyldopa and/or amlodipine. Women should be advised that there is an increased risk of congenital abnormalities if ACE-inhibitors were taken during pregnancy.

6.4.4 GESTATIONAL HYPERTENSION

See to PHC Chapter 6: Obstetrics and gynaecology, Sections 6.4.2.2: Gestational hypertension: no severe features, and 6.4.2.3: Gestational hypertension: with severe features.

6.5 CORONAVIRUS DISEASE-19 (COVID-19) IN PREGNANCY

U07.1/U07.2

*Notifiable medical condition.

ANTENATAL CARE:

» Antenatal care is an essential service and should not be scaled down during lockdown periods.

» Screening and testing criteria for SARS-CoV-2 infection during pregnancy is the same as for the general population.

» Vaccination against COVID-19 and influenza is safe at all gestations of pregnancy and during COVID-19 pandemic it is important that pregnant women take up the COVID-19 and influenza vaccine to reduce their risk of contracting either. (See PHC Section 13.7: Other vaccines.)

» The clinical course and outcome of COVID-19 is not different in pregnancy and most pregnant women who are infected with SARS-CoV-2 will experience only mild or moderate symptoms.

» Up to 75% of infected women in pregnancy may be asymptomatic, and appropriate PPE must be used for all deliveries, regardless of the status of the mother. All pregnant women attending hospital, including women in labour, should wear masks.

» Maternal COVID-19 is associated with an approximately three times greater risk of preterm birth and women should be counselled on warning signs of spontaneous preterm labour. *LoE:IIIb*[xx]

» Risk factors for more severe disease or admission to hospital with COVID-19 include:
  - Obesity (pre-pregnancy BMI >30 kg/m^2). *LoE:IIIb*[xxi]
  - Co-morbidity, such as pre-existing diabetes (see Section 6.2: Diabetes mellitus in pregnancy) and chronic hypertension (see Section 6.4.3: Chronic hypertension).
  - Age >35 years

» SARS-CoV-2 infection is not associated with an increase in the incidence of congenital abnormalities.

THROMBOPROPHYLAXIS:

All pregnant women admitted with confirmed or suspected COVID-19 should be offered prophylactic LMWH or unfractionated heparin for 10 days, unless birth is expected within 12 hours. See Section 2.8: Venous thrombo-embolism.

DELIVERY:

» COVID-19 infection is not an indication for delivery, unless delivery is required as part of maternal resuscitation to improve maternal oxygenation.
» When a woman with COVID-19 presents with spontaneous preterm labour, suppression of labour (to delay delivery in order to administer antenatal corticosteroids) should not be done.
» All women with confirmed or suspected SARS-CoV-2 infection must preferably deliver in a dedicated COVID-19 hospital or ward.

MEDICINE TREATMENT

Observe oxygen saturation measurement hourly.

- Oxygen, if saturation is <94%.

Symptomatic relief of headache:

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

Note: Avoid morphine analgesia if patient is respiratory compromised.

In pregnant patients who require supplemental oxygen:

» Corticosteroids crosses the placenta and may have long-term deleterious effects on the child.

If corticosteroids are also needed to accelerate fetal lung maturity: See Section 6.11.1: Preterm labour (PTL) and preterm prelabour rupture of membranes (PPROM).

If corticosteroids are not needed for fetal lung maturity:

- Corticosteroids, e.g.:
- Dexamethasone, IV, 6 mg daily for up to 10 days, or until discharge.

If there is a concern over in-utero steroid exposure, use alternative therapy (with less placental transfer):

- Prednisone, oral 40 mg daily, for up to 10 days, or until discharge.
  OR
  Hydrocortisone, IV, 80 mg 12 hourly for up to 10 days, or until discharge.

Anaesthetic: *LoE:IIa*[xxii]

- Spinal anaesthesia is the anaesthetic of choice in the absence of contra-indications. See Section 12.7: Anaesthesia, spinal (intrathecal). The patient

should wear a surgical facemask for the duration of the perioperative period.

POSTPARTUM:

» Infection with SARS-CoV-2 is not a contra-indication to breast feeding.
» There is no contra-indication to the use of post-partum contraception. (See PHC Chapter 7: Family planning.)

6.6 HIV IN PREGNANCY

O98.7 + (Z21/B24)

Consult the most recent National Department of Health Guideline for Vertical Transmission Prevention of Communicable Infections

All pregnant women should receive routine counselling and voluntary HIV testing at their very first antenatal visit.

All women who test negative or who decline testing, should be offered repeat HIV testing at every routine visit throughout pregnancy (8 visits in all), at labour/delivery, at the 6-week EPI visit, and three monthly throughout breastfeeding.

WLHIV should be clinically staged and have a blood sample taken for CD4 cell count and serum creatinine on the same day as diagnosis. The results must be obtained within a week.
Initiate lifelong ART in all pregnant or breastfeeding women on the same day of diagnosis regardless of CD4 count or infant feeding practice.

Provide adequate support and counselling, particularly addressing ART adherence.

Discuss postpartum contraceptive use in the antenatal period.

Educate all women during the antenatal period about the benefits of exclusive breastfeeding for the first 6 months and breastfeeding with complimentary feeding from 6 months until at least 2 years after delivery. (Only in circumstance where the mother has confirmed 2nd or 3rd line ART regimen failure (VL >1000 copies/mL), advise not to breastfeed and prescribe replacement feeds.)

Perform a TB symptom screen for all pregnant women at each visit. If any of the answers to the screening questions are positive, do further TB investigations. A TB-NAAT test must be done for all pregnant women with a new diagnosis of HIV disease or known HIV- infected women with a new pregnancy.

Screen and treat all patients for syphilis and other STIs, in line with basic antenatal care.
Test partner for HIV and perform routine cervical cancer screening.

Assist women with unwanted pregnancies <20 weeks' gestation with access to TOP services.

MEDICINE TREATMENT

» Patients should receive ART at the first antenatal visit, whether newly diagnosed or known to be living with HIV but not on ART.

» Tenofovir should not be used in pregnant women with a serum creatinine ≥85 micromol/L (a more sensitive measure of renal impairment in pregnancy than calculated creatinine clearance).

» Pregnant women may be initiated on/switched to a dolutegravir-containing regimen.

LoE:IIb[xxiii]

» Initiate antenatal supplementation (see PHC Section 6.4.1: Antenatal supplements), noting that calcium and DTG should not be taken together on an empty stomach, but can be taken together with food.

1st ANC visit	
Pregnant women not on ART, with normal renal function, **without** TB.	• TDF, oral, 300 mg daily. **AND** • 3TC, oral, 300 mg daily. **AND** • DTG, oral, 50 mg daily. Provided as a fixed dose combination (FDC).
Pregnant women not on ART, with normal renal function, **with** TB. (DTG requires boosting with TB treatment.)	• TDF, oral, 300 mg daily. **AND** • 3TC, oral, 300 mg daily. **AND** • DTG, oral, 50 mg daily. Provided as a fixed dose combination (FDC). **WITH** DTG, oral 50 mg 12 hours later.
Pregnant woman on TDF + FTC + EFV.	Switch to TDF+3TC+DTG.
Pregnant woman already on ART with a VL between 50-1000 copies/ml.	See Section 10.1: Antiretroviral Therapy.
2nd ANC visit (1 week later)	
Creatinine ≤85 micromol/L.	Continue ART as an FDC
Creatinine >85 micromol/L. (TDF is contraindicated)	Replace TDF with ABC as part of a FDC: • ABC, oral, 600 mg daily **AND** • 3TC, oral, 300 mg daily. **AND** • DTG, oral, 50 mg daily.

LoE:IIIb[xxiv]

Caesarean Delivery (CD):
Provide antibiotic prophylaxis to all pregnant women, including HIV-infected pregnant women prior to surgery (See Chapter 11: Surgical antibiotic prophylaxis).

Women with the following risk factors may be at higher risk of infection post Caesarean delivery:
» Advanced immunosuppression.
» Prolonged rupture of membranes (>18 hours).
» Multiple vaginal examinations during labour (>5 PVs).
» Second stage CD.
Monitor carefully and treat infection appropriately.

HIV-infected pregnant women not on ART undergoing elective Caesarean delivery/or in labour:

- NVP, oral, 200 mg as a single dose.

WITH

- TDF, oral, 300 mg as a single dose.

AND

- 3TC, oral, 300 mg as a single dose.

AND

- DTG, oral, 50 mg as a single dose (as a FDC 4 hours before Caesarean delivery).

Followed by lifelong:

- TDF+3TC+DTG (provided as an FDC).

For management of the HIV-exposed infant, see PHC Section 11.5: The HIV exposed infant.

For more information on HIV management, see Section 10.1: Antiretroviral Therapy.

6.7 SYPHILIS

O98.1

DIAGNOSTIC CRITERIA

Most pregnant women infected with syphilis are asymptomatic.
See PHC Section 12.8: Syphilis serology and treatment.

GENERAL MEASURES

Inform contact(s).

MEDICINE TREATMENT

Mother (treat as either early or late latent/unknown stage of syphilis):

For late latent syphilis or syphilis of unknown duration

- Benzathine benzylpenicillin (depot formulation), IM, 2.4 million units diluted in 6 mL 1% lidocaine without adrenaline (epinephrine), weekly for 3 doses.

Note: If the mother has received <3 doses, treat the baby for congenital syphilis.

For early syphilis *LoE:IIIb*[xxv]

- Benzathine benzylpenicillin (depot formulation), IM, 2.4 million units diluted in 6 mL 1% lidocaine without adrenaline (epinephrine), immediately as a single dose.

Severe penicillin allergy (Z88.0)

For penicillin sensitive pregnant women: penicillin desensitisation.

Perform only in an ICU setting or in a setting where recognition and management of anaphylaxis can be assured. See "How to Use These Guidelines" for detailed information.

Oral penicillin desensitisation protocol

A: Prepare stock solution of oral phenoxymethylpenicillin 250mg/ 5mL and dilutions for steps 1-7 and 8-10.
B: Administer increasing doses of penicillin strictly at 15 minutes intervals.

Step	Medicine mg/mL	Amount to administer (mL)
To make 0.5 mg/mL solution: Add 0.5 mL of stock phenoxymethylpenicillin solution to 49.5 mL water (total volume 50mL).		
1	0.5 mg/mL solution (1000 units/mL)	0.1 mL orally
2		0.2 mL orally
3		0.4 mL orally
4		0.8 mL orally
5		1.6 mL orally
6		3.2 mL orally
7		6.4 mL orally
To make 5 mg/mL solution: Dilute 1 mL of stock phenoxymethylpenicillin solution with 9 mL water (total volume 10mL).		
8	5 mg/mL solution (10000 units/mL)	1.2 mL orally
9		2.4 mL orally
10		4.8 mL orally
Stock phenoxymethylpenicillin 250 mg/5 mL = 50 mg/mL.		
11	50 mg/mL (80000 units/mL)	1.0 mL orally
12		2.0 mL orally
13		4.0 mL orally
14		8.0 mL orally

After step 14, observe for 30 minutes, then administer desired dose of intramuscular penicillin.

Note:

- Repeat desensitisation is not required for subsequent doses of the same treatment course (e.g., to complete 3 doses of benzathine benzylpenicillin for late latent syphilis or syphilis of unknown duration).
- However, second and third doses must be administered in a hospital setting.

Asymptomatic, well baby:
Mother has syphilis and has not been treated, or was only partially treated:

- Benzathine benzylpenicillin (depot formulation), IM, 50 000 units/kg as a single dose into the antero-lateral thigh. A

Symptomatic baby

- Procaine penicillin, IM, 50 000 units/kg daily for 10 days. A (Not for IV use.)

OR

Benzylpenicillin (Penicillin G), IV, 50 000 units/kg, 12 hourly for 10 days. A

6.8 HEPATITIS B IN PREGNANCY

O98.4

DESCRIPTION

Hepatitis B virus (HBV) is transmitted sexually or by percutaneous exposure to infectious body fluids, i.e., blood, saliva, vaginal fluid, and semen. Diagnosis is confirmed serologically by a positive hepatitis B surface antigen (HBsAg).

Screening in pregnancy for HBsAg should ideally be performed in the first trimester. HBeAg positive pregnant women are more infectious than HBsAg positive women, as they have higher rates of HBV replication.

GENERAL MEASURES

Screen sexual contact(s); if they are sero-negative, give hepatitis B vaccination.
All infected patients should be counselled with regard to lifestyle modifications to reduce hepatotoxicity, including alcohol, substance abuse, and co-prescription of herbal and traditional medicines.

MEDICINE TREATMENT

Indications for medical therapy in HIV-negative pregnant women are the same as for non-pregnant adults.

» For management of chronic hepatitis B, **without** chronic HIV infection, see Section 1.2.4.2 Hepatitis B, chronic (non-HIV coinfection).
» For management of chronic hepatitis B **with** chronic HIV infection, see Chapter 10: HIV and AIDS. (ART for women with chronic Hepatitis B should always include ARVs active against hepatitis B.)

Note:
» Ensure normal renal function before starting treatment with TDF (serum creatinine <85 micromol/L or creatinine clearance >60 mL/minute).
» Monitor ALT and HBV DNA viral load at 6 months after commencing treatment.
» An adequate virological response is an HBV DNA VL<2000 IU/mL.

Prevention of perinatal transmission
» Caesarean delivery is reserved for obstetric indications only.
» Delivery should take place in a facility that can offer Hepatitis B vaccination to the baby at birth.
» Administration of ARVs active against HBV from 28 weeks of pregnancy will further reduce risk of vertical transmission.

Pregnant women who are HBsAg/ HBeAg positive and HIV negative
» All HIV negative pregnant women are eligible for HIV Pre-exposure prophylaxis (PrEP) (see PHC STGs and EML, section 11.11: Pre-exposure prophylaxis (PrEP)). TDF, which is included in the oral PrEP regimen, has anti-HBV activity, and will reduce the risk of vertical transmission of HBV.
» Women who are HIV negative and HBsAg positive who decline PrEP must be counselled that TDF will reduce risk of vertical transmission of Hepatitis B to the baby, particularly if HBeAg is positive or HBV viral load is high.
» TDF 300 mg daily should be administered from 28 weeks of pregnancy until birth to women with a high hepatitis viral load (≥200 000 IU/mL), or positive HBeAg, or where HBeAg/viral load result is unavailable at 28 weeks.
» For care of babies born to: (1) mothers with acute hepatitis B infection at the time of delivery, (2) mothers who are HBsAg-positive, or (3) mothers who are HBeAg-positive, see Primary Health Care STGs and EML, section 6.6.5: Hepatitis B exposed infant.
» Obtain infectious disease specialist or internal medicine physician opinion before stopping TDF as there is a risk for postpartum hepatitis flare.
» Consider continued treatment for HBV after delivery where indicated (see Section 1.2.4.2 Hepatitis B, chronic (non-HIV coinfection)).

For Pregnant women who are HBsAg/ HBeAg positive and HIV negative

- TDF, oral, 300 mg daily (from 28 weeks of pregnancy until birth).

LoE:IVb[xxvi]

REFERRAL
» Cirrhosis.
» Liver failure.
» Renal dysfunction (TDF is contraindicated in renal impairment. Tenofovir alafenamide (TAF) should be prescribed in place of TDF).
» Refer all infected babies to a specialist paediatrician for further management.

6.9 JAUNDICE IN PREGNANCY
O26.6

DESCRIPTION
The most common causes of jaundice in pregnancy are not pregnancy specific. They include viral hepatitis, and adverse drug reactions.
Pregnancy-specific causes include:
» intrahepatic cholestasis of pregnancy,
» acute fatty liver of pregnancy (acute yellow atrophy of the liver),
» severe pre-eclampsia or eclampsia, and
» hyperemesis gravidarum.

REFERRAL
All, as certain causes of jaundice in pregnancy have a high mortality.

6.10 HYPEREMESIS GRAVIDARUM
O21.0/1/9

DESCRIPTION
Recurrent vomiting leading to ketosis, generally in the first trimester.
Exclude:
» medical causes, e.g., thyrotoxicosis, and
» molar pregnancy.

GENERAL MEASURES
Counselling.
Frequent small, dry meals.
Avoid fatty and spicy foods.
Restrict oral intake for 24–48 hours but ensure adequate intravenous hydration.

MEDICINE TREATMENT
Correct electrolyte imbalance with IV fluids.

- Pyridoxine, oral, 25 mg 8 hourly.

AND

- Vitamin B complex, IV, 10 mL.

AND

- Promethazine, oral/IM/IV 25 mg 8 hourly as needed.

LoE:IIIb[xxvii]

If no/poor response:

ADD

- Metoclopramide, oral/IV, 10–20 mg 6 hourly as needed.

LoE:IIIb[xxviii]

In refractory cases:

Administer daily until hyperemesis is controlled:

- Dexamethasone, IM/IV, 4–8 mg daily.

AND

- Ondansetron, IV, 4–8 mg over 5 minutes, daily.
  - **Note:** There is uncertainty regarding the safety of ondansetron in the first trimester. Use with caution and only when necessary.

LoE:IIIb[xxix]

6.11 PRETERM LABOUR

6.11.1 PRETERM LABOUR (PTL) AND PRETERM PRELABOUR RUPTURE OF MEMBRANES (PPROM)

O60.0/O42.0-2/O42.9

DESCRIPTION

Preterm: <37 weeks' gestation.
Most problems occur at <34 weeks' gestation.
Confirm ruptured membranes by sterile vaginal speculum.
Preterm labour confirmed by regular uterine contractions with progressive cervical changes.

GENERAL MEASURES

Assess fetal wellbeing.
Estimate fetal weight.
Deliver if chorio-amnionitis suspected.

MEDICINE TREATMENT

If gestation <34 weeks:

Pre-hydrate before administration of nifedipine:

- Sodium chloride 0.9%, IV, 200 mL.

AND

- Nifedipine, oral, 20 mg.
  - If contractions persist, follow with 10 mg after 30 minutes then 10 mg 4 hourly for up to 48 hours.

If gestation <32 weeks and where nifedipine contra-indicated:

- Indomethacin, oral, 50 mg immediately then 25 mg 4 hourly for up to 48 hours.

LoE:Ia[xxx]

Note: Indomethacin may cause oligohydramnios, and its use is associated with a risk of premature closure of the ductus arteriosus. Use only if there is intolerance to nifedipine.

To improve fetal lung maturity at 26–34 weeks: (Z29.2)

- Betamethasone, IM, 12 mg, 2 doses 24 hours apart. LoE:Ia[xxxi]

If betamethasone is not available:

- Dexamethasone, IM, 8 mg, 3 doses 8 hours apart. LoE:Ia[xxxii]

Note: Corticosteroids are maximally effective about 24 hours after administration of the first dose. Therefore, give as soon as possible following diagnosis of PTL or PPROM.

Antibiotic therapy (Z29.2)

- Ampicillin, IV, 1 g 6 hourly for 48 hours. A

Follow with:

- Amoxicillin, oral, 500 mg 8 hourly for a further 5 days. A

AND

- Azithromycin 1g orally as a single dose. W LoE:IIIa[xxxiii]

Severe penicillin allergy: (Z88.0)

- Clindamycin, IV, 600 mg 8 hourly for 48 hours. A

Follow with:

- Clindamycin, oral, 450 mg 8 hourly for a further 5 days. A

AND

- Azithromycin 1g orally as a single dose. W LoE:IIIa[xxxiv]

Prepare for appropriate care of preterm infant.

REFERRAL

» Fetus that may require neonatal intensive care, e.g. estimated weight <1.5 kg or gestation <32 weeks.
» Fetus requiring specialised treatment after birth, e.g. surgery.
» Severely ill mother.

6.11.2 PREVENTION OF PRETERM LABOUR

Z35.2

DESCRIPTION

Women with a previous spontaneous preterm delivery are at higher risk for preterm delivery in the next pregnancy. In certain high-risk cases, pregnancy may be prolonged by the careful consideration of either cervical cerclage or vaginal progesterone therapy.

The following high-risk women should undergo cervical screening and offered

a choice of cerclage or progesterone if the cervical length is **≤25 mm**:

» A history of 2nd trimester miscarriage (between 16 and 26 weeks) suggestive of cervical incompetence: (Painless dilatation with a quick labour, and birth of a live baby or fresh stillbirth) after excluding other causes of mid-trimester losses, e.g. intra-uterine death that required induction, abruptio placentae, fetal abnormalities, polyhydramnios, and medical terminations.
» Previous history of spontaneous preterm birth between 27 and 34 weeks (exclude non-spontaneous causes e.g. iatrogenic delivery for pre-eclampsia, or syphilis). No need to refer previous late preterm deliveries (34-37 weeks).
» Twin gestations (dichorionic or monochorionic), regardless of the previous history, as twin pregnancies are at increased risk (7-10 fold) of preterm labour

Do not screen for cervical length in low-risk women routinely, as it is not cost-effective.

GENERAL MEASURES

Cervical length must be measured by a skilled operator using transvaginal ultrasound.
Cervical measurement can be done between 16 and 24 weeks.
A cervical length of ≤25 mm indicates a higher risk for recurrent preterm labour. Discuss the risks and benefits of both options with the patient to make an informed shared decision of the most appropriate treatment.

MEDICINE TREATMENT

Women should be counselled that 20 cerclage procedures will prevent one preterm delivery (NNT 17 to 20) and that progesterone is successful in 1 out of every 8 cases (NNT 6 to 8), to assist them in making an informed decision.

LoE:IIb[xxxv]

Consider prophylactic vaginal progesterone ***or*** cervical cerclage (MacDonald suture) for women with:

» history of spontaneous preterm birth (27-34 weeks) or mid-trimester loss (16-24 weeks), ***and***
» cervical length ≤ 25 mm confirmed on ultrasound (16-24 weeks).

- Progesterone, PV, 200 mg daily. *LoE:IIb*[xxxvi]
  - Stop treatment at 34 weeks and refer to antenatal services at primary level of care for further management.

Consider prophylactic cervical cerclage (MacDonald suture) ***only*** for women with:

» cervical length ≤ 25 mm confirmed on ultrasound (16-24 weeks),

AND

» history of preterm prelabour rupture of membranes (PPROM), ***or***
» history of cervical trauma.

Rescue cerclage:

» If the cervix is already open and the membranes exposed, but unruptured, consider a rescue cervical cerclage (16-27 weeks).
» Do not insert a rescue cerclage if there are contractions, active vaginal bleeding or signs of infection.

Cerclage should be removed at 36 weeks, and thereafter the patient can be referred to antenatal services at primary level of care. *LoE:IIb*[xxxvii]

REFERRAL
Women with recurrent losses and previous cerclage that tore out (severe cervical trauma), as they may require an abdominal cerclage.

6.12 SUPPRESSION OF LABOUR FOR FETAL DISTRESS
O68.0-3/8-9 + (Z51.2)

DESCRIPTION
Tocolysis is useful to treat fetal distress in labour and to suppress labour in women needing transfer or awaiting Caesarean delivery. Also used prior to external cephalic version.

MEDICINE TREATMENT
- Salbutamol bolus, 250 mcg IV, slowly over 2 minutes.
  - Reconstitute the solution as follows:
    - Add 1 mL (i.e., 0.5 mg/mL) salbutamol to 9 mL sodium chloride 0.9% to make a solution of 50 mcg/mL. Administer 5 mL (250 mcg) of this solution.
    - Monitor pulse. Do not administer if mother has cardiac disease.
    - Place the mother in the left lateral position.
    - If pulse increases >120 bpm, discontinue salbutamol.

LoE:IIb[xxxviii]

6.13 LABOUR INDUCTION
Z35.9/Z51.2

If induction of labour is indicated, for medical reasons, for example pre-eclampsia, diabetes, or post-term pregnancy.

GENERAL MEASURES
Counsel the woman about the risks: failed induction or uterine hyperstimulation syndrome, which may require emergency Caesarean delivery.

Cervix favourable and confirmed HIV-uninfected mother
Artificial rupture of the membranes.

Cervix unfavourable (Bishop score <7)
Extra-amniotic Foley catheter with/without saline infusion:
Pass a Foley catheter with 30 mL bulb through cervix with sterile technique.

Inflate bulb with 50 mL water or sodium chloride 0.9%.
Tape catheter to thigh with light traction.
Alternatively, attach sodium chloride 0.9% 1 L with giving set to catheter, and infuse sodium chloride 0.9% at 50 mL/hour. Remove after 24 hours.

LoE:IVb

MEDICINE TREATMENT

Cervix unfavourable (Bishop score <7)

Extra-amniotic Foley catheter (as above) **PLUS** one of the options below:

Prostaglandins, e.g.: *LoE:IIb[xxxix]*

- Dinoprostone gel, intravaginally, 1 mg.
  - Repeat after 6 hours.
  - Do not exceed 4 mg.

OR

- Dinoprostone tablets, intravaginally, 1 mg.
  - Repeat after 6 hours.
  - Do not exceed 4 mg.

LoE:IIIb[xl]

OR

- Misoprostol, oral, 20 mcg 2 hourly until in labour, or up to 24 hours.
  - Oral misoprostol may be given as freshly made-up solution of one 200 mcg tablet in 200 mL water, i.e., 1 mcg/mL solution. Give 20 mL of this solution 2 hourly.
  - Stop misoprostol administration when in established labour.
  - Maximum 24 hours.
  - Never use oxytocin and misoprostol simultaneously.
  - Misoprostol and other prostaglandins are contraindicated in women with previous Caesarean sections and in grand multiparous women.

LoE:IIIb[xli]

Note:

» Misoprostol in larger doses than indicated here for labour induction at term, may cause uterine rupture.
» Only to be prescribed by a doctor experienced in Maternal Health.

Non-stress test and cardiotocography:

Note: Perform a non-stress test (NST), before starting the induction, and cardiotocography (CTG) within an hour of each dinoprostone insertion, to evaluate the fetal condition during labour induction.
When using oral misoprostol, do a baseline NST before commencing IOL, followed by CTG 4-hourly (prior to every alternate dose).
Repeat CTG once contractions have started, or more frequently only if clinically indicated.

LoE:IVb

Cervix favourable (Bishop score ≥7)

Amniotomy followed 2 hours later by:

- Oxytocin, IV, 2 units in 200 mL sodium chloride 0.9%.

LoE:IIIb[xlii]

- Start at an infusion rate of 12 mL/hour (i.e. 2 milliunits/minute). If absent or inadequate contractions, increase infusion rate according to the table below:

Time after starting (minutes)	Oxytocin dose (milliunits/minute)	Dilution: 2 units in 200 mL sodium chloride 0.9% (mL/hour)
0	2	12
30	4	24
60	6	36
90	8	48
120	10	60
150	12	72
180	14	84
210	16	96
240	18	108
270	20	120

Note:

» It is safe to perform amniotomy in pregnant women living with HIV on ART who have an undetectable plasma VL at delivery.

LoE:IIIb[xliii]

» Avoid oxytocin in women with previous Caesarean section or parity ≥5.
» Continuous electronic fetal heart rate monitoring is essential.
» Aim for adequate uterine contractions (3–5 contractions in 10 minutes). Once adequate contractions achieved, do **not** increase rate further.
» Most women will experience adequate contractions at a dose of 12 milliunits/minute.
» If tachysystole develops (>5 contractions in 10 minutes), reduce or stop the oxytocin infusion to achieve 3-5 contractions in 10 minutes. If there are fetal heart rate abnormalities which persist despite stopping the oxytocin, administer salbutamol as above.

6.14 LABOUR PAIN, SEVERE

O62.9 +(Z51.2)

GENERAL MEASURES

Antenatal counselling.
Psychological support from family member, friend or volunteer ‘doula’.
The need for analgesics may be reduced by keeping the woman informed about the progress of labour, providing reassurance and carefully explaining the procedures performed.
Anticipate the need for analgesia rather than waiting for severe distress.

MEDICINE TREATMENT

- Morphine, IM, 0.1 mg/kg 4 hourly as needed, to a maximum of 10 mg.

Titrate dose and dose frequency according to pain. LoE:IVb[xliv]
Supplement with premixed nitrous oxide 50%/ oxygen 50% in late first stage.

Epidural anaesthesia
Offer this service only at hospitals with anaesthetic expertise, monitoring, capacity and equipment for epidural. (See Chapter 12: Anaesthesiology, and intensive care.)

Perineal analgesia: R10.2

- Lidocaine, 1 or 2%, infiltration, locally or by a pudendal block.

Postpartum and post-episiotomy pain O90.9 + (R10.2 + Z51.2)

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

OR

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals.

OR

- Morphine, IM, 0.1 mg/kg 4 hourly as needed, to a maximum of 10 mg.

LoE:IVbl[xlv]

6.15 DEHYDRATION/KETOSIS IN LABOUR

O99.2 + (E86)

DESCRIPTION

Subclinical dehydration is often missed in labour.

GENERAL MEASURES

Encourage adequate oral fluid intake.

MEDICINE TREATMENT

Mild dehydration
Give oral fluids.

Moderate/severe dehydration
Administer intravenous fluids, e.g.:

- Sodium chloride 0.9%, IV, 250 mL/hour.

Re-evaluate hydration hourly.

6.16 POSTPARTUM FEVER

O85/O86.0-4/O86.8

DESCRIPTION

During delivery the woman's protective barrier against infections is temporarily reduced and this may lead to infections.
The cause of fever may be a serious complication.
Consider excessive use of misoprostol for PPH (doses >600 mcg) as a possible non-infectious cause of postpartum fever.

GENERAL MEASURES

Prevent deep vein thrombosis.
Complete evacuation of uterine contents.
Hysterectomy may be indicated in severe uterine sepsis.
Attention to breast engorgement.

MEDICINE TREATMENT

Antibiotic treatment, where appropriate, should be guided by the presumed source of infection.

Empiric antibiotic therapy

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly, until patient apyrexial for 24 hours. A

LoE:IVb

Follow with:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly. A

REFERRAL

» No clinical response to 48 hours of antibiotic treatment.
» Septic shock.

6.17 POSTPARTUM HAEMORRHAGE

O72.1-3 + (Z51.2)

DESCRIPTION

Blood loss >500 mL after birth of the baby or any blood loss which results in haemodynamic instability (tachycardia and/or hypotension).

GENERAL MEASURES

Bimanual compression of the uterus.
Ensure delivery of placenta is complete.
Check for local causes of bleeding.
Balloon tamponade of the uterine cavity should be considered if the patient is to be transferred to another facility.

MEDICINE TREATMENT

Prevention Z29.2

Active management of the 3rd stage of labour:

- Oxytocin, IM, 10 units.

Note:

» Delay cord clamping and cutting (after 1 minute)
» Deliver the placenta by controlled cord traction.

Treatment

Resuscitate.
Put up two IV lines of crystalloid, one of which should contain oxytocin 20 IU.
Cross match and hold blood for transfusion.
Monitor BP and pulse, and response to uterotonics every 15 minutes.

- Oxytocin, IV, 20 units in 1 L sodium chloride 0.9% at 250 mL/hour.

If uterus remains atonic (palpable above the umbilicus) after the oxytocin infusion has started:

- Ergometrine, IM, 0.5 mg.
  or
  a combination of oxytocin, IM, 5 units and ergometrine, IM, 0.5 mg.
  - Avoid ergometrine in women with hypertension or cardiac disease, except in severe cases where the benefit is considered to outweigh the risk (discuss with a specialist).
  - Repeat ergometrine 0.5 mg IM after 15 minutes if no response.

AND *LoE:Ia*[xlvi]

- Tranexamic acid 1 g, IV, slowly over 10 minutes.
  - Repeat after 30 minutes if there is ongoing vaginal bleeding.

In settings where oxytocin had NOT been administered as prophylaxis at birth:

- Misoprostol, sublingual, or rectal, 600 mcg as a single dose.

LoE:IIb[xlvii]

6.18 THE RHESUS NEGATIVE WOMAN

O36.0 + (Z29.1)

GENERAL MEASURES

Maternal serum antibodies absent

Prevention

Test for maternal serum antibodies at 'booking', 28- and 34-weeks' gestation.
During pregnancy, give prophylactic anti-D immunoglobulin to the mother within 72 hours of a potentially sensitising event.

MEDICINE TREATMENT

After a termination of pregnancy (TOP), miscarriage, ectopic pregnancy or amniocentesis 13-22 weeks:

LoE:IIIb[xlviii]

- Anti-D immunoglobulin, IM, 50 mcg.

After external cephalic version or potentially sensitizing event ≥22 weeks:

- Anti-D immunoglobulin, IM, 100 mcg.

At birth, determine the Rh status of the cord blood and request a Coomb's test:
Cord blood Rh negative - no treatment.
Cord blood Rh positive, Coomb's negative:

- Anti-D immunoglobulin, IM, 100 mcg.

If a large feto-maternal haemorrhage is suspected:

- Anti-D immunoglobulin, IM, 300 mcg for every 30 mL haemorrhage.
  - Maximum dose: 1 200 mcg.

AND
Do a maternal blood Kleihauer test (consult a specialist).

Rh positive, Coomb's positive:
In these cases, the mother will also have antibodies.
Do not administer anti-D immunoglobulin.

Maternal serum antibodies present.
Consult a specialist.

6.19 URINARY TRACT INFECTION (UTI) IN PREGNANCY

6.19.1 CYSTITIS

O23.1

DESCRIPTION

This condition usually presents with lower abdominal pain, frequency of micturition, and/or dysuria. There are no features of sepsis, e.g., fever. Urine dipstick testing usually shows nitrites, with/without leukocytes; and/or blood.

GENERAL MEASURES

Encourage oral fluid intake.
Midstream urine for microscopy, culture and sensitivity.

MEDICINE TREATMENT

Empiric treatment (symptoms present with nitrites positive **AND** leukocytes positive on dipstick):

- Fosfomycin, oral, 3 g as a single dose — LoE:IIIb[xdix] / LoE:Ib[l]

OR

- Nitrofurantoin, oral, 100 mg, 6 hourly for 5 days.

REFFERAL/CONSULTATION

LoE:IIbli

No response to treatment, or resistant organism on culture.

6.19.2 PYELONEPHRITIS, ACUTE

O23.0

DESCRIPTION

This condition is more serious than cystitis and may result in preterm labour.
Features of pyelonephritis include:

» temperature ≥ 38ºC,
» renal angle tenderness (often bilateral),
» other features of sepsis, i.e., vomiting, tachypnoea, tachycardia, confusion and hypotension.

GENERAL MEASURES

Admit to hospital.
Ensure adequate hydration with intravenous fluids, up to 3 L of sodium chloride 0.9% over 24 hours.
Midstream urine for microscopy, culture and sensitivity.

MEDICINE TREATMENT

Empiric therapy:

- Ceftriaxone, IV, 1 g, daily for 48 hours, or until fever subsides. W

OR

- Gentamicin, IV, 6 mg/kg, daily (ensure normal renal function). A

Switch to oral therapy as soon as the patient is able to take oral fluids:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 7 days. A

Change antibiotics according to culture and sensitivity results. After treatment, ensure that two urine specimens are negative to confirm eradication.

[i] Department of Health, Republic of South Africa. 2016. Guidelines for Maternity care in South Africa, 4th edition. https://www.knowledgehub.org.za/e-library

[ii] South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[iii] Ferrous (Iron) supplements, oral - intermittent dosing: National Department of Health: Affordable Medicines, EDP-Primary Health Care level. Medicine Review: Intermittent iron supplementation in pregnancy, 6 November 2017. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Ferrous (Iron) supplements, oral - intermittent dosing: Peña-Rosas JP, De-Regil LM, Gomez Malave H, Flores-Urrutia MC, Dowswell T. Intermittent oral iron supplementation during pregnancy. Cochrane Database Syst Rev. 2015 Oct 19;(10):CD009997. https://www.ncbi.nlm.nih.gov/pubmed/26482110

[iv] Iron (treatment of iron-deficiency anaemia): Reveiz L, Gyte GM, Cuervo LG, Casasbuenas A. Treatments for iron-deficiency anaemia in pregnancy. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD003094. http://www.ncbi.nlm.nih.gov/pubmed/21975735

[v] Therapeutic response to iron (Rise in Hb): Pavord S, Daru J, Prasannan N, Robinson S, Stanworth S, Girling J; BSH Committee. UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol. 2020 Mar;188(6):819-830. https://pubmed.ncbi.nlm.nih.gov/31578718/

Therapeutic response to iron (Rise in Hb): Joint Formulary Committee. British National Formulary. 80. London: BMJ Group and Pharmaceutical Press; 2020.

[vi] Diagnostic criteria for gestational diabetes: NICE. Guideline: Diabetes in pregnancy: management from preconception to the postnatal period, 16 December 2020. https://www.nice.org.uk/guidance/ng3

[vii] Stepwise gestational diabetes approach: NICE. Guideline: Diabetes in pregnancy: management from preconception to the postnatal period, 16 December 2020. https://www.nice.org.uk/guidance/ng3

[viii] Thresholds for diagnosing gestational diabetes: Farrar D, Duley L, Dowswell T, Lawlor DA. Different strategies for diagnosing gestational diabetes to improve maternal and infant health. Cochrane Database Syst Rev. 2017 Aug 23;8:CD007122. https://www.ncbi.nlm.nih.gov/pubmed/28832911

Thresholds for diagnosing gestational diabetes: National Collaborating Centre for Women's and Children's Health (UK). Diabetes in Pregnancy: Management of Diabetes and Its Complications from Preconception to the Postnatal Period. London: National Institute for Health and Care Excellence (UK); 2015 Feb. https://www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-from-preconception-to-the-postnatal-period-51038446021

[ix] Insulin dosing in pregnancy: NICE. Guideline: Diabetes in pregnancy: management from preconception to the postnatal period, 16 December 2020. https://www.nice.org.uk/guidance/ng3

[x] Insulin dosing (pregnancy): Nachum Z, Ben-Shlomo I, Weiner E, Shalev E. Twice daily versus four times daily insulin dose regimens for diabetes in pregnancy: randomised controlled trial. BMJ. 1999 Nov 6;319(7219):1223-7. https://www.ncbi.nlm.nih.gov/pubmed/10550081

[xi] Spironolactone, oral (contra-indicated in pregnancy): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xii] Antihypertensive combination therapy: Hypertension guideline working group, Seedat YK, Rayner BL, Veriava Y. South African hypertension practice guideline 2014. Cardiovasc J Afr. 2014 Nov-Dec;25(6):288-94.http://www.ncbi.nlm.nih.gov/pubmed/25629715

[xiii] Calcium channel blocker (amlodipine/ nifedipine): Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2018 Oct 1;10(10):CD002252. https://pubmed.ncbi.nlm.nih.gov/30277556/

Calcium channel blocker (amlodipine/ nifedipine): Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Ananth Karumanchi S et al. The Hypertensive Disorders of Pregnancy: The 2021 International Society for the Study of Hypertesion in Pregnancy Classification, Diagnosis & Management Recommendations for International Practice, Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health (2021). https://doi.org/10.1016/j.preghy.2021.09.008

Calcium channel blocker (amlodipine/ nifedipine): Moodley J, Soma-Pillay P, Buchmann E, Pattinson RC. Hypertensive disorders in pregnancy: 2019 National guideline. S Afr Med J. 2019 Sep 13;109(9):12723. https://pubmed.ncbi.nlm.nih.gov/31635598/

[xiv] Nifedipine (dosing interval): Prevost RR, Akl SA, Whybrew WD, Sibai BM. Oral nifedipine pharmacokinetics in pregnancy-induced hypertension. Pharmacotherapy. 1992;12(3):174-7. http://www.ncbi.nlm.nih.gov/pubmed/1951561

Nifedipine (dosing interval): Committee on Obstetric Practice. Committee Opinion No. 623: Emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period. Obstet Gynecol. 2015 Feb;125(2):521-5. http://www.ncbi.nlm.nih.gov/pubmed/25611642

Nifedipine (dosing interval): Mol BW, Roberts CT, Thangaratinam S, Magee LA, de Groot CJ, Hofmeyr GJ. Pre-eclampsia. Lancet. 2015 Sep 2. pii: S0140-6736(15)00070-7. http://www.ncbi.nlm.nih.gov/pubmed/26342729

[xv] Labetalol, IV infusion: Raheem IA, Saaid R, Omar SZ, Tan PC. Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomised trial. BJOG. 2012 Jan;119(1):78-85. http://www.ncbi.nlm.nih.gov/pubmed/21985500

[xvi] Oxytocin, IM: Department of Health, Republic of South Africa. 2016. Guidelines for Maternity care in South Africa, 4th edition. https://www.knowledgehub.org.za/e-library

[xvii] Aspirin, dose - prevention of preeclampsia: Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev. 2019 Oct 30;2019(10):CD004659. https://pubmed.ncbi.nlm.nih.gov/31684684/

Aspirin, oral - prevention of preeclampsia (safety from 6 weeks' gestation): Hoffman MK, Goudar SS, Kodkany BS, Metgud M, Somannavar M, Okitawutshu J et al; ASPIRIN Study Group. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial. Lancet. 2020 Jan 25;395(10220):285-293. https://www.ncbi.nlm.nih.gov/pubmed/31982074

Aspirin, oral - prevention of preeclampsia (safety from 6 weeks' gestation): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Review: Safety of aspirin in pregnancy, February 2020. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xviii] Calcium: Hofmeyr GJ, Lawrie TA, Atallah ÁN, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. 2018 Oct 1;10(10):CD001059. https://pubmed.ncbi.nlm.nih.gov/30277579/

Calcium: WHO. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia, 2011. http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548335/en/

[xix] Doppler screening: Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Ananth Karumanchi S et al. The Hypertensive Disorders of Pregnancy: The 2021 International Society for the Study of Hypertesion in Pregnancy Classification, Diagnosis & Management Recommendations for International Practice, Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health (2021). https://doi.org/10.1016/j.preghy.2021.09.008

Doppler screening: Alfirevic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev. 2017 Jun 13;6(6):CD007529. https://pubmed.ncbi.nlm.nih.gov/28613398/

Doppler screening: Frusca T, Todros T, Lees C, Bilardo CM; TRUFFLE Investigators. Outcome in early-onset fetal growth restriction is best combining computerized fetal heart rate analysis with ductus venosus Doppler: insights from the Trial of Umbilical and Fetal Flow in Europe. Am J Obstet Gynecol. 2018 Feb;218(2S):S783-S789. https://pubmed.ncbi.nlm.nih.gov/29422211/

[xx] Risk of preterm birth (COVID-19): Chinn J, Sedighim S, Kirby KA, Hohmann S, Hameed AB, Jolley J, Nguyen NT. Characteristics and Outcomes of Women With COVID-19 Giving Birth at US Academic Centers During the COVID-19 Pandemic. JAMA Netw Open. 2021 Aug 2;4(8):e2120456. https://pubmed.ncbi.nlm.nih.gov/34379123/

[xxi] Risk of hospitalisation (Obese COVID-19 pregnant women): Chinn J, Sedighim S, Kirby KA, Hohmann S, Hameed AB, Jolley J, Nguyen NT. Characteristics and Outcomes of Women With COVID-19 Giving Birth at US Academic Centers During the COVID-19 Pandemic. JAMA Netw Open. 2021 Aug 2;4(8):e2120456. https://pubmed.ncbi.nlm.nih.gov/34379123/

[xxii] Corticosteroid therapy (pregnancy): National Department of Health: Affordable Medicines, EDP-NEMLC COVID-19. Rapid review: Corticosteroids for COVID-19: evidence review of the clinical benefit and harm, 24 October 2020. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Corticosteroid therapy (pregnancy): WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020 Sep 2;324(13):1–13. https://pubmed.ncbi.nlm.nih.gov/32876694/

[xxiii] Dolutegravir (WOCP & pregnancy): National Department of Health: Affordable Medicines, EDP-PHC/Adult Hospital level. Medicine Review: Dolutegravir in pregnancy, June, 2021. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xxiv] ART regimens (pregnancy): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

ART in pregnancy: National Department of Health: National Consolidated Guidelines for the Management of HIV in Adults, Adolescents, Children and Infants and Prevention of Mother-to-Child Transmission, June 2020. https://www.knowledgehub.org.za/elibrary/national-consolidated-guidelines-management-hiv-adults-adolescents-children-and-infants

[xxv] Benzathine benzylpenicillin (late latent syphilis/of unknown duration): Workowski KA, Bolan GA. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015 [published correction appears in MMWR Recomm Rep. 2015 Aug 28;64(33):924] MMWR Recomm Rep. 2015;64(RR-03):1-137. https://pubmed.ncbi.nlm.nih.gov/26042815/

Benzathine benzylpenicillin (late latent syphilis/of unknown duration): World Health Organization: WHO Guidelines for the treatment of Treponema palladum (syphilis), 2016. https://www.who.int/reproductivehealth/publications/rtis/syphilis-treatment-guidelines/en/

[xxvi] Tenofovir (Pregnant women: HBsAG/ HBeAG positive & HIV negative): National Department of Health: Affordable Medicines, EDP- PHC and Adult Hospital level. Medicine Review: Use of antivirals in the third trimester of pregnancy, in HIV Negative women with chronic active Hepatitis B infection who are HBeAG positive, to prevent vertical transmission of Hepatitis B, May 2024. http://www.health.gov.za/.

[xxvii] Promethazine, oral/parenteral (first-line therapy for hyperemesis gravidarum): The Royal College of Obstetricians and Gynaecologists. The Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum (Green-top Guideline No. 69), 22 June 2016. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg69/

[xxviii] Metoclopramide, oral/parenteral (second-line therapy for hyperemesis gravidarum): The Royal College of Obstetricians and Gynaecologists. The Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum (Green-top Guideline No. 69), 22 June 2016. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg69/

[xxix] Ondansetron, parenteral (in pregnancy): Kaplan YC, Richardson JL, Keskin-Arslan E, Erol-Coskun H, Kennedy D. Use of ondansetron during pregnancy and the risk of major congenital malformations: A systematic review and meta-analysis. Reprod Toxicol. 2019;86:1-13. https://pubmed.ncbi.nlm.nih.gov/30849498/

Ondansetron, parenteral (in pregnancy): Huybrechts KF, Hernández-Díaz S, Straub L, et al. Association of Maternal First-Trimester Ondansetron Use With Cardiac Malformations and Oral Clefts in Offspring. JAMA. 2018;320(23):2429-2437. https://pubmed.ncbi.nlm.nih.gov/30561479/

Ondansetron, parenteral (in pregnancy): Huybrechts KF, Hernandez-Diaz S, Straub L, et al. Intravenous Ondansetron in Pregnancy and Risk of Congenital Malformations [published online ahead of print, 2019 Nov 15]. JAMA. 2019;323(4):372-374. https://pubmed.ncbi.nlm.nih.gov/31730152/

[xxx] Indomethacin: Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ. Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. BMJ. 2012 Oct 9;345:e6226. https://pubmed.ncbi.nlm.nih.gov/23048010/

[xxxi] Betamethasone, IM: McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2020 Dec 25;12(12):CD004454. https://pubmed.ncbi.nlm.nih.gov/33368142/

Betamethasone, IM: FIGO Working Group on Good Clinical Practice in Maternal-Fetal Medicine. Good clinical practice advice: Antenatal corticosteroids for fetal lung maturation. Int J Gynaecol Obstet. 2019 Mar;144(3):352-355. https://pubmed.ncbi.nlm.nih.gov/30710360/

[xxxii] Dexamethasone, IM: McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2020 Dec 25;12(12):CD004454. https://pubmed.ncbi.nlm.nih.gov/33368142/

Dexamethasone, IM: FIGO Working Group on Good Clinical Practice in Maternal-Fetal Medicine. Good clinical practice advice: Antenatal corticosteroids for fetal lung maturation. Int J Gynaecol Obstet. 2019 Mar;144(3):352-355. https://pubmed.ncbi.nlm.nih.gov/30710360/

[xxxiii] Antibiotic therapy (PROM): Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev. 2013 Dec 2;(12):CD001058. https://pubmed.ncbi.nlm.nih.gov/24297389/

Antibiotic therapy (PROM): Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010 Nov 19;59(RR-10):1-36. https://pubmed.ncbi.nlm.nih.gov/21088663/

Antibiotic therapy (PROM): ACOG. Prelabor Rupture of Membranes: ACOG Practice Bulletin, Number 217. Obstet Gynecol. 2020 Mar;135(3):e80-e97. https://pubmed.ncbi.nlm.nih.gov/32080050/

Antibiotic therapy (PROM): Navathe R, Schoen CN, Heidari P, Bachilova S, Ward A, Tepper J et al. Azithromycin vs erythromycin for the management of preterm premature rupture of membranes. Am J Obstet Gynecol. 2019 Aug;221(2):144.e1-144.e8. https://pubmed.ncbi.nlm.nih.gov/30904320/

[xxxiv] Penicillin allergic - antibiotic therapy (PROM): Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev. 2013 Dec 2;(12):CD001058. https://pubmed.ncbi.nlm.nih.gov/24297389/

Penicillin allergic - antibiotic therapy (PROM): Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010 Nov 19;59(RR-10):1-36. https://pubmed.ncbi.nlm.nih.gov/21088663/

Penicillin allergic - antibiotic therapy (PROM): ACOG. Prelabor Rupture of Membranes: ACOG Practice Bulletin, Number 217. Obstet Gynecol. 2020 Mar;135(3):e80-e97. https://pubmed.ncbi.nlm.nih.gov/32080050/

Penicillin allergic - antibiotic therapy (PROM): Navathe R, Schoen CN, Heidari P, Bachilova S, Ward A, Tepper J et al. Azithromycin vs erythromycin for the management of preterm premature rupture of membranes. Am J Obstet Gynecol. 2019 Aug;221(2):144.e1-144.e8. https://pubmed.ncbi.nlm.nih.gov/30904320/

[xxxv] Prevention of preterm labour: Alfirevic Z, Stampalija T, Medley N. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. Cochrane Database Syst Rev. 2017 Jun 6;6:CD008991. https://www.ncbi.nlm.nih.gov/pubmed/28586127

Prevention of preterm labour: Jarde A, Lutsiv O, Beyene J, McDonald SD. Vaginal progesterone, oral

progesterone, 17-OHPC, cerclage, and pessary for preventing preterm birth in at-risk singleton pregnancies: an updated systematic review and network meta-analysis. BJOG 2019; 126: 556–567. https://www.ncbi.nlm.nih.gov/pubmed/30480871

Prevention of preterm labour: NICE Guidelines: Preterm Labour and Birth, August 2019 https://www.nice.org.uk/guidance/ng25

[xxxvi] Progesterone, PV: Jarde A, Lutsiv O, Beyene J, McDonald SD. Vaginal progesterone, oral progesterone, 17-OHPC, cerclage, and pessary for preventing preterm birth in at-risk singleton pregnancies: an updated systematic review and network meta-analysis. BJOG 2019; 126: 556–567. https://www.ncbi.nlm.nih.gov/pubmed/30480871

Progesterone, PV: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Progesterone, vaginal for prevention of preterm labour, October 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Progesterone, PV: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Progesterone, vaginal for prevention of preterm labour In Twin Pregnancies, February 2026. https://www.health.gov.za/nhi-edp-stgs-eml/

[xxxvii] Cerclage: Alfirevic Z, Stampalija T, Medley N. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. Cochrane Database Syst Rev. 2017 Jun 6;6:CD008991. https://www.ncbi.nlm.nih.gov/pubmed/28586127

Cerclage: NICE Guidelines: Preterm Labour and Birth, August 2019 https://www.nice.org.uk/guidance/ng25

[xxxviii] Salbutamol, IV: Neilson JP, West HM, Dowswell T. Betamimetics for inhibiting preterm labour. Cochrane Database Syst Rev. 2014 Feb 5;2:CD004352. http://www.ncbi.nlm.nih.gov/pubmed/24500892

Salbutamol, IV: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxxix] Extra-amniotic Foley catheter: PLUS prostaglandin protocol: Al-Ibraheemi Z, Brustman L, Bimson BE, Porat N, Rosenn B. Misoprostol With Foley Bulb Compared With Misoprostol Alone for Cervical Ripening: A Randomized Controlled Trial. Obstet Gynecol. 2018 Jan;131(1):23-29. https://www.ncbi.nlm.nih.gov/pubmed/29215514

Extra-amniotic Foley catheter: PLUS prostaglandin protocol: Osoti A, Kibii DK, Tong TMK, Maranga I. Effect of extra-amniotic Foley's catheter and vaginal misoprostol versus vaginal misoprostol alone on cervical ripening and induction of labor in Kenya, a randomized controlled trial. BMC Pregnancy Childbirth. 2018 Jul 12;18(1):300. https://www.ncbi.nlm.nih.gov/pubmed/30001195

Extra-amniotic Foley catheter: PLUS prostaglandin protocol: World Health Organisation. WHO recommendations for induction of labour, Clinical Practice Guideline, 2011. https://pubmed.ncbi.nlm.nih.gov/23586118/

[xl] Dinoprostone: West HM, Jozwiak M, Dodd JM. Methods of term labour induction for women with a previous caesarean Section. Cochrane Database Syst Rev. 2017 Jun 9;6(6):CD009792. https://pubmed.ncbi.nlm.nih.gov/28599068/

Dinoprostone: Andrikopoulou M, Lavery JA, Ananth CV, Vintzileos AM. Cervical ripening agents in the second trimester of pregnancy in women with a scarred uterus: a systematic review and metaanalysis of observational studies. Am J Obstet Gynecol. 2016 Aug;215(2):177-94. https://pubmed.ncbi.nlm.nih.gov/27018469/

Dinoprostone: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xli] Dinoprostone (contraindication): NICE. Guideline: Inducing labour, 4 November 2021. https://www.nice.org.uk/guidance/NG207

Dinoprostone (contraindication): Pfizer: Prandin E2 vaginal gel package insert.

[xlii] Oxytocin, IV (Cervix favourable (Bishop score ≥7): NICE Clinical Guideline: 70 - Induction of labour, 2008. https://www.nice.org.uk/guidance/cg70/evidence/cg70-induction-of-labour-full-guideline2

[xliii] Amniotomy in HIV-infected pregnant women: Peters H, Byrne L, De Ruiter A, Francis K, Harding K, Taylor GP, Tookey PA, Townsend CL. Duration of ruptured membranes and mother-to-child HIV transmission: a prospective population-based surveillance study. BJOG. 2016 May;123(6):975-81. https://www.ncbi.nlm.nih.gov/pubmed/26011825

[xliv] Morphine, IM: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xlv] Morphine, IM: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xlvi] Tranexamic acid, IV: WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet 2017; 6736(17)30638-4. https://www.ncbi.nlm.nih.gov/pubmed/28456509

Tranexamic acid, IV: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Tranexamic acid, IV, for management of post partum haemmhorhage in pregnant women, 11 October 2017. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xlvii] Misoprostol: Essential Steps in Managing Obstetric Emergencies (ESMOE), facilitator's guide. Misoprostol: Hofmeyr GJ, Gülmezoglu AM, Novikova N, Lindow SW, Pereira S, Piaggio G. Misoprostol to prevent

and treat postpartum haemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects. Bull World Health Organ. 2009 Sep;87(9):666-77. http://www.ncbi.nlm.nih.gov/pubmed/19784446

Misoprostol: Department of Health, Republic of South Africa. 2016. Guidelines for Maternity care in South Africa, 4th edition. https://www.knowledgehub.org.za/e-library

Misoprostol: International Federation Of Gynecology And Obstetrics. Treatment of postpartum hemorrhage with misoprostol. Int J Gynaecol Obstet. 2012 Dec;119(3):215-6. http://www.ncbi.nlm.nih.gov/pubmed/23036964

xlviii Anti-D Immunoglobulin, iM (20 weeks): NICE Clinical Guideline: 156 - Routine antenatal anti-D prophylaxis for women who are rhesus D negative, 2008. https://www.nice.org.uk/guidance/ta156/resources/routine-antenatal-antid-prophylaxis-for-women-who-are-rhesus-d-negative-pdf-82598318102725

xlix Dipsticks (positive nitrites or leukocytes): Mambatta AK, Jayarajan J, Rashme VL, Harini S, Menon S, Kuppusamy J. Reliability of dipstick assay in predicting urinary tract infection. J Family Med Prim Care. 2015 Apr-Jun;4(2):265-8. https://www.ncbi.nlm.nih.gov/pubmed/25949979

Dipsticks (positive nitrites or leukocytes): Demilie T, Beyene G, Melaku S, Tsegaye W. Diagnostic accuracy of rapid urine dipstick test to predict urinary tract infection among pregnant women in Felege Hiwot Referral Hospital, Bahir Dar, North West Ethiopia. BMC Res Notes. 2014 Jul 29;7:481. https://www.ncbi.nlm.nih.gov/pubmed/25073620

l Fosfomycin, oral: Falagas ME, Vouloumanou EK, Togias AG, Karadima M, Kapaskelis AM, Rafailidis PI, Athanasiou S. Fosfomycin versus other antibiotics for the treatment of cystitis: a meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2010 Sep;65(9):1862-77. http://www.ncbi.nlm.nih.gov/pubmed/20587612

Fosfomycin, oral: Lewis DA, Gumede LY, van der Hoven LA, de Gita GN, de Kock EJ, de Lange T, Maseko V, Kekana V, Smuts FP, Perovic O. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. S Afr Med J. 2013 Mar 15;103(6):377-81. http://www.ncbi.nlm.nih.gov/pubmed/23725955

li Nitrofurantoin: Zalmanovici Trestioreanu A, Green H, Paul M, Yaphe J, Leibovici L. Antimicrobial agents for treating uncomplicated urinary tract infection in women. Cochrane Database Syst Rev. 2010 Oct 6;(10):CD007182. https://www.ncbi.nlm.nih.gov/pubmed/20927755

Nitrofurantoin: Lewis DA, Gumede LY, van der Hoven LA, de Gita GN, de Kock EJ, de Lange T, Maseko V, Kekana V, Smuts FP, Perovic O. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. S Afr Med J. 2013 Mar 15;103(6):377-81.http://www.ncbi.nlm.nih.gov/pubmed/23725955

Nitrofurantoin: Nordeng H, Lupattelli A, Romøren M, Koren G. Neonatal outcomes after gestational exposure to nitrofurantoin. Obstet Gynecol. 2013 Feb;121(2 Pt 1):306-13. http://www.ncbi.nlm.nih.gov/pubmed/23344280

SOUTH AFRICAN NATIONAL DEPARTMENT OF HEALTH
NEMLC SUMMARY REPORT ON UPDATES MADE TO THE THE STANDARD TREATMENT GUIDELINES AND ESSENTIAL MEDICINE LIST GUIDANCE PRODUCTS
BROAD REPRODUCTIVE
ADULT HOSPITAL LEVEL
CHAPTER 6 OBSTETRICS

Document Version

Report Version	**Date**	**Detail**
V1.0	*26 February 2026*	Labour pain, severe – pethidine not added to the therapeutic interchange database
V 2.0	*26 March 2026*	Prevention of Preterm Labour – addition of progesterone per vagina for twin pregnancies The Rhesus Negative Woman – instructions on Anti-D Immunoglobulin amended

Specific guidance products (Tick relevant and specify chapter number)

No	Guidance Product	*Tick*	*Number*
1.	Primary Health Care Level STGs	✓	6.2 Miscarriage
2.	Adult Hospital Level STGs	✓	6.14 Labour Pain, Severe 6.11.2 Prevention of Preterm Labour 6.18 The Rhesus Negative Woman
3.	Paediatric Hospital Level STGs		
4.	Tertiary and Quaternary EML		

Refer to PHC NEMLC Report for rationale and changes to the PHC Level

Summary Tables

Medicine Amendments

Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG).

STG/SECTION	**GUIDANCE PRODUCTS (Tick relevant)**				**MEDICINE / MANAGEMENT**	**ADDED / DELETED / AMENDED**	**TI* CONSIDERATIONS (if applicable)**
	PHC STGs & EML	AH STG & EML	PaedH STG & EML	TQ EML			
Report Version v1.0							
6.11.2 PREVENTION OF PRETERM LABOUR		X			Progesterone, PV	Added for twin pregnancies	Not applicable
6.14 LABOUR PAIN,		X			Pethidine, IM	Not added	Not added

SEVERE							
		X			Propofol, IM	Retained	Pethidine IM not added
6.18 THE RHESUS NEGATIVE WOMAN	X	X			Anti-D Immunoglobulin	Retained – Instructions amended	Not applicable

The report provides an update on the following:

1. Addition of progesterone per vagina for prevention of preterm labour for twin pregnancies
2. Consideration of Pethidine IM to the Therapeutic interchange database as an alternative to Morphine IM for the obstetric indication of labour pain, severe.
3. The Rhesus Negative Woman – revision of Anti D immunoglobulin administration

Report V1.0

6.14 LABOUR PAIN, SEVERE

Pethidine, IM: Not added to the therapeutic interchange database
Morphine, IM: Retained

Historically, pethidine IM was listed as an essential medicine for labour pain, severe, but safety issues, especially in doses >50mg, was a reason it was replaced by morphine in the STGs. In the 2016-2018 review cycle NEMLC recommended morphine replace pethidine on the STGs and EML for the indication of labour pain, severe as morphine IM was safer for mother and baby.

NEMLC REPORT OF PHC OBSTETRICS AND GYNAECOLOGY CHAPTER, 2016-2018 REVIEW:
Analgesia:
Recommendation: Morphine, IM replaces pethidine, IM as analgesia during first stage of labour with cervical dilatation < 10 cm.
Rationale: Regulation 31 replaces regulation 47 of the Medicines and related substances Act 101 of 1965 i.e. access to pethidine is replaced by access to schedule 5 and 6 medicines in order to provide intrapartum care. In addition, there are safety concerns regarding pethidine's active metabolite, normeperidine that is potentially neurotoxic.
Level of Evidence: Regulations[1], Guidelines[2]

However, a query arose in the contracting process if pethidine should be added to the therapeutic interchange (TI) database for labour pain, severe during intrapartum care for example in the case of stock shortages or morphine allergy, noting that there is currently high usage of pethidine, but indication unclear. Although morphine allergy is rare, pethidine can also cause adverse reactions and will not be a completely safe alternative, given at midwife level.

[1] Regulation 31 of the Medicines and related substances Act 101 of 1965.

[2] SAMF, 2022.

According to the TI policy[3] a medicine can only appear on the TI database if it is a therapeutic alternative to the less expensive option on tender for a specific indication (i.e. for the indication in question the word example would appear in the Standard Treatment Guidelines (STGs)). As previously deliberated by NEMLC, morphine is preferred to pethidine for the broad reproductive indication of labour pain, severe as it is safer for mother and child i.e. no class indication applied here. Therefore, pethidine is not an explicit therapeutic alternative to morphine and cannot appear on the TI database as the therapeutic alternative to morphine for the indication of labour pain, severe as morphine is the preferred agent for this indication. In the case of severe stock challenges of morphine IM the issue will be revisited to discuss approaches to handle the stock challenges and direction will be provided by the National Department of Health.

Report V2.0

6.11.2 PREVENTION OF PRETERM LABOUR

Progesterone, PV: Added

Vaginal progesterone was an essential medicine at Adult Hospital Level in South Africa in singleton pregnancies in: (1) mid- trimester cervical shortening (defined as ≤25 mm before 24 weeks gestation) with no prior spontaneous singleton preterm birth, and/or (2) women with a history of spontaneous preterm birth or mid-trimester loss.[4]

In March 2026 NEMLC strongly recommended the use of vaginal progesterone in twin pregnancies given that a review of the literature[5] showed that when vaginal progesterone is compared to placebo in twin pregnancies in women with short cervixes, vaginal progesterone likely reduces preterm births < 34 week and that there may be little to no difference in stillbirth or neonatal death.[6]

The STG was updated as follows:

From

6.11.2 PREVENTION OF PRETERM LABOUR (SINGLETON PREGNANCIES ONLY)

Z35.2

DESCRIPTION

Women with a previous spontaneous preterm delivery are at higher risk for preterm delivery in the next pregnancy. In certain high-risk cases, pregnancy may be prolonged by the careful consideration of either cervical cerclage or vaginal progesterone therapy.

The following high-risk women should undergo cervical screening and offered a choice of cerclage or progesterone:

A history of 2nd trimester miscarriage (between 16 and 26 weeks) suggestive of cervical incompetence: (Painless dilatation with a quick labour, and birth of a live baby or fresh stillbirth) after excluding other causes of mid-trimester losses, e.g. intra-uterine death that required induction, abruptio placentae, fetal abnormalities, polyhydramnios, and medical terminations.

[3] National Department of Health. 2026. Therapeutic Interchange Policy.

[4] National Department of Health. Adult Hospital Level Medication Review Process Component: Obstetrics. Review of the use of progesterone for prevention of preterm birth in a select "at risk" population

[5] National Department of Health. Adult Hospital Level Medication Review Process Component: Obstetrics. Review of the use of progesterone for prevention of preterm birth in a select "at risk" population

» Previous history of spontaneous preterm birth between 27 and 34 weeks (exclude non-spontaneous causes e.g. iatrogenic delivery for pre-eclampsia, or syphilis). No need to refer previous late preterm deliveries (34-37 weeks).

Do not screen in low-risk women routinely, as it is not cost-effective.

GENERAL MEASURES

Cervical length must be measured by a skilled operator using transvaginal ultrasound.
Cervical measurement can be done between 16 and 24 weeks.
A cervical length of ≤25 mm indicates a higher risk for recurrent preterm labour.
Discuss the risks and benefits of both options with the patient to make an informed shared decision of the most appropriate treatment.

MEDICINE TREATMENT

Women should be counselled that 20 cerclage procedures will prevent one preterm delivery (NNT 17 to 20) and that progesterone is successful in 1 out of
every 8 cases (NNT 6 to 8), to assist them in making an informed decision.

Consider prophylactic vaginal progesterone ***or*** cervical cerclage (MacDonald suture) for women with:
» history of spontaneous preterm birth (27-34 weeks) or mid-trimester loss (16-24 weeks), ***and***
» cervical length ≤ 25 mm confirmed on ultrasound (16-24 weeks).

- Progesterone, PV, 200 mg daily.
  - Stop treatment at 34 weeks and refer to antenatal services at primary level of care for further management.

(Note: Vaginal progesterone may be considered for high-risk women with a normal cervix length on ultrasound.)

Consider prophylactic cervical cerclage (MacDonald suture) ***only*** for women with:
» cervical length ≤ 25 mm confirmed on ultrasound (16-24 weeks),
AND
» history of preterm prelabour rupture of membranes (PPROM), ***or***
» history of cervical trauma.

Rescue cerclage:
» If the cervix is already open and the membranes exposed, but unruptured, consider a rescue cervical cerclage (16-27 weeks).
» Do not insert a rescue cerclage if there are contractions, active vaginal bleeding or signs of infection.

Cerclage should be removed at 36 weeks, and thereafter the patient can
be referred to antenatal services at primary level of care.

REFERRAL

Women with recurrent losses and previous cerclage that tore out (severe cervical trauma), as they may require an abdominal cerclage.

To

6.11.2 PREVENTION OF PRETERM LABOUR

Z35.2

DESCRIPTION

Women with a previous spontaneous preterm delivery are at higher risk for preterm delivery in the next pregnancy. In certain high-risk cases, pregnancy may be prolonged by the careful consideration of either cervical cerclage or vaginal progesterone therapy.

The following high-risk women should undergo cervical screening and offered a choice of cerclage or progesterone if the cervical length is **≤25 mm**:
» A history of 2nd trimester miscarriage (between 16 and 26 weeks) suggestive of cervical incompetence: (Painless dilatation with a quick labour, and birth of a live baby or fresh stillbirth) after excluding other causes of mid-trimester losses, e.g. intra-uterine death that required induction, abruptio placentae, fetal abnormalities, polyhydramnios, and medical terminations.
» Previous history of spontaneous preterm birth between 27 and 34 weeks (exclude non-spontaneous causes e.g. iatrogenic delivery for pre-eclampsia, or syphilis). No need to refer previous late preterm deliveries (34-37 weeks).
» Twin gestations (dichorionic or monochorionic), regardless of the previous history, as twin pregnancies are at increased risk (7-10 fold) of preterm labour

Do not screen for cervical length in low-risk women routinely, as it is not cost-effective.

GENERAL MEASURES
Cervical length must be measured by a skilled operator using transvaginal ultrasound.
Cervical measurement can be done between 16 and 24 weeks.
A cervical length of ≤25 mm indicates a higher risk for recurrent preterm labour.
Discuss the risks and benefits of both options with the patient to make an informed shared decision of the most appropriate treatment.

MEDICINE TREATMENT
Women should be counselled that 20 cerclage procedures will prevent one preterm delivery (NNT 17 to 20) and that progesterone is successful in 1 out of
every 8 cases (NNT 6 to 8), to assist them in making an informed decision.

Consider prophylactic vaginal progesterone ***or*** cervical cerclage (MacDonald suture) for women with:
» history of spontaneous preterm birth (27-34 weeks) or mid-trimester loss (16-24 weeks), ***and***
» cervical length ≤ 25 mm confirmed on ultrasound (16-24 weeks).

- Progesterone, PV, 200 mg daily.
  - Stop treatment at 34 weeks and refer to antenatal services at primary level of care for further management.

Consider prophylactic cervical cerclage (MacDonald suture) ***only*** for women with:
» cervical length ≤ 25 mm confirmed on ultrasound (16-24 weeks),
AND
» history of preterm prelabour rupture of membranes (PPROM), ***or***
» history of cervical trauma.

Rescue cerclage:
» If the cervix is already open and the membranes exposed, but unruptured, consider a rescue cervical cerclage (16-27 weeks).
» Do not insert a rescue cerclage if there are contractions, active vaginal bleeding or signs of infection.

Cerclage should be removed at 36 weeks, and thereafter the patient can
be referred to antenatal services at primary level of care.

REFERRAL
Women with recurrent losses and previous cerclage that tore out (severe cervical trauma), as they may require an abdominal cerclage.

6.18 THE RHESUS NEGATIVE WOMAN

Anti-D Immunoglobulin: Retained (Instructions amended)

An external comment was received from a Provincial Pharmaceutical Therapeutics Committee member through provincial pharmaceutical services raising that there is a contradiction/vagueness between the Primary level and AHL essential medicines list (EML), regarding Anti-D immunoglobulin, administration, for miscarriage or termination of pregnancy. The AHL Hospital level EML only recommends anti-D for the 2nd trimester while the PHC EML recommends Anti-D immunoglobulin if a surgical procedure is done, which presumably would include 1st trimester cases. This discussion at provincial level emanated because of the stock supply constraints of Anti-D immunoglobulin by the supplier. A circular is in place from NDOH (2021) advising on the restricted use as there is no alternative.

In pregnancies of up to 9 weeks gestation, the theoretical risk of maternal Rh sensitization associated with termination of pregnancy (TOP), or miscarriage is very low. Consequently, determining Rh status and offering anti-D prophylaxis are not regarded as essential prerequisites for early TOP or early pregnancy loss. This is in alignment with the South African TOP guideline[7]. Between 9 and 12 weeks, the risk remains sufficiently low that

[7] National Department of Health. 219. National Clinical Guideline for Implementation of the Choice on Termination of Pregnancy Act.

professional societies advise against routine administration of Anti-D immunoglobulin, considering both the low likelihood of sensitisation and the logistical challenges related to limited Anti-D immunoglobulin supply. Therefore, as anti-D immunoglobulin administration in the first trimester is not harmful, no specific cautionary statements are required.

The Standard Treatment Guideline was Updated as Follows:

From:

6.18 THE RHESUS NEGATIVE WOMAN

O36.0 + (Z29.1)

GENERAL MEASURES

Maternal serum antibodies absent

Prevention

Test for maternal serum antibodies at 'booking', 28- and 34-weeks' gestation.
During pregnancy, give prophylactic anti-D immunoglobulin to the mother within 72 hours of a potentially sensitising event.

MEDICINE TREATMENT

<u>After a termination of pregnancy (TOP), miscarriage, ectopic pregnancy or amniocentesis <20 weeks:</u>

- Anti-D immunoglobulin, IM, 50 mcg.

<u>After external cephalic version or potentially sensitizing event ≥20 weeks:</u>

- Anti-D immunoglobulin, IM, 100 mcg.

<u>At birth, determine the Rh status of the cord blood and request a Coomb's test:</u>
Cord blood Rh negative - no treatment.
Cord blood Rh positive, Coomb's negative:

- Anti-D immunoglobulin, IM, 100 mcg.

<u>If a large feto-maternal haemorrhage is suspected:</u>

- Anti-D immunoglobulin, IM, 300 mcg for every 30 mL haemorrhage.
  - Maximum dose: 1 200 mcg.

AND

Do a maternal blood Kleihauer test (consult a specialist).

<u>Rh positive, Coomb's positive:</u>
In these cases, the mother will also have antibodies.
Do not administer anti-D immunoglobulin.

Maternal serum antibodies present.
Consult a specialist.

To

6.18 THE RHESUS NEGATIVE WOMAN

O36.0 + (Z29.1)

GENERAL MEASURES

Maternal serum antibodies absent

Prevention

Test for maternal serum antibodies at 'booking', 28- and 34-weeks' gestation.
During pregnancy, give prophylactic anti-D immunoglobulin to the mother within 72 hours of a potentially sensitising event.

MEDICINE TREATMENT

After a termination of pregnancy (TOP), miscarriage, ectopic pregnancy or amniocentesis 13-22 weeks:

- Anti-D immunoglobulin, IM, 50 mcg.

After external cephalic version or potentially sensitizing event ≥22 weeks:

- Anti-D immunoglobulin, IM, 100 mcg.

At birth, determine the Rh status of the cord blood and request a Coomb's test:
Cord blood Rh negative - no treatment.
Cord blood Rh positive, Coomb's negative:

- Anti-D immunoglobulin, IM, 100 mcg.

If a large feto-maternal haemorrhage is suspected:

- Anti-D immunoglobulin, IM, 300 mcg for every 30 mL haemorrhage.
  - Maximum dose: 1 200 mcg.

AND

Do a maternal blood Kleihauer test (consult a specialist).

Rh positive, Coomb's positive:
In these cases, the mother will also have antibodies.
Do not administer anti-D immunoglobulin.

Maternal serum antibodies present.
Consult a specialist.

In parallel, at the primary care level, access to ultrasound may be limited, making precise gestational dating difficult. In the interest of equity and operational simplicity, it was advisable to remove the first-trimester Rh section from the primary care guideline and adopt the same approach outlined in the Adult STG and the NDoH circular[8], which is based on the current constraints in Anti-D immunoglobulin availability.

[8] National Department of Health. 2021. Recommendations for restricted use of Anti-D immunoglobulin.

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

South African National Department of Health, National Essential Medicines List Committee

Progesterone, per vagina, for prevention of preterm labour In Twin Pregnancies[1]

DATE: 2 December 2025

Medicine Class	Progesterones (Progestins)	*If applicable* *Please consider therapeutic interchange policy*
Medicine/s name **-INN:** **- South African name (if differs from INN)**	Progesterone	*http://www.whocc.no/atc_ddd_index/*
Medicine/s (ATC5):	G03DA	*http://www.whocc.no/atc_ddd_index/*
Indication (ICD-10 code):	Z35.2	*https://www.health.gov.za/icd-10-master-industry-table/*
SAHPRA Approved	Yes	SAHPRA registered health products database *https://medapps.sahpra.org.za:6006/*
Dosage form/s	Pessary, vaginal tablet	
Route of administration/s	Vaginal	
Patient population	Pregnant woman with twin gestations, including both dichorionic and monochorionic twins, between16–26 weeks with a short cervix (≤ 25 mm) on ultrasound	

[1] The review template is a tool utilised to systematically synthesise evidence and aid decision-making by the National Essential Medicines Committee (NEMLC) on amendments to the Standard Treatment Guidelines and Essential Medicines List. The template was revised through collaboration between the South African Medical Research Council, University of Stellenbosch, NEMLC, the Essential Drugs Programme (EDP) and SA GRADE Network and approved for piloting by the NEMLC in February 2025. The template is to be reviewed annually, utilised along with the relevant NEMLC approved policies, guidelines, methodology and processes and naming of review documents must adhere to the naming conventions set by the EDP. Current version updated post tabling at NEMLC meeting held 16th October 2025.

Prevalence and/or incidence of condition	The rate of early preterm birth reported in twin pregnancies is approximately 10 %, compared to 1–2 % in singleton pregnancies.[1]	
Level of Care	Adult Hospital Level	
Prescriber level	Doctor prescribed	

EXECUTIVE SUMMARY

- We conducted a rapid review of available evidence that assessed the effect of vaginal progesterone compared to standard of care or placebo in pregnant woman with twin gestations, including both dichorionic and monochorionic twins, between16–26 weeks with a short cervix (≤ 25 mm) on ultrasound (restrictions: none).
- We searched the Guidelines International Network (GIN) library, the National Institute for Health and Care Excellence (NICE) website, the American College of Obstetrics and Gynaecology (ACOG), the Society for Maternal Fetal Medicine (SMFM), and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) for relevant guidelines [November 2025]. We identified five clinical practice guidelines and included two of these, and also included the evidence synthesis which informed the NICE NG137 guideline[2].
- Two clinical practice guidelines were included: (1) ACOG a practice bulletin for obstetrician-gynaecologists in the United States[3,4] published in 2021 as an update to 2012 guidance. The guideline addresses the prediction and prevention of spontaneous preterm birth in both single and multiple pregnancies. (2) The NICE guideline was published in 2024. The NICE guideline focuses on management guidance for twin and triplet pregnancies[5].
- A duplicate AGREE assessment rated the NICE guideline[5] as high quality, and the AMSTAR II of the underlying effectiveness review was moderate quality. The effectiveness results are summarised below.
- Summary of effectiveness results[5] for vaginal progesterone vs placebo. All comparisons were made to placebo only.
    - **Reduction in preterm birth < 34 weeks:** When vaginal progesterone (100 to 600mg per day) is compared to placebo in twin pregnancies in women with short cervixes, vaginal progesterone likely reduces preterm births < 34 weeks (moderate certainty)
        - Spontaneous preterm births < 34 weeks: RR 0.58 (95% Confidence interval (CI) 0.38 to 0.89), 273 fewer per 1000 (from 404 fewer to 72 fewer per 1000), NNT 4. (moderate certainty evidence)
        - Preterm birth <32 weeks: RR 0.56 (95% CI 0.33 to 0.93), 205 fewer per 1000 (from 312 fewer to 33 fewer), NNT 7. (moderate certainty evidence)
    - **NICU stay/prolonged hospital stay:**
        - Not reported
    - **Neonatal mortality:** When vaginal progesterone (100 to 600mg per day) is compared to placebo in twin pregnancies in women with short cervixes, there may be little to no difference in neonatal deaths or stillbirths (low certainty).
        - Neonatal deaths: RR 0.51 (95% CI 0.2 to 1.28), 51 fewer per 1000 (from 84 fewer to 29 more), NNT 16. (Low certainty evidence)
        - Stillbirths: RR 0.54 (95% CI 0.17 to 1.77), 21 fewer per 1000 (from 39 fewer to 36 more), NNT -90. (Low certainty evidence)
    - **Safety: serious adverse events and adverse events:**
        - Not reported
- Vaginal progesterone is currently an essential medicine at Adult Hospital Level in South Africa in singleton pregnancies in: (1) mid- trimester cervical shortening (defined as ≤25 mm before 24 weeks gestation) with no prior spontaneous singleton preterm birth, and/or (2) women with a history of spontaneous preterm birth or mid-trimester loss.[6]

KEY RECOMMENDATIONS

Type of ERC recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
	☐	☐	☐	X

High level summary of conclusions from Evidence to Decision Framework – See link	The review of the literature shows that when vaginal progesterone is compared to placebo in twin pregnancies in women with short cervixes, vaginal progesterone likely reduces preterm births < 34 weeks. There may be little to no difference in stillbirth or neonatal death.					
NEMLC Ratification	**Date**	**Comments**				
	26/02/26					
EML Status	EML[2]	Non-EML – contingent on stated reference price threshold in Rand Value classified as **NEML-PT (Non EML Price Threshold)**		Non-EML		
	X	☐		☐		
Therapeutic Interchange Considerations (if applicable)	If YES:	Alternative medicine/s name (INN)	Alternative/s SAHPRA registered?	Formulation/s	Equipotent dose/ Dose range and dosing interval	If NO, tick box
						X
Trigger for review	Alternative therapeutic agent at a lower price. Update based on new trial results.					

REVIEW TEAM

Review contributors as detailed below:

[2] An item designated as 'EML' indicates that item is not subject to price threshold set by NEMLC however may be subject to benchmark reference pricing during the contracting process as per the Framework for the Inclusion of Items in National Pharmaceutical Contracts: Therapeutic Classes, Reference Pricing, and Series-Based Specification

Name & Affiliation	Declaration of Interests	Defining the PICO	Protocol development	Literature search	Study selection	Data extraction & characteristics of included studies	Quality appraisal	Data analysis	GRADE assessment	Write up and referencing	Clinical Expertise & interpretation	Quality assurance
Dr Natasha Gloeck[1,2]	None to declare	X	X	X	X	X	X	X	X	X	X	X
Dr Millidhashni Reddy[3]	None to declare	X	X		X	X	X			X	X	X
Prof Stefan Gebhardt[4]	None to declare	X		X	X						X	X

1. Health Systems Research Unit, South African Medical Research Council,
2. South African GRADE Network
3. Pharmaceutical Consultant: Health Technology Assessment and Policy, National Department of Health
4. Stellenbosch University and Tygerberg Hospital

ACKNOWLEDGEMENTS

The members of the Expert Review Committee (ERC), and National Essential Medicines List Committee. This research was supported by the E2D Collaboration, which brings together the NDoH, the Health Systems Research Unit (HSRU) and Cochrane South Africa at the South African Medical Research Council (SAMRC), and the Centre for Evidence-based Health Care (CEBHC) at Stellenbosch University.

EVIDENCE TO DECISION FRAMEWORK

Question	
Should Progesterone(micronized vaginal progesterone) 200mg versus Standard of care or placebo be used in pregnant woman with twin gestations, including both dichorionic and monochorionic twins, between16–26 weeks with a short cervix (≤ 25 mm) on ultrasound?	
Population:	Pregnant woman with twin gestations, including both dichorionic and monochorionic twins, between16–26 weeks with a short cervix (≤ 25 mm) on ultrasound
Intervention:	Progesterone (micronized vaginal progesterone) 200mg, vaginally, at bedtime
Comparison:	Standard of care or placebo

Setting:	**PUBLIC SECTOR SOUTH AFRICA**
Perspective:	**PUBLIC HEALTH/ POPULATION**

ASSESSMENT

Problem Priority (optional)
Why is this medicine being evaluated?

The rate of early preterm birth reported in twin pregnancies is approximately 10%, compared to 1–2% in singleton pregnancies. In twin pregnancies an increase in risk for early preterm labour is observed in women with cervical length <25 mm[1]. Vaginal progesterone is currently an essential medicine at Adult Hospital Level in South Africa in singleton pregnancies in: (1) mid- trimester cervical shortening (defined as ≤25 mm before 24 weeks gestation) with no prior spontaneous singleton preterm birth, and/or (2) women with a history of spontaneous preterm birth or mid-trimester loss. In 2025, NEMLC requested a review of the literature to determine if the recommendation for singleton pregnancies as outlined above should be expanded to include twin pregnancies.[6]

Desirable Effects
How substantial are the desirable anticipated effects (i.e., benefits)?

Judgement	Research evidence	Additional considerations (by committee)
○ Trivial ○ Small ○ **Moderate** ○ Large ○ Varies (if so, why?) ○ Don't know	1. **Reduction in preterm birth < 34 weeks[5]:** Vaginal progesterone VS placebo in twin pregnancies in women with short cervixes, vaginal progesterone likely reduces preterm births < 34 weeks – Spontaneous preterm birth <34 weeks: One included study (IPD Review (Conde-Agudelo 2022[7]) RR 0.58 (0.38 to 0.89), 95 participants, moderate quality evidence. – 273 fewer per 1000 spontaneous preterm births <34 weeks, ranging from 72 fewer to 404 fewer per 1000. – Preterm birth < 32 weeks: One included study (IPD Review (Conde-Agudelo 2022[7]) RR 0.56 (0.33 to 0.93), 95 participants, moderate quality evidence. – 205 fewer per 1000 preterm births <32 weeks, ranging from 33 fewer to 312 fewer per 1000.	*The ERC judged that the reduction in preterm birth <34 weeks in the relevant population constituted a moderate desirable effect.*

	2. **NICU stay/prolonged hospital stay -** Not reported. 3. **Neonatal mortality[5]:** Vaginal progesterone VS placebo in twin pregnancies in women with short cervixes, there may be little to no difference in neonatal deaths or stillbirths. – Neonatal death: One included study (IPD Review (Conde-Agudelo 2022[7]) RR 0.51 (0.2 to 1.28), 190 participants, low quality evidence. – 51 fewer neonatal deaths per 1000, ranging from 84 fewer to 29 more per 1000. – Stillbirth: One included study (IPD Review (Conde-Agudelo 2022) RR 0.54 (0.17 to 1.77), 190 participants, low quality evidence. – 21 fewer stillbirths per 1000, ranging from 39 fewer to 36 more per 1000. 4. **Safety:** AEs, SAEs Not reported.	
Undesirable Effects **How substantial are the undesirable anticipated effects (i.e., harms and toxicity)?**		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ Large ○ Moderate ○ Small ○ **Trivial** ○ Varies (if so, why?) ○ Don't know	1. **Safety:** AEs, SAEs Not reported. The previous NEMLC approved review on the use of progesterone for prevention of preterm birth in a select "at risk" population reported that in women who choose to take progesterone for preterm birth prevention, it appears to be safe with no major adverse events. These results have been noted in follow-up studies up to two years.[6,8]	*The ERC noted/judged that, based on previous NEMLC review, the undesirable effects are likely trivial.*
Certainty of evidence[3] **What is the overall certainty of the evidence of effects (across all critical outcomes)?**		
Judgement	**Research evidence**	**Additional considerations (by committee)**

[3] **CERTAINTY OF EVIDENCE**
High certainty: confident in the evidence / We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: mostly confident, but further research may change the effect / We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: some confidence, further research likely to change the effect / Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

○ Very low ○ **Low** ○ **Moderate** ○ High ○ No included studies	Low (GRADE ratings ranged from low to moderate certainty evidence)	

Values
Is there important uncertainty in how people with conditions, caregivers, healthcare providers or decision-makers value the main outcomes?

Judgement	Research evidence	Additional considerations (by committee)
○ Important uncertainty ○ Possibly important uncertainty ○ **Probably no important uncertainty** ○ No important uncertainty	**Reduction in preterm birth < 34 weeks:** When vaginal progesterone is compared to placebo in twin pregnancies in women with short cervixes, vaginal progesterone likely reduces preterm births < 34 weeks **Neonatal mortality:** When vaginal progesterone is compared to placebo in twin pregnancies in women with short cervixes, there may be little to no difference in neonatal deaths or stillbirths.	*The ERC judged that there was no reason to suspect varying values among the affected population identified in the evidence.*

Balance of effects
Does the balance of effects favour the medicine being considered an essential medicine? Do the desirable effects outweigh the undesirable effects?

Judgement	Research evidence	Additional considerations (by committee)
○ **Yes (*Favours the intervention*)** ○ Probably Yes (*Probably favours the intervention*) ○ Probably No (*Probably favours the comparison*) ○ No (*Favours the comparison*) ○ Varies (if so, why?) ○ Don't know	1. **Reduction in preterm birth < 34 weeks[5]:** Vaginal progesterone VS placebo in twin pregnancies in women with short cervixes, vaginal progesterone likely reduces preterm births < 34 weeks – Spontaneous preterm birth <34 weeks: One included study (IPD Review (Conde-Agudelo 2022[7]) RR 0.58 (0.38 to 0.89), 95 participants, moderate quality evidence. – 273 fewer per 1000 spontaneous preterm births <34 weeks, ranging from 72 fewer to 404 fewer per 1000. – Preterm birth < 32 weeks: One included study (IPD Review (Conde-Agudelo 2022[7]) RR 0.56 (0.33 to 0.93), 95 participants, moderate quality evidence.	*The ERC determined that, on balance of health effects, progesterone was favoured over standard of care/placebo in pregnant women with twin pregnancies and a short cervix because due to the desirable effects outweighing the undesirable effects.*

Very low certainty: findings indicate uncertain effect / We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect

	– 205 fewer per 1000 preterm births <32 weeks, ranging from 33 fewer to 312 fewer per 1000. 2. **NICU stay/prolonged hospital stay -** Not reported. 3. **Neonatal mortality[5]:** For Vaginal progesterone vs placebo in twin pregnancies in women with short cervixes, there is little to no difference in neonatal deaths or stillbirths. – Neonatal death: One included study (IPD Review (Conde-Agudelo 2022) RR 0.51 (0.2 to 1.28), 190 participants, low quality evidence. – 51 fewer neonatal deaths per 1000, ranging from 84 fewer to 29 more per 1000. – Stillbirth: One included study (IPD Review (Conde-Agudelo 2022[7]) RR 0.54 (0.17 to 1.77), 190 participants, low quality evidence. – 21 fewer stillbirths per 1000, ranging from 39 fewer to 36 more per 1000. 4. **Safety:** AEs, SAEs Not reported.	

Resources required
How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations (by committee)
○ Large costs ○ Moderate costs ○ **Negligible costs or savings** ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Price of medicines/ treatment course Medicine | Tender price ZAR)* | SEP (ZAR)* December 2025 Cyclogest 200mg – 15 pessaries | | 407,84 Utrogestan, 200mg 15 pessaries | | 300,41	*The ERC judged that there was no reason to suspect different costs from that presented in the evidence.*

Equity*
What would be the impact on health equity?

Judgement	Research evidence	Additional considerations (by committee)
○ Reduced ○ Probably reduced ○ Probably no	Currently the product is only available for singleton pregnancies. Including the item on the EML for twin pregnancies would improve	

impact ○ **Probably increased** ○ Increased ○ Varies ○ Don't know	equity, given the evidence of efficacy in reducing preterm birth in twin pregnancies.	

Acceptability*
Is the option acceptable to recommend as an essential medicine to key stakeholders?

Judgement	Research evidence	Additional considerations (by committee)
○ No ○ Probably no ○ **Probably yes** ○ Yes ○ Varies (if so, why?) ○ Don't know	We examined a study on the acceptability of a trial of vaginal progesterone for the prevention of preterm birth among HIV-infected women in Lusaka, Zambia: a mixed methods study, participants reported a preference of a vaginal medication over injectable described their familiarity with the vaginal product, a fear of needles and resulting pain, and inconvenience of a weekly clinic visit. Those who preferred weekly injections cited fewer doses to remember.[9]	

Feasibility*
Is the option feasible to implement?

Judgement	Research evidence		Additional considerations (by committee)
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies (if so, why?) ○ Don't know	Alternative Medicine/s (INN)	Not applicable	•
	Is the alternative SAHPRA registered?		
	Formulation/s		
	Equipotent Dose/ Dose range		
	N/A		

SUMMARY OF JUDGEMENTS

Indicate the relevant judgements below per domain in **bold**

	Judgement						
Desirable effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	**Trivial**		Varies	Don't know
Certainty of evidence	Very low	**Low**	**Moderate**	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison		**Probably favors the intervention**	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
Equity	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION[4]

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	X

CONCLUSIONS

Recommendation

For pregnant woman with twin gestations, including both dichorionic and monochorionic twins, between 16–26 weeks with a short cervix (≤ 25 mm) on ultrasound, the NEMLC recommends the use of progesterone 200mg per vagina over standard of care/placebo (strong recommendation, [low to moderate the certainty of evidence]).

Justification

N/A

Monitoring and evaluation

N/A

Research priorities

- Review results when new trials are published

[4] **STRENGTH OF THE RECOMMENDATION:**
Strong recommendation
Strong recommendations are those recommendations for which the guideline development group is confident that the desirable consequences of implementing the recommendation outweigh the undesirable consequences. Strong recommendations can be adopted as practice (most patients should receive the recommended medicine) or policy (adapted as policy) in most situations. For patients, most people would want the recommended medicine and only a small proportion would not.
Conditional recommendation
The guideline development group is less certain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences or when the anticipated net benefits are very small. Therefore, discussion (or substantial debate) may be required before a conditional recommendation can be adopted as practice or policy. For patients, the majority if people would want the recommended medicine, but many would not.

Restrictions

N/A

Implementation considerations

N/A – this is already standard practice in singleton pregnancies in women with a cervix ≤25mm.

Table of contents

REPORT

BACKGROUND

In December 2019 the National Essential Medicine List Committee (NEMLC), based on an evidence review conducted by the Adult Hospital Level Committee[6], aligned with NICE Guidelines[10], recommended daily vaginal progesterone treatment up to 34 weeks of gestation for singleton pregnancies in:

- mid- trimester cervical shortening (defined as ≤25 mm before 24 weeks gestation) with no prior spontaneous singleton preterm birth, and/or
- women with a history of spontaneous preterm birth or mid-trimester loss.

This recommendation for singleton pregnancies was based on recommendations that were informed by a systematic review and meta-analysis that included the OPPTIMUM study[11]. Although the OPPTIMUM study showed conflicting results of no benefit of vaginal progesterone in preventing preterm labour, a subgroup analysis and individual participant data meta-analysis of low to moderate quality evidence showed that for women with a history of spontaneous preterm birth, or women with a short cervix (≤25mm), vaginal progesterone decreases the number of preterm births (at < 34 weeks' gestation) compared to placebo. It was also noted that from a feasibility and acceptability point of view pharmacological management with vaginal progesterone is non-invasive and less costly compared to cerclage (intervention that used a strong suture to reinforce the cervix during pregnancy).

The rate of early preterm birth reported in twin pregnancies is approximately 10%, compared to 1–2% in singleton pregnancies. In South Africa, the Saving Babies report (2020–2023) identified spontaneous preterm labour as the leading obstetric cause of death, accounting for 21% of deaths. The perinatal mortality rate was reported as 30.2 per 1,000 for singleton deliveries and 80.5 per 1,000 for multiple gestations. It is important to highlight that most clinical trials investigating the use of progesterone for the prevention of preterm birth were conducted in high-income countries, where access to advanced neonatal intensive and high-care facilities is substantially greater. Consequently, any reduction in the risk of preterm labour is likely to have a more profound impact on neonatal morbidity in low- and middle-income countries (LMICs). Supporting this, the Saving Babies report further noted that prematurity was the primary cause of neonatal mortality in South Africa, contributing to 46% of all neonatal deaths.[12]

In twin pregnancies the increase in risk for preterm labour is observed in women with cervical length <25 mm.[13] In 2025, NEMLC requested a review of the literature to determine if the recommendation for singleton pregnancies as outlined above should be expanded to include twin pregnancies.[6]

Table 1: PURPOSE/OBJECTIVE i.e., PICO question:

Population Subgroups	Pregnant woman with twin gestations, including both dichorionic and monochorionic twins, between 16–26 weeks with a short cervix (≤ 25 mm) on ultrasound
Intervention(s)	Progesterone (micronized vaginal progesterone) 200mg, vaginally, at bedtime

Comparator(s)	Standard of care or placebo
Outcome(s)	• Reduction in preterm births < 34 weeks • Neonatal morbidity: NICU stay/prolonged hospital stay • Neonatal mortality • Safety: AEs, SAEs
Study types	Clinical practice guidelines (CPGs), Systematic Reviews of Randomised Controlled Trials (RCTs) or other, RCTs

METHODS

1. **Data Sources**
   Clinical practice guidelines: We searched the Guidelines International Network (GIN) library, the National Institute for Health and Care Excellence (NICE) website, the American College of Obstetrics and Gynaecology (ACOG), the Society for Maternal Fetal Medicine (SMFM), and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) for relevant guidelines.

2. **Search Strategy**
   We searched the relevant guideline repositories using keywords “twin”, “multiple”, and “multiple gestation”.

3. **Study selection and eligibility criteria, data extraction and analysis, and evidence synthesis**
   Relevant clinical practice guidelines were identified by one reviewer and checked by a second reviewer. Guidelines were screened using a tool that matched the guideline PICO with our PICO and guidelines included or excluded accordingly (see Figure 1 Search flow Chart). Relevant recommendations were extracted from the included guidelines by one reviewer (NG) and checked by a second reviewer (MR). Data were extracted from the included systematic review (NICE) by one reviewer (NG) and checked by a second reviewer (MR). Any disagreements were resolved through discussion.

4. **Assessment of methodological quality**
   We used the AGREE II tool[14] to assess clinical practice guidelines, and the AMSTAR II[15] tool to assess the evidence review within the included NICE and ACOG guideline.

5. **GRADE assessment**
   We adopted the GRADE assessment in the evidence review by NICE[2,5].

RESULTS

1. **Result of the search**
   We identified seven guidelines through searching guideline databases (see figure 1). We excluded five of these guidelines. The German guideline[16,] was excluded as their

recommendation was based on older NICE guidance than the included NICE guidance. The RANZCOG[17,18,19] guidance was excluded due to a PICO mismatch and one of the ACOG guidelines[3] was excluded due to the wrong intervention being included. The two included guidelines are described and discussed below.

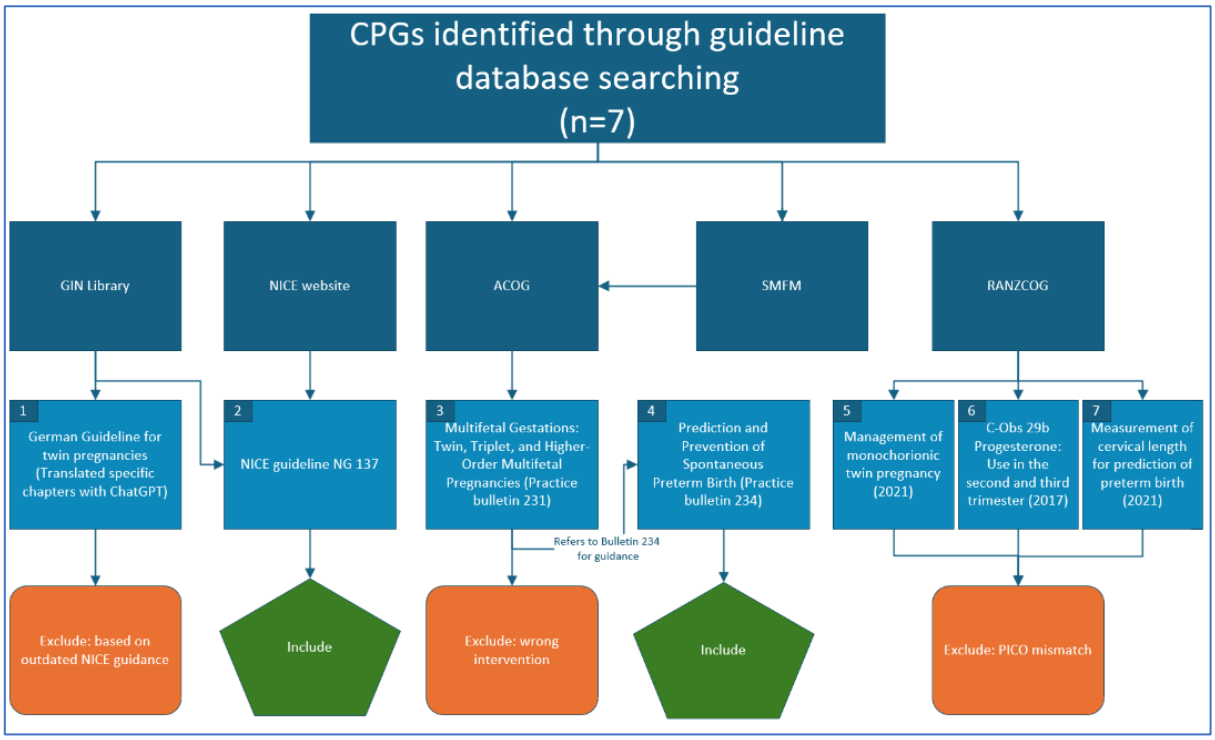

Figure 1 Search flow chart

2. Description of included studies (clinical practice guidelines, systematic reviews and RCTs) and critical appraisal

Table 2 reports a summary of the guideline recommendations, Table 3: PICO table from NICE review and Table 4 reports the main characteristics and outcomes of the studies included in the systematic review. Appendix 1 provides the full AGREE II scoring for the guidelines and Appendix 2 provides the AMSTAR 2 Appraisal of the systematic review, in duplicate.

2.1. Clinical Practice Guidelines

We included two clinical practice guidelines.

The first guideline by ACOG is a practice bulletin for obstetrician-gynaecologists in the United States[4]. It was published in 2021 as an update to previous guidance from 2012. The guideline addresses the prediction and prevention of spontaneous preterm birth in both single and multiple pregnancies. The evidence rating system used was according to methods outlined by the US Preventative Service Task Force. The recommendations relevant to our PICO are summarised below in Table 1. Two reviewers (NG, MR) assessed the quality of this guideline using the AGREE II tool and it was rated as moderate quality (Appendix 1)

The second included guideline by NICE was published in 2024[5]. This guideline focuses on management guidance for twin and triplet pregnancies. The GRADE evidence rating system was used to assess the quality of evidence and the relevant recommendations are summarised in Table 1. Two reviewers (NG, MR) assessed the quality of this guideline using the AGREE II tool and it was rated as high quality (See Appendix 1 for both reviewer assessments and scoring per domain). A secondary appraisal of the guidelines for overall timeousness and credibility was also conducted. The top-scoring guidance in this assessment was the NICE guidance[5].

Table 2 Recommendations from included clinical practice guidelines

Citation	Recommendation	AGREE II (combined)
American College of Obstetricians and Gynaecologists: Committee on Practice Bulletins. Prediction and prevention of spontaneous preterm birth: number 234. ACOG Practice Bulletin. 2021.	"Cervical pessary is not recommended for prevention of preterm birth in twin pregnancies with a short Cervix." Level A[5] evidence	– Scope and purpose (D1) 72% – Stakeholder involvement (D2) 33% – Rigour of development (D3) 43% – Clarity of presentation (D4) 89% – Applicability (D5) 4% – Editorial independence (D6) 29% **Overall 45%**
National Institute for Health and Care Excellence (NICE). NG 137 Twin and triplet pregnancy. 2024.	Under section 1.5 Preventing Preterm Birth "Offer a single cervical length scan between 16 and 20 weeks to women or pregnant people with a twin or triplet pregnancy. [2024]" "Offer progesterone 200 mg vaginal capsules once a day at bedtime to women or pregnant people with a twin or triplet pregnancy and a cervical length of 25 mm or less. Continue treatment until 34 weeks (or birth if sooner). [2024]" "If a cervical length of 25 mm or less is found incidentally on a scan conducted between 20 and 24 weeks, offer progesterone 200 mg vaginal capsules once a day at bedtime. Continue treatment until 34 weeks (or birth if sooner). [2024] In April 2024, this was an off-label use of progesterone 200 mg vaginal capsules. See NICE's information on prescribing medicines."	– Scope and purpose (D1) 97% – Stakeholder involvement (D2) 86% – Rigour of development (D3) 93% – Clarity of presentation (D4) 94% – Applicability (D5) 79% – Editorial independence (D6) 83% **Overall 89%**

2.2. *Systematic reviews*

We included the systematic review which informed relevant recommendations within the NICE guideline[2]. This systematic review examined effectiveness of progesterone use (vaginal, oral or intramuscular) from 16 to 37 weeks gestational age compared to standard of care, placebo or progesterone given through different routes in women at risk of preterm birth in twin and triplet pregnancies – this population was further stratified by cervical length (short ≤25mm and long>25mm) and whether there had been a previous preterm birth or not.

Critical outcomes included stillbirth or neonatal death, preterm birth at 22+0 to 27+6 weeks, 28+0 to 31+6 weeks, and 32+0 to 36+6 weeks, and spontaneous preterm birth < 34 weeks of gestation.

[5] Level A: Recommendations are based on good and consistent scientific evidence.

Important outcomes included a composite outcome of serious neonatal complications[6], and a composite of adverse maternal outcomes[7]. The PICO is summarised in the table below. This review included two randomised controlled trials, and two individual patient data (IPD) reviews – all studies compared vaginal progesterone to placebo or control (no intervention) in women with twin pregnancies. We judged it as having a moderate AMSTAR II rating (see Appendix 2 for judgements). GRADE evidence ratings as judged by the team at NICE are included below the effectiveness of the intervention section.

Table 3: PICO table from NICE review[2]

Population	Women at risk of preterm birth in twin and triplet pregnancy Strata Cervical length - Women with a short cervix (≤25mm) - Women with a longer cervix (>25mm) Previous preterm birth - Women with previous preterm birth - Women with no previous preterm birth
Intervention	• Vaginal progesterone • Oral progesterone • Intramuscular 17-hydroxyprogesterone caproate (17-OHPC) *Progesterone use in first, second and third trimester (part) will be included as all are relevant
Comparison	Placebo or control or standard of care or With each other
Outcomes	**Critical** • Stillbirth or neonatal death* (to report neonatal death outcome separately if reported) • Preterm birth** at 22+0 - 27+6 weeks • Preterm birth** at 28+0 - 31+6 weeks • Preterm birth** at 32+0 - 36+6 weeks • Spontaneous preterm birth <34 weeks of gestation (this will include spontaneous preterm birth <33 weeks) *Stillbirth defined as "a baby that dies after 24 weeks of pregnancy but before they are born", and a neonatal death defined as "death within 28 days after birth" **This includes spontaneous preterm birth and indicated preterm birth (in which a baby is delivered by early induction of labour or caesarean birth due to maternal or fetal illness). **Important** • Composite of serious neonatal complications (for example, severe necrotising enterocolitis stages 2–3, intraventricular haemorrhage grades 3–4, retinopathy of prematurity stage 3 or worse, bronchopulmonary dysplasia, confirmed sepsis, patent ductus arteriosus, and neonatal infection) • Composite of adverse maternal outcomes (for example, gestational hypertension, pre-eclampsia, gestational diabetes, and maternal infection including chorioamnionitis)

[6] This could include severe necrotising enterocolitis stages 2–3, intraventricular haemorrhage grades 3–4, retinopathy of prematurity stage 3 or worse, bronchopulmonary dysplasia, confirmed sepsis, patent ductus arteriosus, and neonatal infection
[7] This could include gestational hypertension, pre-eclampsia, gestational diabetes, and maternal infection such as chorioamnionitis

Table 4: Characteristics of the study included in the NICE Systematic Review that informed our PICO (Extracted from NICE Evidence Review)[2]:

Study	Population	Intervention	Comparison	Outcomes
Conde-Agudelo 2022[7] International	N=95, Vaginal progesterone: N=52, Placebo: N=43 N=6 RCTs investigating vaginal progesterone for the prevention of preterm birth in women with a twin pregnancy and short cervix (≤25 mm) or women with an unselected twin pregnancy and short cervix. Participants characteristics not reported	Vaginal progesterone (100-600 mg per day)	Placebo	• Stillbirth (fetal death) • Neonatal death • Preterm birth <28 weeks Preterm birth <32 weeks • Preterm birth <37 weeks • Spontaneous preterm birth <34 weeks • Composite of serious neonatal complications

2.3. *Randomised controlled trials (RCTs)*

During review of the above systematic review, we identified the PROSPECT trial (NCT02518594).[20] This is a randomised controlled trial of 630 women evaluating the use of vaginal progesterone compared to placebo to prevent early preterm birth in women pregnant with twins and with a cervical length less than 30mm. The primary outcome was delivery or foetal loss of either twin prior to 35 weeks gestation. Secondary outcomes included interval from randomisation to delivery or foetal demise, gestational age at delivery, preterm delivery or foetal demise prior to 28 weeks, 32 weeks, and 37 weeks gestation, spontaneous preterm delivery (following preterm labour or preterm rupture of membranes) < 32 weeks and 35 weeks gestation, indicated preterm delivery < 35 weeks gestation, caesarean delivery, foetal or neonatal death, small for gestational age, composite neonatal outcome, and length of hospital stay, need for NICU or immediate care admission and length of stay if admitted. The trial started in November 2015 and concluded in February 2025. There are no published results available – we have reached out to study investigators to request access to results.

EFFECTIVENESS OF THE INTERVENTION

Comparison	Number of included studies
Vaginal progesterone compared to SoC or placebo	one

Comparison 1

1. **Reduction in preterm birth < 34 weeks:** When vaginal progesterone is compared to placebo in twin pregnancies in women with short cervixes, vaginal progesterone likely reduces preterm births < 34 weeks (moderate certainty evidence)
   - Spontaneous preterm birth <34 weeks: One included study (IPD Review (Conde-Agudelo 2022[7])) RR 0.58 (95% Confidence interval (CI) 0.38 to 0.89), 95 participants, moderate certainty evidence rated down for serious imprecision due to the confidence interval crossing one minimally important difference. In absolute terms, there were 273 fewer per 1000 spontaneous preterm births <34 weeks, ranging from 72 fewer to 404 fewer per 1000.
   - Preterm birth < 32 weeks: One included study (IPD Review (Conde-Agudelo 2022[7])) RR 0.56 (95% CI 0.33 to 0.93), 95 participants, moderate certainty evidence rated down for serious imprecision due to the confidence interval crossing one minimally important difference. In absolute terms, there were 205 fewer per 1000 preterm births <32 weeks, ranging from 33 fewer to 312 fewer per 1000.

2. **NICU stay/prolonged hospital stay**
   Not reported.

   A composite outcome of serious neonatal complications was reported in the review which included neonatal morbidity/mortality, including respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis proven neonatal sepsis, or neonatal death. As this

composite outcome combined both neonatal morbidity and mortality we did not report this outcome.

3. **Neonatal mortality:** When vaginal progesterone is compared to placebo in twin pregnancies in women with short cervixes, there may be little to no difference in neonatal deaths or stillbirths (low certainty evidence).
   - Neonatal death: One included study (IPD Review (Conde-Agudelo 2022[7]) RR 0.51 (95% CI 0.2 to 1.28), 190 participants, low certainty evidence rated down for very serious imprecision due to the low event rate. In absolute terms, there were 51 fewer neonatal deaths per 1000, ranging from 84 fewer to 29 more per 1000.
   - Stillbirth: One included study (IPD Review (Conde-Agudelo 2022[7]) RR 0.54 (95% CI 0.17 to 1.77), 190 participants, low certainty evidence rated down for very serious imprecision due to the low event rate. In absolute terms, there were 21 fewer stillbirths per 1000, ranging from 39 fewer to 36 more per 1000.

4. **Safety:** AEs, SAEs
   Not reported.

GRADE EVIDENCE TABLE (Table 11 copied from NG 137 evidence review)[2]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone	Placebo	Relative (95% CI)	Absolute		
Stillbirth (fetal death, adjusted analysis) (baby or fetus)												
1 (Conde-Agudelo 2022)	IPD review	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	None	6/104 (5.8%)	4/86 (4.7%)	RR 0.54 (0.17 to 1.77)	21 fewer per 1000 (from 39 fewer to 36 more)	LOW	CRITICAL
Neonatal death (adjusted analysis) (baby or fetus)												
1 (Conde-Agudelo 2022)	IPD review	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	None	4/104 (3.8%)	9/86 (10.5%)	RR 0.51 (0.2 to 1.28)	51 fewer per 1000 (from 84 fewer to 29 more)	LOW	CRITICAL
Preterm birth <32 weeks (pregnant women)												
1 (Conde-Agudelo 2022)	IPD review	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	16/52 (30.8%)	20/43 (46.5%)	RR 0.56 (0.33 to 0.93)	205 fewer per 1000 (from 33 fewer to 312 fewer)	MODERATE	CRITICAL
Spontaneous preterm birth <34 weeks (pregnant women)												
1 (Conde-Agudelo 2022)	IPD review	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	20/52 (38.5%)	28/43 (65.1%)	RR 0.58 (0.38 to 0.89)	273 fewer per 1000 (from 72 fewer to 404 fewer)	MODERATE	CRITICAL

CI: confidence interval; IPD: individual participant data; OIS: optimal information size; RR: risk ratio
[1] <150 events
[2] 95% CI crosses 1 MID

DISCUSSION

Summary of results
The review of the literature shows that when vaginal progesterone is compared to placebo in twin pregnancies in women with short cervixes, vaginal progesterone likely reduces preterm births < 34 weeks. There may be little to no difference in stillbirth or neonatal death.

Limitations in the review process
ICU stay and adverse events was not reported in the NICE guideline. However, a previous NEMLC approved review on the use of progesterone for prevention of preterm birth in a select “at risk” population reported that in women who choose to take progesterone for preterm birth prevention, it appears to be safe with no major adverse events. These results have been noted in follow-up studies up to two years. [6,8]

CONCLUSION

International guidelines including the NICE guidelines[5] reviewed here have accepted the levels of evidence to recommend vaginal progesterone in twin pregnancies in women with short cervixes as vaginal progesterone likely reduces preterm births < 34 weeks. In South Africa vaginal progesterone is recommended for prevention of preterm labour in singleton pregnancies. The evidence shows that that when vaginal progesterone is compared to placebo in twin pregnancies in women with short cervixes, vaginal progesterone likely reduces preterm births < 34 weeks for twin pregnancies too.

REFERENCES

[1] da Fonseca EB, Vasconcelos de Castro TB, Dias T, Araujo L, Aires D. Cervical assessment. Best Pract Res Clin Obstet Gynaecol. 2025 Mar;99:102590. doi: 10.1016/j.bpobgyn.2025.102590. Epub 2025 Mar 11. PMID: 40090290.

[2] Progesterone for preventing spontaneous preterm birth in twin and triplet pregnancy: Twin and triplet pregnancy: Evidence review K. London: National Institute for Health and Care Excellence (NICE); 2024 Apr. PMID: 38829974.

[3] Multifetal Gestations: Twin, Triplet, and Higher-Order Multifetal Pregnancies: ACOG Practice Bulletin, Number 231. Obstet Gynecol. 2021 Jun 1;137(6):e145-e162. doi: 10.1097/AOG.0000000000004397. PMID: 34011891.

[4] Prediction and Prevention of Spontaneous Preterm Birth: ACOG Practice Bulletin, Number 234. Obstet Gynecol. 2021 Aug 1;138(2):e65-e90. doi: 10.1097/AOG.0000000000004479. PMID: 34293771.

[5] Twin and triplet pregnancy. London: National Institute for Health and Care Excellence (NICE); 2024 Apr 9. PMID: 31513365.

[6] National Department of Health. Adult Hospital Level Medication Review Process Component: Obstetrics. Review of the use of progesterone for prevention of preterm birth in a select “at risk” population.

[7] Romero R, Conde-Agudelo A, Rehal A, Da Fonseca E, Brizot ML, Rode L, Serra V, Cetingoz E, Syngelaki A, Tabor A, Perales A, Hassan SS, Nicolaides KH. Vaginal progesterone for the prevention of preterm birth and adverse perinatal outcomes in twin gestations with a short cervix: an updated individual patient data meta-analysis. Ultrasound Obstet Gynecol. 2022 Feb;59(2):263-266. doi: 10.1002/uog.24839. PMID: 34941003; PMCID: PMC9333094.

[8] Cuijpers CJJ, Van't Hooft J, Schneeberger C, Van Der Lee JH, Simons NE, Van Os MA, Van Der Ven J, De Groot CJM, Mol BWJ, Van Wassenaer-Leemhuis AG. Progesterone for prevention of preterm birth in women with short cervical length: 2-year infant outcomes. Ultrasound Obstet Gynecol. 2021 Mar;57(3):431-439. doi: 10.1002/uog.23126. Epub 2021 Feb 12. PMID: 32959909; PMCID: PMC7986902.

[9] Price JT, Mabula-Bwalya CM, Freeman BL, Carda-Auten J, Phiri WM, Chibwe K, Kantumoya P, Vwalika B, Stringer JSA, Golin CE. Acceptability of a trial of vaginal progesterone for the prevention of preterm birth among HIV-infected women in Lusaka, Zambia: A mixed methods study. PLoS One. 2020 Sep 24;15(9):e0238748. doi: 10.1371/journal.pone.0238748. Erratum in: PLoS One. 2021 Jan 28;16(1):e0246489. doi: 10.1371/journal.pone.0246489. PMID: 32970697; PMCID: PMC7514015.

[10] NICE. NICE Guideline: Preterm labour and birth, Updated in August 2019. Available at: https://www.nice.org.uk/guidance/ng25 .

[11]Norman JE, Marlow N, Messow CM, Shennan A, Bennett PR, Thornton S, Robson SC, McConnachie A, Petrou S, Sebire NJ, Lavender T, Whyte S, Norrie J, OPPTIMUM study group. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double blind trial. Lancet. 2016;387(10033):2106. Epub 2016 Feb 24.

[12] National Department of Health. Saving Mothers and Babies 2017-2019: Executive Summary

[13] da Fonseca EB, Vasconcelos de Castro TB, Dias T, Araujo L, Aires D. Cervical assessment. Best Pract Res Clin Obstet Gynaecol. 2025 Mar;99:102590. doi: 10.1016/j.bpobgyn.2025.102590. Epub 2025 Mar 11. PMID: 40090290.

[14] APPRAISAL OF GUIDELINES fOR RESEARCH & EVALUATION II. https://www.agreetrust.org/wp-content/uploads/2013/10/AGREE-II-Users-Manual-and-23-item-Instrument_2009_UPDATE_2013.pdf

[15]A MeaSurement Tool to Assess systematic Reviews. AMSTAR II https://amstar.ca/

[16] von Kaisenberg C, Klaritsch P, Ochsenbein-Kölble N, Hodel ME, Nothacker M, Hecher K. Screening, Management and Delivery in Twin Pregnancy. Ultraschall Med. 2021 Aug;42(4):367-378. English, German. doi: 10.1055/a-1248-8896. Epub 2020 Oct 5. PMID: 33017845.

[17] Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Management-Monochorionic-Twin-Pregnancy. March 2011. Available at: https://ranzcog.edu.au/resource-hub/

[18] Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Measurement of cervical length for prediciton of preterm birth. November 2021. Available at: https://ranzcog.edu.au/resource-hub/

[19] Royal Australian and New Zealand College of Obstetricians and Gynaecologists. C Obs 29 b Progesterone: Use in the second and third trimester. July 2017 with interim upate November 2023. Available at: https://ranzcog.edu.au/resource-hub/

[20] Clinical Trials.ORG. A Trial of Pessary and Progesterone for Preterm Prevention in Twin Gestation With a Short Cervix (PROSPECT). Available at: https://clinicaltrials.gov/study/NCT02518594

Appendix 1: AGREE II Individual reviewer ratings

AGREE II assessment scores																							
ACOG Guidance																							
72																							
	Scope and purpose			**Stakeholder involvement**			**Rigour of development**								**Clarity of presentation**			**Applicability**				**Editorial independence**		**Overall assessment**
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1 (NG)	7	7	3	1	1	6	5	1	5	4	5	6	1	4	7	6	7	1	1	1	1	1	4	4
Appraiser 2 (MR)	7	7	1	3	2	5	5	3	4	2	4	5	1	2	5	6	7	2	1	2	1	1	5	3
Item Total	14	14	4	4	3	11	10	4	9	6	9	11	2	6	12	12	14	3	2	3	2	2	9	7
Domain Total	32			18			57								38			10				11		166
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	**72%**			**33%**			**43%**								**89%**			**4%**				**29%**		**45%**

Twin and triplet pregnancy - NICE																								
Scoring the guidelines																								
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	7	7	7	5	7	7	5	7	6	7	7	6	7	7	6	6	3	6	7	6	6	6	6
Appraiser 2	7	6	7	6	5	7	7	7	6	7	6	6	7	7	7	7	7	4	6	7	7	5	7	6
Item Total	14	13	14	13	10	14	14	12	13	13	13	13	13	14	14	13	13	7	12	14	13	11	13	12
Domain Total	41			37			105								40			46				24		293
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	**97%**			**86%**			**93%**								**94%**			**79%**				**83%**		**89%**

Using an approach used in Mc Allister *et al*. Advancing guideline quality through country-wide and regional appraisal of CPGs: a scoping review, 22 September 2022, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-1850020/v1][20]

	Scope and purpose	Stakeholder involvement	Rigour of development	Clarity of presentation	Applicability	Editorial independence	Overall Assessment Score
Guideline	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	
NICE	97%	86%	93%	94%	79%	83%	89%
ACOG	72%	33%	43%	89%	4%	29%	45%

Low: < 40%	Moderate: 40% - 59%	High: ≥ 60%

Assessment of Timeliness and Credibility of Guidelines				
Guideline	Timeliness	Credibility	Use of GRADE	Overall Assessment Score
NICE	3	5	5	13
ACOG	3	3	2	8

Key to Scoring:

Timeliness (CPG level)

- Guideline is out-of-date and likely to miss important recent evidence 1
- Guideline is recent and unlikely to miss recent important evidence 3

Credibility (CPG level)

- Guideline is not credible (e.g., < 60% overall for Domain 1, 3 and 6) 1
- Guideline is credible but has significant limitations (e.g., > 60% in either D1, D3 or D6) 3
- Guideline is credible (e.g., high overall scores across domains) 5

Use of GRADE (CPG Level)

- Does not use/report GRADE or GRADE EtD 1
- Guidelines uses GRADE 2
- Guidelines reported GRADE EtD tables 3

Appendix 2: AMSTAR 2 Judgements

AMSTAR 2 assessment of [Progesterone for preventing spontaneous preterm birth in twin and triplet pregnancy: Twin and triplet pregnancy: Evidence review K. London: National Institute for Health and Care Excellence (NICE); 2024 Apr. PMID: 38829974.]

		Reviewer 1 (NG)		Reviewer 2 (MR)	
No.	**Criteria**	**Comments**	**Y/ PY/ N#**	**Comments**	**Y/ PY/ N#**
1	Research questions and inclusion criteria for the review included the components of PICO	Table included with PICO	Y	Eligibility criteria are outlined in Table 1 as Population, Intervention, Comparison and Outcome (PICO) characteristics of the review.	Y
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	Protocol is available for review (Appendix A) – no significant deviations reported	Y	Appendix A outlines a protocol. Unclear if there were no deviations in the review as no explicit explanations of deviations or non-deviations. are provided. Deviations in the individual study appraisals included in the review were considered.	PY
3	Review authors explained selection of the study designs for inclusion in the review	Review done as per NICE manual guidelines	PY	The literature search was systematic and conducted in terms of the Developing NICE guidelines: the manual, searches were restricted b systematic reviews or randomised control trials (RCTs) and RCTs.	Y
4*	Review authors used a comprehensive literature search strategy	Yes (Appendix B)	Y	Outlined in Appendix B Literature search strategies	Y
5	Review authors perform study selection in duplicate	"potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary"	PY	Not explicitly stated, however methods conducted according to the Developing NICE guidelines: the manual which implies duplicate search	PY
6	Review authors perform data extraction in duplicate	"One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer"	PY	Not explicitly stated, however methods were conducted according to the Developing NICE guidelines: the manual which implies duplicate search and dual sifting was performed on at least 10% of records; requiring 90% agreement.	PY
7*	Review authors provided a list of excluded studies and justify the exclusions	Appendix J	Y	Excluded studies for review question: What is the clinical and cost-effectiveness of progesterone in preventing spontaneous preterm birth in twin and triplet pregnancy? And reasons for exclusion were provided.	Y
8	Review authors described the included studies in adequate detail	"Table 2: Summary of included studies" page 9	Y	Summary of included studies are provided in tables and narrative.	Y

9*	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	"Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • Wang et al checklist for assessing the methodological quality of IPD meta-analysis https://www.bmj.com/content/bmj/373/bmj.n736.full.pdf"	Y	Quality assessment of individual studies will be performed using the following checklists: ROBIS tool for systematic reviews , Cochrane RoB tool v.2 for RCTs and quasi-RCTs and Wang et al checklist for assessing the methodological quality of IPD meta-analysis https://www.bmj.com/content/bmj/373/bmj.n736.full.pdf	Y
10	Review authors reported on the sources of funding for the studies included in the review.	Included in the evidence tables	Y	Relevant outcome data and source of funding was included in the protocol for data extraction and considered in the critical appraisals.	Y
11*	For meta-analyses, review authors used appropriate methods for statistical combination of results	Plan for MA is available in the protocol Appendix A	Y	Where possible, meta-analyses was conducted using Cochrane Review Manager software.	Y
12	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	"The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/"	Y	Risk of Bias reviewed at all steps through the assessment and presented in GRADE	Y
13*	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Authors used GRADE to assess review quality and reflected on this when interpreting results	Y	Risk of Bias reviewed at all steps through the assessment and presented in GRADE	Y
14	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Authors had a plan for managing heterogeneity but there was no specific need to explain or discuss further	PY	In the protocol it is explicitly stated that heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Not reported.	Y
15*	For quantitative synthesis, review authors carried out adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	Authors considered publication bias when assessing included studies	PY	Considered in review of studies	Y
16	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	"Declarations of interest were recorded according to NICE's conflicts of interest policy. " – although it is not so easy to find this document. It is stated that the review was funded by NICE	PY	Declarations of interest were recorded according to NICE's conflicts of interest policy.	Y
OVERALL QUALITY ASSESSMENT:		**Moderate quality**			
Rationale and conclusion:				See below for respective rating	

[#] Y= Yes, PY = Partial yes, N = No

** Critical domains = 2, 4, 7, 9, 11, 13, 15*

*** Berild JD, et al. A Systematic Review of Studies Published between 2016 and 2019 on the Effectiveness and Efficacy of Pneumococcal Vaccination on Pneumonia and Invasive Pneumococcal Disease in an Elderly Population. Pathogens. 2020 Apr 3;9(4):259. doi: 10.3390/pathogens9040259.*

Rating overall confidence in the results of the review

- *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
- *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that *were* included in the review
- *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the *question* of interest
- *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).