SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 6: OBSTETRICS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 -2019)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the obstetrics chapter.

A: NEW SECTIONS ADDED

CONDITION	MEDICINE MANAGEMENT	MEDICINE ADDED
6.9 Hepatitis B in pregnancy	Yes	*Mother:* Tenofovir, oral Tenofovir+Emtricitabine+Efavirenz, oral (FDC) *Neonate* Hepatitis B vaccine Hepatitis B immunoglobulin
6.13 Prevention of preterm labour (singleton pregnancies only)	Yes	Progesterone, vaginal, 200 mg

6.9 HEPATITIS B IN PREGNANCY

The following STG was developed, taking into consideration the recently NEMLC approved PHC STG[1].

Description
Hepatitis B virus (HBV) is transmitted sexually or by percutaneous exposure to infectious body fluids, i.e. blood, saliva, vaginal fluid & 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 and perinatal transmission.

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-uninfected 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 should include ARV active against hepatitis B).

Note:
» Ensure normal renal function before starting treatment with tenofovir (serum creatinine <85 umol/L or creatinine clearance >60 mL/min).
» 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.
» Babies born to mothers with acute hepatitis B infection at the time of delivery or to mothers who are HBsAg-positive or HBeAg-positive, see Primary Health Care STGs and EML, section 6.6.5: Hepatitis B exposed infant.

Referral
» Cirrhosis
» Liver failure
» Renal dysfunction (eGFR<60mL/min)
» Treatment failure.
» Refer co-infected babies to a specialist paediatrician for further management.

Level of Evidence: I Systematic review[2], Open-label study[3]

[1] NEMLC minutes of the meeting, 2 March 2017.
[2] Lee C, Gong Y, Brok J, Boxall EH, Gluud C. Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis. BMJ. 2006 Feb 11;332(7537):328-36. https://www.ncbi.nlm.nih.gov/pubmed/16443611

6.13 PREVENTION OF PRETERM LABOUR (SINGLETON PREGNANCIES ONLY)

The STG was developed, following receipt an evidence alert.

Refer to the medicine review, progesterone to prevent preterm delivery (October 2019):

Progesterone to Prevent Preterm deli

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review, the Adult Hospital Level Committee recommends daily vaginal progesterone treatment through to 34 weeks of gestation 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.

Of note is that in the South African setting, routine cervical screening is not practiced in low-risk women as this is considered to be unpractical and unaffordable - sonography (ultrasound imaging) is not readily available at all facilities.

Rationale:

- Guidance aligned with NICE Guideline recommendations that were informed by systematic review and meta-analysis that included the OPPTIMUM study which showed conflicting results of no benefit of vaginal progesterone in preventing preterm labour.
- 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.
- Furthermore, pharmacological management with vaginal progesterone is non-invasive and less costly compared to cerclage.

Level of Evidence: II Systematic review and meta-analysis of low to moderate quality RCTs, Guidelines[4]

The following STG was added to the chapter:

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.
» 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 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 midtrimester loss (16-24 weeks), ***and/or***
» cervical length ≤ 25 mm confirmed on ultrasound (16-24 weeks).

Progesterone, PV, 200 mg daily.

[3] Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, Washington MK, Germanidis G, Flaherty JF, Schall RA, Bornstein JD, Kitrinos KM, Subramanian GM, McHutchison JG, Heathcote EJ. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow up study. Lancet. 2013;381:468–75. http://www.ncbi.nlm.nih.gov/pubmed/23234725

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

- Stop treatment at 34 weeks and refer to antenatal services at primary level of care for further management.

(**Note**: Vaginal progesterone may be considered in high-risk women with a normal cervix length confirmed 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 torn out (severe cervical trauma), as they may require an abdominal cerclage.

B: AMENDMENTS TO MEDICINE TREATMENT

SECTION	MEDICINE	ADDED/DELETED/AMENDED
6.1 Anaemia in pregnancy	Folic acid, oral	Deleted & cross-reference to the PHC STGs and EML, 2018
	Ferrous sulfate, oral	Retained
	Ferrous fumarate, oral	Added
	Iron, IV	Retained
	Blood transfusions	Not added
6.2 **Diabetes mellitus in pregnancy**		
- Diagnosis of GDM	Diagnostic criteria for Gestational Diabetes Mellitus (GDM)	Not amended
	Blood glucose thresholds	Not amended
	HbA1C	Not added as a diagnostic test
- Preferred insulin regimen	Insulin	Dosing amended
6.3 Heart disease in pregnancy	Contraception	Added
	Spironolactone, oral	Contra-indication in pregnancy added
	Enoxaparin, SC	Indication(s) amended
	Unfractionated heparin, IV/SC	Indication(s) amended
6.4 Hypertensive disorders in pregnancy	Methyldopa, oral	Dosing not amended
- Prevention of pre-eclampsia	Aspirin	Directions for use and dosing amended
6.7 HIV in pregnancy	Tenofovir+Emtricitabline+Efavirenz, oral (TEE)	indication amended to <6weeks gestation or wishing to conceive again
	Tenofovir+Lamivudine+Dolutegravir, oral (TLD)	Added
- Active psychiatric illness in HIV-infected pregnant women (EFV contraindicated)	Tenofovir + lamivudine + dolutegravir, oral (TLD)	Added
- Active psychiatric illness in HIV-infected pregnant women and DTG not suitable	Nevirapine + Tenofovir + Emtricitabine, oral	Not added
	Nevirapine + Zidovudine + Lamivudine, oral	Not added
	Lopinavir/ritonavir + Tenofovir + Emtricitabine, oral	Added
	Lopinavir/ritonavir + Zidovudine + Lamivudine, oral	Added
-HIV-infected pregnant women in labour not on ART:	Nevirapine+Tenofovir+Emtricitabine, oral (single dose)	Deleted
	Nevirapine, oral (single dose)	Added
	Tenofovir+lamivudine+dolutegravir, oral (single dose)	Added
-HIV-infected pregnant women undergoing Caesarean section not on ART:	Nevirapine+Tenofovir+Emtricitabine, oral (single dose)	Deleted
	Zidovudine, oral (3 hourly until delivery)	Deleted
	Nevirapine, oral (single dose)	Added
	Tenofovir+lamivudine+dolutegravir, oral (single dose)	Added
6.8 Syphilis *- Pregnancy and breastfeeding*	Benzathine benzylpenicillin, IM	Dosing amended
6.9 Hepatitis B in pregnancy	Management of hepatitis B	Cross referenced to section 1.2.4.2 Hepatitis B, chronic (non-HIV coinfection) and chapter 10: HIV and AIDS
	Perinatal transmission of hepatitis B	Cross referenced to PHC STGs and EML,

		2018 (until such time as Paediatric Hospital Level STG is developed)
6.11 Hyperemesis gravidarum	Ondansetron, IV	Retained and caution note added
	Granisetron, IV	Not added
6.14 Labour induction (Cervix favourable (Bishop score ≥7)	Foley catheter	Protocol updated to include extra-amniotic foley catheter with prostaglandins
	Non-stress test and cardiotocography	Monitoring updated
	Amniotomy	Guidance added for HIV-infected pregnant women on ART
	Oxytocin, IV	Dosing table amended
6.18 Postpartum haemorrhage	Dinoprost, parenteral	Deleted
	Tranexamic acid, IV	Not amended
	Carbetocin, parenteral (room temperature stable)	Not added
	Oxytocin, IM	Retained
6.19 The Rhesus negative woman	Anti-D immunoglobulin	Dose amended
6.20.1 Cystitis		
- Diagnosis for empiric antibiotic therapy	Dipstick (nitrites or leukocytes)	Retained
- Empiric antibiotics	Nitrofurantoin, oral	Retained
	Fosfomycin, oral	Added
	Cefuroxime, oral	Not added
Appendix III: Medicines used in pregnancy		
Table of teratogenic medicines	Macrolides, oral	Added, with a note indicating that evidence suggests risk associated with erythromycin, but there is uncertainty regarding associated risk with azithromycin and clarithromycin

Pfizer South Africa had submitted comments for the Obstetrics and Gynaecology chapters advising that misoprostol was recommended for off-label use in the STGs and EML; and that Pfizer would thus, not take responsibility for any litigation cases. Therefore, the following statement is recommended for inclusion to the preface of the Adult Hospital Level STGs and EML: *"Some recommendations might not be aligned with the SAHPRA/MCC registered label/package insert; but are guided by health needs assessment and the best available scientific evidence."*

6.1 ANAEMIA IN PREGNANCY

Prophylaxis

Folic acid, oral: *deleted with cross-reference to the PHC STGs and EML, 2018*
Ferrous sulfate, oral: *retained*
Ferrous fumarate, oral: *added*

Aligned with the PHC STGs and EML, 2018 that recommends an additional oral iron preparation. In addition, folic acid was deleted for prophylaxis of anaemia in pregnancy, aligned with chapter 2: Blood and blood forming organs, section 2.2: Anaemia, iron deficiency and the PHC STGs and EML, 2018 (see PHC NEMLC report below). However, a cross reference to Primary Health Care STGs and EML, section 6.4.1: Antenatal supplements was added for guidance on folic acid supplementation to prevent neural tube defects.

Re: PHC NEMLC report (2016-8), where folic acid, oral was removed for prophylaxis of anaemia in pregnancy:

"**Folic acid deficiency:** Guidance for folate deficiency was removed, aligned with the Adult hospital level STG (2015).
Rationale: Folate deficiency is now a rare cause of anaemia in pregnancy in South Africa. There is folate fortification of basic foods. Other causes of anaemia in pregnancy may be more common.
Level of Evidence: III Expert opinion

Megaloblastic anaemia: Folate deficiency is the commonest cause of megaloblastic anaemia, but this is a rare condition in South Africa and thus, folic acid was not added to iron supplementation to treat or prevent anaemia in pregnancy.
Rationale: Megaloblastic anaemia is an uncommon condition in pregnancy and evidence suggests that addition of folic acid to iron supplementation is not beneficial for prophylaxis of anaemia or to treat women with postpartum anaemia.
Level of Evidence: II Systematic review (low quality) [5], RCT (low quality) [6], Guidelines[7] [8] [9] [10], Expert opinion

[5]Yakoob MY, Bhutta ZA.Effect of routine iron supplementation with or without folic acid on anemia during pregnancy.BMC Public Health.2011 Apr 13;11Suppl3:S21. https://www.ncbi.nlm.nih.gov/pubmed/21501439
[6] Van Der Woude DA, De Vries J, Van Wijk EM, Verzijl JM, Pijnenborg JM. A randomized controlled trial examining the addition of folic acid to iron supplementation in the treatment of postpartum anemia.Int J Gynaecol Obstet. 2014 Aug;126(2):101-5. https://www.ncbi.nlm.nih.gov/pubmed/24839916
[7]ACOG Committee on Practice Bulletins. ACOG practice bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 44, July 2003. (Replaces Committee Opinion Number 252, March 2001) Obstet. Gynecol. 2003;102(1):203–213.
[8]U.S. Preventive Services Task Force. Folic acid for the prevention of neural tube defects: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009 May 5;150(9):626-31.

Treatment

Background: At the NEMLC meeting of 11 April 2019, the NEMLC recommended that the Adult Hospital Level Committee do a cost comparison of blood transfusion vs parenteral iron for anaemia in pregnancy – estimated costing follows below:

Direct medicine prices:

Medicine/Management	Price	Reference
• *Iron, IV administration*	*R271.80 – R1,221.70*	*Sec 6.1 Anaemia in pregnancy*
Iron sucrose, IV (600 mg in 3x200mL sodium chloride)	R 271.80	Contract circulars RT297-2019, RT299-2017.
Iron dextran, IV	R 1,221.70	
• *Blood transfusion*	*R9515.85*	*Sec 20.11.1.2.1 Massive transfusion*
Unit of blood x 1	R 2,201.26	SANBS State Patient Price List 2019-2020. https://sanbs.org.za/product-price-list/
FDP x 1	R 1,1141.49	
Platelets x 1	R 8,374.36	

The commonest reason for oral iron treatment failure is notably poor tolerance. However, other considerations includes the scarcity of blood as a resource, hospitalisation is required to do a blood transfusion; whilst parenteral iron can be administered as an outpatient/day patient.

A research question for the next review cycle is whether a treatment course of parenteral iron is comparable to a unit of transfused blood in terms of effectiveness and safety.

6.2 DIABETES MELLITUS IN PREGNANCY

Diagnostic criteria for Gestational Diabetes Mellitus (GDM)

Blood glucose thresholds: *not amended*

Thresholds: Guidelines are not universally accepted; and differ in different countries. The International Association of Diabetes and Pregnancy Study Groups (IADPSG)[11] recommend lower thresholds than the current STGs (adopted by most regions in South Africa) for the diagnosis of gestational diabetes. IADSPG thresholds are for fasting plasma glucose: 5.1 mmol/L and plasma glucose: 8.5 mmol/L two hours after an oral glucose tolerance test vs. STG recommendations of 5.6 mmol/L and 7.8 mmol/L, respectively. IADPSG criteria will result in an increased number of GDM cases and there is insufficient evidence for adopting these criteria in South Africa.

HbA1C: Diagnosing GDM using HbA1C was not accepted, as this has not been validated in the South African population. Refer to the October 2017 evidence summary: Should HbA1C be used as a diagnostic test for diabetes mellitus?

HbA1C for Diagnosising DM_A

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

An external comment was subsequently received from the South African Medical Association motivating to use threshold for gestational diabetes mellitus (GDM) as recommended by the International Association of Diabetes and the Pregnancy Study Groups (IADPSG). The current STG aligns with the NICE guidelines[12]. The commentator stated that *"the justification for not amending thresholds based on more recent recommendations should be more substantive than simply "it will increase the number of GDM cases".....given the complications, which have been*

[9]RCOG.Nutrition in Pregnancy: Scientific Impact Paper No. 18.

[10] Wilson RD; Genetics Committee, Wilson RD, Audibert F, Brock JA, Carroll J, Cartier L, Gagnon A, Johnson JA, Langlois S, Murphy-Kaulbeck L, Okun N, PastuckM; Special Contributors, Deb-Rinker P, Dodds L, Leon JA, Lowel HL, Luo W, MacFarlane A, McMillan R, Moore A, Mundle W, O'Connor D, Ray J, Van den Hof M. Pre-conception Folic Acid and Multivitamin Supplementation for the Primary and Secondary Prevention of Neural Tube Defects and Other Folic Acid-Sensitive Congenital Anomalies. J ObstetGynaecol Can. 2015 Jun;37(6):534-52.

[11] International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva Ad, Hod M, Kitzmiler JL, Lowe LP, McIntyre HD, Oats JJ, Omori Y, Schmidt MI. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010 Mar;33(3):676-82. https://www.ncbi.nlm.nih.gov/pubmed/20190296

[12] 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

associated with GDM, as well as the benefits in pregnancy outcomes, which have been associated with the appropriate treatment of the condition".

Evidence:

Adam and Rheeder et al (2017)[13]: Local study using the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria diagnosed an additional 25% pregnant women with GDM.

Risk vs benefit: Risks associated with applying the IADPSG criteria[14] was that more pregnant women would be diagnosed requiring management for diabetes mellitus; labour induction and C-section deliveries would increase (amongst women with impaired glucose tolerance and diabetes mellitus) with the newborn requiring management in High-care units. Clinically significant benefit for lowering the threshold is very limited, as this does not contribute to improving peri-natal mortality; though birth weights may be increased.

IADPSG criteria: The criteria was based on findings from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study[15], designed to achieve consensus in the diagnosis of GDM by investigating the impact of maternal glycemia, less severe than overt diabetes, on the risk of adverse pregnancy and neonatal outcomes. A linear increase in the risk of primary outcomes (LGA, cord C-peptide, clinical neonatal hypoglycemia (NH), and primary CS) with increasing degrees of hyperglycemia, as assessed by a fasting 75-g OGTT at fasting, 1 and 2 h was shown.

Arbitary cut-offs: Dichotomous targets for the fasting, 1- and 2-h values was selected even though the risks of adverse outcomes demonstrated strong linear relationships with these variables. An odds ratio of 1.75 times the mean was selected through expert opinion, for the outcomes of increased neonatal body fat, LGA, and cord c-peptide greater than the 90th percentile to arrive at the recommended diagnostic criteria for GDM. Plasma glucose levels corresponding to ≥OR of 1.75 were fasting ≥ 5.1 mmol/l; 2 h ≥ 8.5 mmol/l. GDM was diagnosed if one or more values were met, increasing the prevalence of GDM to a maximum of 25.5%[16]. Authors of a Cochrane review[17], concluded that "*There is insufficient evidence to suggest which strategy is best for diagnosing GDM. Large randomised trials are required to establish the best strategy for correctly identifying women with GDM".*

Cost-effectiveness and long-term benefit: IADSPG criteria could possibly be considered, if the costs of diagnosis and treatment can be controlled, lifestyle optimised and evidence of benefit can be shown for improving pregnancy and neonatal outcomes as well as long-term cardiometabolic benefits to mother and offspring. [18]

Recommendation: Diagnostic criteria for GDM be retained as the two-step OGTT.

Rationale: There is insufficient evidence showing that the IADSPG criteria for diagnosing GDM is clinically superior to the conventional two-step OGTT approach. In addition, an enabling environment would be required for the use of these criteria (see above).

Level of Evidence: I Systematic review[19], Guideline[20]

Preferred insulin regimen

Insulin: *dosing amended*

The test of the STG was updated as follows:

Starting dose may be based on previous insulin requirements, if known, or empiric starting dose: • ~~Insulin, intermediate acting, 12 units at bedtime with a bedtime snack.~~

[13] Adam S, Rheeder P. Screening for gestational diabetes mellitus in a South African population: Prevalence, comparison of diagnostic criteria and the role of risk factors. S Afr Med J. 2017 May 24;107(6):523-527. https://www.ncbi.nlm.nih.gov/pubmed/28604326

[14] International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva Ad, Hod M, Kitzmiler JL, Lowe LP, McIntyre HD, Oats JJ, Omori Y, Schmidt MI. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010 Mar;33(3):676-82. https://www.ncbi.nlm.nih.gov/pubmed/20190296

[15] Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358(19):1991–2002. https://www.ncbi.nlm.nih.gov/pubmed/18463375

[16] Brown FM, Wyckoff J. Application of One-Step IADPSG Versus Two-Step Diagnostic Criteria for Gestational Diabetes in the Real World: Impact on Health Services, Clinical Care, and Outcomes. Curr Diab Rep. 2017 Aug 10;17(10):85. https://www.ncbi.nlm.nih.gov/pubmed/28799123

[17] 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

[18] Of note is that consensus was not reached amongst IADPSG members, with 60% opting for the IADPSG criteria; whilst 30% preferred the two-step method - Ogunyemi DA, Fong A, Rad S, Fong S, Kjos SL. Attitudes and practices of healthcare providers regarding gestational diabetes: results of a survey conducted at the 2010 meeting of the International Association of Diabetes in Pregnancy Study Group (IADPSG) Diabet Med. 2011;28(8):976–986. https://www.ncbi.nlm.nih.gov/pubmed/21535123

[19] 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

[20] 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

~~Insulin, soluble, short acting8 units 30 minutes before each of the three main meals (breakfast, lunch and supper).~~

- Insulin, short acting with all 3 meals to maintain the post prandial levels.

AND

- Insulin, intermediate acting at bedtime (with a bedtime snack) to maintain preprandial levels.

Insulin dosing:

  - Total daily dose: 0.5 units/kg/day,
  - One third of the total dose: intermediate acting insulin at bedtime.
  - The remaining two thirds divided into three equal doses are given before each meal (breakfast, lunch and supper).

Adjust insulin dosage daily according to blood glucose profiles, until control is adequate.

Where the above recommended regimen is not feasible

Twice-daily regimen with biphasic insulin.

~~Empiric starting dose if previous insulin requirements are not known:~~

- Insulin, biphasic.

Level of Evidence: I RCT[21]

6.3 HEART DISEASE IN PREGNANCY

Spironolactone: *contra-indication added*

Spironolactone crosses the placenta, is anti-androgenic and is associated with feminisation of male fetuses in animals. Contra-indication to spironolactone in pregnancy was added to the text of the STG.

Level of Evidence: III Guidelines[22]

Enoxaparin, SC: *indication(s) amended (valvular heart disease only; women with prosthetic heart valves referred)*

Unfractionated heparin, IV/SC: *indication(s) amended (valvular heart disease only; women with prosthetic heart valves referred)*

Contraception counselling: *guidance strengthened*

A medicine review was commissioned to compare the efficacy and safety of low molecular weight heparin (LMWH) and unfractionated heparin (UFH) compared to current standard of care in the management of pregnant women with prosthetic health valves. (The review is currently in draft format, undergoing further development, to inform management at tertiary level of care).

Recommendation: Based on this evidence review, the Adult Hospital Level Committee recommended that for women with mechanical heart valves, who conceive despite contraception, termination of pregnancy (TOP) should be offered routinely. This should be done as early in pregnancy as possible. Women who decline TOP must receive the care of a specialist team that should include an obstetrician and cardiologist. Access to echocardiography and laboratory services are essential. Care should be centralised, where possible.

This medicine review and proposed treatment algorithm will be able to inform management of pregnant women with mechanical heart valves, at Tertiary and Quaternary level of care – to be referred to the Tertiary and Quaternary Expert Review Committee.

Rationale: Available evidence shows an unacceptably high maternal mortality rate and considerable maternal morbidity associated with valvular heart disease (requiring prosthetic valves) and its treatment.

Level of Evidence: III Systematic review of observational studies, Guidelines

Review indicator: Tertiary and Quaternary level review

The STG was amended accordingly providing the following guidance:

- *Indications:* Guidance for anticoagulation therapy be restricted to pregnant women with valvular heart disease; whilst pregnant women with prosthetic valves be offered the option of TOP or be referred to tertiary level of care for management by a multi-disciplinary team.
- *Contraception:* Young women with prosthetic valves should be offered contraception; whilst those with valvular heart disease should be guided to consider completing their family early followed by appropriate family planning, before progressing to requiring mechanical valves.

[21] 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

[22] SAMF, 2016

6.4 HYPERTENSIVE DISORDERS IN PREGNANCY

Methyldopa, oral: *dosing not amended*

Query regarding the discrepancy between the NDoH Maternal Health Care Guidelines, 2012 and Adult Hospital Level STGs and EML, 2015 for methyldopa for management of hypertension in pregnancy, was received.

FIGO Guidelines: NDoH Maternal Care Guidelines aligned with International Federation of Gynecology and Obstetrics (FIGO) guidelines[23], recommending methyldopa 500 mg 8 hourly, oral.

Pharmacokinetic study: Adult Hospital STGs and EML, recommends, *"Methyldopa, oral, 250 mg 8 hourly as a starting dose - increase to a maximum of 750 mg 8 hourly, according to response".* It is noted that this aligns with the SAMF, 2016[24]; whilst a pharmacokinetic study[25] suggests that 12 hourly dosing is feasible.

Recommendation: Methyldopa, oral dosing retained as, **"***250 mg 8 hourly as a starting dose - increase to a maximum of 750 mg 8 hourly, according to response*".

Level of Evidence: III Pharmacokinetic study, Guidelines

Prevention of pre-eclampsia

Aspirin, oral: *directions for use and dosing amended*

i. Directions for use:

Refer to evidence summary: Safety of aspirin in pregnancy, February 2020.

Aspirin in pregnancy_Adultsre

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

The recently published ASPIRIN trial[1] showed that low-dose aspirin – when taken between 6 weeks & 16 weeks gestation – significantly reduced perinatal mortality, fetal death, early preterm birth, as well as preterm delivery among pregnant women with hypertensive disorders. Aspirin use in early pregnancy was not associated with fetal loss, miscarriage, excessive vaginal bleeding, birth defects or medical TOP.

Recommendation: Aspirin be initiated from 6 weeks gestation for the prevention of pre-eclampsia.

Level of Evidence: I RCT

ii. Dosing:

NEMLC MEETING OF 26 SEPTEMBER 2019:

Further deliberations were made by NEMLC at the meeting of 26 September 2019, noting that the current tender price of "100 mg" is more expensive than the "150 mg"[26].

Recommendation: Aspirin be recommended as a daily dose of 150 mg throughout the STGs, until such time that there is price parity. Doses of 100 mg and 81 mg to be added to the Adult Hospital Level Therapeutic Interchange database.

Level of Evidence: III Expert opinion

6.7 HIV IN PREGNANCY

Tenofovir + emtricitabline + efavirenz, oral (TEE): *indication amended to <6weeks gestation or wishing to conceive again*

Tenofovir + lamivudine + dolutegravir, oral (TLD): *added*

[23] International Federation of Gynecology and Obstetrics. The FIGO Textbook of Pregnancy Hypertension. http://www.safemotherhood.ucsf.edu/wp-content/uploads/2013/01/FIGO-Pregnancy_Hypertension-Final.pdf

[24] SAMF, 2016

[25] Wright JM, Orozco-Gonzalez M, Polak G, Dollery CT. Duration of effect of single daily dose methyldopa therapy. Br J Clin Pharmacol. 1982 Jun;13(6):847-54. https://www.ncbi.nlm.nih.gov/pubmed/7093115

[26] Tender price – contract circular RT289-2019: Aspirin 100 mg single tablet = R 0.502; Weighted average price of aspirin 300 mg tablet = R0.211 [Accessed 8 October 2019]

Aligned with 2019 NDoH PMTCT Guidelines[27] that recommends TEE for pregnant women <6 weeks gestation and/or wishes to conceive more children; whilst TLD recommended for pregnant women presenting at > 6 weeks gestation or who choose TLD once understanding the risk and benefits of DTG. Switching between regimens requires a suppressed viral load of less than 50 copies/ml in the last 6 months.
Level of Evidence: III Guidelines

Active psychiatric illness in HIV-infected pregnant women (EFV contraindicated):
Tenofovir + lamivudine + dolutegravir, oral (TLD): *added*
Aligned with 2019 PMTCT HIV Guidelines.

Active psychiatric illness in HIV-infected pregnant women and DTG not suitable:
Nevirapine + Tenofovir + Emtricitabine, oral: *not added*
Nevirapine + Zidovudine + Lamivudine, oral: *not added*
Lopinavir/ritonavir + Tenofovir + Emtricitabine, oral: *added*
Lopinavir/ritonavir + Zidovudine + Lamivudine, oral: *added*

NEMLC MEETING OF 30 JANUARY 2020:
The NEMLC recommended that nevirapine not be considered as an ART regimen in HIV-infected pregnant women, due to the toxicity associated with nevirapine. It is noted that this is not aligned with the 2019 PMTCT HIV Guidelines and the NEMLC recommended that the National Programme be advised accordingly.

HIV infected pregnant women in labour not on ART:
Nevirapine + Tenofovir +Emtricitabine, oral (single dose): *deleted*
Nevirapine,oral (single dose): *added*
Tenofovir + lamivudine + dolutegravir, oral (TLD): *added*
Aligned with 2019 PMTCT HIV Guidelines, noting that the HIV-exposed infant would receive appropriate antiretroviral treatment according to risk category.
Level of Evidence: III Guidelines

HIV infected pregnant women undergoing Caesarean section not on ART:
Nevirapine + Tenofovir +Emtricitabine, oral (single dose): *deleted*
Zidovudine, oral (3 hourly until delivery): *deleted*
Nevirapine,oral (single dose): *added*
Tenofovir + lamivudine + dolutegravir, oral (TLD): *added*
Aligned with 2019 NDoH PMTCT Guidelines, noting that the HIV-exposed infant would receive appropriate antiretroviral treatment according to risk category.
Level of Evidence: III Guidelines

NEMLC MEETING OF 6 DECEMBER 2018:
The PMTCT Technical working group (TWG) presented the proposed changes to the NDoH PMTCT Guidelines to NEMLC.

The NEMLC requested that the PMTCT Technical working group provide the evidence for single dose tenofovir+lamivudine+dolutegravir (TLD) to prevent MTCT of HIV in women presenting in labour not on ART, as evidence presented was for 10-14 days of antiretroviral therapy:
"RCT evidence[28] showed that at two weeks postpartum viral suppression (< 50 copies/ml) with DTG- was significantly higher compared to EFV, 69% (20) and 39% (12), p = 0.02. Pharamacokinetic data showed that 10-day DTG monotherapy reduced VL < 50 copies/mL[29]".

[27] South African National Department of Health South Africa. Guideline for the Prevention of Mother to Child Transmission of Communicable Infections, October 2019. https://www.knowledgehub.org.za/elibrary/guideline-prevention-mother-child-transmission-communicable-infections
[28] Orrell C, Kintu K, Coombs JA, Amara A, Myer L, et al. DolPHIN-1: randomised controlled trial of dolutegravir (DTG) - versus efavirenz (EFV)-based therapy in mothers initiating antiretroviral treatment in late pregnancy. 22nd International AIDS Conference (AIDS 2018), Amsterdam, abstract THAB0307LB, July 2018. http://programme.aids2018.org/Abstract/Abstract/13144
[29] Article circulated after the meeting: Min S, Sloan L, DeJesus E, Hawkins T, McCurdy L, Song I, Stroder R, Chen S, Underwood M, Fujiwara T, Piscitelli S, Lalezari J. Antiviral activity, safety, and pharmacokinetics/ pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults. AIDS. 2011 Sep 10;25(14):1737-45.

Electronic discussion[30] after the NEMLC meeting of 6 December 2018:

PMTCT TWG acknowledged NEMLC recommendations and proposed a "more evidence-based option" for women presenting in labour and not yet on ART:

1. A single dose of NVP, together with
2. A single dose of TLD

Rationale: Evidence[31] exists for the effectiveness of NVP as a single immediate dose administered in labour and it therefore will remain in the regimen. FTC+TDF was used to "cover the tail" in the era where not all women were eligible for ART post-delivery. For AZT 3-hourly there was never really any evidence. It was just what we had at the time, and what was thought would be effective way back at the start of the program. However, all women now qualify for ART, and an immediate single dose of TLD provides the first dose of a lifelong regimen, and removes the need for either FTC+AZT or AZT 3-hourly during labour. cART is to be continued the following day after understanding her fertility intentions and counselling her appropriately on the risk of DTG-associated NTD for her subsequent pregnancies. TLD can be continued if she is willing to use effective contraception. Alternatively, an EFV containing regimen (TEE) can be prescribed if DTG is not appropriate.

Level of Evidence: I Systematic review, Expert opinion

NEMLC accepted the updated proposed recommendation.

6.8 SYPHILIS

Pregnancy and breastfeeding

Benzathine benzylpenicillin, parenteral: *dosing amended*

Background: A query had been received from the Mental Health Directorate, via the Clinton Health Access Initiative regarding the apparent misalignment of the Adult Hospital Level STGs and EML, 2019 edition with the WHO Syphilis Guidelines, 2016.

The recommendations are as follows:

Cited WHO Syphilis Guidelines, 2016[32]	Adult Hospital Level STGs and EML, 2019 edition[33]
Pregnant women: **Recommendation 3** In pregnant women with early syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units once intramuscularly over no treatment.	**Section 6.8: Syphilis** **Mother** • 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.

Testing for syphilis: Syphilis testing in pregnancy is a rapid test, which does not show the stage of disease. A cross-reference to Primary Health Care STGs and EML, section 12.8: Syphilis serology and treatment, was added.

Local setting: Pregnant women generally report late for antenatal care and are asymptomatic.

WHO Guidelines: WHO Guidelines also recommends that unknown stages of disease be treated as late syphilis, which is the current standard of care in pregnancy.

NEMLC MEETING OF 11 JUNE 2020:

Early vs late-latent syphilis: The STG guidance for benzathine benzylpenicillin (x3 doses) was for pregnant women of unknown stages of disease or with late –latent syphilis. In public sector, pregnant women generally report late for antenatal care and are asymptomatic. However, given the supply constraints of benzathine benzylpenicillin, it was recommended that guidance be included for managing pregnant women with single dose of benzathine benzylpenicillin when they present with early syphilis.

NEMLC RECOMMENDATION: Guidance in the STG was amended from:

[30] E-mail on file: 18 December 2018 from Dr J Wessels.

[31] Siegfried N, van der Merwe L, Brocklehurst P, Sint TT. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. Cochrane Database Syst Rev. 2011 Jul 6;(7):CD003510. https://www.ncbi.nlm.nih.gov/pubmed/21735394

[32] World Health Organization: WHO Guidelines for the treatment of Treponema palladum (syphilis), 2016. https://www.who.int/reproductivehealth/publications/rtis/syphilis-treatment-guidelines/en/

[33] National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, 2019. http://www.health.gov.za/

~~**Mother (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.~~

To:

Mother (treat as either early or late latent/unknown or early 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

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

Level of Evidence: III Guidelines[34] [35]

6.11 HYPEREMESIS GRAVIDARUM

Ondansetron, IV: *retained and caution note added*

Background: Dear Healthcare provider letter received from Novartis/South African Health Products Regulatory Authority providing medicine safety information regarding the increased risk of cleft lip and/or cleft palate associated with ondansetron during the first 12 weeks of pregnancy.

United Kingdom Teratology Report, September 2019: Available evidence is conflicting[36] [37] and it is uncertain if there is an association between fetal cleft palate and maternal ondansetron use in the first trimester. If there is a risk, the absolute risk (considering the background risk) was reported to be small equating to approximately two additional cases of cleft palate in every 10,000 ondansetron-exposed pregnancies relative to the expected background rate of 5.7 per 10,000.

Huybrechts et al, 2020[38]*:* Analysis of a previous population cohort (1 880 594 pregnancies) found no significant association of maternal oral ondanetron, administered in the first trimester, and congenital malformations; but a small increased risk of oral clefts could not be excluded.[6]

Analysis of the same dataset showed that ondansetron, IV was not associated with an increase in the risk of cardiac malformations, oral clefts, or congenital malformations overall:

- Oral clefts: aRR 0.95 (95%CI,0.63 to 1.43) and the aRD−0.5 (95%CI, −4.5 to 3.5) per 10000 births.
- Cardiac malformations: aRR 0.97 (95% CI, 0.86 to1.10) and the aRD −2.9 (95% CI, −15.7 to 9.8) per 10000 births.
- Congenital malformations, overall: RR 1.02 (95% CI, 0.96-1.08) and RD 7.1 (95% CI, −17.9 to 32.2) per 10000 births.

(RR=relative risk; RD=risk difference; a=adjusted after propensity score matching)

However, limitations include risk of bias and potential for residual confounding in this observational study.

Recommendation: The text of the STG was updated as follows, describing the uncertainty of the risk of fetal cleft palate associated with maternal ondansetron use in the first trimester:

[34] World Health Organization: WHO Guidelines for the treatment of Treponema palladum (syphilis), 2016. https://www.who.int/reproductivehealth/publications/rtis/syphilis-treatment-guidelines/en/

[35] Workowski KA, Bolan GA: Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2015.MMWR Recomm Rep. 2015;64; RR-3):1-140. http://www.cdc.gov/std/tg2015/tg-2015-print.pdf

[36] 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/

[37] 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/

[38] 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/

Correct electrolyte imbalance with IV fluids.

- Pyridoxine, oral, 25 mg 8 hourly.

AND

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

AND

- Vitamin B complex, IV, 10 mL.

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.

Level of Evidence: III Observational studies

Gransiteron, IV*: not added*

Evidence for gransiteron, IV and the possible class effect of 5-HT3 inhibitors l in hyperemesis gravidarum is limited.

6.14 LABOUR INDUCTION

Cervix favourable (Bishop score ≥7)

Oxytocin, IV: *dosing table amended*

Dosing table was amended as follows, aligned with NICE Guidelines[39]:

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

Foley catheter: *protocol updated to include extra-amniotic foley catheter **with** prostaglandins*

Refer to the March 2019 summery report, Foley catheter bulb for induction of labour:

FoleyCatheterBulb-LabourInduction_Ac

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recently published RCT (2018) [40] aligns with 2018 study done in Botswana[41], Cochrane review (2012) [42] and WHO recommendations[43]; for induction of labour, with regards to using foley catheter with prostaglandins. Protocol in the STG was updated, accordingly.

Level of Evidence: I RCTs, Systematic review, Guidelines

Non-stress test and cardiotocography: *monitoring updated*

[39] NICE Clinical Guideline: 70 - Induction of labour, 2008. https://www.nice.org.uk/guidance/cg70/evidence/cg70-induction-of-labour-full-guideline2

[40] 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.

[41] 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.

[42] Jozwiak M, Bloemenkamp KW, Kelly AJ, Mol BW, Irion O, Boulvain M. Mechanical methods for induction of labour. Cochrane Database Syst Rev. 2012 Mar 14;(3):CD001233.

[43] Jozwiak M, Bloemenkamp KW, Kelly AJ, Mol BW, Irion O, Boulvain M. Mechanical methods for induction of labour. Cochrane Database Syst Rev. 2012 Mar 14;(3):CD001233.

Cardiotograph monitoring during labour induction was updated, guided by expert opinion (Prof Justus Hofmeyer) as there is a lack of evidence in this clinical setting.
Level of Evidence: III Expert opinion

Amniotomy: *guidance added for HIV-infected pregnant women on ART*
Evidence from an observational study[44] suggests that it is safe to perform amniotomy in pregnant women with HIV on ART who have an undetectable plasma VL at delivery. STG text updated to mention this.
Level of Evidence: II Observational study

6.18 POSTPARTUM HAEMORRHAGE

Treatment
Dinoprost, parenteral: *deleted*
Tranexamic acid, parenteral: *not amended*

Dinoprost: Global discontinuation of parenteral dinoprost warrants deletion of this medicine from the Adult Hospital EML. The alternative agent carboprost is currently not available in the South African market and to date no application for registration appears to have been submitted to the South African Health Products Regulatory Authority.

Tranexamic acid: Refer to the medicine review, tranexamic acid injection for PPH (October 2017):

TranexamicAcid for PPH_AdultsReview_1

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review, the Adult Hospital Level Commitee recommended that the current treatment algorithm for PPH with TXA after oxytocinin and ergometrine be retained in the STG.
Rationale: As per RCT recommendations tranexamic acid should be given within three hours after bleeding onset.
Level of Evidence: I RCT[45]

TXA, IV at primary level of care:
The National Committee of Confidential Enquires into Maternal Deaths (NCCEMD) requested that consideration be made to access TXA injection at primary level of care for PPH cases not responding to oxytocin and ergometrine. Currently, TXA IV is only included in the Adult Hospital Level EML.

WOMAN trial: E-mail communication from the investigators verified that risk factors for PPH were not collected and that the trial was done in the emergency situation.[46]

Rationale provided for inclusion of TXA, IV on the PHC EML:
Savings Mother report (2011-2013)[47] reported that 15.9% (684) PPH cases caused maternal deaths; of which 2% occurred at primary level of care; whilst 36.7% occurred at secondary level facilities. The PHC STG recommends that where blood loss is greater than 500 mL, oxytocin/ergometrine to be administered with referral to secondary level of care.

CRASH-2 study: Both the CRASH-2[48] and the WOMAN studies showed a mortality benefit if TXA IV was administered within 3 hours of trauma or PPH. The WOMAN trial showed no additional statistical significant benefit or harm if TXA, IV was administered to women with PPH due to uterine atony beyond 3 hours.

Pragmatic implications: From a pragmatic perspective, early access to TXA IV at primary level of care may be beneficial due to the quick onset and severity of PPH and early administration of TXA, once it is clear that there has

[44] 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
[45] 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
[46] E-mail communication from WOMAN trial investigator, 28 November 2017, on file.
[47] National Department of Health: National Committee for the Confidential Enquiries into Maternal Deaths Saving Mothers Report, 2011-2013.
[48] CRASH-2 Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised placebo-controlled trial. Lancet 2010; 376: 23-32. https://www.ncbi.nlm.nih.gov/pubmed/20554319

been no response to initial oxytocin/ergometrine treatment. Access to TXA at midwife obstetric units (MOUs) may reduce referrals for PPH up to a higher level of care. Furthermore, there may be considerable delay in transferring women with PPH from an MOU to a higher level of care, either due to the long distance to the nearest hospital, or the from delay awaiting arrival of emergency medical services (EMS) at the MOU. This would necessitate additional training regarding intrapartum and emergency obstetric care for primary level healthcare workers.

NEMLC RECOMMENDATION:

The NEMLC did not accept the proposal to include TXA IV on the primary health care EML. (However, inclusion on the Adult Hospital Level EML was acceptable).

Rationale:

- "The **composite primary endpoint of death** from all causes or hysterectomy was not reduced with tranexamic acid (534 [5·3%] deaths or hysterectomies in the tranexamic acid group vs 546 [5·5%]
- in the placebo group, RR 0·97, 95% CI 0·87-1·09; p=0·65)"; **statistically not significant.** Death due to bleeding where tranexamic acid was administered within 3 hours of birth was a secondary endpoint. The effect size was small: ARR of 0.5% with NNT of 200 (1.2% in the tranexamic acid group vs 1.7% in the placebo group).
- Generalisability of the results of the WOMANS Trial to the local primary health care setting was not possible, as the trial was done in an emergency hospital setting.
- Referral to higher level of care for appropiate management from primary level may be delayed.

Level of Evidence: I RCT

Review indicator: Evidence of efficacy and safety in primary care setting.

Prevention

Carbetocin, parenteral (room temperature stable, rts): *not added*

Oxytocin, IM: *retained*

Refer to the medicine review, carbetocin for the prevention of PPF (January 2019):

Carbetocin for prevention of PPH_A

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review the Adult Hospital Level Expert Review Committee (ERC) acknowledges that the evidence of efficacy shows that carbetocin rts is not inferior to oxytocin for the prevention of PPH. However, the ERC reccomends that carbetocin not be included on the EML for PPH prophylaxis, until there is a substantial price reduction comparable to oxytocin which is the current standard of care.

Where oxytocin is unavailable, oxytocin and ergometrine combination can be considered, provided there are no complications of heart disease and hypertension.

Level of Evidence: II Network meta-analysis of disease oriented RCTs[49], disease oriented RCT[50]

Review indicator: Price reduction

Additional considerations:

- *World Health Organisation information:* The supply cost of carbetocin rts is approximately 20 times more than that of oxytocin. Evidence on effects suggests that for most priority outcomes, its effects are similar or possibly superior to those of oxytocin. However, if the supply cost of carbetocin rts becomes comparable to that of oxytocin (as indicated in the memorandum of understanding signed between WHO and manufacturer of a heat-stable formulation of carbetocin) then moderate to large cost savings can be expected in the longer term given that other resource requirements (e.g. staff and supplies) are similar between carbetocin rts and oxytocin.
- *Systems issues:* NCCEMD Saving Mothers report: 3rd most common cause of death was postpartum

[49] Gallos ID, Williams HM, Price MJ, Merriel A, Gee H, Lissauer D, Moorthy V, Tobias A, Deeks JJ, Widmer M, Tunçalp Ö, Gülmezoglu AM, Hofmeyr GJ, Coomarasamy A. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database Syst Rev. 2018 Apr 25;4:CD011689. https://www.ncbi.nlm.nih.gov/pubmed/29693726

[50] Widmer M, Piaggio G, Nguyen TMH, Osoti A, Owa OO, Misra S, Coomarasamy A, Abdel-Aleem H, Mallapur AA, Qureshi Z, Lumbiganon P, Patel AB, Carroli G, Fawole B, Goudar SS, Pujar YV, Neilson J, Hofmeyr GJ, Su LL, Ferreira de Carvalho J, Pandey U, Mugerwa K, Shiragur SS, Byamugisha J, Giordano D, Gülmezoglu AM; WHO CHAMPION Trial Group. Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth. N Engl J Med. 2018 Aug 23;379(8):743-752.

haemorrhage, after C-section. The report described the root-cause as systems- rather than medicine-related issues; and the Adult Hospital Level Committee was of the opinion that this needs to be addressed.

- *Oxytocin/ergometrine:* Uptake of oxytocin/ergometrine was currently reported to be very low.
- *Cost minimisation analysis:* University of Cape Town post-graduate student volunteered to assist with an economic evaluation on this technology for due diligence purposes. However, during the scoping of this project, the Adult Hospital Level Committee realised that a cost minimisation analysis (comparison of direct medicine prices) was merely required, especially as all primary health care facilities in South Africa are required to have a fridge on site (as per the Ideal Clinic requirements). Thus, carbetocin rts can be considered for inclusion to the EML when the price is the same as oxytocin.

NEMLC MEETING OF 5 DECEMBER 2019:
NEMLC accepted the Adult Hospital Level Committee's proposal not to include carbetocin, room temperature stable formulation on the Adult Hospital Level EML as it is currently cost-prohibitive.
Rationale: Health systems strengthening was required through an adequate service delivery platform to ensure adequate cold chain distribution and appropriate storage of the currently recommended medicine, oxytocin, IV. It was considered unreasonable to pay for a more expensive medicine, because the health system was insufficient and fridges were not available at all healthcare facilities.
It was further recommended that the National Department of Health engage with relevant parties to access carbetocin rts at the agreed upon price that was available to low middle income countries.

6.19 THE RHESUS NEGATIVE WOMAN

Anti-D immunoglobulin: *dose amended*

Doses amended to align with Guidelines:

After a termination of pregnancy (TOP), miscarriage, ectopic pregnancy or amniocentesis <20 weeks:
- Anti-D immunoglobulin, IM, 50 ~~100~~ mcg.

After external cephalic version or potentially sensitizing event ≥20 weeks:
- Anti-D immunoglobulin, IM, 100 mcg.

Level of Evidence: III Guidelines[51]

Wastage: National Bioproduct Institute is the sole supplier of anti-D immunoglobulin and there are concerns that as this product is only available as a 100 mcg formulation, wastage occurs when only 50 mcg is required. It was recommended that the NDoH discusses this matter with the supplier.

6.19.1 CYSTITIS

Nitrofurantoin, oral: *retained*
Fosfomycin, oral: *retained*
Cefuroxime, oral: *not added*

Nitrofurantoin and Fosfomycin, oral
Recommendations aligned to Chapter 7: Nephrological and urological conditions, section 7.3.2: Urinary tract infection (UTI) (refer to the respective NEMLC report).

Cefuroxime
Refer to the medicine review, cefuroxime for UTI in pregnancy (November 2017):

[51] 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

Cefuroxime for UTI in pregnancy_Adults

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Cefuroxime: Refer to the review: Cefuroxime for UTI in pregnancy, 21 November 2017.
Fosfomycin is an expensive medicine for use in the public healthcare sector.
ORACLE data: There is an increased risk of necrotising enterocolitis in preterm neonates in women with PPROM that are administered co-amoxyclav, as shown in the Oracle I RCT[52]. However, in the Oracle II RCT[53], women in spontaneous preterm labour with intact membranes (i.e no rupture of membranes) and no evidence of clinical infection were randomised to antibiotics (including co-amoxyclav); and it was shown that antibiotics were not effective and the neonates experienced no adverse effects. However, local susceptibility study indicated higher susceptibility of gram negative bacilli to fosfomycin, cefuroxime and nitrofurantoin compared to co-amoxyclav.[54]

Recommendation: Based on the review of the evidence, the Adult Hospital Level Committee recommended that cefuroxime be recommended in the event nitrofurantoin is not available.
Rationale: Cefuroxime is comparable to fosfomycin in terms of effectiveness and safety. However, better compliance is anticipated with fosfomycin that is administered as a single dose. In view of the price disparity between fosfomycin versus cefuroxime, fosfomycin should only be recommended if there's a substantial reduction in price, similar to its price in parts of Europe.
Level of Evidence: I Systematic review[55], RCTs[56] [57], Susceptibility data, Expert opinion

NEMLC MEETING OF 1 FEBRUARY 2018, 21 FEBRUARY 2019 AND 11 APRIL 2019
The NEMLC did not accept the Adult Hospital Level Committee recommendation to include cefuroxime on the Adult Hospital Level EML.

Rationale:
- Nitrofurantoin and fosfomycin recommended for uncomplicated cystitis was considered to be sufficient.
- Cefuroxime could be considered if these agents are out of stock, but should be recommended via a circular. Furthermore, introducing a second generation cephalosporin, cefuroxime, to the EML for this indication would probably result in indication creep.

Level of Evidence: III Expert opinion
Review indicator: Current susceptibility studies.

APPENDIX III: MEDICINES IN PREGNANCY

Macrolides, oral: listed as a teratogenic medicine as a class (

Evidence review:
A retrospective study, of children born between 1990-2016, of mothers exposed to macrolides from 1st trimester of

[52] Kenyon SL, Taylor DJ, Tarnow-Mordi W et al. Broad-spectrum antibiotics for preterm prelabour rupture of fetal membranes: the ORACLE I randomised trial. Lancet 2001; 357: 979-88.
[53] Kenyon SL, Taylor DJ, Tarnow-Mordi W; ORACLE Collaborative Group. Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial. ORACLE Collaborative Group. Lancet. 2001 Mar31;357(9261):989-94.
[54] Lewis DA, Gumede LYE, van der Hoven LA, de Gita GN, de Kock EJE, de Lange T, et al. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. S Afr Med J 2013; 103(6): 377-81. http://www.ncbi.nlm.nih.gov/pubmed/23725955
[55] Vazquez JC, Abalos E. Treatments for symptomatic urinary tract infections during pregnancy. Cochrane Database Syst Rev. 2011 Jan 19;(1):CD002256. https://www.ncbi.nlm.nih.gov/pubmed/21249652
[56] Usta TA, Dogan O, Ates U, Yucel B, Onar Z, Kaya E. Comparison of single-dose and multiple-dose antibiotics for lower urinary tract infection in pregnancy. Int J Gynaecol Obstet. 2011 Sep;114(3):229-33. https://www.ncbi.nlm.nih.gov/pubmed/21696732
[57] Estebanez A, Pascual R, Gil V, Ortiz F, Santibáñez M, Pérez Barba C. Fosfomycin in a single dose versus a 7-day course of amoxicillin-clavulanate for the treatment of asymptomatic bacteriuria during pregnancy. Eur J Clin Microbiol Infect Dis. 2009 Dec;28(12):1457-64. https://www.ncbi.nlm.nih.gov/pubmed/19768649

pregnancy[58], found an association between macrolide exposure in the first trimester and congenital anomalies, specifically cardiovascular malformations. Beyond 13 weeks gestation, an association of macrolides with genital malformations was reported.

- *Study methodology:*
  - Macrolides were compared to penicillin – but there are additional confounders that includes the type of infection and the severity of infection, and it is not reported whether this was accounted for in both study cohorts. Thus, there is uncertainty as to whether the baseline study groups were comparable. An additional confounder that was not considered was that maternal infection transmitted to the fetus may result in birth defects.
  - Baseline demographics in the two study cohorts differed with more alcohol misuse, tobacco misuse, illicit drug use reported in the macrolide group (though propensity scores were adjusted). And, details of chronic therapy in hypertensive and epileptic pregnant women were not provided, to determine if any were teratogenic. Also, co-morbid diabetes is an additional confounder that could contribute to birth defects.
  - Data on adherence to treatment has likewise not been reported, noting that patients were not interviewed/surveyed regrading compliance. Macrolides may be considerable less tolerable than penicillin, especially erythromycin that is associated with gastro-intestinal side effects. Thus, there is uncertainty regarding the completion of antibiotic treatment courses.
  - Macrolides were evaluated as a class, though the article does state, *"Findings for clarithromycin had wide confidence intervals and analyses for azithromycin were precluded because of few events".* Of the 8632 women, 151 women took azithromycin (and the trimester was not specified), 7987 took erythromycin and 494 took clarithromycin. Although 92.6% of macrolide exposures were associated with erythromycin, there is uncertainty whether or not this is a class effect. Associations with clarithromycin exposure in the supplementary table S8 are in the same direction as for erythromycin, although the estimates lack precision. The number of events associated with azithromycin and clarithromycin has not been reported and additional data has been requested from the investigators of this study.

Recommendation: Macrolide class be listed in the teratogenic table of medicine in Appendix III in the Adult Hospital Level STGs and EML, 2019 edition, as follows:

Macrolides	In a large population-based cohort study, when compared to penicillin, first trimester macrolide exposure was associated with increased risk of cardiovascular malformations, and macrolide exposure in any trimester was associated with increased risk of genital malformations. The majority of macrolide exposures in this study (93%) were to erythromycin, but a class effect cannot be ruled out. Macrolides should only be prescribed in pregnancy when clearly indicated.

Rationale: Observational evidence suggests that macrolides may be associated with a risk of cardiovascular malformations in the first trimester, and an increased risk of genital malformations in any trimester. Majority of exposures was attributable to erythromycin, but data is insufficient to determine an association with clarithromycin or azithromycin - further research is required. Despite the safety of azithromycin and clarithromycin not being established in pregnancy (due to uncertainty of the evidence), the macrolide class effect on congenital malformations cannot be ruled out. Until further evidence is forthcoming, azithromycin should be considered during pregnancy where the benefit has been weighed against the risk and where other alternative options are not available.

Level of Evidence: III Systematic review of observational studies, Expert opinion

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)
- ***Note:*** *Information sourced from NEMLC ratified minutes and NEMLC-approved documents.*

[58] Fan H, Gilbert R, O'Callaghan F, Li L. Associations between macrolide antibiotics prescribing during pregnancy and adverse child outcomes in the UK: population based cohort study. BMJ. 2020 Feb 19;368:m331. https://www.ncbi.nlm.nih.gov/pubmed/32075790