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SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 6: OBSTETRICS & GYNAECOLOGY CONDITIONS
NEMLC RECOMMENDATIONS FOR MEDICINE MANAGEMENT (2016 – 2018)

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

SECTION	MEDICINE	ADDED/DELETED/AMENDED
OBSTETRICS		
6.2.Miscarriage	Anti-D immunoglobulin	Retained
6.2.1 Management of incomplete miscarriage in the 1st trimester, at primary health care level	Misoprostol, oral/PV	Deleted
	Pethidine, IM	Not added
	Morphine, IM	Added
	Paracetamol, oral	Added
	Ibuprofen, oral	Added
6.2.2 Antepartum haemorrhage	Sodium chloride 0.9%, IV	Retained
6.3.1 Management of termination of pregnancy at primary health care level: gestation ≤12 weeks (and 0 days)	Mifepristone, oral	Added
	Misoprostol	Added
	Paracetamol, oral	Added
	Morphine, IM	Added
	Ibuprofen, oral	Added
	Anti-D Immunoglobulin, IM	Added
6.4.1 Antenatal supplements	Folic acid, oral	Added
	Ferrous sulphate compound BPC, oral	Added
	Ferrous fumarate, oral	Added
	Calcium carbonate, oral	Added
6.4.2.1 Chronic hypertension	Methyldopa, oral	Amended (All cases referred)
6.4.2.2 Gestational hypertension: mild to moderate	Methyldopa, oral	Directions for use not amended
6.4.2.3 Gestational hypertension: severe	Nifedipine, oral	Directions of use amended
	Sodium chloride 0.9% IV	Deleted
	Labetalol, IV	Not added
6.4.2.4 Pre-eclampsia (prevention)	Aspirin, oral	Not added
	Calcium, oral	Indication; directions of use amended
6.4.2.5 Eclampsia	Magnesium sulfate, IV	Amended
	Calcium gluconate, IV	Added
	Nifedipine, oral	Added
	Labetalol, IV	Not added
6.4.3 Anaemia in pregnancy	Folic acid, oral	Deleted for folate deficiency and not added for megaloblastic anaemia
	Ferrous, oral (fumarate and sulphate compound BPC)	Directions of use not amended (beverage-drug interaction).
- Established anaemia	Ferrous, oral (fumarate and sulphate compound BPC)	Dosing amended
6.4.4 Syphilis in pregnancy *- Severe penicillin allergy*	Azithromycin, oral	Not added (refer for penicillin desensitisation)
	Lidocaine 1% injection	Directions for use not amended
6.4.5.1 Cystitis, in pregnancy	Nitrofurantoin, oral	Added and dosing interval not amended
6.4.5.2 Pylelonephritis	Ceftriaxone, IV	Added
6.4.7 Preterm labour (PTL)	Betamethasone, IM	Dosing amended
6.4.7.2 Preterm prelabour rupture of membranes (PPROM)	Betamethasone, IM	Dosing amended
- Initial antibiotic therapy	Amoxicillin, oral	Added

SECTION	MEDICINE	ADDED/DELETED/AMENDED
	Metronidazole, oral	Added
- *Severe penicillin allergy*	Azithromycin, oral	Added
	Metronidazole, oral	Added
6.4.7.3 Prelabour rupture of membranes at term (PROM) Initial antibiotic therapy:	Ampicillin, IV	Retained
	Metronidazole, oral	Retained
- *Severe penicillin allergy*	Azithromycin, oral	Added
	Metronidazole, oral	Added
6.5 Intrapartum care	Morphine, IM	Added
	Pethidine, IM	Deleted
	Paracetamol, oral	Added
	Ibuprofen, oral	Added
6.6.3 Care of sick and small neonates:		
- *If blood glucose < 1.4mmol/L or remains < 2.6mmol/L after an oral feed:*	Dextrose, 10%, IV	Added
6.6.5 Perinatal transmission of hepatitis B		
	Hepatitis B immunoglobulin, IM	Added
	Hepatitis B vaccine, IM	Added
6.7.1 Postpartum haemorrhage (PPH)	Oxytocin, IV	Retained as preferred option
	Misoprostol	Retained as an option where oxytocin is not available
	Ergometrine	Retained
6.7.2 Puerperal sepsis	Ceftriaxone, IV	Added
	Metronidazole, oral	Added
6.8 HIV in pregnancy		
- *CD4 < 100 cells/mm3, CrAg +ve*	Fluconazole, oral:	Indication amended
- *CD4 < 100 cells/mm3, CrAg +ve*	Fluconazole, oral	Amended (from 2nd trimester)
- *2nd ANC visit, renal impairment*	Zidovudine	Deleted
	Abacavir, oral	Added as part of triple ART therapy (doctor consultation)
GYNAECOLOGY		
6.11.1 Abnormal vaginal bleeding during reproductive years	Ferrous, oral	Dosing amended
	Tranexamic acid, oral	Not added
6.13 Hormone therapy (HT)	Hormone therapy	Amended (aligned with Adult Hospital level STGs and EML, 2015)

6.2 MISCARRIAGE

Anti-D immunoglobulin: *retained*

An external comment was received querying the administration of anti-D immunoglobulin for uncomplicated spontaneous miscarriages < 12 weeks. The PHC Committee acknowledged that there are insufficient data available to evaluate the practice of anti-D administration in an unsensitised Rh-negative mother after spontaneous miscarriage. Thus, until high-quality evidence becomes available, the practice of anti-D Immunoglobulin prophylaxis after spontaneous miscarriage for preventing Rh alloimmunisation cannot be generalised[1].

Recommendation: Anti-D immunoglobulin be retained in the STG for all miscarriages in Rh-negative, non-sensitised women.

Rationale: There are insufficient data available to evaluate the practice of anti-D administration in an unsensitised Rh-negative mother after spontaneous miscarriage. Previous recommendation of anti-D Immunoglobulin prophylaxis in Rh-negative, non-sensitised women after spontaneous miscarriage was thus retained.

Level of Evidence: II Systematic review (low quality), Expert opinion

[1]Karanth L, Jaafar SH, Kanagasabai S, Nair NS, Barua A. Anti-D administration after spontaneous miscarriage for preventing Rhesus alloimmunisation. The Cochrane database of systematic reviews. 2013(3):Cd009617.https://www.ncbi.nlm.nih.gov/pubmed/23543581

6.2.1 MANAGEMENT OF INCOMPLETE MISCARRIAGE IN THE 1ST TRIMESTER, AT PRIMARY HEALTH CARE LEVEL

Manual vacuum aspiration

Misoprostol, oral/PV: *deleted*
Pethidine, IM: *not added*
Morphine, IM: *added*
Paracetamol, oral: *added*
Ibuprofen, oral: *added*

The indication for misoprostol oral/PV was corrected. Administration to ripen the cervix before manual vacuum aspiration is required for termination of miscarriage and not for incomplete miscarriage. The following was deleted from the text of the STG for correctness:

~~Before MVA, to ripen the cervix:~~
~~Misoprostol, oral/vaginal, 400 mcg as a single dose.~~

In addition, the STG was made consistent with the Adult Hospital Level STGs and EML, 2015, for completeness.

Level of Evidence: III Guidelines

6.2.2 ANTEPARTUM HAEMORRHAGE

Sodium chloride 0.9%, IV: *retained*
Sodium chloride 0.9% was retained as the crystalloid of choice in this clinical setting.

6.3.1 MANAGEMENT OF TERMINATION OF PREGNANCY AT PRIMARY HEALTH CARE LEVEL: GESTATION ≤12 WEEKS (AND 0 DAYS)

The following new STG was added to the chapter, as safe access to medical termination of pregnancy is required at facilities that have been accredited by the Choice on Termination of Pregnancy Act Amendment 1 of 2008, to provide TOP services. Criteria for TOP procedures was aligned with the Choice of Termination of Pregnancy Act, 1996, as amended

Adapted from the Adult Hospital Level STG and EML, 2015:

General measures

» Confirm pregnancy with urine pregnancy test.
» Determine gestational age with ultrasound. If ultrasound unavailable, use dates (LMP) and bimanual (pelvic) examination: if unsure of dates, examination disagrees with dates or uterus palpable abdominally, arrange pre-procedure ultrasound.
» Counselling.
» Outpatient procedure by nursing staff with specific training.
» Screen for STIs (if treatment needed, do not delay TOP).
» Arrange Pap smear if needed.
» Check HIV status.
» Counsel and start contraception post TOP, before leaving facility. Arrange contraception follow-up.

Medicine treatment

Medical TOP (if < 9 weeks gestation):

- Mifepristone, oral, 200 mg, immediately as a single dose.

Followed 24–48 hours later by:

- Misoprostol, PV, 800 mcg.
  - If expulsion does not occur within 4 hours of misoprostol administration, a second dose of misoprostol 400 mcg oral/PV may be given.

For pain relief:

After administration of mifepristone, start:

- Paracetamol, oral, 1 g 4–6 hourly when required to a maximum of 4 doses per 24 hours.
  - Maximum dose: 15 mg/kg/dose.

- Maximum dose: 4g in 24 hours.

ADD

After expulsion is complete:

- Ibuprofen, oral, 400 mg 8 hourly with meals.

OR

TOP using manual vacuum aspiration (MVA):

- Misoprostol, PV, 400 mcg 3 hours before vacuum aspiration of the uterus.

Routine analgesia for vacuum aspiration:

- Morphine, IM, 0.1 mg/kg 30 minutes before aspiration procedure, to a maximum of 10 mg.

Alternatively, consider paracervical block if trained in technique.

Oral analgesia as required for 48 hours:

- Paracetamol, oral, 1 g 4–6 hourly when required to a maximum of 4 doses per 24 hours.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4g in 24 hours.

AND

- Ibuprofen, oral, 400 mg 8 hourly with meals.

For both medical and surgical TOPs (MVA):

In Rh-negative, non-sensitised women:

- Anti-D immunoglobulin, IM, 50–100 mcg preferably within 72 hours but may be given up to 7 days following TOP.

Review all patients after 7 days: if bleeding persists, arrange urgent ultrasound.

Referral

» Gestation ≥13 weeks (or gestation uncertain).
» If any signs or symptoms of ectopic pregnancy or other early pregnancy complications.
» Co-morbid conditions (heart disease, asthma, diabetes, anaemia, clotting disorder, seizure disorder, substance abuse, hypertension).
» Large fibroids (may interfere with determining gestation age and/or MVA)
» Any signs of sepsis (tachycardia, hypotension, pyrexia, tachypnoea, offensive vaginal discharge)
» If MVA not available or declined, refer for medical TOP if ≥ 9 weeks gestation.

Ultrasound: The STG was adapted from the Adult STGs and EML, 2015, with the caveats that TOP may only be performed at an accredited facility, designated by the Member of Executive Council at provincial level and aligned with the Royal College of Obstetrics and Gynaecology Guidelines[2] that states, *"Routine pre-abortion ultrasound scanning is unnecessary but, if available, may be useful if there are concerns about complications such as ectopic pregnancy".* (Refer to the medicine review: "Can TOPs be accomplished safely and effectively without ultrasound", for detailed information). A gestational limit of < 9 weeks was stipulated, and where a gestational limit cannot be determined, patient should be referred.

Recommendation: Medical TOP be indicated for < 9 weeks' gestation in the primary healthcare setting as opposed to < 13 weeks' gestation, as at primary healthcare, TOP is recommended in 1st trimester without mandatory ultrasound screening.

Rationale: Safe access to medical termination of pregnancy is required. Medical TOP would be offered in accredited facilities at PHC facilities, without mandatory ultrasound screening. However, the risk of failed medical TOP increases with gestational age[3]. Medical TOP beyond 9 weeks should ideally be conducted as an inpatient procedure.

Level of Evidence: III Guidelines[4] [5] [6], Case series, Expert opinion

[2]Royal College of Obstetrics and Gynaecology Guidelines. The Care of Women Requesting Induced Abortion (Evidence-based Clinical Guideline No. 7), 2011. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/the-care-of-women-requesting-induced-abortion/

[3]Hamoda H, Ashok PW, Flett GM, Templeton A. Medical abortion at 9-13 weeks' gestation: a review of 1076 consecutive cases. Contraception. 2005 May;71(5):327-32.http://www.ncbi.nlm.nih.gov/pubmed/15854631

[4] The Royal College of Obstetricians and Gynaecologists: Best practice in comprehensive abortion care, 2015. https://www.rcog.org.uk/globalassets/documents/guidelines/best-practice-papers/best-practice-paper-2.pdf

[5] The American College of Obstetricians and Gynaecologists: Best practice in comprehensive abortion care, 2014. http://www.acog.org/~/media/Practice%20Bulletins/Committee%20on%20Practice%20Bulletins%20--%20Gynecology/Public/pb143.pdf?dmc=1&ts=20140703T1932230602

[6] WHO. Safe abortion: technical and policy guidance for health systems, 2014. http://www.who.int/reproductivehealth/publications/unsafe_abortion/en/

Refer to the review: Can TOPs be accomplished safely and effectively without ultrasound?

Ultrasound and TOP_PHC_Review_12

6.4.1 ANTENATAL SUPPLEMENTS

Separate STG was developed providing guidance on antenatal supplements (i.e. iron, folate and calcium supplementation).

Description

Supplements before and during pregnancy and lactation can help to prevent, or lessen the effect, of a number of conditions or complications associated with pregnancy. Specifically:

» Folic acid, given for at least one month prior to conception and during pregnancy (particularly the first 12 weeks) can help to prevent neural tube defects (abnormal development of spinal cord/brain).
» Iron can help to prevent anaemia.
» Calcium can help to prevent pre-eclampsia.

General measures

» Eat a balanced diet to prevent nutritional deficiency.
» Avoid unpasteurised milk, soft cheeses, raw or undercooked meat, poultry, raw eggs and shellfish.
» Cut down on caffeine. Reduce intake of tea. Do not drink tea within 2 hours of taking iron tablets.

Medicine treatment

Prevention of Neural Tube Defects (NTD)

- Folic acid, oral, 5 mg daily:
  - All women intending to become pregnant or pregnant women (first trimester of pregnancy).
  - If high risk, throughout pregnancy, i.e.:
    - on anticonvulsants - especially valproate and carbamazepine,
    - previous child with NTD; or
    - family history of NTD.

Prevention of anaemia:

During pregnancy, after delivery and during lactation:

- Ferrous sulphate compound BPC, oral, 170 mg once daily, (± 65 mg elemental iron), with meals.

OR

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

- Taking iron tablets with meals decreases iron absorption, but improves tolerability. (**Note:** Do not take iron tablets with milk).

If daily iron is poorly tolerated, intermittent iron supplementation may be administered:

- Ferrous sulphate compound BPC, oral, 340 mg per week, (± 130 mg elemental iron), with meals.

OR

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

- Taking iron tablets with meals decreases iron absorption, but improves tolerability. (**Note:** Do not take iron tablets with milk).

Note: Established anaemia i.e. Hb <10 g/dL, see Section 3.1: Anaemia.

Prevention of pre-eclampsia:

From confirmation of pregnancy:

- Calcium carbonate, oral 12 hourly (equivalent to 1 g elemental calcium daily).
  - Although the benefit is greatest in high-risk women, consider use of this agent in all pregnant women. See Section 6.4.2.4: Pre-eclampsia.
  - Calcium reduces iron absorption from the gastro-intestinal tract. Take supplements 4 hours apart from each other.

Folic acid: Main indication of peri-conceptual use of folic acid is the primary prevention of neural tube defects (NTDs). Folic acid dose varies from 0.4-5 mg, dependant on woman's risk status (e.g. on

anticonvulsant therapy, previous NTDs, family history of NTDs)[7] [8] [9] [10]. However, 5 mg folic acid tablet is mostly available on the South African market. There is no available evidence for the harms associated with higher dose folic acid in low risk women.

Recommendation: Folic acid, oral, 5 mg daily as an antenatal supplement for the prevention of neural tube defects.

Rationale: Antenatal supplementation of folic acid is indicated for the prevention of neural tube defects, and the required daily dose is 0.4 mg. However, 5 mg formulations are currently available locally and although food is fortified with folate, consideration should be made for women without access to commercial maize (e.g. reliant on subsistence farming).

Level of Evidence: I Systematic reviews[11] [12] [13], Guidelines, Expert opinion

Caution regarding valproic acid in pregnancy

The following caution was added to the STG, following the European Medicine Agency's Pharmacovigilance Risk Assessment Committee (PRAC) assessment and recommendation to strengthen the caution to avoid valproate exposure in pregnancy.

CAUTION
Children born to women taking valproic acid are at significant risk of birth defects (10%) and persistent developmental disorders (40%).
Valproic acid is contra-indicated and should be avoided in pregnancy and women of child-bearing potential.

Level of Evidence: III Registry data[14]

Iron: (Refer to the medicine review: Intermittent iron supplementation in pregnancy, 6 November 2017).

IntermitIronSupp in Pregnancy_PHC_Mec

Recommendation: Based on the evidence review, the PHC Committee was of the opinion that intermittent iron is not appropiate as antenal supplemenattion for all pregnant women. Iron supplementation in pregnancy should be recommended as daily iron dosing. However, if iron is poorly tolerated, intermittent iron supplemenattion should be considered as an alternative.

[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.

[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] Atta CA, Fiest KM, Frolkis AD, Jette N, Pringsheim T, St Germaine-Smith C, Rajapakse T, Kaplan GG, Metcalfe A. Global Birth Prevalence of Spina Bifida by Folic Acid Fortification Status: A Systematic Review and Meta-Analysis. Am J Public Health. 2016 Jan;106(1):e24-34. https://www.ncbi.nlm.nih.gov/pubmed/26562127

[12] De-Regil LM, Peña-Rosas JP, Fernández-Gaxiola AC, Rayco-Solon P. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. Cochrane Database Syst Rev. 2015 Dec 14;(12):CD007950. https://www.ncbi.nlm.nih.gov/pubmed/26662928

[13] Viswanathan M, Treiman KA, Kish-Doto J, Middleton JC, Coker-Schwimmer EJ,Nicholson WK. Folic Acid Supplementation for the Prevention of Neural Tube Defects: An Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2017 Jan 10;317(2):190-203.

[14] Valproic acid – caution in pregnancy: European Medicines Agency - Pharmacovigilance Risk Assessment Committee. Assessment report EMA/198940/2018 - valproate exposure in pregnancy, 8 February 2018. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_2017_31/Position_provided_by_CMDh/WC500250221.pdf

Valproic acid – caution in pregnancy: Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008 Sep;81(1):1-13. https://www.ncbi.nlm.nih.gov/pubmed/18565732

Rationale: Current low quality evidence suggests that intermittent iron supplementation is as efficacious as daily dosing in pregnant women. Furthermore, local prevalence study estimates that 30-40% of pregnant women have anaemia.
Level of Evidence: I Systematic review[15], Prevalence study[16]

Calcium: Aligned with guidance for prevention of pre-eclampsia in section 6.4.2.4 Pre-eclampsia (See page 6 of this NEMLC report).

6.4.1 HYPERTENSIVE DISORDERS OF PREGNANCY

Guidance for management of hypertension in pregnancy was delineated as follows for ease of reference to the audience of the PHC STGs and EML:

6.4.1 Hypertensive disorders I pregnancy
- **6.4.1.1 Chronic hypertension**
- **6.4.1.2 Gestational hypertension: mild to moderate**
- **6.4.2.3 Gestational hypertension: severe**
- **6.4.3.4 Pre-eclampsia**
- **6.4.4.5 Eclampsia**

6.4.2.1 CHRONIC HYPERTENSION

Methyldopa, oral: *amended*
All women with chronic hypertension, who are now pregnant, require referral for evaluation and management. Women may have been on complex and teratogenic antihypertensive medication and ultrasound scanning to evaluate the fetus for abnormalities, and/or switching to safer medication and initiation of prophylactic aspirin and calcium for pre-eclampsia occurs at secondary level of care.
Level of Evidence: III Expert opinion

6.4.2.2 GESTATIONAL HYPERTENSION: MILD TO MODERATE

Methyldopa, oral: *directions for use not amended*
Campbell *et al* (1988) showed that blood pressures increased by varying amounts in 5 methyldopa-stable hypertension patients within 2 weeks of initiating oral ferrous sulfate therapy (325 mg 3 times/day)[17]. The BP increases exceeded 15 mm Hg systolic and 10 mm Hg diastolic. The absorption of methyldopa in 12 normal subjects was decreased from 29% to 8% when administered with a 325 mg dose of ferrous sulfate. Campbell *et al* (1991) further showed that bioavailability of methyldopa was decreased by 42%, 55%, and 83% in normal subjects when taken 2 hours before, 1 hour before, or simultaneous with, an oral dose of ferrous sulfate[18]. It was suggested that ferric iron likely forms a poorly absorbed chelate with methyldopa in the gastrointestinal tract[19].
Recommendation: Recommendation not to administer methyldopa with iron be retained in the STG.
Rationale: Pharmacokinetic studies suggest drug-drug interaction between oral ferrous preparations and methyldopa.
Level of Evidence: III Pharmacokinetic study

[15] Pena-Rosas JP, De-Regil LM, Gomez Malave H, Flores-Urrutia MC, Dowswell T. Intermittent oral iron supplementation during pregnancy. The Cochrane database of systematic reviews. 2015(10):CD009997. https://www.ncbi.nlm.nih.gov/pubmed/26482110
[16] Tunkyi K, Moodley J. Prevalence of anaemia in pregnancy in a regional health facility in South Africa. S Afr Med J. 2015;106(1):101-4. https://www.ncbi.nlm.nih.gov/pubmed/26792317
[17]Campbell N, Paddock V, and Sundaram R. Alteration of Methyldopa Absorption, Metabolism, and Blood Pressure Control Caused by Ferrous Sulphate and Ferrous Gluconate.ClinPharmacolTher, 1988, 43:381-6.
[18] Campbell NR and Hasinoff BB, "Iron Supplements: A Common Cause of Drug Interactions," Br J ClinPharmacol, 1991, 31:251-5.
[19] Campbell NR, Campbell RR, Hasinoff BB, "Ferrous sulfate reduces methyldopa absorption: methyldopa: iron complex formation as a likely mechanism," Clin Invest Med, 1990, 13(6):329-32.

6.4.2.1 GESTATIONAL HYPERTENSION: SEVERE

Nifedipine, oral: *directions of use amended*
Severe hypertension (BP >160/110 mmHg) always requires immediate referral and nifedipine, oral is administered prior to referral. Dosing interval for repeat doses amended from "60" to "30" minutes, aligned with Adult Hospital Level STGs and EML, 2015 and NDoH Maternity Care Guidelines, 2016.

Sodium chloride 0.9% IV: *deleted*
Removal of sodium chloride 0.9 % infusion for pre-loading was deleted aligned with the Adult Hospital Level STGs and EML, 2015 to minimize irrational medicine use.
Rationale: A large number of deaths from pulmonary oedema especially in pre-eclamptics (some of whom may have peripartum cardiomyopathy) have been reported in South Africa.

Labetalol, IV: *not added*
The PHC Committee was of the opinion that labetalol, IV was not recommended for use at primary health care level. All cases of severe hypertension in the pregnant woman are referred to secondary level for management (Adult Hospital Level STGs and EML, 2015 provides further guidance).
Rationale: Severe hypertension in this setting requires to be lowered cautiously in a controlled setting as too precipitous a drop in blood pressure would be hazardous (provided for in the Adult Hospital Level STGs and EML, 2015).
Level of Evidence: III Guidelines[20] [21]

6.4.2.4 PRE-ECLAMPSIA

Prevention of pre-eclampsia

Aspirin: *not added*
Aspirin for this indication (preventive treatment for women at high risk of pre-eclampsia, e.g. pre-eclampsia in a previous pregnancy, chronic hypertension, diabetes, antiphospholipid syndrome or systemic lupus erythematosus) is not initiated at primary health level of care.
Level of Evidence: III Expert opinion

Calcium, oral: *indications and directions for use amended*
Aligned with the Adult Hospital Level STGs and EML, 2015 that states that, "*Although the benefit is greatest in high-risk women, consider use of this agent in all pregnant women*". This is based on Cochrane review[22] that showed that calcium supplementation in all pregnant women (regardless of the risk of hypertensive disorders) appears to reduce the risk of pre-eclampsia, preterm birth and the occurrence of the composite outcome 'death or serious morbidity'.
Recommendation: The option of calcium, oral supplementation for all pregnant women regardless of risk of hypertensive disorder, be included in the STG.
Rationale: Evidence of a reduction in risk of pre-eclampsia, preterm birth and the occurrence of the composite outcome 'death or serious morbidity'; with anomalous increase in HELLP syndrome (reported to be low) associated with calcium supplementation in pregnant women (irrespective of the risk of pre-eclampsia).
Level of Evidence: I Systematic review and metaanalysis

When to use calcium, oral, for the prevention of pre-eclampsia amended from *" 14 weeks gestation onwards"* to *""from confirmation of pregnancy".*
Level of Evidence: III Expert opinion

[20] Adult Hospital Level STGs and EML, 2015.
[21] National Department of Health: Maternity Care Guidelines, 2016.
[22] Hofmeyr GJ, Lawrie TA, Atallah AN, Duley L, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. 2014 Jun 24;6:CD001059.http://www.ncbi.nlm.nih.gov/pubmed/24960615

6.4.2.5 ECLAMPSIA

Magnesium sulfate: *amended (precautions added)*
Calcium gluconate 10%, IV: *added*
Nifedipine, oral: *added*
Labetalol, IV: *not added*
STG was aligned with the Adult Hospital level STG (2015) and precautions relating to magnesium sulfate with reference to knee reflexes, urine output, respiratory depression or persistent seizures were added to the text of the STG.

The focus of management of eclampsia at primary level of care is to control the seizures with urgent referral. Emergency dosing with oral nifedipine was added to the STG in cases where patient is alert and BP ≥ 110/160 mmHg; whilst labetalol IV was not considered appropriate for primary level of care.
Level of Evidence: III Guidelines, Expert opinion

6.4.3 ANAEMIA IN PREGNANCY

Folic acid, oral: *deleted for folate deficiency and not added for megaloblastic anaemia*

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)[23], RCT (low quality)[24], Guidelines[25 26 27 28], Expert opinion

Ferrous, oral (fumarate and sulphate compound BPC): *directions of use not amended (beverage-drug interaction)*
There is evidence that shows a significant association of tea and non-absorption of iron.[29]Further aligned with the Adult STGs and EML, 2015 recommending that there is no obligation to take iron preparations with a meal.
Level of Evidence: III Pharmacokinetic study, Guidelines

[23]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
[24] 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
[25]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.
[26]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.
[27]RCOG.Nutrition in Pregnancy: Scientific Impact Paper No. 18.
[28] 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.
[29]- Killip S1, Bennett JM, Chambers MD. Iron deficiency anemia. Am Fam Physician. 2007 Mar 1;75(5):671-8.
- Disler, P B. The effect of tea on iron absorption. Gut.1975 vol:16 iss:3 pg:193 -200

Established anaemia

Ferrous, oral (fumarate and sulphate compound BPC): *dosing amended*

The dosing was amended from "8 hourly" to "12 hourly", aligned with the Adult Hospital level STG and EML (2015) supported by a Cochrane review (2011)[30] that concluded "Daily low-dose iron supplements may be effective at treating anaemia in pregnancy with less gastrointestinal side effects compared with higher doses".

Level of Evidence: I Systematic review

6.4.4 SYPHILIS IN PREGNANCY

Pregnant women

Lidocaine 1% injection: *directions for use not amended*

The recommendation to dilute benzathine benzylpenicillin 2.4 MU in 6 mls lidocaine 1 5 was aligned with the UK national guidelines on the management of syphilis 2015[31].

Level of Evidence: III Guidelines

Severe penicillin allergy

Azithromycin, oral: *not added*

Referral for penicillin desensitisation was retained as the treatment option for severe penicillin allergic pregnant women with syphilis, as macrolides are ineffective and the alternate option, doxycycline is contra-indicated in pregnancy.

Level of Evidence: III Guidelines[32]

6.4.5.1 CYSTITIS

The following STG was included in the chapter, as the condition commonly presents at primary level.

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 and/or leukocytes; protein and/or blood may also be detected.

General measures

» Encourage oral fluid intake

» Midstream urine for microscopy, culture and sensitivity

Medicine treatment

Empiric treatment (nitrites positive OR leukocytes positive on dipstick):

- Nitrofurantion, oral, 100 mg 6 hourly for 7 days.

Referral

» No response to treatment, or resistant organism on culture.

» Features of pyelonephritis (See Section 6.3.4.2: Pyelonephritis, acute).

Local antibiotic susceptibility patterns indicate that nitrofurantoin is a good first choice, with the advantage of use in penicillin allergic patients too[33]. A registry study[34](that included 180 120 pregnancies with 5 794 nitrofurantoin exposures) showed no increased risk of fetal malformations

[30]Reveiz L, Gyte GM, Cuervo LG, Casasbuenas A. Treatments for iron-deficiency anaemia in pregnancy. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD003094.

[31] Kingston M, French P, Higgins S, McQuillan O, Sukthankar A, Stott C, McBrien B, Tipple C, Turner A, Sullivan AK; Members of the Syphilis guidelines revision group 2015, Radcliffe K, Cousins D, FitzGerald M, Fisher M, Grover D, Higgins S, Kingston M, Rayment M, Sullivan A. UK national guidelines on the management ofsyphilis 2015. Int J STD AIDS. 2016 May;27(6):421-46. https://www.ncbi.nlm.nih.gov/pubmed/26721608

[32] SAMF, 2014

[33] 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

[34] 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

when used in the first trimester (compared to other antibiotics or infants not exposed to any antibiotics). The same study showed an increased risk of neonatal jaundice when compared to infants who were not exposed to antibiotics, but this was not significant when compared to those exposed to other antibiotics: OR 1.31 (95% CI 1.02 to 1.70) and 1.25 (95% CI 0.93 to 1.69) respectively, both adjusted for prematurity, sex, year of birth, neonatal antibiotic treatment and maternal oxytocin treatment, age, parity, and smoking.

Supply: Historically, nitrofurantoin had supply challenges due to erratic availability. However, the supplier is in the process of correcting this to ensure consistent availability of this medicine.

Level of Evidence: III Guidelines[35], Observational studies

Nitrofurantoin, oral: *dosing interval not amended*

Previously NEMLC[36] had recommended that the treatment dose of nitrofurantoin, "100 mg 6 hourly for 5 days" be reviewed as non-compliance would be an issue. It was noted that SAMF 2016 recommends an alternate dosing option of "100 mg 8 hourly". However, based on the current formulation and half-life of nitrofurantoin, dosing is to be retained as 6 hourly. This dosing regimen was used in RCTs reviewed in a Cochrane review.[37] Of note is that a modified release nitrofurantoin formulation is currently not available on the South African market.

Recommendation: Nitrofurantoin, oral dosing be retained as "100 mg 6 hourly".

Rationale: Nitrofurantoin, oral is dosed as 6 hourly in RCTs and the half-life of nitrofurantoin and the current immediate-release formulation available on the South African market warrants a dosing interval of "6 hourly" for the treatment of cystitis in pregnancy.

Level of Evidence: I Systematic review

6.4.5.2 PYELONEPHRITIS, ACUTE, IN PREGNANCY

Following STG was added to the chapter, aligned with the Adult Hospital Level STGs and EML, 2015.

Description

Features of pyelonephritis include: temperature ≥ 38°C, renal angle tenderness, vomiting, tachypnoea, tachycardia, hypotension, confusion.

This condition is more serious and may result in preterm labour.

General measures

» Midstream urine for microscopy and culture and sensitivity

» Ensure adequate hydration with IV fluids while awaiting transfer

Medicine treatment

Empiric therapy:

- Ceftriaxone, IV, 1 g as a single dose.

CAUTION: USE OF CEFTRIAXONE

Do not administer calcium containing fluids, e.g. Ringer-Lactate, concurrently with ceftriaxone.

Referral

All cases.

Level of Evidence: III Guidelines

6.4.6 LISTERIOSIS

The following was added to the Obstetrics and gynaecology chapter, aligned with NICD Guidelines:

Note: If you have any questions or concerns, visit www.nicd.ac.za or call the NCID hotline on 082 883 9920.

Description

Listeriosis is a preventable and treatable bacterial disease spread through food. Most listerial infections are sporadic but outbreaks do occur. Pregnancy is a predisposing factor for developing serious Listeriosis.

Patients present with a flu-like illness (with fever). They may also have sore joints, backache, diarrhoea and vomiting, and/or signs of meningitis (headache, neck stiffness, confusion).

[35] Adult Hospital Level STGs and EML, 2015

[36] NEMLC minutes of the meeting of the 15 September 2016.

[37] 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

Listeriosis has been added to the national list of notifiable diseases.

General measures

Educate your patients on how to prevent it: wash hands, knives, and cutting boards after handling uncooked food, avoid luncheon meats/delicatessen meats, wash raw vegetables thoroughly, avoid unpasteurised milk, thoroughly cook raw food from animal sources.

Medicine treatment

During outbreaks, if sign of meningitis, give pre-referral treatment (see Section 15.4.2: Meningitis, acute).

Referral

All cases.

Level of Evidence: III Guidelines[38]

6.4.7 PRETERM LABOUR (PTL)

To improve fetal lung maturity at 26–34 weeks

Betamethasone, IM: *dosing amended*

Dosing recommendations aligned with the Adult Hospital Level STG and EML, 2015[39].

Level of Evidence: I Systematic review

6.4.7.2 PRETERM PRELABOUR RUPTURE OF MEMBRANES (PPROM)

To improve fetal lung maturity at 26–34 weeks

Betamethasone, IM: *dosing amended*

Dosing recommendations aligned with the Adult Hospital Level STG and EML, 2015[40].

Level of Evidence: I Systematic review

Initiation of antibiotic therapy, prior to referral

Amoxicillin, oral: *added*

Metronidazole, oral: *added*

Antibiotic recommendations in the PHC STG was aligned to the Adult Hospital Level STG, 2015 for continuity of care. Antibiotics commenced, prior to referral of all cases of PPROM.

Rationale: Alignment of initial oral antibiotic therapy, prior to referral to secondary level of care, with the Adult Hospital Level STGs and EML, 2015 to ensure continuity of care.

Level of Evidence: III Guidelines

Severe penicillin allergy

Azithromycin, oral: *added*

Metronidazole, oral: *added*

Level of Evidence: III Guidelines[41], Expert opinion

[38] National Institute of Communicable Diseases. Listeriosis: Clinical recommendations for diagnosis and treatment, 5 December 2017. http://www.nicd.ac.za/

[39] **Adult Hospital STGs & EML, 2015:**

- Betamethasone, IM be retained as 1st line option to improve fetal lung maturity.

Rationale:

- The relative risk reduction for respiratory distress syndrome was shown to be greater for betamethasone compared to dexamethasone.
- Evidence is unclear regarding optimal dose of corticosteroids to enhance lung maturation; however, guidelines recommend that it would be reasonable to use any dosing regimen as long as 24 mg of either betamethasone or dexamethasone is given within a 24–48-hour period.

- Betamethasone, IM: Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2006 Jul 19;(3):CD004454. http://www.ncbi.nlm.nih.gov/pubmed/16856047

- Betamethasone, IM: Royal College of Obstetricians and Gynaecologists. Green-top Guideline No.7: Antenatal corticosteroids to reduce neonatal morbidity and mortality. October 2010. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_7.pdf

[40] Adult Hospital STGs & EML, 2015: (See rationale for betamethasone, IM, above).

[41] Adult Hospital Level STGs and EML, 2015.

6.4.7.3 PRELABOUR RUPTURE OF MEMBRANES AT TERM (PROM)

It is noted that women with PROM at term require referral the same day for induction of labour.

Initial antibiotic therapy:
Ampicillin, IV: *retained*
Metronidazole, oral: *retained*

Severe penicillin allergy
Azithromycin, oral: *added*
Metronidazole, oral: *added*
Level of Evidence: III Guidelines[42], Expert opinion

6.5 INTRAPARTUM CARE

Nurse prescribing
Legislative provisions: Section 56 of the Nursing Act 33 of 2005 as amended (the Nursing Act) provides a mechanism for nurses to perform certain functions including the prescribing of medicine. Section 56(6) (Special provisions relating to certain nurses) of the Nursing Act states that:

- *"Despite the provisions of this Act, the said Medicines and Related Substances Act, 1965, the Pharmacy Act, 1974 (Act 53 of 1974), and the Health Professions Act, 1974 (Act 56 of 1974), a nurse who is in the service of -...".*
- *Pharmacists and pharmacy support personnel may dispense a prescription issued by a nurse authorised to prescribe medicine in terms of Section 56(6) of the Nursing Act, provided that the nurse has only prescribed medicine which he/she has been authorised to prescribe in terms of the authority issued to him/her. A nurse may, however, not dispense a repeat of a prescription for specialised or hospital level medicines prescribed by a medical practitioner.*

Midwives permits: Prescribing of medicines by midwives is provided for by regulation 31 that replaces regulation 47 of the Medicines and related substances Act 101 of 1965 i.e. previous provision of access to pethidine is replaced by access to schedule 5 and 6 medicines in order to provide intrapartum care. Therefore, the STG 'Section 6.5: Intrapartum care has been expanded to ensure access to all relevant medicines as per the midwives' scope of practice (with cross-referencing to relevant sections (i.e. to sections 6.7.1: Postpartum haemorrhage (PPH); 6.5: Care of the neonate and 6.7.3 Neonatal Resuscitation) to allow for adequate care of mother and infant by the authorised midwife.
Preamble: The foreword to the PHC EML will provide some information regarding section 56(6) and regulation 31; and will describe the intention of the statements, "doctor prescribed" and "doctor initiated".

Pethidine, IM: *deleted*
Morphine, IM: *added*
Paracetamol, oral: *added*
Ibuprofen, oral: *added*

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 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.

[42] Adult Hospital Level STGs and EML, 2015.

Level of Evidence: III Regulations[43], Guidelines[44]

Pain after delivery:
Paracetamol, oral and ibuprofen, oral recommended for postpartum and post-episiotomy pain, aligned with the Adult Hospital Level STGs and EML, 2015.
Level of Evidence: III Guidelines

6.6.3 CARE OF SICK AND SMALL NEONATE

If blood glucose < 1.4mmol/L or remains<2.6mmol/L after an oral feed:

Dextrose, 10%, IV: *added*
Hypoglycaemia management in this clinical setting was aligned with 2014 Guidelines for Integrated Management of Childhood Illness (IMCI)[45] and Neonatal care charts[46].

6.6.5 PERINATAL TRANSMISSION OF HEPATITIS B

Hepatitis B immunoglobulin, IM: *added*
Hepatitis B vaccine, IM: *added*

Perinatal/vertical transmission of hepatitis B
NAGI had not recommended routine hepatitis B vaccination of all newborns. However, the NEMLC recommended that guidance be provided for newborns born to mothers with confirmed hepatitis B infection. Standard of care as recommended in the Paediatric Hospital Level STGs and EML was included in the PHC STG.
Rationale: Alignment with the Paediatric Hospital Level STGs and EML.
Level of Care: III Guidelines[47]

The following new STG was added to the chapter:

Description
Babies born to mothers with acute hepatitis B infection at the time of delivery or to mothers who are HBsAg-positive or HBeAg-positive.

Medicine treatment

- Hepatitis B immunoglobulin, IM, 0.5 mL within 12 hours of delivery.

AND

- Hepatitis B vaccine, IM, 0.5 mL, first dose within 12 hours of delivery.
  - Continue hepatitis B immunisation according to the recommended immunisation schedule.

» Check the baby's hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (HBsAb) at 9 months:
  – If HBsAg positive: baby has hepatitis B infection – refer.
  – If HBsAg negative and HBsAb negative: repeat vaccination with hepatitis B containing vaccine, with a repeat dose in 1 month. Repeat HBsAb one month after the second dose; if still HBsAb negative then refer.
  – If HBsAb positive: baby is immune to hepatitis B. Reassure parents, no further testing required.

Note: Do not check hepatitis B serology before 9 months of age as antibodies from the birth dose of immunoglobulin might still be present. Refer if hepatitis B serology is not available.

6.7.1 POSTPARTUM HAEMORRHAGE (PPH)

This section was moved from Section: 6.5 Intrapartum care to be a stand-alone STG.

[43]Regulation 31 of the Medicines and related substances Act 101 of 1965.
[44] SAMF, 2016
[45] National Department of Health: Integrated Management of Childhood Illness (IMCI) Guidelines, 2014.
[46] Guidelines for the care of all newborns in District Hospitals, Health Centres and Midwife Obstetric Units in South Africa: Neonate care charts, March 2014.
[47]Paediatric Hospital STGs and EML, 2013. http://www.health.gov.za/

Third stage

Prevention of post-partum haemorrhage (PPH):

Oxytocin, IV: *retained as preferred option*

Misoprostol: *retained as an option where oxytocin is not available*

Evidence suggests that oxytocin 10 IU IM is superior to misoprostol 600 mcg for the prevention of PPH[48] and that misoprostol is no better than placebo for the treatment of PPH, once oxytocin has been used for the prevention of PPH[49]. Furthermore, the dose of misoprostol 600 mcg is aligned with the WHO 2012 recommendations[50].

Level of Evidence: I Systematic review[51], RCTs

Ergometrine: *retained*

The use of ergometrine in hypertensive women is a relative contra-indication. PPH results in tachycardia, hypotension and hypovolaemic shock and ergometrine would probably restore BP. Of note is that pregnant women with pre-existing heart disease (0.1% of all pregnant women) should be referred to a regional/tertiary facility for both antenatal care and delivery.

Level of Evidence: III Standard of care

6.7.2 PUERPERAL SEPSIS

New section added to the chapter, as puerperal infections was amongst the leading causes of maternal death[52] and would probably present at primary healthcare facilities. Initial antibiotic therapy aligned to antibiotic management in miscarriage (i.e. ceftriaxone and metronidazole for gram-positive and anaerobic coverage), prior to referral.

Description

Clinical features include a temperature ≥ 38°C (usually for at least 2 days), often accompanied by offensive vaginal discharge (lochia) and/or abdominal pain within the first 10 days postpartum.

General measures

» Monitor vital parameters, e.g. Haemoglobin (Hb), pulse, BP, temperature.
» Treat for shock if indicated.

Medicine treatment

- Ceftriaxone, IV, 1 g as a single dose.

CAUTION: USE OF CEFTRIAXONE

Do not administer calcium containing fluids, e.g. Ringer-Lactate, concurrently with ceftriaxone.

AND

- Metronidazole, oral, 400 mg as a single dose.

Referral

All cases.

Level of Evidence: III Expert opinion

6.8 HIV IN PREGNANCY

[48]Gülmezoglu AM, Villar J, Ngoc NT, Piaggio G, Carroli G, Adetoro L, Abdel-Aleem H, Cheng L, Hofmeyr G, Lumbiganon P, Unger C, Prendiville W, Pinol A, Elbourne D, El-Refaey H, Schulz K; WHO Collaborative Group To Evaluate Misoprostol in the Management of the Third Stage of Labour. WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. Lancet. 2001 Sep 1;358(9283):689-95. http://www.ncbi.nlm.nih.gov/pubmed/11551574

[49]Widmer M, Blum J, Hofmeyr GJ, Carroli G, Abdel-Aleem H, Lumbiganon P, Nguyen TN, Wojdyla D, Thinkhamrop J, Singata M, Mignini LE, Abdel-Aleem MA, Tran ST, Winikoff B. Misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage: a multicentre, double-blind randomised trial. Lancet. 2010 May 22;375(9728):1808-13. http://www.ncbi.nlm.nih.gov/pubmed/20494730

[50] World Health Organisation. WHO recommendations for the prevention and treatment of postpartum haemorrhage, 2012. http://apps.who.int/iris/bitstream/10665/75411/1/9789241548502_eng.pdf

[51]Hofmeyr GJ, Gülmezoglu AM, Novikova N, Linder V, Ferreira 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

[52] Saving Mothers 2011-2013: Sixth report on the Confidential Enquiries into Maternal Deaths in South Africa. Short report. http://www.kznhealth.gov.za/mcwh/Maternal/Saving-Mothers-2011-2013-short-report.pdf

Pregnant Women with CD4 < 100 cells/mm^3, CrAg+

Fluconazole, oral: *indication amended*

Registry study[53] showed no increase in the prevalence of birth defects with fluconazole exposure. However, an association between fluconazole exposure and Tetralogy of Fallot was suggested, OR 3.2 (95% CI 1.5 to 6.8).Subsequent smaller study of the same Danish registry data[54] showed a significantly increased risk of spontaneous abortion associated with fluconazole exposure (HR, 1.48; 95% CI, 1.23 to 1.77); but no significant association between fluconazole exposure and stillbirth (HR, 1.32 [95% CI, 0.82 to 2.14]).

Of note is that fluconazole exposure was analysed across 2 trimesters (11-22 weeks), and it is difficult to assess whether the risk of spontaneous miscarriage remains elevated after 13 weeks' gestation.

Recommendation: Pre-emptive fluconazole therapy be retained in the STG for HIV-infected pregnant women with a CD4 <100 cells/mm^3 and CrAg positive, but only from the 2nd trimester onwards.

Rationale: Conflicting evidence regarding the associated risk of oral fluconazole and stillbirths and spontaneous abortions (evaluated on source registry data). In addition, these safety concerns have not been sufficiently studied in pregnant women > 13 weeks. The authors of the registry studies recommend further study to verify if there is an associated safety risk.

Level of Evidence: III Registry studies

Referral

Referral criteria of CrAG+ pregnant women*: amended*

The current 2013 Southern African HIV Clinicians Society[55] recommends that in CrAg+, asymptomatic patients, "*A lumbar puncture may be considered if available*". NICD recommends that a CrAg+ screen should prompt a careful evaluation for signs/ symptoms of meningitis and a lumbar puncture if feasible. However, data is limited and study by Wakefield et al[56] showed that "*Blood cryptococcal antigen (CrAg) titers are associated with concurrent subclinical cryptococcal meningitis in at least a third of CrAg-positive patients with advanced HIV*". The current guidelines are in the process of being reviewed. Pending further evidence, the PHC Committee recommends not including a recommendation to refer all asymptomatic CrAg+ patients for lumbar puncture.

However, the referral criteria were further expanded and clarified pertaining to the safety issues of fluconazole in the 1st trimester of pregnancy.

Recommendation:

The text of the STG was updated to:

- Refer mothers suspected of non-adherence early.
- Creatinine > 85 mmol/L.
- ALT > 100 IU/L.
- Pregnant women who are CrAg+, and
  - symptomatic (headache, confusion), or
  - asymptomatic, but in the 1st trimester.

Level of Evidence: III Registry studies

Renal dysfunction

Zidovudine: *deleted*

Abacavir: *added as part of triple ART therapy (doctor consultation)*

Aligned with the Adult Hospital Level STGs and EML, 2015 and PMTCT Sub-Committee recommendation to switch tenofovir to abacavir, rather than zidovudine in renal failure, as zidovudine

[53]Mølgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. N Engl J Med. 2013 Aug 29;369(9):830-9. http://www.ncbi.nlm.nih.gov/pubmed/23984730

[54]Mølgaard-Nielsen D, Svanström H, Melbye M, Hviid A, Pasternak B. Association Between Use of Oral Fluconazole During Pregnancy and Risk of Spontaneous Abortion and Stillbirth. JAMA. 2016 Jan 5;315(1):58-67. http://www.ncbi.nlm.nih.gov/pubmed/26746458

[55] Govender et al. Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-infected persons: 2013 update. S Afr J HIV Med 2013;14(2):76-86. DOI:10.7196/SAJHIVMED.930

[56] Wake RM, Britz E, Sriruttan C, Rukasha I, Omar T, Spencer DC, Nel JS, Mashamaite S, Adelekan A, Chiller TM, Jarvis JN, Harrison TS, Govender NP. High Cryptococcal Antigen Titers in Blood are Predictive of Subclinical Cryptococcal Meningitis Among HIV-Infected Patients. Clin Infect Dis. 2017 Oct 5. https://www.ncbi.nlm.nih.gov/pubmed/29028998

is associated with anaemia in pregnancy. Furthermore,triple therapy ART should not be deferred, and the pregnant woman should be switched to ABC+FTC+EFV, as recommended in the Adult Hospital Level STG and EML, 2015 in consultation with a doctor, prior to referral for further management.

Recommendation: Pregnant women intolerant to TDF, due to renal impairment, diagnosed at the 2nd antenatal care visit, should be initiated on alternate triple therapy: ABC+FTC+EFV in consultation with a doctor prior to referral to secondary level of care for further management.

Rationale: Triple therapy ART (ABC+FTC+EFV) was considered more feasible in pregnant women already initiated on TDF+FTC+EFV, but diagnosed with renal impairment at the second antenatal care visit, prior to referral as opposed to AZT 300mg 12 hourly. Aligned with the Adult Hospital Level STGs and EML, 2015 for continuum of care.

Level of Evidence: III Guidelines[57], Expert opinion

The following table was included, adapted from the Adult Hospital Level STG, 2015:

FIRST-LINE ART REGIMENS		
1ST ANC VISIT		
All pregnant women not on ART (any gestational age). **AND** All breastfeeding women not on ART.	• TDF, oral, 300 mg daily. **AND** • FTC, oral, 200 mg daily **AND** • EFV, oral, 600 mg at night. Provide as fixed dose combination (FDC).	» Contraindication to TDF: renal insufficiency, other nephrotoxic medicines e.g. aminoglycosides. » Contraindication to EFV: active psychiatric illness.
If active psychiatric illness (EFV may be contraindicated).	• TDF, oral, 300 mg daily. **AND** • FTC, oral, 200 mg daily **AND** • NVP, oral, 200 mg daily for 2 weeks, then 200 mg 12 hourly. **OR** • LPV/r 400/100 mg 12 hourly). (Doctor consult).	» High-risk pregnancy: doctor consult or refer immediately if acute psychiatric illness. » <u>CD4 < 250</u> • Replace EFV with NVP: o Do an ALT test before starting NVP. Avoid NVP if ALT elevated. If ALT elevated, replace EFV with LPV/r. » <u>CD4 ≥ 250</u> • Replace EFV with LPV/r.
If renal insufficiency or other nephrotoxic medicines e.g. aminoglycosides (TDF may be contraindicated)	Start alternative regimen (Doctor consult): • ABC, oral, 600 mg daily **AND** • 3TC, oral, 300 mg daily **AND** • EFV, oral, 600mg daily.	
Pregnant women currently on ART	• Continue current ART regimen.	» Do a VL as soon as pregnancy is confirmed. » Pregnant women with confirmed 2nd or 3rd line ART regimen failures should not breastfeed their infants, if they can safely formula feed.
2ND ANC VISIT (1 WEEK LATER)		
Creatinine ≤ 85 micromol/L	• Continue FDC: TDF+FTC+EFV	
Creatinine > 85 micromol/L (TDF is contra-indicated)	• Stop FDC: TDF+FTC+EFV. Start alternative regimen (Doctor consult): • ABC, oral, 300mg, 12 hourly **AND** • 3TC, oral, 150mg, 12 hourly **AND** • EFV, oral, 600mg daily.	» High-risk pregnancy: change to alternate triple therapy within 2 weeks (doctor consult) and refer for renal dysfunction investigation.

[57] Adult Hospital Level STGs and EML, 2015.

6.9 MATERNAL MENTAL HEALTH

STGs for mental disorders in pregnancy and postpartum were developed as these conditions commonly present at PHC level of care.[58] [59]

The following was included in the chapter:

Conditions affecting a pregnant and postpartum woman need to be recognized and managed because of the significant negative impact this has on the mother's ability to carry the pregnancy to term and to care for her baby. This has consequences for the health and development of the child.
The unique hormonal changes, changes to sleep wake cycles, and the stress of caring for a newborn make the peri-partum period high risk for any psychiatric disorder to manifest.
Sufferers of peri-partum psychiatric conditions are at high risk for similar episodes in future pregnancies and the need for family planning should be emphasised.

6.9.1 ANTEPARTUM DEPRESSION

The following was included in the chapter:

Description
Symptoms can mimic those of pregnancy itself and the diagnosis can therefore be missed. See section 16.4.1: Depressive disorder, for symptoms and management.
Untreated depression in pregnancy can lead to intrauterine growth problems, low birth weight, preterm delivery or pregnancy loss, poor adherence to antenatal care and can lead to postpartum depression.

General measures
Identification of risk factors for the development of depression, e.g.:
» poor social support,
» absent, abusive or unsupportive partner,
» past history of depression or anxiety,
» recent traumatic life event(s),
» precious pregnancy or unplanned pregnancy
Provide supportive counselling and mobilise available support systems.
Screen for suicide risk.

Referral
» All patients.

6.9.2 POSTPARTUM DEPRESSION

The following was included in the chapter:

Description
Postpartum "blues":
» Presents with irritability, tearfulness, anxiety;
» Begins by day 3 to 5 postpartum;
» Usually resolves spontaneously within 48 to 72 hours of onset;
If these symptoms persist for longer than a week, screen for postpartum depression.

Postpartum depression:
» Usually begins within a month of delivery,but can be evident up to a year after delivery.
See section 16.4.1: Depressive disorders, for symptoms and management.

General measures
» Mobilise patient's support system.
» Reassure and advise on practical aspects of childcare and adjusting to new lifestyle.
» Organisations such as Postnatal Depression South Africa (PNDSA) are a useful resource. http://www.pndsa.org.za/
» Edinburgh Postnatal Depression Scale can be a useful screening tool. https://psychology-tools.com/epds/

[58] Mannikam L, Burns JK. Antenatal depression and its risk factors: An urban prevalence study in KwaZulu-Natal. SAMJ 2012:12(102)
[59] Peltzer K, Habil, Shikwane ME. Prevalence of postnatal depression and associated factors among hiv-positive women in primary care in nkangala district, south africa. SAJHIVmed. 2011:12(4).

» Identify risk factors requiring urgent admission and invoke the MHCA if necessary
- Suicide risk.
- Risk to infant.
- Psychotic features including command auditory hallucinations.

Referral
All patients with postpartum depression.

6.9.2 ANTEPARTUM PSYCHOSIS

The following was included in the chapter:

Is a medical emergency and requires urgent hospitalisation.

Description
Development of bizarre behaviour and/or delusions and/or hallucinations in the month postpartum.
Can be due to primary psychotic disorder or delirium, but most commonly due to a severe postpartum mood episode.

General measures
» Ensure safety of staff, patient and infant.
» De-escalation techniques and non-threatening approach.
» Risk assessment.
» Exclude delirium or general medical condition, if possible.
» Invoke the MHCA and sedate if necessary (see section 16.1: Aggressive Disruptive behaviour management).
» Social worker involvement.

Referral
Refer all cases urgently.

6.11.1 ABNORMAL VAGINAL BLEEDING DURING REPRODUCTIVE YEARS

Tranexamic acid, IV: *not added*
Tranexamic acid[60] is available on the Adult Hospital level EML (2015) for management of menorrhagia, but the PHC Committee was of the opinion that it would not be pragmatic to include this expensive medicine[61] at all PHC facilities.
Level of Evidence: III Expert opinion

If blood loss has been severe or there are signs of anaemia:
Ferrous, oral: *dosing amended*
Dosing was aligned to "12 hourly" as in section 6.3.2 Anaemia in pregnancy.
Level of Evidence: I Systematic review[62]

6.13 HORMONE THERAPY (HT)

Hormone therapy: *amended*
Aligned with the Adult STGs and EML, 2015.
Level of Evidence: III Guidelines

[60] Lethaby A, Farquhar C, Cooke I. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev. 2000;(4):CD000249. http://www.ncbi.nlm.nih.gov/pubmed/11034679
[61] Contract circular HP09-2016SD: R278.87 for TXA 500mg, 100 tabs - Treatment course of 1 g 6 hourly on days 1–4 of the cycle (32 tabs) = R 89.25.
[62] 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