SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 6: OBSTETRICS & GYNAECOLOGY
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020 -2024 REVIEW CYCLE)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG).

SECTION A

MEDICINE AMENDMENTS:

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED
6.2 Miscarriage	Anti-D immunoglobulin, IM	Amended
6.2.1 Management of incomplete miscarriage in the 1st trimester, at primary health care level - *medical evacuation*	Misoprostol, SL/PV/buccal	Directions for use amended
	Ibuprofen, oral	Directions for use amended
	Pregnancy test	Added
	Paracervical block (lidocaine 1%)	Added
6.3 Termination of pregnancy (TOP) - *venue*	TOP criteria	Amended
6.3.1 Management of termination of pregnancy at primary health care level: gestation up to 12 weeks and 0 days	Mifepristone, oral	Directions for use not amended
	Misoprostol, SL	Directions for use amended
	Paracervical block (lidocaine 1%)	Added (doctor only)
	Ibuprofen, oral	Directions for use amended
6.4.1 Antenatal supplements	Iron, oral	Not amended
	Calcium, oral	Retained, with an amendment showing only the elemental calcium requirement i.e. not the calcium carbonate salt dose
	Aspirin, oral	Added
6.4.2 Hypertensive disorders in pregnancy	Categories of gestational hypertension	Amended
6.4.2.1 Chronic hypertension	Methyldopa, oral	Dose and directions for use not amended
6.4.2.5 Eclampsia	Labetalol, IV	Not added
6.4.4 Syphilis in pregnancy	Lidocaine 1%, parenteral	Not amended
6.4.7.1 Preterm labour (PTL) *and* **6.4.7.2 Preterm pre-labour rupture of membranes (PPROM)**	Betamethasone, parenteral	Dosing amended
6.4.7.2 Preterm prelabour rupture of membranes (PPROM) - *Antibiotic therapy*	Ampicillin, IV	Added
	Amoxicillin, oral	Retained
	Metronidazole, oral	Deleted
	Aztihromycin, oral	Added
- *Severe penicillin allergy*	Metronidazole, oral	Deleted
	Aztihromycin, oral	Dose amended
	Clindamycin, oral	Not added
6.4.7.3 Prelabour rupture of membranes at term (PROM): *>12 hours*	Antibiotic prophylaxis	Retained
6.5 Intrapartum care	Morphine, parenteral	Retained
	Pethidine, parenteral	Not added
	Anti-D immunoglobulin	Directions for use amended
6.6.2 Neonatal resuscitation	Naloxone, IV	Retained
	Resuscitation algorithm	Amended
6.8 HIV in pregnancy	Tenofovir + lamivudine + dolutegravir, oral	Indication amended
	HIV testing	Amended
- *CrAg positive*	Lumbar puncture	Added
6.13 Hormone therapy	Mammogram	Deleted

	Transdermal hormone therapy patches	Not added to the STG, but added to the therapeutic interchange database
Further change after publication of chapter: 6.7.1 Postpartum haemorrhage (PPH)	Tranexamic acid, parenteral	Added

**Throughout the chapter Paracetamol, oral dosing range has been aligned to AHL Chapter 25: Pain including a reiteration of the maximum dose.*

6.2 MISCARRIAGE

Anti-D immunoglobulin, IM: *amended*

Local resource constraints of Anti-D immunoglobulin warrants restricted use of Anti-D immunoglobulin, from "*all Rh-negative women who had a surgical procedure*" to "*only in Rh-negative, non-sensitised women who had surgical procedure for miscarriage*".

The STG was amended as follows:

~~For all miscarriages in Rh-negative, non-sensitised women:~~

For all Rh-negative non-sensitised women, who had a surgical procedure to manage a miscarriage:

- Anti-D immunoglobulin, IM, 50 mcg preferably within 72 hours but may be given up to 7 days following management of miscarriage.

~~Omit anti-D in the first trimester when there are supply constraints~~

Do not offer Anti-D prophylaxis to women who:

» only received medical management for a miscarriage or
» had a threatened miscarriage or
» had a complete miscarriage.

Level of Evidence: Low certainty evidence[1,2], Guidelines[3]

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

Medical evacuation

Misoprostol, SL/PV/buccal: *directions for use amended*

The STG text was amended to align with NICE[4] and WHO[5] guidelines as follows:

- ~~Misoprostol, PV, 800 mcg every 3 hours for 2 doses.~~
  - ~~Repeat after 24 hours if necessary.~~

~~**OR**~~

- ~~Misoprostol, SL, 600 mcg every 3 hours for 2 doses~~
  - ~~Repeat after 24 hours if necessary~~
- Misoprostol, SL/PV/buccal, 800 mcg immediately as a single dose.
  - Repeat after 24 hours if necessary.

Level of Evidence: Low certainty evidence

Ibuprofen, oral: *directions for use amended*

The STG text was aligned with narrative within this chapter, noting harms associated with routine use of ibuprofen:

- Ibuprofen, oral, 400 mg 8 hourly with or after a meal, as needed for 2-3 days.

Pregnancy test: *added*

[1] Karanth L, Jaafar SH, Kanagasabai S, Nair NS, Barua A. Anti-D administration after spontaneous miscarriage for preventing Rhesus alloimmunisation. Cochrane Database Syst Rev. 2013 Mar 28;(3):CD009617. https://pubmed.ncbi.nlm.nih.gov/23543581/

[2] Hamel C, Esmaeilisaraji L, Thuku M, Michaud A, Sikora L, Fung-Kee-Fung K. Antenatal and postpartum prevention of Rh alloimmunization: A systematic review and GRADE analysis. PLoS One. 2020;15(9):e0238844.

[3] Schmidt-Hansen M, Lord J, Hawkins J, Cameron S, Pandey A, Hasler E, et al. Anti-D prophylaxis for rhesus D (RhD)-negative women having an abortion of a pregnancy up to 13+6 weeks' gestation: a systematic review and new NICE consensus guidelines. BMJ Sex Reprod Health. 2020 Jan 20;bmjsrh-2019-200536.

[4] NICE. Guideline: Abortion Care, 25 September 2019. https://www.nice.org.uk/guidance/ng140

[5] WHO. Guideline: Medical management of abortion, 2018. https://www.who.int/reproductivehealth/publications/medical-management-abortion/en/

Pregnancy test as follow up management was added, aligned with NICE guidance.[6]A 3-week period before testing is recommended to minimise false-positives (bHCG 25miu/ml is the cut-off for a positive pregnancy test).[7] Women with a positive pregnancy test to be referred, accordingly.

Perform a pregnancy test three weeks after medical management

Level of Evidence: Low certainty evidence

6.2.1 MANAGEMENT OF INCOMPLETE MISCARRIAGE IN THE 1ST TRIMESTER, AT PRIMARY HEALTH CARE LEVEL *and* 6.3.1 MANAGEMENT OF TERMINATION OF PREGNANCY AT PRIMARY HEALTH CARE LEVEL: GESTATION UP TO 12 WEEKS AND 0 DAYS

Paracervical block (lidocaine 1%): *added*

Guidance was added for paracervical block with lidocaine 1%, parenteral with a cross-reference to the Adult Hospital Level STGs and EML, section 5.9.1: TOP: management of pregnancies ≤14 weeks of gestation, where detailed information is provided on directions for use.

The South African Nursing Council (SANC) *"maintains that Paracervical block is an invasive procedure which is outside the current Scope of Practice of Registered Nurses and Midwives. For this reason, training of nurses to perform such a procedure is not supported by SANC"*[8], and thus guidance for paracervical block has been included as "doctor only".

6.3 TERMINATION OF PREGNANCY (TOP)

Venue

TOP criteria: *amended*

The Choice on Termination of Pregnancy Act, 1996 (as amended by Act 38 of 2004), provides expanded access to abortions; allows registered nurses, as well as registered midwives, to perform abortions up to the twelfth week of pregnancy. The following additional STG text was added:

~~An accredited facility with staff trained in performing TOP, designated by the Member of Executive Council at provincial level.~~ Any facility that has a 24-hour maternity service can provide TOP service without specific designation - *The Choice on Termination of Pregnancy Act, 1996 (as amended by Act 38 of 2004), expanded access to abortions, allowed registered nurses, as well as registered midwives, to perform abortions up to the twelfth week of pregnancy.*

6.3.1 MANAGEMENT OF TERMINATION OF PREGNANCY AT PRIMARY HEALTH CARE LEVEL: GESTATION UP TO 12 WEEKS AND 0 DAYS

Medical TOP

Mifepristone, oral: *directions for use not amended*

Timing of administration of misoprostol, following mifepristone is recommended by RCOG Best Practice guide[9] as 24-48 hours; whilst NICE guidelines[10] recommends 36-48 hours (and a shorter time interval, based on women's preference). However, for pragmatic purposes 24-48 hours was retained.

Level of Evidence: Low certainty evidence

Misoprostol, SL: *directions for use amended*

The RCOG Best Practice guide[11] recommends that > 14 weeks medical TOP should be performed in a facility, but it can be presumed that in South Africa it may be unsafe to abort 9-12 weeks at home or en-route to a hospital. Therefore,

[6] Medical abortion (follow-up pregnancy test): NICE. Guideline: Abortion Care, 25 September 2019. https://www.nice.org.uk/guidance/ng140

[7] Barnhart K, Sammel MD, Chung K, Zhou L, Hummel AC, Guo W. Decline of serum human chorionic gonadotropin and spontaneous complete abortion: defining the normal curve. Obstet Gynecol. 2004 Nov;104(5 Pt 1):975–81. https://pubmed.ncbi.nlm.nih.gov/15516387/

[8] The SANC Circular 8/2019**:** https://www.sanc.co.za/2019/11/26/circular-30-84-2/

[9] 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/

[10] Medical abortion (follow-up pregnancy test): NICE. Guideline: Abortion Care, 25 September 2019. https://www.nice.org.uk/guidance/ng140

[11] 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/

the STG text was amended to include the additional pragmatic guidance:

- Misoprostol, SL, 800 mcg by self-administration at home*.
  - If expulsion does not occur within 4 hours of misoprostol administration, a second dose of misoprostol 400 mcg, oral/PV may be given.
  - *From >9 weeks to ≤ 12 weeks - return to the facility within 48 hours to take misoprostol on-site (early morning) due to the risk of heavy bleeding.

Level of Evidence: Low certainty evidence

Pain

Ibuprofen, oral: *directions for use amended*

The STG text was aligned with narrative within this chapter, noting harms associated with routine use of ibuprofen:

- Ibuprofen, oral, 400 mg 8 hourly with or after a meal, as needed for 2-3 days.

6.4.1 ANTENATAL SUPPLEMENTS

Iron, oral: *not amended*

The STG currently provides guidance for dosing of oral iron in those with poor tolerance, supported by previously reviewed evidence.[12] [13]

Calcium, oral: *not amended*

Dosing for calcium was not amended. WHO guidance[14] recommends 1.5 - 2g in divided doses. The recent International Society for the Study of Hypertension in Pregnancy (ISSHP)[15] recommends 'at least 500g per day', assessed as 'weak evidence'. Authors of an updated Cochrane review[16] concluded, "*High-dose calcium supplementation (≥ 1 g/day) may reduce the risk of pre-eclampsia and preterm birth*", and that, "*The limited evidence on low-dose calcium supplementation suggests a reduction in pre-eclampsia, hypertension and admission to neonatal high care, but needs to be confirmed by larger, high-quality trials*".

Level of Evidence: Low certainty evidence

See also Section B for further changes after publication of chapter.

6.4.2 HYPERTENSIVE DISORDERS IN PREGNANCY

Categories of gestational hypertension: *amended*

Aligned with the Adult Hospital Level STGs and EML, 2019; Section 6.4: Hypertensive disorders in pregnancy.

STG text was amended from:

~~LEVELS OF SEVERITY OF HYPERTENSION~~

~~Level of hypertension~~	~~BP Level mmHg~~		
	~~Systolic~~		~~Diastolic~~
~~mild~~	~~140–149~~	~~or~~	~~90–99~~
~~moderate~~	~~150–159~~	~~or~~	~~100–109~~
~~severe~~	~~≥160~~	~~or~~	~~≥110~~

To:

Categorising hypertensive disease:

[12] Ferrous (Iron) supplements, oral - intermittent dosing: National Department of Health: Affordable Medicines, EDP-Primary Health Care level. Medicine Review: Intermittent iron supplementation in pregnancy, 6 November 2017. https://www.knowledgehub.org.za/e-library

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

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

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

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

» A diastolic BP of 90-109 mmHg and/or systolic BP of 140-159 mmHg; but with **NO** symptoms or organ dysfunction is classified as hypertensive disease without severe features.

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

6.4.2.1 CHRONIC HYPERTENSION

Methyldopa, oral: *dose not amended*

The dose of methyldopa for chronic gestational hypertension was not amended, as this is aligned to the Adult Hospital Level STGs and EML, 2019 – refer to the extract from the NEMLC report for the Adult Hospital Level Obstetrics chapter (2017-19 review cycle), below:

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[17], 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[18]; whilst a pharmacokinetic study[19] 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

Level of Evidence: Low certainty evidence

Methyldopa, oral: *directions for use not amended*

The STG text was not amended as iron supplements have been found to decrease methyldopa absorption[20]. Taking methyldopa two hours before or after iron-containing products can help avoid this interaction.

6.4.2.5 ECLAMPSIA

Labetalol, IV: *not added*

The NEMLC had not approved this in the previous review cycle, due to affordability and pragmatic implications at primary level of care.

NEMLC report for the 2016-2018 review of the PHC STGs and EML, 2018 edition:
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

[17] International Federation of Gynecology and Obstetrics. The FIGO Textbook of Pregnancy Hypertension. http://www.safemotherhood.ucsf.edu/wpcontent/uploads/2013/01/FIGO-Pregnancy_Hypertension-Final.pdf
[18] SAMF, 2022
[19] 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
[20] Campbell NR, Campbell RR, Hasinoff BB. Ferrous sulfate reduces methyldopa absorption: methyldopa: iron complex formation as a likely mechanism. Clin Invest Med. 1990 Dec;13(6):329-32. https://pubmed.ncbi.nlm.nih.gov/2078911/

6.4.4 SYPHILIS IN PREGNANCY

Lidocaine 1%, parenteral*: not amended*

Recommendations for the administration of lidocaine 1% which is used as a diluent for less painful administration of intramuscular benzathine benzylpenicillin were not amended. The volume of lidocaine 1% as a diluent is aligned with Amir et al's study[21] and the UK 2008 STI guidelines[22] as previously cited.

6.4.7.1 PRETERM LABOUR (PTL) *and* 6.4.7.2 PRETERM PRELABOUR RUPTURE OF MEMBRANES (PPROM)

Betamethasone, parenteral: *dosing amended*

The administration of antenatal betamethasone has been shown to improve improve fetal lung maturity at 26–34 weeks, confirmed by the updated 2020 Cochrane review[23]. High certainty evidence showed that antenatal corticosteroids reduced the risk of:

- perinatal death (RR 0.85, 95% CI 0.77 to 0.93; 9833 infants; 14 RCTs; 2.3% fewer, 95% CI 1.1% to 3.6% fewer)
- neonatal death (RR 0.78, 95% CI 0.70to 0.87; 10,609 infants; 22 RCTs; 2.6% fewer, 95% CI 1.5% to 3.6% fewer)
- respiratory distress syndrome (RR 0.71, 95% CI 0.65 to 0.78; 11,183 infants; 26 RCTs; 4.3% fewer, 95% CI 3.2% to 5.2% fewer)

The dosing interval for commonly used regimen of two doses of betamethasone, IM 12 mg was corrected from "~~*12 hours apart"*~~ to "*24 hours apart*", aligned with the International Federation of Gynecology and Obstetrics clinical practice guide on maternal-fetal medicine[24].

Level of Evidence: High certainty evidence

6.4.7.2 PRETERM PRELABOUR RUPTURE OF MEMBRANES (PPROM)

Ampicillin, IV: *added*
Amoxicillin, oral: *retained*
Metronidazole, oral: *deleted*
Aztihromycin, oral: *added*

Antibiotics for PPROM reduces maternal and neonatal complications – a Cochrane review[25] showed that any antibiotic vs placebo results in:

- Less chorioamnionitis - any antibiotic vs placebo, RR 0.57; 95% CI 0.37 to 0.86.
- Less preterm birth - any antibiotics vs placebo; delivery within 7 days after admission RR 0.8; 95% CI 0.71 to 0.9.
- Less neonatal infection - any antibiotic vs placebo; neonatal infection RR 0.68; 95% CI 0.53 to 0.87.

However, women with PPROM have a high risk of group B streptococcal (GBS) infection. The recommended antibiotic for intrapartum GBS prophylaxis is penicillin.[26] Broad spectrum antibiotics are recommended to prolong latency (due to the colonization with vaginal and rectal organisms). [27]

Of note is that the Cochrane review[25] included 22 RCTs, of which only one RCT (from 1997) used metronidazole. From the available evidence, the Cochrane review recommends erythromycin as a better choice. When different regimens of azithromycin or erythromycin were compared, there was no difference in latency to delivery, incidence of

[21] Amir J, Ginat S, Cohen YH, Marcus TE, Keller N, Varsano I. Lidocaine as a diluent for administration of benzathine penicillin G. Pediatr Infect Dis J. 1998 Oct;17(10):890-3.
[22]Kingston M, French P, Goh B, Goold P, Higgins S, Sukthankar A, et al.; Syphilis Guidelines Revision Group 2008, Clinical Effectiveness Group. UK National Guidelines on the Management of Syphilis 2008. Int J STD AIDS. 2008 Nov;19(11):729-40. Erratum in: Int J STD AIDS. 2011 Oct;22(10):613-
[23] IM: McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2020 Dec 25;12(12):CD004454. https://pubmed.ncbi.nlm.nih.gov/33368142/
[24] FIGO Working Group on Good Clinical Practice in Maternal-Fetal Medicine. Good clinical practice advice: Antenatal corticosteroids for fetal lung maturation. Int J Gynaecol Obstet. 2019 Mar;144(3):352-355. https://pubmed.ncbi.nlm.nih.gov/30710360/
[25] Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev. 2013 Dec 2;(12):CD001058. https://pubmed.ncbi.nlm.nih.gov/24297389/
[26] Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010 Nov 19;59(RR-10):1-36. https://pubmed.ncbi.nlm.nih.gov/21088663/
[27] ACOG. Prelabor Rupture of Membranes: ACOG Practice Bulletin, Number 217. Obstet Gynecol. 2020 Mar;135(3):e80-e97. https://pubmed.ncbi.nlm.nih.gov/32080050/

chorioamnionitis, or neonatal outcomes. There also appears to be no additional benefit for an extended course of azithromycin beyond the single-day dosing.[28]
Level of Evidence: Moderate certainty evidence

Severe penicillin allergy
Metronidazole, oral: *deleted*
Aztihromycin, oral: *dose amended*
Clindamycin, oral: *not added*
As clindamycin is not currently included in the PHC EML, a single pre-referral dose of azithromycin 1 g is recommended with urgent referral (refer to discussion on azithromycin above).

6.4.7.3 PRELABOUR RUPTURE OF MEMBRANES AT TERM (PROM)

> 12 hours
Antibiotic prophylaxis*: retained*
Antibiotic prophylaxis for term or near-term premature rupture of membranes is not associated with any benefits in either maternal or neonatal outcomes. In women with latency longer than 12 hours, prophylactic antibiotics are associated with significantly lower rates of chorioamnionitis by 51% and endometritis by 88%.[29] The STG recommends a pre-referral dose of antibiotics with urgent referral.

6.5 INTRAPARTUM CARE

Morphine, parenteral: *retained*
Pethidine, parenteral: *not added*
Morphine was approved by NEMLC in the previous review cycle, as it has less side effects/less effect on the baby.

NEMLC report for the 2016-2018 review of the PHC STGs and EML, 2018 edition:
Analgesia:
Recommendation: *Morphine, IM replaces pethidine, IM as analgesia during first stage of labour with cervical dilatation < 10 cm.*
Rationale: Regulation 31 replaces regulation 47 of the Medicines and related substances Act 101 of 1965 i.e. access to pethidine is replaced by access to schedule 5 and 6 medicines in order to provide intrapartum care. In addition, there are safety concerns regarding pethidine's active metabolite, normeperidine that is potentially neurotoxic.
Level of Evidence: III Regulations[30], Guidelines[31]

Anti-D immunoglobulin: *directions for use amended*
Rational use of Anti-D immunoglobulin is warranted due to continual supply challenges. The following additional text was added to the STG:

» Check baby's Rh status; do not given anti-D if the baby is Rh-negative, or if the mother has Anti-Rh antibodies.

6.6.2 NEONATAL RESUSCITATION

Naloxone, IV: *retained*
The PHC/Adult Hospital Level Committee noted that naloxone, IV was not used in practice for initial neonatal resuscitation in the delivery room anymore. Maternally administered opioids in this clinical setting may cause neonatal respiratory depression, but evidence could not be sourced for naloxone, noting that ventilation and oxygenation may be sufficient for neonatal resuscitation.

[28] Navathe R, Schoen CN, Heidari P, Bachilova S, Ward A, Tepper J et al. Azithromycin vs erythromycin for the management of preterm premature rupture of membranes. Am J Obstet Gynecol. 2019 Aug;221(2):144.e1-144.e8. https://pubmed.ncbi.nlm.nih.gov/30904320/
[29] Saccone G, Berghella V. Antibiotic prophylaxis for term or near-term premature rupture of membranes: metaanalysis of randomized trials. Am J Obstet Gynecol. 2015 May;212(5):627.e1-9. https://pubmed.ncbi.nlm.nih.gov/25555659/
[30]Regulation 31 of the Medicines and related substances Act 101 of 1965.
[31] SAMF, 2022

NEMLC MEETING OF 24 JUNE 2021:

NEMLC Recommendation: *The NEMLC recommended that naloxone be retained for the indication stated in the STG: If the mother is known or suspected to have had narcotic pain relief and the baby has normal heart rate and colour response to bag-mask ventilation, but has not initiated sustained regular respiratory effort".*
However, concern of irrational use of naloxone in clinical practice was raised, and NEMLC deliberated on removing naloxone from the STG. However, as maternal opioid misuse was considered to be relatively common, the NEMLC recommended that naloxone be retained for the indication above, but that a statement be added that ***"Naloxone is not routinely indicated for neonatal resuscitation".***

The Resuscitation Council of Southern Africa's newborn resuscitation algorithm was updated from the 2015 version to the 2021 version.[32]

6.8 HIV IN PREGNANCY

(Note: Recommendations were aligned with updated[33] chapter 11: HIV and AIDs, as appropriate).

Tenofovir + lamivudine + dolutegravir, oral: *amended*
Indication expanded from ≥6 weeks gestation to ALL women
Refer to the medicine review: Dolutegravir in pregnancy, June 2021:

NDoH_PHC-Adult Medicine review_DT

Recommendation: The PHC/Adult Hospital Level Committee recommends that dolutegravir should be part of the preferred first line ART regimen for all adults and adolescents living with HIV, including pregnant women and women of child-bearing potential. The existing contra-indication in pregnancy should be removed from the STG.
Rationale: The risk of neural tube defects in infants exposed to dolutegravir in early pregnancy that was first identified in the Tsepamo observational study in Botswana has diminished over time, with the accumulation of further data. The risk difference between dolutegravir and efavirenz is no longer significant.
Dolutegravir (especially when combined with tenofovir alafenamide) is associated with more weight gain during pregnancy than efavirenz, but the difference is unlikely to be clinically relevant.
Randomised controlled trials have shown non-inferiority in terms of maternal viral suppression rates at 48 weeks. Dolutegravir causes more rapid viral suppression than efavirenz, resulting in increased viral suppression rates by time of delivery in randomised controlled trials of ART initiation in the second and third trimester of pregnancy. This has not yet translated into a demonstrable difference in mother-to-child transmission risk, but event rates are very low with both regimens.
A standardised regimen for all adults and adolescents living with HIV is likely to be easier for nurses to provide.
Based on those findings and observations, the PHC/Adult Hospital Level Committee feel that the potential long-term benefits to pregnant women and WOCP (Women of Child Bearing Potential), as well as potential short-term benefits to their infants, outweigh the risks.
Level of Evidence: Moderate certainty of evidence
Review indicator: New evidence of harms

NEMLC MEETING OF 24 JUNE 2021:
NEMLC Recommendation: The NEMLC accepted the recommendation as proposed by the PHC/Adult Hospital Level Committee, which would support the universal test-and-treat (UTT) strategy of the National HIV Programme.
It was also duly noted that the South African Health Products Regulatory Authority were currently reviewing the label of dolutegravir products registered on the South African market.

[32] Published with permission from the Resuscitation Council of Southern Africa. https://resus.co.za/
[33] South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023.

HIV testing: *amended*
Guidance for HIV-testing was amended to align with guidance recommended in the Prevention of Mother-to-Child Transmission of HIV (PMTCT) and the management of HIV in Children, Adolescents and Adults, current Guidelines for Maternity Care in South Africa - i.e. at every Basic Antenatal Care (BANC) visit (8 in total).

CrAg positive
Lumbar puncture: *added*
The following was added to the STG text:

Note: All CrAg positive women need a LP, unless contra-indicated, regardless of symptoms.

6.13 HORMONE THERAPY (HT)

Mammogram: *deleted*
The following STG text was deleted, specifically noting that no facilities are available at primary level of care:

~~» Where the facility is available, arrange mammography before starting HT. However, lack of access to mammography should not delay HT if indicated for severe menopausal symptoms if the woman has no other special risk factors for breast cancer (e.g.: family history of breast cancer in first degree relative).~~

Transdermal hormone therapy patches: *not added to the STG, but added to the therapeutic interchange database*
Refer to the evidence summary on transdermal HT patches, July 2021, v2:

Transdermal HT Patches_Evidence Sum

Evidence for alternative routes for HT administration was reviewed, owing to reported supply constraints with oral HT. Oral and transdermal HT were both effective in terms of management of menopausal symptoms. Observational studies showed that the risk of thrombosis was higher with oral oestrogen compared to transdermal oestrogen. The PHC ERC therefore proposed that transdermal HT be added to the STG, but restricted to women at high risk of thrombosis, owing to cost. However, the two routes have not been compared directly in women with a high risk of thrombosis, and transdermal HT isn't specifically indicated/registered for this population.

NEMLC MEETING OF 19 DECEMBER 2021
Discussion: The risk for first time thrombosis was reported to be higher amongst women on oral HT compared to those using transdermal HT[34]. However, the number of women needing HT who have a high risk of thromboembolism was anticipated that this would be a small number[35]. Citalopram is recommended for treatment of menopausal symptoms in women at high risk of thromboembolism at secondary level of care. Furthermore, NEMLC raised concerns regarding the high price of transdermal HT.

Recommendation: NEMLC deliberated on the proposal suggested by the PHC/Adult Hospital Level Committee, and recommended that HT transdermal patches be removed from the STG, but be added to the therapeutic interchange database as an alternative to oral estrogens.
Rationale: The number of women requiring HT at high risk of thromboembolism is anticipated to be small. Transdermal HT is expensive compared to oral HT preparations. Citalopram is included on the secondary level EML for management of perimenopausal or menopausal syndrome where "oral" HT is contra-indicated, poorly tolerated or ineffective.
Level of Evidence: Conditional recommendation, moderate certainty evidence

Review: equivalence of hormones

[34] Sweetland S, Beral V, Balkwill A, Liu B, Benson VS, Canonico M, et al.; Million Women Study Collaborators. Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. J Thromb Haemost. 2012 Nov;10(11):2277-86. https://pubmed.ncbi.nlm.nih.gov/22963114/
[35] Previously, NEMLC had recommended venlafaxine, oral (for hormone with hormone-dependant cancers) not be included on the national EML for secondary level of care; but rather for consideration at tertiary and quaternary level of care – NEMLC minutes of the meeting of 14 December 2017.

Hormone replacement therapy (HRT) reduce vasomotor symptoms in a dose-dependent fashion, and the standard treatment guidelines recommend that prescribers start with the lowest dose available and titrate upwards according to symptoms.[36] There are no head-to-head comparisons of the various formulations in relieving vasomotor symptoms.

Estrogens: Conjugated estrogen (CE) 0.625mg orally is considered a 'standard dose' of HRT and is equivalent to 1-2mg of oral estradiol.[3] A serum estradiol concentration of 76.8 pg/mL is achieved with CE 0.625 mg daily. For 1 mg and 2 mg doses of oral estradiol, serum concentrations of estradiol attained are 65.8 pg/mL and 107.6 pg/mL respectively. Although the optimal range for serum estradiol concentration to achieve therapeutic efficacy has not been established, a serum estradiol concentration of 60 pg/mL is needed to prevent osteoporosis[37] and reduce 50% of hot flashes.[38] During a normal menstrual cycle in the mid-follicular phase plasma estradiol concentrations are 60-150pg/ml.[4] Experimental studies in castrated animals and human studies in postmenopausal women suggest that a plasma estradiol concentration of approximately 100 pg/ml is optimal for treatment of hot flushes, prevention of bone loss and cardiovascular protection.[4]

Progestogens: Serum progesterone concentrations greater than 5 ng/mL must be achieved to inhibit endometrial mitosis and to induce a secretory change (endometrial protection). This threshold concentration is based on the observation that during a normal menstrual cycle, the corpus luteum produces circulating progesterone concentrations that are in the range of approximately 5 to 20 ng/mL.[39]

Norethisterone vs medroxyprogesterone acetate: The WHO 18th Expert Committee of the Selection and Use of Essential Medicines[40] systematically reviewed the evidence (1 systematic review[41] and 3 RCTs[42] [43] [44]) and concluded that low-dose HT be used to manage menopausal symptoms (doses of 5mg norethisterone not recommended as the risks outweigh the benefits). Combining estrogen with progestogen minimises the risk of endometrial hyperplasia which can develop into endometrial cancer in menopausal women with an intact uterus; and low dose estrogen plus progestogen (1 mg norethisterone or 1.5 mg medroxyprogesterone acetate) appears safe for the endometrium, taken either continuously or sequentially.[45]

The therapeutic interchange database for hormone therapy was updated as per the following table aligned with products currently available on the South African market listed in the SAMF, 2020 edition
NEMLC recommended that transdermal hormone therapy patches not be included on the PHC EML, but recommended that the patches should be added to the therapeutic interchange database and be grouped therapeutically with the other EML-recommended oral hormone preparations – the evidence (safety and efficacy) reviewed did not show value for investing in the transdermal HT patches, but could be considered as an alternative to the oral HT preparations when there are supply issues of the latter, or for scale of volume procurement purposes.

Indication	Therapeutic class	INN	Strength (mg)	formulation
Menstruation > 1 year ago	Progestogens and estrogens, fixed combinations (lowdose)	Norethisterone/estrogen*	0.5/1	oral

[36] Kim S-M, Kim SE, Lee D-Y, Choi D. Serum estradiol level according to dose and formulation of oral estrogens in postmenopausal women. Sci Rep. 2021 Feb 11;11:3585.
[37] de Lignieres B. Hormone replacement therapy: clinical benefits and side-effects. Maturitas. 1996 May;23 Suppl:S31-36.
[38] Steingold KA, Laufer L, Chetkowski RJ, DeFazio JD, Matt DW, Meldrum DR, et al. Treatment of hot flashes with transdermal estradiol administration. J Clin Endocrinol Metab. 1985 Oct;61(4):627–32.
[39] Stanczyk FZ, Paulson RJ, Roy S. Percutaneous administration of progesterone: blood levels and endometrial protection. Menopause. 2005 Apr;12(2):232–7.
[40] World Health Organization. 18th Expert Committee on the Selection and Use of Essential Medicines- Section 18.7: Progestogens, March 2011. [Accessed 17 March 2022] Available at: https://www.who.int/selection_medicines/committees/expert/18/applications/Norethisterone.pdf
[41] Zweifel JE, O'Brien WH. A meta-analysis of the effect of hormone replacement therapy upon depressed mood. Psychoneuroendocrinology. 1997 Apr;22(3):189-212. doi: 10.1016/s0306-4530(96)00034-0. Erratum in: Psychoneuroendocrinology 1997 Nov;22(8):655.
[42] Cagnacci A, Arangino S, Baldassari F, Alessandrini C, Landi S, Volpe A. A comparison of the central effects of different progestins used in hormone replacement therapy. Maturitas. 2004 Aug 20;48(4):456-62. doi: 10.1016/j.maturitas.2003.10.003.
[43] Magos AL, Brewster E, Singh R, O'Dowd T, Brincat M, Studd JW. The effects of norethisterone in postmenopausal women on oestrogen replacement therapy: a model for the premenstrual syndrome. Br J Obstet Gynaecol. 1986 Dec;93(12):1290-6. doi: 10.1111/j.1471-0528.1986.tb07868.x.
[44] Boschetti C, Cortellaro M, Nencioni T, Bertolli V, Della Volpe A, Zanussi C. Short- and long-term effects of hormone replacement therapy (transdermal estradiol vs oral conjugated equine estrogens, combined with medroxyprogesterone acetate) on blood coagulation factors in postmenopausal women. Thromb Res. 1991 Apr;62(1-2):1-8. doi: 10.1016/0049-3848(91)90663-h.
[45] Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Database Syst Rev. 2012 Aug 15;2012(8):CD000402. doi: 10.1002/14651858.CD000402.

Menstruation > 1 year ago	Progestogens and estrogens, fixed combinations (lowdose)	estradiol/ Norethisterone **	0.62/2.7	transdermal patches
Menstruation > 1 year ago	**Progestogens and estrogens, fixed combinations (standard dose)**	**Estradiol/Norethisterone ***	**1/1**	**oral**
Menstruation > 1 year ago	Progestogens and estrogens, fixed combinations (standard dose)	estradiol/Norethisterone **	3.2/11.2	transdermal patches
Menstruation > 1 year ago	**Progestogens (used with estrogens) - continuous combined therapy**	**Medroxyprogesterone acetate***	**2.5 to 5**	**oral**
Menstruation > 1 year ago	Progestogens (used with estrogens) - continuous combined therapy	Norethisterone**	1.25 to 2.5	oral
Menstruation > 1 year ago	**Estrogens (used with progestogens) - continuous combined therapy**	**Estradiol***	**1 to 2**	**oral**
Menstruation > 1 year ago	Estrogens (used with progestogens) - continuous combined therapy	Conjugated estrogens**	0.3 to 0.625	oral
Menstruation < 1 year ago/present	**Progestogens and estrogens, sequential preparations (low dose)**	**Norethisterone+estrogen/estrogen***	**1/2**	**oral**
Menstruation < 1 year ago/present	Progestogens and estrogens, sequential preparations (low dose)	Dydrogesterone+estrogen/estrogen**	10/1	oral
Menstruation < 1 year ago/present	**Progestogens and estrogens, sequential preparations (standard dose)**	**Norgestrel+estrogen/estrogen***	**0.5/2**	**oral**
Menstruation < 1 year ago/present	Progestogens and estrogens, sequential preparations (standard dose)	Cyproterone+estrogen/estrogen**	1/2	oral
Menstruation < 1 year ago/present	Progestogens and estrogens, sequential preparations (standard dose)	Norethisterone+estrogen/estrogen**	1/2	oral
Menstruation < 1 year ago/present	**Progestogens (used with estrogens) - sequential opposed therapy**	**Medroxyprogesterone acetate***	**5 to 10**	**oral**
Menstruation < 1 year ago/present	Progestogens (used with estrogens) - sequential opposed therapy	Norethisterone**	1.25 to 2.5	oral
Menstruation < 1 year ago/present	**Estrogens (used with progestogens) - sequential opposed therapy**	**Estradiol***	**1 to 2**	**oral**
Menstruation < 1 year ago/present	Estrogens (used with progestogens) - sequential opposed therapy	Conjugated estrogens**	0.3 to 0.625	oral
Uterus absent (post hysterectomy)	**Estrogens**	**Estradiol***	**1 to 2**	**oral**
Uterus absent (post hysterectomy)	Estrogens	Conjugated estrogens**	0.3 to 0.625	oral
Uterus absent (post hysterectomy)	Estrogens	Estradiol**	25 to 75	transdermal patches

**Listed in the STG*

***Listed in the therapeutic interchange database*

SECTION B

Further changes after publication of chapter:

6.4.1 ANTENATAL SUPPLEMENTS

Aspirin, oral: *Added*

Historically, the National Essential Medicines List Committee retained aspirin for secondary level initiation in all women with chronic hypertension, who are pregnant as the patient would require referral to the secondary level of care for evaluation and management.[46,47,48] NEMLC highlighted that pregnant women with chronic hypertension may have been on complex and teratogenic antihypertensive medication and ultrasound scanning to evaluate the foetus for abnormalities, and/or switching to safer medication would be appropriate for secondary level and therefore initiation of prophylactic aspirin and calcium for pre-eclampsia would also only be appropriate for secondary level of care. Expert opinion was cited as the evidence for strict secondary level aspirin initiation for prevention of pre-eclampsia.[49] However patients with historical risk factors (e.g. previous history of pre-eclampsia) might not be referred immediately to secondary care, but only at a scheduled appointment, which may be a few weeks later. These patients will then potentially miss out on the benefit of early initiation of aspirin prophylaxis.

The evidence for the use of aspirin in women at risk for early-onset pre-eclampsia is regarded as strong[50] and well documented.

Level of Evidence: Systematic Reviews, Randomised Control Trials & Guidelines

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

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

[48] National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Review: Safety of aspirin in pregnancy, February 2020. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[49] National Department of Health. South African Primary Healthcare Level Essential Medicines List Chapter 6: Obstetrics & Gynaecology Conditions. National Essential Medicines List Committee (NEMLC) Recommendations for Medicine Management (2016 – 2018)

[50] Ngene NC, Moodley J. Preventing maternal morbidity and mortality from preeclampsia and eclampsia particularly in low- and middle-income countries. Best Pract Res Clin Obstet Gynaecol. 2024 Feb 15;94:102473. doi: 10.1016/j.bpobgyn.2024.102473. Epub ahead of print. PMID: 38513504.

From a safety perspective the literature shows [50] low-dose aspirin has been widely regarded as safe in pregnancy, although there are small increases in bleeding risk; mostly intrapartum and postpartum bleeding and a small (0.06%) increase in neonatal intracranial bleeds. Most of these risks can be mitigated by discontinuing aspirin by 36 weeks, based on the lack of effectiveness for prevention of term pre-eclampsia.

Aspirin is widely available, inexpensive and has a favourable fetal and maternal safety profile and research shows that aspirin prophylaxis for women at risk of hypertensive related diseases of pregnancy particularly in low- and middle-income countries results in reduction in the risk of early onset preeclampsia.[50]

The Committee therefore recommended to alter the prescribing level of aspirin, 150mg, oral for reduction in the risk of early onset pre-eclampsia in pregnancy to PHC level for nurse initiation, in alignment with NDOH maternity and hypertension in pregnancy guidelines.

In line with local National Maternity Care Guideline[51] and the International Society for the Study of Hypertension in Pregnancy[52] the aspirin dosing is recommended at bedtime to prevent gastric irritation and initiated from 6 weeks of gestation (but preferably before 16 weeks) until 36 weeks. Additional guidance regarding taking aspirin preferably not an empty stomach was also added.

PHC/Adult ERC Recommendation: 2 May 2024
The PHC /AHL ERC supports the use of aspirin 150mg oral, until 36 weeks of pregnancy, for prevention of pre-eclampsia for all levels of care.

NEMLC Recommendation: 16 May 2024

NEMLC accepted the proposal as recommended by the PHC/Adult ERC (see above)

The description section of the STG was updated as follows:

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 before 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.
» Low dose aspirin can reduce the risk for early onset pre-eclampsia in women at risk.

Calcium, oral: *retained with an amendment showing only the elemental calcium requirement i.e. not the calcium carbonate salt dose*

A provincial query was received by NDOH requesting clarity on the STG dose for calcium which was regarded as ambiguous as it contained both the calcium carbonate salt dose & elemental calcium dose. It was also raised that the that calcium doses are not standardized in the PHC (Obstetrics & Gynecology) AHL (Obstetrics) & AHL (Nephrology) chapters. Going forward, NEMLC has recommended that the STG recommendation should only contain the elemental calcium requirement as this is the actual calcium content contained in the tablet (i.e. the calcium carbonate salt dose, should not be included in the STG). Additionally, the recommended elemental calcium dose is now in line with how the peadiatric Hospital STG is currently phrased.

[51] NDOH. National Maternity Care Guidelines. Updated 2024.
[52] International Society for the Study of Hypertension in Pregnancy. Available at: https://isshp.org/guidelines/.

The medicine section for the prevention of pre-eclampsia of the STG was updated as follows:

Prevention of pre-eclampsia:
From confirmation of pregnancy (all women):

- Calcium, elemental, oral, 1 g daily ~~(given as calcium carbonate), 12 hourly~~.
  - 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.

From confirmation of pregnancy (all women with risk factors. including: pre-eclampsia in a previous pregnancy, chronic hypertension, diabetes, antiphospholipid syndrome, or systemic lupus erythematosus (SLE)):

- Aspirin, oral, 150 mg, taken at bedtime, preferably not on an empty stomach, until 36 weeks
  - Start at 6 weeks of gestation but preferably before 16 weeks
  - Stop at 36 weeks to reduce risk of bleeding during labour
  - Administration at bedtime reduces the risk of gastric irritation
- Refer to the next level of care as appropriate for the condition (see below). Women with a prior history of pre-eclampsia, but otherwise well, can be referred for the next available appointment, preferably around 20 weeks.

Editorially, the prevention of pre-eclampsia guidance was removed from section 6.4.2.2 pre-eclampsia, as it was updated under prevention of pre-eclampsia in section 6.4.1 antenatal supplements. A cross reference was added in section 6.4.2.2 pre-eclampsia to the updated prevention of pre-eclampsia guidance in section 6.4.1 antenatal supplements.

6.7.1 POSTPARTUM HAEMORRHAGE (PPH)

Tranexamic acid, parenteral: *Added*

Previously reviewed by NEMLC and not approved for inclusion on the PHC EML.

NEMLC report for the 2017-2019 review of the Adult Hospital Level STGs and EML, 2019 edition:
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.[53]

Rationale provided for inclusion of TXA, IV on the PHC EML:
Savings Mother report (2011-2013)[54] *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[55] *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 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:

[53] E-mail communication from WOMAN trial investigator, 28 November 2017, on file.
[54] National Department of Health: National Committee for the Confidential Enquiries into Maternal Deaths Saving Mothers Report, 2011-2013.
[55] 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

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 appropriate management from primary level may be delayed.

Level of Evidence: I RCT

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

In 2023, a motivation to include TXA, IV at PHC level was received arguing that it is reasonable to extrapolate the WOMAN trial findings to the PHC level and that the total price of the TXA, IV in the original review was incorrectly calculated.

At the NEMLC meeting, 30th March 2023, NEMLC recommended[56] that:

- Previous deliberations be revisited in response to the motivation received.
- PHC/Adult Hospital Level ERC review updated data (specifically safety and efficacy on use of TXA IV outside of hospitals i.e., extrapolatable for PHC use).

The E-MOTIVE (WHO) trial[57] published in May 2023 provides the updated evidence for the use of TXA, IV which can be extrapolated to PHC level. The E-MOTIVE trial was the Early detection of Postpartum Haemorrhage and treatment using the WHO MOTIVE 'first response' bundle: a parallel cluster-randomized trial that included a baseline control phase, along with mixed-methods evaluation in 210 132 low risk women undergoing vaginal delivery.

- E MOTIVE was performed mainly at Level one/district hospitals in South Africa (more than 18 000 women), Nigeria, Kenya and Tanzania (78 hospitals) and the Intervention included **E**arly detection with a calibrated blood collection drape. When 500mls was noted in the drape and/or clinical assessment of PPH, a bundle of care was immediately given with all components as close together as possible: Uterine **M**assage, **IV** fluids, **O**xytocin and **T**ranexamic acid and examination of the genital; tract with **E**scalation of care when needed. The control hospitals used an uncalibrated drape and usual care.
- Midwives were authorized to diagnose and treat PPH (including IV TXA) without the need for confirmation or authorization by a doctor. This would be similar to what would happen at a PHC level if TXA were available at PHC Level.
- A primary-outcome event (a composite of severe postpartum hemorrhage (blood loss, ≥1000 ml), laparotomy for bleeding, or maternal death from bleeding occurred in 794 of 48,678 patients (1.6%) in the intervention group and in 2139 of 50,044 (4.3%) in the usual-care group (risk ratio, 0.40; 95% confidence interval [CI], 0.32 to 0.50; P<0.001).
- This equates to a risk difference of 26 fewer per 1000 (2.6%), ranging from 55 to 40 fewer per 1000 for severe outcomes. This is based on the RR of 0.4 (95% CI from 0.32-0.5).
- For numbers needed to treat; you need to treat (apply the full bundle) to 37 cases of PPH to prevent one event of severe outcome (a composite of death, laparotomy, or severe blood loss). However, those 37 women will require treatment for PPH regardless.
- Compliance to the bundle was 92% in the E-MOTIVE group and 19% in the usual care group.
- The authors did not report on thrombotic events in the puerperium (not included in the trial design).

[56] National Department of Health. Minutes of the NEMLC Meeting. 30 March 2023.

[57] Gallos I, Devall A, Martin J, Middleton L, Beeson L, Galadanci H, et al. Randomized Trial of Early Detection and Treatment of Postpartum Hemorrhage. New England Journal of Medicine. 2023 May 9;0(0):null

In summary, the WHO E-MOTIVE trial[57]has shown that a bundle of care that includes TXA given by midwives at district hospital level reduces PPH by 60%. The results of this study can be extrapolated to community health center/Midwifery Obstetrics Unit (MOU) level, as all the interventions in the trial were given by midwives without intervention from a doctor[57] and all women with a significant bleed will be urgently transferred to the next level of care, so further management will be under doctor or specialist care.

Cost and economic considerations:

Tranexamic Acid; 500mg/5ml; injection; 5 ml is R37,60.
Therefore, a 1-gram dose would cost R75,20 (2 x 500mg vials).

Additionally, an economic evaluation of the WOMAN trial in Nigeria and Pakistan concluded that early treatment of post-partum haemorrhage with tranexamic acid, IV, is cost-effective in Nigeria and Pakistan, and is likely to be cost-effective in countries in sub-Saharan Africa with similar incidence of PPH.[58]

Refer to the full evidence summary report below

Tranexamic_Acid_IV_
PHC_Summary_Final_

PHC/Adult ERC Recommendation: 8 June 2023
The PHC /AHL ERC supports the use of tranexamic acid (TXA) 1g IV (by slow injection or infusion in 200mls of N Saline over 10 minutes) for PPH for all levels of care.

NEMLC Recommendation: 20 July 2023
NEMLC supports the use of tranexamic acid (TXA) 1g IV (by slow injection or infusion in 200mls of N Saline over 10 minutes) for PPH for all levels of care, which may be initiated by a nurse, but only with prior approval of a medical practitioner.

Randomised Controlled Trial: GRADE IIIb

The STG was amended as follows:

MEDICINE TREATMENT

Replace fluids:
Sodium chloride 0.9%, IV, infused as fast as possible in one IV line.
AND
Oxytocin, IV 20 units in 1 000 mL sodium chloride 0.9% infused at 250 mL/hour in 2nd IV line.
AND
Tranexamic acid, IV, 1g in 200 mL sodium chloride 0.9% over 10 minutes, or 1g by slow IV injection,
which may be initiated by a nurse, but only with prior approval of a medical practitioner.

[58] Li B, Miners A, Shakur H, Roberts I; WOMAN Trial Collaborators. Tranexamic acid for treatment of women with post-partum haemorrhage in Nigeria and Pakistan: a cost-effectiveness analysis of data from the WOMAN trial. Lancet Glob Health. 2018 Feb;6(2):e222-e228. doi: 10.1016/S2214-109X(17)30467-9. PMID: 29389542; PMCID: PMC5785366