South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Obstetrics

Medicine review
To review the use of progesterone for prevention of preterm birth in a select "at risk" population

Date: October 2019
Medicine (INN): Progesterone (vaginal)
Medicine (ATC): G03DA04
Indication (ICD10 code): Short cervix within 1st 24 weeks of gestation
Patient population: Pregnant women at risk for recurrent preterm labour until 24 weeks gestation
Prevalence of condition: n/a
Level of Care: Secondary hospitals
Prescriber Level: Doctor
Current standard of Care: Ultrasound indicated cerclage
Efficacy estimates: (preferably NNT)
Vgainal progesterone vs placebo

- Reduced preterm births <34 weeks: OR 0.50, 95% CI 0.33 to 0.75, I^2=60%; ARR 7.76%; NNT 13; Low to moderate quality of evidence
  (NICE Guideline update - systematic review and meta-analysis[5])

Motivator/reviewer name(s): Dr G Timothy, Prof GS Gebhardt, Ms TD Leong, Dr H Dawood
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Author affiliation and conflict of interest details:
Primary reviewer(s):

- *Dr G Timothy:* Discovery Health Medical Aid, Member of the Adult Hospital Level Expert Review Committee (2017-2020); No conflicts of interest declared.
- *Ms TD Leong:* National Department of Health, Essential Drugs Programme, Secretariat to the Adult Hospital Level Expert Review Committee (2017-2020); No conflicts of interest declared.

Secondary reviewer(s):

- *Prof GS Gebhardt*: Stellenbosch University and Tygerberg Hospital, Adult Hospital Level Committee (2017-2020); No conflicts of interest declared.
- *Dr H Dawood:* Greys hospital, UKZN Department of health; Caprisa, University of KwaZulu-Natal; Adult Hospital Level Committee (2017-2020); NEMLC Committee member; *Conflicts of interest:* MSD: ECMID 2018 - Conference attendance; ACTA study - DSMB member (crypto meningitis); Adcock Ingram - HIV discussion with general practitioners.

Executive summary:
Preterm birth is the leading cause of death of babies in South Africa- 48% of all cause mortality within the first month in babies born alive is due to prematurity (about 4000 babies per year). Those that survive have significant morbidity

related to vision, hearing and neurodevelopmental delay resulting in long-term burden on health care and education. A subset of women at risk for preterm birth can be identified (previous history of preterm labour and/or short cervix on ultrasound) and successfully treated with vaginal progesterone (currently vaginal progesterone is prescribed). This medicine is not included in the EML, but is self- funded by the patient in certain instances.

Cervical length screening is only offered until 24 weeks of pregnancy, as there are no preventative strategies to treat a short cervix after this gestation stage (cerclage or progesterone is ineffective when initiated after this time).

The following women would qualify for cervical screening:

1. Patients with a history of 2nd trimester miscarriage suggestive of cervical incompetence: (Painless dilatation of the cervix with a short labour duration) after excluding other causes of mid-trimester losses such as : intra-uterine deaths requiring induction, abruptions, fetal abnormalities, polyhydramnios, and medical terminations.
2. Previous history of spontaneous preterm birth between 27 and 34 weeks.

The following clinical scenarios would be routinely screened with cervical length measurement, as it is not cost-effective:

1. Low risk women with no history of previous preterm birth or T2 miscarriage suggestive of cervical incompetence
2. Previous late preterm birth (34-37 weeks) as interventions at this stage are not very effective in decreasing late preterm delivery.

The benefits of vaginal progesterone in the prevention of preterm labour have yielded mixed results in different studies to date.. This review aims to determine the level of evidence. New studies has been published and hence the need to review if vaginal progesterone should be considered for inclusion on the National EML. The NICE guidelines on preterm labour was also updated (August 2019) with the new evidence.

Introduction:

There are several ways in which progesterone contributes to pregnancy maintenance:

1. It is produced by the corpus luteum until the placenta takes over this function at 7-9 weeks gestation. Without this progesterone production an abortion would occur before 7 weeks.
2. It maintains uterine quiescence in the latter half of pregnancy.
3. It prevents apoptosis in fetal membrane explants

Progesterone supplementation appears to reduce the rate of spontaneous singleton preterm birth in women who have had a previous spontaneous preterm singleton birth and in women with a short cervix on ultrasound examination in the current pregnancy. Studies have also shown that women with certain characteristics, such as vaginal bleeding, gonorrhea, or chlamydia infection in the current pregnancy; a late preterm birth in a past pregnancy; or penultimate preterm birth, are less likely to have a significant risk reduction. [1,2.]

In 2012, a systematic review and meta-analysis of individual patient data (IPD) from randomized controlled trials comparing vaginal progesterone with placebo in women with a singleton gestation and a cervical length ≤25 mm in the midtrimester[3] reported that the administration of vaginal progesterone was associated with a significant reduction in the risk of preterm birth occurring from <28 weeks of gestation through <35 weeks of gestation. Following this

publication, vaginal progesterone was recommended for patients with a singleton gestation and a short cervix by the:

- Society for Maternal-Fetal Medicine (SMFM),
- American College of Obstetricians and Gynecologists (ACOG),
- International Federation of Gynecology and Obstetrics (FIGO), and
- National Institute for Health and Care Excellence (NICE), amongst others.

In 2016, the OPPTIMUM study[4] was released - a randomized controlled trial comparing vaginal progesterone versus placebo in women at risk of preterm birth because of previous spontaneous preterm birth <34 weeks of gestation, or a cervical length ≤25 mm, or because of a positive fetal fibronectin test combined with other clinical risk factors for preterm birth. This trial showed that vaginal progesterone did not significantly reduce the risk of preterm birth or perinatal morbidity and mortality in the entire population, or in the subgroup of women with a cervical length ≤25 mm. This study added to the controversy on vaginal progesterone for preterm labour at the time.

Subsequent to this, further meta-analysis have been published showing a different result.[5,6]

Objective: To review the evidence for the use of vaginal progesterone for use in women at high risk for preterm birth (based on previous history) if they are found to have a shortened cervix under 24 weeks gestation.

PICO question:

-P Pregnant women up to 24 weeks gestation at risk for recurrent preterm delivery with a shortened cervix(≤25 mm).
-I Vaginal progesterone
-C Placebo
-O Preterm Delivery

There is a paucity of evidence directly comparing cerclage to vaginal progesterone and thus, the comparator in the PICO question was amended from "cervical cerclage (MacDonald suture)" to "placebo".

Of note is that the NICE Guidelines[6] have recently been updated (August 2019) following an evidence review of the clinical effectiveness of prophylactic progesterone in preventing preterm labour.
(https://www.nice.org.uk/guidance/ng25/evidence)

AGREE II appraisal of these Guidelines has been assessed to be of good quality, and thus the evidence reviewed in the NICE Guideline Update mostly informed this medicine review.

A. CERCLAGE

It is noted that use of cerclage was not considered in the updated NICE Guidelines as the previous Guidelines recommended progesterone and cerclage. The indications for progesterone has also not changed (a history of preterm birth and a short cervix). As there is a paucity of evidence directly comparing progesterone and cerclage, the NICE Guideline does recommend that the "choice of cerclage or progesterone should be determined after discussion between the woman and health care professionals".

B. VAGINAL PROGESTERONE

Systematic review performed by the NICE included one Cochrane systematic review (Dodd 2013); 5 RCTs (Ashoush 2017, Azargoon 2016, Crowther 2017, Norman 2018, van Os 2015) and 1 individual patient data (IPD) meta-analysis (Romero 2018). The table below provides a brief summary of the included studies.

Table 2: Summary of included studies

Study	Participants	Intervention	Control	Outcomes
Ashoush 2017 RCT Egypt	N=187 women with history of spontaneous preterm birth	Oral progesterone (100 mg every 6 hours) Treatment started between 14 and 18 weeks' gestational age	Placebo	• Infant mortality • Gestational age at birth
Azargoon 2016 RCT Iran	N=100 women with a history of preterm birth (52%) or previous history of preterm birth and short cervix (≤28 mm) (27%)	Vaginal progesterone (400 mg/day) Treatment started between 16 and 22 weeks' gestational age	Placebo	• Preterm birth <34 weeks' • Infant mortality • Gestational age at birth
Crowther 2017 RCT Australia, New Zealand, Canada	N=799 women with history of spontaneous preterm birth	Vaginal progesterone (100mg/day) Treatment started at 20 weeks' gestational age, or from randomisation (if this occurred after 20 weeks)	Placebo	• Stillbirth • Infant mortality • Early neonatal sepsis • Health-related quality of life
Dodd 2013 Cochrane systematic review Iran, Brazil, US, India	K=9 • Akbari 2009 • Cetingoz 2011 • da Fonseca 2003 • Fonseca 2007 • Glover 2011 • Hassan 2011 • Majhi 2009 • O´Brien 2007	Vaginal progesterone (90 to 200 mg): • Akbari 2009 • Cetingoz 2011 • da Fonseca 2003 • Fonseca 2007 • Hassan 2011 • Majhi 2009 • O´Brien 2007	Placebo	• Preterm birth <34 weeks' • Stillbirth • Infant mortality • Gestational age at birth • Neonatal sepsis

Study	Participants	Intervention	Control	Outcomes
	• Rai 2009 N=1892 women with a history of spontaneous preterm birth or short cervix on ultrasound scan	Oral progesterone (100 to 200 mg): • Glover 2011 • Rai 2009 Treatment start week ranged between 16 and 24 weeks' gestational age		
Norman 2018 RCT UK	N=1225 women with risk factors for preterm birth (including previous preterm birth, cervical length ≤25mm, second trimester loss, preterm premature rupture of the membranes or history of cervical procedure to treat abnormal smears)	Vaginal progesterone (200 mg/day) Treatment started between 22 and 24 weeks' gestational age	Placebo	• Preterm birth <34 weeks' • Stillbirth • Infant mortality • Gestational age at birth • Health-related quality of life • Bayley-III cognitive composite score • Moderate or severe neuro-developmental impairment • Visual impairment • Hearing impairment
Romero 2018[a] IPD meta-analysis UK, USA, Turkey	K= 5 • Cetingoz 2011 • Fonseca 2007 • Hassan 2011 • Norman 2016 • O'Brien 2007 N=974 with a short cervix (≤25 mm)	Vaginal progesterone (90 to 200 mg/day) Treatment start week ranged between 18 and 24 weeks' gestational age	Placebo	• Preterm birth <34+0 weeks' • Stillbirth • Infant mortality • Gestational age at birth • Proven neonatal sepsis • Health-related quality of life • Bayley-III cognitive composite score • Moderate or severe neuro-developmental impairment • Visual or hearing impairment

Study	Participants	Intervention	Control	Outcomes
van Os 2015 RCT The Netherlands	N=80 women with a short cervix (≤30 mm)	Vaginal progesterone (200 mg) Treatment started at 22 weeks' gestational age	Placebo	• Preterm birth <34 weeks' • Infant mortality • Neonatal sepsis

[a]*Romero 2018 contacted the principal investigators of the eligible trials. Data included in the IPD meta-analysis may have not been reported in the main trials.*
mg: milligrams; mm: millimetres; RCT: randomised controlled trial; IPD: individual patient data

Source: NICE preterm labour and birth Guideline, update (August 2019). Appendix A: Evidence review for clinical effectiveness of prophylactic progesterone in preventing preterm labour.

EVIDENCE STATEMENTS MADE IN THE NICE GUIDELINE

i. Vaginal progesterone vs placebo

a. Preterm birth <34weeks'

Low quality evidence suggests that vaginal progesterone decreases the number of preterm births (at <34 weeks' gestation), vs placebo. However, trials were very heterogeous (I^2 = 60%), which resolved after conducting pre-specified subgroup analysis.

- **Subgroup analysis:** *Women with a history of spontaneous preterm birth*
  Moderate quality evidence showed that for women with a history of spontaneous preterm birth, vaginal progesterone decreases the number of preterm births (at <34 weeks' gestation), vs placebo.
- **Subgroup analysis:** *Women with a short cervix (<30 mm)*
  Low quality evidence showed that for women with a short cervix (<30 mm), vaginal progesterone decreases the number of preterm births (at <34 weeks' gestation), vs placebo.
- **Individual participant data meta-analysis:** *Women with a short cervix (≤25 mm)*
  Low quality evidence showing that for women with a short cervix (≤25mm), vaginal progesterone decreases the number of preterm births (at <34 weeks' gestation), vs placebo.

b. Stillbirth

Very low quality evidence showed no clinically important difference in the number of stillbirths between those who received vaginal progesterone vs placebo.

c. Infant mortality

Moderate quality evidence showed a clinically important decrease in infant mortality for those who received vaginal progesterone vs placebo

- **Subgroup analysis:** *Women with a history of spontaneous preterm birth*
  Low quality evidence suggests that for women with a history of spontaneous preterm birth, there may be a clinically important decrease in infant mortality in those who received vaginal progesterone vs placebo, as there is uncertainty around the estimate (RR 0.53, 95% CI 0.25 to 1.12).
- **Subgroup analysis:** *Women with a short cervix (<30 mm)*
  Low quality evidence suggests that, for women with a short cervix (<30 mm), there may be a clinically important

decrease in infant mortality in those who received vaginal progesterone vs placebo, as there is uncertainty around the estimate (RR 0.42, 95% CI 0.16 to 1.08).

- **Individual participant data meta-analysis:** *Women with a short cervix (≤25 mm)*
  Low quality evidence showed that for women with a short cervix (≤25 mm), there may be a clinically important decrease in infant mortality in those who received vaginal progesterone vs placebo, as there is uncertainty around the estimate (RR 0.45, 95% CI 0.18 to 1.08).

d. Gestational age at birth (mean weeks')

Very low quality evidence showed no clinically important difference in gestational age at birth between those who received vaginal progesterone or placebo. Substantial heterogeneity between trials reviewed (I^2=82%), warrants caution when interpreting results.

- **Subgroup analysis:** *Women with a history of spontaneous preterm birth*
  Very low quality evidence showed no clinically important difference in gestational age at birth between those who received vaginal progesterone or placebo. Substantial heterogeneity between trials reviewed (I^2=91%).
- **Individual participant data meta-analysis:** *Women with a short cervix (≤25 mm)*
  Moderate quality evidence to showed that, for women with a short cervix (≤25 mm), there was a clinically important increase in gestational age at birth for those who received vaginal progesterone vs placebo.

e. Early onset neonatal sepsis (up to 72 hours)

Low quality evidence showed that infants experienced a clinically important decrease in the occurrence of neonatal sepsis when delivered by women who received vaginal progesterone vs placebo.

- **Subgroup analysis:** *Women with a history of spontaneous preterm birth*
  Moderate quality evidence showed that for women with a history of spontaneous preterm birth, vaginal progesterone decreases the occurrence of neonatal sepsis vs placebo.
- **Subgroup analysis:** *Women with a short cervix (<30 mm)*
  Very low quality evidence showed that for women with a short cervix (<30 mm), there was no clinically important difference in the occurrence of neonatal sepsis between administration of vaginal progesterone or placebo.
- **Individual participant data meta-analysis:** *Women with a short cervix (≤25 mm)*
  Moderate quality evidence suggests that for women with a short cervix (≤25mm), there may be a clinically important decrease in neonatal sepsis for infants when comparing vaginal progesterone vs placebo, but there is uncertainty around the estimate (RR 0.61, 95% CI 0.34 to 1.09).

Critical outcomes, preterm birth <34 weeks', stillbirth and infant mortality prior to discharge were selected as the most direct indicators of the efficacy and safety of prophylactic progesterone in women at risk of preterm birth. However, other outcomes were reviewed including maternal satisfaction/ health-related quality of life (HRQoL), and neurodevelopmental outcome at ≥ 18 months.

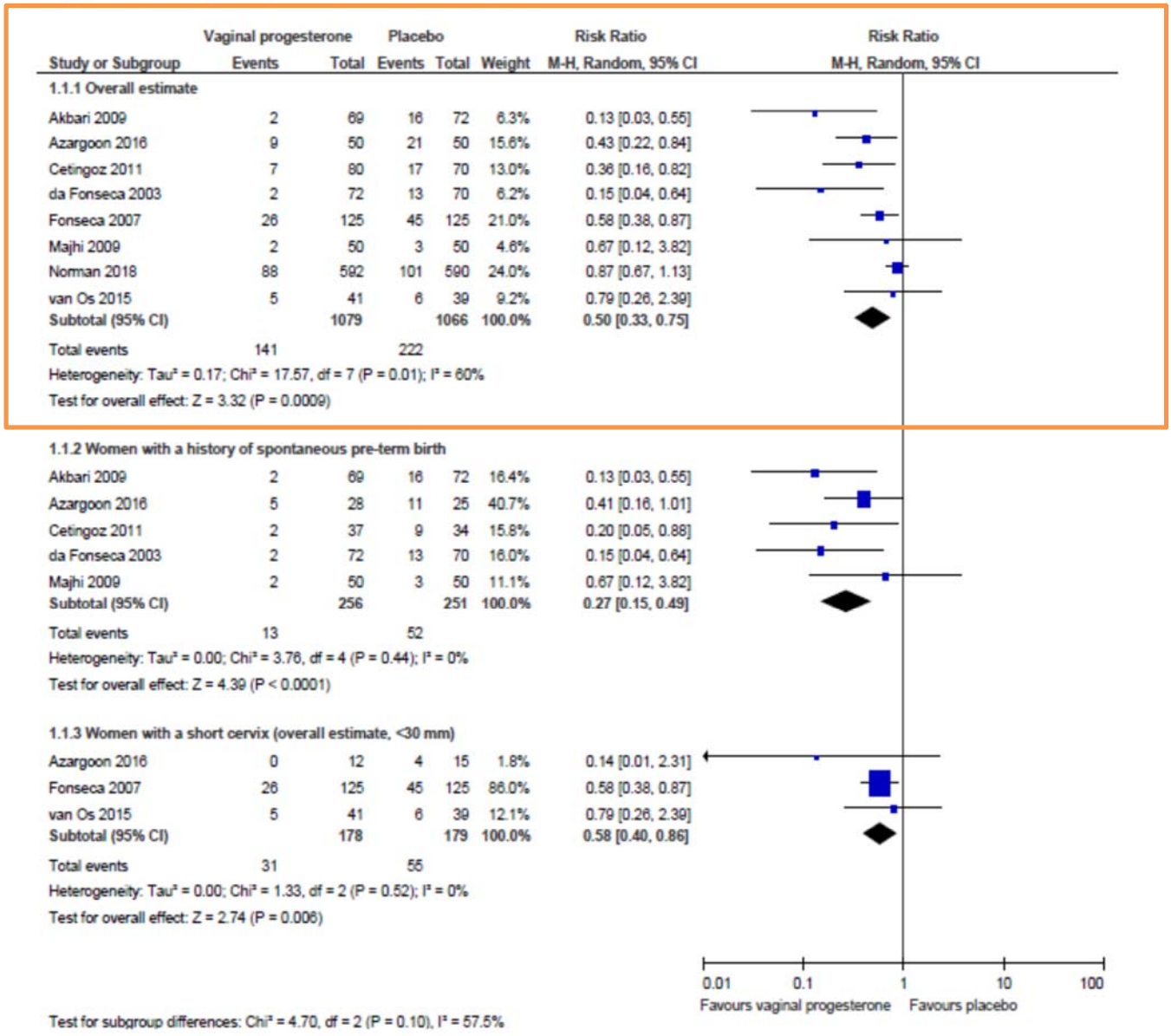
QUALITY OF THE EVIDENCE REVIEWED IN THE NICE SYSTEMATIC REVIEW

The quality of the evidence ranged from very low to high, but was downgraded due to risk of bias (randomisation and blinding not reported, or study treatment was not concealed); high heterogeneity (and predefined subgroup analyses were performed where I^2 >50%); and imprecision (trials were underpowered and thus estimates reported had wide confidence intervals).

OPPTIMUM trial: Data from this UK based trial (Norman et al, 2018) that showed no benefit of vaginal progesterone in the prevention of preterm birth for women with recognised risk factors was included in the NICE evidence review. The OPPTIMUM study however did not alter the overall conclusion of the NICE review and meta-analysis (see forest plot, below). It is suggested that the heterogeneity of the underlying population may have contributed to this (previous

preterm birth, cervical length ≤25mm, preterm premature rupture of the membranes or previous procedure to treat abnormal cervical smears) and data for subgroup analysis was not forthcoming.

Figure 1: Preterm birth <34+0 weeks



Source: NICE preterm labour and birth Guideline, update (August 2019). Appendix A: Evidence review for clinical effectiveness of prophylactic progesterone in preventing preterm labour.

CONCLUSION

Progesterone supplementation may reduce the risk of preterm birth in women with a singleton pregnancy who have had a previous spontaneous singleton preterm birth and in women with a short cervix on ultrasound examination in the current pregnancy.

Based on the evidence it is suggested that for women with a singleton pregnancy who have had a previous spontaneous singleton preterm birth, progesterone treatment is a reasonable option.

For women with mid-trimester cervical shortening (defined as ≤25 mm before 24 weeks) and no prior spontaneous singleton preterm birth, it is suggested that daily vaginal progesterone treatment through 34 weeks of gestation be offered. The studies show that reasonable options include a vaginal suppository (100 or 200 mg), gel (90 mg), or tablet (100 mg micronized progesterone).

The NICE guideline recommends that cervical cerclage be considered in women with a cervix length ≤25mm with previous history of cervical trauma or previous preterm pre-labour rupture of membranes.

For women who choose to take progesterone for preterm birth prevention, it appears to be safe with no major adverse events noted in follow-up studies up to two years.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	See evidence review above – note that vaginal progesterone should be used in specific patient cohorts only.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	No harms were identified.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [X] No [ ] List the members of the group. Cervical Cerclage List specific exclusion from the group:	Alfirevic et al[7]. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. Cochrane Database Syst Rev. 2017 Jun 6;6:CD008991. Rationale for exclusion from the group: n/a References: n/a
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [X] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	The Committee was of the opinion that pharmacological management may be preferred to a surgical procedure in women.

RESOURCE USE

How large are the resource requirements?

More intensive	Less intensive	Uncertain
	X	

Prices of medicines

Medicine	Cost (ZAR)
Vaginal progesterone 200 mg, 15	327.42*

* SEP database [Accessed 6 November 2019]

Price comparison of the different treatment protocols, as proposed by NICE Guidelines (2019)

Scenarios:

1. History of spontaneous preterm birth or mid-trimester loss
2. Cervical length ≤ 25mm (diagnosed 16-24wks) AND with NO history of spontaneous preterm birth or mid-trimester loss
3. Cervical length ≤ 25mm (diagnosed 16-24wks) AND with history of PPROM and /or cervical trauma (Only cerclage recommended for this clinical setting)

Assumptions:

1. Cervical cerclage procedure requires 2-day admission
2. No complications from cervical cerclage requiring additional care
3. Removal is an outpatient procedure and does not require anaesthetic
4. MacDonald stitch is the standard of care

Treatment protocols and cost for various scenarios:

Scenario	Treatment	Cost (ZAR)
1	Progesterone 200 mg, PV daily (initiated from between 16 to 24 wks and continued until 34 wks)	2750.33
2		
3	Cervical cerclage (MacDonald)	6788.00

Comparative ICERs

Medical management	NNT	Cost (ZAR)	ICER
Cervical cerclage	17 [7]	R12 356,00	R115 396.00
Progesterone, PV: PTB < 34 wks	13 [5]	R2 750,33	R35 754.26

PV = per vagina; PTB = preterm birth; wks = weeks; NNT = number needed to treat to prevent a PTB; ICER = incremental cost effective ratio

References:

- SEP database [Accessed 6 November 2019]
- Uniform Patient Fee Schedule, 2019 www.health.gov.za
- NICE Guidelines: Preterm Labour and Birth, August 2019 https://www.nice.org.uk/guidance/ng25
- Alfirevic Z, Stampalija T, Medley N. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. Cochrane Database Syst Rev. 2017 Jun 6;6:CD008991.

Additional resources: n/a

EQUITY

Would there be an impact on health inequity?

Yes	No	Uncertain
	X	

Inclusion of vaginal progesterone on the National EML would probably improve access to health care .

FEASIBILITY

Is the implementation of this recommendation feasible?

Yes	No	Uncertain
X		

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	X	☐

Recommendation

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

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

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

Rationale:

- Guidance aligned with NICE Guideline recommendations that were informed by systematic review and meta-analysis that included the OPPTIMUM study which showed conflicting results of no benefit of vaginal progesterone in preventing preterm labour.
- Subgroup analysis and individual participant data meta-analysis of low to moderate quality evidence showed that for women with a history of spontaneous preterm birth, or women with a short cervix (≤25mm), vaginal progesterone decreases the number of preterm births (at <34 weeks' gestation) compared to placebo.
- Furthermore, pharmacological management with vaginal progesterone is non-invasive and less costly compared to cerclage.

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

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
☐	X	☐

VEN status:

Vital	Essential	Necessary
☐	X	☐

NEMLC MEETING OF 5 DECEMBER 2019:

NEMLC accepted the recommendation and supporting evidence and rationale, as provided for by the NICE Guidelines for preterm labour and birth, that was recently updated in August 2019.

Monitoring and evaluation considerations:

Auditing to measure the uptake of vaginal progesterone for high-risk pregnancies to prevent preterm births.

Research priorities: Perceptions and acceptance of vaginal progesterone.

References

1) Manuck TA, Esplin MS, Biggio J, et al. Predictors of response to 17-alpha hydroxyprogesterone caproate for prevention of recurrent spontaneous preterm birth. Am J Obstet Gynecol 2016;214:376.e1.
2) Manuck TA, Stoddard GJ, Fry RC, et al. Nonresponse to 17-alpha hydroxyprogesterone caproate for recurrent spontaneous preterm birth prevention: clinical prediction and generation of a risk scoring system. Am J Obstet Gynecol 2016; 215:622.e1.
3) Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. Am J Obstet Gynecol. 2012; 206:124.e1–19. [PubMed: 22284156]
4) Jarde A, Lutsiv O, Beyene J, McDonald SD. Vaginal progesterone, oral progesterone, 17-OHPC, cerclage, and pessary for preventing preterm birth in at-risk singleton pregnancies: an updated systematic review and network meta-analysis. BJOG 2019; 126: 556–567.
5) NICE. NICE Guideline: Preterm labour and birth, Updated in August 2019. Available at: https://www.nice.org.uk/guidance/ng25
6) Norman JE, Marlow N, Messow CM, Shennan A, Bennett PR, Thornton S, Robson SC, McConnachie A, Petrou S, Sebire NJ, Lavender T, Whyte S, Norrie J, OPPTIMUM study group. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. Lancet. 2016;387(10033):2106. Epub 2016 Feb 24.
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