Risk-Based Cervical Length Screening and use of Progesterone in the Prevention of Preterm Birth

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Definitions and Legend ___ ***1***

Questions we need to answer from best available evidence ___ ***2***

Do we give vaginal progesterone to everyone with a prior spontaneous PTB or just those identified to have a short cervix? ___ **2**

Table 1. Review of best available evidence for vaginal progesterone ___ 2

How do we identify women with a short cervix? ___ **3**

To whom do we offer ultrasound-indicated cerclage vs vaginal progesterone? ___ **3**

Figure 1. Screening for Singleton Pregnancies with Prior sPTB < 34 weeks ___ 4

Figure 2. Singletons with prior sPTB between 34w0d-36w6d ___ 5

Figure 3. Singletons with NO Prior Spontaneous PTB < 37 weeks (Asymptomatic) ___ 5

Should we offer 17OHP to women with a prior spontaneous PTB for primary prophylaxis? ___ **6**

Who should be offered a transabdominal cerclage? ___ **6**

Additional Notes ___ ***6***

Appendix ___ ***7***

Table s1. Cerclage Checklist ___ **7**

Definitions and Legend

- TAS = Transabdominal sonography
- TVS = Transvaginal sonography
- TA = Transabdominal
- TV = Transvaginal
- CL = cervical length
- PPROM – preterm premature rupture of membranes
- PTL – preterm labor
- PTB - preterm birth
- sPTB – spotaneous preterm birth, PTB due to PPROM or PTL <37 weeks (up to 36w6d)
- Short cervix – TV CL $\leq$ 2.5cm
- Unsuccessful TV cerclage – sPTB between 14-28 weeks despite history- or ultrasound-indicated TV cerclage
- History-indicated cerclage (also known as prophylactic cerclage) – cerclage placed for a history of one or more second-trimester pregnancy losses related to painless cervical dilation and in the absence of labor or abruptio placentae or for a history of exam-indicated cerclage
- Exam-indicated cerclage – cerclage placed for painless cervical dilation (defined as $\geq$1cm dilation) in the second trimester
- Ultrasound-indicated cerclage – cerclage placed for a short cervix $\leq$2.5cm identified on TV ultrasound and no dilation detected on digital exam.

Questions we need to answer from best available evidence

1. Do we give vaginal progesterone to everyone with a prior spontaneous PTB or just those identified to have a short cervix?
2. Do we perform cervical length screening only in those with a prior spontaneous PTB <34 weeks or <37 weeks?
3. To whom do we offer ultrasound-indicated cerclage?
4. Do we offer 17OHP for women with a prior SPTB?

Do we give vaginal progesterone to everyone with a prior spontaneous PTB or just those identified to have a short cervix?

***Table 1**. Review of best available evidence for vaginal progesterone*

Study	Study type	Population	Intervention	Primary Outcome	Results
DeFonseca et al. 2007	DB, PC RCT, "opt in" 8 centers (London and Chile)	1. Singletons and twins between 20-25 weeks 2. TV CL ≤ 15mm 3. 15% with ≥1 sPTB 4. ~10% twins	200mg micronized Progesterone vs placebo	sPTB <34 weeks	1. N=250 2. Vag Prog ↓sPTB <34 wks (19.2% vs 34.4%, RR 0.56, CI 0.36-0.86) 3. No sig reduction in neonatal morbidity
Hassan et al. 2011	DB, PC, RCT 44 centers, 10 countries	1. Singleton 2. 19w0d-23w6d 3. TV CL 10-20mm 4. No signs of PTL	90mg vaginal progesterone gel (Crinone 8%) vs placebo	sPTB <33 weeks	1. N=458 2. Vag Prog ↓sPTB <33 wks (8.9% vs 16.1%, RR 0.55, CI 0.33-0.92, p=0.02) 3. ↓sPTB, 28, 35 weeks 4. ↓RDS, any neo morbidity and BW<1500gm
Normal et al. 2016 OPPTIMUM study	DB, PC, RCT 65 UK NHS centers, 1 Swedish hospital	1. Singleton 2. Prior PTB 3. ± short cervix 4. +FFN with other risk factor	Vag P vs placebo	1. Fetal death or birth <34 weeks 2. Composite neonatal 3. Standardized cognitive score at 2 yo	Vag P did not reduce PTB<34w, neonatal outcomes or long-term benefit or harm on children at 2 yo.
EPPICC group et al 2021	Meta-analysis of IPD from 31 RCTs 9 trials of vag P vs placebo	1. Singletons, multifetal gestations 2. Prior PTB ± short cervix	Vag P vs placebo or standard care	sPTB <37w, <34w, <28w	1. ↓PTB <34w by 22% 2. But no apparent benefit in women with prior PTB and CL>30mm
Conde-Agudelo et al. 9/2022	Meta-analysis and systematic review, RCTs 10 studies, n=2958 7 small studies, only 1 low risk of bias 3 large studies, all low risk of bias	1. Singletons 2. Prior sPTB	Vag P vs placebo	PTB <37w and <34w	↓PTB <37w and <34w When restricted to studies with "low risk of bias", Vag P did not reduce PBT <37w or <34w
Nelson et al. 10/2022	Prospective obs trial "Before and after design"	1. Singletons 2. Prior sPTB	Vag P vs placebo 3:1 match with historical controls	PTB <35 weeks	Vag P did not reduce PTB <35 weeks (PTB occurred in 24% Vag P group vs 16% of historical cohort)
Conde-Agudelo and Romero 12/2022	Research Letter Post-hoc subgroup analysis	1. Singletons 2. Prior sPTB 3. CL >25mm	Vag P vs placebo	PTB <37w and <34w	Vag P did not reduce PTB <37w or <34w in women with prior sPTB and CL>25mm

- Insufficient evidence exists to recommend vaginal progesterone as a primary prophylaxis in women with a prior PTB.
- BCM OB/Gyn Perinatal Guidelines Committee recognizes the uncertainty this poses to patients who have experienced a successful pregnancy outcome while on 17OHP even though evidence does not support continued use due to lack of benefit. In this situation, vaginal progesterone as primary prophylaxis can be discussed using a shared decision-making process but lack of evidence for efficacy as primary prophylaxis should be discussed and clearly documented.

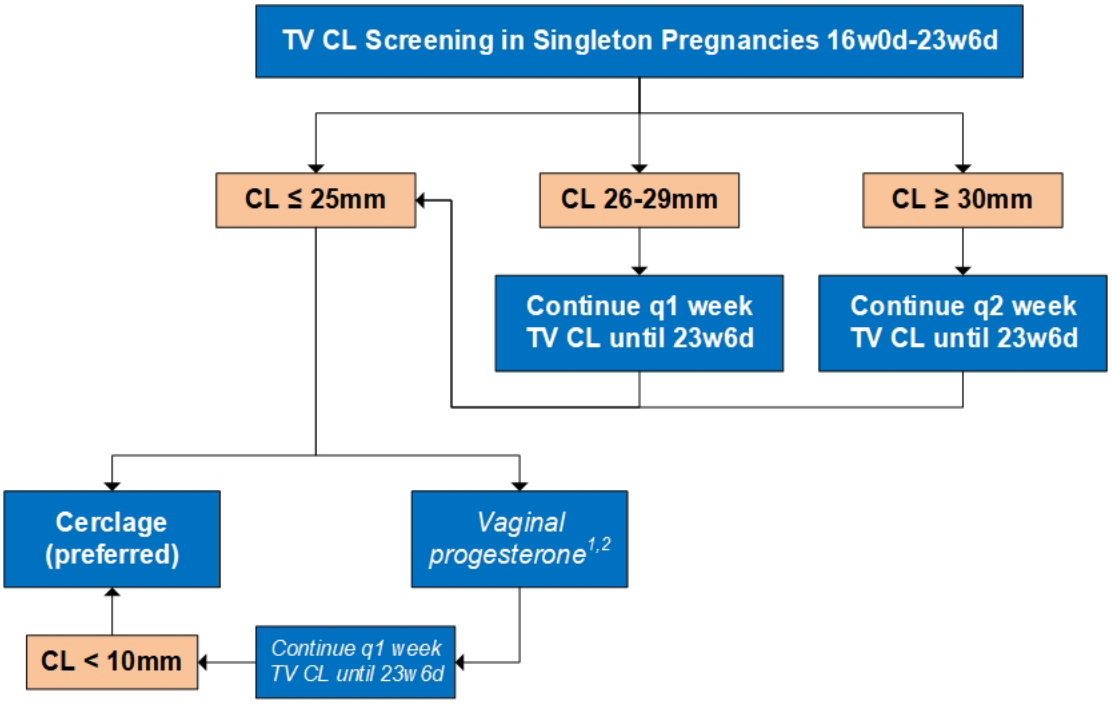
How do we identify women with a short cervix?

- In women with a singleton IUP and prior sPTB *<37 weeks*, we recommend serial transvaginal cervical length screening between 16-23w6d.
    - Ultrasound- or exam-indicated cerclage may be placed up to 23w6d, however the ultimate decision to place or withhold cerclage placement will depend upon the clinical circumstances of each individual patient (e.g. presence or absence of regular contractions, prolapsing membranes)
- BCM OB/Gyn Perinatal Guidelines Committee does *not* recommend universal TV CL screening
- BCM OB/Gyn Perinatal Guidelines Committee recommends transabdominal subjective assessment of the cervix between 16-23w6d on all women, regardless of PTB history, undergoing anatomic survey. If there is a suspicion of a short cervix on TA assessment or the cervix is not visualized, then TV assessment and measurement of the CL should be performed**. A short cervix is defined as a TV CL ≤2.5cm.**

To whom do we offer ultrasound-indicated cerclage vs vaginal progesterone?

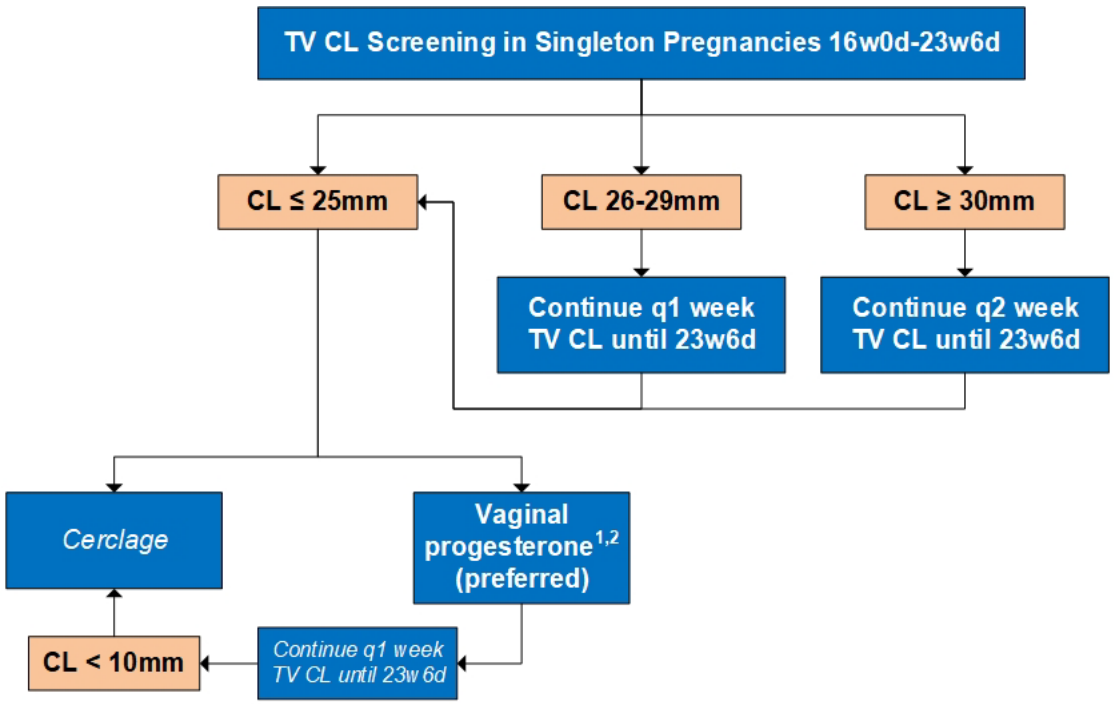
- BCM OB/Gyn Perinatal Guidelines Committee recommends that women with a singleton IUP and prior spontaneous PTB <34 weeks who are identified to have a TV CL ≤2.5cm be offered a TV cerclage as first-line intervention based on the best available evidence.
- In women who decline a TV cerclage placement, vaginal progesterone may provide some benefit based on indirect data and is a reasonable second-line option given safety profile.
- **BCM OB/Gyn Perinatal Guidelines Committee recommends that women with a singleton IUP and prior sPTB between 34w0d – 36w6d who are identified to have a TV CL ≤2.5cm be offered vaginal progesterone as first-line intervention based on the best available evidence.**
- Women who receive vaginal progesterone for a short cervix, regardless of PTB history, should continue weekly CL screening until 23w6d to identify progressive cervical shortening. If a TV CL <10 mm is identified before 24 weeks, a cerclage should be considered as vaginal progesterone does not appear to be effective at or below this cervical length ~~(see slides 16, 17)~~.
- **These recommendations are meant to be a guideline to clinical decision-making. BCM OB/Gyn Perinatal Guidelines Committee acknowledges that our understanding of PTB is evolving and therefore clinical situations will exist that may not fit into either gestational age epoch as described. In these cases, a unique treatment plan is encouraged after individualization of care and shared decision-making regarding cerclage vs vaginal progesterone.** Direct communication with the patient's physician is advised to maintain consistency in care.

Figure 1. *Screening for Singleton Pregnancies with Prior sPTB < 34 weeks*



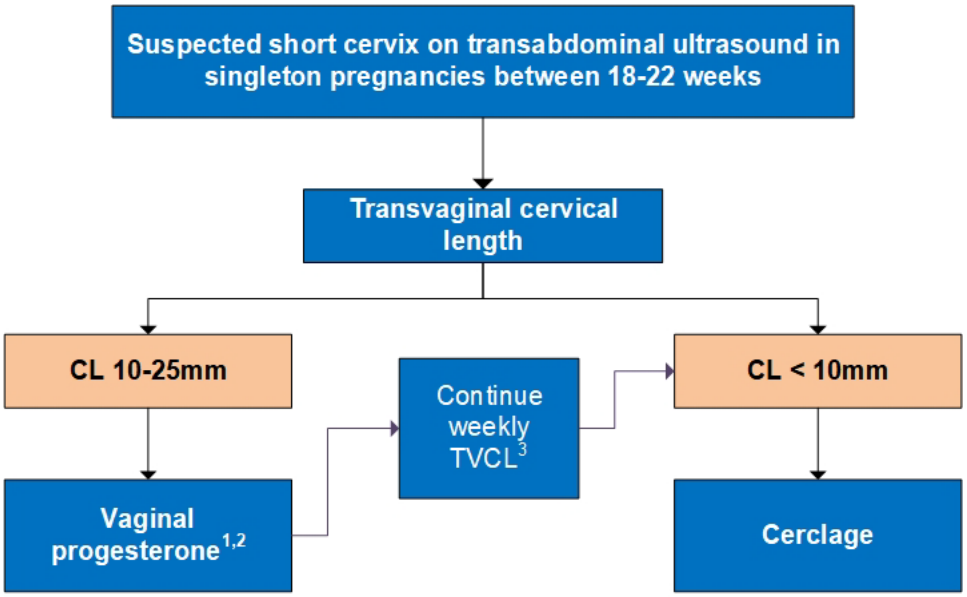
[1]Crinone 8% vaginal gel (90mg) or 200mg micronized progesterone nightly until 36 weeks
[2]Consider cervical exam to rule out cervical dilatation

Figure 2. *Singletons with prior sPTB between 34w0d-36w6d*



[1]Crinone 8% vaginal gel (90mg) or 200mg micronized progesterone nightly until 36 weeks
[2]Consider cervical exam to rule out cervical dilatation

Figure 3. *Singletons with NO Prior Spontaneous PTB < 37 weeks (Asymptomatic)*



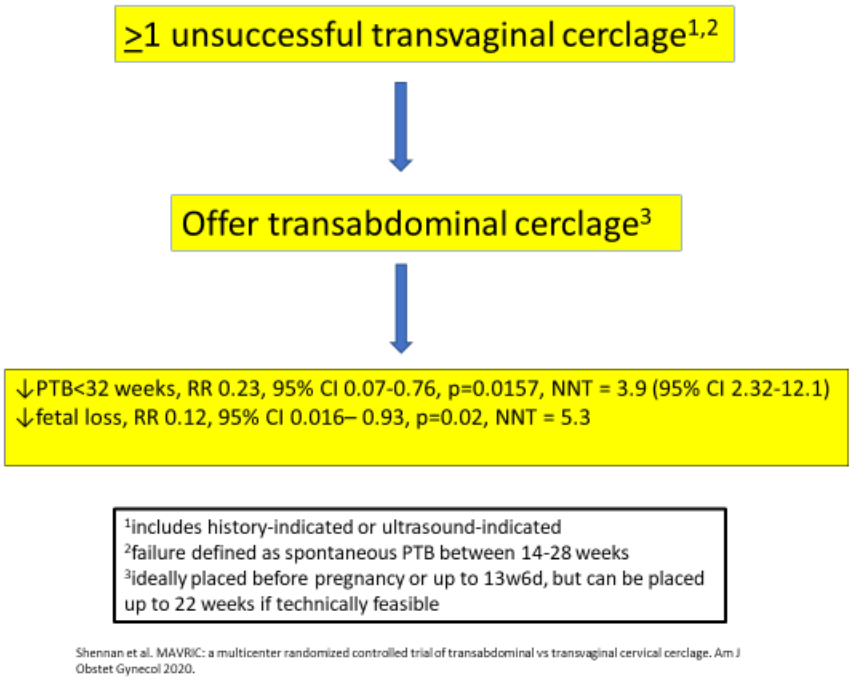
[1]Crinone 8% (90mg) vaginal gel or 200mg micronized progesterone qHS until 36 weeks
[2]Consider cervical exam to rule out cervical dilatation
[3]Continue weekly CL until 23w6d to identify progressive shortening < 10mm for which a cerclage would be indicated

Should we offer 17OHP to women with a prior spontaneous PTB for primary prophylaxis?

- BCM OB/Gyn Perinatal Guidelines Committee recommends that 17OHP not be offered to women with a prior spontaneous PTB.

Who should be offered a transabdominal cerclage?

- Women with a ≥1 unsuccessful history- or ultrasound-indicated TV cerclage should be considered for a transabdominal cerclage.
- Placement of a TA cerclage should be performed before conception but can be placed up to 21w6d, if technically feasible.
- Women with a history of an unsuccessful exam-indicated cerclage should be offered a history-indicated cerclage in their subsequent pregnancy.



Shennan et al. MAVRIC: a multicenter randomized controlled trial of transabdominal vs transvaginal cervical cerclage. Am J Obstet Gynecol 2020.

Additional Notes

- A bimanual exam to check for cervical dilation should be considered in the setting of a short cervix.

- In patients who start vaginal progesterone but then require a cerclage for progressive cervical shortening, it is reasonable to continue vaginal progesterone based on limited evidence.
- Continued cervical length screening is not indicated after cerclage placement.
- In the setting of an exam-indicated cerclage, the perioperative addition of Indomethacin and Cefazolin may prolong latency period. The regimen is as follows:
    - Cefazolin (weight-based dosing: 1 gm if <100kg, 2 gm if ≥100kg): first dose preoperatively and then every 8 hours for 2 doses postoperatively for a total of 3 doses
    - Those with a PCN allergy should receive Clindamycin 600mg instead
    - Indomethacin 50mg PO immediately postoperatively, and then every 8 hours for 2 additional doses for a total of 3 doses
    - If cervical insufficiency is suspected based on a prior pregnancy loss of a multiple gestation, a history-indicated cerclage can be offered after shared decision-making.

Appendix

Table s1. Cerclage Checklist

Indications for Cerclage	[] History-indicated - History of one or more second-trimester pregnancy losses related to painless cervical dilation and in the absence of labor or abruptio placentae - History of exam-indicated cerclage [] Exam-indicated - Painless cervical dilation in the second trimester [] Ultrasound-indicated - Current singleton pregnancy, prior spontaneous preterm birth at less than 34 weeks of gestation, and short cervical length (less than 25 mm) before 24 weeks of gestation - Cervical length less than 10 mm without a history of prior preterm birth, without evidence of cervical dilation [] Transabdominal cerclage - Unsuccessful transvaginal cerclage, defined as singleton delivery before 28 0/7 weeks of gestation from sPTB after placement of history- or ultrasound-indicated cerclage - Anatomic factors that preclude placement of transvaginal cerclage, such as extensively amputated cervix, trachelectomy, recurrent LEEP procedures or a congenitally extremely short cervix
Contraindications for cerclage	Intrauterine infection Active preterm labor PPROM Fetal demise Active bleeding
Scheduling Considerations	[] Schedule ideally between 13-14 weeks for history-indicated cerclage but pending patient presentation for care [] Schedule pending diagnosis for ultrasound- or exam-indicated cerclage - If between 22 and 24 weeks, counsel patient on periviability implications - Ultrasound-indicated cerclages ideally should be placed within 72 hours of diagnosis and referral for US-indicated cerclage should be made to the PFW MFM RN coordinators to be scheduled in the PFW OR or scheduled in the BT OR.

	- Exam-indicated cerclages ideally should be placed within 24 hours of diagnosis if the patient is beyond 14 weeks; a period of observation to eliminate preterm labor as the cause is reasonable
Pre-Operative Evaluation	[] Pelvic examination including sterile speculum examination and digital examination [] Aneuploidy screening or diagnostic testing, if desired [] T&S, CBC [] Evaluation for infection - Work-up based on symptoms - Evaluation for intraamniotic infection, including amniocentesis if clinically indicated (can consider with exam-indicated cerclage) [] Ultrasound as appropriate [] Anesthesia consultation [] History and physical [] Surgical consent (Risks include bleeding, infection, damage to surrounding structures, rupture of membranes, failure of the cerclage leading to pre-viable, peri-viable or preterm delivery with the potential for adverse outcomes in the current and any future pregnancy, cervical trauma in the setting of labor) [] Discuss planned observation after procedure [] Post-procedural plan for any prophylactic antibiotics and tocolytics [] Length of stay determination after procedure and whether tocometry monitoring is necessary [] Fetal heart rate documented prior to cerclage (day of surgery)
Intraoperative	[] Counseling of patient on intra-operative findings and/or complications [] Discussion if intra-operative findings warrant tocolysis and prophylactic antibiotics
Postoperative	[] Assessment of fetal heart tones after procedure [] Anesthetic considerations (if discharging day of surgery) - Ambulation - Urination - Alert anesthesia of any concerns postoperatively [] Provide patient education – what to expect [] Review activity level with patient [] Discuss use of progesterone if patient was using prior to cerclage placement [] Postoperative analgesia [] Follow-up scheduled within 2 weeks with primary Obstetrician [] Employment absence documentation as needed [] No further routine cervical length assessment recommended

Checklist references:

1. Society for Maternal-Fetal Medicine (SMFM); Mateus Nino J, Combs CA, Davidson C; SMFM Patient Safety and Quality Committee. Electronic address: smfm@smfm.org. Society for Maternal-Fetal Medicine Special Statement: Checklists for transabdominal cerclage. Am J Obstet Gynecol. 2023 Oct;229(4):B2-B6.
2. Cate J, Bauer S. Cerclage Checklist. Duke University