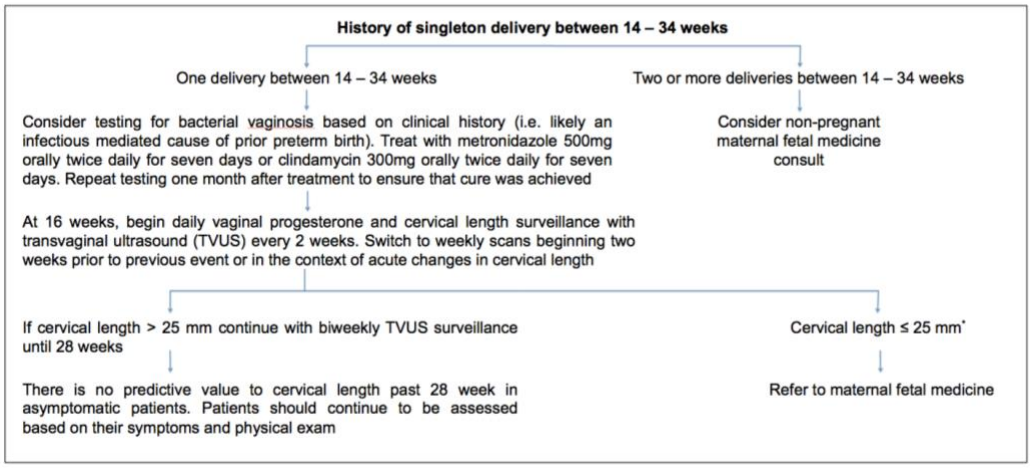
SOON Network Standardized Protocol for the Prevention of Preterm Birth

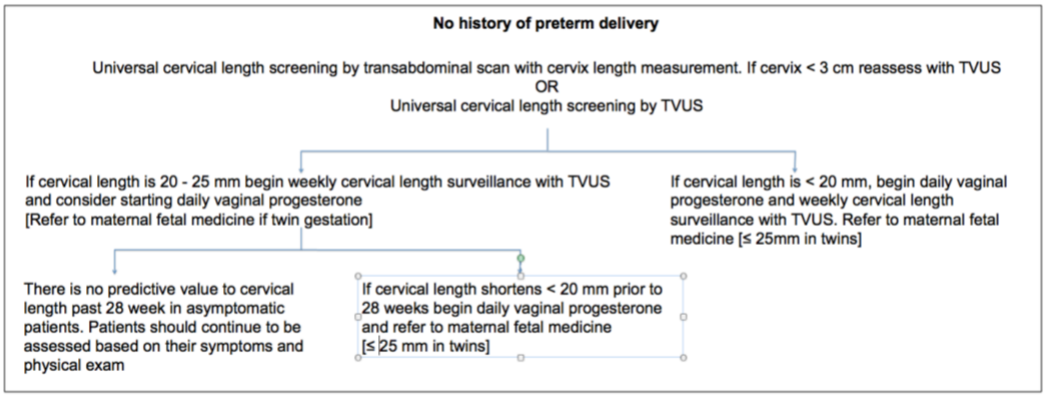
Based on the International Classification of Disease, preterm birth is defined as a baby born alive before 37 completed weeks of pregnancy. In 2010, 15 million babies or 11% of livebirths world wide were born pre-term and 1 million of these babies died due to direct causes related to prematurity. In Canada, preterm births account for 8% of all births, which translates to ~24000 babies in 2010, which has increased by almost 25% over the past decade.

Two-thirds of preterm births are due to spontaneous preterm labour, cervical insufficiency, or preterm premature rupture of membranes. The purpose of the following document is to summarize the available evidence and the proceedings of a consensus meeting to develop a network-wide protocol for the prevention of preterm birth from these causes[1]. The findings, protocols, and recommendations are consistently updated as new evidence becomes available.

Most recent update: September 2018

Summary flow charts





Management of women with known history of preterm birth

The etiology of a preterm birth is often difficult to ascertain when a woman presents in a subsequent pregnancy. Spontaneous preterm birth (ie: not iatrogenic) is usually caused by spontaneous preterm labour, cervical insufficiency, or preterm premature rupture of membranes. These can be mediated by placental, infectious, or cervical mechanisms. When the etiology is unclear, most practitioners will screen for these various causes and treat based on any clues that evolve.

Obtaining a complete and thorough history is critical to understanding the likely etiology of the previous preterm birth, which can help to guide decision-making regarding treatment

Investigations:

Initial investigations are performed to seek causes that may be infectious, placental, or cervical.

i) Bacterial vaginosis

- SOGC guideline[2] recommends screening and treating women at high risk of preterm birth
- Cochrane review[3] shows benefit to screening the general population, but when studies are reduced to look at women at risk of preterm birth, there is no proven benefit to treatment: no reduction in rate of PTB<37 weeks, no reduction in rate of PPROM, some trend to reduction of late miscarriage.
- Meta-analysis from 2011[4] shows reduction in risk of PTB < 37 weeks when screened and treated with oral clindamycin

Consensus:

- No firm suggestion that the entire network should screen and treat
- Make your own choice on who to screen
    - If we're going to screen, screen at the first OB visit 12-16 weeks has been recommended in the literature
    - Oral treatment
        - More research is required. Until then, oral treatment as per SOGC
        - Oral clindamycin proven in multiple studies.

ii) Other vaginal microbiology testing

- Should be more individualized treatment depending on patient's history
- Older trials suggest benefit of Ureaplasma screening and treating in reduction of colonization, but not in reduction of PTB
- Only applicable to high-risk population

Consensus: No screening for Ureaplasma for general preterm population (low risk population or in women with history of 1 preterm birth) UNLESS there is something in her history that makes you suspect could have played a role

- Screen high risk population and treat

iii) Urine – treatment of asymptomatic bacteriuria, UTI

- Treatment of women with asymptomatic bacteriuria and a history of PTB has been shown reduce the risk of subsequent PTB when treated before 20 weeks[5]
- Asymptomatic patient – inexpensive, treatment helps to reduce PTB in a population of preterm birth
- Often get borderline reports of multiple organisms –won't treat them at the time of result. Will often repeat test at next visit. Will only treat if a specific bacteria is found with a colonization of greater than 10^6
- Urine culture – everyone screens at first visit. Some will screen again at 24-28 weeks along with GCT
    - At 28 weeks – if they have growth at level of UTI, will treat patients

Consensus:

- Screen and treat at booking visit before 20 weeks.
- Uncertainty re: benefit of screening asymptomatic women and treating at 24-28 weeks for the reduction of PTB

iv) Placental assessment by uterine artery Doppler measurements

- Optimal remodelling of maternal spiral arteries is at 20-22 weeks
- Consider in those with a history of placentally-mediated preterm birth
- Uterine artery Doppler is not part of a screening program - difficult to obtain at outside centres
- Inconsistent literature on who to screen or timing of the test

v) Is there a role for (first and second) trimester serum analytes?

- If people measure these analytes as part of FTS or IPS and obtain abnormal values, should tell patients their associations with these lab values
- Goetzinger 2012[6] showed low PAPP-A and higher frequency of abnormal first-trimester uterine artery Dopplers in women delivering <34 weeks, but no improved prediction when model executed
    - No improved prediction beyond prediction based on maternal characteristics
- SOGC 2008[7] cites association of abnormal analytes with increased rates of PTB, but does not give a clear protocol for management (this technical update is currently under review)
- Some evidence for use in those with a history of placentally-mediated preterm birth, but insufficient to recommend for screening
- RCT[8, 9] data shows trend to reduction in preterm birth with low-dose ASA administration after 12 weeks

Consensus:

Interesting from a research perspective, however not enough research to warrant screening or management options using serum analytes or uterine doppler unless the patient has a clear history of a placental mediated preterm birth.

- Protocol has to clarify spontaneous PTB and NOT iatrogenic PTB.
- Although we should include that if someone with a placental mediated (IUGR, preeclampsia) PTB – patient should be on aspirin

Progesterone as primary prevention

Progesterone treatment has been studied in women who have undergone spontaneous preterm birth, regardless of it being due to cervical, infectious, or placental causes.

i) When to initiate:

- In women with a history of preterm birth, progesterone treatment to begin 16-20 weeks.
    - SMFM guideline 2014: If there is a history of PTB, studies have started progesterone between 16-20 weeks. Meta-analysis[10] includes OPTIMUM study and found benefit to administration of progesterone when cx <25mm mid-trimester

- What to do with women from fertility clinic that are on progesterone until 12 weeks and have a history of preterm birth?
    - Note: the dose of progesterone varies with fertility treatment; usually vaginally although some may have been prescribed oral medication
    - If they come on 600mg per day and then taper down slowly to accepted dose

Consensus: Progesterone to be started at 16-20 weeks in singleton gestations with a history of preterm birth. Also role for history-indicated cerclage depending on OB and patient preference and nuances from history of preterm birth.

ii) How to monitor: repeat TVUS cervical length measurements q1-2week
iii) When to move to cerclage in women treated with progesterone (what cut –off cervical length): Usually inserted at <15mm
iv) When to discontinue:

- No consensus in literature, continue until risk of PTB is low 34-36 weeks
    - Intuitively, wouldn't want to create an iatrogenic progesterone withdrawal before term. But also by continuing them on progesterone later are we putting women at higher risk for postterm births?

Consensus: Stopping at 34-36 weeks

Role of combined treatment with cerclage and progesterone

- In which patients?
    - Usually combined treatment in women who were started on progesterone and then underwent an ultrasound-indicated cerclage
    - No evidence to guide this management:
        - Small retrospective studies (Jung, E Addition of adjuvant progesterone, J of obstetrics gynecol research 2016, Stetson, 2016, obs and gyn, outcomes with cerclage) show no improvement in outcomes

ii) what monitoring?
iii) when to remove cerclage?

- Using both is not an unreasonable option because there is insufficient data to currently guide us. Which one you will decide to use first will depend on the patient
    - No study comparing progesterone vs. cerclage

- What do people do with monitoring with a cerclage?
    - U/S q1-2 weeks
    - Monitoring not because you will be offering them an additional treatment because can help make them a decision about bringing them to a tertiary center, celestone, hospitalization, reassurance, stress reduction
- Removal – if 35 weeks why would you take it? Concerned that women will go into labour
    - Most people take cerclages out at 38+weeks and inducing them at 41 weeks. Take 1-2 days to go into labour. Very uncommon to go into labour shortly after taking out a cerclage
    - Reasonable to take it out because of risk of cervical tearing
    - If done at 35 weeks, often incomplete removal because procedure is often done without an epidural
    - SOGC recommends 36-38 weeks

Consensus: F/u with U/S q2-4 weeks depending on what the initial cervix was and patient hx

<u>Celestone</u>

- How do we optimize the timing of celestone?
- We should be more cautious about giving celestone
- If you're monitoring someone serially with a stitch and then you see that they have dropped in length or cervix is dilated -> would give celestone more imminently

Consensus:

- Consider monitoring q 2 weeks in people with a stitch. May alter management, lifestyle, education, steroids
- No steroids routinely at 24 weeks but if monitor and significant change then consider steroids

Management of women without a history of PTB and a finding of short cervix

Universal screening for cervical length

- Transabdominal U/S – since most patients will have a cervix of 3-4 cm and have a full bladder – the transabdominal u/s could be used as an initial screening tool
    - Could we use as a transabdominal u/s as discriminatory method?
        - Saul, 2008: Using an empty bladder and a cutoff of 3cm, trans-adominal scanning captured all cervixes that were <2.5cm[11].
        - Rhoades, 2016: Prospective study comparing TA to TV – cutoff of 3.5cm excludes cervix <3cm on TVS and avoids TV study in 68%[12]

- Push towards universal screening in low-risk population as a means to reduce preterm birth
    - Fonseca, 2007[13]: routine scan 20-25 weeks, <15mm cervix
    - Crosy, 2016[14]: Meta-analysis. Universal TVS and progesterone for all those whose cervix is <15mm – reduction in delivery before 34 weeks by 27.7% Cost study done showing this is a cost-effective intervention

Potential drawbacks to universal screening by TVUS:

- Many patients in the community go to different U/S clinics – but could community OBs identify the radiologists that they each prefer within the community?
- If we have an infrastructure for routine screening – will already have a mechanism for identifying short cervix and information could be inputted prospectively
- Possibly can attach that if a TVUS < 2cm AND treat with progesterone as standard of care

Consensus:

- Transabdominal U/S as universal screening for cervical length. If CL <3cm on transabdominal U/S than OB should refer for transvaginal U/S
- Transvaginal US as universal screening for cervical length where possible

Primary treatment

- Progesterone if cervix ≤ 25 mm at 18-24 weeks (Updated 2018: IPD meta-analysis initiating progesterone at cervix length ≤ 25mm prevented PTB at all weeks <36 - < 33 weeks)[15]
- If patient ≤ 15mm
    - Refer to tertiary center
    - Offer the option of a cerclage
    - No evidence – have to use clinical judgment
- What is short?
    - ≤ 25mm - increase surveillance and initiate progesterone
- Cerclage
    - In women with a finding of short cervix, progesterone and cerclage have been found to have equal benefit in several studies and in a recent indirect comparison meta-analysis.[16] The decision for cerclage should be individualized to the specific clinical situation until more concrete recommendations can be made. The consensus of the meeting was to offer cerclage if the cervix is ≤ 15mm or if there is rapid decline in the absence of any contraindications.
- Repeat measurements are recommended every 1-2 weeks
- Admission and steroids?
    - Admission does not prolong pregnancy[17] but can be done for short term monitoring, administration of steroids, and counseling and planning.

Consensus: If CL < 25mm increased surveillance of q1-2 weeks interval of monitoring and begin progesterone. Discussion of cerclage may be considered between patient and clinician

Consideration for Twins:

- Progesterone is considered safe[18] when given routinely in twin pregnancies, however, routine, universal administration has had inconsistent effects in reducing rates of preterm birth.[19,20]
- A recent individual patient data meta-analysis[21] of administration of progesterone in twin gestations where a short cervix (≤ 25 mm) was found at a mid-trimester ultrasound shows benefit in reducing rates of preterm birth at <35 weeks up to <30weeks (RRs ranging from 0.47 to 0.83) and neonatal morbidity and mortality.
- If cervical length in twins found to be ≤ 25mm – recommend initiation of daily vaginal progesterone and referral to MFM centre for consultation re: ongoing care.

Consensus: Serial cervical length screening by TVUS in twins. Progesterone and referral to maternal fetal medicine centre if ≤ 25mm

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