Preterm Prevention Clinic Treatment Pathway

Owner: Catherine Hillman	Job title: Consultant Obstetrician
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Key Amendment

Date	Amendment	Approved by

Preterm Prevention Clinic Treatment Pathway

Background:

Every year worldwide approximately 13 million premature deliveries babies are born premature, with a global incidence of up to 12%. Preterm birth is defined as birth before 37 weeks' gestation. It is a major contributor to neonatal and infant morbidity and mortality[1]. Spontaneous preterm birth accounts for about three-quarters of these births and births before 30 weeks of gestation account for most neonatal deaths[2]. The costs of preterm labour are significant, costing the US economy 26.2 billion dollars in 2005. The rate of spontaneous preterm birth in 2017 at Worcestershire Acute Hospitals Trust was around 9%. Preterm birth also has marked psychological, physical and emotional sequelae for those families affected[3].

The incidence of spontaneous preterm birth is continuing to rise. The reasons driving this increase remain unclear[4]. There are certain clinical measures employed that aim to prevent preterm labour, although most of these are still under evaluation. Nevertheless, current interventions could potentially eliminate up to 50% of recurrent preterm births[4]. Management needs to target those women at greatest risk of preterm delivery in order to improve care and ultimately outcome for both mother and baby. Interventions such as cervical cerclage, pre-delivery steroids for fetal lung maturation, progesterone, antibiotics, tocolytics and timely in-utero transfer may form part of a broader package of care offered to women demonstrated to be at greatest risk of early delivery.

Women with a history of a previous preterm labour or a second trimester loss are at high risk of having a further preterm delivery[5]. Other risk factors include previous cervical surgery, terminations of pregnancy, repeated dilatation and curettage and trachelectomy[6] and caesarean at full dilatation. There are many other "softer" risk factors implicated in the pathogenesis of preterm labour. These include age, parity, body mass index, ethnicity, socio-economic status, smoking, anxiety and depression also associated with premature labour[5]. The most challenging element of this clinical conundrum is that preterm delivery is a multifactorial problem, with multiple aetiologies. More recently, the "Saving Babies lives Bundle version 2" has reiterated the importance of reducing preterm birth and through its 5th element made it a requirement to formalize the risk assessment and management of women at risk. As part of this, the prediction of women at greatest risk is of paramount importance. Interventions to reduce risk can then be implemented.

Prediction of Preterm delivery:

Cervical sonography:

The cervix provides mechanical strength and helps to prevent ascending infection from the vagina penetrating the intra-uterine space. Cervical insufficiency, categorized as painless cervical dilatation, is the inability of the uterine cervix to retain a pregnancy in the absence of contractions or labour. Transvaginal ultrasound is the gold standard for assessment of cervical length. It has been reliably shown that the shorter the sonographic cervical length in the mid-trimester, the higher the risk of spontaneous preterm labour, presumably due to an "insufficient cervix"

There is no consensus as to what constitutes a sonographically short cervix. Some studies use a cervical length of <25mm, whilst others reduce this further to <15mm. Despite this clinical conflict, a shortening cervix remains the single most powerful predictor for preterm birth in the index pregnancy. Furthermore, a shortening cervix is far more informative than a history of previous preterm birth. With shortening of the cervix to <15 mm, there is almost

a 50% risk of preterm birth at 32 weeks[7.] Therefore, through cervical length screening, interventions should be offered to those women at greatest risk in a timely fashion[8].
Nevertheless, the use of cervical length scanning as a risk assessment tool has its limitations when used in isolation. Previous studies by Romero et al. indicate that only 8% of all patients with a mid-trimester cervical length ≤15mm [9] deliver preterm at <32 weeks' gestation.

Interventions for the prevention of preterm birth:

Interventions available at Worcester Royal for the prevention of preterm birth include:

- Cervical Cerclage
- Progesterone
- Aspirin
- Arabin Pessary

Cervical cerclage

Cervical cerclage involves the insertion of a surgical suture in the hope of being able to reinforce the mechanical strength of a shortening cervix. This can either be done as an emergency rescue procedure or as a planned prophylactic intervention for a woman with a poor previous obstetric history.

Emergency cerclage:

These should only be inserted where a patient presents at <24/40 gestation with a dilated cervix with intact membranes, in the absence of bleeding or contractions. It is crucial to assess for maternal well-being through basic observations and measurement of the CRP and white cell count. Where there is concern over possible sepsis, cerclage should be omitted. Patients should be thoroughly counseled regarding the risks of cerclage (bleeding, rupture of the membranes and subsequent infection) together with the potential that it may not ultimately.

Patients should remain as inpatients following the procedure for at least 3 days to watch for the development of sepsis. Four hourly observations and daily white cell counts should be taken following cerclage for three days. Should a patient experience ruptured membranes with a cerclage in situ, the stitch should be removed to minimize the risk of ascending infection on the clear counselling that this may result in preterm labour or late trimester miscarriage.

Evidence:

The Vaginal Ultrasound Cerclage Trial compared women who had received cervical cerclage with those who had not. Recurrent preterm birth (≤35 week's gestation) occurred in 32% of women with a cervical cerclage, compared with 42% of those who did not receive cerclage (OR, 0.67; 95% CI, 0.42–1.07; P 053)[14]. The incidence of preterm birth (≤35 weeks gestation) was particularly decreased in the 64 women whose cervical length was less than 15mm at randomization, who subsequently received cerclage. Women with cervical lengths between 15 and 25mm treated with cerclage delivered infants with significantly less morbidity[14]. Historically other studies have found no benefit from cervical cerclage, but this may relate to the previous inability to predict preterm labour and therefore patient mix within

the trials. Consequently, cerclage does remain a controversial intervention, although the Royal College of Obstetricians and Gynecologists recommend its use in women with a history of preterm labour and a cervical length of <25mm[8].

Results from randomized trials show similar rates of preterm birth in women with prior preterm births who undergo a history-indicated, prophylactic cerclage compared with those followed by ultrasound who were treated with cerclage only if the cervix shortened.

Therefore, cervical surveillance using transvaginal scanning can help to select appropriate candidates who would benefit most from cerclage, thus reducing needless surgical intervention and its complications.

Complications of cerclage are not inconsiderable and include infection, risk of bleeding, risk from the anaesthetic and also potential increased risk of miscarriage. As such, it is an intervention that should only ever be targeted at those for whom the risk of preterm delivery is significant and in whom the potential for benefit is greatest.

Progesterone:

There is evidence that vaginal progesterone reduces the risk of recurrent preterm birth[20-22]. In a trial sponsored by The Fetal Medicine Foundation, the overall reduction of preterm birth with vaginal progesterone administered in women with a cervical length of <15mm was 44%[21]. These results have been replicated by others studies[22-23].

NICE recommend the use of vaginal progesterone in certain situations (see below). This decision should be made following counselling of the woman by a Consultant.

- Offer a choice of prophylactic vaginal progesterone or prophylactic cervical cerclage to women who have both:

    - a history of spontaneous preterm birth (up to 34+0 weeks of pregnancy) or mid-trimester loss (from 16+0 weeks of pregnancy onwards) and

    - results from a transvaginal ultrasound scan…. that show a cervical length of 25 mm or less. Discuss the risks and benefits of both options with the woman, and make a shared decision on which treatment is most suitable. [2019]

- Consider prophylactic vaginal progesterone (Cyclogest 400mg/PV/nocte) for women who have either:
    - a history of spontaneous preterm birth (up to 34+0 weeks of pregnancy) or mid-trimester loss (from 16+0 weeks of pregnancy onwards) or results from a transvaginal ultrasound scan carried out between 16+0 and 24+0 weeks of pregnancy that show a cervical length of 25 mm or less. [2019]

Aspirin:

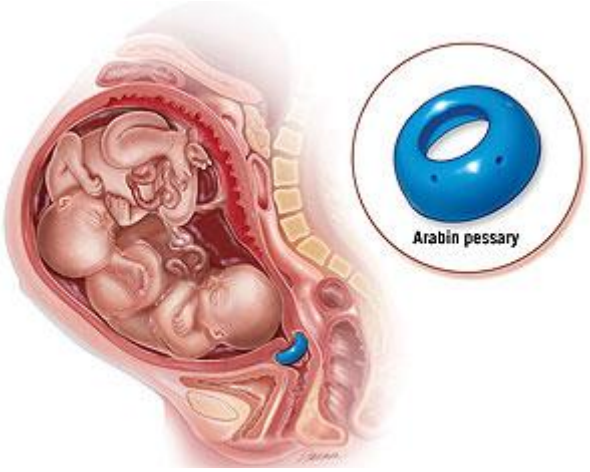
Aspirin is recognised to reduce the risk of pre-eclampsia (16 fewer per 1000 women treated), preterm birth (16 fewer per 1000 treated), the baby being born small-for-gestational age (seven fewer per 1000 treated) and fetal or neonatal death (five fewer per 1000 treated). Overall, administering antiplatelet agents to 1000 women led to 20 fewer pregnancies with serious adverse outcomes.

Aspirin slightly increased the risk of postpartum haemorrhage (>500 mls). Antiplatelet agents marginally increase the risk of placental abruption, but again the quality of the evidence was moderate due to low event numbers and thus wide 95% CI. Overall, aspirin is considered to improve outcome and appears to be safe.

Arabin Pessary:

The Arabin pessary is a donut shaped device that sits around the cervix. It has been shown to be beneficial as an alternative to formal cerclage for women with a cervical length <25mm who either decline cerclage or perhaps who present at a gestation which would make cerclage less acceptable. The pessary has been shown to reduce the number of deliveries before 34 weeks of pregnancy (early preterm birth) from 27% in women who did not use the pessary to 6% in those who did. It is inserted much in the same way a pessary is sited for the management of prolapse and sits around the cervix with the pessary lips pointing away from the cervix to provide additional mechanical strength. The woman should not be aware of it once sited (see diagram below).

Arabin Pessary:



Preterm Prevention Clinic (PPC)

The Preterm Prevention Clinic at Worcester Royal Hospital will see women as soon as possible following booking at around 14 weeks gestation. These women will have been referred from the community if risk factors for preterm delivery have been highlighted (see below). During this appointment, women would be assessed for clinical risk factors for preterm birth. Depending on the history women may be offered a prophylactic cerclage +/- progesterone supplementation. Women who have had a failed cerclage in the past should be discussed with Birmingham Women's Hospital.

Irrespective of the presence of a suture, transvaginal ultrasound assessment of the cervix will be performed at the 18 week review. If the cervix is found to be short, i.e. measuring <25mm, the patient will be offered FFN swab testing. Using the QUiPP algorithm, the FFN result will be combined with the cervical length to generate a risk of delivery. Following discussion, the patient may be offered further surgical or medical intervention in the form of cervical cerclage or vaginal progesterone treatment. Women would be seen again at 22 weeks and again at 24 weeks. Women who have undergone screening and have had no intervention may be transferred back into routine care from 24 weeks gestation. Midwifery care is appropriate should there be no further risk factors.

Women who have undergone an intervention e.g. cerclage or progesterone therapy should remain under the Preterm Prevention Clinic until 36 weeks.

Protocol for referral to Preterm Prevention Clinic:

Risk factor	Pathway
High risk • Previous preterm birth or mid-trimester loss (16-34 weeks gestation) • Previous preterm prelabour rupture of membranes (<34/40) • Previous cerclage • Previous trachelectomy • Uterine anomalies	**Management** • Refer to PPC by 12 weeks • Take history • Consider need for history indicated cerclage • Offer transvaginal cervical length scanning 2-4 weekly between 18-24 weeks • Quantitative fibronectin if cervix measuring <25mm • Use QUiPP to generate risk of delivery • Offer intervention as appropriate based on either history or additional screening tests having discussed risks and benefits based on up-to-date guidance from UK Preterm clinical network/NICE. • Interventions may include cervical cerclage, arabin pessary and progesterone.
Intermediate risk • Previous delivery by LSCS at full dilatation • LLETZ (>10mm depth) • >1 LLETZ performed • Cone biopsy (knife or laser)	**Management** • Refer to PPC by 12 weeks • Offer a single transvaginal cervical length between 18-24 weeks gestation as a minimum • Quantitative fibronectin if cervix measuring <25mm

Important note:

Women with a **history of LLETZ and subsequent term delivery** can be scanned by the radiology department and be cared for outside the PPC. They should have a cervical length performed at 18 and 22 weeks gestation as a minimum. Referral to preterm clinic should be done if there are any concerns around cervical length i.e. <25mm.

General principles:

- Patients should have BP, urine dip, SFH check (if appropriate) and fetal heart check at each visit.

- Consider prophylactic antibiotics if strong history of recurrent UTI.

- Consider a prophylactic cervical suture if history of recurrent late miscarriage or preterm birth, or if there is a history of probable cervical incompetence. Stitch should be sited as soon as possible following first trimester screening.

- Consider aspirin (150mg/OD) for women with a history of prior preterm labour or late trimester loss related to PET or placental dysfunction e.g. IUGR. Aspirin is especially important for women with a prior history of placental disease. Women with hepatic or renal disease should have a reduced dose (75mg/OD/PO). Ensure there is no maternal contraindication to taking aspirin.

- Assess smoking status and perform CO monitoring for all women at booking and at 36 weeks gestation. Confirmed smokers should have CO monitoring at every visit. Offer smoking cessation support as appropriate. Aim to be smoking free prior to 16 weeks gestation.

- Screen all women for asymptomatic bacteriuria through sending MSU for culture and sensitivity at booking. Treat UTI promptly to reduce the risk of subsequent preterm labour.

- Ensure that women are asked about domestic violence via the routine enquiry and document in the notes. Where necessary alert safeguarding midwife and offer additional support.

- Do not give steroids if FFN is negative, even if the cervix measures short.

- If the cervix is <25mm with FFN negative, recall to clinic in 1 week for a repeat ultrasound and FFN

- In patients with a history of prior PPROM, consider treatment for potential vaginal infection at 18/40 and 22/40.

- Aim to remove cervical suture or arabin pessary pre-labour at 37/40

- Remove cervical suture or arabin pessary if SROM or signs of labour

- If women present with potential preterm labour please refer to the WAHT Management of preterm labour guideline and ensure the appropriate administration of steroids, tocolysis and magnesium per protocol.

How to take a fibronectin (fFN) swab:

- Quantitative fFN can be taken from 18/40.
- Avoid gel on the speculum as it will increase the risk of false positives.
- Also beware taking a swab if the patient has bled or has had recent sexual intercourse.
- Using the swab, sample the posterior fornix for 10 seconds.
- Place the swab into the fluid medium provided.
- This sample is now ready to be analysed by the Hologic fFN reader.

How to calibrate the fFN reader:

- Machine must be calibrated every morning by clinic staff.
- Switch on the Hologic machine (switch at the back of the machine).
- Input your user name (ok to use your usual log in for the desktop).
- The cassette for calibration is in the locked cupboard in the clean utility.
- To calibrate the machine, press the central square marked calibrate.
- Then insert the calibration cassette and press next.
- The machine will calibrate, providing you with a “pass” sticker.
- The machine is now ready to use.
- If there is a failure to calibrate, the machine cannot be used and the Hologic Rep will need to be contacted.

How to test a patient sample:

- Once the machine has been calibrated, press “test patient”.
- Input your user details as mentioned above.
- Using the bar code reader scan the LOG number on the side of the box containing the fFN test cassettes.
- Press the button for “numbers”.
- Input the patient hospital number and press “next”.
- Insert the test cassette into the machine until you hear a click.
- Using the pipette provided, administer 200mcl to the test well.
- Press start and the machine will start to measure the sample.
- The test takes 10 minutes to complete after which a result will automatically print.
- Using the QuIPP APP, combine the fFN result with the cervical length to generate the risk of delivery, as explained above.
- Counsel the patient regarding the risk of delivery over the next 1 week, 2 weeks and 4 weeks and document in notes.

QuIPP

The QUiPP app is a clinical decision-making tool with the potential to revolutionize preterm birth prediction for women with symptoms of threatened preterm labour as well as asymptomatic high-risk women. Accurate diagnosis of preterm labour is desirable in order to prevent the maternal and fetal risks incurred by the majority of women who are over-managed, without missing true cases.

The QuIPP application has been designed for health, allied health and health research professionals who look after pregnant women to calculate individualised percentage risks scores of delivery within pre-specified clinically relevant timeframes. It is designed to be used with women as an educational tool and to arrive at shared decisions regarding the management of their pregnancy.

It is designed for use in two clinical settings:

1. For management of asymptomatic women at high-risk for preterm birth (delivery before 37 weeks’ gestation) who are attending preterm surveillance clinics

2. For management of women with symptoms suggestive of abnormal or premature uterine activity (e.g. abdominal pain, contractions, tightenings).

It relies on a relevant clinical history having been taken regarding the woman's risk factors for preterm birth and her current symptoms. It relies on existing point-of-care testing: quantitative fetal fibronectin (fFN) sampling of the cervico-vaginal fluid and/or transvaginal ultrasound cervical length (CL) measurements. Therefore the user is expected to have significant midwifery or obstetric experience in order to use QUiPP app or is working closely with a team-member who does.

How to counsel

Using a 5% risk of delivery within 7 days according to the QUiPP App as the threshold for intervention, 9/9 women with threatened preterm labour would have been treated correctly, giving a sensitivity of 100% (97.5% CI, 66.4%) and a negative predictive value of 100% (95% CI, 98.9–100%). The positive predictive value for delivery within 7 days was 30.0% (95% CI, 11.9–54.3%) for women presenting before 30 weeks and 20.0% (95% CI, 4.3–49.1%) for women presenting between 30 and 34 weeks. If this 5% threshold had been used to triage women presenting between 24 and 29+6 weeks, 89.4% (n=168) of admissions could have been safely avoided, compared with 0% for a treat-all strategy. No true case of preterm labour would have been missed, as no woman who was assigned a risk of <10% delivered within 7 days.

For women with threatened preterm labour, the QUiPP App can accurately guide management at risk thresholds for sPTB of 1%, 5% and 10%, allowing outpatient management in the vast majority of cases. A treat-all approach would not have avoided admission for any woman, exposed 188 mothers and their babies to unnecessary hospitalization and steroid administration and increased the burden on network and transport services owing to unnecessary in-utero transfers. Prediction of sPTB should be performed before 30 weeks to determine management until there is evidence that such a high level of unnecessary intervention, as suggested by the treat-all strategy, does less harm than the occurrence of rare false negatives.

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Flow chart for Preterm Prevention Clinic

Offer prophylactic Cerclage/Arabin following first trimester screening if history of preterm delivery or mid-trimester loss with evidence of cervical incompetence as soon as possible

General principles

BP

Urine dip/Send MSU

TV USS from 18 weeks

Fetal Fibronectin (FFN) if cervical length <25mm on TV USS

Generate QUiPP risk

If shortening cervix (<25mm) discuss Options if +ve FFN:

- Cerclage
- Arabin
- Progesterone

Arabin pessary ok >24/40

From >23/40 consider Steroids and Magnesium if delivery thought imminent (refer to QUiPP result)

Dalacin cream 0.5mg PV nocte for 7 days at 18/40 and 22/40 if history of recurrent BV

<14/40 → HVS/Chlamydia (if <25 years) Start aspirin if appropriate

18/40 → TV USS +/-FFN

Consider Dalacin if prior history of PPROM

22/40 → TV USS +/- FFN

Consider Dalacin if prior history of PPROM

24/40 → TV USS +/- FFN

Discharge to routine care if no interventions

>24/40 → TV USS +/- FFN
+/- Steroids
+/- Magnesium
Consider transfer to tertiary unit if delivery considered imminent

Care to be individualised