Specialised preterm prevention care, preterm prevention clinics and specialist preterm prevention advisors

Background Information

Introduction

Over the last 20-30 years, with a growing understanding of the contributing factors for preterm birth and the importance of risk stratification to guide the use of interventions to prevent preterm birth, specialised preterm birth services have been established. The majority are focused on spontaneous preterm birth and aim to provide specialist multidisciplinary pregnancy care in a dedicated clinic setting for asymptomatic wāhine/people with an increased chance of preterm birth due to pre-existing obstetric and/or gynaecological history (considered as indirectly modifiable risk factors).

The key components of a preterm prevention clinic or service include addressing modifiable risk factors (such as advice on becoming smoke-free, and screening and treating infection), surveillance of cervical length by transvaginal ultrasound scan through the mid-trimester, and providing evidence-based interventions of vaginal progesterone and cervical cerclage when indicated. They provide coordinated, supportive and individualised care to wāhine/people with a higher chance of spontaneous preterm birth, in partnership with a usual pregnancy care provider.

Although there is strong evidence supporting many practices used in preterm prevention clinics, evidence for preterm prevention clinics as a package is limited and evolving. This is in part due to the limited number of studies in the field and because many studies are old (prior to 1990) and no longer reflect practice in modern-day preterm prevention clinics.[2,3] Furthermore, as preterm prevention clinics are promoted and recommended widely across many settings,[4-6] further research via 'gold-standard' randomised trials, is less likely to be considered.

Inclusion of preterm prevention clinics in national preterm birth recommendations in countries like the United Kingdom[6] and Australia[5] has been justified by the ongoing poor outcomes from preterm birth, the availability of multiple evidence-based interventions, and the ability to provide coordinated and individualised care that is welcomed by wāhine/people using the services. For example, within an Aotearoa setting, care through a preterm prevention clinic has been associated with significant improvements in psychological wellbeing during the second trimester.[7] Wāhine/people attending the clinic also perceived that the clinic care reduced their pregnancy-related anxiety, whilst highlighting the beneficial effect of medical support, close monitoring and timely intervention, and the reassurance that care through a preterm prevention clinic was able to provide.[7]

Whilst evidence remains limited to guide day-to-day practice within preterm prevention clinics, significant variations in the referral criteria, investigations beyond cervical length measurement, interventions, and frequency and duration of care have been identified.[2] The advent of national and international consensus guidelines and national preterm birth prevention programmes is likely to result in greater consistency and equitable access to these services.

The geography and population size of Aotearoa pose significant challenges for the delivery of consistent and equitable specialist services and clinics in more rural areas and smaller units, including the majority of secondary maternity units. This includes capacity and resources to support preterm prevention clinics, as well as the training and peer mentorship for obstetricians and midwives to become upskilled and maintain confidence and competency in their practice.

An alternative to formal specialised preterm prevention clinics, in particular, for smaller units, may be preterm prevention specialist advisors. These clinicians may work through general obstetric services supported by specialist midwives, sonographers and the local paediatric team. To enable the establishment and development of specialised preterm prevention services (clinics or advisors), a Community of Practice has been proposed as a potential solution. A Community of Practice is defined as 'a group of people who engage in a process of collective learning with a shared domain of human endeavour'.[8] It includes three crucial elements which can be easily applied to specialised preterm prevention services: a domain, a community and a practice. Results from a 12-month pilot study of such a Community of Practice in Aotearoa (the Carosika Community of Practice), show highly encouraging results. There was a significant improvement in preterm birth care knowledge and confidence across obstetric and midwifery participants (overall adjusted knowledge scores increased from 36.9 to 45.5, $p<0.0001$) (unpublished data). This, along with very high levels of engagement and support for continuation, changes towards more consistent national practice, and an increase in preterm prevention clinic and specialist advisor numbers (unpublished data) support ongoing activity for the Carosika Community of Practice.

Adjunct prediction tests for spontaneous preterm birth in specialised preterm prevention care

Not all wāhine/people with indirectly modifiable risk factors for spontaneous preterm birth, will require an elective or planned treatment, and/or will go into labour or experience PPROM before 37 weeks. Adjunct prediction tests have the potential to be used in combination with risk factor assessment, or alone, to identify those with a higher chance of spontaneous preterm birth, and to allow resources and interventions to be used for those most likely to benefit.

These adjunct prediction tests for spontaneous preterm birth include ultrasound cervical length assessment and vaginal biomarker tests. This section focuses on their use in the population with indirectly modifiable risk factors and being cared for through specialised preterm prevention clinics.

For the use of adjunct prediction tests for spontaneous preterm birth and second trimester miscarriage relevant to pregnancy care for all wāhine/people, recommendations of practice for pregnancy care are provided in 'Prediction and prevention of spontaneous preterm birth in the general population'.

For wāhine/people with signs or symptoms of preterm labour (threatened preterm labour) and/or PPROM, recommendations of practice on the prediction and prevention of spontaneous preterm birth in these clinical scenarios, including adjunct prediction tests, are provided in 'Preterm prelabour rupture of membranes (PPROM) and threatened and active preterm labour'.

Ultrasound cervical length assessment

Cervical shortening is part of the common pathway to preterm labour and PPROM, either as a consequence and/or an initiator of the labour process. Although not all wāhine/people with a short

cervix in the mid-trimester will have a preterm birth, it is associated with an elevated chance.[9] Furthermore, a shortened cervix may occur weeks or even months before preterm birth, and hence may be viewed as part of the latent phase of preterm labour, providing opportunity for effective preventative interventions.

There is much debate about the value of universal cervical length surveillance, and significant variation in recommended practice regarding its inclusion as a standard part of the mid-trimester scan in the general population.[4,10-14] In those already identified to be at a higher chance of spontaneous preterm birth, there is less debate about its use within specialised preterm prevention care. This is further supported by evidence of benefit with cervical cerclage and vaginal progesterone use for wāhine/people with a short cervix.[15,16]

Consistency and reproducibility of measurement are essential for cervical length assessment to have value as an adjunct test for predicting spontaneous preterm birth. The transabdominal approach is likely to overestimate cervical length due to artificial elongation of the cervix from a full bladder or excessive probe pressure, and cannot always provide adequate visualisation of the cervix,[17] due to factors such as acoustic attenuation commonly seen with an elevated body mass index and/or shadowing from fetal or maternal structures.[4] The transvaginal approach adds time[11] and inconvenience, but offers better visualisation and more accurate measurement.[4] It is the recommended approach for screening populations already identified to have a higher chance of spontaneous preterm birth.[4,18] Transvaginal imaging with effective counselling is highly acceptable to wāhine/people, with very low decline rates.[19,20] In addition to the use of a transvaginal approach, a standardised technique that includes trained personnel, an empty bladder, appropriate positioning, identification of key structures, image capture, measurement technique and reporting is well described and limits inter- and intra-observer variation.[4,18]

Cervical length is typically stable between 14 and 28 weeks, and then gradually shortens towards term.[21,22] A reference range for cervical length at 16 to 36 weeks has been identified from more than 6500 transvaginal cervical length measurements taken in routine antenatal care for singleton pregnancies.[22] The median cervical length is reported to be 43 mm at 16 weeks and 30 mm at 36 weeks.[22] In comparison, the 1st centile is 27 mm at 16 weeks, 23 mm at 20 weeks, 19 mm at 24 weeks and 7 mm at 36 weeks.[22]

A systematic review including 14 cohort studies has assessed the predictive ability of mid-trimester cervical length measurement in asymptomatic wāhine/people considered to be at a higher chance of spontaneous preterm birth based on their pre-existing obstetric and/or gynaecological history.[23] It demonstrated an inverse relationship between cervical length and the risk of spontaneous preterm birth, with improved prediction at shorter cervical length cut-offs.[23] The most commonly used cervical length cut-off of <25 mm prior to 24 weeks, had test sensitivity 65.4%, specificity 75.5%, positive predictive value (PPV) 33.0% and negative predictive value (NPV) 92.0% for the prediction of preterm birth <35 weeks.[23] For simplicity, 25 mm has been adopted by the majority as the cut-off to define a ‘short’ cervix.[4] In a general population, only 1.6% and 4.2% of all pregnancies at 20 and 24 weeks will have a short cervix by this definition.[22] The incidence of a short cervix in a population with pre-existing risk factors is higher, and varies according to the nature and severity of risk.

Curvature of the cervical canal is commonly seen with a normal cervical length - 51% of cervical length measures >25 mm, but very rarely in a short cervix - no cases where the cervix was ≤15 mm in a cohort of 301 transvaginal cervical length assessments at 23 weeks.[24] In cases with significant curvature, the cervical length is likely to be longer when measured in two segments or traced along the curvature than in a straight-line measurement. However, as a significantly short cervix always

appears to be straight, the universal use of a straight-line measurement is recommended to promote consistency in care.[4]

Cervical funnelling, considered as the effacement of the internal aspect of the cervix with protrusion of the amniotic membranes past the internal os and into the cervical canal, has been associated with subsequent preterm birth. However, its presence does not substantially improve predictive ability compared with cervical length alone.[11] Recording the presence of cervical funnelling may be beneficial to clinicians when planning a cervical cerclage for a short cervix.

Intra-amniotic debris, also referred to as 'sludge', is considered as echogenic material within the amniotic cavity, often seen close to the internal os. It represents solid particles such as blood clot, vernix and meconium and may also reflect pus and microbes. In wāhine/people with a short cervix, intra-amniotic debris is an independent risk factor for preterm birth[25] and has also been associated with chorioamnionitis.[26] However, there is no consensus regarding the need for additional diagnostic tests or alternative treatment when debris is present.[4]

Most studies to date have assessed the predictive ability of cervical length assessment from 14-16 weeks until 24 weeks.[23] Cervical length screening is not recommended beyond 24 weeks for several reasons. Firstly, this is the typical upper gestation limit to consider preventative interventions of cervical cerclage and vaginal progesterone. In addition, beyond 23-24 weeks (considered the limits of survival), preparation for preterm birth is likely to be more effective for pēpi survival. However, interventions, such as *in utero* transfer and antenatal administration of corticosteroids and magnesium sulphate, are only effective within days and hours of birth. Hence, cervical length in asymptomatic wāhine/people at >24 weeks is less useful as it is poor in predicting imminent birth.

The frequency of cervical length surveillance in specialised preterm prevention care is based on considerations of the pathophysiological mechanisms and timing of cervical change, as well as the type and severity of pre-existing risk factors and local practice.[2,6] Evidence to support the frequency of cervical length surveillance is very limited. In the largest trial evaluating the use of ultrasound-indicated cervical cerclage in wāhine/people with a prior spontaneous preterm birth,[27] transvaginal cervical length assessment was performed fortnightly from 16^{+0} to 22^{+6} weeks, and increased to weekly if the cervix was 25-29 mm.[27] Cerclage for a short cervix (<25mm) using this practice was associated with improved outcomes.

Cervical length assessment in twin and higher-order multiple pregnancy may still be considered. As with singleton pregnancies, 25 mm is used as the cut-off to define a 'short' cervix.[4] However, this occurs much more frequently in twin pregnancies (11%),[28] and evidence of the benefit of vaginal progesterone or cervical cerclage when multiple pregnancy is the only risk factor for spontaneous preterm birth is less conclusive. Directing cervical length surveillance in multiple pregnancy to only those with pre-existing risk factors is likely to have more impact.

Vaginal biomarkers

Fetal fibronectin (fFN) was previously used as an adjunct predictive test for spontaneous preterm birth for asymptomatic wāhine/people with recognised risk factors and receiving specialised preterm prevention care (alone and in combination with cervical length). Since the withdrawal of fFN from the global market, no other vaginal biomarker is available to support screening in this asymptomatic population. Both cervical phosphorylated insulin-like growth factor binding protein-1 (phIFGBP-1), marketed as Actim Partus, and placental alpha microglobulin-1 (PAMG-1), marketed as Partosure,

have modest predictive value for those with signs and symptoms of preterm labour, but they have not been evaluated as a screening tool within an asymptomatic population.

Combination risk assessment tools

The QUiPP (Quantitative Instrument for the Prediction of Preterm Birth) App has been developed as a clinical decision-making tool used to predict spontaneous preterm birth in both asymptomatic wāhine/people receiving specialised preterm prevention care and in those who were symptomatic, including from a more general population.[29] It originally incorporated pre-existing risk factors (previous preterm birth, second trimester loss and cervical surgery), along with current gestation, number of pēpi, shortest cervical length and quantitative fFN level, resulting in risk prediction for birth within one, two and four weeks and by 30, 34 and 37 weeks.[30] It continues to function without the inclusion of fFN, but is likely to be less accurate.

This type of tool, used in specialised preterm prevention care, has utility in supporting decisions on the use of preventative interventions. However, it is likely to be most useful to support conversations with whānau close to the limits of survival and at the very highest chance of imminent preterm birth. A 5-10% chance of birth within one week, has been considered a reasonable threshold to prompt discussion with wāhine/people and whānau and to consider the use of interventions that optimise outcomes after preterm birth at these gestations, where the number needed to treat is low and potential for impact is high.

Interventions for the prevention of spontaneous preterm birth in specialised preterm prevention care

Cervical cerclage

Cervical cerclage is a surgical procedure involving the placement of a stitch around the cervix to provide support in pregnancy. It was first introduced into clinical practice in the 1950-60s with a transvaginal placement for the care of wāhine/people at a very high-chance of second trimester miscarriage.[31,32] Indications have now been extended to include those also at risk of spontaneous preterm birth, and may be placed in pregnancy or preconception (interval), via a transvaginal or transabdominal route, with consideration based on history, ultrasound evidence of a short cervical length, or when the cervix is already open.

Cervical cerclage is thought to prevent spontaneous preterm birth through two main mechanisms. Firstly, it provides mechanical support to the cervix to retain the pregnancy. Secondly, it maintains cervical length and the mucous plug, supporting cervical integrity and preventing ascending infection from the lower genital tract.[33]

Since its introduction more than six decades ago, there has been much debate and controversy about the role and efficacy of cervical cerclage in preterm birth prevention. Large randomised trials have been undertaken to help provide an evidence-based approach to management. Despite this, there remains uncertainty about which wāhine/people are most likely to benefit, and the optimal surgical techniques to use.

Transvaginal cervical cerclage is generally considered to have three types according to the indication for its use:

- History-indicated – with pre-existing risk factors for spontaneous preterm birth

- Ultrasound-indicated – with a short cervix (considered to be ≤25 mm at ≤24^{+6} weeks)
- Rescue – with an open cervix and exposed fetal membranes.

Transabdominal cervical cerclage is a history-indicated procedure for those at the highest chance of spontaneous preterm birth.

History-indicated transvaginal cervical cerclage

A history-indicated cervical cerclage is considered based on pre-existing obstetric and/or gynaecological history and predominantly focused on those wāhine/people with previous preterm birth and/or second trimester miscarriage. Randomised trials assessing the efficacy of history-indicated transvaginal cervical cerclage are old. The largest of these, a 1980s UK-led international trial, included almost 1300 wāhine/people considered to be at an increased risk of spontaneous preterm birth and whose obstetricians were uncertain whether to recommend a cervical cerclage.[34] Participants were randomised to cerclage or no treatment. The majority of participants had a history of prior spontaneous preterm birth/second-trimester miscarriage or cervical surgery.[34] Cervical cerclage was associated with a lower rate of birth <33 weeks compared with those managed without cerclage (83/647, 13% versus 110/645, 17%, OR 0.72, 95% CI 0.53-0.97, number needed to treat [NNT] 25).[34] Wāhine/people with ≥3 prior second-trimester miscarriages or preterm births were the most likely to benefit, with a rate of birth <33 weeks of 8/54, 15% with cerclage versus 17/53, 32% without ($p<0.05$, NNT 6).[34] Wāhine/people managed with cervical cerclage had a higher chance of puerperal pyrexia (6% versus 3%, OR 2.12, 95% CI 1.08-4.16).[34]

The most recent Cochrane review (2017) includes three further randomised trials of history-indicated cerclage compared with no cerclage (an additional 781 participants).[35] Cerclage was not associated with a significant reduction in preterm birth <37 weeks (RR 0.86, 95% CI 0.59-1.27), <34 weeks (RR 0.76, 95% CI 0.40-1.46) or <28 weeks (RR 0.82, 95% CI 0.59-1.13).[35] Similar risk ratios were also observed for perinatal loss, serious neonatal morbidity and neonatal death before discharge – all favouring towards cervical cerclage use, but as a non-significant trend.[35]

Interpretation and application of these findings to current practice is challenging. Even in the 1980s, clinicians were only willing to include wāhine/people in randomised trials where they were 'uncertain whether to recommend a cervical cerclage,' and hence those at highest risk may not have been included (creating bias that leads to an underestimation of effect). As history-indicated cerclage and/or alternative surveillance and treatment regimens are now considered as standards of care for those with recognised risk factors for preterm birth, further randomised trials of cerclage or no cerclage are very unlikely to be undertaken.

Ultrasound-indicated transvaginal cervical cerclage

As the majority of wāhine/people with pre-existing risk factors for spontaneous preterm birth will give birth at term in a subsequent pregnancy, and a short cervix is associated with subsequent preterm birth, cervical length assessment has been introduced as an adjunct test and triage tool. This allows better identification of those most likely to benefit from intervention and limits unnecessary intervention for others. Cervical cerclage for a short cervix is one of the two interventions used, and when used in these circumstances, it is referred to as an ultrasound-indicated cervical cerclage.

Ultrasound-indicated cervical cerclage may be used for those with a short cervix and pre-existing risk factors (usually previous preterm birth or second trimester miscarriage) or for those in the general population (as part of a screening process or as an 'incidental' finding). All clinical trials to date

assessing ultrasound-indicated cervical cerclage are significantly underpowered, and numbers remain relatively small even in meta-analyses.

A systematic review and meta-analysis including five randomised trials and 908 wāhine/people with a previous spontaneous preterm birth and a short cervix (<25 mm at <24 weeks) compared transvaginal cervical cerclage with expectant management (no cerclage).[15] Of those in the cerclage group, 28.4% had a birth <35 weeks compared to 41.3% for those managed expectantly (RR 0.70, 95% CI 0.55-0.89).[15] Ultrasound-indicated cerclage was also associated with a reduced chance of birth <24, <28, <32 and <37 weeks (RR ranging from 0.48-0.70, upper 95% CI <1.0 for all) and reduced chance of perinatal mortality or morbidity (15.6% with cerclage versus 24.8% without, RR 0.64, 95% CI 0.45-0.91, NNT 6).[15]

For those in the general population without previous spontaneous preterm birth but who are found to have a short cervix in pregnancy, a 2025 systematic review and individual participant-level data (IPD) meta-analysis provides new evidence to guide practice. It included six randomised trials and 507 asymptomatic wāhine/people with a short cervix (≤25 mm).[36] There was no difference in birth <37 weeks in those managed with ultrasound-indicated cerclage compared to expectant management (no cerclage), 33.5% versus 39.8%, RR 0.88, 95% CI 0.59-1.31, or in birth <24 weeks, <28 weeks and <34 weeks, or for any pēpi outcomes.[36] However, in planned subgroup analysis, wāhine/people with a cervical length ≤20 mm at <24 weeks who were managed with cerclage had a lower rate of preterm birth <37 weeks compared to those who were managed expectantly, 30.9% vs 41.5%, RR 0.75, 95% CI 0.56-0.99 (414 participants).[36] The effect size supporting cerclage treatment was greater for shorter cervical lengths at the time of inclusion, birth <37 weeks for cervical length ≤5mm 48.5% vs 79.4%, RR 0.61, 95% CI 0.41-0.90, and birth <37 weeks for cervical length ≤10mm 36.7% vs 54.7%, RR 0.67, 95% CI 0.49-0.93).[36]

Rescue transvaginal cervical cerclage

A rescue cerclage, also referred to as an emergency or physically-indicated cervical cerclage is considered for wāhine/people presenting with an open cervix and exposed fetal membranes (with or without fetal membranes prolapsed beyond the cervical external os) in the second trimester. The chance of PPROM, chorioamnionitis, sepsis, miscarriage and extreme preterm birth in these pregnancies is very high and hence considered as a 'rescue' and 'emergency' scenario.

Evidence supporting rescue cervical cerclage has been obtained from observational cohort and case-control studies. A 2023 systematic review identified 96 such studies.[37] However, observational data without comparative control groups have major limitations in informing practice. Only 14 of the 96 studies included comparison groups (with expectant management without cervical cerclage), reporting on 746 pregnancies with 445 rescue cervical cerclage and 301 expectantly managed, including singletons (n=729) and twins (n=36).[37] The mean gestational age at diagnosis of an open cervix was 21.9 weeks, with a mean cervical dilatation of 3-4cm and fetal membranes prolapsed beyond the cervical external os in 98%.[37] The intraoperative PPROM rate was 6%. Pregnancy prolongation after rescue cervical cerclage was 54 and 27 days for singleton and twin pregnancies respectively, compared with only 14 and 5 days respectively, with expectant management.[37] Overall perinatal survival was higher after rescue cervical cerclage compared with expectant management, 70.9% vs 27.9%, pooled ratio 1.7, 95% CI 1.2-2.1.[37] This improved perinatal survival was greatest for twin pregnancies, 44.1% vs 2.6%, pooled ratio 16.8, 95% 2.3-120.3, although still significant in singleton pregnancies, 73.0% vs 35.5%, pooled ratio 1.6, 95% 1.2-2.1).[37] Within these studies the use perioperative antibiotics and tocolysis was high in both cervical cerclage and expectant management groups, progesterone therapy was less commonly reported.[37]

These data are helpful for counselling wāhine/people with an open cervix in the second trimester, but remain observational and have some additional limitations. Of particular note is the mean cervical dilatation 3-4cm and almost universal prolapse of fetal membranes beyond the cervical external os. Many of these studies were completed prior to the use of cervical length surveillance, and hence cervical findings were likely to have been confirmed after presentation with symptoms. In current practice, using cervical length surveillance in a specialised preterm prevention service or review at the time of the mid-trimester anatomy scan, it is likely that an open cervix may be diagnosed earlier for many (whilst asymptomatic) and hence with less cervical dilatation and membrane prolapse, potentially resulting in better outcomes than seen previously. Furthermore, factors such as gestational age at cervical change, pre-existing evidence of ascending infection and risks of birth at the limits of survival should be included in the assessment of the overall chance of success to support whānau-led decisions on care.

Transvaginal cervical cerclage technique

Two techniques were originally described for the placement of transvaginal cervical cerclage, and both have been used for history-indicated, ultrasound-indicated and rescue/emergency cervical cerclage. The original Shirodkar technique describes anterior and posterior vaginal mucosa dissection to reflect the bladder, allow the suture to be subcutaneous (buried) through the majority of the circumference of the cervix, and for the knot to be buried posteriorly.[31] The McDonald technique does not include vaginal mucosa dissection and uses a purse-string style suture with four to five bites of cervical tissue in a circumferential manner, with the knot usually tied anteriorly.[32] Neither technique should breach the cervical canal.

Most randomised trials assessing transvaginal cervical cerclage have not included data on the techniques used for placement, and several modifications to the original procedures have been reported and are used in practice, making comparisons challenging. Only one head-to-head trial, including just 68 participants, has compared techniques.[38] Hence, meta-analyses have included non-randomised studies, predominantly retrospective cohorts. These meta-analyses generally report in favour of the Shirodkar technique.[39,40] However, methodological constraints, including multiple confounding factors, limit the impact of these findings. This is highlighted by the loss of significance in relative risk reduction in preterm birth associated with use of the Shirodkar technique once sensitivity analyses remove studies with a serious risk of bias.[39]

Additional factors, including pre-existing risk status, surgeon experience and the need for regional anaesthesia for removal of a cerclage placed with dissection (due to burial of the knot), should also be considered. It is likely that the key factor for success is the placement of the cerclage as close to the level of the cervical internal os, and clinical judgement is required on how best to achieve this using a purse-string or buried style technique. Vaginal mucosa dissection to expose more of the cervical body is likely to enable higher placement, especially where the vaginal portion of cervix is less adequate, but this does not necessarily require other components of the traditional Shirodkar technique. In current practice, this type of transvaginal cervical cerclage is referred to as a high transvaginal cervical cerclage or cervical cerclage with vaginal dissection.

Two main suture materials are used for transvaginal cervical cerclage. Braided and monofilament sutures have both been identified to have benefits and risks. A retrospective cohort, supported by a prospective longitudinal vaginal microbiome and cervico-vaginal cytokine study, suggested that a monofilament suture had significant advantages over a braided suture.[41] A monofilament suture was associated with reduced preterm birth and perinatal loss, a less dysbiotic microbiome, and a

significant reduction in several pro-inflammatory cytokines.[41] However, improved clinical outcomes were not demonstrated in the large UK multicentre C-STITCH trial, including 2049 wāhine/people receiving a history-indicated or ultrasound-indicated transvaginal cervical cerclage and randomised to monofilament or braided suture.[42] Miscarriage, stillbirth or neonatal death in the first week of life occurred in 80/1003 (8.0%) in the monofilament suture group and 75/993 (7.6%) in the braided suture group (adjusted RR 1.05, 95% CI 0.79-1.40).[42] Of note, maternal sepsis and chorioamnionitis were less common with monofilament compared with braided suture, 3.9% versus 6.8%, adjusted RR 0.58, 95% CI 0.40-0.82 and 2.7% versus 6.0%, adjusted RR 0.45, 95% CI 0.29-0.71, respectively.[42] Rates of reported cerclage removal complications were high in both groups, but more common with a monofilament suture, 56.5% versus 42.2%, adjusted RR 1.25, 95% CI 1.15-1.36).[42]

Transabdominal cervical cerclage (TACC)

TACC involves placement of a cervical cerclage (one or two sutures) via the abdominal route using laparotomy or laparoscopy. It allows higher placement of the cerclage directly at the level of the cervical internal os. Due to its more invasive and resource-intense nature (for placement and birth), it is reserved for the wāhine/people considered to be at the highest risk for spontaneous preterm birth. This is generally considered to be those who have had an unsuccessful history- or ultrasound-indicated cerclage, or those with such extensive cervical surgery that there is minimal cervical tissue remaining, making placement of transvaginal cervical cerclage more challenging.

Multiple observational studies have identified major improvements in perinatal survival and preterm birth associated with TACC.[43] These findings have been confirmed in the only randomised trial including TACC. The Multicentre Abdominal vs Vaginal Randomised Intervention of Cerclage (MAVRIC) trial compared TACC with 'low' transvaginal cerclage (without dissection) and 'high' transvaginal cerclage (with dissection).[44] Wāhine/people with a previous unsuccessful (defined as birth <28 weeks) transvaginal history- or ultrasound-indicated cervical cerclage were included.[44] TACC was placed preconception or <14 weeks, and vaginal cervical cerclage was placed <16 weeks. Of the 111 wāhine/people who were included and conceived during the study period, 39 had TACC, 39 had high vaginal cerclage, and 33 had low vaginal cerclage.[44] Those with TACC had lower rates of birth <32 weeks compared to those with a low transvaginal cerclage (8% versus 38%, RR 0.23, 95% CI 0.07-0.76, NNT 3.9) as well as fewer perinatal losses (3% versus 21%, RR 0.12, 95% CI 0.016-0.93, NNT 5.3).[44] There were no differences in the rates of birth <32 weeks for high and low transvaginal cervical cerclage. The conclusions reported were that TACC should be the treatment of choice for wāhine/people with an unsuccessful transvaginal cervical cerclage, with numbers needed to treat that are sufficiently low to justify the abdominal surgery and caesarean birth that is required in this select group.

Within the MAVRIC trial and historically, TACC have generally been placed by laparotomy and may be placed preconception (interval) or early in pregnancy. TACC placement by laparoscopic methods is increasingly reported, although predominantly as an interval procedure. There are no direct comparisons of the two approaches to TACC. Meta-analysis suggests similar perinatal survival rates (overall 91.2%) and gestation at birth (36.6 weeks) for each.[43] The laparoscopic approach is likely to be associated with significantly less blood loss and a shorter hospital stay, but a longer operation duration than TACC placed by laparotomy.[43]

Reinforcing/second transvaginal cervical cerclage

Cervical cerclage is successful for the majority. However, ongoing review of wāhine/people after a history- or ultrasound-indicated cerclage may reveal signs of 'failure'. This may be considered as a

shortening cervix (≤25mm) or, more concerningly, when there is prolapse of the fetal membranes through the cervical cerclage, which may be evident via ultrasound assessment or seen on speculum examination. The efficacy of a second or 'reinforcing' transvaginal cerclage when there is suspected 'failure' of the primary cerclage is unclear with two systematic reviews demonstrating conflicting results, one suggesting improved pregnancy outcomes with a reinforcing cerclage,[45] and the other suggesting harm (reduced pregnancy latency and increased preterm birth).[46] All included studies were observational only, and high heterogeneity across studies makes interpretation difficult. Where fetal membranes have prolapsed through a cervical cerclage, risks should be considered to be at least as high as when the cervix is open and when rescue cerclage is being contemplated.

Progestogen therapy

Progesterone is a 'pro-pregnancy' hormone that has an important role in maintaining uterine quiescence through pregnancy. It counteracts the inflammatory cascade that leads to labour by reducing the production of stimulatory prostaglandins and inhibiting the expression of contraction-associated protein genes within the myometrium.[47,48] Although maternal serum progesterone levels do not change significantly in the weeks preceding labour, there is evidence that the onset of labour (both at term and preterm) is associated with a functional withdrawal of progesterone activity in the uterus.[47]

The potential therapeutic role of progesterone for the prevention of preterm birth has been extensively studied over many years. Two main types of progestogens have been considered, 17α-hydroxyprogesterone (17α-OHP) and natural micronised progesterone. Like cervical cerclage, progesterone use may be history-indicated and based on pre-existing risk factors for spontaneous preterm birth, or ultrasound-indicated, based on a short cervix (with or without pre-existing risk factors).

17α-hydroxyprogesterone

17α-OHP is a semi-synthetic steroid hormone with a different, but related, chemical structure to progesterone. It acts as a progesterone receptor agonist. It is given as a weekly intramuscular injection of hydroxyprogesterone caproate. Based on the findings of a single randomised trial published in 2003, and FDA accelerated approval, its use across the USA was rapidly implemented.[48] In that single placebo-controlled trial, including 463 wāhine/people with a prior spontaneous preterm birth, weekly use of 17α-OHP from 16 to 36 weeks was effective in reducing birth <37 weeks (36.3% vs 54.9%, RR 0.66, 95% CI 0.54-0.81).[49] However, subsequent trials, including the FDA-requested confirmatory trial (PROLONG), have failed to replicate these findings of benefit.[50] 17α-OHP injections are no longer approved for the prevention of recurrent preterm birth in the USA, and use has significantly declined. 17α-OHP is not available in Aotearoa.

Natural micronised progesterone

Natural micronised progesterone is the most commonly studied and used progestogen for the prevention of preterm birth. It may be administered as a vaginal gel or suppository, or by oral capsules.

There are a large number of studies exploring the potential of natural progesterone for the prevention of preterm birth, including by several routes of administration, as well as a variety of doses, timing and duration of treatment. The Evaluating Progestogen for Prevention of Preterm Birth

International Collaborative (EPPPIC) study is an individual participant data (IPD) meta-analysis incorporating data from 31 of 47 identified randomised trials and 11 644 wāhine/people and their 16 185 pēpi.[16] It provides the highest quality evidence available to inform practice. The EPPPIC study includes 14 placebo-controlled trials of vaginal progesterone and two placebo-controlled trials of oral progesterone (with 183 participants only).[16] None of the trials assessed progesterone therapy via the rectal route.

Vaginal progesterone

For the vaginal progesterone trials included in the EPPPIC study, singleton and twin pregnancies are included. Of the singleton pregnancies (3816 participants), 69% had a prior history of preterm birth and information on cervical length was known for two-thirds of participants (cervix ≤25mm in 27%). Of the twin pregnancies (2068 participants), only 3% had a prior history of preterm birth and information on cervical length was known for 60% participants (cervix ≤25mm in 3.5%).[16] Based on variations in each of the trials' eligibility criteria, wāhine/people without a previous preterm birth mostly had a short cervix (ultrasound-indicated use), and those with a previous preterm birth mostly did not have a short cervix (history-indicated use) at trial entry. To limit the impact of this confounding, cervical length and preterm birth covariates were jointly analysed and supplementary two-stage analyses of subpopulations were categorised by previous preterm birth status and cervical length, using ≤25 mm to define a short cervix.[16]

Overall, the use of vaginal progesterone in singleton pregnancies reduced the chance of birth <34 weeks (RR 0.78, 95% CI 0.68-0.90) and had a consistent but non-significant effect for birth <28 and <37 weeks.[16] Vaginal progesterone was associated with significant improvements in some pēpi outcomes including the chance of birthweight <2500 g (RR 0.82, 95% CI 0.74-0.91), birthweight <1500 g (RR 0.70, 95% CI 0.49-0.99), neonatal intensive care unit admission (RR 0.78, 95% CI 0.68-0.90), respiratory distress syndrome (RR 0.73, 95% CI 0.58-0.93) and the need for respiratory support (RR 0.77, 95% CI 0.61-0.99).[16] When including only those participants with cervical length recorded, the relative treatment effect did not appear to vary between those with a short cervix (≤25mm) and those with a normal cervical length (>25mm). [16] However, in subgroup analyses including those with a normal cervical length only (and hence likely to be considered history-indicated use), any reduction in birth <34 weeks was non-significant, even for those with a prior history of preterm birth (RR 0.91, 95% CI 0.69-1.20).[16]

Vaginal progesterone treatment in twin pregnancies had no effect on the chance of birth <34 weeks (RR 1.01, 95% CI 0.84-1.20), or <28 and <37 weeks, or on any pēpi outcomes.[16] However, for the vast majority of included twin pregnancies, there was no history of a prior preterm birth, and cervical length was either unknown or normal (>25mm), only 72 wāhine/people had a short cervix.[16] An alternative systematic review using trial-level meta-analysis enabled the inclusion of more studies/participants with a twin pregnancy and short cervix (six trials and 303 participants).[51] In this analysis, vaginal progesterone treatment was associated with a reduction in preterm birth (<33 weeks RR 0.69, 95% CI 0.51-0.93),[51] suggesting that with better identification of those with additional risk factors for spontaneous preterm birth, progesterone treatment may still be beneficial in twin pregnancies.

Of particular relevance is that most of the trials evaluating vaginal progesterone in singleton and twin pregnancies included in EPPPIC did not include wāhine/people with a very short cervix (<10mm),[16] when non-randomised treatment including cervical cerclage was likely to be preferentially offered. Hence, EPPPIC results are generalisable to populations with a cervical length ≥10mm. The role of vaginal progesterone as a treatment for a short (but not very short) cervix, is further supported by

an earlier study including individual participant data from five trials.[52] In this study, vaginal progesterone had no effect for wāhine/people with a cervical length <10mm (birth <33 weeks RR 0.83, 95% CI 0.49-1.41) but an almost halving of risk when the cervix was 10-20mm (birth <33 weeks RR 0.52, 95% CI 0.35-0.76).[52]

The EPPPIC study did not demonstrate any evidence of difference in effect by vaginal progesterone preparation or dose.[16] In Aotearoa, Utrogestan capsules are the only form of micronised progesterone available. Across all trials assessing vaginal progesterone therapy, micronised capsules were used at daily doses of 100mg[53] or 200mg.[54] Gestational age at commencing treatment varied by trial, ranging from 18 to 24 weeks and continuing to 34-37 weeks.[54] It is recommended as a night-time dose to allow passive absorption whilst supine.

Cerclage and/or vaginal progesterone

Direct comparisons of cervical cerclage with vaginal progesterone for the prevention of preterm birth based on pre-existing obstetric and/or gynaecological history, and/or ultrasound evidence of a short cervix are very limited.[55] Indirect comparisons cannot fully account for differences in pre-existing risk status, but suggest that there are no differences in rates of preterm birth or adverse outcomes for pēpi when comparing cervical cerclage and vaginal progesterone. Meta-analysis of five trials comparing vaginal progesterone to placebo (265 wāhine/people) and five trials comparing cerclage to no cerclage (504 wāhine/people) showed that each treatment reduced preterm birth and improved some measures of pēpi wellbeing including a composite perinatal morbidity and mortality outcome.[56] When indirectly compared with each other, there was no difference in effect on birth <35 weeks (RR 0.97, 95% CI 0.66-1.44), perinatal mortality (RR 0.97, 95% CI 0.35-2.69) or in all other assessed gestational age at birth thresholds and neonatal outcomes.[56] A similar lack of difference was noted, including only those wāhine/people with cervical length ≤15mm, however, the number of participants included in the assessment and thresholds for inclusions in studies varied by type of intervention.[56]

Evidence to inform practice on the use of vaginal progesterone in addition to cervical cerclage is limited to non-randomised studies and predominantly from observational cohorts. For example, in the UK multicentre C-STITCH trial comparing monofilament or braided suture,[42] data were collected on the concomitant use of progesterone. Secondary analysis demonstrated that approximately half of all participants also received progesterone treatment, and this was associated with a lower incidence of the trial primary outcome (miscarriage and perinatal mortality), 49/832 (5.9%) vs 91/1103 (8.3%), adjusted risk ratio 0.70, 95% CI 0.50-0.99.[57] This analysis adjusted for indication for cerclage, obstetric history, surgical technique, and maternal age but was unable to fully account for progesterone prescription, which is likely to have been at each clinician's discretion and hence will include several confounding factors.[57]

Cervical pessary

Cervical pessaries, often referred to as Arabin pessaries, were originally developed for the management of vaginal wall prolapse in pregnancy, but were subsequently adopted for use for the prevention of spontaneous preterm birth. They have been in use for almost as long as cervical cerclage, but with significantly less evidence available to inform clinical practice. A cervical pessary is a silicone ring with an inner diameter that fits around the cervix and an outer diameter that fits against the pelvic floor. It can be placed within an outpatient care setting. It is intended to tilt the cervix back towards the posterior fornix and alter the utero-cervical angle. It is suggested that this

results in redistribution of weight to the vaginal floor, retro-symphyseal structures and Pouch of Douglas, whilst retaining the cervical mucous plug and stopping pēpi head descending onto the cervical internal os.

Despite demonstration of effectiveness in altering the utero-cervical angle,[58] cervical pessary use in singleton pregnancies with a short cervix is not associated with any improvement in pregnancy outcomes.[59] In over 900 wāhine/people with a singleton pregnancy and a cervical length ≤25mm at 20^{+0} to 24^{+6} weeks randomised to receive cervical pessary or no pessary use, birth <34 weeks occurred for 55/460 (12.0%) using a pessary and 50/464 (10.8%) without pessary use OR 1.12, 95% CI 0.75–1.69.[59] There was also no difference in perinatal outcomes including adverse neonatal events, 30/450 (6.7%) and 26/456 (5.7%), OR 1.18, 95% CI 0.69- 2.13).[59] Cervical pessary use in twin pregnancies similarly does not reduce the chance of preterm birth.[60] However, when focused only on those with a short cervix ≤25mm in a trial of 137 pregnancies, cervical pessary was associated with a reduction in birth <34 weeks, 11/68 (16.2%) vs 26/66 (39.4%), RR 0.41 95% CI 0.22-0.76, but no improvement in adverse perinatal outcome 8/68 (5.9%) vs 12/66 9.1%, RR 0.64 95% CI 0.27 – 1.50.[61]

Cervical pessaries are not currently commercially available in Aotearoa.

References

References are included with those used in the Recommendations and About sections of 'Prediction and prevention of spontaneous preterm birth in specialised preterm prevention care'. These are listed under the About section.