Prediction and prevention of spontaneous preterm birth - understanding the risk factors and adjunct tests

Background Information

Introduction

Spontaneous preterm birth may occur following the spontaneous onset of labour and/or PPROM <37^{+0} weeks gestation. The lower limit of preterm birth may be considered as birth from 20^{+0} weeks (as the timepoint requiring birth registration in Aotearoa New Zealand), although pēpi survival is only possible from 22-23 weeks. The mechanisms leading to spontaneous second-trimester miscarriage (considered from 14^{+0} weeks of gestation)[1] are similar to those causing spontaneous preterm birth. Therefore these two conditions (preterm birth and second trimester miscarriage) should be considered as the same pathophysiological entity with similar risk factors, risk modification, prediction and prevention. Due to the shared pathophysiological mechanisms and similar approaches to care, reference to spontaneous preterm birth in this section of Taonga Tuku Iho includes all births from 14^{+0} to 36^{+6} weeks.

Despite significant research efforts, there are no proven therapies to stop labour once it has established.[1] Prevention of spontaneous preterm birth, therefore, relies on the early prediction of those with a higher chance of preterm labour and/or PPROM. Identification of risk factors for spontaneous preterm birth allows for modification of risk where possible, and the use of additional evidence-based prediction measures and treatments prior to the onset of labour and/or PPROM, where they may effectively prevent preterm birth.

This document provides background information on the risk factors for spontaneous preterm birth and the adjunct tests that support improved prediction of risk.

Risk factors for spontaneous preterm birth

There are numerous established risk factors for spontaneous preterm birth, and many of these risk factors can be identified prior to, or in early pregnancy. However, additional risk factors may also develop during pregnancy. Identification of risk factors and their appropriate management relies on early engagement of wāhine/people in pregnancy care, usually with their Lead Maternity Carer (LMC) or primary care provider, along with clear pathways for obstetric referral where indicated.

Risk factors for spontaneous preterm birth may be considered to be:

- **Directly modifiable** – the risk factor can be removed or altered
- **Indirectly modifiable** – the risk factor cannot be taken away, but interventions are available to reduce risk
- **Non-modifiable** - the risk factor cannot be taken away or changed, but awareness may still be beneficial.

Directly modifiable risk factors for spontaneous preterm birth

Urinary/renal tract infection and asymptomatic bacteriuria

Physiological changes in pregnancy may predispose wāhine/people to colonisation of the urinary tract and asymptomatic bacteriuria is common, affecting 2-15% of all pregnancies.[8] Asymptomatic bacteriuria (often defined as $>10^5$ colony-forming units per ml) is associated with preterm birth, and when left untreated, acute pyelonephritis may occur in up to 30% of wāhine/people.[9] A 2019 Cochrane review including 15 studies and >2000 wāhine/people, comparing screening and antibiotic treatment for asymptomatic bacteriuria in pregnancy to no treatment or placebo, demonstrated the elevated chance of preterm birth (17.4%) and the impact of timely treatment.[10] Antibiotic treatment was associated with a major reduction in pyelonephritis (RR 0.24, 95% CI 0.13-0.41).[9] A similar effect size was observed in the rate of birth at $<37^{+0}$ weeks: 17.4% for wāhine/people with untreated asymptomatic bacteriuria, compared to only 5.9% after treatment with antibiotics (RR 0.34, 95% CI 0.13-0.88).[9] However, only three studies with 327 participants contributed evidence on preterm birth (low-certainty evidence).[9]

Sexually transmitted infections (chlamydia, trichomonas, gonorrhoea, syphilis, HIV)

All sexually transmitted infections increase the risk of spontaneous preterm birth (Table 1). Chlamydia is the most prevalent sexually transmitted infection in Aotearoa,[11] although rates of syphilis and gonorrhoea are rising.[12,13]

Treatment of chlamydia, gonorrhoea and syphilis in pregnancy is associated with a reduction in preterm birth (Table 1). The timing and gestation of treatment are likely to have a significant impact on the chance of preterm birth. For example, in a systematic review and meta-analysis assessing the impact of treatment for syphilis, the overall chance of preterm birth for wāhine/people with infection was 14.1% (compared to 7.2% for those without syphilis), for those untreated, or treated in the third trimester, rates of preterm birth were 23.2% and 17.6% respectively.[14] Wahine/people with HIV infection may have a spontaneous preterm birth risk 3-4 fold higher than those without HIV infection, although evidence is limited and conflicting.[15]

Table 1: Risk of preterm birth with sexually transmitted infections

Infection in pregnancy	**Odds ratio (95% CI) for preterm birth $<37^{+0}$ weeks**	**Preterm birth risk reduction by treatment in pregnancy**
Chlamydia	2.28 (1.64-3.16)[16]	42%[17]
Trichomonas	1.27 (1.08-1.50)[18]*	†
Gonorrhoea	1.90 (1.14-3.19)[19]	53%[20]
Syphilis	1.91 (1.35-2.69)[21]	52%[17]

** PPROM OR 1.87 (95% CI 1.53-2.29) [18] for trichomonas.*

† Studies assessing the impact of treatment of trichomonas in pregnancy have inconsistent results, including a potential increase in preterm birth when treated with metronidazole. [22] However, due to the potential for other harmful effects of infection, treatment is recommended.

Systemic and other infections

Systemic infection and the subsequent proinflammatory state are contributors to preterm labour and PPROM. Beyond urinary and renal tract infection, pneumonia and periodontal disease are commonly implicated in preterm birth.[23,24]

The influenza and COVID-19 vaccines are safe and recommended for use in pregnancy, and funded by Te Whatu Ora.[25] The quadrivalent influenza vaccine reduces the chance of wahine/person having influenza viral infection in pregnancy, and hence removes an additional risk for preterm birth. Use of the COVID-19 vaccine in pregnancy is also safe and associated, not only with less COVID-19 infection, but also with a significantly lower chance of preterm birth (recently demonstrated in a review where three out of four studies, showed significant reductions with adjusted hazard and odds ratios ranging from 0.72 to 0.93).[26]

Conversely, despite periodontal disease being associated with preterm birth, treatment in pregnancy is not associated with a reduction in risk. In a 2017 Cochrane review, including 11 randomised trials of periodontal treatment compared with no treatment, the rate of birth <37^{+0} weeks was 11.4% vs 13.1%, RR 0.87, 95% CI 0.70-1.10.[27]

Cigarette smoking

Cigarette smoking is associated with an approximately three-fold increase in the chance of spontaneous preterm birth, including adjustment for confounding factors.[7,28] Rates of cigarette smoking have decreased in recent years in Aotearoa. Te Whatu Ora Maternity Clinical Indicators show 7.3% wāhine/people smoked throughout pregnancy (defined as maternal tobacco use at two weeks post birth) in 2021, reduced from 12.0% in 2015.[29] Despite this overall reduction, there remains ongoing wide variation in rates of smoking in pregnancy by area of residence e.g. 13.6% in Northland, 6.4% in Canterbury and 2.1% in Auckland, and by ethnicity e.g. 19.5% for wāhine Māori, 5.4% for Pacific People and 3.9% for European (2021 data).[29]

Becoming smoke-free in early pregnancy is associated with significant benefit in reducing the chance of spontaneous preterm birth. In the Aotearoa-led SCOPE (Screening for Pregnancy Endpoints) Study, wāhine/people who continued to smoke in pregnancy had higher rates of spontaneous preterm birth than non-smokers with adjustment for demographic factors, alcohol use and early pregnancy bleeding (adjusted OR 3.21, 95% CI 1.42-7.23).[7] Those who became smoke-free by 15 weeks had similar rates of spontaneous preterm birth compared with non-smokers (adjusted OR 1.03, 95% CI 0.49-2.18).[7]

The association between smoking and spontaneous preterm birth is likely related to placental factors. Cigarette smoking is known to cause placental vasoconstriction, leading to placental damage and an increased systemic inflammatory response.[28]

Use of vaping (also known as electronic cigarettes) is increasingly common. There is currently limited evidence on the effects of vaping in pregnancy, including the impact on preterm birth.[30]

Recreational drug and alcohol use

The use of recreational drugs in pregnancy is associated with an increased chance of spontaneous preterm birth, independent of cigarette smoking and socio-economic status.[31,32] Marijuana use is increasing worldwide, and changes in legalisation have resulted in increased access and acceptability of its use in many countries.[33-35] In the SCOPE Study, 4.5% of wāhine/people in Aotearoa and 5.6% of the overall cohort reported use of marijuana prior to or during pregnancy.[31] Those who reported continued marijuana use at 20 weeks (1.0% of the study population) had a higher chance of spontaneous preterm birth, independent of cigarette smoking (adjusted OR 2.28, 95% CI 1.45-3.59) and socioeconomic index (adjusted OR 2.17, 95% CI 1.41-3.34).[31]

Methamphetamine is the second most commonly used recreational drug in Aotearoa.[36] Whilst accurate estimates for its use in pregnancy in Aotearoa are not available, other local methamphetamine statistics parallel worldwide trends.[37] In a large American study, 5.2% of

wāhine/people reported methamphetamine use at some point during their pregnancy,[38] and users are more likely (adjusted OR 2.9, 95% CI 2.7-3.1) to have a spontaneous preterm birth compared to non-users, including after adjustment for multiple confounding factors.[39]

The mechanism behind the association between recreational drug use and spontaneous preterm birth is unclear. Potential theories include placental vasoconstriction, like that seen with cigarette smoking. However, unaccounted for confounding factors may also have a role.[39,40]

Wāhine/people who continue to use alcohol in pregnancy may have other confounding factors that contribute to their chance of preterm birth e.g. cigarette smoking, recreational drug use and mental health disorders. However, when analyses adjust for these confounders, the impact of heavy alcohol-exposure persists, (adjusted OR 1.32, 95% CI 1.19-1.46) for preterm birth in comparison to no-heavy prenatal alcohol-exposure.[41] Heavy-alcohol exposure in this study was determined via a hospital attendance for a fully alcohol-attributable diagnosis or use of prescription drugs to treat alcohol dependence one year before or during pregnancy, or a prenatal alcohol-related diagnosis given to the child after their birth.[41] Less is known about the impact of lower levels of alcohol exposure in pregnancy on preterm birth.

Low body mass index (BMI)

The relationship between pre-pregnancy BMI and the chance of spontaneous preterm birth is complex.[42] Wāhine/people who are underweight (BMI <18.5 kg/m^2) have higher rates of spontaneous preterm birth than wāhine/people with a normal BMI (18.5 – 24.9 kg/m^2) following adjustment for age, education, ethnicity, cigarette smoking and antenatal care (adjusted OR 1.41, 95% CI 1.37-1.45).[43] However, the association between higher BMI (BMI ≥30 kg/m^2) and spontaneous preterm birth is less clear, with conflicting findings in both individual studies and by systematic review.[42,44-46]

Proposed mechanisms for the association between low BMI and spontaneous preterm birth include the effects of māmā/person malnutrition on *in utero* pēpi growth and development, increased production of stress hormones, and an increased susceptibility to infection.[43]

Stress and mental health conditions

Stress, anxiety and depression in pregnancy are each associated with an increased chance of spontaneous preterm birth.[28,47] Whilst confounding factors are likely to have a significant role, they are unlikely to completely explain this association.[48] A 2015 systematic review of 39 studies considering the effects of depression, anxiety, and perceived stress in pregnancy on preterm birth, included 134,488 pregnant wāhine/people.[47] Depression was associated with an increased chance of preterm birth (estimate of effect ranged from OR 1.13 to 3.93) in all but one of 14 studies.[47] Anxiety was reviewed in four studies, and three demonstrated a significant association (estimate of effect ranged from OR 1.48 to 2.73).[47] Perceived stress was examined in five studies, consistently demonstrating a statistically significant relationship (estimate of effect ranged from OR 1.14 to RR 1.75).[47] The elevated chance of preterm birth was reported to be associated with spontaneous, rather than provider-initiated, preterm birth.[47]

Interventions aimed at reducing stress in pregnancy have been associated with a reduction in preterm birth. Ten studies including 4,816 wāhine/people undertaking stress-reducing activities (pilates, yoga, multidisciplinary stress reduction program, hypnosis and combination therapy of mindfulness, yoga, music, baby bonding and education).[49] The incidence of preterm birth was significantly lower in the intervention groups, 6.3% compared with 12.7% the control groups (RR 0.50, 95% CI 0.35-0.71).[49] However, this meta-analysis was unable to differentiate spontaneous and

provider-initiated preterm birth, and the overall quality of included studies was low, with a high risk of bias.[49]

The exact causative mechanisms by which stress and mental health conditions contribute to spontaneous preterm birth are unclear. Increased levels of stress hormones such as cortisol and catecholamines are likely to play a role, contributing to placental hypoperfusion and inflammation.[48]

Low socioeconomic status

Preterm birth is associated with a lack of socioeconomic advantage. There are multiple determinants of socioeconomic status including education, marital status, occupation, income, and area of residence, as well as contributing behavioural and psychosocial factors such as stress, housing conditions, smoking, and discrimination. They all have the potential to impact on the chance of preterm birth. The effect of each of these variables on the chance of spontaneous preterm birth is difficult to quantify due to the complexities of these factors.[50] Although support can be provided to improve socioeconomic status during pregnancy, these broader determinants of health cannot be easily overcome over the course of a pregnancy.

Poor access to medical and pregnancy care

There is significant variation in access to medical and pregnancy care across Aotearoa, including by place of residence and ethnic group. Despite this, there are limited data on how inequity in access to care may impact on preterm birth, and specifically on spontaneous preterm birth. Multiple studies internationally demonstrate that being 'unbooked', with no or minimal pregnancy care, is associated with preterm birth. Using a city-based (London) cohort as an example, unbooked wāhine/people were more than six times more likely to have a preterm birth than those booked for pregnancy care (OR 6.44, 95% CI 2.24-18.50).[51] Factors contributing to unbooked pregnancy status included young age, unemployment, being single/unmarried, and being non-English speaking.[51] Although unreported in this study, the impact is likely to be on both spontaneous and provider-initiated preterm birth.

Providing equitable access to high-quality antenatal care that meets the wider cultural and social, as well as medical needs of whānau is likely to positively impact preterm birth. The Australian 'Birthing in our Community' programme provides an excellent example of how co-design of a service, including continuity of midwifery care alongside an increased indigenous workforce, focused on strengths-based family wellbeing and culturally-responsive care, may reduce preterm birth.[52] In this cohort study, the rate of preterm birth was 6.9% for those receiving care via the new service compared with 11.6% for those receiving standard care, matched adjusted OR 0.50, 95% CI 0.31-0.83.[52] A number of Māori-led initiatives are now established across Aotearoa, providing continuity of care through a Te Ao Māori lens, supported by, and integrated into the wider health system. The impact on preterm birth is still to be determined.

Continuity of care may improve access to medical and pregnancy care and hence influence preterm birth. Midwife-led continuity of care has been associated with improvements in rates of preterm birth in the general population.[53,54] Community-based midwife continuity of care has also been associated with reduced rates of preterm birth and specifically improved outcomes amongst ethnic minority wāhine/people and those living in deprived areas.[55]

Family and intimate partner violence

Family and intimate partner violence (physical, emotional and sexual) often increases in pregnancy and is associated with multiple adverse pregnancy outcomes, including preterm birth (adjusted OR 1.89, 95% CI 1.43-2.48).[56] Both international and Aotearoa-specific data show that Indigenous and non-Indigenous wāhine/people experience violence in pregnancy differently.[57,58] Within an Aotearoa

study including 54,980 younger wāhine/people (<25 years of age), 0.4% of the population experienced assault during pregnancy, and it was more common for wāhine Māori (0.7%) than for non-Māori (0.2%), p<0.001. Wāhine Māori also experienced more severe physical violence but lower rates of hospitalisation for injury.[58] The overall rate of preterm birth in this population was 8.5%. After an assault in pregnancy, preterm birth was significantly higher; or non-Māori 25.3% (adjusted RR 2.6, 95% CI 2.0-3.4) and for Māori 33.8% (RR 2.5, 95% CI 2.1-3.0).[58]

Multiple factors, including racism, discrimination, drug and alcohol use and socioeconomic status, are likely to contribute to the differences in preterm birth rates seen following violence in pregnancy, and additional differences by Indigeneity. The mechanisms by which violence may lead to preterm birth are also likely to be multifactorial, including antepartum haemorrhage and rupture of membranes after direct assault, genitourinary infection and emotional stress, and impacts on behaviour such as withdrawal from pregnancy care or increased drug and alcohol use.

Indirectly modifiable risk factors for spontaneous preterm birth

Previous spontaneous preterm birth and second trimester miscarriage and/or PPROM
Previous spontaneous preterm birth is one of the most significant risk factors for subsequent preterm birth, with a highly variable recurrence risk of 15-85%, depending on the number of prior preterm births and the gestation at which these occurred.[2,28,59,60] A 2017 systematic review and meta-analysis included those with at least one spontaneous preterm live birth <37 weeks, and at least one subsequent singleton pregnancy resulting in a live birth (including 32 studies and 55,197 wāhine/people). The absolute risk of recurrence for spontaneous preterm birth was 30% (95% CI 27%-34%).[2]

A large population-based cohort study from the United States assessed 19,025 wāhine/people with three consecutive singleton pregnancies; the chance of recurrence of preterm birth was highest in those with two prior preterm births, at 42%.[60] The chance of recurrence was inversely related to the gestational age at each prior preterm birth, ranging from 38% in wāhine/people with two previous moderate preterm births (32 to 36 weeks) and up to 57% if they had two previous very preterm births (21 to 31 weeks).[60] Wāhine/people with a previous preterm birth followed by a term birth had a lower risk of recurrent preterm birth of 12-15% in their third pregnancy.[60]

Congenital uterine and/or cervical anomaly
Congenital uterine and/or cervical anomalies are relatively common, affecting up to 5.5% in an unselected population.[61] The most common uterine anomalies are canalisation differences (i.e. septate anomalies), followed by unification differences (i.e. bicornuate and unicornuate anomalies).[61] Congenital uterine anomalies have been associated with an up to seven-fold increase in the chance of spontaneous preterm birth.[3] A United Kingdom 2019 study assessed the risk of spontaneous preterm birth. This study included 319 wāhine/people with a prepregnancy diagnosis of a congenital uterine anomaly.[62] Rates of spontaneous preterm birth were 26% (7/27) for unicornuate uterus, 21% (7/34) for uterine didelphys, 16% (31/189) for bicornuate uterus, 13% (7/56) for septate uterus, and 31% (4/13) for arcuate uterus.[62] The numbers within this study are relatively small, limiting the exact quantification of elevated risk.

The mechanisms for an increased chance of spontaneous preterm birth are likely to vary according to the type of anomaly, with theories including reduced uterine capacity, differences in vascularity and connective tissue leading to increased myometrial contractility, and the presence of coinciding cervical anomalies and consequent cervical insufficiency.[63] Wāhine/people who have had surgery for uterine anomalies such as septum resection may have a persisting increased chance of spontaneous preterm birth.

Previous cervical surgery

Wāhine/people who have had a large loop excision of the transformation zone (LLETZ) or knife cone biopsy have an increased chance of spontaneous preterm birth compared to those without cervical surgery. In a 2016 systematic review and meta-analysis (71 included studies, >6.3 million participants and 65,082 with cervical surgery), local cervical treatment for preinvasive and early invasive disease significantly increased the chance of preterm birth at all gestational age groups, including for extreme preterm birth. (Table 2).[64]

Table 2: Chance of preterm birth by gestational age at birth after treatment for cervical preinvasive and early invasive disease.[64]

	Relative risk (RR) by treatment type (95% CI)*		
Preterm birth gestation	LLETZ	Knife cone biopsy	Any treatment
Preterm birth <37 weeks	1.56 (1.36-1.79)	2.70 (2.14-3.40)	1.78 (1.60-1.98)
Preterm birth <32-34 weeks	2.13 (1.66-2.75)	3.07 (1.72-5.49)	2.40 (1.92-2.99)
Preterm birth <28-30 weeks	2.57 (1.97-3.35)	4.52 0.83-24.54)	2.54 (1.77-3.63)

**No cervical treatment used as the comparator.*
LLETZ - large loop excision of the transformation zone.

The chance of preterm birth is also increased for wāhine/people who have had more than one treatment compared to no treatment (13.2% vs 4.1%, RR 3.78, 95% CI 2.65-5.39) and with increasing depth of excision (table 3).[64]

Table 3: Rates and chance of preterm birth by depth of excision of treatment for cervical preinvasive and early invasive disease.[64]

Depth of excision	Preterm birth <37 weeks	Relative risk (95% CI)*
≤10-12 mm	7.1%	1.54 (1.09-2.18)
≥10-12 mm	9.8%	1.93 (1.62-2.31)
≥15-17 mm	10.1%	2.77 (1.95-3.93)
≥20 mm	10.2%	4.91 (2.06-11.68)

**No cervical treatment as comparator (rate of preterm birth <37 weeks 3.4%).*

The likely mechanisms accounting for the increased chance of spontaneous preterm birth following excisional cervical surgery include a change in the mechanical function of the cervix and shortened cervical length, both of which may contribute to an increased risk of ascending infection.[65]

Previous caesarean section at advanced cervical dilatation and/or with a uterine incision extension through cervix +/- vagina

The impact of prior caesarean section in labour is increasingly recognised as a risk factor for subsequent spontaneous preterm birth.[6,66,67] The first published cohort included 189,021 paired first and second births in a Canadian population.[67] Caesarean section at full cervical dilatation, when compared to previous spontaneous vaginal birth, was associated with increased subsequent spontaneous preterm birth (5.3% vs 3.4%, RR 1.57, 95% CI 1.43-1.73 for birth <37 weeks and 0.9% vs 0.4%, RR 2.12, 95% CI 1.67-2.68 for birth <32 weeks).[67] Several further studies have explored additional factors relating to caesarean section birth that may contribute to the chance of preterm labour and PPROM, including stage of labour, cervical dilatation, duration of second stage of labour, fetal station, use of an instrument to deliver the fetal head, uterine incision type, fetal disimpaction, caesarean section method, uterine wall thickness, method of uterine closure and unintended uterine incision extension.[68]

Aotearoa-specific data includes 20,031 pairs of consecutive live births at Te Toka Tumai, Auckland City Hospital.[68] Caesarean section in labour with cervical dilatation from ≥5cm up to full cervical dilatation was associated with an increasingly higher chance of subsequent spontaneous preterm birth. However, like other studies, the absolute chance of subsequent spontaneous preterm birth was not high e.g. spontaneous preterm birth <37^{+0} weeks after caesarean section at full cervical dilatation was 4.8%, compared with 3.0% after a vaginal birth (adjusted RR 2.8, 95% CI 1.8-4.2).[68] But importantly, prior caesarean section was more significantly associated with extreme preterm birth. For example, rate of birth <28^{+0} weeks was 1.3% after caesarean section at full cervical dilatation compared to 0.2% after vaginal birth (adjusted RR 7.7, 95% CI 3.9-15.3). Major uterine incision extensions significantly increased risk (8.8% for spontaneous preterm birth) and this was as high as 29% if the tear extended through the cervix into the vagina.[68]

Although not fully elucidated, it is likely that the pathophysiological pathway to subsequent preterm birth after caesarean section includes cervical injury via an inadvertently low incision (more common at advanced cervical dilatation) or a tear into the cervicoisthmic tissue, leading to cervical insufficiency.[66,68]

Previous uterine instrumentation

Cervical dilatation and curettage and evacuation of retained products of conception are associated with an increased chance of spontaneous preterm birth, and the chance increases with the number of instrumentations.[5] In the SCOPE Study, including participants from Aotearoa, wāhine/people with a single dilatation and curettage for the management of miscarriage or termination of pregnancy had an increased chance of spontaneous preterm birth in a future pregnancy compared to those with no previous pregnancy loss or termination (adjusted OR 1.66, 95% CI 1.14-2.42).[5] This is likely due to the uterine instrumentation itself, as wāhine/people whose pregnancy losses were managed medically had no increased risk of preterm birth, and the chance was further elevated by an increasing number of procedures (adjusted OR 2.33, 95% CI 1.88-2.88 after two or three dilatation and curettage).[5]

Although the exact mechanism is unknown, it is proposed that mechanical dilatation of the cervix causes cervical damage and subsequent cervical insufficiency.[5] Additionally, disruption of the endometrium leads to alterations in the expression of genes involved in inflammation, which may play a contributory role.[5]

Connective tissue disorders

Rare connective tissue disorders such as Ehlers-Danlos syndrome are commonly associated with spontaneous preterm birth, often following PPROM. Altered collagen synthesis and function impacts on fetal membrane integrity and cervical sufficiency. Rates of PPROM are reported to vary between 25-75% and appear to be dependent on the type of Ehlers-Danlos syndrome (PPROM most common in Classical type I, and least common in Hypermobility type III).[69]

Medical conditions

Medical conditions such as diabetes and hypertension increase the risk of both spontaneous and provider-initiated preterm birth. Wāhine/people with pre-existing diabetes have a higher chance of spontaneous preterm birth than those without diabetes (OR 1.6, 95% CI 1.2-2.2).[70] Those who develop gestational diabetes also have an increased chance of spontaneous preterm birth even following adjustment for hypertension, polyhydramnios and birthweight (adjusted OR 1.42, 95% CI 1.15-1.77).[71] It is postulated that the increased chance of spontaneous preterm birth may be due to an increased risk of urogenital infection associated with poor glycaemic control.[70]

Meta-analysis including almost 800,000 pregnancies identified a significantly elevated chance of preterm birth for wāhine/people with chronic hypertension compared to the general pregnant

population (RR 2.7, 95% CI 1.9-3.6).[72] Spontaneous preterm birth likely contributed to around one-third of these, given findings from another study in which 32.5% of all preterm births in wāhine/people with chronic hypertension were the result of spontaneous labour.[73] The underlying mechanism behind this association is likely to be at least in part explained by high rates of superimposed preeclampsia in wāhine/people with chronic hypertension. Preeclampsia is a systemic intravascular inflammatory state and is associated with an almost two-fold increase in spontaneous preterm birth from 33 to 36 weeks (RR 1.9, 95% CI 1.3-2.8).[74]

Identification of wāhine/people with recognised risk factors for these medical conditions, and use of preventative measures where appropriate (e.g. aspirin for prevention of preeclampsia) and/or close surveillance and good control (e.g. glycaemic control for those with diabetes in pregnancy) will help to limit the impact of these medical conditions on spontaneous preterm birth.

Multiple pregnancy
Wāhine/people with twin or higher order multiple pregnancies have significantly increased chance of both spontaneous and provider-initiated preterm birth. There are some variations in rates of preterm birth across populations.[75] The most detailed data in Aotearoa from Te Toka Tumai, Auckland City Hospital (2024 data) includes a rate of preterm birth of 70.4% for twins (36.4% were spontaneous), and 100% for triplets.[76]

Approximately half of all preterm births for multiple pregnancies are spontaneous. Uterine over-distension likely plays a major role in the pathophysiological mechanism leading to PPROM and preterm labour.[28]

Cervical change, threatened preterm labour and PPROM
Wāhine/people may develop signs and symptoms during pregnancy that should be identified as significant risk factors for spontaneous preterm birth. These include the development of a short or open cervix; signs and symptoms of threatened preterm labour; and PPROM, known to precede approximately 40% of spontaneous preterm births.

Microbiological studies suggest that infection is a factor in 25-40% of all spontaneous preterm births.[23] Ascending infection is the most common route of transmission, with microorganisms from the lower genital tract responsible for the majority of intrauterine infection (chorioamnionitis).[24] Chorioamnionitis from ascending infection may be a secondary consequence of a shortened and/or dilated cervix, with the primary cervical change due to another factor.

Non-modifiable risk factors for spontaneous preterm birth

Ethnicity
Māori, Pacific and Indian whanāu experience less privilege in rates of spontaneous preterm birth; 8.8% for Māori, 8.4% for Pacific, 8.1% for Indian, 7.2% for Asian (excluding Indian), and 6.8% for European and other people over the period 2020-2024.[77] Historically national datasets have not allowed for differentiation of preterm birth by spontaneous and provider-initiated status. Te Toka Tumai Auckland City Hospital annual data is able to make this differentiation, and of those birthing at the unit (including those transferred for neonatal intensive care facilities), differences by ethnicity persist when examining only spontaneous preterm birth; 10.0% for Māori, 6.4% for Pacific, 5.3% for Indian, 4.0% for European and 6.1% for Asian (2024 data).[76] The reasons for these differences are likely to be multifactorial and include effects of colonisation and racism, equity of access to care including culturally-responsive care, and other confounding factors such as socioeconomic status, age and cigarette smoking. Metabolic factors may also have an influence.[78]

Extremes of age

There is a 'U-shaped' distribution of spontaneous preterm birth according to age of the wahine/person. The majority of age-related differences are likely due to confounders, including higher rates of smoking and recreational drug use, and lower access to care in younger wāhine/people, and higher rates of medical and obstetric complications and use of assisted reproductive technologies in older wāhine/people.[79] However, there is also evidence to support a modest independent association between spontaneous preterm birth and age.[79,80] In a large Canadian study, younger (20-24 years) and older (>40 years) wāhine/people had higher rates of spontaneous preterm birth when compared to a reference group aged 30-34 years, following adjustment for primiparity, use of reproductive technologies, medical history, cigarette smoking and drug use, hypertensive complications, gestational diabetes and placenta praevia (adjusted OR 1.08, 95% CI 1.01-1.15 and adjusted OR 1.20, 95% CI 1.06-1.36 respectively).[79] The underlying pathophysiology for this association is unclear, and differences in socioeconomic status which cannot be adjusted for or other unrecognised confounding factors may have a role.[79]

Short inter-pregnancy interval

An inter-pregnancy interval, from prior birth to conception, of <6 months is an independent risk factor for spontaneous preterm birth (adjusted OR 2.2, 95% CI 1.3-3.6 for births at 24 to 32 weeks, and adjusted OR 1.6, 95% CI 1.3-2.0 for births at 33 to 36 weeks).[81] Although wāhine/people who have a poor outcome in a prior pregnancy (perinatal death, fetal growth restriction or preterm birth) are more likely to have a short inter-pregnancy interval, the association with spontaneous preterm birth persists when the first pregnancy was a live term birth.[81] Proposed mechanisms include insufficient time for contraction-associated proteins to return to pre-pregnancy levels, affecting the usual process of labour initiation; and depletion of nutritional reserves of the wahine/person.[81]

Early pregnancy bleeding

Vaginal bleeding in the first and second trimesters is associated with an increased chance of spontaneous preterm birth.[28] Having more than one episode of bleeding in early pregnancy was associated with an almost two-fold increase in risk of spontaneous preterm birth in the SCOPE Study (OR 2.33, 95% CI 1.08-5.04).[82] The release of thrombin from decidual-placental haemorrhage and subsequent haemosiderin deposition are inflammatory triggers. They are likely to in part, or wholly contribute to the risk of spontaneous late miscarriage, PPROM and preterm labour following bleeding in pregnancy.

A*ntepartum haemorrhage*

Whilst a significant proportion of preterm births due to placental abruption or placenta praevia are provider-initiated due to wahine/person and/or pēpi compromise, the release of thrombin from decidual-placental haemorrhage and subsequent haemosiderin deposition are also inflammatory triggers for preterm labour in wāhine/people where immediate birth is not indicated.[83]

In a study of 502 wāhine/people with placental abruption, the risk of spontaneous preterm birth was high, even when adjusting for common confounders such as smoking, recreational drug use and hypertensive disorders (adjusted RR 6.6, 95% CI 5.4-7.9 for birth at <37 weeks; adjusted RR 16.3, 95% CI 11.5-22.9 for birth at <32 weeks).[84] Meta-analysis demonstrates that wāhine/people with placenta praevia also have an increased chance of preterm birth (RR 5.32, 95% CI 4.39-6.45), however the contribution of provider-initiated versus spontaneous preterm birth was not reported.[85]

Bacterial vaginosis and other genital tract infections

Bacterial vaginosis is a clinical syndrome characterised by a loss of vaginal *Lactobacilli*, and increased numbers of diverse anaerobic bacteria including *Gardnerella vaginalis.* [86] Bacterial vaginosis is present in up to 20% of wāhine/people during pregnancy, the majority of whom will be

asymptomatic.[87] Substantial evidence has demonstrated that bacterial vaginosis is associated with spontaneous preterm birth. Meta-analyses (32 studies and 30,518 participants) have shown that bacterial vaginosis more than doubles the risk of preterm birth (OR 2.16, 95% CI 1.56-3.00) and second trimester miscarriage (OR 6.32, 95% CI 3.65-10.94) in asymptomatic wāhine/people.[88]

Whilst antibiotic treatment may be effective at eradicating bacterial vaginosis during pregnancy, treatment including before 20 weeks does not reduce the risk of preterm birth. This was demonstrated in a 2013 Cochrane review including five trials and 4088 participants, with no reduction in preterm birth after antibiotic use, RR 0.85, 95% CI 0.62-1.17.[87] The lack of treatment benefit persisted when considering only those wāhine/people at high-risk based on their previous preterm birth history (three trials, 421 participants, RR 0.78, 95% CI 0.43-1.48).[87] A more recent systematic review and individual participant data meta-analysis including 23 eligible trials (13 studies contributed data for 4887 participants and for the remaining studies, data were imputed) further supports that treatment of bacterial vaginosis in pregnancy does not reduce preterm birth risk (for metronidazole adjusted OR 0.95, 95% 0.81-1.11, and for clindamycin OR 0.90, 95% 0.72-1.12). These findings persisted for all preterm gestational ages (<37, <34 and <32 weeks) and with, or without, inclusion of twin pregnancies.[89]

There has been some debate about the significance of asymptomatic vaginal Candida colonisation and pregnancy outcomes. A systematic review and meta-analysis from 2020 assessed the association with spontaneous preterm birth (8 studies and 16,948 participants).[90] There was no difference in spontaneous preterm birth rates in wāhine/people with or without Candida infection (OR 1.13, 95% CI 0.97-1.31).[90]

Invasive testing including chorionic villous sampling and amniocentesis
Historically, chorionic villous sampling and amniocentesis, usually performed in the second trimester, have been associated with an increased chance of late miscarriage of approximately 2% and 1% respectively. However, more recent studies are more specific to procedure-related loss and now estimate these to be 0.2% (95% CI -0.13 to 0.52%) for chorionic villous sampling and 0.3% (95% CI 0.11-0.49%) for amniocentesis (systematic review of eight studies with 13,011 chorionic villous sampling, and 12 studies with 63,723 amniocentesis).[91] For studies that were able to consider similar risk profiles for those undergoing invasive testing and those not, the procedure-related risk is further reduced, becoming negligible, -0.11% (95% CI -0.29 to 0.08%) for chorionic villous sampling and 0.12% (95% CI -0.05 to 0.30) for amniocentesis.[91]

There are more limited data on the impact of later amniocentesis and the chance of preterm birth. The indications for later gestation testing are likely to be significant confounders, making it difficult to truly determine the procedure-related risk. A 2023 systematic review and meta-analysis included five studies and 911 wāhine/people undergoing amniocentesis after 24 weeks.[92] When amniocentesis was performed <32 weeks, birth before 37 weeks occurred in 5.8% (95% CI 3.4-8.8%) and within one week for 1.5% (95% CI 0.4-3.2%).[92]

Polyhydramnios
The presence of excess amniotic fluid is associated with an increased chance of preterm birth, along with other pregnancy complications. As demonstrated in cohort studies, wāhine/people with polyhydramnios are more likely to give birth preterm than those without polyhydramnios (19% versus 12%, p<0.001 when amniotic fluid index of ≥25 cm), and the vast majority (85%) of these are spontaneous.[93] The underlying cause for polyhydramnios influences the chance of spontaneous preterm birth, and was highest amongst pregnancies with a congenital fetal anomaly (39%), followed by pregnancies complicated by diabetes (22%).[93] Interestingly, the severity of polyhydramnios did

not appear to significantly increase the chance of preterm birth, suggesting that uterine stretch is unlikely to be the sole causative mechanism.[93]

Pregnancy complications - preeclampsia, fetal growth restriction (FGR), obstetric cholestasis
Both preeclampsia and FGR are associated with provider-initiated preterm birth, where concerns for māmā/person and/or pēpi wellbeing determine that birth is safer than ongoing pregnancy. However, as conditions of uteroplacental insufficiency, they are also associated with placental and systemic inflammation, and hence, the chance of spontaneous preterm birth is also increased.[74,94] For example, with preeclampsia, there is an almost two-fold increase in spontaneous birth from 33 to 36 weeks (RR 1.9, 95% CI 1.3-2.8).[74]

Preterm birth may be recommended (provider-initiated) for wāhine/people with severe obstetric cholestasis (peak bile acids ≥100 µmol/L) to reduce the chance of stillbirth. However, meta-analysis of eight cohort studies and >125,000 participants, confirms that obstetric cholestasis is also associated with spontaneous preterm birth, 13.4% compared with 4.0%, OR 3.47 (95% CI 3.06-3.95).[95] Spontaneous preterm birth is more common when peak bile acids are ≥100 µmol/L compared with 40-99 µmol/L and <40 µmol/L.[95] The proposed mechanisms by which preterm labour and/or PPROM may be induced include the effect of bile acids, increasing the early expression of oxytocin receptors.

Adjunct prediction tests for spontaneous preterm birth in the general population

Despite a wide variety of risk factors for spontaneous preterm birth, the majority of wāhine/people with one or more of these factors give birth at term, and some wāhine/people with none of these risk factors may still 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, 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 a general population without indirectly modifiable risk factors that may be modified through specialised preterm birth pregnancy care.

Ultrasound cervical length assessment
Universal cervical length assessment at the time of the mid-trimester 'anatomy' scan has been proposed as a population-wide screening tool for spontaneous preterm birth.[96-99] High-quality evidence to support this approach is lacking, and there is significant variation across guidelines internationally.[100] Proposed screening programmes also vary. Some recommend the gold-standard transvaginal approach for cervical length assessment for all wāhine/people, while others suggest an initial transabdominal scan, followed by a transvaginal scan for some, dependent on the cervical length measure.

There is no randomised evidence to inform a universal cervical length screening programme. The potential impact is inferred from population-based cohort studies or extrapolated from small intervention studies. A large retrospective cohort study in a United States population assessed the effectiveness of the universal addition of transvaginal cervical length at the mid-trimester scan. It included 46,598 participants before the programme introduction in 2011, and 17,609 after.[101] Participants were nulliparous or multiparous with no previous preterm birth, wāhine/people with other risk factors, such as previous cervical surgery, were included. Universal cervical length screening was associated with a small but significant decrease in spontaneous preterm birth at <37

weeks (4.8% pre-screen vs 4.0% in the screened group, aOR 0.79, 95% CI 0.72-0.86), <34 weeks (1.3% vs 1.0%, aOR 0.72, 95% CI 0.60-0.86) and <32 weeks (0.7% vs 0.5%, aOR 0.70, 95% CI 0.55-0.89).[101] Other confounding factors that may have influenced changes in preterm birth rates over time cannot be fully accounted for in a study of this nature. Furthermore, despite the majority of wāhine/people (17,590, 99.9%) agreeing to a transvaginal scan, very few (157, 0.89%) had a short cervix (≤25 mm).[101] Of note, only 74 (47%) of those with a short cervix received progesterone and/or cerclage, and the majority of births <37 weeks still occurred in those with a 'normal' cervical length at the midtrimester scan. This included 1001 preterm births, and 651 spontaneous preterm births in those with cervical length >25mm, compared with 50 preterm births in those with a short cervix.

Routine measurement of cervical length during the mid-trimester scan is included in the package of care promoted by the Australian Preterm Birth Prevention Alliance.[102] This national multifaceted prevention programme recommends an initial transabdominal assessment of cervical length and a subsequent transvaginal scan if the cervix is <35mm. The overall programme had an initial impact on moderate-late preterm birth (32^{+0} to 36^{+6} weeks), but not $<32^{+0}$ weeks.[103] To date, the rates of spontaneous and provider-initiated preterm birth have not been reported, and the effect of each intervention within the package is unknown. Other elements, e.g. smoking cessation and routine vaginal progesterone use for all wāhine/people with a prior spontaneous preterm birth, may have significantly contributed to the impact.

Without strong evidence of benefit, the challenges of a universal cervical length screening programme should also be considered. This includes the invasive nature of transvaginal scans for a general population. Furthermore, guidelines from Aotearoa and Australia acknowledge that the inclusion of a transvaginal examination adds approximately 10 minutes to the duration of a mid-trimester scan, and that busy units may not be able to absorb the additional time without impact on other services.[97] Wāhine/people in geographically remote areas are likely to have limited access to transvaginal assessment and, hence, be further disadvantaged in preterm birth prevention care.[97] Furthermore, a systematic review of cost-effectiveness studies from the United States suggests there may be a small increase in overall medical costs associated with routine transvaginal screening for low-risk, singleton pregnancies.[104] Currently, there are no data available on the cost-effectiveness of universal screening in Aotearoa or Australia.[97]

Vaginal biomarkers

Vaginal biomarkers with potential as adjunct predictive tests for spontaneous preterm birth are cervical phosphorylated insulin-like growth factor binding protein-1 (phlFGBP-1), marketed as Actim Partus, and placental alpha microglobulin-1 (PAMG-1), marketed as Partosure. These tests have modest predictive value for spontaneous preterm birth in wāhine/people who develop symptoms of preterm labour, but have no role in screening within an asymptomatic general population.

References are incorporated with those also used in the Recommendations and About sections, and are listed under the About section.