Optimising the care of women at high risk of spontaneous preterm birth

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Abstract

Background

Preterm birth is the leading cause of neonatal death and has lifelong health consequences for many survivors. The majority of cases are a consequence of the spontaneous onset of labour.

Aims

To identify strategies that optimise the care of women at high risk of spontaneous preterm birth.

Methods

Vaginal biomarker use in symptomatic women

1. A quality improvement project assessed the effect of a multi-faceted implementation programme on compliance with the use of a fetal fibronectin clinical practice guideline.
2. A prospective observational study compared the impact of different vaginal biomarker tests on clinical care.

Preterm birth clinics

3. A systematic review assessed current practice in preterm birth clinics worldwide.
4. An observational study reviewed five years of practice in the first preterm birth clinic in New Zealand.
5. A longitudinal cohort survey assessed the psychological wellbeing of women attending a preterm birth clinic and the potential impact of clinic care on their wellbeing.

Birth at peri-viable gestations

6. A single-centre case series assessed antenatal counselling and perinatal care for babies born at 23-24 weeks over a two year period.

Results

Vaginal biomarker use in symptomatic women

1. A multi-faceted implementation programme improves compliance to a clinical practice guideline.
2. Use of quantitative fFN could decrease the rate of antenatal admissions without compromising care for babies born preterm.

Preterm birth clinics

3. There is wide variation in practice in preterm birth clinics.
4. Most women underwent cervical surveillance as their primary management. Pregnancy outcomes were consistent with published literature.
5. Women seen in preterm birth clinics have high rates of anxiety. Anxiety reduced over time whilst attending the clinic. Women's perceptions of clinic care were favourable.

Birth at peri-viable gestations

6. All families opted for active intervention when this was offered. Some aspects of care can be improved, including magnesium sulphate administration, delayed cord clamping and documentation of plans for delivery.

Conclusions

There are opportunities to optimise the care of women at high risk of spontaneous preterm birth. Findings will contribute to the development of a national preterm birth prevention programme for New Zealand.

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I would like to begin by expressing my heartfelt gratitude to my principal supervisor Associate Professor Katie Groom, who has provided me with invaluable guidance and unwavering support. Thank you for inspiring me to pursue research alongside my clinical career, I think you knew I was destined for academia before I did! I would also like to thank Associate Professor Jason Waugh, who stepped in as a co-supervisor towards the end of my first year, and provided much wisdom, pragmatism, and encouragement. I am also very grateful to Professor Lesley McCowan who was a co-supervisor for part of my first year, and enabled me to commence my Doctor of Medicine studies whilst working as a Clinical Fellow in the Department of Obstetrics and Gynaecology. I truly appreciate the opportunities this allowed me.

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Glossary

°C	Degrees Celsius
17α-OHP	17 alpha hydroxyprogesterone
17OHP-C	17 alpha hydroxyprogesterone caproate
ADHB	Auckland District Heath Board
aOR	Adjusted odds ratio
aRR	Adjusted relative risk
BMI	Body mass index
CASP	Critical Appraisal Skills Programme
C-STICH	Cerclage Suture Type for an Insufficient Cervix and its effect on Health
CI	Confidence interval
cm	Centimetres
ELISA	Enzyme-linked immunosorbent assay
EPDS	Edinburgh Postnatal Depression Scale
EPOC	Effective Practice and Organisation of Care
EPPPIC	Evaluating Progestogen for Prevention of Preterm Birth International Collaborative
FDA	Food and Drug Administration
fFN	Fetal fibronectin
g	Grams
GBS	Group B streptococcus
IM	Intramuscular
IVF	*In vitro* fertilisation
IVH	Intraventricular haemorrhage
kg/m^2	Kilograms per metre squared
LEEP	Loop electrosurgical excision procedure
LLETZ	Large loop excision of the transformation zone
MAVRIC	Multicentre Abdominal versus Vaginal Randomised Investigation of Cerclage
MeSH	Medical Subject Headings
µg/L	Microgram per litre
mg	Milligrams
mm	Millimetres
mmHg	Millimetres of Mercury
MOS	Medical Outcomes Study

MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
NEC	Necrotising enterocolitis
N	Number
ng/mL	Nanograms per millilitre
NNT	Numbers needed to treat
NPV	Negative predictive value
NZ	New Zealand
OR	Odds ratio
PAMG-1	Placental alpha microglobulin-1
PDA	Patent ductus arteriosus
pIGFBP-1	Phosphorylated insulin like growth factor binding protein-1
PMMRC	Perinatal and Maternal Mortality Review Committee
PPV	Positive predictive value
PPROM	Preterm pre-labour rupture of membranes
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PTB	Preterm birth
PTBC	Preterm birth clinic
QUiPP	Quantitative Instrument for the Prediction of Preterm Birth
RCOG	Royal College of Obstetricians and Gynaecologists
RDS	Respiratory distress syndrome
ROC	Receiver operator curves
ROP	Retinopathy of prematurity
RR	Relative risk
SCOPE	Screening for Pregnancy Endpoints
SD	Standard deviation
SF-36	36-Item Short Form Survey
sPTB	Spontaneous preterm birth
STAI	State-Trait Anxiety Inventory
TV USS	Transvaginal ultrasound scan
UK	United Kingdom
USD	United States dollars

Chapter 1 Overview

1.1 Overview of thesis

Preterm birth is an important global health problem with approximately 1 in 10 babies born prematurely each year (March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012). Preterm birth is the leading cause of neonatal death worldwide and many survivors have significant perinatal morbidity and lifelong health consequences (March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012). More than half of all preterm births are due to the spontaneous onset of labour or preterm pre-labour rupture of membranes (PPROM), which is referred to collectively as spontaneous preterm birth (Goldenberg, Culhane et al. 2008; March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012). Despite considerable research in this field, there is no effective treatment to stop preterm labour once it has established (Hamilton & Mullan 2016; Haram, Mortensen et al. 2015). The emphasis of current management is therefore on two main strategies: the prevention of preterm labour; and the accurate identification of women at highest risk of spontaneous preterm birth, so that they can be targeted for antenatal interventions that improve perinatal outcomes for babies born preterm. This thesis examines ways to optimise the care of women at high risk of spontaneous preterm birth through both of these strategies. This is achieved through six studies within three main themes: (1) assessing the use of vaginal biomarkers in the prediction of spontaneous preterm birth; (2) the role of specialised preterm birth clinics; and (3) opportunities to optimise care when birth is expected at peri-viable gestational ages.

Women at high risk of spontaneous preterm birth can be broadly classified into two groups depending on the presence or absence of symptoms. Women who present with symptoms of preterm labour (also known as threatened preterm labour) are referred to as ‘symptomatic women’, and may or may not have other risk factors for spontaneous preterm birth. In contrast, ‘asymptomatic women’ are those at high risk due to their previous obstetric or gynaecological history and do not have symptoms of preterm labour.

1.1.1 Vaginal biomarkers in symptomatic women

The majority of women with threatened preterm labour do not go on to have a spontaneous preterm birth, and assessment based on symptoms alone is a poor predictor (Copper, Goldenberg et al. 1990; Peaceman, Andrews et al. 1997). The consideration of additional diagnostic tools

such as ultrasound assessment of cervical length and the use of vaginal biomarkers, such as fetal fibronectin (fFN), can improve risk stratification (Iams, Casal et al. 1995; Sotiriadis, Papatheodorou et al. 2010). This allows time for antenatal interventions that improve perinatal outcomes to be given to those at highest risk of spontaneous preterm birth, whilst avoiding unnecessary interventions for the majority.

The first two studies in this thesis assess the use of vaginal biomarkers in optimising the care of symptomatic women at high risk of spontaneous preterm birth. The first study assesses whether a multi-faceted implementation strategy improves compliance to a clinical practice guideline for fFN use for women with threatened preterm labour. The second study compares the potential impact of three different vaginal biomarker tests on clinical practice when used in women with symptoms of preterm labour.

1.1.2 Specialised preterm birth clinics

Specialised preterm birth clinics have developed over the last two decades due to a growing understanding of the risk factors for spontaneous preterm birth and availability of interventions known to reduce this risk. These clinics focus on the care of asymptomatic, high risk women. The key components include addressing modifiable risk factors, regular mid-trimester transvaginal ultrasound cervical length surveillance, and providing evidence-based interventions such as vaginal progesterone or cervical cerclage when indicated. Although there is good evidence to support many of the practices that occur in preterm birth clinics, specific evidence to support the utility of preterm birth clinics as a whole is still evolving (Malouf & Redshaw 2017; Vernet, Watson et al. 2017; Whitworth, Quenby et al. 2011). The third study in this thesis is a systematic review assessing practice in specialised preterm birth clinics globally. The fourth study describes the experience and outcomes of five years of practice in the first preterm birth clinic in New Zealand.

Women with high risk pregnancies have increased levels of anxiety, however there is little research on the psychological wellbeing of women at high risk of preterm birth nor on the effect of care through a preterm birth clinic. Whilst it seems likely that care in a preterm birth clinic reduces pregnancy-related anxiety, it has also been hypothesised that identification of high risk status and additional clinic visits may increase anxiety. It has been recommended that future research on preterm birth clinics should include the experiences and perceptions of women who attend such clinics (Malouf & Redshaw 2017). The fifth study in this thesis examines the

psychological wellbeing of women at high risk of spontaneous preterm birth and the potential impact of care in a preterm birth clinic on wellbeing.

1.1.3 Care when birth is expected at peri-viable gestations

In recent years there has been a shift to a more pro-active approach to resuscitation at extremely early gestational ages. Although few babies are born at these extremely preterm gestations, they have the highest rates of mortality and morbidity (Raju, Mercer et al. 2014). This provides another opportunity for optimisation of care. The threshold of viability is often referred to as the 'peri-viable' period, defined here as 23^{+0} to 24^{+6} weeks of gestation. Many factors impact on the rates of survival and survival free of major morbidity, but local hospital practice regarding the offer of resuscitation is the most significant at these extremely early gestations (Rysavy, Li et al. 2015). In New Zealand, inconsistencies in care have been identified for babies who are born extremely preterm (Perinatal and Maternal Mortality Review Committee 2018). The sixth and final study in this thesis examines opportunities to optimise the care of women at high risk of birth at 23 and 24 weeks of gestation in a single institution. Learning points are also relevant for optimisation of perinatal care at later preterm gestations and in other institutions.

1.1.4 Summary of thesis structure

In summary, this thesis assesses strategies to optimise care for both symptomatic and asymptomatic women at high risk of spontaneous preterm birth. This is achieved through six research studies across three main themes; each study will be described in detail in Chapters 4 to 9 (Figure 1.1).

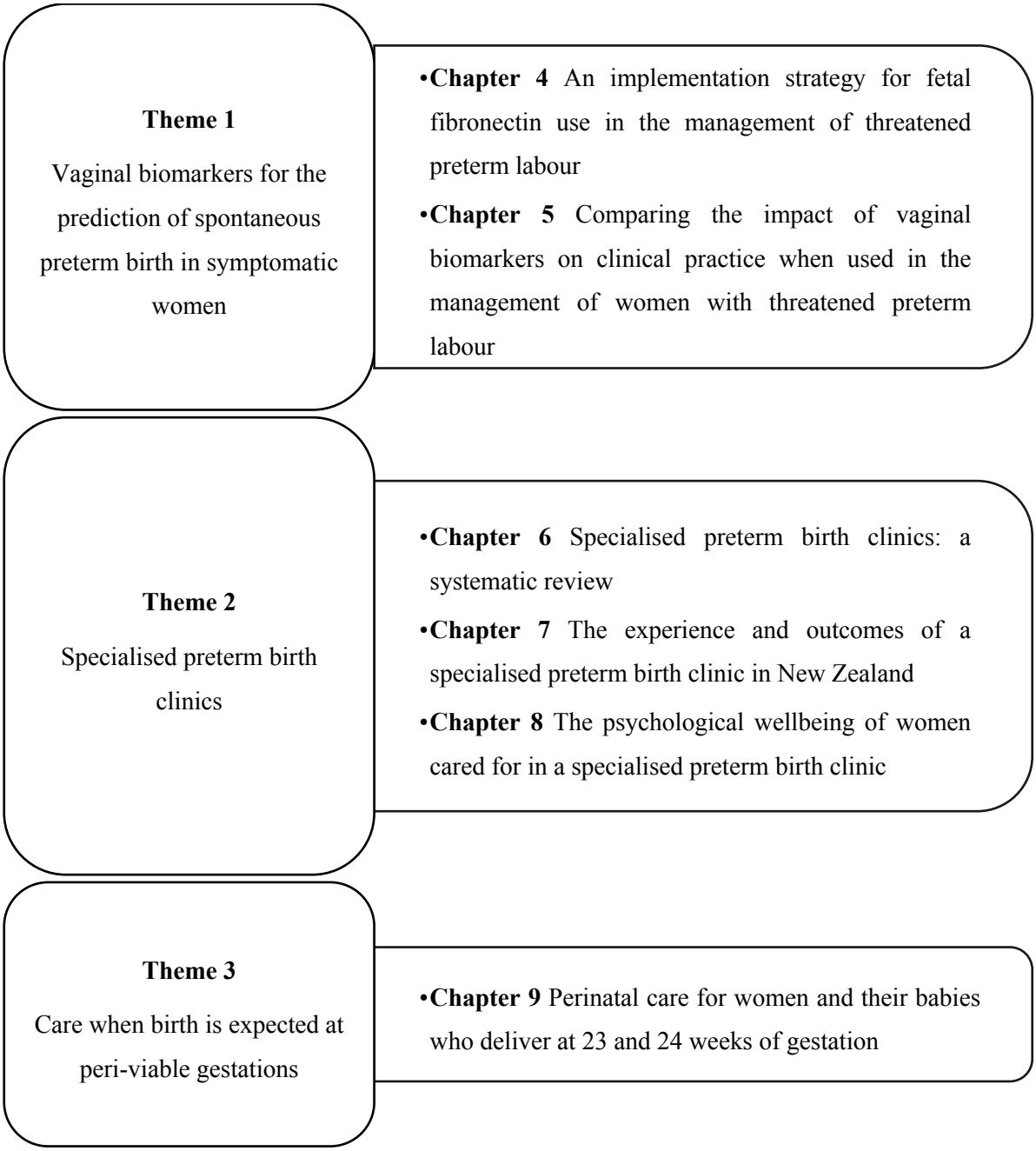

Figure 1.1 Overview of thesis structure

1.2 Overview of preterm birth

1.2.1 Definitions

Preterm birth is defined by the World Health Organisation as birth prior to 37 weeks of gestation (or less than 259 days since the first day of the woman's last menstrual period) (World Health Organisation 1977). The lower limit of gestational age varies by location; 20^{+0} weeks will be used in this thesis unless otherwise specified. Preterm birth can be further classified by the gestational age at delivery, with extremely preterm birth at $<28^{+0}$ weeks, very preterm birth at 28^{+0} to 31^{+6} weeks, and moderate-to-late preterm birth at 32^{+0} to 36^{+6} weeks (March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012).

Preterm labour is defined as the onset of regular uterine contractions, accompanied by significant cervical dilatation of ≥3 cm, prior to 37 weeks of gestation. The terms 'threatened preterm labour' or 'symptoms of preterm labour' are used interchangeably to describe the presence of uterine contractions with no, or limited cervical change at the same gestation.

There is no standard definition for peri-viability, and in its broad sense it can refer to gestations from 20^{+0} through to 25^{+6} weeks (Raju, Mercer et al. 2014). Until recently, babies born at 22 weeks were thought to have very little chance of survival and from 25 weeks there is a general consensus that active management should be offered in countries where neonatal intensive care facilities are available (Guillén, Weiss et al. 2015; Royal College of Obstetricians and Gynaecologists 2014). Thus, a more practical definition of peri-viability is gestational ages from 23^{+0} to 24^{+6} weeks. This is the definition used in the New Zealand consensus statement on peri-viable birth and will be used in this thesis (Newborn Clinical Network 2019). However, recently published guidelines from the United Kingdom advise consideration of neonatal resuscitation from 22^{+0} weeks (British Association of Perinatal Medicine 2019). It is unlikely that this lower gestational age will be adopted in New Zealand in the near future due to existing inequities in care and resource implications even for births at 23 weeks of gestation.

When referring to a single gestational age in weeks, this is intended as the completed number of weeks of gestation and the following six days, for example, 23 weeks refers to 23^{+0} through to 23^{+6} weeks of gestation.

Preterm birth can be classified as spontaneous or medically-indicated. Spontaneous preterm birth is usually defined as birth following the spontaneous onset of labour or PPROM, irrespective of whether the mode of delivery is vaginal or by caesarean section (Goldenberg, Culhane et al. 2008). Medically-indicated preterm birth (also known as iatrogenic or provider-initiated preterm birth) is defined as delivery for maternal and/or fetal indications, whereby labour is induced or delivery is by pre-labour caesarean section (Goldenberg, Culhane et al. 2008).

1.2.2 Incidence of preterm birth

The incidence of preterm birth varies significantly between countries (Figures 1.2 and 1.3), and there are challenges with obtaining accurate data, especially in low income settings. These challenges include data gaps in both numbers of preterm births and overall births, along with potential inaccuracies in pregnancy dating in areas where ultrasound is not routinely available (March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012). Global estimates from 2014 report an overall preterm birth rate of 10.6%, translating to around 15 million babies per year (Chawanpaiboon, Vogel et al. 2019). Estimated rates vary from just 5% in some Northern European countries, to 18.1% in Malawi (March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012). The preterm birth rate in New Zealand was 7.5% in 2017 (Ministry of Health 2019a).

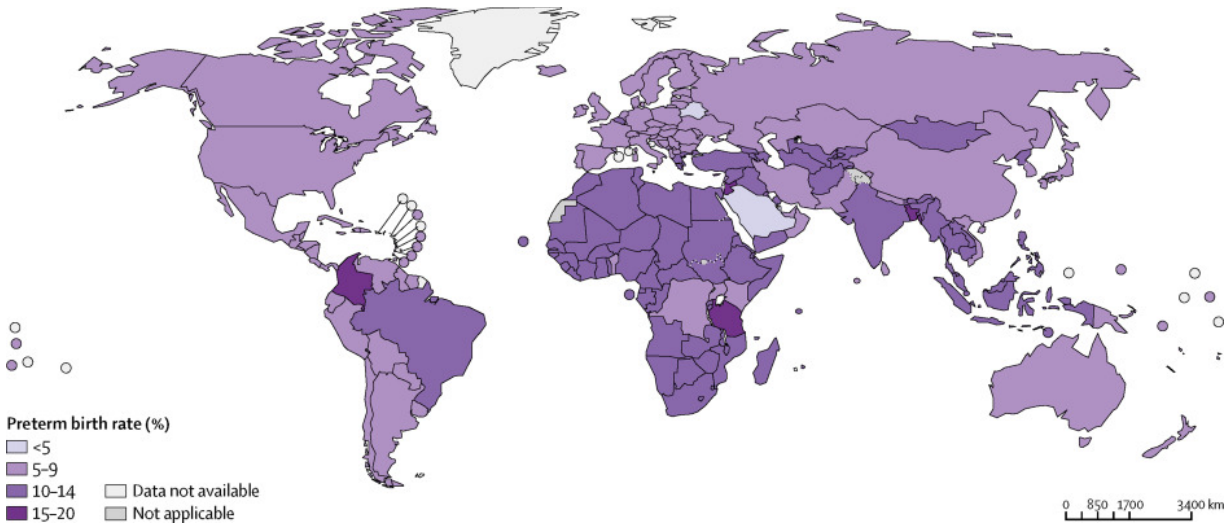

Figure 1.2 Estimated preterm birth rates in 2014

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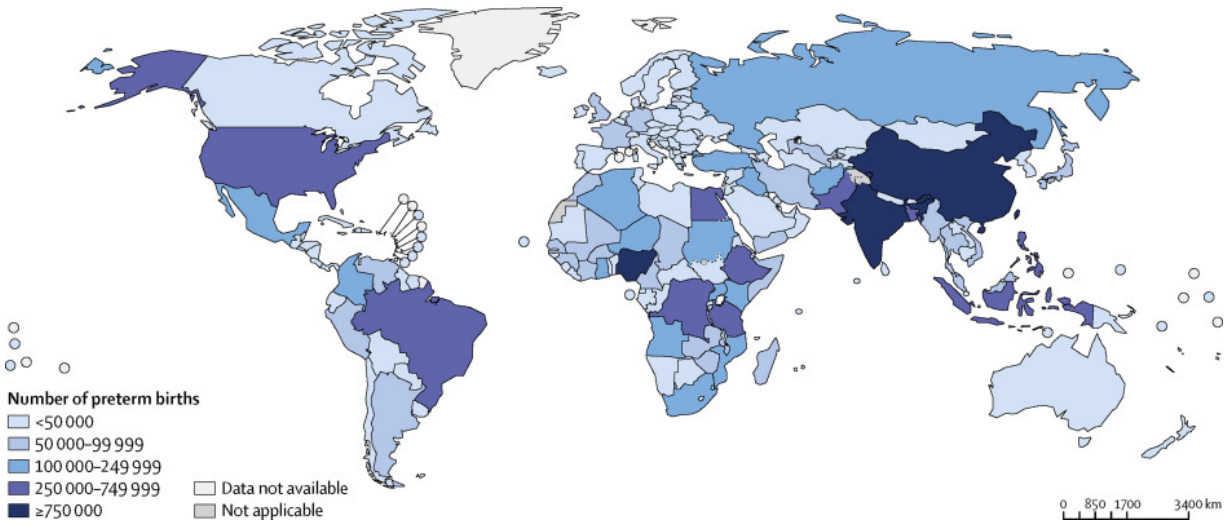

Figure 1.3 Estimated numbers of preterm births in 2014

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Moderate-to-late preterm births contribute the largest proportion of all preterm births globally at an estimated 84.7%, with very preterm births and extremely preterm births making up 11.3% and 4.1% of all preterm births respectively (Chawanpaiboon, Vogel et al. 2019). The relative proportions of spontaneous and medically-indicated preterm births vary between countries. Almost 40% of preterm births in the United States and France are medically-indicated, compared to just over 20% in Scotland and the Netherlands (March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012). This is likely due to differing recommendations regarding timing of birth for obstetric conditions such as poor fetal growth, but may also reflect differences in preterm birth classifications, for example pre-labour caesarean section or induction of labour for PPROM. In low and middle income countries, rates of medically-indicated preterm birth are even lower due to limited access to medical care, with most pregnancies running their natural course (March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012).

Despite significant global efforts, overall preterm birth rates and absolute numbers of babies born preterm continue to rise, increasing the burden on global health (March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012).

1.2.3 Aetiology of preterm birth

Preterm birth is a syndrome with multiple underlying causes and mechanisms. There are differing risk factors for spontaneous and medically-indicated preterm birth, although there is some overlap.

I. Spontaneous preterm birth

The onset of preterm labour is complex and incompletely understood but ultimately involves a common shared pathway of uterine contractility, cervical dilatation and rupture of the fetal membranes (Romero, Dey et al. 2014). A number of risk factors are thought to contribute to the transition from normal uterine quiescence to preterm labour and many involve the activation of inflammatory pathways (Goldenberg, Culhane et al. 2008). No clear cause can be identified in around half of all spontaneous preterm births (Menon 2008).

Risk factors for spontaneous preterm birth include:

- Previous spontaneous preterm birth and/or PPROM
- Congenital uterine anomalies
- Cervical surgery
- Uterine instrumentation
- Caesarean section at full cervical dilatation
- Cigarette smoking
- Recreational drug use
- Extremes of maternal age
- Low body mass index
- Short inter-pregnancy interval
- Low socioeconomic status
- Ethnic/racial differences
- Maternal medical conditions such as diabetes and hypertension
- Stress and psychological distress
- Multiple pregnancy
- Infection
- Antepartum haemorrhage
- Polyhydramnios

These risk factors are explored in more detail in Chapter 2.

II. Medically-indicated preterm birth

Medically-indicated preterm births are usually performed due to maternal and/or fetal considerations that warrant early delivery. However induction of labour or pre-labour caesarean section may be carried out at preterm gestations without good medical justification and thus the term provider-initiated preterm births is now also used. The rate of provider-initiated births in some counties is concerning; up to 57% of provider-initiated late preterm births in the United States are non-evidenced based (Gyamfi-Bannerman, Fuchs et al. 2011).

Common indications for medically-indicated preterm birth include:

- Severe pre-eclampsia
- Placental abruption
- Placenta praevia or accreta
- Uterine rupture
- Fetal growth restriction with abnormal markers of fetal wellbeing
- Suspected fetal hypoxia
- Fetal complications of multiple pregnancy

Maternal medical conditions such as renal disease, hypertension, obesity and diabetes are also risk factors for medically-indicated preterm birth (March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012). This is likely to be due to an increased risk of obstetric complications such as pre-eclampsia and fetal growth restriction, along with the need for early delivery due to deterioration of the pre-existing medical condition itself, for example with renal disease. The number of medically-indicated preterm births is likely to rise due to an increasing number of women embarking on pregnancy with pre-existing medical conditions (in part due to advancing maternal age).

1.2.4 Consequences of preterm birth

Preterm birth is the direct cause of 35% of the world's 3.1 million neonatal deaths each year, and is the highest cause of mortality in under-5 year olds (Liu, Oza et al. 2016). Furthermore, being born preterm increases the risk of dying from other causes, especially infectious illness,

and preterm birth is associated with 50% of all neonatal deaths when indirect causes are included (Lawn, Gravett et al. 2010). Although survival rates from preterm birth vary considerably between countries, babies born at <32 weeks have the highest risk of death (Lawn, Gravett et al. 2010). Improvements in neonatal care in high income countries have led to improved survival and long term outcomes for babies born extremely preterm. In these high income settings, babies born at 24 weeks have a 50% chance of survival when neonatal intensive care is provided (Blencowe, Cousens et al. 2013; Lawn, Gravett et al. 2010). However, even basic health care is lacking in many low-to-middle income countries and 50% survival rates for preterm babies are not achieved until 34 weeks of gestation in many parts of the world (Blencowe, Cousens et al. 2013). Whilst this thesis focuses on optimising the care of women at high risk of preterm birth in high income countries, a substantial reduction in the global burden of preterm birth is only possible with advances in basic health care in low-to-middle income countries. There is an ongoing commitment for improvements in health care globally in the United Nations Sustainable Development Goals for 2030 (United Nations 2016).

Babies born preterm are at risk of both short and long term complications, with some resulting in lifelong disability for survivors. The risk of complications are inversely related to gestational age (Saigal & Doyle 2008). Short term complications of preterm birth include:

- **Intraventricular haemorrhage (IVH):** this major complication of prematurity typically initiates in the germinal matrix, a highly vascularised collection of precursor neuronal and glial cells in the developing brain (Ballabh 2010). The aetiology is multifactorial but primarily attributed to vulnerability of the fragile vasculature to haemorrhage (Ballabh 2010). IVH affects 20% of very low birthweight preterm babies (<1500 grams) and up to 45% of those <750 grams (Ballabh 2010). It predominantly occurs within the first 48 hours of life (Ballabh 2010). The severity of disease is graded based on the extent of haemorrhage on cerebral ultrasound, ranging from mild (grade 1-2) to moderate-to-severe (grade 3-4) (Ballabh 2010). Worse outcomes from IVH correlate with increasing severity of disease, and include death and neurodevelopmental disability (Ballabh 2010). Approximately 45-85% of survivors with moderate-to-severe IVH will have major cognitive deficits and the majority of these will need special assistance in school (Vohr, Allan et al. 2003).

- **Respiratory distress syndrome (RDS):** this common breathing disorder predominantly affects preterm babies and is caused by surfactant deficiency and structural immaturity of the lungs (Sweet, Carnielli et al. 2013). RDS is characterised by increased respiratory effort,

hypoxia and a 'ground glass' appearance on chest x-ray (Sweet, Carnielli et al. 2013). Although the incidence of RDS has decreased with widespread use of antenatal corticosteroid therapy, it remains one of the most common complications of prematurity and is a strong predictor of chronic lung disease (Ward & Beachy 2003). RDS affects 88-92% of babies born at 24 to 27 weeks, 76% at 28 to 29 weeks and 57% at 30 to 31 weeks (Sweet, Carnielli et al. 2013). If left untreated, RDS can result in death from progressive hypoxia and respiratory failure (Sweet, Carnielli et al. 2013).

- **Necrotising enterocolitis (NEC):** this inflammatory disorder is thought to develop after an injury to the gastrointestinal tract and subsequent invasion of gas-producing bacteria, leading to mucosal erosion, bowel necrosis, perforation and sepsis (Ward & Beachy 2003). NEC affects approximately 1-5% of babies admitted to the neonatal unit, and the frequency, severity and age of onset is inversely proportional to gestational age and birthweight (Ward & Beachy 2003). The disease is described in stages; stage 1 is suspected NEC; stage 2 is confirmed NEC with pneumatosis intestinalis (the pathognomonic radiological sign of intramural gas collection); and stage 3 is definite NEC with severe disease including hypotension, metabolic acidosis and coagulopathy, with or without perforation (Walsh & Kliegman 1986). Overall mortality is around 30%, with long term morbidity in survivors related to complications from bowel strictures, malnutrition, and short bowel syndrome following surgical management (Ward & Beachy 2003).

- **Sepsis:** infection resulting in systemic manifestations (sepsis), or organ dysfunction and tissue hypoperfusion (severe sepsis) can be a catastrophic complication of prematurity. Early-onset sepsis occurs within the first three days of life and is typically caused by vertical transmission of organisms from the mother before or at the time of birth (Hornik, Fort et al. 2012). Late-onset sepsis is defined as sepsis between days 4 and 120 of life and may be caused by pathogens acquired at delivery or during the course of hospital care (Hornik, Fort et al. 2012). Preterm and very low birthweight babies are at risk of both early- and late-onset neonatal sepsis due to their underdeveloped immune systems, need for invasive medical procedures including central venous access, and prolonged hospital admissions (Hornik, Fort et al. 2012). Very low birthweight babies have an incidence of early-onset sepsis of 1-2% and late-onset sepsis of 21-25% (Hornik, Fort et al. 2012). Babies with both early- and late-onset sepsis have an increased risk of death when controlling for other confounding factors (odds ratio, OR 1.45, 95% confidence interval, CI 1.21-1.73 and OR 1.30, 95% CI 1.21-1.40 respectively) (Hornik, Fort et al. 2012).

- **Retinopathy of prematurity (ROP):** this potentially blinding condition occurs in preterm babies who have received neonatal care (Hellström, Smith et al. 2013). It almost exclusively affects babies born at <32 weeks or with a birthweight of <1500 grams who receive oxygen therapy (Ward & Beachy 2003). ROP occurs due to the susceptibility of immature retinas to hyperoxia, which disrupts neurovascular growth and if left untreated can result in retinal detachment and blindness (Hellström, Smith et al. 2013). The initial stages (Stages 1 and 2) often resolve spontaneously, but if more advanced disease develops (Stage 3) there is a high risk of progression to blinding retinal detachment (Stages 4 and 5) and laser treatment is recommended (Hellström, Smith et al. 2013). The overall reported incidence of ROP varies widely from 33-73% for births at <28 weeks (Austeng, Källen et al. 2009; Markestad, Kaaresen et al. 2005). Severe disease is less common, affecting 10% of babies born at <32 weeks or with birthweight <1500 grams in a study from Australasia (Darlow, Hutchinson et al. 2005).

- **Persistently patent ductus arteriosus (PDA):** the ductus arteriosus is a physiological shunt which diverts ventricular outflow away from the lungs and to the placenta whilst the fetus is *in utero* (Hamrick & Hansmann 2010). For the first three days of life, a PDA in a healthy term or preterm baby is normal (Hamrick & Hansmann 2010). However, the ductus arteriosus is persistently patent in approximately one third of preterm babies with a birthweight <1500 grams and in 55% of those born <1000 grams (Hamrick & Hansmann 2010). This can have significant clinical consequence, especially during the recovery phase from RDS when improvements in oxygen and ventilation result in falling pulmonary vascular resistance, augmenting the left-to-right shunt through the ductus arteriosus, leading to pulmonary oedema and worsening cardiopulmonary function (Hamrick & Hansmann 2010). The resulting need for prolonged ventilation is strongly associated with the development of chronic lung disease.

Long term complications of preterm birth include:

- **Neurodevelopmental sequelae**: survivors of preterm birth have an increased risk of cerebral palsy, intellectual disability, developmental delay and visual and hearing impairments (Saigal & Doyle 2008). Babies born extremely preterm have the highest risk of significant neurodevelopmental complications, with 21-35% of those born at <28 weeks affected (Saigal & Doyle 2008). However, a much higher proportion of children will have difficulties at school, even in the absence of diagnosed intellectual or sensorineural

disability. One study showed 72% of adolescents with a birthweight of <750 grams and 53% with a birthweight between 750 and 1000 grams required remedial assistance at school, compared to 13% of normal birthweight controls (Saigal, Hoult et al. 2000).

- **Behavioural sequelae:** in addition to neurodevelopmental complications, survivors of preterm birth also have high rates of dysfunction in other cognitive areas including attention, visual processing, academic achievements and executive functioning (Saigal & Doyle 2008). Not only does this have implications for schooling (as illustrated above), but also for social function, with increased rates of attention deficit hyperactivity disorder, withdrawal, social maladaptation, anxiety and depression (Saigal & Doyle 2008).

- **Chronic lung disease of prematurity:** up to 40% of babies who are born extremely preterm will be affected by chronic lung disease (Greenough 2013). Some will require supplemental oxygen at home for several months, with a few still requiring this beyond two years of age (Greenough 2013). Children with chronic lung disease are more likely to be hospitalised for respiratory illness and tend to have a reduced exercise tolerance (Greenough 2013).

- **Long term cardiovascular consequences and non-communicable disease:** there is accumulating evidence that adult survivors of preterm birth have higher rates of non-communicable diseases such as hypertension, asthma and obesity (March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012). For example, former preterm or very low birthweight infants have modestly increased systolic blood pressure in adulthood when compared to those born at term (3.8 mmHg, 95% CI 2.6-5.0) (de Jong, Monuteaux et al. 2012). Additionally, adult survivors of preterm birth, especially men, have a markedly increased fat mass and altered fat distribution compared to men who were born at term (body mass index 32.4 versus 28.4 kg/m^2, p=0.021) (Mathai, Derraik et al. 2013). Both changes contribute to an increased risk of cardiovascular disease. Potential mechanisms include organ immaturity and unintended consequences of antenatal interventions and intensive care (Raju, Buist et al. 2017). Research in this area of developmental origins of health and disease is ongoing.

The morbidity associated with preterm birth can incur great psychological and economic costs to families, society and the health care system over the child's lifetime (March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012). Not only can preterm birth disrupt the family unit due to geographical reasons with prolonged hospital admissions, but

mothers of premature infants also have higher rates of psychological distress with family-wide implications (Davis, Edwards et al. 2003). The costs to the health care system are significant. In the United Kingdom, the health-related cost for a preterm baby surviving to 18 years of age is estimated at £61,781 for babies born at <33 weeks and £94,740 for babies born at <28 weeks (Mangham, Petrou et al. 2009). In the United States, the cost of medical care is substantially higher and for the first year alone is USD $95,000 for babies born between 28 and 31 weeks of gestation (Lawn, Davidge et al. 2013).

1.3 Thesis aims

Despite global efforts, preterm birth rates are rising, and the spontaneous onset of labour contributes to the majority of early births. There are multiple tools and interventions available to aid the prediction and prevention of spontaneous preterm birth, and to improve outcomes when preterm birth cannot be prevented, providing many opportunities for optimisation of care. The overall goal of this thesis is to assess strategies to optimise the care of both symptomatic and asymptomatic women at high risk of spontaneous preterm birth. This is achieved through six key aims:

1. To assess whether the use of a multi-faceted implementation strategy improves adherence to a clinical practice guideline for the use of fFN testing in women with threatened preterm labour.
2. To compare the impact of three vaginal biomarker tests on clinical practice when used in women with threatened preterm labour.
3. To assess current practice in specialised preterm birth clinics globally.
4. To assess the experience and outcomes from five years of practice in the first specialised preterm birth clinic in New Zealand.
5. To report the prevalence of symptoms of anxiety and depression in women cared for in a specialised preterm birth clinic and to assess the impact of care from a preterm birth clinic on psychological wellbeing over time.
6. To assess the antenatal counselling and perinatal care provided to mothers and their babies when birth occurs at 23 and 24 weeks of gestation and to report pregnancy and neonatal outcomes for this cohort.

Chapter 2 Introduction and background

Despite significant research efforts, there is still no proven treatment to stop preterm labour once it has established (Hamilton & Mullan 2016; Haram, Mortensen et al. 2015). We therefore rely on the accurate identification of women at high risk of spontaneous preterm birth prior to the onset of labour to allow evidence-based interventions to be given to prevent preterm labour, and the accurate identification of those with symptoms who will go onto preterm birth to allow interventions to be given to improve perinatal outcomes (UK Preterm Clinical Network 2019).

I will consider symptomatic and asymptomatic women separately, although there is some overlap. For example, a woman who has previously been identified as high risk based on risk factor assessment may later present with symptoms. There is also considerable overlap in the tests used in the prediction of spontaneous preterm birth and I will provide a brief overview of these in Section 2.1 prior to evaluating the evidence for their use in both symptomatic and asymptomatic women. In this chapter, I will also summarise the evidence for the interventions used to prevent spontaneous preterm birth and/or optimise perinatal outcomes. Lastly, I will introduce the role of specialised preterm birth clinics in the care of asymptomatic high risk women, and the potential psychological impact of being identified as high risk.

2.1 Prediction of spontaneous preterm birth

2.1.1 Risk factor assessment

Spontaneous preterm labour is a syndrome initiated by multiple mechanisms (Goldenberg, Culhane et al. 2008). A wide range of risk factors have been identified; common risk factors are outlined below. Even when risk factors are identified in pregnancy, most women will still deliver at term.

- **Previous spontaneous preterm birth and/or preterm pre-labour rupture of membranes (PPROM):** the risk of recurrent preterm birth ranges from approximately 15-50%, depending on the number of previous preterm births and the gestational age at which they have occurred (Goldenberg, Culhane et al. 2008; McManemy, Cooke et al. 2007; Mercer, Goldenberg et al. 1999). In a large population-based cohort study of 19,025 women with three consecutive singleton pregnancies, the overall risk of recurrent preterm birth was highest in women with two prior preterm births, at 42% (McManemy, Cooke et al. 2007). The risk of recurrence was inversely related to the gestational ages at each prior preterm birth, ranging from 38% in women with two previous moderate preterm births (32 to 36 weeks), up to 57% if they had two previous very preterm births (21 to 31 weeks) (McManemy, Cooke et al. 2007). Comparatively, women with a previous preterm birth followed by a term delivery had only a 12-15% risk of recurrent preterm birth in the third pregnancy (McManemy, Cooke et al. 2007).

- **Congenital uterine anomalies:** maternal uterine anomalies are associated with an up to seven-fold increase in the risk of spontaneous preterm birth (Hua, Odibo et al. 2011). Congenital uterine anomalies result from the abnormal formation, fusion or resorption of the Müllerian ducts during fetal life and are present in up to 10% of the general population (Chan, Jayaprakasan et al. 2011). A recent study has assessed the specific risk of spontaneous preterm birth in 319 women with a pre-pregnancy diagnosis of a congenital uterine anomaly, with spontaneous preterm birth rates of 26% for unicornuate uterus (7/27), 21% for uterine didelphys (7/34), 16% for bicornuate uterus (31/189), 13% for septate uterus (7/56), and 31% for arcuate uterus (4/13) (Ridout, Ibeto et al. 2019). The mechanisms for the increased risk of spontaneous preterm birth are likely to vary according to the type of defect, with theories including reduced uterine capacity, differences in vascularity and

connective tissue leading to increased myometrial contractility, and presence of coinciding cervical anomalies (Chan, Jayaprakasan et al. 2011).

- **Cervical surgery:** women with cervical conisation by large loop excision of the transformation zone (LLETZ) or knife cone biopsy have a two- to four-fold increase in the risk of spontaneous preterm birth compared to women without cervical surgery (Jakobsson, Gissler et al. 2007; Kyrgiou, Koliopoulos et al. 2006; Noehr, Jensen et al. 2009). In a large Danish study, the risk of spontaneous preterm birth was related to the depth and number of excisions, but not with the severity of cervical intraepithelial neoplasia nor duration of time since the procedure (Noehr, Jensen et al. 2009). The estimated odds ratio (OR) for spontaneous preterm birth after a LLETZ with a depth of excision of 10 mm is 1.46 (95% confidence interval, CI 1.11-1.92), when compared to no prior LLETZ (Noehr, Jensen et al. 2009). This increases to an estimated OR of 2.85 with a depth of excision of 20 mm (95% CI 2.15-3.77) (Noehr, Jensen et al. 2009). Furthermore, there is an almost four-fold increase in spontaneous preterm birth following two LLETZ procedures (11.4%, OR 3.78, 95% CI 2.58-5.53) compared to no prior LLETZ (Noehr, Jensen et al. 2009). The likely mechanisms accounting for this increased risk include a change in the mechanical function of the cervix and an increased risk of ascending infection due to a shortened cervical length (Shennan & Jones 2004).

- **Uterine instrumentation:** cervical dilatation and curettage and evacuation of retained products of conception are associated with an increased risk of spontaneous preterm birth, and the risk increases with the number of instrumentations (McCarthy, Khashan et al. 2013). In the international SCOPE (Screening for Pregnancy Endpoints) Study, women with a single dilatation and curettage for the management of miscarriage or termination of pregnancy had an increased risk of spontaneous preterm birth compared to those with no previous pregnancy loss or termination (adjusted OR, aOR 1.64, 95% CI 1.08-2.50 and aOR 1.83, 95% CI 1.35-2.48 respectively). This is likely due to the uterine instrumentation itself as women managed medically had no increased risk of preterm birth (McCarthy, Khashan et al. 2013). Although the exact mechanism is unknown, it is likely that mechanical dilatation of the cervix causes cervical damage and future cervical weakness (McCarthy, Khashan et al. 2013). Additionally, there is evidence that disruption of the endometrium causes an alteration to the expression of genes involved in inflammation (McCarthy, Khashan et al. 2013).

- **Caesarean section at full cervical dilatation:** recent evidence has identified prior caesarean section at full cervical dilatation as a significant risk factor for spontaneous preterm birth (Wang, Kirby et al. 2019; Watson, Carter, David et al. 2017; Wood, Tang et al. 2017). In a large Canadian study, there was an increased risk of spontaneous preterm birth in pregnancies following a caesarean section at full cervical dilatation (relative risk, RR 1.57, 95% CI 1.43-1.73 for birth <37 weeks and RR 2.12, 95% CI 1.67-2.68 for birth <32 weeks), when compared to women with a previous normal vaginal birth (Wood, Tang et al. 2017). This increased risk is likely due to an inadvertently low incision being made into the cervicoisthmic tissue at the time of delivery, leading to a weakened cervix (Watson, Carter, David et al. 2017).

- **Cigarette smoking:** this is associated with an approximately three-fold increase in the risk of spontaneous preterm birth once adjustment is made for confounding factors (Goldenberg, Culhane et al. 2008; McCowan, Dekker et al. 2009). Approximately 15% of New Zealand women smoke in pregnancy, although there are wide variations by area of residence and ethnicity; smoking is most common amongst Māori women during pregnancy at 35% (Ministry of Health 2019a; Smokefree 2019). In the SCOPE Study, women who continued to smoke in pregnancy had higher rates of spontaneous preterm birth than non-smokers following adjustment for demographic factors, alcohol use and early pregnancy bleeding (aOR 3.21, 95% CI 1.42-7.23) (McCowan, Dekker et al. 2009). However, those who became smoke-free by 15 weeks had no significant difference in spontaneous preterm birth rates compared to non-smokers (aOR 1.03, 95% CI 0.49-2.18, p=0.66), providing support for smoking cessation advice in early pregnancy (McCowan, Dekker et al. 2009). The pathophysiology behind this association is likely related to placental factors. Cigarette smoking is known to cause placental vasoconstriction, leading to placental damage and an increased systemic inflammatory response (Goldenberg, Culhane et al. 2008).

- **Recreational drug use:** the use of recreational drugs in pregnancy is associated with an increased risk of spontaneous preterm birth independent of cigarette smoking and socio-economic status (Corsi, Walsh et al. 2019; Leemaqz, Dekker et al. 2016). The use of marijuana is increasing worldwide and legalisation changes have improved access and acceptability of use in many countries (Brown, Sarvet et al. 2017; Volkow, Han et al. 2019; Young-Wolff, Sarovar et al. 2019). In the SCOPE Study, 4.5% of New Zealand women and 5.6% of the overall cohort reported use of marijuana prior to or during pregnancy (Leemaqz, Dekker et al. 2016). Those who reported continued marijuana use at 20 weeks (1.0% overall)

had higher rates of spontaneous preterm birth, independent of cigarette smoking (aOR 2.28, 95% CI 1.45-3.59) and socioeconomic index (aOR 2.17, 95% CI 1.41-3.34) (Leemaqz, Dekker et al. 2016). Methamphetamine is the second most widely used recreational drug in New Zealand (LaGasse, Wouldes et al. 2011). Whilst accurate estimates for the use of methamphetamine in pregnancy are not available for New Zealand, other local methamphetamine statistics parallel worldwide trends (Wu, LaGasse et al. 2013). In a large American study 5.2% of women reported methamphetamine use at some point during their pregnancy (Arria, Derauf et al. 2006). Methamphetamine users were more likely to have a spontaneous preterm birth compared to non-users after adjustment for multiple confounding factors (aOR 2.9, 95% CI 2.7-3.1) (Gorman, Orme et al. 2014). The mechanism behind the association between recreational drug use and spontaneous preterm birth is unclear. Potential theories include placental vasoconstriction similar to in cigarette smoking, but unaccounted for confounding factors may also have a role (Chabarria, Racusin et al. 2016; Gorman, Orme et al. 2014).

- **Extremes of maternal age:** there is a 'U-shaped' distribution of spontaneous preterm birth according to maternal age. The majority of age-related differences are likely due to confounders including higher rates of smoking and recreational drug use in younger women, and higher rates of medical and obstetric complications and use of assisted reproductive technologies in older women (Fuchs, Monet et al. 2018). However, there is also evidence to support a modest independent association between spontaneous preterm birth and maternal age (Fuchs, Monet et al. 2018; McIntyre, Newburn-Cook et al. 2009). In a large Canadian study, younger women (20-24 years) and older women (>40 years) 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, smoking and drug use, hypertensive complications, gestational diabetes and placenta praevia (aOR 1.08, 95% CI 1.01-1.15 and aOR 1.20, 95% CI 1.06-1.36 respectively) (Fuchs, Monet et al. 2018). The underlying pathophysiology for this association is unclear, and differences in socioeconomic status not able to be adjusted for or other unrecognised confounding factors may have a role (Fuchs, Monet et al. 2018).

- **Low body mass index (BMI):** the relationship between maternal pre-pregnancy BMI and the risk of spontaneous preterm birth is complex (Shaw, Wise et al. 2014). Women who are underweight (BMI <18.5 kg/m^2) have higher rates of spontaneous preterm birth than women with a normal BMI following adjustment for maternal age, education, race, smoking and

antenatal care (aOR 1.41, 95% CI 1.37-1.45) (Salihu, Mbah et al. 2009). However, the association between obesity and spontaneous preterm birth is less clear, with conflicting findings in both individual studies and systematic review (Hendler, Goldenberg et al. 2005; McDonald, Han et al. 2010; Shaw, Wise et al. 2014; Torloni, Betrán et al. 2009). Regardless, any potential reduction in spontaneous preterm birth associated with increased BMI is likely to be countered by an increased risk of medically-indicated preterm birth (McDonald, Han et al. 2010; Torloni, Betrán et al. 2009). Proposed mechanisms behind the association between low BMI and spontaneous preterm birth include the effects of maternal malnutrition on fetal growth and development, increased production of stress hormones, and an increased susceptibility to infection (Salihu, Mbah et al. 2009).

- **Short inter-pregnancy interval:** an inter-pregnancy interval of <6 months is an independent risk factor for spontaneous preterm birth (aOR 2.2, 95% CI 1.3-3.6 for births at 24 to 32 weeks, and aOR 1.6, 95% CI 1.3-2.0 for births at 33 to 36 weeks) (Smith, Pell et al. 2003). Although women who have a poor outcome in a prior pregnancy are more likely to have a short inter-pregnancy interval, the association with spontaneous preterm birth persists even when the first pregnancy was a live term birth (Smith, Pell et al. 2003). 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 maternal nutritional reserves (Smith, Pell et al. 2003).

- **Low socioeconomic status:** preterm birth is associated with social disadvantage (Murphy 2007; Smith, Draper et al. 2007; Thompson, Irgens et al. 2006). In a large study from the United Kingdom women living in the most deprived decile had almost twice the risk of preterm birth <33 weeks compared to those in the least deprived decile (incidence rate ratio 1.94, 95% CI 1.73-2.17); however data on the relevant contribution from spontaneous and medically-indicated preterm births were not available (Smith, Draper et al. 2007). There are many determinants of socioeconomic status including education, marital status, occupation, income, and area of residence. The effect of each of these variables on the risk of spontaneous preterm birth is difficult to quantify due to the complexities of these factors (Tucker & McGuire 2004). It is also likely that confounding factors play a major role in the disparities seen. For example, in a large population-based study from Nova Scotia, women in the lowest family income group had a significantly higher risk of spontaneous preterm birth when compared to the highest income group (RR 1.14, 95% 1.03-1.25), however this difference did not persist following adjustment for parity, smoking status, weight, marital

status and previous poor obstetric history (adjusted RR, aRR 0.99, 95% CI 0.85-1.15) (Joseph, Fahey et al. 2014). There is limited New Zealand specific data, but in an urban maternity unit, women residing in the two most deprived quintiles had a spontaneous preterm birth rate of 4.5% compared to 3.4% for women living in the two least deprived quintiles (Auckland District Health Board 2019a).

- **Ethnic/racial differences:** women from certain ethnicities are over-represented in spontaneous preterm birth statistics. In New Zealand, Māori women have higher rates of spontaneous preterm birth than non-Māori; 6.5% versus 3.7% in a large maternity hospital in Auckland in 2018 (p=0.003) (Auckland District Health Board 2019a). This is likely to be due to confounding factors such as younger maternal age and smoking, as well as inequities in access to antenatal care (Auckland District Health Board 2017). Black women are also over-represented in preterm birth rates worldwide when compared to white women (aOR 2.0, 95% CI 1.8-2.2) (Schaaf, Liem et al. 2013). These differences are also likely to be multifactorial with socioeconomic status, health behaviours, access to care and genetic and metabolic factors all likely to have influence (Kramer & Hogue 2009).

- **Maternal medical conditions:** medical conditions such as diabetes and hypertension increase the risk of both spontaneous and medically-indicated preterm birth. Women with pre-existing diabetes have a higher risk of spontaneous preterm birth than healthy controls (OR 1.6, 95% CI 1.2-2.2) (Sibai, Caritis et al. 2000). Women who develop gestational diabetes also have an increased risk of spontaneous preterm birth even following adjustment for hypertension, polyhydramnios and birthweight (aOR 1.42, 95% CI 1.15-1.77) (Hedderson, Ferrara et al. 2003). It is postulated that the increased risk of spontaneous preterm birth may be due to an increased risk of urogenital infection associated with poor glycaemic control (Sibai, Caritis et al. 2000). Women with chronic hypertension also have an increased risk of preterm birth compared to the general pregnant population in meta-analysis (RR 2.7, 95% CI 1.9-3.6) (Bramham, Parnell et al. 2014). Spontaneous preterm birth likely contributes to around one third of these given findings from another study in which 32.5% of all preterm births in women with chronic hypertension were the result of spontaneous labour (Kase, Carreno et al. 2013). The underlying mechanism behind this association is likely to be at least in part explained by high rates of superimposed preeclampsia in women with chronic hypertension. Preeclampsia is a systematic 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) (Ananth, Savitz et al. 1997).

- **Stress and psychological distress:** maternal stress, anxiety and depression are each associated with an increased risk of spontaneous preterm birth (Copper, Goldenberg et al. 1996; Goldenberg, Culhane et al. 2008). Whilst confounding factors are likely to have a significant role, they are unlikely to completely explain the association (Grote, Bridge et al. 2010). In the Preterm Prediction Study, stress was associated with an increased risk of spontaneous preterm birth even after adjustment for maternal demographics, psychosocial status and substance use (aOR 1.16, CI 1.05-1.29) (Copper, Goldenberg et al. 1996). Likewise, women with mild and moderate-to-severe depressive symptoms each had an increased risk of spontaneous preterm birth when adjusted for age, weight, unplanned pregnancy, and substance use (aOR 2.22, 95% CI 1.64-3.00 and aOR 3.67, 95% CI 2.09-6.46 respectively) (Sanchez, Puente et al. 2013). Lastly, women with both mild and moderate-to-severe symptoms of anxiety had an increased risk of spontaneous preterm birth (aOR 1.72, 95% CI 1.11-2.67 and aOR 2.76, 95% CI 1.83-4.16 respectively) (Sanchez, Puente et al. 2013). The exact causative mechanisms are unclear but it is thought that increased levels of stress hormones such as cortisol and catecholamines play a role, as they can lead to placental hypoperfusion and inflammation (Grote, Bridge et al. 2010).

- **Multiple pregnancy:** women with twin or higher order multiple pregnancies have an almost ten-fold increased risk of preterm birth than singleton pregnancies (RR 8.2, 95% CI 7.9-8.5 in an Austrian cohort, RR 10.5, 95% CI 9.8-11.1 in a Finish cohort), with approximately half due to the spontaneous onset of labour (Blondel, Macfarlane et al. 2006). The increased risk is likely due to uterine over-distension (Goldenberg, Culhane et al. 2008). The rising use of artificial reproductive technology is partly responsible for the increasing incidence of multiple pregnancies (March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012). A policy of selective single embryo transfer has been shown to reduce the incidence of multiple pregnancy from 32% to 1% in meta-analysis, with no reduction in pregnancy rates when combined with a second frozen embryo cycle (McLernon, Harrild et al. 2010). There has been an increased uptake of single embryo transfer in New Zealand and Australia (76.3% in 2013, 89.4% in 2017), with an associated decrease in multiple pregnancies (5.6% in 2013, 3.6% in 2017) (Newman, Fitzgerald et al. 2019). If fertility clinics adopted a single embryo transfer policy globally, the burden of preterm birth

associated with multiple pregnancies from *in vitro* fertilisation would be significantly reduced.

- **Infection:** microbiological studies suggest that infection is a factor in 25-40% of all spontaneous preterm births (Romero, Espinoza et al. 2006). Ascending infection is the most common route of transmission, with microorganisms from the lower genital tract responsible for the majority of intrauterine infection (chorioamnionitis) (Romero, Dey et al. 2014). Chorioamnionitis that results from ascending infection may be a secondary consequence of a shortened and/or dilated cervix in some cases, with the primary cervical change due to other factors. Systemic infection with haematogenous spread is another possible cause of preterm labour and the most common sources are urinary tract infection, pneumonia, malaria, and periodontal disease (Romero, Dey et al. 2014; Romero, Espinoza et al. 2006). Infection is more likely to be implicated in extremely and very early preterm births (Goldenberg, Culhane et al. 2008).

- **Antepartum haemorrhage:** vaginal bleeding in the first and second trimester, along with bleeding in later pregnancy from placental abruption and placenta praevia, are each associated with an increased risk of spontaneous preterm birth (Goldenberg, Culhane et al. 2008). 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) (Dekker, Lee et al. 2012). Whilst a significant proportion of preterm births due to placental abruption or placenta praevia are medically-indicated due to maternal and/or fetal compromise, the release of thrombin from decidual-placental haemorrhage and subsequent haemosiderin deposition are also inflammatory triggers for preterm labour in women where immediate delivery is not indicated (Ananth & VanderWeele 2011). In a study of 502 women 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 (aRR 6.6, 95% CI 5.4-7.9 <37 weeks; aRR 16.3, 95% CI 11.5-22.9 <32 weeks) (Ananth, Berkowitz et al. 1999). Women with placenta praevia have an overall increased risk of preterm delivery in meta-analysis (RR 5.32, 95% CI 4.39-6.45), however the contribution of medically-indicated versus spontaneous preterm birth was not reported (Vahanian, Lavery et al. 2015).

- **Polyhydramnios:** the presence of excess amniotic fluid is associated with an increased risk of preterm birth, along with other maternal and fetal complications. Women with

polyhydramnios (amniotic fluid index of ≥25 cm) were more likely to deliver preterm than those without polyhydramnios in a large cohort study (19% versus 12%, p<0.001), with 85% of preterm births in the polyhydramnios group due to the spontaneous onset of labour (Many, Hill et al. 1995). The underlying cause for polyhydramnios influenced the risk of spontaneous preterm birth, and was highest amongst pregnancies with a congenital fetal anomaly (39%), followed by pregnancies complicated by diabetes (22%) (Many, Hill et al. 1995). Interestingly, the severity of polyhydramnios did not appear to significantly increase the risk of preterm birth, suggesting that uterine stretch is unlikely to be the sole causative mechanism (Many, Hill et al. 1995).

Risk is likely to be cumulative and women with multiple risk factors are likely to be at highest risk of spontaneous preterm birth (Martius, Steck et al. 1998). Whilst there have been several attempts to develop accurate risk factor based scoring systems for preterm birth prediction, the low sensitivity of these scoring systems have limited their clinical utility (Holbrook, Laros et al. 1989; Mercer, Goldenberg et al. 1996; Shiono & Klebanoff 1993). However, incorporation of clinical risk factor assessment along with other factors such as cervical length and fetal fibronectin (fFN), as discussed later, may be more successful in identifying those truly at risk of spontaneous preterm birth.

2.1.2 Symptoms of preterm labour

Most women who present with symptoms of preterm labour will not have a spontaneous preterm birth. In a United Kingdom based multi-centre study of 300 women who presented with threatened preterm labour, only 5.7% had a spontaneous preterm birth within 14 days of presentation, with 8.7% delivering <34 weeks and 12% <37 weeks (Abbott, Radford et al. 2013). The preterm birth rate was even lower in a large multi-centre American study of 796 women with threatened preterm labour; 1.3% had a spontaneous preterm birth within seven days and 2.9% within 14 days (Wing, Haeri et al. 2017). Both studies included predominantly low risk symptomatic women, although approximately 20% had a history of previous preterm birth (Abbott, Radford et al. 2013; Wing, Haeri et al. 2017).

Whilst studies have shown an association between the frequency of uterine contractions and preterm birth, the presence of contractions does not perform well as an accurate predictor of preterm birth due to a significant overlap with normal pregnancy (Goldenberg, Culhane et al. 2008; Iams, Newman et al. 2002; Nageotte, Dorchester et al. 1988). Other symptoms including

vaginal discharge, bleeding, pressure, backache and diarrhoea were also poor predictors of spontaneous preterm birth in a cohort of initially asymptomatic high risk women who were provided education and asked to report these symptoms through pregnancy (Copper, Goldenberg et al. 1990).

Despite the low positive predictive value (PPV) of symptom assessment for the prediction of preterm birth, a 'treat all' approach for everyone presenting with symptoms has generally been undertaken in the desire not to miss the small group that do go onto early birth. However, this has the negative effect of 'unnecessary' treatment for the majority, with potential for detrimental side effects, anxiety and cost.

2.1.3 Vaginal biomarkers

Vaginal biomarkers have clinical utility in both symptomatic and asymptomatic high risk women. Vaginal biomarkers are widely used in countries where risk stratification rather than a treat-all approach is employed in the management of women at high risk of spontaneous preterm birth. However, there are still unanswered questions regarding the clinical utility of vaginal biomarkers and the National Institute for Health and Care Excellence (NICE) has called for further research on the accuracy of these tests and their effect on clinical outcomes (National Institute for Health and Care Excellence 2018).

There are several vaginal biomarker tests commercially available. The three most commonly used vaginal biomarkers for the prediction of spontaneous preterm birth are fetal fibronectin (fFN), which is available as a qualitative or quantitative test; placental alpha microglobuin-1 (PAMG-1), marketed as PartoSure®; and phosphorylated insulin like growth factor binding protein-1 (pIGFBP-1), marketed as Actim® Partus.

2.1.3.1 Fetal fibronectin

fFN is a glycoprotein found in amniotic fluid and extracts of placental tissue, and can be thought of as 'trophoblast glue' that promotes cellular adhesion at uterine-placental and decidual-fetal membrane interfaces (Lockwood 2012). fFN is released through mechanical or inflammatory-mediated damage to the membranes or placenta before birth. Elevated levels of fFN in the cervicovaginal secretions of both symptomatic and asymptomatic women from 22^{+0} to 34^{+6}

weeks of gestation are associated with an increased risk of preterm labour (Abbott, Hezelgrave et al. 2015; Iams, Casal et al. 1995).

The fFN test is taken at speculum examination by lightly rotating a sterile polyester tipped swab across the posterior vaginal fornix for ten seconds to absorb cervicovaginal secretions (Hologic 2016c). The swab is then placed in a specimen transport tube and can be processed immediately in either the laboratory or as point-of-care testing in a dedicated analyser. Alternatively, it can be refrigerated at 2-8°C and assayed within three days of collection, or frozen and assayed within three months without risk of analyte degradation. The fFN test should be performed prior to any other examination or manipulation of the cervix and lubricant should be avoided, as these can interfere with the test result (Hologic 2016c). Sexual intercourse within the preceding 24 hours and presence of vaginal bleeding may cause a false positive result, however a negative result in these circumstances is valid (Hologic 2016c).

The test analyser utilises an enzyme-linked immunosorbent assay (ELISA) containing FDC-6 monoclonal antibody to detect fFN (Honest, Bachmann et al. 2002). A fFN concentration of ≥50 ng/mL has been established as the threshold to define a positive test result (Hologic 2016b; Honest, Bachmann et al. 2002). fFN was originally introduced as a qualitative test, with the result reported as positive or negative. In more recent years, a quantitative fFN test has become available with ELISA-based quantification allowing absolute fFN concentrations (0 to 500 ng/mL) to be reported and used by clinicians.

2.1.3.2 Placental alpha microglobuin-1

PAMG-1 is another vaginal biomarker that has recently become commercially available, as the PartoSure® time-to-delivery test. PAMG-1 is a protein found in very high concentrations in amniotic fluid and in very low concentrations in normal vaginal secretions and was initially used to detect rupture of membranes as the AmniSure® test (Nikolova, Bayev et al. 2014). It is thought that the inflammatory processes associated with impending labour allow trace amounts of PAMG-1 to pass through micro-perforations in the amniotic membranes (Nikolova, Bayev et al. 2014). The presence of PAMG-1 in the vaginal sections of symptomatic women with intact membranes from 20^{+0} to 36^{+6} weeks of gestation is associated with an increased risk of preterm labour (Nikolova, Bayev et al. 2014).

The PartoSure® test is taken by placing a sterile swab within the vagina for 30 seconds; the use of a speculum is described as optional (Parsagen Diagnostics 2015). The swab is then gently rotated in the solvent tube for a further 30 seconds and discarded. The PartoSure® test is performed at the bedside in a similar manner to a urinary pregnancy test. A test strip is inserted into the specimen vial and left for up to five minutes or until two lines are visualised (Parsagen Diagnostics 2015). A single line denotes a negative test and the presence of two lines, even if faint or broken, denotes a positive test result. A concentration of ≥1 ng/mL is used as the threshold for a positive result (Parsagen Diagnostics 2018).

2.1.3.3 Phosphorylated insulin like growth factor binding protein-1

pIGFBP-1 is available as the Actim® Partus test (Medix Biochemica 2017). pIGFBP-1 is synthesised by the maternal decidual cells and is released into cervical secretions following mechanical or inflammatory-mediated disruption of the fetal-decidual interface, in a similar fashion to fFN (Bruijn, Vis et al. 2016). pIGFBP-1 is predominantly used in symptomatic women and can be used from 22 weeks until delivery (Medix Biochemica 2017).

The Actim® Partus test is taken by placing a dedicated swab in the endocervix for 10-15 seconds (Medix Biochemica 2017). The swab is then rotated in the specimen collection tube for a further 10-15 seconds to extract the specimen (Medix Biochemica 2017). A test strip is inserted into the specimen tube to activate the test, and the results read after five minutes in the same manner as the PartoSure® test, with one or two lines denoting a negative or positive test respectively (Medix Biochemica 2017). Alternatively, a dedicated analyser can be used to electronically read the result. A pIGFBP-1 concentration of ≥10 μg/L is used to define a positive test result (Medix Biochemica 2017).

2.1.4 Cervical length assessment

Ultrasound assessment of cervical length is a predictor of spontaneous preterm birth in all groups where this has been studied, including women with symptoms of preterm labour, asymptomatic high risk women, and the general low risk population (Grimes-Dennis & Berghella 2007). A transvaginal approach is the gold standard for cervical length assessment, allowing best visualisation and accuracy of measurement (Larma & Iams 2012). Transabdominal cervical length scans are used as an initial screening tool in some population-based screening programmes, with a transvaginal scan performed if a short cervix is suspected. Clinical

assessments of cervical length have high inter-examiner variability and are not a good predictor for spontaneous preterm birth (Berghella, Tolosa et al. 1997; Holcomb & Smeltzer 1991).

There is a standardised technique for transvaginal cervical length assessment. Women should be asked to empty their bladder just prior to the scan, as a full maternal bladder can artificially elongate the cervix and obscure the presence of cervical funnelling (Kagan & Sonek 2015; To, Alfirevic et al. 2004). A magnified longitudinal view of the cervix should be obtained by placing the ultrasound probe in the anterior vaginal fornix, ensuring the internal and external os, and cervical canal are clearly identified. Pressure from the ultrasound probe can also artificially elongate the cervix and should be reduced to the minimum required for adequate visualisation. A straight line measurement from the internal os to the external os is the most common technique used, however when the cervix is curved, a straight line measurement may under-estimate cervical length and it can be measured in two or more segments (Kagan & Sonek 2015; Retzke, Sonek et al. 2013). In women with a pathologically short cervix, the cervical canal will be straight and this adjustment in measurement technique is unnecessary (Kagan & Sonek 2015). At least three measurements should be taken and the shortest, best quality measurement used. Given the dynamic nature of the cervix, the duration of examination should be three to five minutes to ensure that any changes in cervical length are seen, for example due to uterine contractions (Kagan & Sonek 2015). The effect of increased intra-abdominal pressure on the stability of the cervix can be assessed by applying suprapubic and/or fundal pressure. The presence of funnelling, defined as protrusion of the amniotic membranes into the cervical canal; and amniotic fluid sludge, defined as echogenic material close to the internal os, may also be noted (Kagan & Sonek 2015). Whilst these additional findings are considered important factors to some clinicians, funnelling was not found to add significantly to the predictive ability of cervical length in a study including 590 scans, where funnelling was present in 33% (Berghella, Owen et al. 2007). Figure 2.1 shows an example of a normal cervical length measurement on transvaginal scan (A) compared to a short cervical length with funnelling (B).

Cervical length normally decreases with increasing gestational age. A normal reference range for cervical length has been identified from 16 to 36 weeks of gestation, based on more than 6500 transvaginal cervical length measurements taken as part of routine antenatal care in singleton pregnancies (Salomon, Diaz-Garcia et al. 2009). The median cervical length is 43 mm at 16 weeks and 30 mm by 36 weeks (Salomon, Diaz-Garcia et al. 2009). 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 (Salomon, Diaz-Garcia et al. 2009). For simplicity, 25 mm is commonly used as the cut-off to

define a 'short' cervix. A cervical length of <25 mm accounts for only 1.6% and 4.2% of all pregnancies at 20 and 24 weeks based on these references ranges (Salomon, Diaz-Garcia et al. 2009).

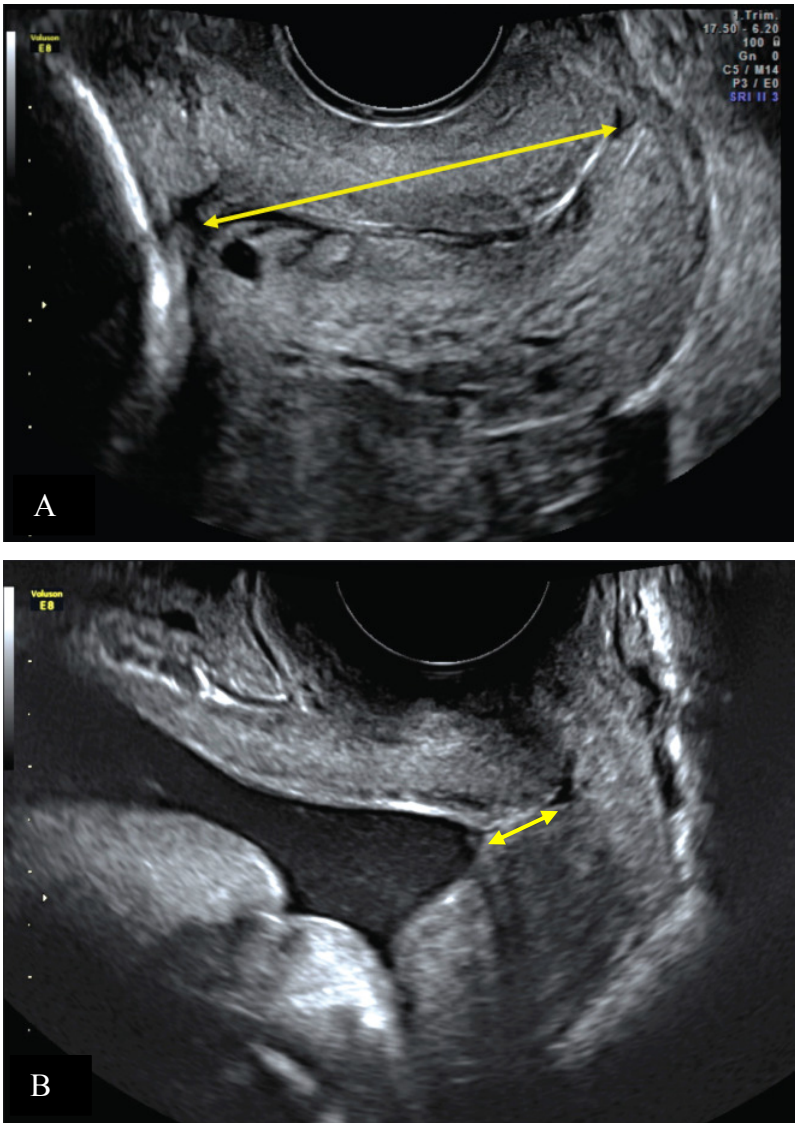

Figure 2.1 Normal cervical length on transvaginal ultrasound scan (A), compared to a short cervical length with funneling (B)

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2.1.5 Assessing efficacy of screening tests

A screening, or predictive, test is applied to a large population to identify those at higher risk of having a condition or disease. In spontaneous preterm birth, screening tests include vaginal

biomarkers and cervical length measurements. Screening tests differ from diagnostic tests in that they assess whether an individual has a higher or lower chance of developing the condition, which may warrant further investigation and/or treatment. They do not provide diagnostic certainty. Generally, screening tests are performed on an asymptomatic population, and so in the context of preterm birth, these tests are often referred to as predictive tests, as they are used in both symptomatic and asymptomatic women. Summary statistics are used to assess and compare the diagnostic accuracy of these predictive tests. The rates of correct identification of patients with and without the condition are known as the test sensitivity and test specificity respectively (Deeks, 2001). Sensitivity and specificity are relatively stable properties of a test, with similar performance across populations. The positive predictive value (PPV) is the probability that a patient with a positive test result truly has the condition, and is heavily influenced by the prevalence of the condition in the population being assessed. The negative predictive value (NPV) is the probability that those with a negative test result do not have the condition and is also influenced by the prevalence of the condition. The test PPV and NPV are less stable parameters and values for the same test can vary widely depending on the prevalence of the condition in the population being assessed. This distinction is particularly important when comparing predictive tests for preterm labour, as the clinical endpoint of spontaneous preterm birth is relatively rare and so comparisons of PPV and NPV alone can be misleading. This is further discussed in section 5.2.5. Receiver operating characteristic (ROC) curves depict the pattern of sensitivities and specificities observed at several different diagnostic thresholds and are therefore useful in the assessment of predictive tests for preterm birth and are used within this thesis.

2.2 Symptomatic women with threatened preterm labour

The onset of symptoms of preterm labour is a common reason for presentation to hospital in pregnancy, yet the majority of women will not deliver early. Most women who present with threatened preterm labour do not have other risk factors for spontaneous preterm birth (Abbott, Radford et al. 2013; Wing, Haeri et al. 2017). The accurate identification of which symptomatic women are likely to deliver early is important so that interventions that improve perinatal outcomes can be given to those most likely to benefit, whilst reducing unnecessary interventions for the majority who do not need it. Tools used to improve the prediction of spontaneous preterm birth were introduced in section 2.1. I will now review the evidence for their use in symptomatic women, along with the evidence for interventions aimed at optimising outcomes when there is a high risk of preterm birth.

2.2.1 Prediction of spontaneous preterm birth in symptomatic women

2.2.1.1 Symptoms and risk factor assessment

The frequency and nature of symptoms of preterm labour (described in section 2.1.2), are of limited clinical value for determining which symptomatic women are at high risk of imminent delivery. A risk factor assessment for preterm birth has some merit, but even in the presence of pre-existing risk factors, most symptomatic women will not deliver preterm. Furthermore, around half of spontaneous preterm births are to women with no identifiable risk factors, so the absence of risk factors does not rule out the risk of progression to established preterm labour. Thus a clinical assessment based on symptoms and risk factors alone is usually insufficient to make decisions for clinical care when a risk stratification rather than treat-all approach to management is utilised. Additional tools such as vaginal biomarkers and cervical length have been shown to be more accurate in the prediction of spontaneous preterm birth than clinical judgement alone.

2.2.1.2 Vaginal biomarkers

The vaginal biomarkers fFN, PAMG-1 and pIGFBP-1 were introduced in section 2.1.3. In this section I will summarise the evidence for their use in symptomatic women.

2.2.1.2.1 Fetal fibronectin

Both qualitative and quantitative fFN have been validated for use in women with threatened preterm labour. One of the first multi-centre studies of fFN assessed the use of the qualitative test in 763 women with symptoms of preterm labour at 24^{+0} to 34^{+6} weeks of gestation (Peaceman, Andrews et al. 1997). There was a positive test (>50 ng/mL) in 20% of cases and these women were significantly more likely to have a preterm birth within seven days (RR 25.9, 95% CI 7.8-86) and 14 days (RR 20.4, 95% CI 8.0-53), compared to women with a negative result (Peaceman, Andrews et al. 1997). The NPV for preterm birth within 7 and 14 days and at <37 weeks were 99.5%, 99.2% and 84.5% respectively (Peaceman, Andrews et al. 1997). This high NPV provides the main clinical utility of fFN, allowing safe discharge from hospital for women with a negative result. The PPV for preterm birth within 7 and 14 days were 13.4% and 16.2% and test sensitivities were 90.5% and 88.5% respectively (Peaceman, Andrews et al. 1997). Subsequent systematic review included 40 studies assessing qualitative fFN in symptomatic women and confirmed the predictive ability of the test, with highest accuracy of prediction at 7 to 10 days from presentation (Honest, Bachmann et al. 2002).

Increasing concentrations of fFN within cervicovaginal secretions correlate positively with the risk of spontaneous preterm birth in women with threatened preterm labour (Abbott, Radford et al. 2013). Absolute fFN concentrations are reported in the quantitative fFN test and this knowledge may improve the clinical application of this vaginal biomarker. In a study of quantitative fFN in 300 women with threatened preterm labour, PPVs for spontaneous preterm birth within 14 days improved from 10.9% to 19.7%, 37.0% and 46.2% with increasing fFN thresholds of 10, 50, 200 and 500 ng/mL respectively (Abbott, Radford et al. 2013). Whilst women with 'intermediate' fFN concentrations of 50-199 ng/mL had an overall increased risk of spontaneous preterm birth at ≤34 weeks, the risk of delivery within seven days was low, and in fact does not appear to be any higher than for women with a negative fFN result of <50 ng/mL, as shown in Table 2.1 (Abbott, Radford et al. 2013). These results suggest that immediate hospital admission and administration of antenatal corticosteroids may be of little benefit to this group of symptomatic women. Thus, using absolute fFN concentrations instead of a dichotomous positive/negative result may allow clinicians to safely reduce interventions for those with lower concentrations of fFN and more appropriately target and individualise care for those at higher risk.

Table 2.1 Quantitative fetal fibronectin and risk of delivery ≤7 days, ≤14 days and ≤34 weeks

fFN level (ng/mL)	**N (%)**	**Spontaneous preterm birth rate**		
		≤7 days [a]	**≤14 days [a]**	**≤34 weeks [a]**
<10	170 (57%)	1%	2%	2%
10-49	62 (21%)	0%	2%	8%
50-199	41 (14%)	0%	8%	12%
200-499	14 (5%)	14%	29%	33%
≥500	13 (4%)	38%	46%	75%

[a] Proportion of deliveries ≤7 days, ≤14 days from testing and at ≤34 weeks gestation/total number of women within each fFN level range.

Adapted from Abbott D, Radford S et al. 2013. Evaluation of a quantitative fFN test for spontaneous preterm birth in symptomatic women. American Journal of Obstetrics and Gynecology.

2.2.1.2.2 Placental alpha microglobulin-1

PAMG-1 has also been assessed in women with threatened preterm labour. In a small study of 101 symptomatic women, PAMG-1 had a NPV of 97.4% and PPV of 78.3% for birth within seven days (Nikolova, Bayev et al. 2014). This suggested PAMG-1 may have a similar NPV to fFN, with an improved PPV. Another study assessed the clinical utility of PAMG-1 compared to standard clinical assessment in 148 women with threatened preterm labour (Lotfi, Faraz et al. 2017). PAMG-1 had a NPV of 97.9% and PPV of 75.0% for spontaneous preterm birth within seven days and better specificity than standard clinical assessment (98% versus 41%, $p<0.0001$) (Lotfi, Faraz et al. 2017). However, the test sensitivities for PAMG-1 were only 66.7% and 53.8% for spontaneous preterm birth within 7 and 14 days respectively (Lotfi, Faraz et al. 2017). This low sensitivity of PAMG-1 has been seen in other studies and is concerning due to potential missed opportunity for interventions that improve neonatal outcomes for infants born preterm.

The predictive abilities of PAMG-1 and qualitative fFN were compared in a large American multi-centre prospective observational study of 711 women with symptoms of preterm labour (Wing, Haeri et al. 2017). The spontaneous preterm birth rate was low in this study, with just 1.3% delivering within seven days and 2.9% within 14 days (Wing, Haeri et al. 2017). PAMG-1 was less likely to be detected than fFN (2.4% compared to 15.5% of cases) (Wing, Haeri et al. 2017). The PPV for spontaneous preterm birth within seven days in singleton pregnancies was higher for PAMG-1 at 23.1%, compared to 4.3% for fFN, with similar NPVs of 99.5% and

99.6% respectively (Wing, Haeri et al. 2017). The authors of this study concluded that PAMG-1 was equivalent to fFN in ruling out spontaneous preterm birth, but demonstrated statistical superiority in predicting it. However a low test sensitivity was again seen for PAMG-1 (50%), with a false negative result in 66.7% (6/9) who had a spontaneous preterm birth within seven days (Wing, Haeri et al. 2017). This combined with concerns about the non-inferiority study design utilised, and the very low spontaneous preterm birth rate for the cohort have led to opinion that current evidence does not support the use of PAMG-1 in clinical practice (Grobman 2017; Kuhrt, Watson et al. 2018).

A recent meta-analysis has compared the predictive abilities of PAMG-1, fFN and pIGFBP-1 and reported a superior statistical performance for PAMG-1 compared to qualitative fFN and pIGFBP-1 for the prediction of spontaneous birth within seven days in symptomatic women (Melchor, Khalil et al. 2018). However more than half of the included participants were from the Wing, Haeri et al. study, and results should be interpreted with caution.

2.2.1.3 Phosphorylated insulin like growth factor binding protein-1

pIGFBP-1 showed initial promise as a predictive test for spontaneous preterm birth in symptomatic women in small studies (Altinkaya, Gungor et al. 2009; Lembet, Eroglu et al. 2002; Paternoster, Muresan et al. 2007). However, subsequent systematic review and meta-analysis of 34 studies has shown the overall predictive ability of this test to be limited, with a pooled sensitivity and specificity for delivery within 14 days of 66% (95% CI 57-74%) and 79% (95% CI 76-81%) respectively (Conde-Agudelo & Romero 2015).

2.2.1.4 Cervical length assessment

Transvaginal cervical length assessment can also be used to predict spontaneous preterm birth in women presenting with threatened preterm labour. In systematic review and meta-analysis, the use of a transvaginal cervical length cut-off of <25 mm gave a pooled sensitivity of 78.3% (95% CI 67.9-86.6%) for the prediction of preterm birth within seven days, with a specificity of 79.6% (95% CI 77.1-81.9%) (Sotiriadis, Papatheodorou et al. 2010). Using a shorter cervical length cut-off of <15 mm improved the specificity of the test to 90.5% (95% CI 89.0-91.9%), but at the expense of sensitivity (59.9%, 95% CI 52.7-66.8%) (Sotiriadis, Papatheodorou et al. 2010). The NPVs for delivery within seven days did not change significantly with different cervical length cut-offs at 94.8%, 96.3% and 95.8% with cervical length cut-offs of 15 mm, 20

mm and 25 mm respectively (Sotiriadis, Papatheodorou et al. 2010). This illustrates the limitation of using the NPV alone to judge the predictive ability of a test. The NPV is strongly driven by the prevalence of the condition tested, and given most women presenting with threatened preterm labour do not deliver imminently, NPVs tend to be high even with a poor test.

Obtaining a cervical length measurement requires the expertise of a trained practitioner (usually a sonographer, radiologist or obstetrician) as well as access to an ultrasound machine with a vaginal probe. This expertise and resource is not always available at the time of initial assessment, even in tertiary hospitals. Cervical length measurements are currently not routinely used in the assessment of women with symptoms of preterm labour in New Zealand, in part due to resource constraints. Vaginal biomarkers are usually used in preference.

2.2.1.5 Combining predictive tests

There is no 'perfect' prediction test to detect which women with threatened preterm labour will have a spontaneous preterm birth. It is likely that tests have better predictive value when used together and studies have assessed the use of a combination of clinical history, vaginal biomarker and cervical length results.

A systematic review assessed nine studies using a combination of fFN and cervical length to predict spontaneous preterm birth in symptomatic women (DeFranco, Lewis et al. 2013). Using a one-step approach of qualitative fFN and cervical length (with individual studies using various cut-offs of <15 mm up to ≤26 mm), the sensitivity and specificity for the prediction for preterm birth within seven days was 71.4% (95% CI 35.9-91.8%) and 96.8% (95% CI 93.1-98.5%), with a PPV and NPV of 45.4% (95% CI 21.3-72.0%) and 98.9% (95% CI 96.1-99.7%) respectively (DeFranco, Lewis et al. 2013). Whilst this combined approach has a lower sensitivity for the prediction of spontaneous preterm birth than the use of either fFN or cervical length alone, the test specificity and PPV improve, which may reduce the rate of interventions (DeFranco, Lewis et al. 2013). However, care should be taken with tests that have a lower sensitivity to ensure that a risk stratification approach does not compromise the care of women and their babies by missing opportunities for intervention in the event of a false negative result.

The QUiPP (Quantitative Instrument for the Prediction of Preterm Birth) App is a clinical decision making tool used to predict spontaneous preterm birth and has been validated in both

symptomatic and asymptomatic high risk women (Kuhrt, Hezelgrave et al. 2016; Kuhrt, Smout et al. 2016; Watson, Carter, Seed et al. 2017). When used in symptomatic women, the QUiPP App incorporates the presence of contractions; risk factors including multiple pregnancy, previous cervical surgery, and previous preterm birth or PPROM <37 weeks; cervical length; and quantitative fFN result (King's College London 2017). The QUiPP algorithm was shown to be an accurate predictor of preterm birth in an evaluation study of 355 women with threatened preterm labour who were retrospectively assigned a QUiPP score (Watson, Carter, Seed et al. 2017). Using a QUiPP result of a ≥5% risk of delivery within seven days as the threshold for intervention gave a test sensitivity of 100% (95% CI 54.1-100%), NPV of 100% (95% CI 97.8-100) and PPV of 17% (95% CI 12.6-21.7%) (Watson, Carter, Seed et al. 2017). Use of QUiPP with this threshold for intervention could avoid 81% of hospital admissions for threatened preterm labour (due to a negative screen result), compared to use of a treat-all approach, with no deliveries within seven days in the women who would have been discharged (Watson, Carter, Seed et al. 2017). A study assessing the accuracy of the QUiPP App as a decision-making tool for *in utero* transfer has recently finished recruitment and results are awaited (Shennan, Carlisle et al. 2018).

2.2.1.6 Clinical practice change

The performance of preterm birth prediction tests are irrelevant if clinicians do not adjust their practice according to the result (Grobman 2017). Observational studies of practice after the introduction of routine fFN testing suggest that clinicians do alter the care they provide according to a fFN result (Dutta & Norman 2010; Foster & Shennan 2014; Giles, Bisits et al. 2000), but that change in practice develops over time suggesting experience and confidence in the test contribute to practice change (Groom, Liu et al. 2006). However, a systematic review of six randomised trials assessing the use of fFN in symptomatic women (revealed fFN result versus concealed result or no fFN test) demonstrated no difference in the antenatal management received, nor in preterm birth rates and perinatal outcomes, with slightly higher hospitalisation costs associated with fFN use (Berghella & Saccone 2016). Publication of this systematic review included editorial comment that the ongoing use of fFN testing in women with threatened preterm labour could not be justified (Macones 2016). However in three of the six trials treatment was left to 'physician's discretion' regardless of whether the fFN result was revealed or, when it was, if the result was positive or negative. The true value of fFN and other preterm birth prediction tests can only be examined if clinicians are aware of the result and alter their practice accordingly.

Clinical practice guidelines and implementation strategies are useful tools to support clinical practice change and provision of evidence-based care. The effectiveness of clinical guideline implementation strategies have been assessed in systematic review, with multi-faceted interventions, use of audit and feedback, interactive education and clinical reminder systems shown to be most beneficial (Chaillet, Dubé et al. 2006; Prior, Guerin et al. 2008). Local opinion leaders can also influence clinician behaviour when introducing new clinical practice guidelines (Chaillet, Dubé et al. 2006).

2.2.2 Preparation for spontaneous preterm birth in symptomatic women

If women remain at high risk of spontaneous preterm birth based on the results of predictive tests, then perinatal interventions shown to improve perinatal outcomes for babies born preterm should be considered. These interventions include antenatal corticosteroids, antenatal magnesium sulphate, and ensuring delivery occurs in a hospital with the appropriate level neonatal unit. The selective use of antibiotics and tocolysis to achieve a short term delay in delivery for these interventions to take effect should also be considered. Antenatal counselling of women and their families is essential, particularly if birth is expected at peri-viable gestations, and parental wishes should be taken into account when planning management. Plans for intrapartum care should include cord clamping management.

2.2.2.1 Antenatal corticosteroids

Antenatal corticosteroids have revolutionised neonatal care. The landmark trial by Liggins and Howie in 1972 demonstrated a significant reduction in respiratory distress syndrome (RDS) and neonatal mortality associated with the administration of antenatal corticosteroids (Liggins & Howie 1972). Since then, numerous studies have confirmed these initial findings, yet it took several decades for some countries to adopt the routine use of antenatal corticosteroids when preterm birth was anticipated (Bonanno & Wapner 2009). The National Institute of Health consensus statement on antenatal corticosteroids was released in 1994 and was followed by improved clinical uptake of this intervention (National Institute of Child Health and Development 1994). Antenatal corticosteroids are now widely used in clinical practice and are recommended by the World Health Organisation (World Health Organisation 2015b). Systematic review and meta-analyses have shown that administration of antenatal corticosteroids reduces the most serious adverse neonatal outcomes related to prematurity, including neonatal death (RR 0.69, 95% CI 0.58-0.89), moderate-to-severe RDS (RR 0.59, 95%

CI 0.38-0.91), intraventricular haemorrhage (IVH) (RR 0.55, 95% CI 0.40-0.76) and necrotising enterocolitis (RR 0.50, 95% CI 0.32-0.78) (Roberts, Brown et al. 2017).

The current New Zealand and Australia guideline recommends administration of a single course of antenatal corticosteroids in women at risk of preterm birth with gestational age is $\leq 34^{+6}$ weeks and delivery is expected within the next seven days, even if likely within 24 hours and irrespective of the cause (Antenatal Corticosteroid Clinical Practice Guidelines Panel 2015). Antenatal corticosteroids are administered as an intramuscular injection with two formulations available; betamethasone 24 mg in divided doses 12 to 36 hours apart, or dexamethasone 24 mg in divided doses 24 to 40 hours apart (Antenatal Corticosteroid Clinical Practice Guidelines Panel 2015). Predictive tests such as fFN and assessment of cervical length are recommended to improve the accuracy of timing of corticosteroid administration (Antenatal Corticosteroid Clinical Practice Guidelines Panel 2015).

There is some debate about the use of repeat doses of antenatal corticosteroids, with varying practice internationally. A Cochrane review of ten studies has shown that weekly repeat doses of corticosteroids given to women who remain at risk of preterm birth seven days after the initial course, reduced the risk of RDS (RR 0.83, 95% CI 0.75-0.91) and serious neonatal morbidity (RR 0.84, 95% CI 0.75-0.94), with no evidence of significant harm (or benefit) seen at two to three year and six to eight year follow up (Crowther, Anderson et al. 2016; McKinlay, Crowther et al. 2012). The authors concluded that repeat doses of antenatal corticosteroids should be considered in view of the neonatal benefits (McKinlay, Crowther et al. 2012). In New Zealand and Australia, repeat doses are recommended if women remain at high risk of preterm birth seven days after their initial course; up to three single repeat weekly doses are recommended up to $\leq 32^{+6}$ weeks of gestation (Antenatal Corticosteroid Clinical Practice Guidelines Panel 2015).

2.2.2.2 Antenatal magnesium sulphate

The antenatal administration of magnesium sulphate is another intervention proven to improve perinatal outcomes for babies born preterm. Giving magnesium sulphate to women at risk of preterm birth substantially reduces the risk of cerebral palsy in their child (RR 0.68, 95% CI 0.54-0.87), in addition to reducing rates of gross motor dysfunction (RR 0.61, 95% CI 0.44-0.85) (Doyle, Crowther et al. 2009). The majority of included trials recruited women at <34 weeks of gestation (Doyle, Crowther et al. 2009). The use of magnesium sulphate for neuroprotection is recommend by the World Health Organisation when there is risk of imminent

birth at $<32^{+0}$ weeks of gestation (World Health Organisation 2015b). National recommendations from Australia have been adopted for use in New Zealand and advise magnesium sulphate administration in women at imminent risk of preterm birth at $<30^{+0}$ weeks of gestation (The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel 2010). Magnesium sulphate should be commenced when birth is planned or definitely expected within 24 hours, with optimal timing as close as possible to four hours before delivery (The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel 2010). The recommended dose is 4 grams intravenously over 20 to 30 minutes as a loading dose followed by a 1 gram per hour maintenance dose until birth or for 24 hours (The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel 2010).

2.2.2.3 Antibiotics

The use of broad spectrum antibiotics following PPROM has been shown to prolong pregnancy and improve short term outcomes for neonates, with lower rates of infection and need for respiratory support and fewer abnormal cerebral ultrasounds in the ORACLE I randomised trial (Kenyon, Boulvain et al. 2013; Kenyon, Taylor et al. 2001). However, these short term improvements do not necessarily translate to long term benefits, with no differences in outcomes in school-age children (Kenyon, Boulvain et al. 2013; Kenyon, Pike et al. 2008a). Despite the lack of evidence for longer term benefit, the improvements in short term outcomes are significant and the routine use of antibiotics for PPROM is widely recommended (Kenyon, Boulvain et al. 2013; Royal College of Obstetricians and Gynaecologists 2010; World Health Organisation 2015a). A ten day course of erythromycin was used in the ORACLE I trial and is the antibiotic regime of choice in many units; co-amoxiclav should be avoided due to an increased risk of necrotising enterocolitis (Kenyon, Boulvain et al. 2013).

In contrast, the routine use of antibiotics to prolong pregnancy and improve neonatal outcomes for women with threatened preterm labour with intact membranes is not recommended, unless there is clinical suspicion for infection. A Cochrane review, which included findings from the ORACLE II randomised trial, identified no improvements in important neonatal outcomes when prophylactic antibiotics were routinely given to prevent preterm labour in women with intact membranes (Flenady, Hawley et al. 2013). Although there was a reduction in rates of maternal infection, long term childhood outcomes identified increased rates of cerebral palsy in the children whose mothers received antibiotics (RR 1.82, 95% CI 0.99-3.34) (Flenady, Hawley et al. 2013; Kenyon, Pike et al. 2008b).

However, intrapartum antibiotics are recommended for women with risk factors for neonatal group B streptococcus (GBS) infection. These risk factors include preterm labour, as although the risk of GBS colonisation may not be different at the time of term or preterm birth, preterm babies are more susceptible to GBS infection and their risk of death consequently is higher. Without prophylactic antibiotics, the incidence of early-onset neonatal GBS infection is between 0.4 to 4 per 1000 for all live births (The Royal Australian and New Zealand College of Obstetricians and Gynaecologists 2019). The overall mortality of neonatal GBS sepsis is 7.5%, and is significantly higher for preterm infants at 19% compared to just 1.7% for those born at term (Håkansson & Källén 2006). Intravenous penicillin is the antibiotic of choice and should be commenced only once in established labour; the optimal timing of administration is at least four hours prior to delivery (The Royal Australian and New Zealand College of Obstetricians and Gynaecologists 2019). The administration of antibiotics prior to the onset of labour has been shown to be ineffective in preventing neonatal GBS infection (The Royal Australian and New Zealand College of Obstetricians and Gynaecologists 2019).

2.2.2.4 *In utero* transfer

Babies that are born in a hospital with the appropriate level neonatal services (inborn babies) do better than babies that are born elsewhere and transferred to an appropriate unit after birth (outborn babies) (Chien, Whyte et al. 2001; Helenius, Longford et al. 2019). *In utero* transfer should therefore be arranged whenever possible. A recent study assessed approximately 2100 matched babies from a cohort of more than 17,000 who were born at <28 weeks of gestation in England from 2008-2015 (Helenius, Longford et al. 2019). Outborn babies who were transferred to a tertiary unit after birth had worse outcomes than matched inborn babies (controls), with significantly increased odds of severe brain injury (OR 2.32, 95% CI 1.78-3.06, number needed to treat, NNT 8) and significantly lower odds of survival without severe brain injury (OR 0.60, 95% CI 0.47-0.76, NNT 9) (Helenius, Longford et al. 2019). However, babies born at <28 weeks in non-tertiary units who were not transferred had even worse outcomes than matched controls, with significantly higher odds of death (OR 1.34, 95% CI 1.02-1.77, NNT 20) (Helenius, Longford et al. 2019), providing evidence to support postnatal transfer if *in utero* transfer cannot be achieved. The differences in outcomes for inborn and outborn babies are likely due to variation in hospital care rather than the transfer itself, with no significant differences in outcomes for babies that required 'horizontal' transfer from one tertiary unit to another when compared to controls (Helenius, Longford et al. 2019).

2.2.2.5 Tocolysis

Tocolysis, the use of medications to inhibit myometrial contractions, was the original focus of management when women presented with preterm labour due to the assumption that halting contractions would stop the labour process (Simhan & Caritis 2007). Commonly used tocolytic agents include calcium channel blockers, prostaglandin inhibitors, betamimetics and oxytocin receptor blockers. Although effective at stopping clinically apparent contractions, systematic review and meta-analysis has shown that the use of tocolysis is not associated with a significant reduction in preterm birth at <30 weeks (OR 1.33, 95% CI 0.53-3.33), <32 weeks (OR 0.81, 95% CI 0.61-1.07) or <37 weeks (OR 0.17, 95% CI 0.02-1.62) (Gyetvai, Hannah et al. 1999). Furthermore, tocolysis did not improve perinatal outcomes, with no significant reduction in perinatal death (OR 1.22, 95% CI 0.84-1.78) nor improvement in neonatal outcomes; RDS (OR 0.82, 95% CI 0.64-1.07), IVH (OR 0.73, 95% CI 0.46-1.15) or necrotising enterocolitis (OR 0.96, 95% CI 0.35-2.65) (Gyetvai, Hannah et al. 1999).

Despite the inability to prevent preterm birth, tocolysis can provide a short term delay in delivery. For example, the use of calcium channel blockers significantly reduces the risk of delivery within 48 hours (RR 0.30, 95% CI 0.21-0.43) when compared to placebo (Flenady, Wojcieszek et al. 2014). This short term delay allows perinatal interventions such as antenatal corticosteroids and magnesium sulphate to be given, and to facilitate *in utero* transfer if required. More recent systematic review and network meta-analysis has suggested that the use of prostaglandin inhibitors and calcium channel blockers may be associated with some improvement in neonatal outcomes, possibly because of time gained for antenatal interventions, however this is still unsubstantiated (Haas, Caldwell et al. 2012). Whilst many countries, including New Zealand, commonly use tocolysis, the World Health Organisation has judged the quality of evidence to be low and insufficient to recommend its use for the purpose of improving neonatal outcomes (World Health Organisation 2015b).

2.2.2.6 Delayed cord clamping

Delayed clamping of the umbilical cord for at least 60 seconds following birth has benefits for term babies, and potential risks and benefits for preterm babies (Fogarty, Osborn et al. 2018; Hutton & Hassan 2007). Whilst the use of delayed cord clamping for babies born preterm has been widely recommended in international guidelines (National Institute for Health and Care Excellence 2015; The American College of Obstetricians and Gynecologists 2017; The

Australian and New Zealand Commitee on Resuscitation 2017; World Health Organisation 2014), an overall benefit for babies at all gestational ages has only recently been confirmed in a large randomised controlled trial and subsequent meta-analysis (Fogarty, Osborn et al. 2018; Tarnow-Mordi, Morris et al. 2017).

Delayed cord clamping reduces hospital mortality by more than 30% (RR 0.68, 95% CI 0.52-0.90) and also reduces the need for neonatal blood transfusion (RR 0.81, 95% CI 0.74-0.87) (Fogarty, Osborn et al. 2018). Improved survival is likely due to a combination of factors, including an increase in the blood volume transferred from the placenta to the neonate, and allowing time for physiological transition (Fogarty, Osborn et al. 2018). Although delayed cord clamping increases the incidence of polycythemia and elevated bilirubin levels for the neonate, no significant differences in the need for exchange transfusion have been seen (RR 0.29, 95% CI 0.05-1.73) (Fogarty, Osborn et al. 2018). Delayed cord clamping also appears to be safe for the mother, with no increased risk of postpartum haemorrhage or need for maternal blood transfusion (Fogarty, Osborn et al. 2018).

2.2.2.7 Early neonatal care

The first 60 minutes of neonatal life is often referred to as the ‘golden hour’. Care during this time can have a significant impact on outcomes for preterm babies and usually includes initial resuscitation and stabilisation and admission to the neonatal intensive care unit (Reynolds, Pilcher et al. 2009; Sharma 2017). Attention has been drawn to this critical time to ensure the provision of evidence-based interventions aimed at reducing the complications of prematurity and improving long term outcomes (Reynolds, Pilcher et al. 2009; Sharma 2017). Key features include delayed cord clamping, prevention of hypothermia and infection, respiratory and cardiovascular support and early nutritional care (Sharma 2017). Good communication within the clinical team and with the family, and clear documentation are essential (Sharma 2017).

2.2.2.8 Special considerations when preterm birth is expected at peri-viable gestational ages

A small proportion of babies are born at the limits of viability each year. In recent years, advances in both obstetric and neonatal care have contributed to significant improvements in survival and long term health outcomes for infants born at peri-viable gestations, leading to a more pro-active approach to perinatal care and resuscitation. Babies born at peri-viable gestations have high rates of mortality and morbidity, and are the most likely to benefit from

interventions to optimise outcomes when preterm birth cannot be prevented. Although antenatal counselling of women and families is an essential part of antenatal care at all preterm gestations, this is especially true around peri-viability as there are some special considerations for care, including the option for comfort care rather than active resuscitation.

The accuracy of global estimates for preterm birth rates at peri-viable gestational ages are limited by the wide range of definitions for peri-viability (as discussed in Section 1.2.1). The incidence of peri-viable birth ranged from 0.03% to 1.9% in a review of 22 studies (Chauhan & Ananth 2013). In New Zealand, extremely preterm birth at <28 weeks accounted for 19.4% of all preterm births and 1.2% of births at all gestations in 2016 (Ministry of Health 2018). National data specifically for the rate of births at 23 and 24 weeks are not readily available. At a large tertiary maternity unit in Auckland, New Zealand, just 0.3% of births occurred at 23 or 24 weeks in 2017 (Auckland District Health Board 2018a).

2.2.2.8.1 Outcomes for birth at peri-viable gestations

Survival rates for infants born at peri-viable gestations vary depending on local practices on whether resuscitation is offered (Rysavy, Li et al. 2015). Accurate knowledge of expected outcomes is an important part of antenatal counselling, and local data should be used wherever possible. Rates of survival to hospital discharge range from 5-7% for births at <23 weeks, 23-27% at 23 weeks, 42-59% at 24 weeks and 67-76% at 25 weeks gestation in data from America, England and Australia over the last 15 years (Ecker, Kaimal et al. 2016). Rates of moderate or severe disability in survivors are approximately 25-50% for babies born at 23 weeks, 20-45% at 24 weeks and 20-40% at 25 weeks (Ecker, Kaimal et al. 2016).

A recent report from the New Zealand Perinatal and Maternal Mortality Review Committee has highlighted ethnic disparities in survival of non-anomalous babies born at 23 to 26 weeks (Perinatal and Maternal Mortality Review Committee 2018). Babies of Māori, Pacific and Indian mothers are more likely to be born at extremely preterm gestations, but are less likely to receive an attempt at resuscitation, and less likely to survive to 28 days (Perinatal and Maternal Mortality Review Committee 2018). These disparities warrant further investigation.

2.2.2.8.2 Antenatal counselling and decision making at peri-viable gestations

When delivery is anticipated at peri-viable gestations, complex decisions need to be made by families and health care professionals (Ecker, Kaimal et al. 2016). This includes whether active intervention and neonatal resuscitation should be performed or whether a more conservative approach with comfort care/palliation should be provided. Several executive summaries and consensus statements have been published to guide clinicians on antenatal family counselling and perinatal management of women anticipated to deliver at peri-viable gestations (British Association of Perinatal Medicine 2019; Ecker, Kaimal et al. 2016; Newborn Clinical Network 2019; Raju, Mercer et al. 2014; Royal College of Obstetricians and Gynaecologists 2014). These management principles are generally consistent with our local approach, although neonatal resuscitation is offered from 23^{+0} weeks in New Zealand, not from 22^{+0} weeks as is now considered in the United Kingdom.

When birth is expected at $<25^{+0}$ weeks of gestation, an individualised management plan should be made to ensure a multidisciplinary and family-centred approach to the care offered. Cases should be discussed with a specialist obstetrician and neonatologist and factors likely to influence neonatal outcome should be reviewed, including assessment of fetal growth, markers of fetal wellbeing (Doppler waveforms and amniotic fluid volume), evidence of ruptured membranes, presence of chorioamnionitis, abnormal fetal heart rate recordings, presence of suspected fetal anomaly, fetal sex (where known), multiple gestation, and whether antenatal corticosteroids and magnesium sulphate have been administered or sufficient time is likely to be available to give them (British Association of Perinatal Medicine 2019; Newborn Clinical Network 2019). Opinion from a maternal fetal medicine specialist should also be obtained where possible. After careful assessment of these factors, active intervention should be offered to parents as an option, but support also given for a more conservative approach for care.

Planned mode of delivery and intrapartum fetal monitoring should also be discussed antenatally. It is likely that a caesarean section performed at a peri-viable gestational age will need to be via a classical or high transverse incision. This has increased risks for maternal health and implications for future pregnancy, yet uncertain fetal benefits in some cases, for example, when performed for abnormal cardiotocograph (Auckland District Health Board 2018b; Ecker, Kaimal et al. 2016). However in cases with breech presentation at <28 weeks, caesarean section is associated with improved intact survival in observational studies (Grabovac, Karim et al. 2018). Thus, a discussion of the risks and benefits for vaginal birth versus caesarean is required,

and it should be acknowledged that a decision for active intervention and resuscitation does not commit parents nor clinicians to perform a caesarean section for fetal indications at these extremely preterm gestations (Newborn Clinical Network 2019). If a decision has been made to not perform a caesarean section for fetal indications, then continuous cardiotocograph monitoring in labour is not recommended. Intermittent auscultation of fetal heart rate should still be performed as this may aid the neonatal team's care after birth.

2.2.2.8.3 Antenatal interventions to improve perinatal outcomes at peri-viable gestations

If active intervention is planned, antenatal corticosteroids, antenatal magnesium sulphate, antibiotics and tocolysis should be administered as per usual practice (Deshmukh & Patole 2017; Ecker, Kaimal et al. 2016; Newborn Clinical Network 2019). Whilst the evidence for giving these interventions prior to 25 weeks is generally less robust than for later preterm gestations, this group of babies have high rates of mortality and morbidity and are therefore the most likely to benefit.

2.3 Asymptomatic women at high risk of spontaneous preterm birth

The accurate identification of women at high risk of spontaneous preterm birth prior to the onset of labour allows clinicians to consider the use of interventions to prevent preterm birth. In this section I will review the evidence for the prediction tools used to identify and risk stratify asymptomatic women at increased risk of spontaneous preterm birth, as well as the treatment options available. I will also discuss the role of specialised preterm birth clinics and the potential psychological impact of being labelled high risk.

2.3.1 Prediction of spontaneous preterm birth prior to the onset of symptoms

2.3.1.1 Risk factor assessment

Common risk factors for spontaneous preterm birth are described in section 2.1.1. Even in the presence of risk factors strongly associated with spontaneous preterm birth, most women will still deliver at term (McManemy, Cooke et al. 2007). For the majority of women, the identification of risk factors should trigger the use of more specific predictive tests, such as cervical length measurement, which in turn can guide the more targeted use of treatments to prevent preterm birth. However, for some women, the presence of risk factors alone will be sufficient to justify the use of elective interventions to reduce the risk of spontaneous preterm birth, for example history-indicated cerclage for women with multiple previous second trimester miscarriages or spontaneous preterm births. The evidence for a history-indicated approach to intervention is discussed in section 2.3.2.

The term ‘cervical incompetence’ (also known as cervical insufficiency) is commonly used in the preterm birth literature, yet there is controversy about its meaning and clinical usefulness. Cervical incompetence was traditionally defined as recurrent second trimester pregnancy loss caused by an inability of the cervix to retain a pregnancy, and was typically characterised by painless cervical dilatation in the absence of contractions or significant bleeding, followed by a rapid delivery (Althuisius, Dekker et al. 2002). For many women, there is a preceding history of trauma to the cervix, for example cervical surgery, or associated congenital uterine anomalies (Althuisius, Dekker et al. 2002). However, there is increasing awareness that cervical incompetence is a continuous variable rather than an exact diagnosis, and the cervix can be more or less ‘competent’ in different scenarios. In the majority of cases, cervical incompetence probably contributes to the wider, multifactorial preterm birth syndrome rather than being the

sole cause. So whilst a history of the characteristic symptoms of cervical incompetence should be taken into account, this alone does not justify the need for elective cerclage in subsequent pregnancies, as most women will not need it and ultrasound surveillance of cervical length is a safe alternative (Althuisius, Dekker et al. 2002).

2.3.1.2 Cervical length assessment

The goal of cervical length assessment in asymptomatic women is to identify those with a short cervix in the mid-trimester, prior to the onset of symptoms, so that preventative interventions can be considered. There are two main approaches to its use. Firstly, cervical length can be used to assess the need for preventative treatments in women already identified as at increased risk of spontaneous preterm birth based on risk factor assessment. More recently cervical length assessment has also been used as a population-wide screening tool for spontaneous preterm birth at the time of the fetal morphology scan.

2.3.1.2.1 Use in high risk women

Measurement of cervical length can be used to predict spontaneous preterm birth in asymptomatic women who have a history of prior spontaneous preterm birth, excisional cervical surgery, multiple uterine instrumentations, or congenital uterine anomaly (Crane & Hutchens 2008; Grimes-Dennis & Berghella 2007). A systematic review of 14 cohort studies assessed the predictive ability of mid-pregnancy cervical length measurements in high risk asymptomatic women and showed an inverse relationship between cervical length and the risk of spontaneous preterm birth, with better prediction at shorter cervical length cut-offs (Crane & Hutchens 2008). The most commonly used cervical length cut-off is <25 mm prior to 24 weeks of gestation, where the test sensitivity is 65.4%, specificity 75.5%, PPV 33.0% and NPV 92.0% for the prediction of preterm birth at <35 weeks (Crane & Hutchens 2008). As previously described in section 2.1.4, cervical length normally decreases with advancing gestation, and most studies have assessed the predictive ability of cervical length from around 14 to 16 weeks up until 24 weeks of gestation (Crane & Hutchens 2008).

Many countries recommend consideration of mid-trimester cervical length scans for asymptomatic women with risk factors such as prior spontaneous preterm birth (McIntosh, Feltovich et al. 2016; Ministry of Health 2019b; The Royal Australian and New Zealand College of Obstetricians and Gynaecologists 2017a; UK Preterm Clinical Network 2019). The frequency

of cervical surveillance depends on risk factor assessment and local practice. In the United Kingdom, women at highest risk based on risk factor assessment (for example, previous spontaneous preterm birth at <34 weeks or mid-trimester loss) are recommended to undergo cervical length assessment two- to four-weekly from 16 to 24 weeks of gestation (UK Preterm Clinical Network 2019). Those at intermediate risk (for example, previous LLETZ >10 mm) are advised to have at least one scan at 18 to 22 weeks of gestation, with additional scans arranged according to individual need and availability of resources (UK Preterm Clinical Network 2019).

2.3.1.2.2 Use in the general population

Around half of all spontaneous preterm births occur in women without identifiable risk factors, so use of an accurate, population-wide screening test for spontaneous preterm birth may provide an opportunity for early intervention for women who may not have otherwise been identified until they presented with symptoms. The use of a routine cervical length assessment in mid-pregnancy has been proposed as an appropriate screening test for spontaneous preterm birth and is already in use in some areas, although controversy over its effectiveness remain (McIntosh, Feltovich et al. 2016; Newnham, White et al. 2017).

Studies assessing the use of cervical length in low risk populations have shown that a short cervix is associated with an increased risk of spontaneous preterm birth (Heath, Southall et al. 1998; Iams, Goldenberg et al. 1996). Heath and colleagues screened over 1200 women from a general clinic population at 23 weeks and assessed spontaneous preterm birth rates for those who were managed expectantly (Heath, Southall et al. 1998). Women had a cervical length of ≤15 mm in 1.7% of cases and this group contributed to 86% of spontaneous preterm births at ≤28 weeks (Heath, Southall et al. 1998). However most women with a 'moderately' short cervix did not have an early preterm birth, and the cervix needed to be very short before the risk of spontaneous preterm birth increased significantly, with only a 4% risk of preterm birth at ≤32 weeks with a cervical length of 15 mm, but a 78% risk with a cervical length of 5 mm (Heath, Southall et al. 1998). The efficacy of cervical cerclage and vaginal progesterone in this group of otherwise low risk women with a short cervix is discussed in section 2.3.2.

The use of cervical length assessment as a population-wide screening test requires a large number of women to be screened to identify the small number of women with a very short cervix who may benefit from interventions to prevent spontaneous preterm birth, and the test has a relatively high false positive rate for early preterm birth. Whilst ultrasound is a safe and

generally well accepted investigation, a transvaginal scan may be considered invasive and uncomfortable to some women, and the availability of ultrasound resources and need for a chaperone should also be taken into account. Furthermore, consideration should be given to the number of women with false positive results who may have unnecessary interventions with the associated risks and implications for resources. To limit the number of women requiring transvaginal scans, some screening programmes, for example in Western Australia, have accepted a transabdominal measurement of cervical length as adequate if the cervix is clearly visualised; a higher cut-off of 35 mm is recommended as transabdominal assessment tends to over-measure the cervix and reduce sensitivity of the test (Hernandez-Andrade, Romero et al. 2012; Newnham, White et al. 2017). A transvaginal scan should then be undertaken if a short cervix is suspected.

Universal transvaginal cervical length screening has been shown to be cost-effective in an American study (Werner, Hamel et al. 2015), but these results do not necessarily translate to other health care systems. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists advise that assessment of cervical length between 18 and 24 weeks in women at low risk of preterm birth can be considered, however acknowledge that this decision requires careful consideration of local factors including acceptability to women, resource availability, education and training, and health economics (The Royal Australian and New Zealand College of Obstetricians and Gynaecologists 2017a). Universal screening of cervical length is not currently offered in New Zealand.

2.3.1.3 Vaginal biomarkers

There are fewer studies assessing the use of vaginal biomarkers for the prediction of spontaneous preterm birth in asymptomatic high risk women compared to in a symptomatic population. Of the three discussed here, fFN has been the most well studied and there is evidence to support its use in this setting for risk stratification and to guide management decisions.

2.3.1.3.1 Fetal fibronectin

In a study of nearly 1500 asymptomatic women at high risk of spontaneous preterm birth, increasing fFN concentrations (taken between 22 and 28 weeks of gestation) were associated with an increased risk of delivery at <34 weeks; 2.7%, 11.0%, 14.9%, 33.9%, and 47.6% with fFN levels of <10, 10-49, 50-199, 200-499 and ≥500 ng/mL respectively (Abbott, Hezelgrave

et al. 2015). The sensitivity, specificity, PPV and NPV of fFN using a threshold of ≥200 ng/mL were 28.7%, 96.4%, 37.7% and 94.7% respectively for spontaneous preterm birth <34 weeks (Abbott, Hezelgrave et al. 2015). The main utility of fFN in asymptomatic women is its high NPV. The majority of women (69.1%) in the Abbott el al. study had a fFN concentration of <10 ng/mL, and these women can be reassured that their risk of early spontaneous preterm birth is very low (2.7%) and they can therefore return to routine antenatal care. In contrast, a high quantitative fFN result, particularly in the presence of a short cervix, may justify additional interventions such as hospital admission and administration of antenatal corticosteroids (further discussed in section 2.3.1.3.4). Women with a cervical length of <25 mm and a fFN of <10 ng/mL had a risk of spontaneous preterm birth at <34 weeks of 9.5% whereas those with a fFN of >200 ng/mL had a risk of 55.1% ($p<0.001$), suggesting that combining fFN and cervical length improves the accuracy of prediction (Abbott, Hezelgrave et al. 2015).

The quantitative fFN test performs better than qualitative fFN for the prediction of spontaneous preterm birth at <34 weeks in asymptomatic high risk women with areas under the curve of 0.78 (95% CI 0.73-0.84) for quantitative fFN and 0.68 (95% CI 0.63-0.73) for the qualitative test (Abbott, Hezelgrave et al. 2015).

2.3.1.3.2 Placental alpha microglobulin-1

No studies assessing the use of PAMG-1 in asymptomatic high risk women were identified and it is not licensed for this use.

2.3.1.3.3 Phosphorylated insulin like growth factor binding protein-1

pIGFBP-1 is not an effective test in asymptomatic women at high risk of spontaneous preterm birth. In a systematic review and meta-analysis of nine studies, pIGFBP-1 had a pooled sensitivity and specificity of 40% and 76% for the prediction of spontaneous preterm birth at <32 weeks (Conde-Agudelo & Romero 2016). pIGFBP-1 is not used for risk prediction in asymptomatic women in New Zealand.

2.3.1.3.4 Combining predictive tests

Combining the results of transvaginal cervical length and quantitative fFN improves prediction of spontaneous preterm birth in asymptomatic high risk women (Bolt, Chandiramani et al. 2011;

Kuhrt, Smout et al. 2016). This approach can be used as a triage tool to aid decisions on additional interventions such as hospital admission and antenatal corticosteroids. Quantitative fFN and cervical length measurements were taken at 23 to 28 weeks gestation in a study of 1130 asymptomatic women cared for in a specialised preterm birth clinic in the United Kingdom (Min, Watson et al. 2016). Women deemed to have a high risk of spontaneous preterm birth based on these tests (defined as poor obstetric history, fFN >50 ng/mL and cervical length of <15 mm) were admitted to hospital, whereas women with a low risk result were discharged from the clinic and underwent routine outpatient antenatal care (Min, Watson et al. 2016). Using this approach only 6% of women were admitted to hospital following asymptomatic screening (Min, Watson et al. 2016). Women who were admitted were much more likely to deliver at <30 weeks than those who were deemed low risk and managed as an outpatient (36.4% versus 1.3%, RR 27.6, 95% CI 15.0-50.1). Most women had their risk of preterm birth appropriately downgraded, allowing them to return to normal pregnancy care (Min, Watson et al. 2016).

Quantitative fFN taken at the earlier gestations of 18 to 21 weeks performs similarly to use at 22 to 27 weeks in asymptomatic high risk women, with areas under the curve of 0.74 (95% CI 0.67-0.80) versus 0.79 (95% CI 0.73-0.86) respectively, p=0.24 (Hezelgrave, Abbott et al. 2016). Thus, use of quantitative fFN at 18 to 21 weeks can also be used to determine which women should have ongoing cervical length scans and which do not need ongoing intensive surveillance (Hezelgrave, Abbott et al. 2016).

The QUiPP App (previously described in symptomatic women in section 2.2.1.5) is a convenient way of combining predictive tests and has been validated for use in an asymptomatic high risk population (Kuhrt, Smout et al. 2016). The QUiPP App combines the presence of risk factors for preterm birth with cervical length and quantitative fFN to provide estimated probabilities for spontaneous preterm birth at various time points (King's College London 2017). QUiPP has been shown to be an accurate predictive test, and using an estimated probability of >10% to indicate a positive test result, the areas under the curve range from 0.77 to 0.99 for each delivery time point (within 2 and 4 weeks, and before 30, 34 and 37 weeks of gestation) (Kuhrt, Smout et al. 2016). Again, this information is useful to allow risk to be downgraded for most women, and provide higher intensity surveillance and interventions such as hospital admission and antenatal corticosteroids for the few who are at greatest risk.

2.3.2 Interventions to prevent spontaneous preterm birth

Once asymptomatic women at high risk of spontaneous preterm birth have been identified from risk factor assessment and/or the use of predictive tools, the focus of care turns to preventative strategies that aim to prolong pregnancy and/or improve perinatal outcomes. Prevention strategies include risk factor modification, for example support to become smoke and drug-free, and screening for, and treating infection. These strategies are also recommended as routine antenatal care regardless of risk status. Other interventions such as cervical cerclage and vaginal progesterone are reserved for women at highest risk of spontaneous preterm birth.

2.3.2.1 Becoming smoke and drug-free

Cigarette smoking and recreational drug use both have modest associations with spontaneous preterm birth (as detailed in section 2.1.1). All women who are identified as cigarette smokers or users of recreational drugs should be provided with cessation advice in early pregnancy and offered referral to cessation support programmes. Women can be advised that there is evidence from observational studies that becoming smoke-free by 15 weeks may reduce the risk of both spontaneous preterm birth and small for gestational age babies to that of a non-smoker (McCowan, Dekker et al. 2009). This may be a significant motivator for women who have additional risk factors for spontaneous preterm birth. A Cochrane review has shown that use of smoking cessation programmes significantly reduces the number of women smoking in late pregnancy (RR 0.94, 95% CI 0.93-0.96) (Lumley, Chamberlain et al. 2009). Furthermore, there is an associated reduction in preterm birth (RR 0.86, 95% CI 0.74-0.98) (Lumley, Chamberlain et al. 2009). There are a range of interventions available to promote smoking cessation, and incentive-based programmes appear to have the highest success rates with 24% of women becoming smoke-free, compared to an overall rate of 6% when other interventions are included in assessment (Lumley, Chamberlain et al. 2009).

2.3.2.2 Screening and treating infection

The activation of inflammatory pathways is thought to be a major contributor to the onset of preterm labour (Romero, Dey et al. 2014). Although it seems logical that early detection and prompt and appropriate treatment of infections in pregnancy would reduce the risk of spontaneous preterm birth, good quality evidence is lacking. A Cochrane review has shown that the use of antibiotic treatment compared to placebo for women with asymptomatic bacteriuria

in pregnancy is associated with a reduction in the incidence of pyelonephritis (RR 0.23, 95% CI 0.13-0.41) and preterm birth (RR 0.27, 95% CI 0.11-0.62), however the quality of evidence was low (Smaill & Vazquez 2015). Although the optimal time for performing urine culture is unknown, it seems appropriate to do this in early pregnancy at the first antenatal booking visit (Smaill & Vazquez 2015). Repeat urine culture following antibiotic treatment as a test of cure is recommended, with repeat treatment as required, but there is currently no evidence to support routine repeat screening throughout pregnancy (Smaill & Vazquez 2015).

Many studies have shown an association between sexually transmitted infections, such as chlamydia, and spontaneous preterm birth (Andrews, Goldenberg et al. 2000; McGregor & French 1991; Rours, Duijts et al. 2011). Antibiotic treatment of chlamydia in pregnancy does achieve microbiological cure and is considered safe (Cluver, Novikova et al. 2017). New Zealand guidelines recommend routine screening and treatment of sexually transmitted infections in pregnancy (New Zealand Sexual Health Society 2017). The optimal timing of screening has not been defined, however testing at the first antenatal booking visit seems a sensible approach. Self-collected swabs are acceptable for asymptomatic women if speculum examination is not required for other indications (New Zealand Sexual Health Society 2017), and is likely to improve compliance from both women and health care professionals.

Bacterial vaginosis in pregnancy is also associated with an increased risk of spontaneous preterm birth (Hillier, Nugent et al. 1995; Kurki, Sivonen et al. 1992). Whilst antibiotic treatment can eradicate bacterial vaginosis in pregnancy, routine treatment has not been shown to reduce the overall risk of preterm birth in systematic review (Brocklehurst, Gordon et al. 2013). Thus, there is little evidence to support universal screening and treatment of bacterial vaginosis in pregnancy (Brocklehurst, Gordon et al. 2013; Carey, Klebanoff et al. 2000), although there are varying opinions and a wide range of practice both nationally and internationally. There is better evidence to support the treatment of bacterial vaginosis in high risk women who have had a previous preterm birth, with a ≥7 day course of metronidazole associated with a reduction in the risk of spontaneous preterm birth at <37 weeks (OR 0.42, 95% CI 0.27-0.67) (Leitich, Brunbauer et al. 2003; McDonald, O'Loughlin et al. 1997).

2.3.2.3 Midwifery-led continuity of care models

Recent studies have highlighted the importance of midwifery-led continuity of care models in reducing preterm birth. Midwifery-led continuity of care has been defined by the Royal College

of Obstetricians and Gynaecologists as a care model where "the midwife is the lead professional in the planning, organisation and delivery of care given to a woman from initial booking to the postnatal period" (Thomas, Paranjothy et al. 2011). Within this model, additional care may be provided by medical staff, however the midwife, in partnership with the woman, remains responsible for the assessment and planning of maternity care and referral to other professionals and services when this is required (Sandall, Soltani et al. 2016). A Cochrane review of 15 trials, including 17,674 women, compared midwifery-led continuity of care with other maternity care models and identified that women receiving midwifery-led continuity of care were less likely to have a preterm birth prior to 37 weeks (average RR 0.76, 95% CI 0.64-0.91) and had fewer fetal losses or neonatal deaths (average RR 0.84, 95% CI 0.71-0.99) (Sandall, Soltani et al. 2016). Subsequent studies have had similar results, and have also shown midwifery-led continuity of care to be effective in reducing preterm birth rates in indigenous women and in those with low socio-economic status (McRae, Janssen et al. 2018; Kildea, Gao et al. 2019). The mechanisms behind this reduction in preterm birth are likely multifactorial, but may include the enabling of trusting relationships between women and care providers along with opportunities for early health and social support interventions that impact positively on birth outcomes (Kildea, Gao et al. 2019). Midwifery continuity of care has been identified as a key strategy in preventing preterm birth, and is recommended by the Australian Preterm Birth Prevention Alliance (Australian Preterm Birth Prevention Alliance 2019).

2.3.2.4 Cervical cerclage

Cervical cerclage was first introduced in the 1950's by Shirodkar, an Indian Gynaecologist who described the transvaginal placement of a cervical suture at 14 weeks of gestation to prevent second trimester miscarriage (Shirodkar 1955). The original Shirodkar procedure involved vaginal dissection to allow placement of a suture at the level of the internal os. An alternative technique was described by McDonald several years later where he used a purse-string style cervical suture to prevent inevitable miscarriage, predominantly in those with an already dilated cervix (McDonald 1957). Although McDonald's initial description is now referred to as a rescue cerclage, the use of a purse-string style cerclage is still widely used for history- and ultrasound-indicated procedures today. Due to the lack of dissection with a McDonald suture, the internal os is often not reached.

There are two main mechanisms by which a cervical cerclage is thought to prevent spontaneous preterm birth. Firstly, a cerclage provides some mechanical support and strength to the cervix,

which may be beneficial in women with a primary cervical problem, such as previous cervical surgery or a congenital anomaly (Abbott, To et al. 2012). Secondly, cerclage helps to maintain cervical length and retain the mucous plug, preventing ascending infection from the lower genital tract (Abbott, To et al. 2012). Thus, cerclage may also be beneficial in women where cervical change occurs as a secondary event, for example due to placental causes.

In the 65 years since the introduction of cervical cerclage, there has been much debate and controversy about the efficacy and role of this common obstetric procedure, with wide variation in clinical practice (Abbott, To et al. 2012; Simcox & Shennan 2007). Although there is evidence to support the use of cervical cerclage, the significant heterogeneity within the population of women at high risk of spontaneous preterm birth makes it difficult to define the group most likely benefit (Abbott, To et al. 2012). Cervical cerclage can be placed as a history-indicated (elective) procedure, as an ultrasound-indicated procedure due to cervical shortening, or as an emergency (rescue) procedure in the presence of cervical dilatation. A history-indicated cerclage can be performed pre-conception, or in early pregnancy, and is usually placed via a transvaginal approach, with a small number placed transabdominally, either by laparotomy or laparoscopy. There are various methods used for insertion of transvaginal cerclage, including the aforementioned Shirodkar and McDonald techniques along with many modifications of each. Various suture materials are available including monofilament and braided sutures and tapes.

2.3.2.4.1 Cerclage techniques

The vast majority of cervical cerclage are placed via a transvaginal approach. There have been no head-to-head randomised trials comparing the Shirodkar or McDonald cerclage techniques, however, indirect comparisons and retrospective studies suggest there are no significant differences in preterm birth rates nor neonatal survival between the two (Harger 1980; Odibo, Berghella et al. 2007). Most clinicians probably use a modification of either technique rather than the exact procedures originally described and a descriptive report is likely to be more helpful in clinical practice, for example, a ‘buried transvaginal cervical cerclage with dissection’ or a ‘transvaginal purse-string style cerclage with no dissection’ (Dawes & Groom 2015). This enables clear direction for the clinician removing the cerclage, as this is the main practical difference between the techniques. A cerclage performed with dissection is more likely to require regional anaesthesia for removal as the knot becomes buried under the vaginal mucosa, whereas cerclage that were inserted without dissection are usually able to be removed without

anaesthesia (Dawes & Groom 2015). Transvaginal cerclage are usually removed electively at 36 to 37 weeks of gestation in preparation for labour and vaginal birth.

Transabdominal cerclage is usually reserved for the highest risk women who have had multiple prior preterm births or mid-trimester losses and a failed transvaginal cerclage, or for women with a history of extensive cervical surgery with inadequate cervical tissue remaining to allow placement of a transvaginal cerclage (Zaveri, Aghajafari et al. 2002). The recently published MAVRIC Study randomised 111 women with a previous failed transvaginal cerclage to a transabdominal cerclage, 'high' transvaginal cerclage (with dissection) or 'low' transvaginal cerclage (without dissection) (Shennan, Chandiramani et al. 2019). Women who received a transabdominal cerclage had significantly lower rates of preterm birth at <32 weeks compared to those managed with a low transvaginal cerclage (8% versus 33%, RR 0.23, 95% CI 0.07-0.76, NNT 3.9) as well as fewer late miscarriages or stillbirths (3% versus 21%, RR 0.12, 95% CI 0.016-0.93, NNT 5.3) (Shennan, Chandiramani et al. 2019). There were no significant differences in spontaneous preterm birth rates between high and low transvaginal cerclage (38% versus 33%, RR 1.15, 95% CI 0.62-2.16) (Shennan, Chandiramani et al. 2019).

Various suture materials are used for cervical cerclage, with little evidence to guide practice. Whilst a braided suture has traditionally been used for its high tensile strength, it has been associated with an increased risk of infection in other surgical procedures (Israfil-Bayli, Toozs-Hobson et al. 2013). A survey of consultants in the United Kingdom showed that whilst 87% of clinicians used a braided suture, 75% of responders were unsure of the best suture material to use (Israfil-Bayli, Toozs-Hobson et al. 2014). A randomised controlled trial (the C-STICH Study) is currently in progress in the United Kingdom and aims to determine whether a monofilament or braided suture material for transvaginal cerclage is more effective (Toozs-Hobson 2014).

2.3.2.4.2 History-indicated cerclage

A history-indicated (elective) cerclage is placed due to obstetric or gynaecological risk factors for spontaneous preterm birth and is usually placed between 12 and 14 weeks after aneuploidy screening, but can also be placed pre-conception. History-indicated cerclage are usually placed transvaginally (with or without dissection), but can be placed as an abdominal procedure in very high risk women as previously described.

There are few randomised trials assessing the use of transvaginal history-indicated cervical cerclage. The largest is the Medical Research Council/Royal College of Obstetricians and Gynaecologists (MRC/RCOG) multi-centre randomised trial which recruited almost 1300 women at increased risk of spontaneous preterm birth whose obstetricians were uncertain whether to recommend a cervical cerclage (MRC/RCOG Working Party on Cervical Cerclage 1993). The majority of women had a prior spontaneous preterm birth or history of cervical surgery. Women randomised to cerclage had a lower rate of preterm birth at <33 weeks compared to those randomised to no cerclage (13% versus 17%, OR 0.72, 95% CI 0.53-0.97, NNT of 25) (MRC/RCOG Working Party on Cervical Cerclage 1993). Women with ≥3 prior second trimester miscarriages or preterm births were most likely to benefit with a preterm birth rate at <33 weeks of 15% with cerclage versus 32% without ($p<0.05$, NNT 6) (MRC/RCOG Working Party on Cervical Cerclage 1993). There were no differences in perinatal mortality, and rates of neonatal morbidity were not reported; women managed with cerclage had an increased risk of puerperal pyrexia (6% versus 3%, OR 2.12, 95% CI 1.08-4.16) (MRC/RCOG Working Party on Cervical Cerclage 1993).

Three systematic reviews assessing the use of history-indicated cerclage were published in 2003, with varying conclusions (Bachmann, Coomarasamy et al. 2003; Drakeley, Roberts et al. 2003; Odibo, Elkousy et al. 2003). A Cochrane review assessed four studies that compared cerclage with no cerclage in a heterogeneous group of women with pre-existing risk factors for spontaneous preterm birth (Drakeley, Roberts et al. 2003). All four studies reported on preterm birth <37 weeks of gestation, and identified no overall statistically significant difference between the two groups (RR 0.88, 95% CI 0.76-1.03) (Drakeley, Roberts et al. 2003). Three studies reported on delivery at <32 weeks and again there was no difference seen between the two groups (RR 1.29, 95% CI 0.67-2.49), however this excluded the MRC/RCOG study which individually showed a significant reduction in preterm birth at <33 weeks as previously described (Drakeley, Roberts et al. 2003; MRC/RCOG Working Party on Cervical Cerclage 1993). The authors concluded that until more data became available, cervical cerclage should not be offered to women at low or medium risk of spontaneous preterm birth, but acknowledged there may be a role for women at very high risk, for example, with ≥3 previous preterm births or second trimester losses or if they developed progressive shortening of the cervix (Drakeley, Roberts et al. 2003). In contrast, Bachmann and colleagues concluded that elective cerclage is effective in reducing preterm birth at <34 weeks in women with significant risk factors (OR 0.75, 95% CI 0.59-0.96) (Bachmann, Coomarasamy et al. 2003). They suggested that the variation in the size of effect between studies was likely to be due to the inclusion criteria of

individual studies which may have excluded women at highest risk who were most likely to benefit (Bachmann, Coomarasamy et al. 2003). Finally, Odibo and colleagues found a trend towards the prevention of preterm delivery at <34 weeks in their meta-analysis (OR 0.77, 95% CI 0.59-0.99) but no improvement in neonatal mortality (OR 0.86, 95% CI 0.56-1.33) (Odibo, Elkousy et al. 2003).

Based on the available evidence, it is likely that history-indicated cerclage for women with one or two prior spontaneous preterm births or second trimester losses provides only a modest reduction in the risk of recurrent preterm birth. An alternative option of cervical length surveillance and ultrasound-indicated cerclage if a short cervix is identified in the second trimester is likely to significantly reduce the number of cerclage performed in this group of women by targeting those most likely to benefit. However, there are wide variations in practice worldwide (Simcox & Shennan 2007). The Royal Australian and New Zealand College of Obstetricians and Gynaecologists and the National Institute for Health and Care Excellence (NICE) do not make recommendations on the use of history-indicated cerclage. An individualised approach to consideration of cerclage is required, taking into account risk factors, clinical examination of the cervix, and women's wishes and perceptions of risk. Women who opt for a history-indicated cerclage should be counselled on the risks and benefits of the procedure and the limitations of the evidence.

2.3.2.4.3 Ultrasound-indicated cerclage in high risk women with a short cervix

The risk of preterm birth increases with decreasing cervical length and this association is strongest in women with other risk factors for spontaneous preterm birth. As previously discussed, there are various definitions of a short cervix, with most using a threshold of <25 mm at <24 weeks of gestation (Care, Ingleby et al. 2019). Alternative thresholds include centile based measurements, for example <1st or <3rd centile for gestational age.

The use of ultrasound-indicated cervical cerclage has been shown to significantly reduce the risk of preterm birth and improve perinatal outcomes in a systematic review of five trials (Berghella, Rafael et al. 2011). Women with a previous spontaneous preterm birth and a short cervix on transvaginal ultrasound scan (<25 mm at <24 weeks) had a preterm birth rate <35 weeks of 28.4% when managed with cerclage, compared to 41.3% in those managed expectantly (RR 0.70, 95% CI 0.55-0.89) (Berghella, Rafael et al. 2011). Ultrasound-indicated cerclage also reduced the risk of preterm birth before 24, 28, 32 and 37 weeks of gestation (RR ranging from

0.48-0.70, upper 95% CI <1.0 for all) and was associated with improvements in a composite score of perinatal mortality and morbidity (15.6% with cerclage versus 24.8% without, RR 0.64, 95% CI 0.45-0.91, NNT 6) (Berghella, Rafael et al. 2011). A multi-centre trial by Owen and colleagues contributed more than half of the participants in this systematic review and used fortnightly transvaginal scans from 16^{+0} until 22^{+6} weeks of gestation, unless the cervix was observed to be 25-29 mm in which case the frequency of scans increased to weekly (Owen, Hankins et al. 2009). In this study, 31% of women with a prior spontaneous preterm birth had a cervical length <25 mm (Owen, Hankins et al. 2009).

The NICE preterm birth guideline recommends that women with a prior mid-trimester loss or spontaneous preterm birth (at 16 to 34 weeks of gestation), who have a cervical length of ≤25 mm on transvaginal scan performed between 16^{+0} and 24^{+0} weeks should be offered a choice of cervical cerclage or vaginal progesterone (National Institute for Health and Care Excellence 2015).

2.3.2.4.4 Ultrasound-indicated cerclage in otherwise low risk women with a short cervix

A large multi-centre study has assessed the use of universal transvaginal cervical length assessment in a generally low risk population and randomised women with a short cervix of ≤15 mm to cervical cerclage or expectant management (To, Alfirevic et al. 2004). Of the 47,123 women who had a transvaginal scan at 22 to 24 weeks gestation, 1% had a cervical length of ≤15 mm (To, Alfirevic et al. 2004). The use of cerclage was not associated with a significant reduction in preterm birth at <33 weeks compared to expectant management (22% versus 26%, RR 0.84, 95% CI 0.54-1.31); nor were there any significant differences in neonatal mortality or morbidity (To, Alfirevic et al. 2004). Although this study did confirm that otherwise low risk women with a very short cervix (mean of 9 mm), had a much higher risk of spontaneous preterm birth at <33 weeks compared to the general population in the United Kingdom (26% versus 1.5%), the mean gestation at delivery was still 35^{+3} weeks even when no treatment was given (To, Alfirevic et al. 2004).

2.3.2.4.5 Rescue cerclage

Rescue cerclage is an emergency procedure which involves the placement of a transvaginal cerclage following detection of an open cervix, usually in the presence of exposed fetal membranes. It can be considered a ‘salvage’ procedure to prolong gestation in women with

advanced cervical changes in the second trimester (Abu Hashim, Al-Inany et al. 2014). Rescue cerclage is a high risk procedure with worse perinatal outcomes than ultrasound- or history-indicated cerclage (Liddiard, Bhattacharya et al. 2011; Nelson, Dola et al. 2009). Cervical dilatation may be detected in asymptomatic women undergoing cervical length surveillance, as an incidental finding at the routine fetal morphology scan, or in symptomatic women following presentation with pain, pressure, vaginal bleeding or discharge.

The evidence for rescue cerclage is predominately based on retrospective cohort studies. In a systematic review of ten studies including 757 women with cervical dilatation between 14 and 27 weeks of gestation, 64% underwent rescue cerclage with the remainder managed expectantly (Ehsanipoor, Seligman et al. 2015). Cerclage was associated with a mean prolongation of pregnancy of 34 days (95% CI 17.9-50.0) compared to expectant management, with improved neonatal survival (71% versus 43%, RR 1.65, 95% CI 1.19-2.28) (Ehsanipoor, Seligman et al. 2015).

An experienced obstetrician should be involved in decisions when rescue cerclage is being considered, with careful counselling regarding the risks of PPROM, chorioamnionitis and failure of the cerclage to prevent a second trimester miscarriage, preterm birth or neonatal death. Consideration should also be given to parental views regarding care and outcomes of babies born around the threshold of viability, as rescue cerclage may prolong pregnancy just long enough to convert a second trimester miscarriage into a peri-viable preterm birth, with relatively high rates of morbidity in survivors.

2.3.2.5 Progesterone

Progesterone is a ‘pro-pregnancy’ hormone which has an important role in maintaining uterine quiescence in the latter part of pregnancy. Progesterone has an anti-inflammatory effect and may counteract the inflammatory cascade that leads to preterm labour by reducing the production of stimulatory prostaglandins and inhibiting the expression of contraction-associated protein genes within the myometrium (Norwitz & Caughey 2011; Berghella 2012). 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 gestations) is associated with a functional withdrawal of progesterone activity at the level of the uterus (Norwitz & Caughey 2011).

There are two different types of progestogens used in preterm birth prevention; 17α-hydroxyprogesterone (17α-OHP) which is given as an intramuscular injection; and natural progesterone which can be given as vaginal or oral preparations (Berghella 2012). These are addressed separately.

17α-OHP is a progestogen steroid hormone related to progesterone and is an agonist of the progesterone receptor. It is given as a weekly injection of hydroxyprogesterone caproate and is used widely in America. Only one early randomised controlled trials showed that weekly use of 17α-OHP from 16 to 36 weeks in women with a prior spontaneous preterm birth was very effective at reducing preterm birth when compared to placebo (26.3% versus 54.9%, RR 0.66, 95% CI 0.54-0.81) (Meis, Klebanoff et al. 2003). As a result of this trial, 17α-OHP received Food and Drug Administration (FDA) approval and has been extensively used in America in women with a prior spontaneous preterm birth (Berghella 2012). However, the Meis et al. study has been criticised due to the very high rate of preterm birth in the placebo group (Greene 2003; Thornton 2007) and a recently published randomised trial with a similar design showed no difference in preterm birth rates with 17α-OHP compared to placebo (Blackwell, Gyamfi-Bannerman et al. 2019). 17α-OHP is not available in New Zealand.

Natural progesterone is the most common type of progestogen used for preterm birth prevention in New Zealand, Australia and the United Kingdom, and is predominantly administered as a daily vaginal dose. Vaginal progesterone has been studied in three groups of women: (1) in all with a previous spontaneous preterm birth who have a normal (or unknown) cervical length; (2) in women with pre-existing risk factors for spontaneous preterm birth who develop a short cervix in the mid-trimester; and (3) in low risk women with a short cervix in the mid-trimester identified through routine screening or as an incidental finding.

There have been a large number of trials and systematic reviews assessing the use of vaginal progesterone for each of these indications, and findings are at times conflicting, resulting in wide variations in practice. The Evaluating Progestogen for Prevention of Preterm Birth International Collaborative (EPPPIC) study is an individual participant data meta-analysis which incorporates data from 31 randomised trials including over 10,000 women (University of York 2019). The results are eagerly awaited.

2.3.2.5.1 History-indicated use of vaginal progesterone

Early studies assessing the prophylactic use of vaginal progesterone in all women with a previous spontaneous preterm birth were promising. A Cochrane review in 2013, showed that progesterone was associated with a significant reduction in perinatal mortality (RR 0.50, 95% CI 0.33-0.75) and morbidity, preterm birth at <34 weeks (RR 0.31, 95% CI 0.14-0.69) and at <37 weeks (RR 0.55, 95% CI 0.42-0.74), when compared to placebo (Dodd, Jones et al. 2013). However, two larger randomised controlled trials, the PROGRESS and OPPTIMUM Studies, have since been published, and did not show these same benefits (Crowther, Ashwood et al. 2017; Norman, Marlow et al. 2016).

In the PROGRESS Trial, 787 women with a previous spontaneous preterm birth at <37 weeks gestation were recruited from 39 Australasian and Canadian centres and randomised to 100 mg vaginal progesterone pessaries or placebo from 20 to 34 weeks gestation (Crowther, Ashwood et al. 2017). There were no significant differences between the two groups for the primary outcome of neonatal RDS (RR 0.99, 95% CI 0.66-1.51), nor in the secondary outcomes of preterm birth <37 weeks (RR 0.98, 95% CI 0.81-1.18) or a composite of serious infant outcomes (RR 0.99, 95% CI 0.82-1.18) (Crowther, Ashwood et al. 2017). The OPPTIMUM study was larger, recruiting 1228 women from 65 centres in the United Kingdom who had either a previous spontaneous preterm birth (approximately 75% of the cohort) or a short cervix (Norman, Marlow et al. 2016). Women were randomised to 200 mg vaginal progesterone capsules or placebo from 22 to 34 weeks gestation. Again, there were no significant differences between the two groups in the co-primary outcomes of fetal death or delivery at <34 weeks (aOR 0.86, 95% CI 0.61-1.22), neonatal morbidity or death (aOR 0.62, 95% CI 0.38-1.03), nor in a cognitive composite score at 2 years (difference in means -0.48, 95% CI -2.77-1.81) (Norman, Marlow et al. 2016).

Giving vaginal progesterone to all high risk women with a previous spontaneous preterm birth therefore appears to have no overall effect on preterm birth or neonatal outcome in high quality randomised controlled trials. Despite these findings, the NICE guideline (updated in 2019) continue to advise ‘consideration’ of prophylactic vaginal progesterone in women with a history of spontaneous preterm birth or mid-trimester loss at 16 to 34 weeks of gestation (National Institute for Health and Care Excellence 2015). This guideline acknowledges the uncertainty over the benefits of progesterone in women with risk factors for preterm birth who have a normal cervical length, and recommendations have been made for further research in this area (National

Institute for Health and Care Excellence 2015). Australasian guidelines also advise consideration of the elective use of vaginal progesterone in women with a prior spontaneous preterm birth, although also acknowledge the heterogeneity of the existing evidence and the need for further studies (The Royal Australian and New Zealand College of Obstetricians and Gynaecologists 2017b). Given the conflicting results from the Cochrane review and the more recent PROGRESS and OPPTIMUM trials, it is unsurprising that there is significant variation in the use of prophylactic vaginal progesterone for high risk women both internationally and within New Zealand. Consistency in care will hopefully improve once findings from the EPPPIC study are available and incorporated into clinical practice guidelines.

2.3.2.5.2 Ultrasound-indicated use of vaginal progesterone in high risk women

The evidence to support the use of vaginal progesterone in women who develop a short cervix is more consistent, and progesterone has been shown to be beneficial regardless of whether women have other risk factors for preterm birth or not. In a systematic review and meta-analysis of individual patient data from five randomised trials of asymptomatic women with a sonographic short cervix of ≤25 mm in the mid-trimester, Romero and colleagues showed that use of vaginal progesterone was associated with a significant reduction in preterm birth at <33 weeks (12% versus 17%, RR 0.62, 95% CI 0.47-0.81) and at <28 weeks (8% versus 11%, RR 0.67, 95% CI 0.45-0.99) when compared to placebo (Romero, Conde-Agudelo et al. 2018). There was also a reduction in RDS (RR 0.47, 95% CI 0.27-0.81) and in the composite outcome of neonatal morbidity and mortality (RR 0.59, 95% CI 0.38-0.91) associated with progesterone use (Romero, Conde-Agudelo et al. 2018). These beneficial effects did not differ significantly between women who had a prior preterm birth and those who did not. There were also no significant differences in outcomes between the doses of vaginal progesterone administered (either 90-100 mg or 200 mg per day) (Romero, Conde-Agudelo et al. 2018).

As vaginal progesterone and cervical cerclage are both effective at reducing preterm birth rates and improving neonatal outcomes in high risk women with a short cervix, this leads to the question of which treatment is more effective? This is currently being assessed in a multi-centre randomised trial based in the United Kingdom (the SuPPoRT Trial), which aims to compare cervical cerclage, vaginal progesterone and cervical pessary for the prevention of preterm birth in women who develop a short cervix and includes women with and without other risk factors for preterm birth (Hezelgrave, Watson et al. 2016). Completion of recruitment is planned for 2021 (Hezelgrave 2015). In the meantime, the best available evidence is an indirect comparison

meta-analysis, where vaginal progesterone and cervical cerclage appear equally effective, with no statistically significant differences in preterm birth rates or perinatal outcomes (Conde-Agudelo, Romero et al. 2018). However, it is important to note that the second largest progesterone trial that contributed to this meta-analysis excluded women with cervical length of <10 mm, with the rationale that these women have a higher rate of intra-amniotic infection/inflammation and are less likely to benefit from progesterone (Hassan, Romero et al. 2011). It may therefore be more appropriate to offer cervical cerclage to high risk women with a very short cervix of <10 mm until results from the SuPPoRT trial are available.

2.3.2.5.3 Ultrasound-indicated use of vaginal progesterone in otherwise low risk women

As described above, vaginal progesterone reduces the risk of preterm birth and improves perinatal outcomes for women with a short cervix, regardless of whether they have other risk factors for spontaneous preterm birth (Romero, Conde-Agudelo et al. 2018). In the PREGNANT Trial, 32,000 predominantly low risk women had a cervical length measurement taken at 19^{+0} to 23^{+6} weeks of gestation, and those with a short cervix of 10 to 20 mm were randomised to vaginal progesterone or placebo (Hassan, Romero et al. 2011). There were 733 women (2.3%) identified to have a short cervix and 465 agreed to participate in the trial and were randomised (Hassan, Romero et al. 2011). Vaginal progesterone was associated with a lower risk of preterm birth at <33 weeks compared to placebo (8.9% versus 16.1%, RR 0.55, 95% CI 0.33-0.92), along with a reduction in a composite of neonatal morbidity and mortality (7.7% versus 13.5%, RR 0.57, 95% CI 0.33-0.99) (Hassan, Romero et al. 2011). These findings were consistent with results from a similar earlier study by Fonseca and colleagues (Fonseca, Celik et al. 2007).

This approach of universal screening and use of vaginal progesterone for a short cervical length reduces the risk of early spontaneous preterm birth for women with a short cervix. However, these studies show that a very large number of low risk women need to be screened to identify the few with a short cervix, and of these, most will not have an early preterm birth; only 16% of the placebo group had a spontaneous preterm birth at <33 weeks despite a median cervical length of 18 mm in the Hassan et al. study. The outcomes of pregnancies with a cervical length >20 mm are not reported and so the number of false negative results and cost-effectiveness of this strategy have not been fully explored. Several economic analyses have been carried out in America (Cahill, Odibo et al. 2010; Jain, Kilgore et al. 2016; Werner, Hamel et al. 2015). Although cost-effectiveness was proven in some studies, this was not the case for all, and

differences in health care systems and health-related costs mean that these results are not directly translatable to other health care settings.

Although the use of universal cervical length screening has not been firmly recommended in the United Kingdom, Australia or New Zealand (as previously discussed), the use of vaginal progesterone is recommended for otherwise low risk women who are identified to have a short cervix of ≤25 mm on transvaginal scan if this is performed between 16^{+0} and 24^{+0} weeks of gestation (National Institute for Health and Care Excellence 2015; The Royal Australian and New Zealand College of Obstetricians and Gynaecologists 2017b).

2.3.2.6 Cervical pessary

Cervical pessaries have been used during pregnancy for more than 50 years, initially for the management of symptoms of vaginal prolapse, but in more recent decades for the prevention of spontaneous preterm birth (Arabin & Alfirevic 2013). The flexible silicon cone-shaped pessary in use today was developed by Hans Arabin in the late 1970s with the aim of surrounding the cervix to provide support and retain the mucous plug, and to alter the utero-cervical angle, redistributing weight to the pelvic floor (Arabin & Alfirevic 2013; Goya, Pratcorona et al. 2012). Advantages of the cervical pessary over cerclage include the ability to place the device in clinic without need for anaesthesia.

Whilst the use of cervical pessary showed promise for prevention of spontaneous preterm birth in initial small studies, larger trials have not confirmed benefit. In a randomised trial of 932 women there were no differences in spontaneous preterm birth rates at <34 weeks in women with a short cervix who were treated with cervical pessary (OR 1.12, 95% CI 0.75-1.69) (Nicolaides, Syngelaki et al. 2016). Research is ongoing with cervical pessary included in the SuPPoRT Trial, however current evidence suggests cervical pessary has a limited role in preterm birth prevention and it is not currently available in New Zealand.

2.3.3 Specialised preterm birth clinics

There are a variety of predictive tools and preventative treatments available for use in the care of women at high risk of spontaneous preterm birth, yet there are still many unanswered questions and evidence continues to evolve. To date no preventative interventions have been found to work conclusively across all groups of women at risk of spontaneous preterm birth

which is likely due to the complex and multi-factorial nature of this condition. The evidence can be difficult to navigate and use in clinical practice, with no clear pathway or algorithm that suits all women. The use of specialised preterm birth clinics can provide integrated, specialised and up-to-date care for women at high risk of spontaneous preterm birth. These clinics may also have a role in reducing anxiety by providing continuity of care and reassurance when appropriate.

Specialised preterm birth prevention clinics have developed over the last two decades due to a growing understanding of the risk factors for preterm birth and the importance of risk stratification to guide the use of interventions aimed at preventing spontaneous preterm birth (Vernet, Watson et al. 2017). They focus on the care of asymptomatic women who are at increased risk of spontaneous preterm birth due to their obstetric and/or gynaecological history. The key components of preterm birth clinics include addressing modifiable risk factors, providing regular transvaginal ultrasound cervical length surveillance through the mid-trimester, and providing evidence-based interventions when indicated.

2.3.3.1 Evidence to support the use of preterm birth clinics

Although there is good evidence to support many of the practices that occur in preterm birth clinics, specific evidence to support the utility of preterm birth clinics as a whole is still evolving (Malouf & Redshaw 2017; Vernet, Watson et al. 2017; Whitworth, Quenby et al. 2011). A Cochrane review from 2011 assessed outcomes from specialised preterm birth prevention clinics compared to standard antenatal care and identified no differences in rates of preterm birth (Whitworth, Quenby et al. 2011). However this review included only three randomised controlled studies, all of which were conducted from 1989-1994 and focused on patient education on the signs and symptoms of preterm labour (Whitworth, Quenby et al. 2011). There have been significant advances over the last thirty years and modern-day preterm birth clinics now utilise proven predictive tools such as transvaginal cervical length scans and quantitative fFN along with evidence-based interventions such as cervical cerclage and progesterone therapy. Care in modern-day preterm birth clinics is therefore significantly different to care in the early 1990's and results from this Cochrane review are not generalisable to current practice.

A more recent systematic review from 2017 included several low-quality cohort studies carried out from 2005-2014 in addition to the older randomised controlled studies previously described (Malouf & Redshaw 2017). This review again concluded that current literature cannot support

nor refute the effect of a preterm prevention clinic in reducing preterm birth (Malouf & Redshaw 2017). Despite the lack of direct evidence on the efficacy of preterm birth clinics for preterm birth prevention, it has been recognised that specialised preterm birth clinics have the advantage of offering coordinated and individualised care (Malouf & Redshaw 2017). There is also expert opinion that the use of preterm birth prevention clinics can be justified due to the poor outcomes from preterm birth and the availability of multiple interventions to reduce the risk and/or improve outcomes (Vernet, Watson et al. 2017). As a result, preterm birth clinics have become common-place in many countries including the United Kingdom and are recommended in the 'Saving Babies' Lives' bundle of care (Care, Ingleby et al. 2019; National Health Service England 2019).

More locally, an observational study has reviewed care from a preterm birth clinic in Melbourne, Australia over a ten year period from 2004 to 2013 (Hughes, Sim et al. 2017). They observed a reduction in the rate of spontaneous preterm birth at all gestational age groups over the study period when adjusted for an increasing risk profile of clinic attendees, as determined by cervical length measurements ($p=0.007$) (Hughes, Sim et al. 2017). This evidence indirectly supports the value of the assessments and interventions introduced into the clinic over the study period and provides valuable local data for Australia.

2.3.3.2 Current practice in preterm birth clinics

A postal survey carried out from 2012 to 2013 assessed practice within preterm birth clinics in the United Kingdom; 23 clinics were identified and included in assessment (Sharp & Alfirevic 2014). Significant heterogeneity in the referral indications and first line treatment of a short cervix were identified (Sharp & Alfirevic 2014). The authors concluded that there was an urgent need for networking, evidence-based guidelines and audit in this area (Sharp & Alfirevic 2014). The NICE guidelines on preterm labour and birth were subsequently published in 2015 (National Institute for Health and Care Excellence 2015) and a repeat survey of practice was carried out in 2017 (Care, Ingleby et al. 2019). There were 33 preterm birth clinics identified in this second survey, a 44% increase in the number of clinics over the five year period (Care, Ingleby et al. 2019). Although there was improved consensus on which high risk women should be targeted for review in specialised preterm birth clinics, there was wider variation in the care provided (Care, Ingleby et al. 2019). Further work to improve consistency in care is required.

The newly released (2019) 'Reducing Preterm Birth: Guidelines for Commissioners and Providers' from the United Kingdom Preterm Clinical Network provides valuable guidance on the recommended referral pathways and management of women at high risk of spontaneous preterm birth (UK Preterm Clinical Network 2019). Recommendations are provided on timing and frequency of cervical length screening, use of quantitative fFN testing, and management options including cervical cerclage, progesterone and cervical pessary, with reference to the NICE guideline on preterm birth.

2.3.3.3 Experience in New Zealand

The first specialised preterm birth clinic in New Zealand was established at National Women's Health, Auckland City Hospital in 2013. The clinic functions similarly to those in the limited published literature, with established referral criteria and processes (Auckland District Health Board 2019b).

There has been a significant reduction in the rate of spontaneous preterm birth at National Women's Health, at both <32 weeks of gestation (from 1.4% to 1.1% p=0.03) and 32 to 36 weeks of gestation (from 3.6% to 2.6% p=0.0003) from 2006 to 2017 (Auckland District Health Board 2018a). The development of a formalised preterm birth clinic is one factor that may have contributed to this reduction, along with potential changes in population demographics, a reduction in the number of women smoking during pregnancy and an improved awareness and identification of risk factors for preterm birth with appropriate intervention in women cared for outside of the preterm birth clinic setting (Auckland District Health Board 2018a).

2.3.4 The psychological wellbeing of women at high risk of spontaneous preterm birth

Psychological disorders such as anxiety and depression and are common in pregnancy and can have wide-ranging impact on the health of mothers, babies and their families (Bennett, Einarson et al. 2004; Dennis, Falah-Hassani et al. 2017; Waldie, Peterson et al. 2015). Women with complicated or high risk pregnancies have higher rates of anxiety and depression compared to the general pregnant population (Dagklis, Tsakiridis et al. 2018; Fairbrother, Young et al. 2017; Thiagayson, Krishnaswamy et al. 2013). Although there is an increased awareness of the importance of postnatal depression from both health care providers and the general public, antenatal anxiety and depression is less well recognised. There is accumulating evidence that women with anxiety and depression in pregnancy have worse perinatal outcomes, and further

attention is required in this area. There is currently little research on the psychological wellbeing of women at high risk of spontaneous preterm birth, and even less on the impact of care from a specialised preterm birth clinic.

2.3.4.1 Anxiety and depression in the general pregnant population

International studies show that around 10% of pregnant women have a major depressive disorder and 18% experience depressive symptoms during the antenatal period (Grigoriadis, VonderPorten et al. 2013). Similar findings have been seen locally. The Growing Up in New Zealand Study assessed an ethnically and socioeconomically diverse group of pregnant women and identified 11.9% as having probable antenatal depression (Waldie, Peterson et al. 2015). The prevalence of depression varies throughout pregnancy. Rates of depression appear to be lowest in the first trimester with 7.4% of women affected, increasing to 12.8% in the second trimester and plateauing at 12.0% in the third trimester (Bennett, Einarson et al. 2004).

Anxiety is also common in pregnancy and frequently coexists with depression (Dennis, Falah-Hassani et al. 2017). The overall prevalence of a clinical diagnosis of an anxiety disorder in pregnancy is 15.2% and self-reported anxiety symptoms are as high as 18.2%, 19.1% and 24.6% in the first, second and third trimesters respectively (Dennis, Falah-Hassani et al. 2017).

There is increasing recognition that psychological wellbeing during pregnancy can affect outcomes. Meta-analyses have shown that women who are depressed during pregnancy have a modestly increased risk of preterm birth, intrauterine growth restriction and low birthweight and have decreased levels of breastfeeding initiation (Grigoriadis, VonderPorten et al. 2013; Grote, Bridge et al. 2010). Whilst there is less literature on the effects of anxiety in pregnancy it has been associated with increased rates of pregnancy-related hypertension and caesarean section, decreased levels of exclusive breastfeeding and increased internalising behaviour and anxiety in the offspring (Field 2017). Improvements in the recognition and treatment of psychological disorders in pregnancy may improve outcomes for both women and children (Giardinelli, Innocenti et al. 2012) .

2.3.4.2 Anxiety and depression in women with high risk pregnancies

Women with high risk pregnancies have higher rates of depressive symptoms compared to the general pregnant population (Dagklis, Tsakiridis et al. 2018). Up to 22% of pregnancies can be

defined as high risk and this includes women at increased risk of spontaneous preterm birth (Rodrigues, Zambaldi et al. 2016). The prevalence of depression in high risk pregnancies ranges from 11% to 28% in studies from the United Kingdom, Singapore, Greece, America and France (Adouard, Glangeaud-Freudenthal et al. 2005; Brandon, Trivedi et al. 2008; Dagklis, Tsakiridis et al. 2018; King, Chambers et al. 2010; Thiagayson, Krishnaswamy et al. 2013). Only one study comparing rates of anxiety between high risk and normal pregnancies was identified. This study reported significant symptoms of anxiety in 45% of women with a medically high risk pregnancy, compared to 17% of women with a low risk pregnancy (King, Chambers et al. 2010).

There are few studies exploring women's experiences of high risk pregnancies. Whilst there is some evidence to suggest that simply labelling a pregnancy high risk may increase anxiety and fear, other studies have found that women embrace this label in a positive way (Simmons & Goldberg 2011; O'Brien, Quenby et al. 2010). A qualitative study assessing women's perceptions of care in a preterm birth clinic showed that women viewed their high risk status positively (O'Brien, Quenby et al. 2010). All 14 women in this small qualitative study reported that regular reassurance from their preterm birth clinic obstetrician was a helpful coping strategy (O'Brien, Quenby et al. 2010). They also felt that other health professionals were not always sensitive to their worries about having another preterm birth (O'Brien, Quenby et al. 2010). These women acknowledged the 'rollercoaster of emotions' that accompanied their visits to a preterm birth clinic. They described increasing anxiety building up prior to their appointment due to the fear of bad news, but also looked forward to the potential reassurance, and usually came away from the appointment 'on a high' (O'Brien, Quenby et al. 2010).

2.3.4.3 Quality of life during pregnancy

Health-related quality of life should also be considered when assessing the psychological wellbeing of women in pregnancy. The World Health Organisation defines quality of life as 'the individual's perception of their life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns' (WHOQOL Group 1994). Research has shown that health-related quality of life decreases even during normal pregnancy (Da Costa, Dritsa et al. 2010; Jomeen & Martin 2005). This is likely explained in part by the physiological changes of pregnancy causing a decline in physical functioning (Da Costa, Dritsa et al. 2010). Depressive symptoms in pregnancy have also been shown to negatively impact on multiple aspects of quality of life (Da Costa, Dritsa et al. 2010).

Furthermore, there is evidence that anxiety and depression in pregnancy can increase somatic symptoms which in turn may impact on quality of life (Kelly, Russo et al. 2001).

2.3.4.4 Screening for anxiety and depression and assessing quality of life in pregnancy

Diagnostic interviews are considered the gold standard in diagnosis of psychiatric conditions such as anxiety and depression, but these are time consuming, require special training for administration and are expensive (Evans, Spiby et al. 2015). Screening tools have therefore been established to assess the likelihood of a psychiatric condition and identify those who should be referred to psychiatric services for diagnostic interview. Commonly used screening questionnaires in pregnancy include the State-Trait Anxiety Inventory (STAI) for anxiety and the Edinburgh Postnatal Depression Scale (EPDS) for depression. Health-related quality of life can also be reliably assessed through the use of questionnaires such as the 36-Item Short Form Survey (SF-36).

The STAI was developed in 1970 by Spielberger to measure the self-reported presence of symptoms of anxiety (Spielberger, Gorsuch et al. 1970) and is available under license from Mind Garden Incorporated, California (Mind Garden 2018). The STAI contains two subscales - a state-anxiety scale and trait-anxiety scale. This allows differentiation between the temporary condition of 'state-anxiety' and the relatively stable and long-standing aspects of anxiety proneness in 'trait-anxiety' (Julian 2011; Mind Garden 2018). The STAI comprises 40 items (20 items for each subscale), with four possible responses for each question (Mind Garden 2018). The STAI takes approximately ten minutes to complete (Julian 2011). Scores can range from 20 to 80 for each subscale, with higher scores indicating greater levels of anxiety (Julian 2011).

The STAI is the most commonly used measure of anxiety during pregnancy (Littleton, Breitkopf et al. 2007). Although initially designed for a non-pregnant population, the STAI has been validated for use in pregnancy and has been shown to be a very good predictor of anxiety compared to diagnostic interview, with excellent internal validity (Grant, McMahon et al. 2008; Gunning, Denison et al. 2010). A cut-off score of >40 corresponds with the highest accuracy for a diagnosis of anxiety, with a sensitivity of 81%, specificity of 80% and PPV of 52% for both the state- and trait-anxiety scales, and was the point where false positive and negative results were minimal (Grant, McMahon et al. 2008). This is consistent with the cut-off score validated for use in non-pregnant women of childbearing age (Grant, McMahon et al. 2008).

The EPDS was developed by Cox, Holden and Sagovsky in 1987 as a screening tool for postnatal depression (Cox, Holden et al. 1987). It was later validated for use in screening for antenatal depression (Adewuya, Ola et al. 2006; Adouard, Glangeaud-Freudenthal et al. 2005; Bunevicius, Kusminskas et al. 2009; Felice, Saliba et al. 2006; Gibson, McKenzie-McHarg et al. 2009; Murray & Cox 1990). The EPDS is a self-reported ten-item scale, with four possible responses for each question, and takes approximately five minutes to complete (Cox, Holden et al. 1987). Scores range from 0 to 30, with higher scores indicating increased symptoms of depression (Cox, Holden et al. 1987). The EPDS is widely available free of charge. The validated cut-off scores for use in an antenatal population are higher than those used postnatally at ≥13 for at least probable minor depression and ≥15 for probable major depression (Gibson, McKenzie-McHarg et al. 2009; Murray & Cox 1990). The higher thresholds for a positive screen in pregnancy may be due to the differing prevalence of depression as well as the emotional, physiological and social changes that occur in pregnancy (Matthey, Henshaw et al. 2006; Murray & Cox 1990). The EPDS has a pooled sensitivity and specificity of 83% and 90% for detection of major depression at a cut-off of ≥13, and a sensitivity and specificity of 61% and 94% for detection of at least minor depression (National Institute of Health and Clinical Excellence 2014).

The SF-36 was developed by Ware and Sherbourne in 1992 as a multi-purpose measure of health-related quality of life and was based on findings from the Medical Outcomes Study (MOS) (Stewart, Hays et al. 1988; Ware & Sherbourne 1992). The SF-36 assesses eight health concepts to form eight quality of life scales: 1) physical functioning; 2) social functioning; 3) role limitations due to physical problems; 4) bodily pain; 5) general mental health; 6) role limitations due to emotional problems; 7) vitality; and 8) general health perceptions (Ware & Sherbourne 1992). The SF-36 is a self-administered questionnaire containing 36 items, with between two and six possible responses for each question and takes five to ten minutes to complete (Ware & Sherbourne 1992). The original scoring system for the SF-36 is complex, but a more straightforward system has been developed and validated by the RAND Corporation (RAND Corporation 2018). The 36 items in both the original MOS SF-36 and RAND 36-Item Health Survey (RAND SF-36) are identical (RAND Corporation 2018). Each item in the RAND SF-36 is scored between 0 and 100, with items in each of the eight scales then averaged together to create the scale score (RAND Corporation 2018). Higher scores define a more favorable health state (RAND Corporation 2018). Prior systematic review has identified a lack of validated quality of life measures for use during pregnancy and called for an appropriate pregnancy-specific tool to be developed (Mogos, August et al. 2013). In the meantime, the SF-36 is

considered an appropriate measure (Da Costa, Dritsa et al. 2010; Jomeen & Martin 2005) and is one of the most common quality of health scales used in pregnancy (Mogos, August et al. 2013).

Chapter 3 Aims and hypotheses

Despite significant research efforts, rates of spontaneous preterm birth continue to rise in most countries where accurate data are available. As illustrated in Chapter 2, there is evidence to support the use of predictive tools and interventions to prevent spontaneous preterm birth and improve perinatal outcomes in both symptomatic and asymptomatic high risk women. This thesis presents the results of six studies that collectively aim to optimise the care of women at high risk of spontaneous preterm birth. In this chapter I will detail the specific aims, hypotheses and objectives for each of the individual studies. Methodology and results are presented for each study in Chapters 4 to 9.

This research will benefit women at high risk of spontaneous preterm birth through improvements in clinical care. It will inform clinicians and policy makers by providing evidence for best practice in the care of women at high risk of spontaneous preterm birth. Work is under way with key stakeholders to develop a proposal for a New Zealand-wide preterm birth prevention programme, as recommended by the Perinatal and Maternal Mortality Review Committee (Perinatal and Maternal Mortality Review Committee 2018). Standardisation of care for women at risk of preterm birth and a targeted introduction of preterm birth clinics across New Zealand will form an integral part of this proposed national initiative.

3.1 Theme 1: Vaginal biomarkers in symptomatic women

3.1.1 An implementation strategy for fetal fibronectin use in the management of threatened preterm labour

Aim: To assess whether the use of a multi-faceted implementation strategy improves adherence to a clinical practice guideline for the use of fetal fibronectin (fFN) testing in women with threatened preterm labour.

Rationale and hypothesis: Clinical practice guidelines can have major impact on health outcomes, however require integration into the clinical setting in order to change clinical practice (Grimshaw, Eccles et al. 2004). In obstetrics, the use of multi-faceted implementation strategies including audit and feedback, with facilitation by local opinion leaders have been shown to be most effective at changing clinician behaviour (Chaillet, Dubé et al. 2006). Poor compliance to an existing clinical practice guideline on fFN use was identified as an area of concern in a large maternity hospital in Auckland, New Zealand, providing opportunity for improvement in care. We hypothesised that the use of a multi-faceted implementation strategy would improve clinician's knowledge on the correct use of fFN in the assessment of women with threatened preterm labour, as well as improve adherence to a clinical practice guideline for the use of fFN testing and subsequent management based on the result. A quality improvement project was designed to investigate this.

Objectives:

- To assess the effect of a multi-faceted educational intervention on:
    - Clinician's knowledge on the correct use of fFN in the assessment of women with threatened preterm labour.
    - Clinician's compliance to a clinical guideline on the use of fFN and subsequent management based on the fFN result.

This study is described in further detail in Chapter 4.

3.1.2 Comparing the impact of vaginal biomarkers on clinical practice when used in the management of women with threatened preterm labour

Aim: To compare the impact of three vaginal biomarker tests on clinical practice when used in women with threatened preterm labour.

Rationale and hypothesis: Whilst the predictive ability of qualitative fFN, quantitative fFN and placental alpha microglobulin-1 (PAMG-1) have been assessed, no prior study has directly compared the performance of these vaginal biomarkers in clinical practice for women with threatened preterm labour. Previous studies have suggested that quantitative fFN and PAMG-1 may perform better than the qualitative fFN test, which is widely used in New Zealand. In a study from the United Kingdom, symptomatic women with an intermediate fFN level of 50-199 ng/mL had an overall increased risk of spontaneous preterm birth, but the risk of delivery over the following seven days was negligible (Abbott, Radford et al. 2013). Knowledge of the absolute fFN concentration may therefore allow clinicians to individualise management and utilise a higher threshold for antenatal hospital admission for threatened preterm labour. Furthermore, an early study suggested PAMG-1 had a superior positive predictive value compared to fFN, with a similar negative predictive value (Nikolova, Bayev et al. 2014). Thus, we hypothesised that a change from qualitative fFN to quantitative fFN and/or PAMG-1 could reduce rates of antenatal admission and unnecessary interventions without compromising antenatal care in women with threatened preterm labour.

Objectives:

- To assess the rates of intervention in women with threatened preterm labour if managed according to qualitative fFN compared to rates of interventions if managed according to pre-defined protocols for qualitative fFN, quantitative fFN and PAMG-1. The interventions include:
    - Antenatal hospital admission.
    - Administration of antenatal corticosteroids.
    - Administration of antenatal magnesium sulphate.
    - *In utero* transfer to an appropriate level neonatal unit.
- To assess whether any reduction in intervention would compromise antenatal care in women with spontaneous preterm birth within seven days of testing, defined as:
    - Delivery ≤34 weeks of gestation without receiving corticosteroids >48 hours and <7 days from delivery, where it was clinically appropriate.

- Delivery <30 weeks of gestation without receiving magnesium sulphate >4 hours and <24 hours from delivery, where it was clinically appropriate.
- Delivery ≤32 weeks of gestation in a hospital without a Level 2 or 3 Neonatal Unit.

This study is described in further detail in Chapter 5.

3.2 Theme 2: Specialised preterm birth clinics

3.2.1 Specialised preterm birth clinics: a systematic review

Aim: To assess current practice in specialised preterm birth clinics globally.

Rationale: Preterm birth clinics are not in common use in New Zealand and Australia, but the development of state-wide and national preterm birth prevention initiatives are likely to result in the introduction of more of these specialised clinics. Until recently there were no national or international guidelines on the protocols and care pathways to be used in preterm birth clinics, with practice often based on local expert opinion. As a result, heterogeneity in practice has been identified as an issue in preterm birth clinics in the United Kingdom (Care, Ingleby et al. 2019). This systematic review of the preterm birth clinic literature was designed to assess current practice in specialised preterm birth clinics, and findings will be used to inform the future development of new preterm birth clinics in New Zealand. Results can also be used to quantify variation in practice, which can be used in future work on improving consistency in care.

Objectives:

- To assess what criteria are used for referral to preterm birth clinics.
- To determine what investigations and interventions are being offered in preterm birth clinics.
- To assess the timing and frequency of review in preterm birth clinics.

This study is described in further detail in Chapter 6.

3.2.2 The experience and outcomes of a specialised preterm birth clinic in New Zealand

Aim: To assess the experience and outcomes from five years of practice in the first specialised preterm birth clinic in New Zealand.

Rationale: Few studies have described the experience and outcomes from specialised preterm birth clinics in Australasia. The first preterm birth clinic in New Zealand was introduced in 2013 in a large maternity hospital in Auckland. A detailed review of the first five years of practice in this clinic provides opportunity to obtain information on resource and training needs that can be used by policy makers and clinicians to inform the future implementation of new preterm birth

clinics in New Zealand. Information on local outcomes can also be used by clinicians in patient counselling.

Objectives:

- To report the demographic details and risk factors for preterm birth for women cared for in a preterm birth clinic in New Zealand.
- To describe the rates of investigations and interventions performed and the results of investigations.
- To assess the pregnancy, birth and perinatal outcomes for women and their babies.
- To compare the outcomes from a New Zealand preterm birth clinic with those published in the international literature.

This study is described in further detail in Chapter 7.

3.2.3 The psychological wellbeing of women cared for in a specialised preterm birth clinic

Aim: To report the prevalence of symptoms of anxiety and depression in women cared for in a specialised preterm birth clinic and to assess the potential impact of care on psychological wellbeing.

Rationale and hypotheses: Anxiety and depression are common in pregnancy and women with high risk pregnancies have higher rates than the general pregnant population (Dagklis, Tsakiridis et al. 2018; Fairbrother, Young et al. 2017). Whilst many believe that care in a specialised preterm birth clinic reduces maternal anxiety, it is possible that the additional information and appointments may increase it. There is little research in this area. We hypothesised that asymptomatic women at high risk of spontaneous preterm birth who are cared for in a preterm birth clinic will have fewer symptoms of anxiety (primary hypothesis) and depression, improved quality of life scores, and decreased pregnancy-related anxiety (secondary hypotheses) after their second consultation in a preterm birth clinic compared to before their first, and that this improvement in psychological wellbeing would be sustained at the end of the second trimester.

Objectives:

- To assess the incidence of symptoms of anxiety and depression, and health-related quality of life in pregnant women at increased risk of spontaneous preterm birth who are being cared for in a preterm birth clinic at three different time points:

    - Prior to their first appointment (baseline, usually around 12-14 weeks).
    - After their second appointment (usually two weeks after the first).
    - After their last appointment (usually around 24 weeks).
- To assess the potential impact of care from a preterm birth clinic on psychological wellbeing.
- To assess women's perceptions of care in a preterm birth clinic.

This study is described in further detail in Chapter 8.

3.3 Theme 3: Care when birth is expected at peri-viable gestations

3.3.1 Perinatal care for women and their babies who deliver at 23 and 24 weeks of gestation

Aim: To assess the antenatal counselling and perinatal care provided to mothers and their babies when birth occurs at 23 and 24 weeks of gestation.

Rationale: Few babies are born at the peri-viable gestations of 23 and 24 weeks, yet they have high rates of mortality and morbidity (Raju, Mercer et al. 2014). Antenatal counselling is an essential aspect of care when birth is expected at these extremely premature gestations to ensure a family-centred approach to care. This study provides an in-depth review of the antenatal counselling and perinatal interventions for all births at these gestational ages over a two year period at a busy tertiary maternity hospital in New Zealand. Information obtained is used to identify areas where care could be optimised for these very high risk pregnancies.

Objectives:

- To assess the documented antenatal counselling provided to women and their families prior to birth at 23 and 24 weeks of gestation.
- To assess the obstetric and neonatal interventions provided to women and their babies when birth occurs at 23 and 24 weeks of gestation.
- To assess the demographic details, risk factors for preterm birth, and pregnancy and neonatal outcomes in this cohort.
- To explore inequities by ethnicity, socioeconomic status and planned location of delivery.

This study is described in further detail in Chapter 9.

Chapter 4 An implementation strategy for fetal fibronectin use in the management of threatened preterm labour

4.1 Preface

Fetal fibronectin (fFN) has been identified as a useful test to predict which women presenting with symptoms of preterm labour will go on to deliver within the following days and hence will benefit from interventions aimed at improving perinatal outcomes such as antenatal corticosteroids and hospital admission. However, it has also been noted that effective use of fFN relies on clinical practice change from clinicians. This chapter outlines the results of a quality improvement project which used a multi-faceted approach to improve clinician compliance to a clinical practice guideline for the use of qualitative fFN in the assessment and management of women with threatened preterm labour.

This chapter has been published as a manuscript in the *European Journal of Obstetrics & Gynecology and Reproductive Biology* (Dawes, Subramoney et al. 2018). The following chapter contains the original manuscript in line with the author's rights to reproduce for scholarly purposes.

4.2 Increasing compliance with a clinical practice guideline for fetal fibronectin testing and the management of threatened preterm labour: A quality improvement project

Dawes LK, Subramoney M, Miller LM, Groom KM.

4.2.1 Abstract

Objective: To increase adherence to a local hospital clinical practice guideline for the use of fFN testing in women presenting with symptoms of threatened preterm labour.

Study design: A quality improvement project using a multi-faceted implementation strategy.

Setting: National Women's Health, Auckland City Hospital; a tertiary referral maternity unit in Auckland, New Zealand.

Population: All obstetricians, junior obstetric doctors and hospital employed midwives.

Methods: A pre-education audit and survey, compulsory interactive educational intervention with audit feedback and provision of reminders followed by a post-education audit and survey one year later.

Main outcome measures: Number of fFN tests performed, proportion of tests performed meeting clinical criteria for testing and proportion of results managed according to hospital guideline.

Results: There was a 25% increase in the number of tests performed with an increase in the proportion that met clinical criteria for testing, 76% (31/41) – 93% (51/55) (OR 4.1, 95% CI 1.2–14.2). Adherence to guidelines for clinical management according to fFN results changed over time, 80% (33/41) – 95% (52/55) (OR 4.2, 95% CI 1.04–17.0). Clinician knowledge on some (but not all) indications for fFN testing improved. Education and reminders did not improve understanding of clinical scenarios that may result in a false positive fFN test.

Conclusions: A multi-faceted approach of audit and clinician feedback, interactive education and reminders supports the implementation of a clinical practice guideline for the use of fFN as a preterm birth prediction test for women presenting with symptoms of threatened preterm labour.

4.2.2 Introduction

Early preterm birth before 34 weeks gestation is associated with significant perinatal mortality and morbidity. Preterm birth is the leading direct cause of neonatal death, accounting for almost one third of neonatal deaths worldwide (Lawn, Gravett et al. 2010). Despite attempts to reduce preterm birth, rates are increasing across almost all countries that report reliable data (March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012). There are no effective treatments that stop preterm labour, so strategies to improve perinatal outcome rely on accurate identification of those at risk of imminent preterm birth to target interventions proven to reduce perinatal mortality and morbidity despite early birth. These interventions include the administration of antenatal corticosteroids for fetal lung maturation (Crowther, McKinlay et al. 2015; Liggins & Howie 1972; Roberts, Brown et al. 2017), the administration of magnesium sulphate for fetal neuroprotection (Antenatal Corticosteroid Clinical Practice Guidelines Panel

2015; Doyle, Crowther et al. 2009), and *in utero* transfer to a facility with appropriate neonatal intensive care support (Chien, Whyte et al. 2001).

Accurate identification of those at risk of spontaneous preterm birth remains a significant challenge. Signs and symptoms of preterm labour are relatively poor indicators of which women will actually go on to deliver preterm, with >70% of women presenting in threatened preterm labour delivering after 37 weeks (Berghella & Saccone 2016). Preterm birth prediction tests such as the vaginal biomarkers fetal fibronectin (fFN) and placental alpha microglobulin-1 (PAMG-1, PartoSure®), may allow us to triage women with symptoms of preterm labour to identify those women at highest risk of preterm birth and to target interventions that reduce perinatal mortality and morbidity most appropriately, whilst reducing unnecessary interventions for those at lower risk (Peaceman, Andrews et al. 1997).

Observational studies of practice after the introduction of routine fFN testing suggest that clinicians alter the care they provide according to fFN result (Dutta & Norman 2010; Foster & Shennan 2014; Giles, Bisits et al.) but that change in practice develops over time suggesting experience and confidence in the test contribute to practice change (Groom, Liu et al. 2006). However, a recent systematic review of six randomised trials of fFN testing (revealed fFN result versus concealed result or no fFN test) demonstrated no difference in the antenatal management received or subsequent rates of preterm birth and perinatal outcome with slightly higher mean hospital costs associated when fFN results were available (Berghella & Saccone 2016). Publication of this review included editorial comment that the continued use of fFN testing in women with threatened preterm labour could not be justified. However in three of the six included trials treatment was left to 'physician's discretion' regardless of whether the fFN result was revealed or, when it was, if the result was positive or negative. The true value of fFN can only be examined if clinicians are aware of the result and alter their practice accordingly.

Clinical practice guidelines at national, regional and local levels include advice not only on the use of fFN testing but also management plans according to the subsequent result (Crowther, McKinlay et al. 2015; National Institute for Health and Care Excellence 2015). However, availability of clinical practice guidelines alone may be insufficient to influence clinicians to make this practice change. Indeed we identified the use of fFN testing in women presenting with symptoms of preterm labour as an area of concern after an audit in our local unit showed that a significant proportion of fFN tests and the management of women with threatened preterm labour did not comply with local hospital guidelines. The Royal College of Obstetricians and

Gynaecologists defines clinical audit as a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change (Cameron 2014). We therefore established this quality improvement project to implement such a change in practice. We used a multi-faceted approach of audit and clinician feedback, interactive education and reminders to enhance adherence to the local hospital clinical practice guideline for the use of fFN testing in women presenting with symptoms of threatened preterm labour.

4.2.3 Methods

This quality improvement project was initiated by the Performance Improvement Team at Auckland District Heath Board (ADHB) and was carried out at National Women's Health, Auckland City Hospital, a tertiary referral maternity unit in Auckland, New Zealand with approximately 7000 births per year. The team consisted of a project manager from the Performance Improvement Team, a senior obstetrician, clinical director of obstetric services, two obstetricians in training and a senior hospital midwife. A five step process was undertaken (Figure 4.1).

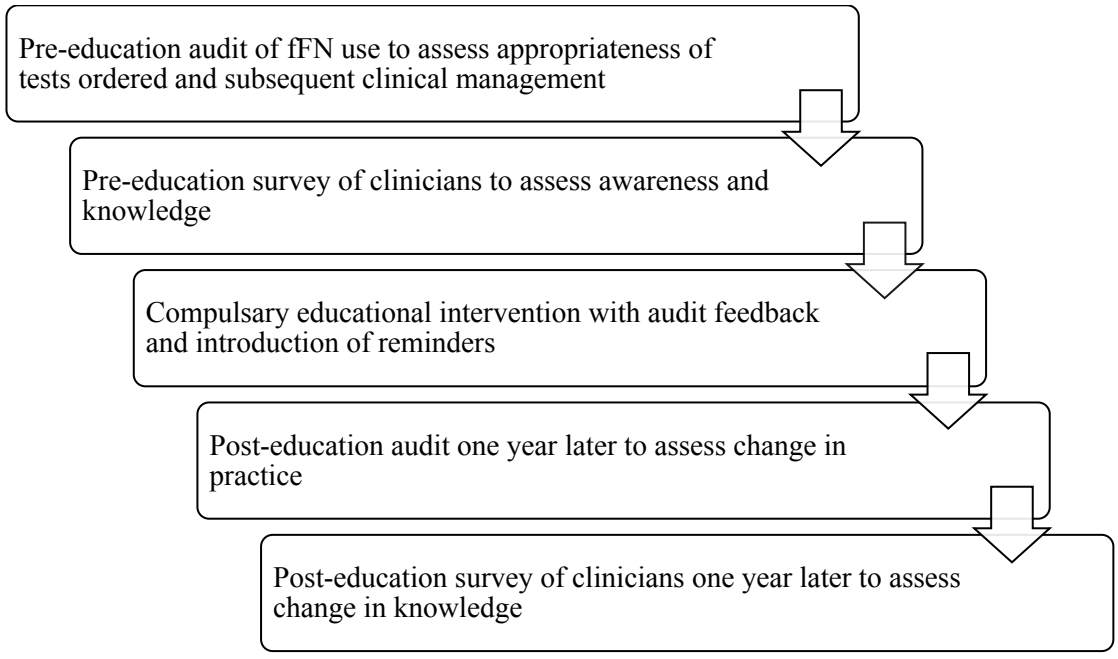

Figure 4.1 Five steps of the quality improvement process

I. Pre-education audit

An audit of fFN testing and subsequent clinical management of tests was carried out. This pre-education audit assessed all fFN tests performed in the four month period from 1 December

2012 until 31 March 2013, as identified from central laboratory records. Two clinicians independently reviewed each woman's electronic clinical records against a pre-defined checklist of criteria, and review from a third senior clinician was utilised to resolve any discrepancies.

Information was collected on age, ethnicity, gestation and clinical details to assess whether the fFN testing met hospital guideline inclusion criteria for testing (Supplementary Table 4.5). The fFN test result (positive >50 ng/mL or negative ≤50 ng/mL) and clinical management was recorded including admission to hospital; administration of antenatal corticosteroids, tocolysis and magnesium sulphate if <30 weeks gestation; use of ultrasound scan and neonatologist review. Information was also collected on gestation at delivery; time interval from fFN testing to delivery; and if preterm birth occurred, whether this was spontaneous or indicated. All information was entered into a Microsoft Access database. Utilising this data, three questions were considered for each case:

1. Did fFN testing meet hospital guideline criteria?
2. Was fFN testing deemed clinically appropriate?
3. Was subsequent clinical management based on the fFN result clinically appropriate?

Clinical appropriateness of fFN testing was considered in addition to whether testing met hospital criteria due to identification of a number of fFN tests that had not been discussed with an obstetric specialist yet met all other hospital criteria and were considered clinically appropriate. Appropriateness of subsequent clinical management according to the fFN result was determined by adherence to recommendations from the hospital guideline, whereby women with a negative fFN and no other clinical concerns should be discharged home with later clinic follow-up, and those with positive results should be admitted to hospital, antenatal corticosteroids administered, tocolysis considered and magnesium sulphate given for fetal neuroprotection if <30 weeks gestation and if delivery is considered imminent.

II. Pre-education survey

An electronic survey was created to assess clinician's knowledge and usual practice. The survey included eight clinical scenarios to assess knowledge of fFN inclusion and exclusion criteria, two clinical scenarios to assess appropriate management of positive and negative results, and questions on cost of fFN, hospital guidelines for its use and clinical situations that would provide a false positive result (Supplementary Table 4.6). The survey was distributed via Survey Monkey to all obstetricians, junior doctors and hospital employed midwives working within the

unit to explore their understanding of indications for fFN testing and subsequent management. A single follow-up email reminder to complete the survey was sent.

III. Compulsory educational intervention

Once the audit and survey were completed all obstetricians, junior doctors and hospital employed midwives working within the unit were invited to attend a compulsory educational session. This was carried out as multiple, small group in-service education sessions. These 30 minute sessions were carried out at a variety of times of the day to improve accessibility for all staff to attend. Attendance was recorded and clinical managers were informed of non-attenders. The interactive educational intervention included presentation of the pre-education audit and survey findings, details of hospital guidelines and evidence to support best practice. Educational posters were displayed in acute service areas, aide memoires were provided to clinicians to carry on their lanyards and a brief summary of recommended management was displayed alongside the fFN result on the hospital electronic results system.

IV. Post-education audit

The audit was repeated one year after the educational intervention (1 December 2012 to 31 March 2014) to assess change in knowledge and practice. The post-education audit process was identical to the pre-education audit, and carried out by the same investigators.

V. Post-education survey

The survey was repeated one year after the educational intervention. The post-education survey was identical to the pre-education survey and was emailed to the same groups of clinicians. A single reminder email was sent prior to closure of the survey.

Clinician practice and clinician knowledge were measured by audit and survey respectively. Pre- and post- educational intervention practice and responses were compared. Odds ratios (with 95% confidence intervals) were estimated, as a measure of size effect comparing pre- and post-intervention rates. This was considered a low risk observational study, in line with the New Zealand Standard Operating Procedures for Health and Disability Ethics Committees, approval from an Ethics Committee was not required (Health & Disability Ethics Committees 2014).

4.2.4 Results

A total of 96 fFN tests were performed over the two audit periods, 19 (19.8%) women had a positive result. Four of 19 women with a positive fFN result delivered within seven days (21.1%) and five within 14 days (26.3%). Of the 77 women with a negative fFN result, two delivered within seven days of testing, both for reasons other than spontaneous preterm labour (caesarean section delivery at time of laparotomy for a bowel obstruction and caesarean section after diagnosis of pre-labour uterine rupture). A further three women with a negative fFN test delivered between seven and 14 days of testing, only one of these went into spontaneous labour <34 weeks gestation.

Over a one month period 116/123 (94.3%) clinicians attended one of 25 in-service education sessions. There were a similar number of survey respondents pre- (48/86, 56%) and post- (50/86, 58.1%) educational intervention. The survey respondents were representative of the clinicians working within the unit at each time point (Table 4.1).

Table 4.1 Clinical roles of respondents in pre- and post-education survey

Respondents	**Pre-education Survey n=48**	**Post-education Survey n=50**
Consultant	17 (35.4)	20 (40.0)
Midwife	11 (22.9)	10 (20.0)
Registrar	9 (18.8)	15 (30.0)
Senior house officer	11 (22.9)	5 (10.0)

Data expressed as number (percentage).

Fetal fibronectin testing practice change

There was a 25% increase in the number of fFN tests performed, from 41 to 55 tests, over the same four calendar month periods pre- and post- educational intervention. There was a similar proportion of positive/negative results pre- and post- educational intervention (Table 4.2). There was no difference seen pre- and post- educational intervention in the proportion of tests performed that met the hospital guidelines for testing. However, after excluding the criteria 'discussion with an obstetric specialist' there was a significant increase in the proportion of cases that met clinical criteria for testing following the educational intervention and use of reminders, 76% (31/41) – 93% (51/55) (OR 4.1, 95% CI 1.2–14.2) (Table 4.2). There was also

improved adherence to guidelines for the clinical management according to fFN results, 80% (33/41) – 95% (52/55) (OR 4.2, 95% CI 1.04–17.0) (Table 4.2).

Clinician knowledge change

There was a significant increase in the proportion of clinicians that were aware of the existence of a local hospital guideline for fFN use following the educational intervention (36/48, 75% – 47/48, 98%, OR 15.7, 95% CI 1.6–126). The majority of respondents were already aware of the gestational ages at which fFN testing should be considered before the educational intervention was introduced but fewer were aware that fFN testing could be done with a short cervical length (seen on transvaginal scan) or when the cervix was 2 cm dilated. Knowledge improved after the educational intervention with regards to cervical dilatation but not cervical length (Table 4.3). The majority of clinicians were aware that recent sexual intercourse and vaginal bleeding may result in a false positive fFN but had less knowledge regarding clinical scenarios that would not result in a false positive and this knowledge did not significantly improve after the compulsory educational intervention (Table 4.3). The pre-education survey showed a lack of knowledge of, or a reluctance to follow, clinical practice guidelines particularly for a woman with contractions but a negative fFN; only 3/44 (7%) of respondents selected discharge home with no tocolysis or corticosteroid treatment in this scenario. In the post-education survey 29/48 (60%) of respondents correctly selected discharge home with no tocolysis or corticosteroid treatment for a woman with a negative fFN (OR 20.9, 95% CI 5.6–77) (Table 4.4). Planned management of positive fFN results was more consistent with hospital guidelines at baseline, however 17/44 (39%) of respondents in the pre-education survey still planned to withhold corticosteroids and tocolysis for a women with a positive fFN result.

Table 4.2 Fetal fibronectin testing practice pre- and post-educational intervention

	Pre-education audit (n=41)	**Post-education audit (n=55)**	**Odds ratio (95% CI)**
Number of positive fFN tests	8/41 (19.5)	11/55 (20.0)	1.0 (0.4-2.7)
Hospital guidelines for testing met	11/41 (26.9)	12/55 (21.8)	0.8 (0.3-2.0)
Clinical criteria for testing met [a]	31/41 (75.6)	51/55 (92.7)	4.1 (1.2-14.2)
Clinical management according to hospital guidelines			
All fFN tests	33/41 (80.5)	52/55 (94.5)	4.2 (1.04-17.0)
Positive fFN	7/8 (87.5)	11/11 (100)	[b]
Negative fFN	26/33 (78.8)	41/44 (93.2)	3.6 (0.9-15.5)

Data expressed as number/total tests (percentage).

fFN – fetal fibronectin.

[a] All inclusion criteria met except 'discussion with specialist obstetrician'.

[b] Event rates includes 0/1 and so no formal testing performed.

Table 4.3 Clinician knowledge pre- and post-educational interventions: indications for fetal fibronectin testing

Survey Question	**Correct Responses Pre-education**	**Correct Responses Post-education**	**Odds ratio (95% CI)**
Awareness of hospital guideline for fFN use	36/48 (75.0)	47/48 (97.9)	15.7 (1.6-126)
Inclusion/exclusion criteria correctly identified in clinical scenarios			
Gestation 23^{+2} weeks	35/48 (72.9)	40/50 (80.0)	1.5 (0.6-3.8)
Gestation 26^{+2} weeks	48/48 (100)	50/50 (100)	[a]
Gestation 33^{+2} weeks	45/48 (93.8)	47/50 (94.0)	1.0 (0.2-5.4)
Gestation 34^{+2} weeks	40/48 (83.3)	44/50 (88.0)	1.5 (0.5-4.6)
TV USS Cervical length 18 mm	29/48 (60.4)	34/50 (68.0)	1.4 (0.6-3.2)
Cervix 2 cm dilated	24/48 (50.0)	43/50 (85.0)	6.1 (2.3-16.3)
Cervix 4 cm dilated	46/48 (95.8)	47/50 (94.0)	0.7 (0.1-4.2)
Ruptured membranes	46/48 (95.8)	49/50 (98.0)	[a]
Discussion with specialist prior to sending fFN to laboratory	20/48 (41.7)	38/50 (76.0)	4.4 (1.9-10.5)
Correct identification of factors that may/may not cause a false positive result			[a]
Intercourse in last 24 hours [b]	47/48 (97.9)	48/50 (96.0)	0.7 (0.2-2.4)
Vaginal bleeding [b]	43/48 (89.6)	43/50 (86.0)	1.3 (0.6-2.8)
Speculum exam in last 24 hours [b]	27/48 (56.3)	31/50 (62.0)	1.8 (0.6-5.3)
Ruptured membranes [c]	6/48 (12.5)	10/50 (20.0)	0.8 (0.4-1.9)
Cervix 4 cm dilated [c]	29/48 (60.4)	28/50 (66.0)	0.7 (0.3-1.7)
Bacterial vaginosis [c]	38/48 (79.2)	36/50 (72.0)	
Correct knowledge of fFN cost	24/44 (55.5)	29/48 (60.4)	1.4 (0.6-3.3)

Data expressed as number/total (percentage). Denominator reflects numbers of respondents that answered each individual question.

fFN – fetal fibronectin, TV USS - transvaginal ultrasound scan.

[a] Event rate includes 0/1 and so no formal testing performed.

[b] May be a cause of false positive result.

[c] Not a cause of false positive result (if positive = true positive).

Table 4.4 Clinician knowledge pre- and post-educational intervention: preferred management according to clinical scenario

Management of fFN result in clinical scenario	**Pre-education Survey**	**Post-education Survey**	**Odds ratio (95% CI)**
For a woman at 29^{+2} weeks with contractions 4 in 10 minutes, a closed cervix 1 cm long, and a NEGATIVE fFN test:			
Admit for observation only	28/44 (63.6)	17/48 (35.4)	0.3 (0.1-0.7)
Admit, corticosteroids and tocolysis	10/44 (22.7)	1/48 (2.1)	[a]
Admit and tocolysis only	3/44 (6.8)	1/48 (2.1)	[a]
Discharge home (correct management)	3/44 (6.8)	29/48 (60.4)	20.9 (5.6-77)
For a woman at 31 weeks with blood stained show, contracting 2 in 10 minutes, with a long closed cervix, and a POSITIVE fFN test:			
Admit for observation only	17/44 (38.6)	11/48 (22.9)	0.5 (0.2-1.2)
Admit, steroids and tocolysis (correct management)	25/44 (56.8)	35/48 (72.9)	2.0 (0.9-4.9)
Admit and tocolysis only	1/44 (2.3)	1/48 (2.1)	[a]
Discharge home	1/44 (2.3)	1/48 (2.1)	[a]

Data expressed as number/total tests (percentage). Denominator reflects numbered of respondents that answered each individual question.

fFN - fetal fibronectin.

[a] Event rate includes 0/1 and so no formal testing performed.

4.2.5 Discussion

Main findings

This quality improvement project demonstrated that a multi-faceted approach of audit and clinician feedback, interactive education and reminders increased the number of fFN tests being performed in our unit. There was an improvement in clinician's knowledge in some aspects of care according to fFN results leading to an increase in the proportion of tests being performed meeting clinical criteria for testing and with improved adherence to clinical management guidelines resulting in a change in practice once testing was performed.

Strengths and limitations

The local hospital clinical guidelines for fFN testing and management for women with threatened preterm labour are similar to other published guidelines, allowing the results of this study to be generalisable. As there were no changes made to the assessment and management of women with threatened preterm labour within our unit during the study period it is likely that the changes seen in this quality improvement project are attributable to the audit and clinician feedback, interactive education and reminders. The independent assessment of clinical notes by two investigators and utilisation of the same investigators for both time-periods of audit limited potential bias in data interpretation and collection. The relatively small number of cases from a single unit may be seen as a limitation of this study however, it does include practice over a 15 month period in a busy tertiary obstetric unit. A further limitation of the study is the change in staff over the duration of the study. There is unlikely to have been significant change in senior obstetricians and hospital employed midwives, however, junior doctors are likely to have rotated through other training units and specialties. Despite this we were still able to demonstrate practice change, supporting this multi-faceted approach to clinical practice guideline implementation as a sustainable one.

Interpretation

Clinical practice guidelines are recommendations for clinicians about the care of patients with specific conditions. They should be systematically developed statements based on published evidence and practice experience. Clinical practice guidelines across most areas of obstetric practice are now widely available but effective implementation remains a challenge. There are a wide variety of methods employed to increase the uptake of clinical practice guidelines including the use of didactic education, interactive education, educational outreach (academic detailing), audit and feedback, reminders, opinion leaders, financial incentives and cost-

effectiveness studies with varying levels of success (Prior, Guerin et al. 2008). Obstetric practice has been identified to differ from other medical specialties with regard to which strategies are most effective for implementation of clinical practice guidelines (Chaillet, Dubé et al. 2006). A systematic review on evidence based strategies for implementing guidelines in obstetrics has shown educational strategies with medical providers are generally ineffective but have mixed effects for para-medical providers (nursing and midwifery staff) and that audit and feedback, use of reminders and multi-faceted strategies were most effective for change in behaviour (Chaillet, Dubé et al. 2006). We are unable to explore further the exact contribution of each factor within our strategic approach and which was most successful. However, the sustained change in practice seen with re-audit and re-survey one year later is encouraging and, like previous research, supports a multi-faceted approach to enhance clinical practice guideline implementation.

4.2.6 Conclusion

Accurate identification of women at risk of preterm birth is a significant challenge. Preterm birth prediction tests only have value if tests are applied appropriately and results interpreted in a standard way including a change in practice. The availability of clinical practice guidelines alone is often insufficient to influence clinicians to make this practice change. A multi-faceted approach of audit and clinician feedback, interactive education and reminders enhance the implementation of a clinical practice guideline for the use of fFN as a preterm birth prediction test for women presenting with symptoms of preterm labour.

4.2.7 Supplementary information

Table 4.5 Local hospital guideline criteria for fetal fibronectin testing

Inclusion Criteria	Exclusion Criteria
▪ 24^{+0}-34^{+0} weeks gestation ▪ Membranes intact ▪ Fetus alive and viable ▪ Cervix <3 cm dilated and >1 cm long ▪ Considering use of steroids +/- tocolysis ▪ Discussed with obstetric specialist	▪ Complications requiring early delivery e.g. abruption ▪ Ruptured membranes ▪ Cervix >3 cm dilated or <1 cm long ▪ Vaginal bleeding [a] ▪ Sexual intercourse in last 24 hours [a] ▪ Digital vaginal examination in last 24 hours [a]

[a] Test can still be taken if considering steroids and tocolysis. A negative result is a true result. A positive result maybe a false positive, but will not alter planned management.

Table 4.6 Survey questions

1. What is your role at ADHB? ☐ Senior house officer ☐ Registrar ☐ Midwife ☐ Consultant
2. Prior to ordering a fFN test, you should: ☐ Consult with the charge midwife ☐ Consult with the consultant ☐ Not consult with anyone ☐ Consult with the charge midwife and consultant
3. In a women presenting with threatened preterm labour and each of the following, would you do a fFN test if: Gestational age 34^{+2} ☐ Yes ☐ No Gestational age 33^{+2} ☐ Yes ☐ No Gestational age 26^{+2} ☐ Yes ☐ No

Gestational age 23^{+2}

- ☐ Yes
- ☐ No

Cervix 4 cm dilated

- ☐ Yes
- ☐ No

Cervix 2 cm dilated

- ☐ Yes
- ☐ No

Transvaginal ultrasound cervical length 18 mm

- ☐ Yes
- ☐ No

Ruptured membranes

- ☐ Yes
- ☐ No

4. In what situations could you get a false positive? (Tick all that apply)
   - ☐ Intercourse in last 24 hours
   - ☐ Bleeding
   - ☐ Ruptured membranes
   - ☐ Speculum examination in last 24 h
   - ☐ Cervix 4 cm dilated
   - ☐ Bacterial vaginosis
5. In a woman at 29^{+2} weeks with ongoing contractions 4 in 10, with a 1 cm long closed cervix, and a NEGATIVE fFN test, you would:
   - ☐ Admit for observation only
   - ☐ Admit and give steroids and tocolysis
   - ☐ Admit and give tocolysis only
   - ☐ Discharge home
6. In a woman at 31 weeks with blood stained show, contracting 2 in 10 but settling, with a long closed cervix, and a POSITIVE fFN test, you would:
   - ☐ Admit for observation only
   - ☐ Admit and give steroids and tocolysis
   - ☐ Admit and give tocolysis only
   - ☐ Discharge home
7. Is there an ADHB policy/guideline on fFN testing?
   - ☐ Yes
   - ☐ No
8. How much does a fFN test cost?

- ☐ $50
- ☐ $150
- ☐ $250
- ☐ $500

ADHB, Auckland District Health Board; fFN, fetal fibronectin.

Chapter 5 Comparing the impact of vaginal biomarkers on clinical practice when used in the management of women with threatened preterm labour

5.1 Preface

This chapter compares the performance of three vaginal biomarker tests used in the assessment and management of women presenting with threatened preterm labour. The aim of this study is to assess the impact of qualitative fetal fibronectin (fFN), quantitative fFN and placental alpha microglobulin-1 (PAMG-1) in symptomatic women, determining which biomarker performs best in clinical practice by reducing antenatal interventions without compromising the antenatal care for those that deliver preterm. This prospective observational study provides evidence to optimise the future clinical care of symptomatic women at increased risk of spontaneous preterm birth.

This chapter has been published as a manuscript in *Acta Obstetricia et Gynecologica Scandinavica* (Dawes, Prentice et al. 2019). The following text contains the original manuscript, reproduced under license from the publisher, John Wiley and Sons.

5.2 The Biomarkers for Preterm Birth Study – A prospective observational study comparing the impact of vaginal biomarkers on clinical practice when used in women with symptoms of preterm labour

Dawes LK, Prentice LR, Huang Y, Groom KM.

5.2.1 Abstract

Introduction: This study aims to compare the use of qualitative fetal fibronectin, quantitative fetal fibronectin and placental alpha microglobulin-1 in women with symptoms of preterm labour, to evaluate which vaginal biomarker performs the best in clinical practice.

Material and methods: This prospective observational study included women who presented with symptoms of preterm labour at 24^{+0} to 34^{+0} weeks of gestation at a large tertiary maternity

hospital in Auckland, New Zealand. Women were managed according to hospital guidelines using qualitative fetal fibronectin. Quantitative fetal fibronectin and placental alpha microglobulin-1 tests were also taken, with clinicians blinded to the results. Management and delivery outcomes were collected from clinical records. The primary outcome was the rate of antenatal hospital admission. Analysis was performed according to pre-defined management protocols for each of the tests.

Results: A total of 128 women had all three biomarkers tests taken. Spontaneous preterm birth rates were 7/128 (5.5%) $\leq 34^{+0}$ weeks and 20/128 (15.6%) $<37^{+0}$ weeks of gestation; 5/128 (3.9%) delivered within seven days of testing. Positive results were recorded in 28 qualitative fetal fibronectin tests, 25 quantitative fetal fibronectin tests with 11 ≥200 ng/mL, and 16 placental alpha microglobulin-1 tests. The use of quantitative fetal fibronectin or placental alpha microglobulin-1 would have lowered antenatal admission rates; 27/128 (21.1%) for qualitative fetal fibronectin, 11/128 (8.6%) for quantitative fetal fibronectin (admission threshold ≥200 ng/mL) and 15/128 (11.7%) for placental alpha microglobulin-1. No additional women with quantitative fetal fibronectin <200 ng/mL delivered within seven days or missed corticosteroids compared with standard care (qualitative fetal fibronectin), however, an additional three cases had a false-negative placental alpha microglobulin-1 and clinical care may have been compromised (no antenatal corticosteroids or admission).

Conclusions: The use of quantitative fetal fibronectin (admission threshold ≥200 ng/mL) has the potential to reduce the rate of antenatal admissions for women with symptoms of preterm labour without compromising use of antenatal interventions that improve outcomes for babies born preterm.

5.2.2 Introduction

Strategies to reduce perinatal mortality and morbidity after preterm birth include the antenatal administration of corticosteroids (Roberts, Brown et al. 2017) and magnesium sulphate (Doyle, Crowther et al. 2009) and delivery in a unit with appropriate neonatal support (Chien, Whyte et al. 2001). Tocolysis provides a short-term delay in delivery (Simhan & Caritis 2007) and women are often admitted to hospital for these interventions to occur. However, the majority of women presenting with symptoms of preterm labour do not deliver early. These symptoms are poor predictors of which women will deliver preterm and gain benefit from interventions (Copper, Goldenberg et al. 1990; Iams, Casal et al. 1995). Additional tools, including cervical length

measurement and vaginal biomarkers, allow more accurate assessment of the risk of spontaneous preterm birth ensuring women at highest risk receive appropriate interventions that improve perinatal outcome, whilst reducing unnecessary treatment and costs for those at less risk.

The qualitative fetal fibronectin (fFN) test (Hologic, Marlborough, MA, USA) has been widely validated for the prediction of spontaneous preterm birth and is used for its strong negative predictive value (NPV) (Honest, Bachmann et al. 2002; Peaceman, Andrews et al. 1997), with a concentration of ≥50 ng/mL established as the threshold to define a positive test (Peaceman, Andrews et al. 1997). However, as increasing fFN concentration correlates with increasing positive predictive value (PPV) (Abbott, Radford et al. 2013) a quantitative fFN test (Hologic) has been introduced, allowing clinicians to use absolute values in their assessment. Placental alpha microglobulin-1 (PAMG-1), the PartoSure test, (Parsagen Diagnostics, Boston, MA, USA) is also now widely available with a concentration of ≥1 ng/mL used to define a positive result (Parsagen Diagnostics 2018). Small studies suggest a superior PPV for PAMG-1 compared with qualitative fFN, but a similar NPV (Melchor, Navas et al. 2018; Nikolova, Bayev et al. 2014).

This study evaluates the use of quantitative fFN, PAMG-1 and qualitative fFN in women with symptoms of preterm labour between 24^{+0} and 34^{+0} weeks of gestation, to determine which biomarker performs best in clinical practice, limiting unnecessary interventions without compromising care for the few who deliver preterm.

5.2.3 Materials and methods

This was a single-centre prospective observational study at National Women's Health, Auckland City Hospital, a tertiary maternity unit in Auckland, New Zealand with approximately 7000 births per year. Women with symptoms of preterm labour at 24^{+0} to 34^{+0} weeks who fulfilled hospital criteria for fFN testing (Auckland District Health Board 2018b) were identified by the assessing clinician and invited to participate. Additional inclusion and exclusion criteria are reported in the Supplementary material (Table 5.6).

Following consent and enrolment, the assessing clinician performed a speculum examination (without lubricant) and fFN and PAMG-1 samples were collected from the posterior fornix using the manufacturers' dedicated swabs. Use of a speculum for sample collection is

recommended for fFN testing and is optional for PAMG-1 testing (Hologic 2016c; Parsagen Diagnostics 2015). Ruptured membranes, cervical dilatation ≥3 cm, or vaginal bleeding precluded the use of a qualitative fFN test, (Auckland District Health Board 2018b), so women in whom these were found were no longer eligible and were excluded. Qualitative fFN was processed as point-of-care testing as per manufacturer's instructions using the Hologic TLI_{IQ} machine (Hologic 2016b). Women were managed according to the result as per standard hospital guidance (Auckland District Health Board 2018b). Following qualitative testing, the remaining fFN specimen was refrigerated at 2–8°C for up to three days, then frozen at –20°C for up to three months until batch processing for quantitative fFN as per the manufacturer's instructions using the Hologic 10Q machine (Hologic 2016a; 2016c). The PAMG-1 swab remained at room temperature and was processed by a senior clinician independent of the clinical care being provided within six hours of collection, as per the manufacturer's instructions (Parsagen Diagnostics 2015). Results were recorded and stored in a sealed envelope for collection by the research team. Participants and health-care providers were blinded to quantitative fFN and PAMG-1 results.

Study eligibility was documented by the assessing clinician. Further information including demographics, antenatal management, and delivery and neonatal outcomes were collected from electronic clinical records by the research team. If delivery occurred elsewhere, delivery and neonatal outcomes were requested from the alternative maternity unit.

All preterm births were classified as spontaneous or medically indicated following clinical record review. Spontaneous preterm birth was defined as birth before 37 weeks of gestation after spontaneous onset of labour or rupture of membranes, regardless of whether labour augmentation or caesarean section was required. Medically indicated preterm birth was defined as birth before 37 weeks of gestation necessitated by one or more obstetric or maternal medical conditions that preceded labour or rupture of membranes.

Data was analysed comparing clinical management directed by qualitative fFN with theoretical management according to pre-defined protocols for each test (Figure 5.1). This allowed estimation of any discrepancy between actual practice and best practice determined by clinical practice guidelines; an issue identified in a previous study in our unit (Dawes, Subramoney et al. 2018). Standard practice directed by qualitative fFN is shown in Figure 5.1. The proposed management directed by quantitative fFN was guided by a multi-centre study assessing 300 women with symptoms of preterm labour in which no woman (0/41) with fFN 50–199 ng/mL

delivered within seven days of testing (Abbott, Radford et al. 2013). We therefore selected a threshold ≥200 ng/mL for hospital admission. Although the risk of spontaneous preterm birth is likely negligible within seven days of testing with fFN 50–199 ng/mL, these women still have an increased risk of spontaneous preterm birth (7.7% ≤14 days, 11.5% ≤34 weeks) (Abbott, Radford et al. 2013). Hence, we opted to include corticosteroids at a threshold ≥50 ng/mL as a 'safety net' as >48 hours is required to achieve maximal effect (Roberts, Brown et al. 2017). The planned obstetric review in one week for women with quantitative fFN 50–199 ng/mL was included to identify those with ongoing symptoms who may benefit from a repeat dose of corticosteroids (Crowther, McKinlay et al. 2015).

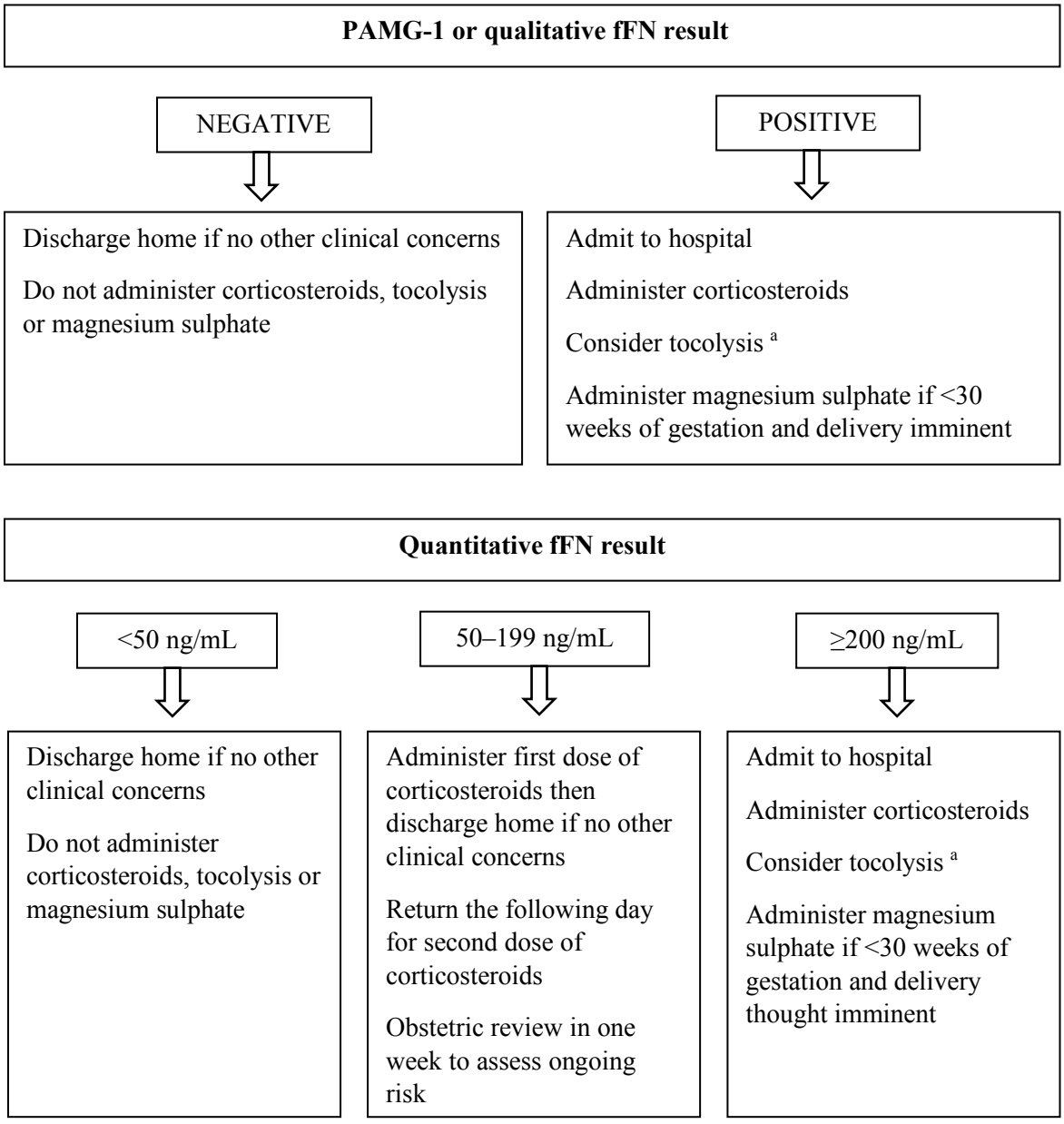

Figure 5.1 Prospective management plans according to biomarker result

Abbreviations: PAMG-1, placental alpha microglobulin-1; fFN, fetal fibronectin.

[a] Tocolytic drug of choice is nifedipine.

The primary outcome was the rate of antenatal hospital admission and secondary outcomes were the rates of corticosteroid and magnesium sulphate administration and *in utero* transfer. These outcomes were selected to allow comparison of rates of antenatal intervention if women were managed according to each vaginal biomarker test. We also assessed whether any reduction in rates of admission or other intervention would compromise care when spontaneous preterm birth occurred within seven days of testing, defined as:

1. Delivery $\leq 34^{+0}$ weeks without antenatal corticosteroids ≥48 hours and <7 days before birth.
2. Delivery $<30^{+0}$ weeks without magnesium sulphate ≥4 hours and ≤24 hours before birth.
3. Delivery $<32^{+0}$ weeks in a hospital without appropriate neonatal support, i.e. does not provide full ventilation and intensive care.

This approach fulfilled the study objective of assessing which vaginal biomarker test performs the best in clinical practice by limiting unnecessary interventions in those who do not deliver within seven or 14 days, without compromising care for those who do.

This observational study was designed to inform clinical practice and consider the safety of change to an alternative biomarker and/or threshold for the assessment of women presenting with symptoms of preterm labour. We took a pragmatic approach to our sample size (planned n = 130) based on the expected number of eligible women and likely recruitment rates for a study of this nature.

Statistical Analyses

Statistical analyses were carried out in IBM SPSS Statistics software (version 25.0) (IBM Corp 2017) and OpenEpi (version 3.01) (Dean, Sullivan et al. 2013). Demographics, obstetric characteristics, and rates of hospital admission and intervention are described using appropriate numerical summary measures. Sensitivity, specificity, PPV, and NPV were calculated as the proportions of spontaneous preterm birth within the time frames described. Wilson score 95% CI are presented. R software (version 3.5.3) (R Core Team 2019) was used to calculate receiver operating characteristic curves for quantitative fFN at different thresholds.

Ethical Approval

Ethical approval was obtained in December 2014 from the New Zealand Health and Disability Ethics Committee (14/NTA/227). Local institutional approval was also obtained in December 2014 from the Auckland District Health Board (A+6424).

5.2.4 Results

Recruitment took place between February 2015 and September 2017; 160 women provided consent to participate and 128 women were included in the final analysis. The majority of exclusions were due to an incomplete set of biomarkers (Figure 5.2), these cases were included in assessment of concordance of biomarker results if two tests had been performed.

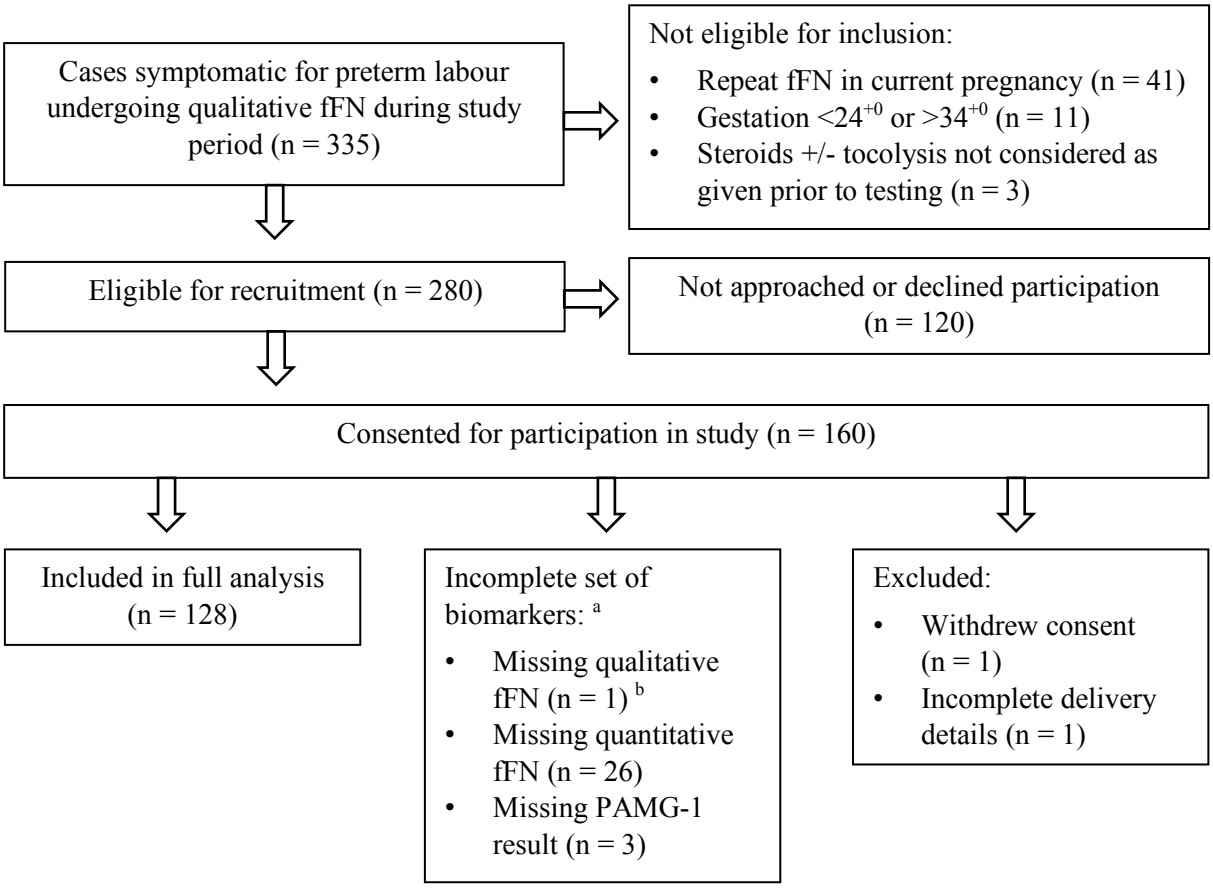

Figure 5.2 Number of women eligible, included in study, follow-up, and analysis

Abbreviations: fFN, fetal fibronectin; PAMG-1, placental alpha microglobulin-1.

[a] Included in analysis of concordant results only.

[b] fFN was taken for qualitative testing, but not processed.

Demographic and obstetric characteristics are described in Table 5.1. The overall rate of spontaneous preterm birth was 20/128 (15.6%). Only 5/128 (3.9%) women had a spontaneous preterm birth within seven days of testing and 6/128 (4.7%) within 14 days of testing. None of the six twin pregnancies delivered within 14 days of testing. Preterm birth was medically indicated in 8/128 (6.3%) pregnancies, all of which occurred after 30^{+0} weeks, and only one within 14 days of testing.

Table 5.1 Participant demographics, obstetric characteristics and birth outcomes

Characteristic	**Participants**	
	n = 128	**% (or SD)**
Maternal age (years)		
Mean ± SD	29.9	± 5.6
Range	16–45	-
Ethnicity		
European	59	46.1
Indian	20	15.6
Pacific Islander	17	13.3
Asian	17	13.3
Māori & Cook Island Māori	9	7.0
Other	6	4.7
Body mass index (kg/m^2) [a]		
Mean ± SD	26.2	± 6.9
Range	18–55	-
Current smokers at booking [b]	15	11.8
Primiparous	55	43.0
Previous preterm birth [b c]		
$<37^{+0}$ weeks of gestation		
None	50	68.5
One	16	21.9
≥Two	6	8.2
$<34^{+0}$ weeks of gestation		
None	63	86.3
One	8	11.0
≥Two	1	1.4
Previous termination of pregnancy [b]		
None	112	88.2
One	9	7.0
≥Two	6	4.6
Previous miscarriage $<20^{+0}$ weeks of gestation [b]		
None	81	63.8
One	28	21.9
≥Two	18	14.1
Plurality		
Singleton	122	95.3

Twins	6	4.7
Vaginal examination or speculum in the 24 hours preceding testing [b]	3	2.4
Sexual intercourse in the 24 hours preceding testing [d]	6	3.9
Gestational age at time of testing (weeks)		
Mean ± SD	30^{+0}	± 18.7 days
Range	24^{+0}–34^{+0}	-
Between 24^{+0} and 29^{+6} weeks of gestation	55	43.0
Gestational age at birth (weeks)		
Mean ± SD	38^{+0}	17.4 days
Range	28^{+0}–42^{+0}	-
Mode of birth		
Normal vaginal delivery	66	51.6
Caesarean section	50	39.1
Instrumental vaginal delivery	12	9.4
Neonatal outcome [e]		
Live born	134	100.0
Early neonatal death	2	1.5
Neonatal intensive care [e]		
Admitted	28	20.9
Mean length of stay (days) ± SD	19.2	18.6

Abbreviation: SD, standard deviation.

[a] Missing data, n = 3.

[b] Missing data, n = 1.

[c] In those with previous pregnancy >20 weeks of gestation.

[d] Missing data, n = 6.

[e] n = 134 babies including six twin pregnancies.

All three test results were concordant in 93/128 (72.7%) cases. Including those where only two biomarker tests were recorded, qualitative and quantitative fFN were concordant in 124/131 (94.7%), and qualitative fFN and PAMG-1 were concordant in 114/154 (74.0%). Of the seven with discordant qualitative and quantitative fFN, the quantitative fFN result was between 40 and 60 ng/mL in three cases. Results were positive in 28/128 (21.9%) of qualitative fFN tests, 25/128 (21.0%) of quantitative fFN tests ≥50 ng/mL, 11/128 (8.6%) ≥200 ng/mL, and 16/128 (12.5%) of PAMG-1 tests.

Table 5.2 summarises the actual rates of antenatal admission and corticosteroid administration by qualitative fFN result and by management according to pre-defined protocols for each test. The antenatal admission rate was 54/128 (42.2%). Of these, 27/54 (50.0%) were admitted despite a negative qualitative fFN; 18/54 (33.3%) had an additional indication for admission (e.g. urinary tract infection), but 9/54 (16.7%) did not and were admitted against standard hospital guidance. If managed according to the pre-defined protocols for each test, admission rates would be 27/128 (21.1%, 95% CI 14.9% to 29%) for qualitative fFN, 11/128 (8.6%, 95% CI 2.7% to 10.9%) for quantitative fFN (threshold ≥200 ng/mL) and 15/128 (11.7%, 95% CI 19.7% to 34.8%) for PAMG-1.

The predicted reduction in antenatal admission and corticosteroid use if managing care by quantitative fFN would not compromise the care provided for women who had a spontaneous birth within 14 days of testing (Table 5.2). However, if managing care by PAMG-1, an additional three women with spontaneous birth within 14 days of testing may have had compromised antenatal care; only 1/6 (16.7%) would have received corticosteroids compared to 4/6 (66.6%) managed by qualitative fFN.

Practice in our unit is to give tocolysis to women with a positive qualitative fFN and ongoing regular and painful uterine contractions. As not all women with a positive biomarker result require tocolysis, we did not analyse theoretical rates of tocolysis for all biomarkers. Tocolysis was administered in 21/128 (16.4%) of cases managed by qualitative fFN result and clinical judgement. All but one of these had a positive qualitative fFN and 17/21 (81.0%) who received tocolysis delivered ≥7 days from testing. Of those that received tocolysis, 7/21 (33.3%) had a quantitative fFN of 50–199 ng/mL and would not have received tocolysis if managed according to the quantitative fFN protocol (Figure 5.1); however, only one of these (14.3%) had a spontaneous preterm birth and this was at 36^{+6} weeks of gestation. None of the additional seven women with quantitative fFN 50–199 ng/mL who did not receive tocolysis delivered within 14 days of testing. PAMG-1 was negative in 16/21 (76.2%) of those who received tocolysis. These 16 women would not have received tocolysis according to PAMG-1 result; however, 4/16 (25.0%) had a spontaneous preterm birth, three of which occurred within seven days of testing.

No women received magnesium sulphate for fetal neuroprotection as a consequence of the qualitative fFN result, as practice in our unit is to wait for cervical dilatation before commencing magnesium sulphate. The administration of magnesium sulphate is therefore less relevant when comparing vaginal biomarker tests. Only one woman had a spontaneous birth at <30 weeks of

gestation within 14 days of testing (positive qualitative fFN, quantitative fFN 480 ng/mL, negative PAMG-1). She received magnesium sulphate five days after testing and this was appropriately timed ≥4 and ≤24 hours from delivery. A second woman delivered spontaneously at <30 weeks of gestation, 17 days after testing, and also received appropriately timed magnesium sulphate (all three biomarkers positive).

All 28 women who delivered preterm were in a hospital with an appropriate-level neonatal unit. If initial assessment and biomarker testing had occurred in a unit without facilities to provide full ventilation and intensive care, *in utero* transfer would be recommended for women with a positive biomarker result if $\leq 32^{+0}$ weeks of gestation (n = 94). In this theoretical scenario, 17/94 (18.1%) would have been transferred if managed by qualitative fFN; 8/94 (8.5%) by quantitative fFN (threshold ≥200 ng/mL); and 12/94 (12.8%) by PAMG-1. Transfer could be considered unnecessary for women who do not deliver within seven days. This would be the case for 14/94 (14.9%) managed by qualitative fFN, 12/94 (12.8%) for quantitative fFN and 9/94 (9.6%) for PAMG-1. There were three women with spontaneous birth ≤32 weeks of gestation and within seven days of testing. All three had positive qualitative and quantitative fFN results (≥200 ng/mL) and would have been transferred appropriately but 2/3 (66.6%) would not have been transferred due to false-negative results if managed by PAMG-1.

Test sensitivity, the ability to detect all with the disease, was 80.0% (95% CI 37.6% to 96.4%) for both qualitative and quantitative fFN, but only 20.0% (95% CI 3.6% to 62.4%) for PAMG-1 for spontaneous preterm birth within one week. We acknowledge that confidence intervals are wide and do cross, suggesting a non-significant finding in the context of small numbers. Table 5.3 provides further comparison of the statistical performance for each test.

Increasing quantitative fFN levels correlated with increasing rates of spontaneous preterm birth (Table 5.4), with the ability of quantitative fFN to predict spontaneous preterm birth improving with increasing fFN thresholds (Table 5.5). The specificity to exclude spontaneous birth within 14 days also improved with increasing fFN thresholds (Table 5.5). Receiver operating characteristic curves for quantitative fFN are available in Supplementary material (Figure 5.3).

Table 5.2 Rates of admission and administration of corticosteroids as a consequence of biomarker result according to management protocol and actual management received by qualitative fetal fibronectin results

Management	**Actual management for qualitative fFN**			**If managed according to protocol for:**								
				Qualitative fFN			**Quantitative fFN**			**PAMG-1**		
	n/N	**%**	**CI**	**n/N**	**%**	**CI**	**n/N**	**%**	**CI**	**n/N**	**%**	**CI**
Overall admission rate	54/128	42.2	34.0–50.8	46/128	35.9	28.2–44.5	30/128	23.4	2.7–10.9	34/128	26.6	19.7–34.8
Admission for preterm labour symptoms only	35/128	27.3	20.4–35.6	27/128	21.1	14.9–29	11/128	8.6	4.9–14.7	15/128	11.7	7.2–18.4
Admission for preterm labour symptoms with positive biomarker and delivery ≥7 days	22/128	17.2	11.6–24.7	23/128	18.0	12.3–25.5	7/128	5.5	2.7–10.9	13/128	10.2	6.0–16.6
Corticosteroids given	34/128	26.6	19.7–34.8	28/128	21.9	15.6–29.8	25/128	19.5	13.6–27.2	16/128	12.5	7.8–19.3
Corticosteroids given and delivery ≥14 days	30/128	23.4	16.9–31.5	24/128	18.8	12.9–26.4	21/128	16.4	11.0–23.8	14/128	10.9	6.6–17.5
First dose corticosteroids ≥48 hours prior to delivery [a] in those ≤34^{+0} weeks with sPTB <7 days [b]	4/5	80.0	28.4–99.5	4/5	80.0	28.4–99.5	4/5	80.0	28.4–99.5	1/5	20.0	0.5–71.6
First dose corticosteroids ≥48 hours prior to delivery [a] in those ≤34^{+0} weeks with sPTB <14 days [b]	4/6	66.6	22.3–95.7	4/6	66.6	22.3–95.7	4/6	66.6	22.3–95.7	1/6	16.7	0.4–64.1

Lower–upper 95% CI, calculated by the Wilson method unless otherwise specified.

Abbreviations: fFN, fetal fibronectin; PAMG-1, placental alpha microglobulin-1; sPTB, spontaneous preterm birth.

[a] Includes two women who delivered <48 hours from testing and so did not receive full course.

[b] Lower–upper 95% CI calculated by the Clopper-Pearson method.

Table 5.3 Statistical performance of qualitative fFN, quantitative fFN and PAMG-1 tests in the prediction of spontaneous preterm birth within 7 and 14 days from testing and at ≤34^{+0} and <37^{+0} weeks of gestation

Statistical measures	**Qualitative fFN**			**Quantitative fFN** [a]			**PAMG-1**		
	%	**n/N**	**CI**	**%**	**n/N**	**CI**	**%**	**n/N**	**CI**
Within 7 days from testing									
Sensitivity	80.0	4/5	37.6–96.4	80.0	4/5	37.6–96.4	20.0	1/5	3.6–62.4
Specificity	80.5	99/123	72.6–86.5	82.9	102/123	75.3–88.6	87.8	108/123	80.9–92.5
PPV	14.3	4/28	5.7–31.5	16.0	4/25	6.4–34.7	6.3	1/16	1.1–28.3
NPV	99.0	99/100	94.6–99.8	99.0	102/103	94.7–99.8	96.4	108/112	91.2–98.6
Within 14 days from testing									
Sensitivity	66.7	4/6	30.0–90.3	66.7	4/6	30.0–90.3	16.7	1/6	3.0–56.4
Specificity	80.3	98/122	72.4–86.4	82.8	101/121	75.1–88.5	87.7	107/122	80.7–92.4
PPV	14.3	4/28	5.7–31.5	16.0	4/25	6.4–34.7	6.3	1/16	1.1–28.3
NPV	98.0	98/100	93.0–99.4	98.1	101/103	93.2–99.5	95.5	107/112	90.0–98.1
≤34^{+0} weeks of gestation									
Sensitivity	71.4	5/7	35.9–91.8	71.4	5/7	35.9–91.8	28.6	2/7	8.2–64.1
Specificity	81.0	98/121	73.1–87.0	83.5	101/121	75.8–89.0	88.4	107/121	81.5–93.0
PPV	17.9	5/28	7.9–35.6	20.0	5/25	8.9–39.1	12.5	2/16	3.5–36.0
NPV	98.0	98/100	93.0–99.5	98.1	101/103	93.2–99.5	95.5	107/112	90.0–98.1
<37^{+0} weeks of gestation									
Sensitivity	40.0	8/20	21.9–61.3	35.0	7/20	18.1–56.7	20.0	4/20	8.1–41.6
Specificity	81.5	88/108	73.1–87.7	83.3	90/108	75.2–89.2	88.9	96/108	81.6–93.5

PPV	28.6	8/28	15.3–47.1	28.0	7/25	14.3–47.6	25.0	4/16	10.2–49.5
NPV	88.0	88/100	80.2–93.0	87.4	90/103	79.6–92.5	85.7	96/112	78.1–91.0

Lower–upper 95% confidence interval, calculated by the Wilson method.

Abbreviations: fFN, fetal fibronectin; PAMG-1, placental alpha microglobulin-1; PPV, positive predictive value; NPV, negative predictive value.

[a] Positive test defined as ≥50 ng/mL.

Table 5.4 Timing of delivery for spontaneous preterm births by quantitative fFN within 7 and 14 days from testing and at ≤34^{+0} and <37^{+0} weeks of gestation

fFN category (ng/mL)	**Total**		**Within 7 days**		**Within 14 days**		**≤34^{+0} weeks**		**<37^{+0} weeks**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
0-9	71	55.5	0	0.0	1	1.4	1	1.4	7	9.9
10–49	32	25.0	1	3.1	1	3.1	1	3.1	6	18.8
50–199	14	10.9	0	0.0	0	0.0	1	7.1	3	21.4
200–499	11	8.6	4	36.4	4	36.4	4	36.4	4	36.4

Abbreviation: fFN, fetal fibronectin.

Table 5.5 The predictive power of quantitative fFN for spontaneous preterm birth within 7 and 14 days from testing and at ≤34^{+0} and <37^{+0} weeks of gestation at cut-off thresholds of ≥10, ≥50 and ≥200 ng/mL for a positive result

Statistical measures	**fFN ≥10 ng/mL**			**fFN ≥50 ng/mL**			**fFN ≥200 ng/mL**		
	%	**n/N**	**CI**	**%**	**n/N**	**CI**	**%**	**n/N**	**CI**
Within 7 days from testing									
Sensitivity	100.0	5/5	56.6–100.0	80.0	4/5	37.6–96.4	80.0	4/5	37.6–96.4
Specificity	57.7	71/123	48.9–66.1	82.9	102/123	75.3–88.6	94.3	116/123	88.7–97.2
PPV	8.8	5/57	3.8–19.0	16.0	4/25	6.4–34.7	36.4	4/11	15.2–64.6
NPV	100.0	71/71	94.9–100.0	99.0	102/103	94.7–99.8	99.2	116/117	95.3–99.9
Within 14 days from testing									
Sensitivity	83.3	5/6	43.7–97.0	66.7	4/6	30.0–90.3	66.7	4/6	30.0–90.3
Specificity	57.4	70/122	48.5–65.8	82.8	101/122	75.1–88.5	94.3	115/122	88.6–97.2
PPV	8.8	5/57	3.8–19.0	16.0	4/25	6.4–34.7	36.4	4/11	15.2–64.6
NPV	98.6	70/71	92.4–99.8	98.1	101/103	93.2–99.5	98.3	115/117	94.0–99.5
≤34^{+0} weeks of gestation									
Sensitivity	85.7	6/7	48.7–97.4	71.4	5/7	35.9–91.8	57.1	4/7	25.1–84.2
Specificity	57.9	70/121	48.9–66.3	83.5	101/121	75.8–89.0	94.2	114/121	88.5–97.2
PPV	10.5	6/57	4.9–21.1	20.0	5/25	8.9–39.1	36.4	4/11	15.2–64.6
NPV	98.6	70/71	92.4–99.8	98.1	101/103	93.2–99.5	97.4	114/117	92.7–99.1
<37^{+0} weeks of gestation									
Sensitivity	65.0	13/20	43.3–81.9	35.0	7/20	18.1–56.7	20.0	4/20	8.1–41.6
Specificity	59.3	64/108	49.8–68.1	83.3	90/108	75.2–89.2	93.5	101/108	87.2–96.8

PPV	22.8	13/57	13.8–35.2	28.0	7/25	14.3–47.6	36.4	4/11	15.2–64.6
NPV	90.1	64/71	81.0–95.1	87.4	90/103	79.6–92.5	86.3	101/117	78.9–91.4

Lower–upper 95% confidence interval, calculated by the Wilson method.

Abbreviation: fFN, fetal fibronectin; PPV, positive predictive value; NPV, negative predictive value.

5.2.5 Discussion

This is the first study to make prospective comparisons of qualitative fFN, quantitative fFN and PAMG-1 in a cohort of women symptomatic of preterm labour and to examine the potential impact of results on antenatal management. We have shown that use of quantitative fFN, with a threshold of ≥50 ng/mL to administer corticosteroids and ≥200 ng/mL for admission to hospital, could reduce hospital admissions by more than half compared to current practice of using qualitative fFN, with no compromise to care for the few women and babies who deliver within 14 days of testing. The use of PAMG-1 could also reduce hospital admissions and corticosteroid administration, but may compromise antenatal care for some who deliver preterm. An additional three women with spontaneous birth within 14 days of testing would have been discharged home with no corticosteroids if managed by PAMG-1 compared to fFN.

The main limitation of our study is the comparison of real-time clinical management to pre-defined theoretical management; however, the inclusion of a pre-defined care plan for qualitative fFN helps to quantify this discrepancy. Results may not reflect current clinical practice but do quantify the rates of interventions if women were managed according to a best-practice protocol. Identification of a discrepancy between actual and best practice highlights the ongoing need for multifaceted approaches to improve compliance to clinical practice guidelines, which has previously been shown to be effective in our unit (Dawes, Subramoney et al. 2018). Furthermore, we acknowledge that management of some women with symptoms of preterm labour will not be solely driven by the initial vaginal biomarker result. Women initially discharged without intervention based on a negative biomarker result may re-present at a later time with persistent or recurring symptoms, and repeat vaginal biomarkers assessment and/or clinical judgement may allow antenatal interventions to be given before spontaneous preterm birth regardless of the initial result. Recurrent presentations were not assessed in this study.

This study included a relatively small sample size from a population served by a single tertiary-level teaching hospital. We believe this is representative of women presenting with symptoms of preterm labour in large urban hospitals in the developed world where management decisions are based on risk assessment rather than a treat-all approach. We have included analysis for *in utero* transfer so results are relevant to smaller and more rural units. Due to the nature of this study, groups were not independent and so it was not appropriate to make direct statistical comparisons across the groups. However, if the study was a direct comparison of qualitative and quantitative fFN tests in two independent populations, our pragmatic sample size of 130

participants would have 80% power to detect a difference in hospital admission rates from 23% to 9% which may be expected with a shift in the threshold for hospital admission from 50 to 200 ng/mL (Abbott, Radford et al. 2013), alpha 0.05, two-sided, and allowing 7% loss to follow up.

Despite a relatively small sample size, our rate of spontaneous preterm birth (3.9%) within seven days of testing is comparable to or higher than other studies (Abbott, Radford et al. 2013), suggesting we sampled an appropriate at-risk population. This is in contrast to a multi-centre American study by Wing et al comparing PAMG-1 and qualitative fFN in 711 women with symptoms of preterm labour, where only 9/703 (1.3%) spontaneous preterm births occurred within seven days of testing (Wing, Haeri et al. 2017).

The primary goal of our study was to assess the impact of each biomarker test on clinical care and it was not powered to determine a difference in the statistical performance of each test, hence our reported confidence intervals are wide. Additionally, the high NPVs are largely driven by the low prevalence of spontaneous preterm birth and this limits the usefulness of comparisons. There is a wide variation in reported PPV for PAMG-1 (Melchor, Navas et al. 2018; Nikolova, Bayev et al. 2014; 2015; Peaceman, Andrews et al. 1997; Wing, Haeri et al. 2017) and fFN (Melchor, Navas et al. 2018; Nikolova, Bayev et al. 2014; 2015; Wing, Haeri et al. 2017), likely due to a differing prevalence of spontaneous preterm birth in each study population and small sample sizes, hence these values should be interpreted with caution. Furthermore, clinicians are likely to treat women even at modest PPV, so a high PPV does not necessarily add value to clinical management. Of more importance is a high test sensitivity to ensure clinicians detect all (or nearly all) women who will have a spontaneous preterm birth within the next 14 days. Low sensitivity due to false-negative results represents potential missed opportunities for antenatal interventions that may improve perinatal outcomes, and limits utility of the test. Hence, although it is preferable to reduce hospital admissions and interventions for those women who do not need them, this should not be at the expense of undertreating women who are likely to benefit. The low sensitivity and high numbers of false-negative results for PAMG-1 in this study, 4/5 women with a spontaneous birth within seven days of testing and 5/6 women within 14 days of testing, is concerning. As previously acknowledged, the confidence intervals for the test sensitivities cross, suggesting non-significant findings, which should be interpreted in the context of small numbers. However a high number of false negative PAMG-1 tests was also seen in the study by Wing et al where 6/9 women with spontaneous preterm birth within seven days had a false-negative PAMG-1 result (Kuhrt, Watson et al. 2018; Wing, Haeri et al. 2017), and hence we remain cautious about this finding. Although the Wing et al

study concluded that PAMG-1 was a stronger predictor of spontaneous preterm birth than fFN, concerns have been raised about the non-inferiority study design utilised, very low spontaneous preterm birth rate and high number of false-negative PAMG-1 results, which has led to conclusions that current evidence does not support the use of PAMG-1 testing in clinical practice (Grobman 2017; Kuhrt, Watson et al. 2018). A subsequent meta-analysis has reported superior statistical performance of PAMG-1 compared with fFN for spontaneous birth within seven days (Melchor, Khalil et al. 2018), but more than half of the included participants were from the Wing et al study, and these results should therefore be interpreted with caution.

The performance of vaginal biomarker tests is irrelevant if clinicians do not adjust their practice according to the result (Grobman 2017). A recent systematic review including six randomised trials of fFN testing (revealed result versus concealed result or no fFN test) demonstrated no difference in the antenatal management received or subsequent rates of preterm birth and perinatal outcomes (Berghella & Saccone 2016). Editorial comment stated that the continued use of fFN testing for women with threatened preterm labour could not be justified (Macones 2016), however in three of the six included trials, treatment was left to 'physician's discretion' regardless of whether the fFN was revealed or, when it was, if the result was positive or negative. The true value of fFN and other vaginal biomarkers can only be examined if clinicians are aware of the result and alter their practice accordingly in a consistent way.

5.2.6 Conclusion

Our study supports a change in practice to the use of quantitative fFN and a shift in threshold for admission. Use of PAMG-1 may also reduce admission rates but it may miss some women who deliver within seven days, potentially compromising antenatal care. A larger prospective study or randomised controlled trial would be required to fully assess any differences in the test characteristics. It is likely that inclusion of additional clinical information, such as cervical length and past history, combined with any of these biomarker tests in prediction models will further enhance the identification of women and babies most likely to benefit from hospital admission; corticosteroid and magnesium sulphate use; tocolysis; and *in utero* transfer (DeFranco, Lewis et al. 2013; Nikolova, Bayev et al. 2015; Watson, Carter, Seed et al. 2017). However, current and future research relies on clinician engagement to implement research findings into practice to ultimately impact on perinatal care and pregnancy outcomes.

5.2.7 Supplementary information

Table 5.6 Eligibility criteria

Inclusion criteria	Exclusion criteria
▪ Gestational age of 24^{+0} to 34^{+0} weeks ▪ No identified complication warranting imminent delivery ▪ Intact fetal membranes ▪ No vaginal bleeding that would preclude a qualitative fFN test (clinician decision) ▪ Fetus alive with no known lethal abnormality ▪ Cervix <3 cm dilated ▪ Antenatal corticosteroids +/- tocolysis +/- magnesium sulphate being considered ▪ Qualitative fFN test being considered ▪ Written informed consent obtained	▪ Higher order multiple pregnancy (≥ triplets) ▪ Previous participation in this study in the current pregnancy

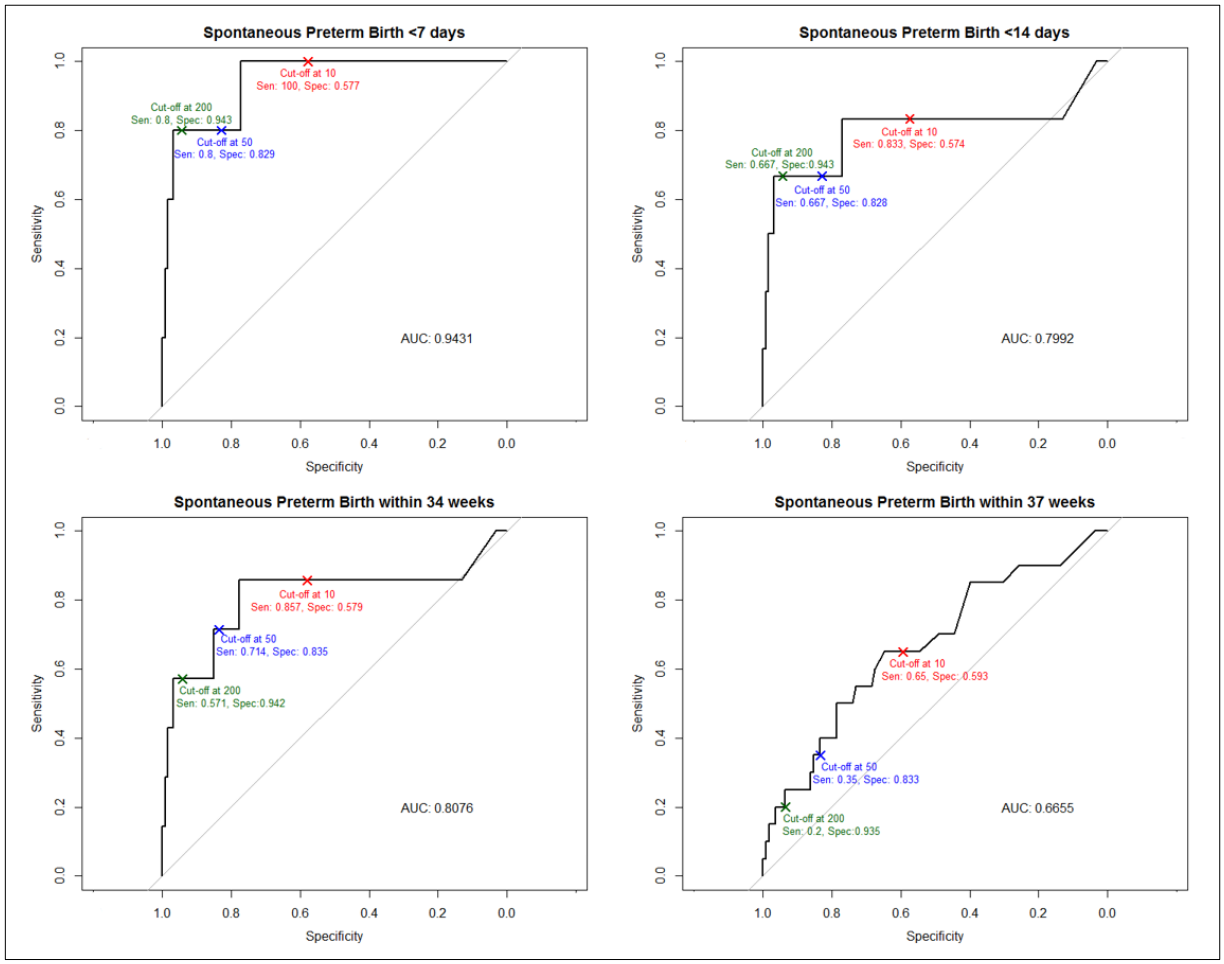

Figure 5.3 Receiver operating characteristic curves examining the ability of quantitative fetal fibronectin to predict spontaneous preterm birth within seven and 14 days and prior to 34 and 37 weeks of gestation

fFN cut-off levels in ng/mL.

Chapter 6 Specialised preterm birth clinics: a systematic review

6.1 Preface

This chapter assesses current practice in specialised preterm birth clinics globally. Until recently, there were no international or national guidelines to direct care in preterm birth clinics. As a result, significant variation in care has been identified as an issue. This chapter includes a systematic review of the literature with the aim of assessing current practice within preterm birth clinics globally, specifically the referral criteria, investigations and interventions offered, and timing and frequency of review. This information can be used to support the development and implementation of preterm birth clinic consensus guidelines and national preterm birth prevention programmes.

This chapter contains a manuscript that has been accepted for publication in *BMC Pregnancy and Childbirth.* The following text contains the original manuscript accepted for publication, reproduced under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

6.2 The use of specialised preterm birth clinics for women at high risk of spontaneous preterm birth: a systematic review

Dawes L, Groom K, Jordan V, Waugh J.

6.2.1 Abstract

Background: Specialised preterm birth clinics care for women at high risk of spontaneous preterm birth. This systematic review assesses current practice within preterm birth clinics globally.

Methods: A comprehensive search strategy was used to identify all studies on preterm birth clinics on the MEDLINE, Embase, PsycINFO, CENTRAL and CINAHL databases. There were no restrictions to study design. Studies were limited to the English language and publications from 1998 onwards. Two reviewers assessed studies for inclusion, performed data extraction and reviewed methodological quality. Primary outcomes were referral criteria, investigations

and interventions offered in preterm birth clinics. Secondary outcomes were the timing of planned first and last appointments and frequency of review.

Results: Thirty-two records fulfilled eligibility criteria and 20 studies were included in the main analysis following grouping of records describing the same study or clinic. Studies were of mixed study design and methodological quality. A total of 39 clinics were described; outcome data was not available for all clinics. Referral criteria included previous spontaneous preterm birth (38/38, 100%), previous mid-trimester loss (34/38, 89%) and previous cervical surgery (33/38, 87%). All clinics offered transvaginal cervical length scans. Additional investigations varied, including urogenital swabs (16/28, 57%) and fetal fibronectin (8/28, 29%). The primary treatment of choice for a sonographic short cervix was cervical cerclage in 10/33 (30%) clinics and vaginal progesterone in 6/33 (18%), with 10/33 (30%) using multiple first-line options and 6/33 (18%) using a combination of treatments. The majority of clinics planned timing of first review for 12-16 weeks (30/35, 86%) and the frequency of review was usually determined by clinical findings (18/24, 75%). There was a wide variation in gestational age at clinic discharge between 24-37 weeks.

Conclusions: There is variation in the referral criteria, investigations and interventions offered in preterm birth clinics and in the timing and frequency of review. Consistency in practice may improve with the introduction of consensus guidelines and national preterm birth prevention programmes.

Systematic review registration number: CRD42019131470.
https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=131470.

6.2.2 Introduction

Preterm birth is the leading cause of neonatal death and is associated with significant perinatal morbidity and lifelong health consequences (March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012). Preterm birth is common and accounts for approximately 10% of births worldwide (March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012). At least half of all preterm births are the result of spontaneous onset of labour or pre-labour rupture of membranes (Goldenberg, Culhane et al. 2008). Despite considerable research efforts there is no effective treatment to stop preterm labour once it has established and current management focuses on prevention (Hamilton & Mullan 2016; Haram,

Mortensen et al. 2015). In recent years, specialised preterm birth clinics have developed due to a growing understanding of risk factors for preterm birth and the importance of risk stratification to guide the use of interventions to prevent preterm labour (Vernet, Watson et al. 2017). To the best of our knowledge, the first modern-day preterm birth clinic was established in the United Kingdom (UK) in 1998.

Preterm birth clinics provide focused and specialised obstetric care to asymptomatic women at increased risk of preterm birth due to their obstetric or gynaecological history. The key components 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 when indicated. The use of transvaginal cervical length assessment and quantitative fetal fibronectin have been proven to aid prediction of spontaneous preterm birth in asymptomatic high risk women and can be used to guide management decisions (Abbott, Hezelgrave et al. 2015; Crane & Hutchens 2008). Interventions such as vaginal progesterone and cervical cerclage have been shown to reduce spontaneous preterm birth and associated neonatal morbidity in asymptomatic, high risk women who develop a sonographic short cervix in the mid-trimester (Conde-Agudelo, Romero et al. 2013; Jorgensen, Alfirevic et al. 2007; Romero, Nicolaides et al. 2012).

Although there is good evidence to support many of the practices that occur in preterm birth clinics, specific evidence to support the utility of preterm birth clinics as a whole is still evolving (Vernet, Watson et al. 2017). Two previous systematic reviews have attempted to assess the efficacy of preterm birth clinics in reducing spontaneous preterm birth and improving neonatal outcomes (Malouf & Redshaw 2017; Whitworth, Quenby et al. 2011). Neither found conclusive evidence to either support or refute the efficacy of specialised preterm birth clinics compared to standard antenatal care (Malouf & Redshaw 2017; Whitworth, Quenby et al. 2011). However, both acknowledged the limited number of studies in this field; only five were randomised controlled trials, all of which were conducted prior to 1990 and no longer reflect practice in modern-day preterm birth clinics. It is unlikely that further randomised controlled trials will be carried out due to the multi-faceted and complex nature of the intervention (Vernet, Watson et al. 2017). Despite the lack of direct evidence to support the use of preterm birth clinics, the poor outcomes from preterm birth, the availability of multiple evidenced-based interventions, and the ability to provide coordinated and individualised care provide sufficient justification for resourcing these clinics (Vernet, Watson et al. 2017). Preterm birth clinics have become standard care in many countries and are recommended in the UK (UK Preterm Clinical Network 2019).

Rationale

Until recently there were no national or international guidelines on the protocols and care pathways to be used in preterm birth clinics, and practice is often based on local expert opinion. The newly released (2019) 'Reducing Preterm Birth: Guidelines for Commissioners and Providers' from the UK Preterm Clinical Network provides guidance on referral pathways for preterm birth prevention (UK Preterm Clinical Network 2019). This includes recommendations on timing and frequency of cervical length assessments and use of quantitative fetal fibronectin testing, along with management options including cervical cerclage, progesterone and cervical pessary, with reference to the National Institute for Health and Care Excellence (NICE) Guidelines for preterm birth (National Institute for Health and Care Excellence 2015; UK Preterm Clinical Network 2019).

This systematic review aims to assess the referral criteria and investigations and interventions offered in preterm birth clinics internationally and the planned timing and frequency of review. It does not attempt to prove the efficacy of preterm clinics as it has already been established that there is currently inadequate evidence available (Malouf & Redshaw 2017; Whitworth, Quenby et al. 2011). The results of this systematic review will be useful for future work in improving consistency in care in both established and new preterm birth clinics. This will in turn allow results from future high-quality observational studies to be more accurately synthesised in systematic review and meta-analyses to assess the efficacy of preterm birth clinics in reducing spontaneous preterm birth and improving offspring outcome.

Objectives

This systematic review has four objectives:

1. To assess the eligibility criteria used for referral to preterm birth clinics.
2. To assess the types of investigations offered in preterm birth clinics.
3. To assess the types of interventions offered in preterm birth clinics.
4. To assess the planned frequency and timing of review in preterm birth clinics.

6.2.3 Methods

Protocol and registration

The protocol was prospectively registered with the PROSPERO International Prospective Register of Systematic Reviews in May 2019, registration number CRD24019131470, available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=131470. This

systematic review has been conducted in line with the standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and written according to the PRISMA checklist of items to include when reporting a systematic review (Moher, Liberati et al. 2009).

Eligibility criteria

All studies on preterm birth clinics were eligible for inclusion, including those that assessed a clinic indirectly i.e. by assessing another intervention in a high risk population cared for in a preterm birth clinic. Preterm birth clinics are also known as preterm birth prevention clinics, preterm surveillance clinics, specialised preterm birth clinics, dedicated preterm birth clinics, miscarriage follow-up clinics and specialised antenatal clinics. There is no comparator group in this review due to the nature of the research objectives. Studies on other types of specialised antenatal clinics such as for multiple pregnancy, hypertension and diabetes were excluded.

There were no restrictions placed on the types of studies eligible for inclusion and both quantitative and qualitative research methods were included. Examples of study designs include randomised controlled trials, cohort studies, case-controlled studies, cross-sectional studies, interviews, surveys and focus groups. Studies were restricted to those published in the English language, for feasibility, and to publications from 1998 onwards, as this is when the first modern-day preterm birth clinic was established.

The primary outcome measures are:

1. Eligibility criteria for referral (for example, previous spontaneous preterm birth prior to a specified gestation, previous cervical surgery of specific type or depth of excision).
2. Types of investigations offered, defined as any test arranged or carried out from the clinic with the aim of reducing the risk of spontaneous preterm birth or improving perinatal outcomes from preterm birth (for example, urine culture, urogenital swabs, cervical length ultrasound, fetal fibronectin). Investigations that form part of standard antenatal care that are not aimed at reducing the risk of spontaneous preterm birth were excluded (for example, aneuploidy screening, fetal anatomy scan).
3. Types of interventions offered, defined as any surgical, medical or non-medical therapy used with the aim of reducing the risk of spontaneous preterm birth (for example, cervical cerclage, progesterone, cervical pessary) or with the aim of improving perinatal outcomes for babies that are born preterm (for example, antenatal corticosteroids, hospital admission).

The secondary outcomes measures are:

4. Timing of planned first and last clinic visit (measured in weeks and days of gestation).
5. Frequency of planned clinic review (measured in number of days or weeks).

Information sources

The MEDLINE, Embase, PsycINFO, CENTRAL and CINAHL databases were searched on 1 May 2019. Additional studies were identified by hand-searching reference lists of included publications.

Search

A comprehensive search strategy was developed using the Peer Review of Electronic Search Strategies (PRESS) Guidelines (McGowan, Sampson et al. 2016) and was adapted for each of the five databases. The search strategy utilised keyword terms for a preterm birth clinic, and MeSH terms for outpatient pregnancy care combined with MeSH terms for preterm birth, pregnancy complications or high risk pregnancy. A human filter was applied along with limits for the English language and for references published from 1998 onwards. The MEDLINE search is available in Supplementary Table 6.7.

Study selection

References identified from each database search were imported into EndNote X8 referencing software (Clarivate Analytics 2016) and then into Covidence systematic review software (Veritas Health Innovation 2019). Duplicates were identified and excluded. References were then screened independently by two reviewers for potential eligibility based on the title and abstract. Full-text articles were retrieved for references that appeared to be relevant and these were also independently assessed for inclusion by two reviewers. Discrepancies were resolved through discussion.

Records were combined if they described the same study, e.g. conference abstracts with full-text articles; and studies that had been updated. For updated studies, the most recent record was used as the study identifier to describe both the original and updated study, and was used for the majority of data collection. Studies were also grouped when there was more than one study describing an individual clinic, with the most relevant study selected following discussion between two investigators. This selected study was used as the study identifier and for the majority of data collection, with the additional studies used for missing data. This approach was necessary to prevent over-representation of clinics that were described in more than one study.

All studies that reported on multiple (named or unnamed) clinics were included at this stage for simplicity and over-representation was addressed later in synthesis.

Data collection process

Electronic data collection forms were used to extract and record data from included studies. Data collection was performed by one reviewer and cross-checked by a second reviewer. Authors were contacted for the names and locations of included preterm birth clinics when this was not reported.

Data items

Primary and secondary outcomes previously specified were collected. Other data items include study source information and funding details, study design, study timeframes, demographic details, risk factors for spontaneous preterm birth, and spontaneous preterm birth rates.

Risk of bias and quality assessments

Two reviewers assessed the methodological quality of included studies. The Cochrane Risk of Bias Tool (Cochrane Effective Practice and Organisation of Care (EPOC) 2017) was used for randomised controlled trials, the Newcastle-Ottawa Scale (Wells, Shea et al. n.d.) for cohort, case controlled studies and other observational studies, the modified Newcastle-Ottawa Scale (Herzog, Álvarez-Pasquin et al. 2013) for cross-sectional studies and the Critical Appraisal Skills Programme (CASP) Checklist (Critical Appraisal Skills Programme 2018) for qualitative studies.

Study measures

Primary and secondary outcomes are described as proportions.

Synthesis of results

The majority of studies included UK based preterm birth clinics, and some reported on multiple clinics. To ensure we avoided over-representation of clinics described in more than one study, authors of UK studies that reported on unnamed clinics were approached (Care, Ingleby et al. 2019; Cohen, Kindinger et al. 2014; Kuhrt, Hezelgrave et al. 2016; Vousden, Hezelgrave et al. 2015). This allowed us to assess whether the largest and most comprehensive study on preterm birth clinics (Care, Ingleby et al. 2019) included all UK clinics described in other studies. All but four clinics in the Care 2019 study were identified and alternative studies including them were excluded from synthesis (Bolt, Chandiramani et al. 2011; Burul, James et al. 2014; Cohen,

Kindinger et al. 2014; Ivandic, Care et al. 2018; Karkhanis, Patni et al. 2012; Kindinger & Teoh 2013; Kindinger, Kyrgiou et al. 2016; Kuhrt, Hezelgrave et al. 2016; O'Brien, Quenby et al. 2010; Watson, Carter, Seed et al. 2017; Yulia, Thomas et al. 2015). Of the four clinics reported anonymously in the Care 2019 study, three are believed to have been reported elsewhere and so these studies were also excluded (Grant & Raouf 2016; Vousden, Hezelgrave et al. 2015). Data from Care 2019 were amalgamated with data from remaining studies, all of which reported on individual clinics outside of the UK, to provide an overall synthesis for the primary and secondary outcomes. A narrative synthesis is provided, structured around the outcome measures, with information also presented in tables. No meta-analysis was performed.

6.2.4 Results

Study selection

The study selection process is detailed in Figure 6.1. Of the 1293 records identified from the search strategy, 32 fulfilled eligibility criteria. Three of these were conference abstracts for included full text articles (Bolt, Chandiramani et al. 2010; Khambay, Bolt et al. 2010; Porter, Henry et al. 2011). One study had been updated and the two publications were combined (Care, Ingleby et al. 2019; Sharp & Alfirevic 2014). A further eight were additional studies reporting on individual clinics already represented by another included study (Alfirevic, Owen et al. 2013; Care, Sharp, & Alfirevic 2014; Care, Sharp, Lane et al. 2014; Duhig, Chandiramani et al. 2009; Khambay, Bolt et al. 2012; Min, Watson et al. 2016; Raouf, Ghazal et al. 2009; Smout, Seed et al. 2010) (detailed in Table 6.1). Twenty studies were therefore included in the main analysis.

Study characteristics

Of the 20 included studies, 15 were full text articles (Bolt, Chandiramani et al. 2011; Care, Ingleby et al. 2019; Danti, Zonca et al. 2014; Hughes, Sim et al. 2017; Ivandic, Care et al. 2018; Karkhanis, Patni et al. 2012; Kindinger, Kyrgiou et al. 2016; Kuhrt, Smout et al. 2016; Manuck, Henry et al. 2011; Newnham, White et al. 2017; O'Brien, Quenby et al. 2010; Stricker, Timmesfeld et al. 2016; Turitz, Bastek et al. 2016; Vousden, Hezelgrave et al. 2015; Watson, Carter, David et al. 2017) and five were conference abstracts (Burul, James et al. 2014; Cohen, Kindinger et al. 2014; Grant & Raouf 2016; Kindinger & Teoh 2013; Yulia, Thomas et al. 2015). Fourteen studies reported on an individual clinic (Bolt, Chandiramani et al. 2011; Burul, James et al. 2014; Danti, Zonca et al. 2014; Grant & Raouf 2016; Hughes, Sim et al. 2017; Ivandic, Care et al. 2018; Karkhanis, Patni et al. 2012; Kindinger & Teoh 2013; Manuck, Henry et al. 2011; Newnham, White et al. 2017; O'Brien, Quenby et al. 2010; Stricker, Timmesfeld et al.

2016; Turitz, Bastek et al. 2016; Yulia, Thomas et al. 2015) and six studies reported on multiple clinics (Care, Ingleby et al. 2019; Cohen, Kindinger et al. 2014; Kindinger, Kyrgiou et al. 2016; Kuhrt, Smout et al. 2016; Vousden, Hezelgrave et al. 2015; Watson, Carter, David et al. 2017).

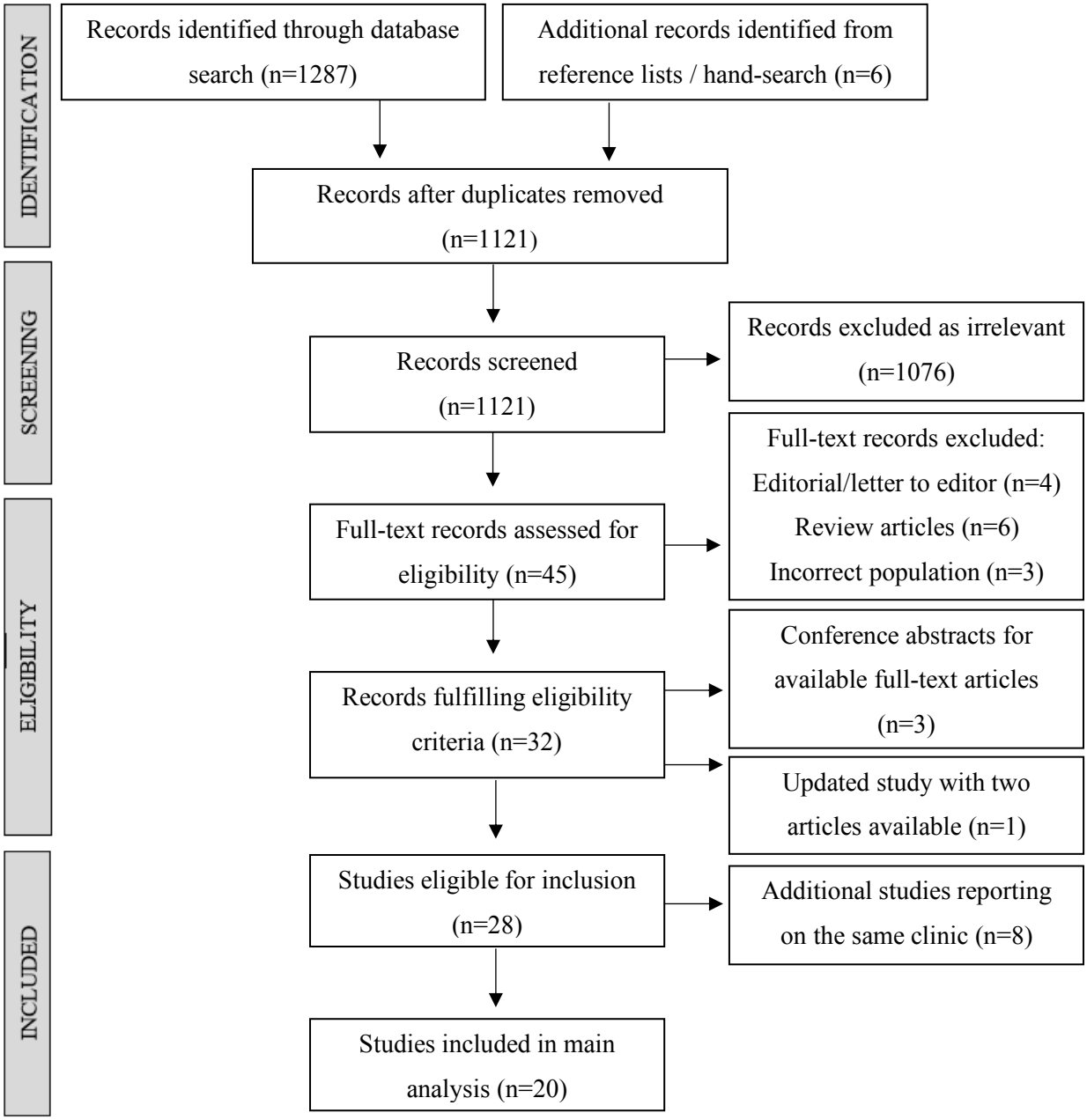

Figure 6.1 PRISMA flow chart of study selection

Table 6.1 Grouping of studies when more than one study reports on an individual clinic

Main study	**Additional studies on the same clinic**	**Name and location of preterm birth clinic**
Bolt 2011	Khambay 2012 Duhig 2009 Min 2016 Smout 2010 [a]	Guys and St Thomas' Hospital, London, United Kingdom
Ivandic 2018	Alfirevic 2013 Care AG 2014 Care A 2014 [a]	Liverpool Women's Hospital, Liverpool, United Kingdom
Karkhanis 2012 [a]	Raouf 2009 [a]	Birmingham Heartlands Hospital, Birmingham, United Kingdom

[a] Conference abstract only.

There were a variety of study designs; seven retrospective audits (Burul, James et al. 2014; Cohen, Kindinger et al. 2014; Hughes, Sim et al. 2017; Ivandic, Care et al. 2018; Karkhanis, Patni et al. 2012; Kindinger & Teoh 2013; Yulia, Thomas et al. 2015), three prospective observational studies (Grant & Raouf 2016; Kuhrt, Smout et al. 2016; Vousden, Hezelgrave et al. 2015), two cross-sectional studies (Care, Ingleby et al. 2019; Turitz, Bastek et al. 2016), two prospective cohort studies (Newnham, White et al. 2017; Watson, Carter, David et al. 2017), two retrospective cohort studies (Manuck, Henry et al. 2011; Stricker, Timmesfeld et al. 2016), two other retrospective observational studies (Bolt, Chandiramani et al. 2011; Kindinger, Kyrgiou et al. 2016), one randomised controlled trial (Danti, Zonca et al. 2014), and one qualitative interpretive study (O'Brien, Quenby et al. 2010). A total of 39 clinics were assessed in data synthesis; 33 clinics (87%) were in the UK, two in America, two in Australia, and one each in Germany and Italy.

Risk of bias and quality assessments

Results of the methodological quality assessments are shown in Supplementary Tables 6.8-6.11. Methodological quality was mixed with studies of low, medium and high quality.

Results of individual studies

The study characteristics and primary and secondary outcomes are summarised in Table 6.2 for studies on individual clinics, and in Table 6.3 for studies reporting on multiple clinics.

Table 6.2 Characteristics of included studies reporting on an individual clinic

Study details	**Characteristics of women cared for in the clinic and spontaneous preterm birth rate**	**Eligibility criteria for referral to the clinic**	**Investigations and interventions offered**	**Timing and frequency of review**
1. **Bolt 2011** Retrospective observational study. 12 month period, dates not reported. Guys and St Thomas' Hospital, London, UK. *Primary and secondary outcome data also obtained from Min 2016, Khambay 2012 and Duhig 2009.*	147 women; White 45%, Black 44%, Asian 4%, other 5% and unknown 3%. Risk factors for spontaneous preterm birth: previous preterm birth >24 weeks 37%, previous late miscarriage 35%, LLETZ 13%, cone biopsy 11%, previous cerclage 16%, current cerclage 27%. Spontaneous preterm birth rate <37 weeks 18%.	Previous preterm birth <37 weeks. Previous PPROM <37 weeks. Previous late miscarriage 16-24 weeks. Extensive cervical surgery e.g. LLETZ, cone biopsy, trachelectomy. Uterine abnormality. Cervical length <25 mm on transvaginal scan. Previous cervical cerclage.	*Investigations:* - Transvaginal cervical length ultrasound scans. - Quantitative fFN at 22-30 weeks. *Interventions:* Cervical cerclage: offered electively if ≥3 previous spontaneous deliveries or losses at 16-34 weeks or ≥2 with an additional risk factor, a previous failed cerclage, or as an ultrasound-indicated procedure if cervical length is <20 mm on transvaginal ultrasound. If considered high risk based on	Timing of planned first visit not reported. Women are seen 2-6 weekly, individualised to clinical need. Women assessed as low risk are discharged at 22-24 weeks. High risk woman are seen up to 30 weeks.

			cervical length and fFN results at 23-28 weeks: - Hospital admission. - Antibiotics if infection suspected. - Tocolysis (nifedipine) if contracting. - Betamethasone.	
2. **Ivandic 2018** Retrospective audit. January 2013 – December 2017. Liverpool Women's Hospital, Liverpool, UK. *Primary and secondary outcome data also obtained from Care AG 2014 and Alfirevic 2013.*	129 women; White 85%, Black African 3%, Asian 2%, Arab 3% and other 7%. Risk factors for spontaneous preterm birth: previous preterm birth or PPROM <34 weeks 76%, LLETZ 21%, knife cone biopsy 9%. Spontaneous preterm birth rate <37 weeks 50%, <34 weeks 29%.	Previous spontaneous preterm birth at 16-34 weeks. Previous PPROM at 16-34 weeks. Significant cervical surgery defined as ≥2 LLETZ or knife cone biopsy. Uterine abnormalities. Incidental finding of short cervix on ultrasound. Following an episode of threatened preterm labour.	*Investigations:* - Transvaginal cervical length ultrasound scans. *Interventions:* Treatment is offered if transvaginal cervical length <3rd centile for gestational age, including: - Cervical pessary. - Vaginal progesterone. - Cervical cerclage.	The first visit is planned for 16 weeks, or earlier if there is a history of significant cervical surgery or cerclage in a previous pregnancy. Women are seen 1-4 weekly depending on the initial cervical length and the gestational age of previous preterm births. Women are discharged at 28 weeks.

3. **Karkhanis 2012** Retrospective audit. November 2007 – November 2009. Birmingham Heartlands Hospital, Birmingham, UK. *Primary and secondary outcome data also obtained from Raouf 2009.*	180 women; ethnicity not reported. Risk factors for spontaneous preterm birth: previous preterm labour or mid trimester loss 88%. Spontaneous preterm birth rate <37 weeks 32%.	Previous preterm birth. Previous mid-trimester loss.	*Investigations:* - Transvaginal cervical length ultrasound scans. - Midstream urine. - Low vaginal swabs. *Interventions:* - Cervical cerclage. - Vaginal progesterone. - Combined treatment.	The first visit is planned for 16 weeks. Frequency of review is not reported. Women are discharged at 34 weeks.
4. **Yulia 2015** Retrospective audit (conference abstract only). January 2011 – December 2013. Chelsea and Westminster Hospital, London, UK	63 women; ethnicity not reported. Risk factors for spontaneous preterm birth: previous late miscarriage or preterm delivery <34 weeks 40%, previous deep cervical treatment 43%, uterine anomaly 8%.	Previous preterm delivery <34 weeks. Previous late miscarriage. Previous deep cervical treatment. Uterine anomalies.	*Investigations:* - Transvaginal cervical length ultrasound scans. *Interventions:* - Cervical cerclage.	Not reported.

	Spontaneous preterm birth rate <37 weeks 16%.			
5. **Kindinger 2013** Retrospective audit (conference abstract only). January 2011 – January 2013. St Mary's Hospital, London, UK.	160 women; ethnicity not reported. Risk factors for spontaneous preterm birth: previous cervical treatment 43%, previous preterm birth <34 weeks 21%, previous mid-trimester loss 26%, uterine anomalies 5%, multiple pregnancy 3%. Spontaneous preterm birth rate <34 weeks 8%.	Previous preterm birth <34 weeks. Previous mid-trimester loss. Previous cervical treatment. Uterine anomalies. Multiple pregnancy.	*Investigations:* - Transvaginal cervical length ultrasound scans. *Interventions:* - Vaginal progesterone. - Cervical cerclage.	Not reported.
6. **Burul 2014** Retrospective audit (conference abstract only). January 2005 – December 2012.	125 women; ethnicity and risk factors for spontaneous preterm birth not reported. Spontaneous preterm birth rate not reported, but median gestation at delivery was 35^{+2} weeks.	Not reported.	*Investigations:* - Not reported. *Interventions:* - Cervical cerclage.	Not reported.

University College London Hospital, London, UK.				
7. **Grant 2016** Prospective observational study (conference abstract only). January 2014 – January 2016. Royal Derby Hospital, Derby, UK.	146 women; ethnicity not reported. Risk factors for spontaneous preterm birth: previous preterm birth <37 weeks 36%, previous second trimester miscarriage 13%, previous failed rescue cerclage 1%, previous LLETZ 49%, previous cone biopsy 2%, previous cervical biopsies 2%, medical history (not further defined) 4%. Spontaneous preterm birth rate <37 weeks 25%.	Previous preterm birth <37 weeks. Previous second trimester miscarriage. Previous failed rescue cerclage. Previous LLETZ. Previous cone biopsy. Previous cervical biopsies. Medical history (not further defined).	*Investigations:* - Transvaginal cervical length ultrasound scans. *Interventions:* - Vaginal progesterone. - Cervical cerclage.	Not reported.

8. **O'Brien 2010** Qualitative interpretive study. Study dates not reported. Manchester, UK.	14 women; White British 93%, Black Caribbean 7%. Risk factors for spontaneous preterm birth and spontaneous preterm birth rate not reported.	Previous preterm birth. Cervical surgery or other gynaecological procedures that increases the risk of cervical incompetence (not further defined).	*Investigations:* - Transvaginal cervical length ultrasound scans. *Interventions:* - Cervical cerclage. - Vaginal progesterone. - Aspirin. - Antibiotics. - Activity restriction. - Hospital admission.	Timing of planned visit is not reported, however it is noted that women are encouraged to attend as soon as they become pregnant. Frequency of review is weekly, fortnightly or monthly depending on individual needs. Timing of last visit is not reported.
9. **Turitz 2016** Cross-sectional study. November 2009 – June 2013. Hospital of the University of Pennsylvania, Pennsylvania, United States of America.	218 women; African American 83%, Caucasian 12%, other 6%. Risk factors for spontaneous preterm birth: previous second trimester loss 39%, previous spontaneous preterm birth <37 weeks 71%. Spontaneous preterm birth rate <37 weeks 36%.	Previous spontaneous preterm birth <37 weeks. Previous second trimester loss 16-24 weeks.	*Investigations:* - Transvaginal cervical length ultrasound scans. *Interventions:* - IM 17OHP-C for all. - Cervical cerclage also recommended if cervical length ≤15 mm or previous preterm birth <34 weeks.	Not reported.

10. **Manuck 2011** Retrospective cohort study. Usual care patients June 2002 – June 2010, preterm birth clinic patients 2008 – 2010. Utah, United States of America.	70 preterm birth clinic patients; Caucasian 83%. (153 usual-care patients). Risk factors for spontaneous preterm birth: previous spontaneous preterm birth <35 weeks 100%. Spontaneous preterm birth rate <37 weeks 49% in preterm birth clinic patients (63% in usual care patients).	Previous spontaneous preterm birth <35 weeks.	*Investigations:* - Transvaginal cervical length ultrasound scans. - Vaginal swab for bacterial vaginosis. - Urine culture. - fFN only if symptoms. *Interventions:* - IM 17OHP-C for all. - Cervical cerclage if cervical length <25 mm at <22 weeks. If cervical length shortening is detected >22 weeks: - Hospital admission. - Activity restriction. - Tocolysis (indomethacin) if contracting. - Betamethasone.	The first visit is planned for 10-18 weeks. Frequency of review is six weekly with additional visits as clinically indicated (every 1-2 weeks if the cervix shortens). Women are discharged at 28-32 weeks.

11. **Hughes 2017** Retrospective audit. 2004 – 2013. Royal Women's Hospital, Melbourne, Australia.	756 women; ethnicity not reported. Risk factors for spontaneous preterm birth: previous spontaneous preterm birth 54%, previous cervical surgery 24%, uterine malformations 11%, incidental finding of short cervix 9%. Spontaneous preterm birth rate <37 weeks 21%.	Previous spontaneous preterm birth. Previous mid-trimester loss. Previous cervical surgery: ≥1 cold knife cone biopsy or ≥2 LLETZ. ≥3 surgical terminations of pregnancy or ≥4 dilatation and curettage procedures. Incidental finding of a short cervix <25 mm on transvaginal scan in the mid-trimester. Uterine malformation.	*Investigations:* - Transvaginal cervical length ultrasound scans. - Cervical swabs for abnormal flora at each visit and for chlamydia at the first visit. - Serum thyroid stimulating hormone and alkaline phosphatase at the first visit. - fFN at the final visit. *Interventions:* Women are offered treatment if cervical length <25 mm, options include: - Vaginal progesterone. - Cervical cerclage. - Arabin pessary (as part of a study only). Appropriate antimicrobials as indicated.	The first visit is planned for 14 weeks. Women are seen fortnightly. Women are discharged at 26 weeks.

12. **Newnham 2017** Prospective population-based cohort study. 2009 – December 2015 (November 2014 – December 2015 for assessment of preterm birth clinic). Perth, Western Australia.	154 women cared for in the preterm birth clinic, but data on 92 concluded pregnancies reported only (233,527 births in whole statewide cohort); ethnicity not reported. Risk factors for spontaneous preterm birth: previous early preterm birth 67%, recurrent pregnancy losses 26%, previous cone biopsy or other ablative procedures of the cervix 14%, uterine anomalies 11%, autoimmune conditions 11%, placental risk factors 10%. Preterm birth <37 weeks 32% (spontaneous preterm birth rate not reported separately).	Previous early preterm birth. Recurrent pregnancy loss. Previous cone biopsy or other ablative procedure of the cervix. Uterine anomalies. Previous stillbirth or neonatal death. Autoimmune conditions. Placental risk factors.	*Investigations:* - Transvaginal cervical length ultrasound scans. *Interventions:* - Vaginal progesterone. - Cervical cerclage. - Mental health support. - 'Medical interventions' not further specified.	Timing of planned visit is not reported, however the median gestational age at first visit was 13^{+6} weeks. Frequency of review and timing of last visit is not reported.

13. **Stricker 2016** Retrospective cohort study. October 2008 – December 2014. Marburg, Germany.	106 women; ethnicity not reported. Risk factors for spontaneous preterm birth: previous preterm birth <37 weeks 33%, previous surgical conisation 19%, previous cervical cerclage for a short cervix 12%, short cervix <3rd centile in current pregnancy 48%. Spontaneous preterm birth rate <37 weeks 44%, <34 weeks 28%.	Previous preterm birth or mid-trimester loss at 16-37 weeks. Previous surgical conisation. Previous cerclage for a short cervix. Short cervical length <3rd centile on transvaginal scan in current pregnancy.	*Investigations:* - Transvaginal cervical length ultrasound scans. *Interventions:* For singleton pregnancies with a short cervix <3rd centile: - Cervical pessary. - Vaginal progesterone. - Cervical cerclage.	Gestation of planned first visit and frequency of review not reported. Women are discharged at 32 weeks.
14. **Danti 2014** Randomised controlled trial. May 2000 – May 2003. Hospital of the University of Brescia and University of Turin, Italy.	87 women; Caucasian 95%, others not reported. Risk factors for spontaneous preterm birth: short cervix ≤25 mm at 24-32 weeks 100%, previous preterm delivery or PPROM 14%, previous mid-	Previous preterm labour and/or PPROM. Previous mid-trimester miscarriage. Previous cervical insufficiency.	*Investigations:* - Transvaginal cervical length ultrasound scans. - Vaginal culture for trichomonas, aerobic and/or anaerobic bacteria, chlamydia.	The first visit is planned for 14 weeks. Frequency of planned review not reported. Women are discharged at 34 weeks.

	trimester miscarriages 3%, uterine anomalies (bifid uterus, uterine septum, myoma) 3%, previous cervical surgery 1%. Spontaneous preterm birth rate <37 weeks 15%.	Previous cervical surgery. Uterine fibromyoma. Uterine malformations Clinical suspicion of cervical shortening.	- Rectal samples for beta haemolytic streptococcus. *Interventions:* - Cervical cerclage. - Vaginal progesterone. - Targeted antibiotic therapy for positive cultures. - Tocolysis (nifedipine) as the study intervention (compared to placebo).	

PPROM, premature pre-labour rupture of membranes; LLETZ, large loop excision of the transformation zone; fFN, fetal fibronectin; IM, intramuscular; 17OHP-C, 17-alpha hydroxyprogesterone caproate; UK, United Kingdom.

Table 6.3 Characteristics of included studies reporting on multiple clinics

Study details	**Characteristics of women cared for in the clinic and spontaneous preterm birth rate**	**Eligibility criteria for referral to the clinic**	**Investigations and interventions offered**	**Timing and frequency of review**
1. **Kindinger 2016** Retrospective observational study. January 2004 to January 2014. Queen Charlotte's Hospital, St Mary's Hospital and Chelsea and Westminster Hospital; London, UK.	725 women; Caucasian 66%, Black 18%, Asian 16%. Risk factors for spontaneous preterm birth: previous excisional cervical treatment to a depth of ≥12 mm 100% (women with other risk factors specifically excluded from this study). Spontaneous preterm birth rate <37 weeks 9%, <34 weeks 2%.	Previous preterm birth <37 weeks. Previous mid-trimester miscarriage >13 weeks. Uterine anomaly. Previous excisional cervical treatment to a depth of ≥12 mm (cone biopsy, LLETZ or LEEP).	*Investigations:* - Transvaginal cervical length ultrasound scans. *Interventions:* - Cervical cerclage.	The first visit is planned for 13-16 weeks. Frequency of planned review not reported. Women are discharged at 20-23 weeks.
2. **Watson 2017** Prospective cohort study.	66 women; White 61%, Black 32%, Asian/Middle-Eastern 8%.	Previous spontaneous preterm birth <37 weeks.	*Investigations:* - Transvaginal cervical length ultrasound scans.	Not reported.

April 2012 – November 2016. Guys and St Thomas' Hospital and University College London Hospital; London, UK.	Risk factors for spontaneous preterm birth: previous spontaneous preterm birth or late miscarriage 100%. Spontaneous preterm birth rate <37 weeks 35%.	Previous spontaneous late miscarriage between 14-24 weeks.	*Interventions:* - Cervical cerclage if cervix <25 mm. - Vaginal progesterone. - Arabin pessary.	
3. **Cohen 2014** Retrospective audit (conference abstract only). January 2013 – May 2014. St Mary's Hospital and Queen Charlotte's Hospital; London, UK.	509 women; Caucasian 59%, Afro-carribean 15%. Risk factors for spontaneous preterm birth: previous preterm labour <34 weeks 26%, previous mid-trimester miscarriage 17%, previous excisional cervical treatment 50%, uterine anomalies 2%, multiple pregnancy 3%. Spontaneous preterm birth rate <37 weeks 11%, <34 weeks 4%.	Previous preterm labour <34 weeks. Previous mid-trimester miscarriage. Previous excisional cervical treatment. Uterine anomalies. Multiple pregnancy.	*Investigations:* - Transvaginal cervical length ultrasound scans. *Interventions:* - Cervical cerclage. - Vaginal progesterone.	Not reported.

4. **Kuhrt 2016** Prospective observational study. October 2010 – July 2014. St Thomas' Hospital, Queen Charlotte's Hospital, University College London Hospital, West Middlesex University Hospital; London, UK; Manchester St Mary's Hospital; Manchester, UK.	1249 women. Ethnicity: White 56%, Black 29%, Asian 8%, other 9%. Risk factors for spontaneous preterm birth: previous spontaneous preterm birth 38%, previous PPROM 19%, previous late miscarriage 22%, previous cervical surgery 44%, short cervix <25 mm 15%. Spontaneous preterm birth rate <37 weeks 15%, <34 weeks 8%.	Previous spontaneous preterm birth <37 weeks. Previous PPROM <37 weeks. Previous late miscarriage 16-24 weeks. Previous cervical surgery. Cervical length <25 mm in the current pregnancy.	*Investigations:* - Transvaginal cervical length ultrasound scans. - Quantitative fFN. *Interventions:* - Cervical cerclage: history-indicated if ≥3 late miscarriages or previous spontaneous preterm births <34 weeks; ultrasound-indicated if cervix <25 mm. - Vaginal progesterone.	Gestation of planned first visit not reported. Women seen every 2-4 weeks. Women are discharged at 30 weeks.
5. **Vousden 2015** Prospective observational study. November 2010 – July 2014. Fifteen hospitals across the UK, nine of which have preterm birth clinics –	54 women; Black 46%, White 35%, other 19%. Risk factors for spontaneous preterm birth: previous preterm birth 44%, previous second trimester miscarriage 72%, previous cervical surgery 7%.	Previous preterm birth. Previous second trimester miscarriage. Previous cervical surgery.	*Investigations:* - Transvaginal cervical length ultrasound scans. *Interventions:* - Cervical cerclage. - Vaginal progesterone.	Not reported.

St Thomas' Hospital, Queen Charlotte's Hospital, University College London Hospital, West Middlesex University Hospital; London; Royal Infirmary of Edinburgh, Edinburgh; Sunderland Royal Hospital; Sunderland; Manchester St Mary's Hospital; Manchester; University Hospital; Coventry; Royal Victoria Infirmary; Newcastle.	Spontaneous preterm birth rate <34 weeks 11%.			
6. **Care 2019** Cross-sectional study (survey). March 2017 – July 2017. Thirty-three unnamed clinics across the UK (list obtained	This study reports on the typical practice of preterm birth clinics, not on individual women cared for in them.	*Percentage of clinics with each referral criteria (n=32 clinics):* Previous preterm birth, 100%, at gestations of: <37 weeks 13%. <35 weeks 3%.	*Investigations (n=32 clinics):* - Transvaginal cervical length ultrasound scans 100%. *Additional Investigations (n=22 clinics from Sharp 2014, not reported in Care 2019):*	*Gestation of planned first visit (n=32 clinics):* - <12 weeks 9%. - 12-14 weeks 38%. - 15-16 weeks 50%. - >16 weeks 3%. - As soon as referred 0%.

from authors, but not reported here). *Primary and secondary outcome data also obtained from Sharp 2014, which was the original study updated by Care 2019.*		<34 weeks 65%. <32 weeks 13%. <28 weeks 3%. Other 3%. Previous PPROM, 91%, at gestations of: <37 weeks 16%. <34 weeks 55%. <32 weeks 13%. <28 weeks 6%. Other 10%. Recurrent second trimester loss 91%. Previous cervical surgery: ≥1 LLETZ 47%. ≥2 LLETZ 100%. Cone biopsy 100%. Uterine anomalies 75%. Recurrent first trimester loss 16%.	- Vaginal flora swabs 59%. - Vaginal acidity 0%. - Cervical stress test 14%. - fFN 32%. *Interventions (n=32 clinics):* Primary treatment choice for asymptomatic women with a short cervix on ultrasound: - Cervical cerclage 30%. - Vaginal progesterone 18%. - IM progesterone 0%. - Arabin cervical pessary 3%. - Combination treatment (most commonly cervical cerclage and vaginal progesterone) 18%. - Multiple first line treatment options 30%. Treatment threshold: - <25 mm 55%. - <15 mm 3%. - Centile charts 15%.	*Frequency of planned review (n=22 clinics from Sharp 2014, not reported in Care 2019):* - Every 2 weeks 18%. - Every 4 weeks 5%. - Based on clinical findings 77%. *Gestation of planned last visit after a diagnosis of short cervix (n=22 clinics from Sharp 2014, not reported in Care 2019):* - 24 weeks 5% - 28 weeks 41%. - 30 weeks 5%. - 34 weeks 36%. - 37 weeks or delivery 14%.

		Threatened preterm labour 13%. Incidental finding of a short cervix 88%.	- Centile chart and/or <25 mm 12%. - Other cervical length cutoff 3%. - QUIPP App 12%. *Additional advice (n=22 clinics from Sharp 2014, not reported in Care 2019):* - Restricting physical activity 45%. - Sick leave 27%. - Refraining from sexual intercourse 41%. - Nutrition 27%. - Bed rest 0%. No further advice 36%.	

PPROM, premature pre-labour rupture of membranes; LLETZ, large loop excision of the transformation zone; LEEP, loop electrosurgical excision procedure; fFN, fetal fibronectin; IM, intramuscular; UK, United Kingdom.

Synthesis of results

Data from 39 clinics were combined to assess the primary and secondary outcomes; 33 UK based clinics from Care 2019 (Care, Ingleby et al. 2019) and six clinics from individual clinic studies outside of the UK (Abbott, Hezelgrave et al. 2015; Danti, Zonca et al. 2014; Hughes, Sim et al. 2017; Manuck, Henry et al. 2011; Stricker, Timmesfeld et al. 2016; Turitz, Bastek et al. 2016). Outcome data was incomplete for some clinics, thus the number of clinics assessed for each outcome varies.

Preterm birth clinic referral criteria is described in Table 6.4. All clinics accepted referrals for women with a previous spontaneous preterm birth, however the gestation of previous preterm birth varied. Just over half (20/38, 53%) set a threshold of <34 weeks for review. Previous late miscarriage or mid-trimester loss was the second most common referral criteria reported in 34/38 (89%) clinics. Most clinics also accepted referrals for women with previous cervical surgery (33/38, 87%), although there was variation in the type of surgery and numbers of excisional biopsies required (Table 6.4).

Data on the types of investigations offered were available for 28 clinics (22 UK, 6 non-UK). All clinics performed transvaginal cervical length ultrasound scans, however use of additional investigations was variable. Urogenital swabs were the second most common investigation performed, with 16/28 (57%) clinics routinely offering this. Fetal fibronectin was used as a risk assessment tool in asymptomatic women in some clinics (8/28, 29%). Other investigations included urine culture, rectal culture for Group B streptococcus, serum thyroid stimulating hormone and alkaline phosphatase which were each described in one clinic.

Table 6.4 Preterm birth clinic referral criteria

Referral criteria (non-exclusive)	**Number of clinics (%), n=38** [a]
Previous spontaneous preterm birth	38 (100)
<37 weeks	6 (16)
<35 weeks	2 (5)
<34 weeks	20 (53)
<32 weeks	4 (11)
<28 weeks	1 (3)
Other	1 (3)
No gestational limit reported	4 (8)
Previous late miscarriage/mid-trimester loss	34 (89) [b]

≥16 weeks	2 (5)
No gestational limit reported	32 (84)
Previous PPROM	30 (79)
<37 weeks	5 (13)
<34 weeks	17 (45)
<32 weeks	4 (11)
<28 weeks	2 (5)
Other	1 (3)
No gestational limit reported	1 (3)
Previous cervical surgery (non-exclusive)	33 (87)
1 LLETZ or no number stated	16 (42)
≥2 LLETZ	32 (84)
Knife cone biopsy	33 (87)
Not further defined	1 (3)
Other gynaecological procedures (non-exclusive)	1 (3)
≥3 Surgical termination of pregnancy	1 (3)
≥4 Dilatation and curettage	1 (3)
Previous cervical cerclage	1 (3)
Uterine abnormality/malformation	27 (71)
Short cervix in current pregnancy	31 (82)
<25 mm	1 (3)
<3rd centile for gestation	1 (3)
'Short' cervix not further defined	29 (76)
Follow up for threatened preterm labour	4 (11)
Previous stillbirth or neonatal death	1 (3)
Autoimmune conditions	1 (3)
Placental risk factors	1 (3)
Multiple pregnancy	0 (0)

UK, United Kingdom; PPROM, preterm pre-labour rupture of membranes; LLETZ, large loop excision of the transformation zone.

[a] Data not available for one clinic.

[b] Includes 29 clinics who accepted referrals for recurrent second trimester miscarriage as referral for a single second trimester miscarriage not reported in Care 2019.

There were differences in how interventions aimed at reducing the risk of spontaneous preterm birth were reported. Table 6.5 lists the range of interventions offered for the six clinics outside of the UK, and separately describes the primary treatment choice for a sonographic short cervix for the 33 clinics within the UK where this information was available. Data on the range of interventions offered in UK clinics was not available for synthesis. Cervical cerclage was offered in all clinics outside of the UK (6/6, 100%). Progesterone was also offered in all clinics, as vaginal progesterone in 4/6 (67%) and intramuscular 17-alpha hydroxyprogesterone caproate (17OHP-C) in the remaining two clinics, both of which were in America. Within UK based preterm birth clinics, the primary treatment choice for women with a sonographic short cervix was cervical cerclage in 10/33 clinics (30%), vaginal progesterone in 6/33 (18%) and cervical pessary in 1/33 (3%). An additional 10/33 clinics (30%) reported utilisation of multiple first line treatment options, and 6/33 (18%) used a combination of treatment, usually cervical cerclage and vaginal progesterone.

Various measures were used to define the threshold for treatment of a 'short' cervix. The most common threshold was a cervical length of <25 mm (21/38, 53%). A cervical length of <15 mm or use of centile charts were used less frequently (2/38, 5% and 6/38, 16% respectively). A further 4/38 clinics (11%) used a combination of thresholds with centile charts and/or a cervical length of <25 mm. Results from the QUiPP App, which combines clinical history, cervical length measurements and fetal fibronectin (Kuhrt, Smout et al. 2016) were used by 4/38 (11%) clinics to determine the need for treatment for a short cervix. One clinic reported using an 'other' threshold and data were unavailable for another.

The use of additional interventions such as hospital admission, antenatal corticosteroid therapy and antimicrobials for high risk, asymptomatic women was not consistently reported across studies and these data were not available from the large surveys of practice in the UK; thus accurate synthesis of information was not possible. Data on additional interventions are provided in Tables 6.2 and 6.3 where this was reported in individual studies.

Many clinics also provided routine lifestyle recommendations. Of the 22 clinics (all in the UK), where these data were available, almost half (10/22, 45%) routinely advised restriction of physical activity, 6/22 (27%) recommended stopping work, 9/22 (41%) advised refraining from sexual intercourse and 6/22 (27%) made dietary recommendations. No clinic recommended routine bed rest and 8/22 (36%) clinics reported that no additional advice was given.

Table 6.5 Preterm birth clinic interventions

Interventions routinely offered (non-exclusive)	**Number of non-UK based clinics (%), n=6**
Cervical cerclage	6 (100)
Vaginal progesterone	4 (67)
IM progesterone (17OHP-C)	2 (33)
Cervical pessary	1 (17)
Primary choice of intervention for women with a sonographic short cervix [a]	**Number of UK based clinics (%), n=33**
Cervical cerclage	10 (30)
Vaginal progesterone	6 (18)
Cervical pessary	1 (3)
Combination therapy [b]	6 (18)
Multiple first-line treatment options	10 (30)

UK, United Kingdom; IM, intramuscular; 17OHP-C, 17-alpha hydroxyprogesterone caproate.

[a] Threshold for a short cervix defined by the individual clinic, further detailed in the text.

[b] Most were combination of cervical cerclage and vaginal progesterone.

Table 6.6 describes the planned timing of preterm birth clinic visits. Data were available for the planned first appointment for 35 clinics (32 UK, 3 non-UK), and for planned last appointment for 26 clinics (22 UK, 4 non-UK). Most clinics planned to see women for their first appointment at 12 to 14 weeks (14/35, 40%) or 15 to 16 weeks (16/35, 46%). The timing of discharge from a preterm birth clinic varied considerably from 24 to 37 weeks. The planned frequency of review was available for 24 clinics (22 UK, 2 non-UK) with the majority (18/24, 75%) individualising this depending on clinical findings. Five clinics (21%) reviewed women fortnightly, and one clinic (4%) four-weekly.

Table 6.6 Timing of planned first and last preterm birth clinic appointments

Gestational age at planned first clinic appointment	**Number (%), n=35** [a]
<12 weeks	3 (9)
12-14 weeks	14 (40)
15-16 weeks	16 (46)
>16 weeks	1 (3)
Other [b]	1 (3)
Gestational age at planned last clinic appointment [c]	**Number (%), n=26** [d]
24 weeks	1 (4)
26 weeks	1 (4)
28 weeks	9 (35)
30 weeks	1 (4)
32 weeks	2 (8)
34 weeks	9 (35)
37 weeks or delivery	3 (12)

UK, United Kingdom.

[a] Data not available for four clinics.

[b] 10-18 weeks.

[c] If a gestational age range was given, the upper gestation is reported.

[d] Data not available for 13 clinics.

6.2.5 Discussion

Summary of evidence

Data were obtained for a number of preterm birth clinics in this systematic review. The majority of clinics were located in the UK, but clinics in America, Germany, Italy and Australia are also identified. All clinics accepted referrals for women with a previous spontaneous preterm birth, however other referral criteria varied. The majority of clinics saw women with previous mid-trimester loss, previous preterm pre-labour rupture of membranes, previous cervical surgery, uterine abnormality or malformation, and a short cervix detected in pregnancy. A minority of clinics also accepted referrals for other indications including history of multiple surgical terminations of pregnancy or dilatation and curettage, as follow up after a diagnosis of threatened preterm labour, and presence of an autoimmune condition. Of interest, no clinic listed previous caesarean section at full dilatation as a referral criteria, despite recent evidence that this

is a significant risk factor for spontaneous preterm birth (Watson, Carter, David et al. 2017; Wood, Tang et al. 2017).

Transvaginal cervical length scans were used to aid decisions on management in all clinics but the use of additional investigations such as urogenital swabs, urine culture and fetal fibronectin varied. Differences in how interventions were reported limited the ability to synthesise these results, however available evidence shows that a range of interventions are available, with significant variation in the choice of primary management for a sonographic short cervix within the UK, where this data was available. The majority of clinics saw women for their first appointment between 12 and 16 weeks of gestation and cared for them through to the late second or early third trimester. The frequency of preterm birth clinic review was usually directed by clinical findings.

Application of results

To the best of our knowledge, this is the first systematic review to assess practice in preterm birth clinics globally, and has shown wide variation in most aspects of care. Inconsistencies in care have also been identified as an issue in national surveys of practice in the UK (Care, Ingleby et al. 2019; Sharp & Alfirevic 2014). This information can be used to support the development and implementation of preterm birth clinic consensus guidelines and national prevention programmes, which are likely to improve consistency and encourage best practice care based on current evidence. The newly introduced 'Reducing Preterm Birth: Guidelines for Commissioners and Providers' (UK Preterm Clinical Network 2019) is likely to fulfil this role in the UK and may also influence care in other countries; re-evaluation of practice following implementation of this guideline will be important to assess its impact. The findings from this review can also be used to assist with service planning as preterm birth clinics continue to be introduced throughout the developed world.

Improving consistency in care will also allow clinics to combine their outcome data in a more meaningful way, enabling high-quality research into the effectiveness of interventions provided in preterm birth clinics, along with comparisons between clinics (Vernet, Watson et al. 2017). The UK Preterm Clinical Network has already developed a bespoke internet-based database that uses an agreed minimal dataset, allowing systematic and standardised collection of clinical data from preterm birth clinics within the network (Carter, Tribe et al. 2018). In 2018, there were seven sites using this database, and an additional 24 sites were registered as Data Collection Centres, four of which are outside of the UK (Carter, Tribe et al. 2018). This collaborative

approach to data collection, if combined with a consistent approach to care in preterm birth clinics, has great potential for the future evaluation of existing and new interventions aimed at optimising the care of asymptomatic women at high risk of spontaneous preterm birth.

Limitations

The main limitation of this review is the potential for incomplete data. Due to the paucity of literature in this area, studies were included that did not specifically assess or report on care in a preterm birth clinic, but reported on another aspect of care in a group of high risk women cared for in a preterm birth clinic. Thus, details about the clinic itself were at times incomplete. We have assumed for the purposes of this review that if a referral criteria, investigation or intervention was not reported, then it was not used. Another limitation is that included data is predominantly from clinics in the UK, so results are likely to favour practice from this region. This is unsurprising as the UK have led the development of modern-day preterm birth clinics and to our knowledge, are the first to recommend the use of preterm birth clinics in national guidelines (UK Preterm Clinical Network 2019). Results from the UK also have a lower risk of publication bias due to the availability and inclusion of studies that had taken a cross-sectional survey approach to assessing preterm birth clinic practice (Care, Ingleby et al. 2019; Sharp & Alfirevic 2014). Results from outside of the UK may reflect care from academic preterm birth clinics which are more likely to have published their data or be involved in other research. National or binational surveys of practice in other localities would be helpful and we intend to explore this in Australasia.

We have taken a unique approach to analysis by combining different studies on the same clinic and in our selection of studies suitable for combination and synthesis. This was necessary as the 'population' of interest was the clinic itself, and thus inclusion of all studies would have resulted in over-representation of certain clinics which were described in multiple studies. The assumption that the three clinics reported in other included UK based studies were included within the four anonymous clinics in Care 2019, is a further limitation of this study. However even if not the case, this is unlikely to have changed findings significantly.

6.2.6 Conclusions

To our knowledge, this is the first systematic review of the practice of preterm birth clinics internationally. Variation in the referral criteria, investigations and interventions, and timing and frequency of review in individual preterm birth clinics was evident. Consistency in care is likely

to be improved with the introduction of consensus guidelines and national preterm birth prevention programmes such as those recently introduced in the UK. A repeat survey of practice in preterm birth clinics in the UK can be used to assess the impact of new consensus guidelines introduced in the UK, and are also required in other localities.

6.2.7 Supplementary information

Table 6.7 MEDLINE search strategy

Line	Search term	Results
1	((preterm or pre-term) adj3 (clinic or clinics)).mp	46
2	(miscarriage adj2 (followup or follow-up) adj2 (clinic or clinics)).mp	0
3	((multidisciplinary or multi-disciplinary) adj2 antenatal adj2 (clinic or clinics)).mp	7
4	(special* adj (antenatal or ante-natal) adj (clinic or clinics)).mp	40
5	((special* adj2 (clinic or clinics)) and (preterm or pre-term)).mp	35
6	((special* adj2 (clinic or clinics)) and (premature adj (delivery or parturition or birth* or labo?r))).mp	16
7	1 or 2 or 3 or 4 or 5 or 6	115
8	Prenatal Care/og [Organization & Administration]	1427
9	Prenatal Care/ and (Ambulatory Care Facilities/ or Outpatient Clinics, Hospital/)	217
10	Perinatal Care/	4153
11	Pregnancy/ and (Ambulatory Care Facilities/ or Outpatient Clinics, Hospital/)	1567
12	8 or 9 or 10 or 11	7070
13	Pregnancy, High-Risk/	4586
14	Premature Birth/	12141
15	Obstetric Labor, Premature/	13071
16	Pregnancy Complications/	87239
17	13 or 14 or 15 or 16	111873
18	12 and 17	1037
19	exp animals/ not humans.sh	4574521
20	(7 or 18) not 19	1142
21	Limit 20 to (english language and yr =”1998-Current”)	887

***** This is a truncation symbol on MEDLINE and was used to retrieve terms with a common root.

Table 6.8 Methodological quality assessment of included studies based on the Newcastle-Ottawa Scale for cohort and case controlled studies

Study	**Selection**				**Comparability**	**Outcome**			**Overall Score** (out of 9)
	Representativeness (⋆)	**Selection of non-exposed cohort (⋆)**	**Ascertainment of exposure (⋆)**	**Outcome not present at start (⋆)**	**By design or control of confounders (⋆⋆)**	**Assessment (⋆)**	**Length of follow-up (⋆)**	**Adequacy of follow-up (⋆)**	
Bolt 2011 [a]	⋆	-	⋆	⋆	- -	⋆	⋆	⋆	6
Ivandic 2018 [a]	⋆	-	⋆	⋆	- -	⋆	⋆	⋆	6
Karkhanis 2012 [a]	⋆	-	⋆	⋆	- -	⋆	⋆	-	5
Yulia 2015 [a]	⋆	-	⋆	⋆	- -	⋆	⋆	-	5
Kindinger 2013 [a]	⋆	-	⋆	⋆	- -	⋆	⋆	-	5
Burul 2014 [a]	⋆	⋆	⋆	⋆	- -	⋆	⋆	-	6
Grant 2016 [a]	⋆	-	⋆	⋆	- -	⋆	⋆	*	6
Manuck 2011	⋆	⋆	⋆	⋆	- ⋆	⋆	⋆	-	7
Hughes 2017 [a]	⋆	-	⋆	⋆	- -	⋆	⋆	*	6

Newnham 2017	⋆	⋆	⋆	⋆	- -	⋆	-	⋆	6
Stricker 2016	⋆	-	⋆	⋆	- -	⋆	⋆	⋆	6
Kindinger 2016 [a]	-	-	⋆	⋆	- -	⋆	⋆	⋆	5
Watson 2017	⋆	⋆	⋆	⋆	- -	⋆	⋆	⋆	7
Cohen 2014 [a]	⋆	-	⋆	⋆	- -	⋆	⋆	-	5
Kuhrt 2016 [a]	⋆	-	⋆	⋆	- -	⋆	⋆	⋆	6
Vousden 2015 [a]	-	-	⋆	⋆	- -	⋆	⋆	⋆	5

[a] Observational study, but not a typical cohort or case controlled study.

Table 6.9 Methodological quality assessment of included studies based on the modified Newcastle-Ottawa Scale for cross-sectional studies

Study	**Selection**				**Comparability**	**Outcome**		**Overall Score** (out of 10)
	Representa-tiveness (⋆)	**Sample size (⋆)**	**Non-respondents (⋆)**	**Ascertainment of the exposure (⋆⋆)**	**By design or control of confounders (⋆⋆)**	**Assessment (⋆⋆)**	**Statistical test (⋆)**	
Turitz 2016	⋆	⋆	⋆	⋆⋆	- -	⋆⋆	⋆	8
Care 2019	⋆	⋆	-	- -	- -	- -	-	2

Table 6.10 Methodological quality assessment of included studies based on the Cochrane Risk of Bias Tool for randomised controlled trials

Study	Danti 2014
Random sequence generation (selection bias)	Low: central computer-generated randomisation.
Allocation concealment (selection bias)	Low: randomised list of balanced blocks for every 10 participants.
Blinding of participants and personnel (performance bias)	Low: patients and clinicians (except pharmacist) blinded.
Blinding of outcome assessment (detection bias)	Low: blinding maintained until after delivery of last participant.
Incomplete outcome data (attrition bias)	Low: outcome data available for all.
Selective outcome reporting (reporting bias)	High: unplanned secondary analysis for women with a short cervix.
Other bias	Unclear: early closure, did not reach planned sample size.

Table 6.11 Methodological quality assessment of included qualitative studies based on the Critical Appraisal Skills Programme Checklist for qualitative research

Study	O'Brien 2010
Study aims	Yes, aims to gain an understanding of the experiences of women attending a preterm birth clinic and to elicit their views.
Appropriate methodology	Yes, qualitative methodology appropriate for the stated aim.
Study design	Yes, research design justified, with use of focus groups and interviews.
Recruitment strategy	Yes, detailed strategy of recruitment from a preterm birth clinic.
Data collection	Yes, through focus groups and one-to-one interviews with transcription of results.
Researcher-participant relationship	Unclear, not well described.
Ethical considerations	Yes, ethical approval obtained.
Data analysis	Yes, description of thematic analysis by two independent researchers, with categories defined by comments made from the women.
Study findings	Yes, three main themes were identified and implications of findings discussed.
Value of the study	Yes, a unique study that identified areas where further research is required.

Chapter 7 The experience and outcomes of a specialised preterm birth clinic in New Zealand

7.1 Preface

This chapter provides a detailed review of the experience and outcomes from five years of practice in the first specialised preterm birth clinic in New Zealand. It includes an in depth assessment of practice within the clinic including the identified risk factors of clinic attendees, investigations performed and results, details of management provided and the maternal and neonatal pregnancy outcomes. This observational study provides local data that can be used in patient counselling, along with valuable information on resource and training needs that can inform the development of future preterm birth clinics in New Zealand and Australia.

This chapter has been submitted as a manuscript to the *Australian and New Zealand Journal of Obstetrics and Gynaecology*; an outcome is awaited. The following manuscript is unaltered from the version submitted for publication.

7.2 The experience and outcomes of a specialised preterm birth clinic in New Zealand

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7.2.1 Abstract

Background: A greater understanding of the risk factors for spontaneous preterm birth and the importance of risk stratification to guide interventions has led to the introduction of preterm birth prevention clinics.

Aim: To evaluate the experience and outcomes of the first specialised preterm birth clinic in New Zealand.

Materials and methods: This observational study reviewed pregnancies cared for in a preterm birth clinic from 2013-2018. Cases were identified and data collected from a maternity database and electronic medical records. Analysis was by referral type.

Results: A total of 345 women were included; 309 elective referrals in pregnancy (275 women), 22 acute referrals and 92 consultations outside pregnancy. For those referred electively in pregnancy, 138/309 (44.7%) fulfilled multiple referral criteria, and 57/309 (18.4%) had ≥2 previous spontaneous preterm births or second trimester losses. Excluding five pregnancies with first trimester miscarriage, 77/304 (25.3%) were managed with a history-indicated cerclage (11 placed preconception) and 217/304 (71.4%) had cervical surveillance as primary management, of which 133 (61.3%) did not require treatment. The remaining had treatment for a short cervix; 37 (17.0%) received an ultrasound-indicated cerclage only, 21 (9.7%) vaginal progesterone only and 26 (12.0%) both. Five women (1.6%) had a second trimester loss at 13^{+0}-19^{+6} and 58/297 (19.5%) had a spontaneous preterm birth at 20^{+0}-36^{+6} weeks. The 'take home baby' rate was 95.4%.

Conclusions: Pregnancy outcomes were similar to those reported by other preterm birth prevention clinics. The majority of women who received cervical surveillance as primary management were able to avoid additional treatment.

7.2.2 Introduction

Preterm birth (PTB) accounts for 7.5% of New Zealand (NZ) births (Ministry of Health 2018) and is the leading cause of neonatal death (Perinatal and Maternal Mortality Review Committee 2018). Approximately half of all PTBs occur after the spontaneous onset of labour or preterm pre-labour rupture of membranes (PPROM) (Auckland District Health Board 2018a; March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012). A growing understanding of the risk factors for spontaneous preterm birth (sPTB) and risk stratification to guide the use of interventions that prevent sPTB and improve neonatal outcomes has led to the development of specialised clinics to care for those identified as high risk. The key components of care in these preterm birth clinics (PTBCs) include addressing modifiable risk factors, mid-trimester transvaginal ultrasound cervical length surveillance, and provision of evidence-based interventions such as cervical cerclage and vaginal progesterone (Vernet, Watson et al. 2017).

To date, systematic reviews have demonstrated only limited evidence that PTBCs reduce sPTB rates, however these reviews included historic studies not reflective of current care (Malouf & Redshaw 2017; Whitworth, Quenby et al. 2011). The benefits of coordinated and individualised care, increasing evidence to support interventions, and the ongoing poor outcomes as a consequence of PTB, provide rationale for these clinics (Malouf & Redshaw 2017; Vernet, Watson et al. 2017). Over the last two decades, PTBCs have become common-place in the

United Kingdom (Care, Ingleby et al. 2019; Sharp & Alfirevic 2014) and are now recommended by the National Health Service (UK Preterm Clinical Network 2019). Their introduction across Australasia has been slower but recent initiatives for preterm birth prevention will likely lead to further development of these services (Newnham & Morris 2019). This study evaluates the experience and outcomes of five years of practice in the first PTBC in NZ; data will inform plans for more clinics across the country.

7.2.3 Materials and methods

This is an observational study of women cared for in a tertiary maternity hospital PTBC from May 2013 to May 2018. Supplementary Tables 7.4 and 7.5 describe clinic referral criteria and standard clinic practice (Auckland District Health Board 2019b). Cases were identified from the maternity database. Data was extracted from this database and electronic medical records by two study investigators. Outcome data was requested when birth occurred elsewhere.

Data was analysed by referral type; (1) elective in pregnancy, (2) acute in pregnancy (cervical length <10 mm in women with pre-existing risk factors and no prior referral, or an incidental finding of a short cervix <25 mm <24 weeks in low risk women), and (3) review outside of pregnancy. Some women were cared for in more than one pregnancy; all pregnancies have been included to allow evaluation of the clinic rather than individuals. Induction of labour and pre-labour caesarean section for PPROM were classified as sPTB.

IBM SPSS Statistics software (version 25.0) was used (IBM Corp 2017). Ethical approval was granted by the Auckland Health Research Ethics Committee (reference 000059).

7.2.4 Results

A total of 345 women were included; 275 (309 pregnancies) elective referrals (244 women in one pregnancy, 29 in two, one in three and one in four), 22 acute referrals (22 pregnancies with one woman also seen electively in a subsequent pregnancy), 92 referrals outside of pregnancy (of which 43 were also cared for in a prior or subsequent pregnancy). Twelve pregnancies were excluded; nine did not fulfil clinic referral criteria, three did not attend appointments offered.

Elective referrals in pregnancy

Demographic details, obstetric characteristics and risk factors for sPTB are described in Table 7.1. Just over half of women resided within the district health board area (160/309, 51.8%), the remainder were from the wider city area (122/309, 39.5%) or tertiary/quaternary referrals from across NZ (27/309, 8.7%). Nearly half of cases fulfilled multiple referral criteria (138/309, 44.7%) (Table 7.1). Of the 236 multiparous pregnancies, 58 (24.6%) had ≥1 prior stillbirth at $\geq 20^{+0}$ weeks and 63 (26.7%) had a prior neonatal death.

Table 7.1 Demographic details and obstetric characteristics for pregnancies seen following elective referral

Characteristic	**Number (%)**
Maternal age (years) †	
Mean ± SD	33.5 ± 5.1
Range	21 - 49
Ethnicity	
European	99 (36.0)
Māori	28 (10.2)
Indian	33 (12.0)
Pacific Peoples	30 (10.9)
Asian	38 (13.8)
Other	47 (17.1)
Body mass index (kg/m^2) †‡	
Mean ± SD	26.9 ± 6.0
Range	17 - 50
Cigarette smoker at first visit †	18 (5.8)
Socio-economic deprivation †§	60 (19.4)
Lead maternity carer † ‖	
Independent midwife	92 (29.8)
Community hospital midwife	47 (15.2)
High risk hospital midwife	120 (38.8)
Private obstetrician	49 (15.9)
Nulliparous	22 (7.1)
Artificial reproductive technology	47 (15.2)
Plurality	
Singleton	300 (97.1)
Twins or triplets	9 (2.9)
Confirmed dating ¶	302 (97.8)

Risk factors for spontaneous preterm birth and criteria for clinic referral: †	
Previous spontaneous preterm birth or PPROM 24^{+0} to 35^{+6} weeks #	119 (38.5)
Previous spontaneous second trimester loss or PPROM 16^{+0} to 23^{+6} weeks	143 (46.3)
One previous LLETZ procedure with >10 mm depth of excision Δ ◊	36 (11.7)
Two or more previous LLETZ procedures ◊	24 (7.8)
Previous knife cone biopsy or trachelectomy ◊	36 (11.7)
Congenital uterine and/or cervical anomaly	30 (9.7)
Short cervix in current pregnancy of 10-25 mm at $<24^{+0}$ weeks	29 (9.4)
Two or more surgical terminations of pregnancy and/or evacuation of retained products of conception	35 (11.3)
Complicated caesarean section at full dilatation	15 (4.9)
Other	17 (5.5)
Multiple previous pregnancies complicated by: †	
Spontaneous preterm birth or second trimester miscarriage from 16^{+0} to 36^{+6} weeks	57 (18.4)
PPROM with or without preterm birth	20 (6.5)

Data represented as number (percentage) unless otherwise stated.

SD, standard deviation; PPROM, preterm pre-labour rupture of membranes; LLETZ, large loop excision of the transformation zone.

† n=309 pregnancies, including 31 women with ≥2 pregnancies.

‡ Missing data for two pregnancies.

§ NZDep2013 Deprivation Index quintile 5 (most deprived).

‖ One pregnancy not booked for maternity care, first trimester miscarriage diagnosed at clinic review.

¶ By sure menstrual dates, first trimester scan, or in vitro fertilisation.

#Also includes survivors born at 23 weeks gestation.

Δ Or depth of excision unknown.

◊ Total of 92 pregnancies with cervical surgery that met referral criteria. Histology was available for 44/92 (47.8%) cases; mean depth of excision 19.7 mm, range 10-45 mm (cumulative if >1 treatment).

The mean gestational age at first consultation was 14^{+0} weeks, range 5^{+3}-24^{+6} weeks. Five women had a miscarriage <12 weeks and were excluded from further analysis. The mean number of clinic visits was 4.7, SD 2.2, range 1-12, with women attending for a single visit in 27/304 (8.9%) pregnancies, usually due to late referral. Results of investigations are shown in Table 7.2. Only one woman declined transvaginal scans. Figure 7.1 summarises management; 142/304 (46.7%) received a cervical cerclage – 77 history-indicated, 61 ultrasound-indicated and four rescue (with exposed fetal membranes); 63/304 (20.7%) received vaginal progesterone – eight history-indicated and 55 ultrasound-indicated

Table 7.2 Results of investigations for pregnancies seen following elective referral

Investigation results	**Number (%)** n=304 †
Urogenital swabs ‡	
Normal	163 (53.6)
Bacterial vaginosis §	49 (16.1)
Candida ‖	45 (14.8)
Group B streptococcus	21 (6.9)
Chlamydia, trichomonas or gonorrhoea ¶	3 (1.0)
Not performed	37 (12.2)
Midstream urine ‡	
Normal	151 (49.7)
Urinary tract infection ¶	18 (5.9)
Not performed	135 (44.4)
Transvaginal cervical length surveillance #	295 (97.0)
Cervical length performed at first visit	293 (96.4)
Mean ± SD (in mm)	31.0 ± 7.7
Range (in mm)	0 – 46
Cervical length performed at last visit	286 (94.1)
Mean ± SD (in mm)	28.5 ± 9.9
Range (in mm)	0 – 45
Shortest cervical length	304 (99.7)
Mean ± SD (in mm)	24.8 ± 9.3
Range (in mm)	0 – 43
<25 mm	131 (43.1)
Qualitative fFN ††	
Negative	31 (79.5)
Positive	8 (20.5)
Quantitative fFN ††	
Mean ± SD (in ng/ml)	57.7 ± 112.0
0 – 49 ng/ml	64 (79.0)
50 – 199 ng/ml	8 (9.9)
200 – 499 ng/ml	8 (9.9)
≥500 ng/ml	1 (1.2)

Data represented as number (percentage) unless otherwise stated.

SD, standard deviation; mm, millimetres; fFN, fetal fibronectin.

† Excludes five pregnancies with first trimester miscarriage diagnosed at first visit. Includes 31 women with ≥2 pregnancies.

‡ Taken at first visit or taken in pregnancy prior to first visit and results available.

§ Treated in 41/49 (83.7%) cases.

‖ Treated in 20/45 (44.4%) cases.

¶ Treated in all cases.

Defined as ≥2 transvaginal ultrasound scans for cervical length.

†† Qualitative fFN taken in 39 pregnancies, replaced by quantitative fFN testing in 2015, taken in 81 pregnancies.

In most pregnancies women had a planned 'exit visit' (265/304, 87.2%); of those not seen, 11 had delivered, three had PPROM, 11 had follow-up in their hometown and six declined or did not attend. The mean gestational age at the exit visit was 23^{+4} weeks, range 19^{+1}-26^{+4} weeks. A fetal fibronectin (fFN) swab was processed at the exit visit in 108/265 (40.8%) pregnancies and at an earlier appointment in another 12 pregnancies (Table 7.2). A QUiPP score combining clinical history, cervical length and fFN (Watson, Carter, Seed et al. 2017) was recorded in 113/120 (94.3%) pregnancies where a fFN result was available; 15/113 (13.3%) had a ≥5% risk of sPTB within two weeks. Antenatal corticosteroids were given in nine of these pregnancies, and in a further three due to antepartum haemorrhage or PPROM; 8/12 (66.7%) delivered <34 weeks. Women were admitted to hospital from their exit visit in only 6/265 (2.3%) pregnancies; two (33.3%) delivered within 14 days and four (66.6%) $<28^{+0}$ weeks. A further seven women with a sPTB $<28^{+0}$ weeks were not administered corticosteroids or admitted to hospital from their exit appointment.

Five women had a second trimester loss at 13^{+0}-19^{+6} weeks; four (80.0%) had received treatment, one history-indicated cerclage and three ultrasound-indicated cerclage of which two also received progesterone. Outcome data was available for 297 of the remaining 299 pregnancies (99.3%); two women relocated overseas (both at 29 weeks) and were not contacted further. Pregnancy complications, delivery details and neonatal and maternal outcomes for pregnancies reaching $\geq 20^{+0}$ weeks are shown in Table 7.3. High rates of antenatal administration of corticosteroids for births $<35^{+0}$ weeks (25/26, 96.2%) and magnesium sulphate for births $<30^{+0}$ weeks (10/12, 83.3%) were achieved. The 'take home baby' rate was 95.4% (288/302) for women whose pregnancy proceeded >12 weeks and outcome was known.

The sPTB rate for women who received cervical surveillance as primary management with no further intervention was 23/133 (17.3%) and only 3/133 (2.3%) delivered <32 weeks. Women

who required treatment for a sonographic short cervix had a higher rate of sPTB (22/84, 26.2%), and half were at <32 weeks (11/22, 50%), including two pregnancies complicated by PPROM and chorioamnionitis <23 weeks.

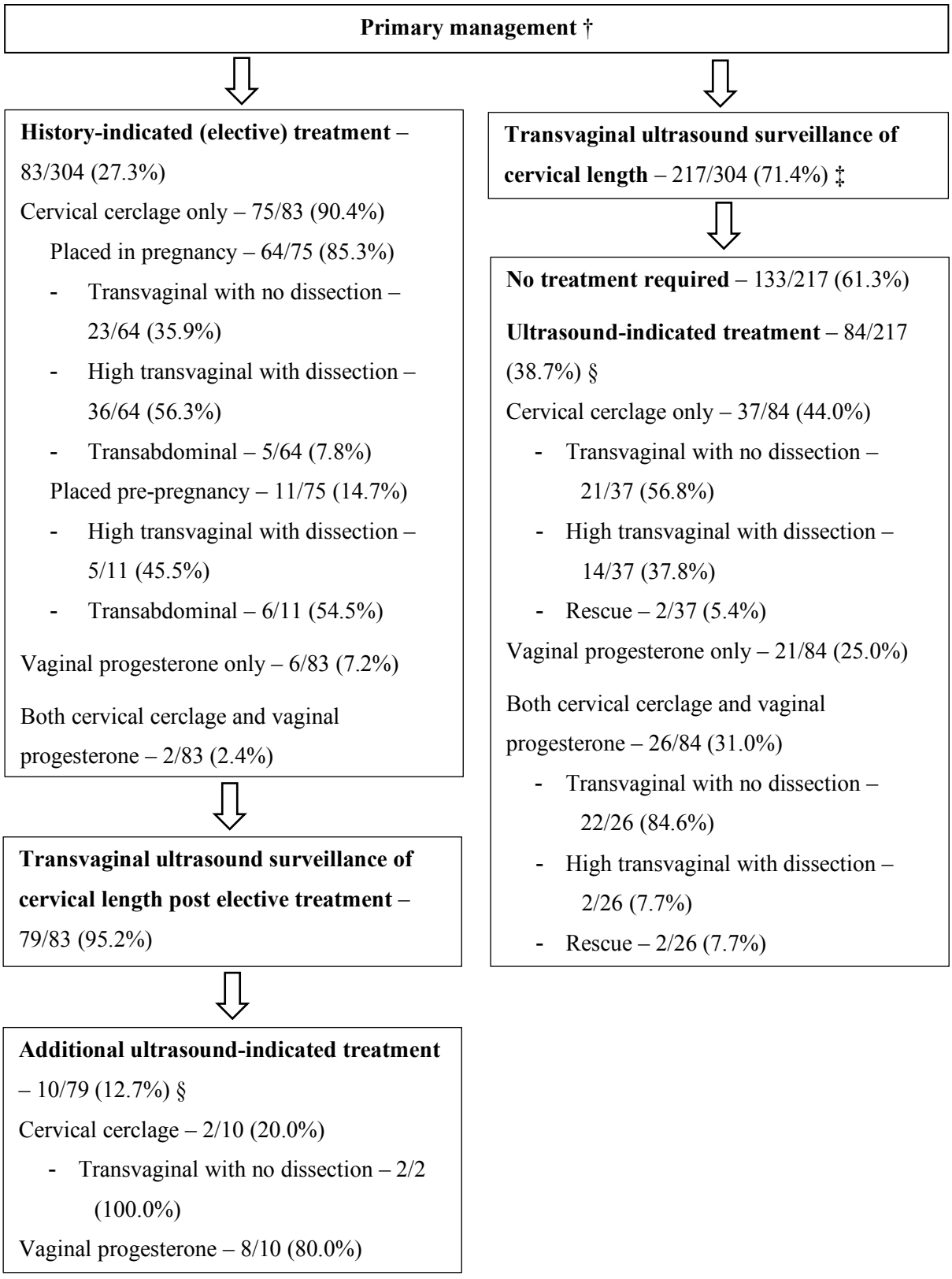

Figure 7.1 Management of pregnancies after elective referral

Data represented as numerator/denominator (percentage) unless otherwise stated.

† n=304 pregnancies, including 30 women with ≥2 pregnancies; excludes five cases with first trimester miscarriage.

‡ An additional four pregnancies had a single visit to the clinic without further treatment or surveillance (three declined, one was found to have ruptured membranes at first visit).

§ Cervical length <25 mm at <24 weeks.

Table 7.3 Antenatal complications, delivery details and neonatal and maternal outcomes for pregnancies that reached beyond 20 weeks of gestation

Complications and outcomes	**Number (%) †**
Antenatal complications	
Antepartum haemorrhage	44 (14.8)
PPROM	37 (12.5)
Chorioamnionitis (clinical diagnosis)	9 (3.0)
Diabetes in pregnancy ‡	46 (16.1)
Preeclampsia	7 (2.4)
Gestational age at delivery	
Spontaneous preterm birth §	58 (19.5)
20^{+0} to 22^{+6} weeks	6 (2.0)
23^{+0} to 24^{+6} weeks	2 (0.7)
25^{+0} to 27^{+6} weeks	11 (3.7)
28^{+0} to 31^{+6} weeks	1 (0.3)
32^{+0} to 36^{+6} weeks	38 (12.8)
Medically-indicated preterm birth	12 (4.0)
Term birth (≥37 weeks)	227 (76.4)
Onset of labour	
Termination of pregnancy ‖	4 (1.3)
Spontaneous labour	143 (48.1)
Induction of labour	77 (25.9)
Pre-labour caesarean section	73 (24.6)
Mode of birth	
Vaginal delivery	181 (60.9)
Caesarean section	116 (39.1)
Neonatal outcomes ¶	
Alive at hospital discharge	295 (96.1)
Stillbirth	6 (2.0)
Early neonatal death	5 (1.6)

Late neonatal death	0 (0.0)
Postneonatal death	1 (0.3)
Major neonatal morbidity #	
Intraventricular haemorrhage	5 (1.7)
Respiratory distress syndrome	29 (9.8)
Necrotising enterocolitis	1 (0.3)
Sepsis (culture-proven)	7 (2.4)
Retinopathy of prematurity	7 (2.4)
Neonatal intensive care admission ¶	66 (19.5)
Maternal harm	
Complications from cervical cerclage ††	2 (0.7)
Intensive care admission	0 (0.0)
Death	0 (0.0)

Data represented as numerator/denominator (percentage) unless otherwise stated.

PPROM, pre-labour premature rupture of membranes.

† n=297 pregnancies unless otherwise stated, including 30 women with ≥2 pregnancies; excludes two pregnancies with unknown outcome.

‡ n=285 pregnancies, excluding 12 pregnancies with unknown diabetes status.

§ Includes induction of labour and pre-labour caesarean following pre-labour premature rupture of membranes.

‖ All four cases who underwent termination of pregnancy had PPROM, with concern for chorioamnionitis in three pregnancies and multiple fetal anomalies in the fourth.

¶ n=307 babies, including eight sets of twins and one set of triplets.

n=296 babies who survived to primary hospital discharge.

†† One due to local infection at insertion site, one cervical laceration at time of removal.

Acute referrals in pregnancy

Most acute referrals (19/22, 86.4%) followed an incidental finding of a short cervix <25 mm at fetal morphology scan. Treatment was commenced prior to the first clinic visit in most pregnancies (15/22, 68.2%) and included cervical cerclage (9), vaginal progesterone (2), and combined therapy (4). The mean cervical length at first clinic visit was 12.9 mm, SD 10.1 mm (post-cerclage measurement in 13 women). In total, 16/22 (72.7%) received cervical cerclage; eight ultrasound-indicated, seven rescue and one pre-pregnancy transabdominal cerclage, and 10/22 (45.5%) received vaginal progesterone, five as sole treatment.

A fFN swab was processed for 18/19 (94.7%) women who had an exit visit with a positive result in 50% of cases (>50 ng/mL). Antenatal corticosteroids were administered from the clinic for

8/19 (42.1%) women who had an exit visit and 6/19 (31.6%) were admitted to hospital. The mean gestational age at birth was 32^{+5} weeks; 10/22 (45.5%) had a sPTB, eight $<28^{+0}$ weeks. Antenatal corticosteroids were given for all births (8/8) $<34^{+0}$ weeks and magnesium sulphate in all but one case (5/6) with birth $<30^{+0}$ weeks. 22/24 babies (91.7%) were alive at hospital discharge, one was stillborn ($<23^{+0}$ weeks) and one had an early neonatal death (born at 23^{+2} weeks with decision for comfort care).

Review outside of pregnancy

Of the 92 women seen outside of pregnancy, one was seen for two episodes with an interval pregnancy (data presented for the first episode). Attendees were European (55.4%), Māori (6.5%), Pacific (13.0%), Asian (13.0%), Indian (9.8%) and other (3.1%). Women resided in the most deprived quintile in 19/92 (20.1%) cases. Reasons for referral were previous sPTB at 24^{+0}-35^{+6} weeks in 31/92 (33.7%); second trimester loss at 16^{+0}-24^{+0} weeks in 43/92 (46.7%) and extensive cervical surgery in 33/92 (35.9%). Only 15/92 (16.3%) had never been pregnant; 8/92 (8.7%) were current smokers.

Pre-pregnancy cerclage was offered to 31/92 (33.7%) women and 22/92 (23.9%) had a cerclage placed; 10 high transvaginal with circumferential dissection and 12 transabdominal cerclage (11 by open approach, one laparoscopic performed elsewhere). All women had a documented plan for future pregnancy and 39/92 (42.4%) returned to the PTBC in a subsequent pregnancy during the study period.

7.2.5 Discussion

This is an observational study of a cohort of women receiving care in the first five years of practice in the only established PTBC in NZ. As this is an established clinic within our hospital, there is no similar high risk group who do not receive this specialised care to allow comparison. We have also not compared women managed with history-indicated and ultrasound-indicated interventions as their pre-existing risk profiles are different. Practice within our clinic is to offer elective cerclage to the 'highest risk' women with multiple second trimester losses/early sPTB or history of extensive cervical surgery. Ultrasound surveillance of cervical length is recommended for the remaining 'moderate risk' women who have had a single prior second trimester loss/sPTB, congenital uterine anomaly, less extensive cervical surgery or multiple uterine instrumentations, with cerclage or vaginal progesterone offered if the cervix shortens to <25 mm.

Women who were referred electively to our PTBC were at high risk of sPTB with many fulfilling multiple referral criteria and/or having multiple previous second trimester losses/sPTBs. Just over two thirds of women seen after elective referral had cervical surveillance as their primary management. Although this is resource intense, further treatment was avoided in most cases and interventions were directed to those at greatest risk, who subsequently were most likely to deliver preterm. Despite being a high risk population, the majority achieved a term delivery with good outcomes for their babies.

Few women were seen following an incidental finding of a short cervix, as expected given there is no policy for routine cervical screening for low risk women in NZ. These women had high rates of sPTB supporting the inclusion of a sonographic short cervix in otherwise low risk women in PTBC referral criteria. Our study does not take into account the number of women screened to detect those with a short cervix, nor the number of false negatives results. Thus, these findings do not necessarily provide support for a universal cervical length screening programme.

Pre-pregnancy consultations represent a moderate amount of the clinic caseload. Just under one third had a pre-pregnancy cerclage placed, half via the transabdominal route. The newly published MAVRIC study results support the use of transabdominal cerclage over repeat transvaginal cerclage in women with a previous failed transvaginal cerclage and hence their use may increase (Shennan, Chandiramani et al. 2019). Pre-pregnancy placement has the advantages of reducing both maternal and fetal risk.

We have recently conducted a systematic review to assess practice in PTBCs globally, there are few studies reporting outcomes from these specialised clinics; only two from Australasia were identified (Hughes, Sim et al. 2017; Newnham, White et al. 2017). Hughes and colleagues have described their ten-year PTBC experience in Melbourne (Hughes, Sim et al. 2017). Comparison of risk status with our study is difficult due to differences in how risk factors have been reported, however, both studies had very similar rates of sPTB (21.3% in our study including elective and acute referrals, 21.4% in the Hughes study) (Hughes, Sim et al. 2017). Studies that report on outcomes from the United Kingdom and America show highly variable rates of sPTB (15-50%), likely reflecting differences in risk status and small study numbers (Bolt, Chandiramani et al. 2011; Ivandic, Care et al. 2018; Kuhrt, Smout et al. 2016; Manuck, Henry et al. 2011).

This is the first study to report on practice from a PTBC in NZ. It provides a significant contribution to the limited international literature in this evolving field. Although PTBCs are not currently widely used in Australasia, state- and nation-wide PTB prevention initiatives are being introduced and PTBCs feature as a key component in some programmes (Newnham & Morris 2019; Newnham, White et al. 2017). Our results can help to plan the more widespread introduction and development of PTBCs across Australasia and inform clinicians and hospital managers on resource and training needs. This study also provides local outcome data that can be used in patient counselling.

PTBCs provide specialised care for women at risk of sPTB, aiming to identify those at greatest risk who are most likely to benefit from interventions to prevent early birth and optimise outcomes for their babies. PTBCs may also have a role in promoting equity by offering standardised care to all with pre-existing risk factors for sPTB. This requires appropriate referral regardless of ethnicity and socio-economic status. Māori women have proportionately higher rates of sPTB than non-Māori (8.3% versus 3.4% in local data from 2017) (Auckland District Health Board 2018a; Perinatal and Maternal Mortality Review Committee 2018). The antecedent causes are likely confounding factors such as younger maternal age, smoking and socio-economic deprivation, which are not criteria for PTBC referral (Auckland District Health Board 2018a). However we would expect to see a higher rate of multiparous Māori women being referred based on their obstetric history. Māori women made up 6.4% of all maternities in 2017 in our hospital (Auckland District Health Board 2018a) and 10.2% of elective referrals to the PTBC in pregnancy, suggesting Māori women are able to access the clinic. However fewer Māori women were seen for review outside of pregnancy (6.5%), raising the possibility of inequity in access to pre-conceptual care.

Women who reside in lower socio-economic areas also have higher rates of sPTB, with local data showing 24.7% of sPTBs were to mothers from the highest deprivation quintile in 2017 (Auckland District Health Board 2018a). Numbers of women from the highest deprivation quintile seen following elective referral (19.4%) and review outside of pregnancy (20.1%) may be lower than expected and disparities by socio-economic status warrants further investigation.

A strength of this study is the large number of cases evaluated over a five-year period, including outcome data in more than 99% of pregnancies. The main limitation is the lack of an appropriate comparison group, as previously described. A further limitation is the inclusion of more than one pregnancy for some women. This limits the ability to make statistical comparisons across

groups (lack of independence), however this was not an objective of this study, and inclusion of all cases provides valuable information on resource implications for future PTBCs. Practice in NZ (Auckland District Health Board 2019b) is similar to most PTBCs in Australia and the United Kingdom, although heterogeneity in practice has been recognised (Care, Ingleby et al. 2019; Sharp & Alfirevic 2014). Cases include local referrals in a large urban maternity hospital, as well as tertiary referrals from throughout the country, allowing findings to be generalisable.

There is increasing recognition of the importance of psychological wellbeing of women who are at high risk of sPTB (Malouf & Redshaw 2017). Reassurance, when appropriate, is an important aspect of PTBC care. A small qualitative study has shown that women embrace their 'high-risk' status and appreciate the close surveillance and expert care these clinics offer (O'Brien, Quenby et al. 2010). Larger studies assessing the psychological impact of PTBCs are required and a prospective study is in progress locally.

7.2.6 Conclusion

Pregnancy outcomes were similar to those reported by other PTBCs providing care for high risk asymptomatic women. Most women who received cervical surveillance as primary management did not require additional treatment. Women referred electively in pregnancy had lower rates of intervention and better outcomes compared to women referred acutely, including those with an incidental finding of a short cervix.

7.2.7 Supplementary information

Table 7.4 Preterm birth prevention clinic referral criteria

Clinic referral criteria:
At least one of the following risk factors for spontaneous preterm birth: a. Previous spontaneous preterm birth or PPROM <36 weeks of gestation b. Previous spontaneous second trimester loss at 16^{+0} to 24^{+0} weeks of gestation c. Previous LLETZ with >10 mm depth of excision or ≥2 procedures of any depth d. Previous knife cone biopsy or trachelectomy e. Congenital uterine and/or cervical anomaly f. Short cervix detected on transvaginal ultrasound scan in current pregnancy of <25 mm at $<24^{+0}$ weeks of gestation g. Other risk factors e.g. ≥2 surgical termination of pregnancy and/or evacuation of retained products of conception procedures, complicated caesarean section at full dilatation, history of diethylstilboestrol exposure (woman or her mother), known collagen or connective tissue disorders
If pregnant, gestation is $<25^{+0}$ weeks

LLETZ, large loop excision of the transformation zone; PPROM, preterm pre-labour rupture of membranes.

Table 7.5 Standard practice at the preterm birth clinic

Standard practice for elective referrals to the clinic include:	
Initial consultation at 10 to 12 weeks	Obstetric and medical review is undertaken to identify risk factors for preterm birth, along with vaginal examination, microbiological swabs, midstream urine for culture and transvaginal ultrasound assessment of the cervix (Auckland District Health Board 2019b). Women are provided with information regarding their individualised risk for preterm birth and counselled on potential interventions including lifestyle and behaviour change (including support for smoking cessation), serial cervical length assessment, cervical cerclage and progesterone therapy, and an individualised plan of care is made. History-indicated (elective) cervical cerclage is generally reserved for women with multiple second trimester miscarriages or spontaneous preterm births, in line with current evidence (Vernet, Watson et al. 2017). Progesterone is not offered as prophylactic treatment and use is considered only in women who develop a short cervix.
Subsequent reviews	In the majority of cases, subsequent visits are fortnightly from 14 to 24 weeks and include a review of pregnancy progress and transvaginal ultrasound assessment of the cervix. Ultrasound-indicated cervical cerclage or vaginal progesterone are recommended if the cervix shortens to <25 mm. Decisions regarding these interventions are made on an individual basis including further review of risk factors, other signs and symptoms and cervical length.
On-going care	Women are discharged back to their lead maternity carer at 23 to 25 weeks. An overall risk assessment for very early preterm birth is made at the final visit and includes the selective use of quantitative fetal fibronectin (fFN) and the QUiPP App for those thought at highest risk. The QUiPP App combines history, cervical length and fFN to predict spontaneous preterm birth within certain timeframes and is used to guide decisions on hospital admission and antenatal corticosteroid use (Kuhrt, Smout et al. 2016). Prior to 2015, a qualitative fFN test was used.

Chapter 8 The psychological wellbeing of women cared for in a specialised preterm birth clinic

8.1 Preface

This chapter assesses the psychological wellbeing of pregnant women at high risk of spontaneous preterm birth who are cared for in a specialised preterm birth clinic. The importance of psychological wellbeing in pregnancy has been realised in recent decades, with anxiety and depression now known to affect pregnancy outcomes (Field 2017; Grigoriadis, VonderPorten et al. 2013; Grote, Bridge et al. 2010). This chapter reports findings from a longitudinal cohort survey that assessed rates of anxiety and depression, and health-related quality of life in high risk pregnant women during the time they receive care from a specialised preterm birth clinic. This study also explores the potential impact of preterm birth clinic care on psychological wellbeing and women's perceptions of their high risk status and the care received.

This chapter contains a manuscript that will be submitted for publication in a peer-reviewed journal once final outcomes are available for the few women who remain pregnant at the time of thesis submission.

8.2 The psychological wellbeing of women at high risk of spontaneous preterm birth cared for in a specialised preterm birth clinic

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8.2.1 Abstract

Importance: Psychological distress in pregnancy can impact on health outcomes.

Objective: To assess the psychological wellbeing of pregnant women at increased risk of spontaneous preterm birth and the impact of care from a preterm birth clinic. The primary hypothesis is women will have fewer symptoms of anxiety after their second clinic visit compared to before their first, which will be sustained to the end of the second trimester.

Design: Single-centre longitudinal cohort survey over one year, 2018-2019.

Setting: Tertiary maternity hospital in Auckland, New Zealand.

Participants: Consent was obtained from 73/97 (75.3%) eligible pregnant women at increased risk of spontaneous preterm birth cared for in a preterm birth clinic; 63/73 (86.3%) completed all questionnaires.

Exposure: Three sets of questionnaires (State-Trait Anxiety Inventory, Edinburgh Postnatal Depression Scale, and 36-Item Short Form Survey) were completed – prior to the first, after the second and after the last appointment at the preterm birth clinic. Study-specific questionnaires explored pregnancy-related anxiety and perceptions of care.

Main outcomes and measures: The primary outcome was the mean state-anxiety score. Secondary outcomes included depression and quality of life measures. Positive screening tests described rates of anxiety and depression.

Results: 73 women were included; 41.1% had a previous preterm birth, 31.5% a second trimester loss and 28.8% cervical surgery; 20.6% had a prior history of psychiatric illness. The adjusted mean state-anxiety score was 39.0 at baseline, which decreased to 36.5 after the second visit (difference -2.5, 95% CI -5.5 – 0.5, p=0.1) and to 32.6 after the last visit (difference -3.9 from second visit, 95% CI -6.4 – -1.5, p=0.002). Rates of anxiety and depression were 38.4%, 34.8%, 19.0%, and 13.7%, 8.7%, 9.5% respectively at the same time periods. Perceptions of care were favourable; 88.9% stated the preterm birth clinic made them significantly or somewhat less anxious and 87.3% would want to be seen again in another pregnancy.

Conclusion and relevance: Women at increased risk of spontaneous preterm birth have high rates of anxiety. Psychological wellbeing improved during the second trimester; women found preterm birth clinic care reduced pregnancy-related anxiety. This provides support for the ongoing use and development of preterm birth clinics.

8.2.2 Introduction

Psychological disorders are common in pregnancy (Bennett, Einarson et al. 2004; Dennis, Falah-Hassani et al. 2017). Women with high risk pregnancies are more likely to suffer psychological distress with higher rates of anxiety and depression than the general pregnant population (Dagklis, Tsakiridis et al. 2018; Fairbrother, Young et al. 2017; Thiagayson,

Krishnaswamy et al. 2013). Few studies have assessed the psychological wellbeing of women who are at high risk of spontaneous preterm birth, and in particular, the potential impact of care from a specialised preterm birth clinic. Preterm birth clinics provide a package of care to asymptomatic women identified to be at increased risk of spontaneous preterm birth based on their obstetric and gynaecological history. This care includes regular visits through the second trimester for ultrasound surveillance of cervical length and provision of treatments to prevent preterm birth such as cervical cerclage and vaginal progesterone therapy when indicated (National Institute for Health and Care Excellence 2015; Vernet, Watson et al. 2017). Close monitoring and reassurance provided through a preterm birth clinic may reduce pregnancy-related anxiety, however, it is also possible that being labelled 'high risk' may increase psychological distress and anxiety (O'Brien, Quenby et al. 2010; Simmons & Goldberg 2011; Stahl & Hundley 2003). Further research in this area has been recommended (Malouf & Redshaw 2017).

There is increasing recognition of the importance of psychological wellbeing in pregnancy. Meta-analyses show that antenatal depression is associated with a modestly increased risk of preterm birth and fetal growth restriction, and decreased rates of breastfeeding initiation (Grigoriadis, VonderPorten et al. 2013; Grote, Bridge et al. 2010). The effect of anxiety is less well evaluated, but is associated with increased pregnancy-related hypertension and caesarean section, decreased rates of exclusive breastfeeding and increased anxiety in the offspring (Field 2017). Antenatal anxiety and depression are also strong predictors of postnatal depression (Robertson, Grace et al. 2004). Strategies for prevention, along with improvements in the recognition and treatment of psychological disorders in pregnancy, are likely to improve outcomes for women and children (Giardinelli, Innocenti et al. 2012).

This study aims to assess rates of anxiety, depression and health-related quality of life in pregnant women at high risk of spontaneous preterm birth who are cared for in a preterm birth clinic. The primary hypothesis is that women will have less anxiety after their second consultation in a preterm birth clinic compared to before their first (baseline), and this improvement will be sustained at the end of the second trimester. Secondary hypotheses are that women will have fewer symptoms of depression, improved quality of life, and less pregnancy-related anxiety over the same period.

8.2.3 Methods

This longitudinal cohort survey was carried out in a tertiary maternity hospital in Auckland, New Zealand. All eligible women attending the preterm birth clinic over a 12 month period from August 2018-2019 were invited to participate prior to their first appointment. Inclusion criteria were gestational age $<24^{+0}$ weeks at first visit; live fetus; eligible for preterm birth clinic review due to ≥1 risk factor for spontaneous preterm birth (Supplementary Table 8.5); written consent obtained; and sufficient English to independently complete questionnaires.

Participants completed three sets of questionnaires: prior to their first clinic appointment (baseline, Set 1), after their second appointment (usually 2-3 weeks later, Set 2), and after their last clinic appointment (usually at 23-24 weeks of gestation, Set 3). A small number of women were seen for only two appointments and returned the Set 3 questionnaires by post two weeks after their last visit. Each set of questionnaires contained three validated measures: the State-Trait Anxiety Inventory (STAI), used under licence from Mind Garden Incorporated (Mind Garden 2018) which contains two subscales to allow differentiation between temporary 'state-anxiety' and the relatively stable and long-standing aspects of anxiety proneness in 'trait-anxiety' (Spielberger, Gorsuch et al. 1970); the Edinburgh Postnatal Depression Scale (EPDS) which is validated for antenatal depression (Murray & Cox 1990); and the RAND 36-Item Short Form Survey (SF-36) to assess quality of life (RAND Corporation 2018; Ware & Sherbourne 1992). Set 1 and 3 also included a study-specific questionnaire to assess psychiatric history, social support, pregnancy-related anxiety and perceptions of care (Supplementary Tables 8.6 and 8.7). The study-specific questionnaires were piloted for the first five women and minor changes made following feedback.

Participants completed hard copy questionnaires independently. The EPDS self-harm question was reviewed at completion and for any women answering 'yes, quite often' or 'sometimes', further assessment of safety was made and referral to maternal mental health services offered. No other changes were made to clinical care. All other responses were seen only by a single investigator not responsible for decisions about referral for psychological support, until completion of the study. Standard clinic practice is described in Supplementary Table 8.8.

Demographic details, pregnancy characteristics, medical history, and pregnancy outcomes were obtained from electronic medical records. At the last visit the discharging clinic obstetrician

used pre-defined criteria to classify women as low, intermediate or high risk for preterm birth (Supplementary Table 8.9).

The primary outcome was the STAI state-anxiety score. Secondary outcomes were the EPDS score, SF-36 summary quality of life scores, and pregnancy-related anxiety from a ten point visual analogue scale (all as continuous measures). The proportion of screen positive scores from the STAI (>40 on the state-anxiety subscale) and EPDS (>12) were calculated to describe rates of significant symptoms of anxiety and depression (referred to as anxiety and depression).

A pragmatic sample size was used. We aimed to invite all eligible women over a one year period to participate. Using data from medically high risk women (King, Chambers et al. 2010), we estimated a sample size of 60 would provide 80% power, with alpha of 0.05, two-sided test and an estimated within subject correlation of 0.75 to detect a decrease in the mean state-anxiety score from 40.0 (SD 12.0) to 36.9.

Descriptive statistics were calculated using SPSS (version 25.0) and R software (version 3.5.3) (IBM Corp 2017; R Core Team 2019). Thematic analysis was carried out on free-text responses using Braun and Clarke methodology (Braun & Clarke 2006). The mixed model for repeated measures analyses, was used to analyse repeatedly measured continuous outcomes and conducted using SAS software (version 9.4) (SAS Institute 2017). These analyses was used to test for time effect adjusting for prior diagnosis of a mental health condition, gestational age at first visit and obstetric history (categorised by no previous pregnancy beyond 12 weeks; loss/preterm birth at 12-28 weeks; loss/preterm birth at 28-37 weeks; or term birth only), and subject was included as a random effect. Kenward-Roger method was used to estimate the denominator degrees of freedom for fixed effects. Two-sided p-value <0.05 determined statistical significance. All confidence intervals (CI) are given at a two-sided 95% level.

Ethical approval was granted by the Health and Disability Ethics Committees (18/NTA/103) and institutional approval by the Auckland District Health Board Research Review Committee (A+8127).

8.2.4 Results

The recruitment rate was 75.3% (73/97); participation is described in Figure 8.1. Demographics, obstetric characteristics and risk factors for preterm birth are detailed in Table 8.1. Some women

had been seen in the clinic in a previous pregnancy (17/73, 23.3%) and/or for pre-pregnancy review (12/73, 16.4%).

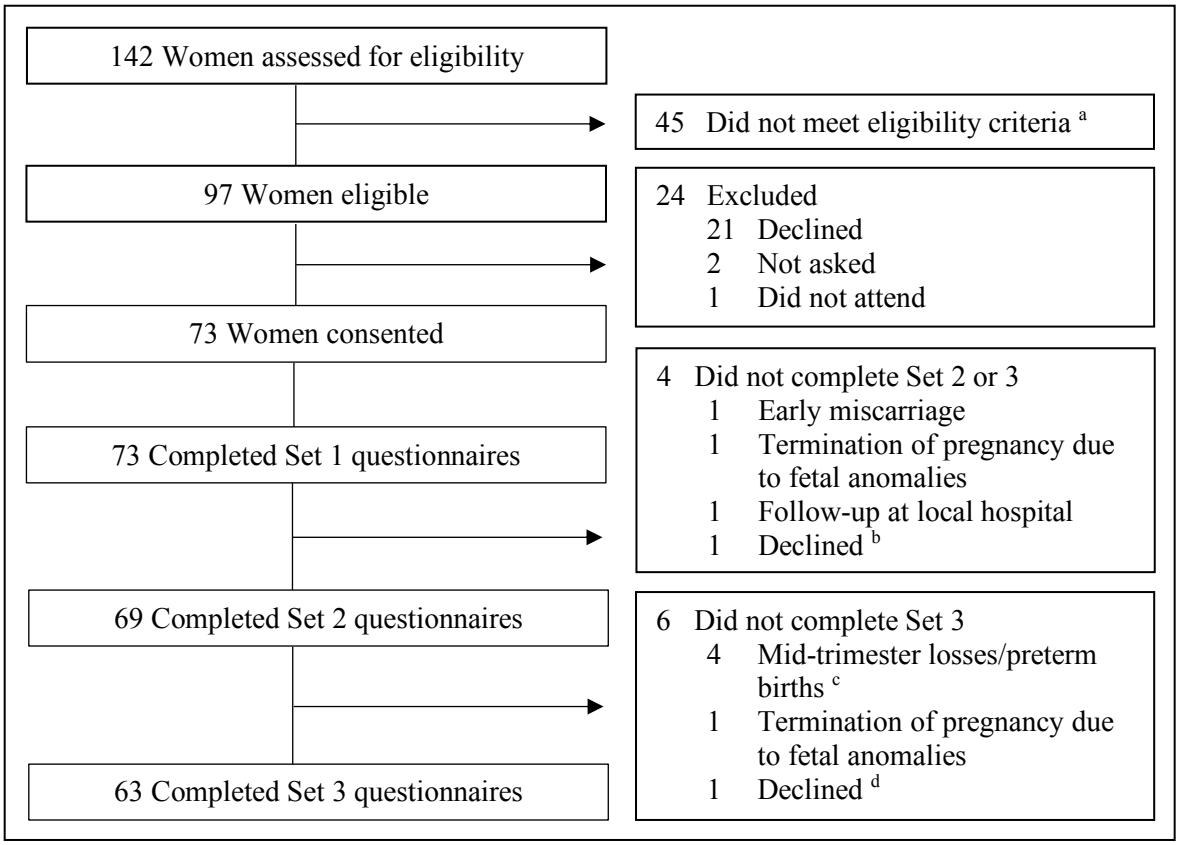


Figure 8.1 Participant recruitment and study flow diagram

[a] Reasons not eligible: 19 were pre-pregnancy consultations, 2 had previously participated in study (both with pregnancy losses), 9 had insufficient English (including one who provided consent but was then identified to have insufficient written English when attempted first set of questionnaires and was withdrawn from the study), 3 were >24 weeks at first visit, and 12 had a single visit planned only.

[b] Distressed with new diagnosis of severe hypertension and fetal growth restriction, subsequently had fetal demise before last visit.

[c] Gestational ages at delivery 16^{+1}, 22^{+3}, 23^{+4} and 24^{+4} weeks.

[d] Recent diagnosis of severe depression with acute distress.

Table 8.1 Demographic details, obstetric characteristics and risk factors for preterm birth

Characteristic	**Participants, n=73**
Ethnicity	
European	36 (49.3)
Māori	7 (9.6)
Pacific	5 (6.8)
Asian	11 (15.1)
Indian	9 (12.3)
Other	5 (6.8)
Age (years)	
Mean (SD)	34.0 (5.1)
Range	22 – 45
Body mass index (kg/m^2) [a]	
Mean (SD)	26.3 (6.4)
Range	19 – 57
Current smoker	5 (6.8)
Has a current partner	72 (98.6)
Previous diagnosis of a mental health condition (non-exclusive) [b]	
Depression	10 (13.7)
Postnatal depression	4 (5.5)
Generalised anxiety disorder	2 (2.7)
Panic disorder	1 (1.4)
Social anxiety disorder	1 (1.4)
Post-traumatic spectrum disorder	3 (4.1)
None	58 (79.4)
Currently taking medication for a mental health condition?	4 (5.5)
Currently under the care of a psychiatrist/psychologist	1 (1.4)
Nulliparous	16 (21.9)
Previous stillbirth or neonatal death $\geq 20^{+0}$ weeks	22 (30.1)
Current twin pregnancy	1 (1.4)
Reasons for preterm birth clinic referral (non-exclusive)	
Previous spontaneous preterm birth/PPROM (24^{+0} to 36^{+0} weeks) [c]	30 (41.1)
Previous second trimester loss (16^{+0} to 23^{+6} weeks)	23 (31.5)
Previous extensive cervical surgery [d]	21 (28.8)
Congenital uterine anomaly	1 (1.4)
Short cervix in current pregnancy <25 mm	5 (6.8)
≥2 surgical terminations and/or other uterine instrumentations	14 (19.2)
Other risk factors for spontaneous preterm birth	4 (5.5)
Multiple reasons for referral to the preterm birth clinic	23 (31.5)

Data represented as number (%) unless otherwise stated.

SD, standard deviation; mm, millimetres; PPROM, pre-labour premature rupture of membranes; LLETZ, large loop excision of the transformation zone.

[a] Missing data n=2.

[b] Self-reported.

[c] Includes survivors born at 23 weeks of gestation.

[d] LLETZ with depth of excision ≥10 mm or >1 procedure, or knife cone biopsy.

The mean gestational ages at questionnaire completion were 13^{+4} weeks (SD 3^{+3}), 16^{+2} weeks (SD 3^{+2}) and 23^{+6} weeks (SD 1^{+2}). Unadjusted and adjusted anxiety, depression and quality of life scores are shown in Tables 8.2 and 8.3 respectively. The adjusted mean state-anxiety score (estimated using the least squares mean) was 39.0 at baseline and decreased to 36.5 after the second visit (least square means difference -2.5, 95% CI -5.5 – 0.5, p=0.1), with a further reduction to 32.6 after the last visit (least squares means difference -3.9 from the second visit, 95% CI -6.4 – -1.5, p=0.002). There were 28/73 (38.4%) women who met the threshold for anxiety (>40) at baseline, and this halved to 12/63 (19.0%) after the last clinic visit. The adjusted mean EPDS score was 7.5 at baseline and decreased to 6.3 after the second visit (least squares means difference -1.2, 95% CI -2.3 – -0.2, p=0.02) and this was sustained until the last visit, with a further non-significant reduction (mean 5.7, least squares means difference -0.6, 95% CI -1.4 – 0.2, p=0.2). The proportion of women with a positive EPDS also decreased from 10/73 (13.7%) at baseline to 6/69 (8.7%) after the second consultation and plateaued at 6/63 (9.5%) after the last visit. There was some improvement in the RAND SF-36 summary scores for mental health over time, with no differences in physical health scores (Table 8.3). Pregnancy-related anxiety scores had decreased by the last clinic visit for most women (44/63, 69.8%).

One woman was referred to the maternal mental health service following review of the EPDS self-harm question. Preterm birth clinic clinicians referred six women to the women's health social work for psychological support and two to maternal mental health services. None of the women who completed the Set 3 questionnaires reported a new diagnosis of a mental health condition during the study period (one missing response), although one woman who declined to complete the last set of questionnaires was diagnosed with severe depression.

Women's baseline knowledge of their risk of preterm birth and perceptions of preterm birth clinic care are described in Supplementary Table 8.10. Women had mixed feelings about referral to the clinic prior to review, but following their last visit 56/63 (88.9%) reported care in the preterm birth clinic made them significantly or somewhat less anxious. The majority (55/63,

87.3%) would want to be cared for in a preterm birth clinic again in another pregnancy. The seven women who did not had already had a term birth since their prior early birth, or were referred for cervical surgery or multiple uterine instrumentations only (only one of these required an intervention greater than surveillance in their current pregnancy).

The predominant themes causing pregnancy-related anxiety at baseline were preterm birth, pregnancy loss, and concern for the baby's health. Many women were anxious about extremely early birth – *"being born too early to do anything about it,"* and were worried about reaching milestones – *"getting to 24 weeks to be deemed to have a 'viable' pregnancy."* Women were worried about history repeating itself – *"I am scared that it might happen again,"* and how they would cope if it did – *"my ability to manage emotions associated with NICU [neonatal intensive care unit] if this baby is early."* A smaller number of women were anxious about the risks of chromosomal problems or fetal anomalies.

When asked at clinic discharge what they found most helpful to relieve pregnancy-related anxiety, the main theme was medical support, including close monitoring, the preterm birth clinic, regular ultrasound scans, and support and communication from doctors – *"the fortnightly visits have really helped me! Lots of reassurance," "follow up from the preterm birth clinic," "the weekly check-ups and reassurance from the doctors and how quickly they acted when there was an issue,"* and *"the support of specialists who are willing to listen."* Other themes included support from family and friends, distraction, relaxation techniques and prayer.

The mean number of preterm birth clinic visits was 5.4 (SD 2.1), range 1-11. Clinic interventions and pregnancy outcomes are reported in Table 8.4. Elective cervical cerclage is reserved for the highest risk women, and was performed in 17/72 cases (23.6%, excludes one woman with local follow up after the first visit as no further data collected), usually at 12-14 weeks gestation. The remaining women had ultrasound surveillance of cervical length as their primary management. Pregnancy outcomes are available for 67 women, with a further five women still pregnant (all >32 weeks) at the time of thesis submission. The overall rate of birth <37 weeks was 15/67 (22.4%), including two spontaneous second trimester losses. One extremely early preterm birth followed pre-labour fetal demise, all other preterm births occurred following spontaneous labour or preterm pre-labour rupture of membranes. Of pregnancies that reached $\geq 20^{+0}$ weeks 62/64 (96.9%) babies were alive at hospital discharge.

Table 8.2 Unadjusted anxiety, depression and quality of life scores

Questionnaire	**Set 1 (baseline), n=73**			**Set 2, n=69**			**Set 3, n=63**		
Mean score	**Mean**	**SD**	**95% CI**	**Mean**	**SD**	**95% CI**	**Mean**	**SD**	**95% CI**
STAI state-anxiety	38.6	11.9	36.8 – 41.3	36.2	11.6	33.5 – 38.9	32.0	9.8	29.6 – 34.4
STAI trait-anxiety	37.3	10.1	35.0 – 39.6	36.5 [a]	9.6	34.2 – 38.8	34.9	10.8	32.2 – 37.6
EPDS	7.3	4.6	6.2 – 8.4	6.0	4.5	4.9 – 7.1	5.4	5.1	4.1 – 6.6
RAND SF-36 summary mental health [b]	63.8 [c]	15.9	60.0 – 67.8	65.7 [d]	17.0	61.5 – 69.9	72.4 [e]	17.9	67.8 – 77.0
RAND SF-36 summary physical health [b]	69.3 [a]	21.5	64.3 – 74.3	66.0 [f]	24.1	60.2 – 71.8	71.3 [a]	22.7	65.6 – 77.0
Pregnancy-related anxiety [g]	4.9 [a]	2.5	4.3 – 5.5	-	-	-	2.7	2.5	2.1 – 3.3
Range									
STAI state-anxiety	20 – 65			20 – 63			20 – 60		
STAI trait-anxiety	20 – 61			20 – 63 [a]			20 – 60		
EPDS	0 – 20			0 – 19			0 – 22		
RAND SF-36 summary mental health [b]	21 – 93 [c]			17 – 93 [d]			16 – 94 [e]		
RAND SF-36 summary physical health [b]	17 – 100 [a]			12 – 99 [f]			21 – 99 [a]		
Pregnancy-related anxiety [g]	0 – 10			-			0 – 10		
Positive screening tests	**Proportion**	**%**	**95% CI**	**Proportion**	**%**	**95% CI**	**Proportion**	**%**	**95% CI**
STAI state-anxiety [h]	28/73	38.4	27.2 – 49.5	24/69	34.8	23.5 – 46.0	12/63	19.0	9.4 – 28.7
STAI trait-anxiety [h]	28/73	38.4	27.2 – 49.5	23/68 [a]	33.8	22.6 – 45.1	15/63	23.8	13.3 – 34.3
EPDS [i]	10/73	13.7	5.8 – 21.6	6/69	8.7	2.0 – 15.3	6/63	9.5	2.3 – 16.8

STAI, State Trait Anxiety Inventory; SD, standard deviation; CI, confidence interval; EPDS, Edinburgh Postnatal Depression Scale; SF-36, 36-Item Short Form Survey

[a] Missing score for one woman as one incomplete question.

[b] Higher scores associated with better quality of life.

[c] Missing scores for nine women as one or more incomplete questions.

[d] Missing scores for five women as one or more incomplete questions.

[e] Missing scores for four women as one or more incomplete questions.

[f] Missing scores for three women as one or more incomplete questions.

[g] Visual analogue scale, 0 = not at all anxious, 10 = extremely anxious. Obtained from study-specific questionnaire at Set 1 and Set 3 time points only.

[h] Positive screen defined as STAI subscale score >40.

[i] Positive screen defined as EPDS >12.

Table 8.3 Mixed model for repeated measures analyses for anxiety, depression and quality of life scores

	STAI state-anxiety			**EPDS**			**RAND SF-36 summary physical health [a]**			**RAND SF-36 summary mental health [a]**		
Fixed effect	**p value [b]**			**p value [b]**			**p value [b]**			**p value [b]**		
Time	<0.0001			0.0001			0.3			<0.0001		
Gestation at first visit	0.7			0.4			0.2			0.2		
Prior mental health condition	0.7			0.09			0.6			0.006		
Obstetric history [c]	0.4			0.04			0.8			0.3		
Least squares means	**Estimate**	**95% CI**		**Estimate**	**95% CI**		**Estimate**	**95% CI**		**Estimate**	**95% CI**	
Time 1 [d]	39.0	35.6 – 42.4		7.5	6.1 – 8.9		70.9	63.9 – 77.8		60.7	55.8 – 65.6	
Time 2 [d]	36.5	33.0 – 40.0		6.3	4.9 – 7.7		67.2	60.1 – 74.4		62.5	57.5 – 67.4	
Time 3 [d]	32.6	29.1 – 36.1		5.7	4.3 – 7.1		71.5	64.3 – 78.6		69.5	64.6 – 74.5	
Least squares means difference	**Estimate**	**95% CI**	**p value [e]**	**Estimate**	**95% CI**	**p value [e]**	**Estimate**	**95% CI**	**p value [e]**	**Estimate**	**95% CI**	**p value [e]**
Time 2 - 1	-2.5	-5.5 – 0.5	0.1	-1.2	-2.3 – -0.2	0.02	-3.7	-10.1 – 2.8	0.3	1.8	-3.1 – 6.6	0.5
Time 3 - 1	-6.4	-8.8 – -4.0	<0.0001	-1.8	-2.6 – -1.0	<.0001	0.6	-4.6 – 5.8	0.8	8.9	4.7 – 13.0	<0.0001
Time 3 - 2	-3.9	-6.4 – -1.5	0.002	-0.6	-1.4 – 0.2	0.2	4.2	-1.1 – 9.6	0.1	7.1	-3.0 – -11.2	0.001

STAI, State Trait Anxiety Inventory; EPDS, Edinburgh Postnatal Depression Scale; SF-36, 36-Item Short Form Survey; CI, confidence interval.

[a] Higher scores associated with better quality of life.

[b] Pr > F. Type 3 tests of fixed effects.

[c] Categorised by no previous pregnancy beyond 12 weeks; loss/preterm birth at 12-28 weeks; loss/preterm birth at 28-37 weeks; or term birth only.

[d] Results from Time 1, 2 and 3 correspond to Set 1, 2 and 3 questionnaires.

[e] Pr > |t|.

Table 8.4 Preterm birth clinic interventions and pregnancy outcomes [a]

Characteristics	**Number (%) or mean (SD)**
Shortest transvaginal cervical length measurement	
Mean (SD) (in mm)	27.0 (9.1)
Range (in mm)	0-39
Number <25 mm (threshold for intervention)	21/72 (29.2)
Treatments given to reduce the risk of preterm birth	
Cervical cerclage only	16/72 (22.2)
Vaginal progesterone only	4/72 (5.6)
Both cervical cerclage and vaginal progesterone	10/72 (13.9)
No treatment	40/72 (55.6)
Antenatal hospital admission from clinic due to preterm birth risk	2/72 (2.8)
Risk of preterm birth for those who had an exit visit [b]	
Low	45/66 (68.2)
Intermediate	18/66 (27.3)
High	3/66 (4.5)
Pregnancy outcome	
Termination of pregnancy for fetal anomalies	2/72 (2.8)
First trimester miscarriage (<13^{+0} weeks)	1/72 (1.4)
Second trimester loss (13^{+1} to 22^{+6} weeks)	2/72 (2.8)
Extremely early preterm birth (23^{+0} to 27^{+6} weeks) [d]	3/72 (4.2)
Very early preterm birth (28^{+0} to 31^{+6} weeks)	1/72 (1.4)
Moderate to late preterm birth (32^{+0} to 36^{+6} weeks) [e]	10/67 (14.9)
Term birth (≥37^{+0} weeks) [e]	48/67 (71.6)
Mode of birth for pregnancies that reached ≥20^{+0} weeks [e f]	
Normal vaginal birth	40/63 (63.5)
Instrumental birth	6/63 (9.5)
Caesarean section	17/63 (27.0)
Neonatal outcome for pregnancies that reached ≥20^{+0} weeks [e f g]	
Alive at hospital discharge	62/64 (96.9)
Early neonatal death	1/64 (1.6)
Stillbirth	1/64 (1.6)

[a] Excludes one woman with all follow up at local hospital after first visit as no further data collected.

[b] Risk assessment defined in Supplementary Table 8.9. Quantitative fetal fibronectin was included in 29/66 (44%) cases. Excludes six women who did not have an exit appointment and includes three women who did not complete Set 3 questionnaires – for two the exit visit was their second visit, both were high risk and delivered prior to planned completion of the Set 3 questionnaires by post; and one who declined.

[d] Includes one pre-labour fetal demise.

[e] Excluding five women still pregnant in their third trimester at time of submission and one termination of pregnancy >20 weeks.

[f] Excludes one termination of pregnancy >20 weeks for fetal anomalies.

[g] Includes one set of twins.

8.2.5 Discussion

This is the first study to assess the psychological wellbeing of women receiving care in a specialised preterm birth clinic. It identifies high rates of psychological distress, with 38.4% and 13.7% of high risk women having significant symptoms of anxiety and depression, respectively, at the beginning of the second trimester. Whilst the change in mean state-anxiety scores after two clinic visits did not reach statistical significance, improvement may still be clinically important. Adjusted mean state-anxiety scores were significantly improved by clinic discharge, with rates of anxiety half that of baseline. Although depression was less common than anxiety, the adjusted mean EPDS score improved by the second clinic visit and this was sustained to the end of the second trimester. Quality of life improved with regard to mental health, but not physical health. Self-reported pregnancy-related anxiety also improved and women perceived care in the preterm birth clinic to be a significant factor in relieving anxiety.

A number of studies have reported rates of anxiety and depression in pregnancy, with a wide range of estimates (Bennett, Einarson et al. 2004; Dennis, Falah-Hassani et al. 2017). In systematic review, the overall prevalence of a clinical diagnosis of an anxiety disorder in pregnancy was 15.2%, with rates of self-reported anxiety of 18.2%, 19.1% and 24.6% in the first, second and third trimesters respectively (Dennis, Falah-Hassani et al. 2017). Women with high risk pregnancies have higher rates of anxiety than low risk women; 45.0% versus 16.7% in one study (King, Chambers et al. 2010). Rates of depression were 7.4%, 12.8% and 12.0% in the general pregnant population in the first, second and third trimesters (Bennett, Einarson et al. 2004), and ranged from 11% to 28% in studies on high risk pregnancies (Adouard, Glangeaud-Freudenthal et al. 2005; Brandon, Trivedi et al. 2008; Dagklis, Tsakiridis et al. 2018; King, Chambers et al. 2010; Thiagayson, Krishnaswamy et al. 2013). The high rates of anxiety seen in our study are consistent with published literature for high risk pregnancies with rates of depression in the lower range of those previously reported.

Although we do not have data for the whole pregnancy, it seems that gestational changes in rates of anxiety in women at high risk of spontaneous preterm birth may not follow the same trends

as in the general pregnant population in which rates rise throughout pregnancy (Dennis, Falah-Hassani et al. 2017). In our study, anxiety was highest at the beginning of the second trimester and then decreased to levels similar to those seen in general pregnant populations by the end of the second trimester. This may be due to reduced anxiety over second trimester loss once this gestational time period is complete (31.5% of our cohort had experienced a second trimester loss previously). However, advancing gestation is unlikely to be the sole factor leading to anxiety levels reaching those of the general pregnant population as the risk of early preterm birth was still ongoing at the time of last clinic visit. This, along with women's perception of care, suggests that preterm birth clinic care may have had a role in improving psychological wellbeing. The provision of an overall ongoing risk assessment at the final clinic visit is likely to be beneficial; the majority of women were then considered to be at relatively low risk of preterm birth and encouraged to return to a low risk model of maternity care.

Whilst there is some evidence that simply labelling a pregnancy 'high risk' may increase anxiety and fear, other studies identified that women embrace this label in a positive way (O'Brien, Quenby et al. 2010; Simmons & Goldberg 2011). A qualitative study has assessed women's perceptions of care in a preterm birth clinic in the United Kingdom, with all women viewing their high risk status positively (O'Brien, Quenby et al. 2010). These women reported that regular reassurance from the clinic was a helpful coping strategy and that other health professionals were not always sensitive to their worries about having another preterm birth (O'Brien, Quenby et al. 2010). Our results are consistent with these findings.

Preterm birth clinics offer individualised, coordinated and evidence-based care with the aim of reducing spontaneous preterm birth and improving perinatal outcome. Any potential to reduce psychological distress is as an additional benefit. Whilst further research with inclusion of a comparator group may more directly quantify the effect of a preterm birth clinic in improving psychological wellbeing, the new knowledge from our study should reassure clinicians and policy makers that preterm birth clinics do not cause psychological harm.

Symptoms of anxiety and depression were under-recognised by clinicians in this study, with low referral rates for psychological support or maternal mental health review based on usual indications. Early recognition of anxiety and depression with provision of support or referral for other interventions may reduce maternal morbidity and improve pregnancy outcomes, and is likely to reduce the risk of postnatal depression (Austin 2004). Our findings suggest there are currently missed opportunities for care and preterm birth clinics should ensure they have referral

pathways and access to psychological assessment and support, or should incorporate this into part of standard care within the clinic.

The main limitation of our study may be perceived as the lack of a comparator group. The most appropriate comparison is with women of similar preterm birth risk who do not receive care in a specialised preterm birth clinic; however, withholding clinic care is not possible when a clinic is already well established and available to all. Use of the general population or a medically high risk group as a comparator is not appropriate as background anxiety levels for these women may increase over gestation due to increasing risk of other pregnancy complications, whereas the risk of preterm birth decreases with advancing gestation. A further limitation is the use of screening tests rather than diagnostic criteria for anxiety and depression. Whilst diagnostic interviews are the gold standard, they are time consuming, require special training for administration and are expensive (Evans, Spiby et al. 2015). Screening tests are reliable and have been validated for use in pregnancy (Adewuya, Ola et al. 2006; Adouard, Glangeaud-Freudenthal et al. 2005; Bunevicius, Kusminskas et al. 2009; Felice, Saliba et al. 2006; Gibson, McKenzie-McHarg et al. 2009; Grant & Raouf 2016; Gunning, Denison et al. 2010; Murray & Cox 1990). The STAI with a cut-off >40 has a sensitivity of 81% and specificity of 80% for diagnosis of an anxiety disorder in pregnancy when compared to DSM-IV criteria (Grant, McMahon et al. 2008). The EPDS is also accurate, with a cut-off of >12 used in pregnancy, giving a sensitivity of 83% and specificity of 90% for detection of major depression (National Institute of Health and Clinical Excellence 2014). Participant dropout may have influenced the study outcome as the majority were due to pregnancy loss or extremely early preterm birth, and these women may have had the highest risk pregnancies and hence highest levels of psychological distress. However, unadjusted analysis of only the 63 women who completed all assessments showed similar results.

Strengths of this study include longitudinal assessment of a high risk cohort with a high recruitment rate in an ethnically diverse group of women. Although undertaken at a single site, referrals are accepted from the wider region, improving generalisability of results. There were multiple clinicians working in the clinic over the study period (two lead obstetricians, three senior obstetric trainees, and three specialist midwives), so an individual clinician is less likely to have had significant influence over outcomes. Variation in practice between preterm birth clinics has been recognised as an issue (Care, Ingleby et al. 2019), however the general principles of care identified by women as factors that reduced anxiety i.e. close surveillance and regular ultrasound scans, are similar across clinics globally.

8.2.6 Conclusions

Women at increased risk of spontaneous preterm birth have high rates of anxiety in early pregnancy. Improvements in psychological wellbeing were seen whilst these women were cared for in a specialised preterm birth clinic through the second trimester. Women's perceptions of a preterm birth clinic were favourable and they attributed the care received as being a significant factor in reducing pregnancy-related anxiety. Findings of this study provide further support for the ongoing use and development of these specialised clinics.

8.2.7 Supplementary information

Table 8.5 Preterm birth clinic referral criteria

Clinic referral criteria:
At least one of the following risk factors for spontaneous preterm birth: a. Previous spontaneous preterm birth or PPROM <36 weeks of gestation b. Previous spontaneous second trimester loss at 16^{+0} to 24^{+0} weeks of gestation c. Previous LLETZ with >10 mm depth of excision or ≥2 procedures of any depth d. Previous knife cone biopsy or trachelectomy e. Congenital uterine and/or cervical anomaly f. Short cervix detected on transvaginal ultrasound scan in current pregnancy of <25 mm at $<24^{+0}$ weeks of gestation g. Other risk factors e.g. ≥2 surgical termination of pregnancy and/or evacuation of retained products of conception procedures, complicated caesarean section at full dilatation, history of diethylstilboestrol exposure (woman or her mother), known collagen or connective tissue disorders

LLETZ, large loop excision of the transformation zone; PPROM, preterm pre-labour rupture of membranes.

Table 8.6 Study specific questionnaire from Set 1

Study specific questionnaire Set 1
1. Which ethnic group do you belong to? Mark the space or spaces which apply to you. □ New Zealand European □ Māori □ Samoan □ Cook Island Māori □ Tongan □ Niuean □ Chinese □ Indian □ Other such as Dutch, Japanese, Tokelauan. Please state: _____
2. Were you aware that you had an increased risk of your baby being born early in this pregnancy before you got pregnant? □ Yes If yes, please go to question 3 □ No If no, please go to question 4
3. Did you contemplate not getting pregnant prior to this pregnancy because you were worried about your increased chance of having a baby born early? □ Yes □ No
4. Once you were pregnant, did your lead maternity carer (midwife, GP or obstetrician) identify that there was an increased chance of your baby being born early in this pregnancy? □ Yes If yes, please go to question 5 □ No If no, please go to question 6
5. How did you feel when your lead maternity carer (midwife, GP or obstetrician) identified that there was an increased chance of your baby being born early in this pregnancy? □ Very anxious □ Somewhat anxious □ No different / the same □ Somewhat reassured □ Very reassured
6. How did you feel after your maternity care provider (midwife, GP or obstetrician) suggested you come to the preterm birth clinic? □ Significantly more anxious □ Somewhat more anxious □ No different / the same □ Somewhat more reassured

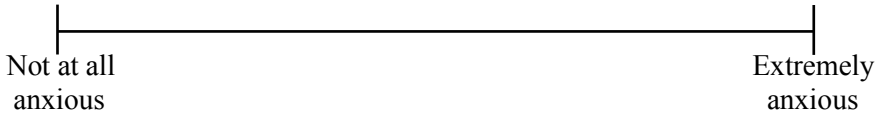
- Significantly more reassured

7. How did you feel after you read the pamphlet about what to expect in the preterm birth clinic that was included with your appointment details?
   - Significantly more anxious
   - Somewhat more anxious
   - No different / the same
   - Somewhat more reassured
   - Significantly more reassured

8. Do you have a partner?
   - Yes
   - No

9. How would you describe your social support network (for example your partner, whānau/family, friends)?
   - Very unsupportive
   - Somewhat unsupportive
   - Neither supportive nor unsupportive
   - Somewhat supportive
   - Very supportive

10. Note how anxious (on average) you have felt about your pregnancy over the past 7 days with a mark (|) on the line below.



11. What are you most anxious about in this pregnancy? *(space for response)*

12. What do you find most helpful to relieve any pregnancy-related anxiety? *(space for response)*

13. Have you ever been diagnosed with any of the following mental health conditions?
   - Depression
   - Postnatal depression
   - Generalised anxiety disorder
   - Post-traumatic stress disorder
   - Social anxiety disorder
   - Panic disorder
   - Obsessive-compulsive disorder
   - Bipolar disorder
   - Schizophrenia
   - Borderline personality disorder
   - Other, please name _____

☐ None
14. Are you currently taking any prescribed medication for a mental health condition? ☐ Yes. If so, what is the name of this medication? _____ ☐ No
15. Have you ever taken any prescribed medication for a mental health condition? ☐ Yes. If so, what is the name of this medication? _____ ☐ No
16. Are you currently under the care of a psychiatrist or psychologist? ☐ Yes. If so, what is this for? _____ ☐ No
17. Have you ever been seen by a psychiatrist? ☐ Yes. If so, when was this and what was it for? _____ ☐ No
18. Are you taking any pregnancy supplements or probiotics, other than folic acid, Elevit or iodine? ☐ Yes. If so, what is the name of the supplement/s? _____ ☐ No

GP, general practioner.

Table 8.7 Study specific questionnaire from Set 3

Study specific questionnaire Set 3
1. How have you found the quality of your general pregnancy care? □ Very low quality □ Low quality □ Neither high or low quality □ High quality □ Very high quality
2. How have you found the quality of your care through the preterm birth clinic? □ Very low quality □ Low quality □ Neither high or low quality □ High quality □ Very high quality
3. Do you think that being seen in a preterm birth clinic made you more or less anxious about your pregnancy? □ Significantly more anxious □ Somewhat more anxious □ Neither more or less anxious □ Somewhat less anxious □ Significantly less anxious
4. If you have another pregnancy, would you want to be cared for through a preterm birth clinic again? □ Yes □ No □ Unsure
5. Note how anxious (on average) you have felt about your pregnancy over the past 7 days with a mark (|) on the line below. Not at all anxious ——— Extremely anxious
6. What are you most anxious about in this pregnancy? *(space for response)*
7. What do you find most helpful to relieve any pregnancy-related anxiety? *(space for response)*
8. Have you been diagnosed with a mental health condition since you were first seen in the preterm birth clinic this pregnancy? □ Yes, if so please provide details_____ □ No

Table 8.8 Standard practice at the preterm birth clinic

Standard practice includes:	
Initial consultation at 10 to 12 weeks	Obstetric and medical review is undertaken to identify risk factors for preterm birth, along with vaginal examination, microbiological swabs, midstream urine for culture and transvaginal ultrasound assessment of the cervix (Auckland District Health Board 2019b). Women are provided with information regarding their individualised risk for preterm birth and counselled on potential interventions including lifestyle and behaviour change (including support for smoking cessation), serial cervical length assessment, cervical cerclage and progesterone therapy, and an individualised plan of care is made. History-indicated (elective) cervical cerclage is generally reserved for women with multiple second trimester miscarriages or spontaneous preterm births, in line with current evidence (Vernet, Watson et al. 2017). Progesterone is not offered as prophylactic treatment and use is considered only in women who develop a short cervix.
Subsequent reviews	In the majority of cases, subsequent visits are fortnightly from 14 to 24 weeks and include a review of pregnancy progress and transvaginal ultrasound assessment of the cervix. Ultrasound-indicated cervical cerclage or vaginal progesterone are recommended if the cervix shortens to <25 mm. Decisions regarding these interventions are made on an individual basis including further review of risk factors, other signs and symptoms and cervical length.
On-going care	Women are discharged back to their lead maternity carer at 23 to 25 weeks. An overall risk assessment for very early preterm birth is made at the final visit and includes the selective use of quantitative fetal fibronectin and the QUiPP App for those thought at highest risk. The QUiPP App combines history, cervical length and fetal fibronectin to predict spontaneous preterm birth within certain timeframes and is used to guide decisions on hospital admission and antenatal corticosteroid use (Kuhrt, Smout et al. 2016).

Table 8.9 Criteria for risk classification for study purposes at discharge from the preterm birth clinic

Risk classification	**Criteria**
Low	Normal cervical length, AND/OR Quantitative fetal fibronectin level of <50 ng/mL if performed (based on usual clinical indications), AND No intervention (progesterone or cerclage) required during the current pregnancy due to cervical change
Intermediate	Shortened cervical length to 11-25 mm, AND/OR Quantitative fetal fibronectin level of 50-199 ng/mL if performed (based on usual indications), AND/OR Need for progesterone and/or cerclage during the current pregnancy due to cervical change
High	Shortened cervical length to <10 mm, AND/OR Quantitative fetal fibronectin level of ≥200 ng/mL if performed (based on usual indications)

Table 8.10 Women's knowledge of their preterm birth risk and their perceptions of preterm birth clinic care

Question and response	Number (%)
Set 1 (baseline)	
1. Were you aware that you had an increased risk of your baby being born early before you got pregnant?	
Yes	59/73 (80.8)
No	14/73 (19.2)
2. Did you contemplate not getting pregnant because you were worried about your increased chance of having a baby born early? [a]	
Yes	19/59 (32.2)
No	40/59 (67.8)
3. Once you were pregnant, did your lead maternity carer (midwife, GP or obstetrician) identify that there was an increased chance of your baby being born early?	
Yes	51/71 (71.8)
No	20/71 (28.2)
4. How did you feel when your lead maternity carer (midwife, GP or obstetrician) identified that there was an increased chance of your baby being born early? [b]	
Very anxious	11/51 (21.6)
Somewhat anxious	20/51 (39.2)
Neither anxious nor relieved	12/51 (23.5)
Somewhat relieved	5/51 (9.8)
Very relieved	3/51 (5.9)
5. How did you feel after your maternity care provider (midwife, GP or obstetrician) suggested you come to the preterm birth clinic?	
Significantly more anxious	8/71 (11.3)
Somewhat more anxious	12/71 (16.9)
Neither more or less anxious	11/71 (15.5)
Somewhat less anxious	24/71 (33.8)
Significantly less anxious	16/71 (22.5)
6. How did you feel after you read the pamphlet about what to expect in the preterm birth clinic that was included with your appointment details?	
Significantly more anxious	1/69 (1.4)
Somewhat more anxious	13/69 (18.8)
Neither more or less anxious	30/69 (43.5)
Somewhat less anxious	20/69 (29.0)

Significantly less anxious	5/69 (7.2)
8. How would you describe your social support network (for example your partner, whānau/family, friends)?	
Very unsupportive	7/72 (9.7)
Somewhat unsupportive	1/72 (1.4)
Neither supportive nor unsupportive	2/72 (2.8)
Somewhat supportive	6/72 (8.3)
Very supportive	56/72 (77.8)
Set 3 (after last visit)	
1. How have you found the quality of your general pregnancy care?	
Very low quality	0/63 (0.0)
Low quality	1/63 (1.6)
Neither high or low quality	4/63 (6.3)
High quality	13/63 (20.6)
Very high quality	45/63 (71.4)
2. How have you found the quality of your care through the preterm birth clinic?	
Very low quality	0/63 (0.0)
Low quality	1/63 (1.6)
Neither high or low quality	1/63 (1.6)
High quality	12/63 (19.0)
Very high quality	49/63 (77.8)
3. Do you think that being seen in a preterm birth clinic made you more or less anxious about your pregnancy?	
Significantly more anxious	2/63 (3.2)
Somewhat more anxious	2/63 (3.2)
Neither more or less anxious	3/63 (4.8)
Somewhat less anxious	14/63 (22.2)
Significantly less anxious	42/63 (66.7)
4. If you have another pregnancy, would you want to be cared for through a preterm birth clinic again?	
Yes	55/63 (87.3)
No	7/63 (11.1)
Unsure	1/63 (1.6)

GP, general practitioner.

Denominator reflects number of respondents that answered each individual question.

[a] Only answered if responded 'Yes' to question 1.

[b] Only answered if responded 'Yes' to question 3.

Chapter 9 Perinatal care for women and their babies who deliver at 23 and 24 weeks of gestation

9.1 Preface

This chapter provides a detailed review of the antenatal counselling and perinatal care provided to women and their babies when birth occurs at the peri-viable gestational ages of 23 and 24 weeks. It assesses all inborn cases over a two year time period at a large tertiary maternity unit in New Zealand. The learning points identified in this study can be used to optimise care when birth occurs at extremely early gestational ages, and can also be translated to care at later preterm gestations.

This chapter contains a manuscript that has been published in the *Australian and New Zealand Journal of Obstetrics and Gynaecology* (Dawes, Buksh et al. 2019). The following text contains the original manuscript, reproduced under license from the publisher, John Wiley and Sons.

9.2 Perinatal care provided for babies born at 23 and 24 weeks of gestation

Dawes L, Buksh M, Sadler L, Waugh J, Groom K.

9.2.1 Abstract

In recent years significant improvements in survival and survival-free of major morbidity in babies born at 23^{+0} to 24^{+6} weeks of gestation have led to a more pro-active approach to resuscitation at these peri-viable gestations. Antenatal counselling and interventions, intrapartum care and postnatal advice should be part of the package of care provided to optimise outcomes for these babies and their families. This observational study assesses the perinatal care provided to mothers and their babies who were born at 23 and 24 weeks of gestations over a two year period at a tertiary maternity hospital in New Zealand.

9.2.2 Introduction

Preterm birth is the leading cause of neonatal death and causes life-long health consequences for many survivors (March of Dimes, Partnership for Maternal Newborn and Child Health et al. 2012). Although few babies are born at peri-viable gestations (defined here as 23^{+0}-24^{+6} weeks), they have the highest rates of mortality and morbidity (Auckland District Health Board 2018a; Raju, Mercer et al. 2014). Many factors impact on the rates of survival and survival-free of major morbidity but local hospital practice regarding the offer of resuscitation (active intervention) is the most significant factor at these very preterm gestations (Rysavy, Li et al. 2015).

Inequities in care for babies born at peri-viable gestations have been reported. In New Zealand (NZ), the Perinatal and Maternal Mortality Review Committee (PMMRC) identified that babies of Māori, Pacific and Indian mothers are more likely to be born at 23-26 weeks, but less likely to receive resuscitation and less likely to survive (Perinatal and Maternal Mortality Review Committee 2018). Differences in care offered across NZ has also been identified, resulting in a PMMRC recommendation for a national consensus pathway for the care of women with birth anticipated before 25 weeks of gestation (Perinatal and Maternal Mortality Review Committee 2018).

When delivery is anticipated at peri-viable gestations, complex decisions need to be made by clinicians, women and their families (Ecker, Kaimal et al. 2016). This includes: assessment of likely survival and survival-free of major morbidity; sensitive and informed discussion; consideration of interventions that impact outcome; and decision of whether active intervention with resuscitation or a more conservative approach of comfort care is taken. International statements guide clinicians on antenatal counselling and perinatal management at peri-viable gestations (Ecker, Kaimal et al. 2016; Raju, Mercer et al. 2014; Royal College of Obstetricians and Gynaecologists 2014). Principles within these statements are consistent with the approach taken in NZ and Australia.

The local preterm labour guideline at National Women's Health, Auckland City Hospital was amended in February 2017 to include specific guidance when birth is expected at 23-24 weeks (Auckland District Health Board 2018b). It encourages a multidisciplinary and family-centred approach with development of an individualised plan including comfort care or active intervention (Auckland District Health Board 2018b). If active intervention is planned, corticosteroids, magnesium sulphate, antibiotics, and tocolysis are recommended (Auckland

District Health Board 2018b). Mode of delivery and intrapartum fetal monitoring should be discussed separately as caesarean section performed at these gestations may require a classical incision. This guideline was updated in 2018 to include delayed cord clamping (Auckland District Health Board 2018b; Fogarty, Osborn et al. 2018; Tarnow-Mordi, Morris et al. 2017). The aim of this study is to assess the antenatal counselling and perinatal care provided to mothers and their babies when birth occurs at 23-24 weeks to identify areas where improvements can be made.

9.2.3 Materials and methods

This observational study reviewed all babies born at 23^{+0}-24^{+6} weeks from 1 January 2017 to 31 December 2018 at National Women's Health, Auckland City Hospital, a tertiary maternity unit in NZ. Singleton and multiple pregnancies and babies born after spontaneous onset of labour or medically indicated delivery were included; pre-labour fetal demise (unless multiple pregnancy with ≥1 survivor) and planned termination of pregnancy were excluded.

Cases were identified from the maternity database and data obtained from maternity and neonatal databases and review of electronic medical records by one investigator. Opinion was sought from additional investigators where there were uncertainties (maternal fetal medicine specialist and neonatologist).

Demographics, obstetric history, risk factors for preterm birth and postnatal care are reported for the whole cohort. Antenatal counselling, perinatal interventions, delivery details and neonatal outcome have been analysed separately for births at 23 (23^{+0}-23^{+6}) and 24 (24^{+0}-24^{+6}) weeks. Cases where active intervention was deemed medically inappropriate were excluded from the latter analysis. IBM SPSS Statistics software (version 25.0) was used.

Ethical approval was obtained from the Auckland Health Research Ethics Committee (reference 000068).

9.2.4 Results

There were 23 eligible pregnancies with 24 babies: 10 born at 23 weeks and 14 at 24 weeks. All were the result of spontaneous onset of labour. Demographic and obstetric characteristics are shown in Table 9.1.

Table 9.1 Patient demographics and obstetric characteristics

Characteristic	**Participants (n=23)**
Maternal age (years)	
Mean ± SD	31.8 ± 5.1
Range	22 – 44
Ethnicity	
New Zealand European	7 (30.4%)
Asian	4 (17.4%)
Māori	3 (13.0%)
Indian	3 (13.0%)
Pacific Peoples	2 (8.7%)
Other	4 (17.4%)
Body mass index (kg/m^2)	
Mean ± SD	26.2 ± 5.2
Range	18 - 35
Primiparous	15 (65.2%)
IVF pregnancy	3 (13.0%)
Confirmed dating [a]	23 (100.0%)
Booked for antenatal care	22 (95.7%)
Pre-existing risk factors for preterm birth	
Twin pregnancy [b]	5 (21.7%)
Previous preterm birth	1 (4.3%)
Previous cervical surgery	3 (13.0%)
Previous caesarean section at full dilatation	2 (8.7%)
Multiple (≥2) uterine instrumentations or surgical terminations of pregnancy	3 (13.0%)
Cigarette smoking	4 (17.4%)
Marijuana use	1 (4.3%)
Socio-economic deprivation [c]	8 (34.8%)
Interventions in current pregnancy	
Cervical cerclage	2 (8.7%)
Vaginal progesterone	3 (13.0%)

Data represented as number (percentage) unless otherwise stated.

SD, standard deviation; IVF, *in vitro* fertilisation.

[a] By sure menstrual dates, first trimester scan, or IVF.

[b] Four of these had pre-labour demise of one twin.

[c] NZDep2013 Deprivation Index deciles 9 and 10.

Median gestation at the delivery admission was 165 days (23^{+4} weeks), range 147-174 days. Six women were transferred from a secondary hospital. The primary reason for admission was rupture of membranes with or without threatened preterm labour (10/23, 43.5%), threatened or established preterm labour with intact membranes (12/23, 52.2%) and antepartum haemorrhage (1/23, 4.3%). The time interval from identification as high risk for imminent delivery until birth was >24 hours in 15/23 (65.2%) cases, median 51.9 hours (range 50 minutes to 17 days).

A recent estimated fetal weight (within two weeks of birth) was available for 18/23 (78.3%) cases, with two fetuses identified as small-for-gestational-age. For one, with an estimated weight of <400 g, it was deemed medically inappropriate to offer active intervention. All remaining 22 women and their families were offered active intervention; however, documented antenatal counselling included the alternative of comfort care in 8/9 (88.9%) births at 23 weeks and in just over half of cases (8/13, 61.5%) at 24 weeks. All who were offered active intervention opted for this. Other aspects of antenatal counselling and plans for perinatal care, where documented, are described in Table 9.2. All women were seen by an obstetrician prior to birth, 11/22 (50.0%) were also seen by a maternal fetal medicine specialist and 17/22 (77.3%) by a neonatologist.

Table 9.2 Documented antenatal counselling, antenatal plans for perinatal care and actual care received when active intervention was offered (n=22 pregnancies)

Aspect of care	**Birth at 23 weeks**	**Birth at 24 weeks**
Neonatal outcomes discussed and documented	8/9 (88.9%)	11/13 (84.6%)
Antenatal corticosteroids		
Use discussed and documented	6/9 (66.7%)	12/13 (92.3%)
At least one dose received	8/9 (88.9%)	13/13 (100.0%)
Complete course received	6/9 (66.7%)	9/13 (69.2%)
Magnesium sulphate		
Use discussed and documented	5/9 (55.6%)	12/13 (92.3%)
Commenced	6/9 (66.7%)	10/13 (76.9%)
≥4 hours received	3/9 (33.3%)	6/13 (46.2%)
Tocolysis		
Received	1/9 (11.1%)	4/13 (30.8%)
Contraindicated if not given [a]	6/8 (75.0%)	5/9 (55.6%)
Intrapartum antibiotics if vaginal birth		
Commenced	6/9 (66.7%)	8/10 (80.0%)

>4 hours received	2/9 (22.2%)	6/10 (60.0%)
Mode of birth		
Discussed and documented	7/9 (77.8%)	11/13 (84.6%)
Vaginal birth planned	7/7 (100.0%)	9/11 (81.8%)
Caesarean section planned	0/7 (0.0%)	2/11 (18.2%)
Actual		
Vaginal birth	9/9 (100.0%)	11/14 (78.6%)
Breech presentation	4/9 (44.4%)	3/14 (21.4%) [b]
Caesarean section	0/9 (0.0%)	3/14 (21.4%)
Breech presentation	0/9 (0.0%)	2/14 (14.3%)
Caesarean for fetal indications		
Discussed and documented	7/9 (77.8%)	8/13 (61.5%)
Decision to perform caesarean for fetal indications if required	0/7 (0.0%)	4/8 (50.0%)
Intrapartum fetal monitoring		
Discussed and documented	6/9 (66.7%)	9/13 (69.2%)
No monitoring planned	2/6 (33.3%)	0/9 (0.0%)
Intermittent auscultation planned	4/6 (66.7%)	8/9 (88.9%)
Continuous cardiotocograph planned	0/6 (0.0%)	1/9 (11.1%)
Received		
No monitoring	4/9 (44.4%)	1/13 (7.7%)
Intermittent auscultation	4/9 (44.4%)	6/13 (46.2%)
Continuous cardiotocograph	1/9 (11.1%)	6/13 (46.2%)
Delayed cord clamping [c]		
Discussed and documented	1/3 (33.3%)	0/5 (0.0%)
Received	1/3 (33.3%)	2/4 (50.0%)
Neonatal resuscitation		
Neonatologist present at birth [d]	7/9 (77.8%)	13/14 (92.9%)
Resuscitation attempted if live born	9/9 (100.0%)	13/13 (100.0%)
Admitted to neonatal unit if live born	5/9 (55.6%)	12/13 (92.3%)

Data represented as numerator/denominator (percentage).

[a] Contraindications include suspected or confirmed chorioamnionitis and active vaginal bleeding.

[b] Includes one second twin (leading co-twin cephalic).

[c] 2018 births only; delayed cord clamping was introduced into the local preterm labour guideline in 2018.

[d] Neonatologist present within 2 minutes for all remaining cases.

Table 9.2 shows the rates of interventions when active intervention was planned. Women who did not receive antenatal corticosteroids, magnesium sulphate and intrapartum antibiotics had a short time period from diagnosis of established labour to birth; 50 minutes in one case when corticosteroids were not given, and five to 65 minutes where magnesium sulphate was not given. However, in the six cases where magnesium sulphate was not given, five women were inpatients prior to established labour and an earlier diagnosis may have been possible. Intrapartum fetal monitoring was carried out as planned and documented for 4/6 (66.7%) births at 23 weeks and 8/9 (88.9%) births at 24 weeks. In the three cases with a discrepancy between planned and actual care, the level of monitoring increased.

Mode of birth is described in Table 9.2. When a plan for mode of birth was documented, this occurred as planned in all births at 23 weeks and 10/11 (91.0%) births at 24 weeks. There was one intrapartum stillbirth (24 weeks). Just over half of babies were alive to primary hospital discharge: 4/9 (44.4%) born at 23 weeks and 9/14 (64.3%) born at 24 weeks (or 9/13, 69.2% at 24 weeks if considering only live births). All surviving babies born at 23 weeks were discharged home on oxygen (4/4), as were 88.9% (8/9) of babies born at 24 weeks. Rates of other major morbidities were low for survivors: intraventricular haemorrhage (grade 1) in only one baby (23 weeks) and retinopathy of prematurity (stage 3/4) in one baby (24 weeks).

Women were seen by an obstetrician for review after birth and prior to hospital discharge in 17/23 (73.9%) cases, however, a documented discussion regarding subsequent risk of preterm birth with advice for future care occurred in only 9/17 (52.9%). Recommendations for future pregnancy care were communicated to the family doctor/lead maternity carer in only one case. Placental histology was obtained in all cases, with relevant findings in all but two cases. Post mortem was offered in all but one case when the baby did not survive; no family accepted a post mortem. A follow-up appointment was arranged with an obstetrician in 10/23 (43.5%) cases and of these, 7/10 (70.0%) attended.

9.2.5 Discussion

In the majority of cases where birth occurs at peri-viable gestation there is time for counselling and provision of perinatal interventions that impact outcome. Within our study all families offered active intervention opted for this, highlighting the need for specialist assessment prior to counselling. Our study identified areas of opportunity to optimise perinatal care. Whilst rates of antenatal corticosteroid use were high, magnesium sulphate administration could be

improved. We acknowledge the challenges of accurately timing magnesium to within four hours of delivery at these extremely preterm gestations. However, given high rates of mortality and morbidity for these extremely preterm babies, magnesium use is a priority and a low threshold for reassessment in the event of changing symptoms is necessary.

Birth at 23-24 weeks gestation is uncommon, and even in a tertiary hospital, many general obstetricians will have limited exposure. Despite local guidelines for care, further education is required, especially regarding decisions for intrapartum fetal monitoring and delayed cord clamping where antenatal plans were often incomplete and care suboptimal. Antenatal plans for mode of delivery and intrapartum fetal monitoring must be clearly documented and available in the event of established labour or an emergency that necessitates rapid delivery.

In our study, 44.4% and 69.2% of live born babies with planned active intervention at 23 weeks and 24 weeks respectively survived to hospital discharge. This compares favourably to the published literature with survival rates of 23-27% at 23 weeks and 42-59% at 24 weeks in studies from America, England and Australia (Ecker, Kaimal et al. 2016). However, comparisons between studies are limited by variations in the population assessed; some studies report outcomes for all live births, whereas others exclude deaths in the delivery room. Furthermore, some studies report outcomes regardless of whether active resuscitation was planned or performed. Differences in outcomes between our study and the published literature may reflect these differences in the populations included as well as different time periods of assessment and our small study number. The rates of major morbidities such as intraventricular haemorrhage in survivors in our study appear to be relatively low, however may reflect the study size, and long term outcomes are not yet available.

Women who have a preterm birth at a peri-viable gestation are at increased risk of subsequent preterm birth. While women and their families are often overwhelmed with events immediately postpartum and may not retain detailed information, brief discussion and advice should be provided and communicated to the family doctor/lead maternity carer, as even when follow-up appointments are made, there is a risk of non-attendance.

The main limitation of this study is the small number of births, preventing planned analysis by ethnicity, socioeconomic status and planned place of birth. In addition, the retrospective design relied on potentially incomplete documentation of discussions. Although this was a single site

study, practice is similar to other tertiary maternity units across NZ and Australia making learning points externally valid.

In conclusion, in the majority of births at 23-24 weeks there is time for counselling and perinatal interventions to improve outcomes and most families choose active intervention. The quality of counselling and perinatal care can be improved.

Chapter 10 Overall discussion and conclusion

The overall goal of this thesis is to explore ways to optimise the care of women at high risk of spontaneous preterm birth. Opportunities were identified across three main themes: (1) the use of vaginal biomarkers in women with symptoms of preterm labour; (2) the role of specialised preterm birth clinics; and (3) perinatal care when birth is expected at peri-viable gestations. Six key aims were developed within these themes and investigated across six research studies.

10.1 Theme 1: Vaginal biomarkers in symptomatic women

10.1.1 An implementation strategy for fetal fibronectin use in the management of threatened preterm labour

Aim

To assess whether the use of a multi-faceted implementation strategy improves adherence to a clinical practice guideline for the use of fetal fibronectin (fFN) testing in women with threatened preterm labour.

Summary of findings

In this quality improvement project I have shown that a multi-faceted educational intervention improves clinician compliance to a clinical practice guideline for the use of fFN in the assessment and management of women with threatened preterm labour. Audit with clinician feedback, interactive education, and reminders resulted in improved clinician knowledge in care around fFN use including best practice management according to the fFN result. It also resulted in clinical practice change, with an increased number of fFN tests performed, an increased proportion of fFN tests meeting clinical criteria for testing and an improved adherence to clinical management guidelines once the test was performed.

Implications for clinical practice

Clinical practice guidelines are widely available across most areas of obstetrics, but effective implementation remains a challenge. As clinical practice guidelines describe best practice care based on current evidence, greater compliance to these guidelines will improve the quality of

clinical care provided. The measurable improvements in clinician compliance seen in my study have direct implications for clinical practice at the study site. Comparable improvements in practice are also likely to be achieved more widely if similar multi-faceted approaches to fFN guideline implementation are used in other units.

We know that the vast majority of women with threatened preterm labour will not deliver within two weeks of presentation (Abbott, Radford et al. 2013; Wing, Haeri et al. 2017), and that use of fFN can improve the accuracy of risk prediction (Peaceman, Andrews et al. 1997). This allows a risk stratification rather than 'treat all' approach to management. Improvements in the appropriate clinical management of fFN results seen in this quality improvement project means fewer women with a negative fFN test are admitted to hospital or given medications that are unlikely to be beneficial, as >99% will still be pregnant in two weeks time (Peaceman, Andrews et al. 1997). Interventions can instead be targeted to women with a positive fFN test who are at higher risk of imminent preterm birth, and improved guideline compliance ensures these women receive appropriate management with hospital admission and administration of antenatal corticosteroids to optimise perinatal outcomes if they deliver preterm.

My study has demonstrated the effectiveness of a multi-faceted educational approach to changing clinician behaviour, and therefore has implications for clinical practice beyond the use of fFN. The general principles from this study can be used in the implementation of other preterm birth risk prediction tools, for example alternative vaginal biomarkers or measurement of cervical length, with similar results expected. These principles can also be applied to other aspects of care in obstetrics and gynaecology, with my study providing evidence to support the use of similar programmes for the implementation of new guidelines within this field or to improve compliance to existing guidelines when this is identified as an issue.

Implications for future research

This quality improvement project has shown that clinical practice change can be achieved at one year post-educational intervention. However, findings from the Biomarkers for Preterm Birth Study suggest that improved guideline compliance may not be sustained over a longer period of time. A discrepancy between actual practice and that according to the fFN clinical practice guideline was again evident in the Biomarkers for Preterm Birth Study, which was commenced at the same site two years after completion of the original multi-faceted educational intervention for fFN use. It is possible that staff changeover contributed to a reduction in compliance over

an extended period of time. Future studies in this area should explore strategies to improve the sustainability of practice change over time and with changing personnel.

10.1.2 Comparing the impact of vaginal biomarkers on clinical practice when used in the management of women with threatened preterm labour

Aim

To compare the impact of vaginal biomarkers on clinical practice when used in the management of women with threatened preterm labour.

Summary of findings

The Biomarkers for Preterm Birth Study provides evidence to support the use of quantitative fFN over qualitative fFN and PAMG-1 in the assessment and management of women with threatened preterm labour. I have shown that knowledge of the actual fFN concentration from the quantitative test allows a more individualised approach to the management of threatened preterm labour and can reduce rates of antenatal hospital admission and other interventions compared to the use of qualitative fFN. These clinical benefits can be achieved without compromising antenatal care for the few babies who are born preterm. Whilst the use of PAMG-1 may also reduce antenatal admissions and other interventions, this may compromise antenatal care for some babies who are born preterm (for example due to missed antenatal corticosteroid administration), and findings from my study do not support its use.

My study confirms that few women with symptoms of preterm labour will go on to deliver imminently, with only 4.7% having a spontaneous preterm birth within two weeks. This is consistent with the existing literature and further supports the concept of risk stratification to guide management rather than a 'treat-all' approach.

Implications for clinical practice

This is the first published study to make prospective comparisons of qualitative fFN, quantitative fFN and PAMG-1 in a cohort of symptomatic women and to examine the potential impact on clinical management. This research provides new evidence to support the use of quantitative fFN testing to optimise the care of women with threatened preterm labour.

As a direct result of my study, quantitative fFN testing was introduced at National Women's Health, Auckland City Hospital (the study site) in June 2018, replacing qualitative fFN. The hospital preterm labour guideline was updated to incorporate this change and utilises the management algorithm from my study (Auckland District Health Board 2018b). We expect other maternity units, both in New Zealand and internationally, to consider the use of quantitative fFN now that results have been presented and published (Dawes, Prentice et al. 2018; Dawes, Prentice et al. 2019).

Reducing hospital admissions and other interventions for symptomatic women identified to be at low risk of imminent spontaneous preterm birth has several advantages. In addition to freeing up hospital beds with the associated benefits for hospital staffing and health care costs, women avoid disruption to family and work life and the associated anxiety this may cause. Furthermore, a reduction in the administration of medications, for example tocolytic agents, decreases the risk of iatrogenic harm.

Implications for future research

I have shown that quantitative fFN has the potential to perform better than qualitative fFN and PAMG-1 in clinical practice, but this test still has a relatively low positive predictive value (PPV) for the prediction of imminent spontaneous preterm birth; a fFN level of 200 ng/mL has a PPV of 37.0% for delivery within 14 days (Abbott, Radford et al. 2013). Future research is required to determine whether the accuracy of preterm birth risk prediction can be further improved in symptomatic women. This includes the development of new biomarkers along with further investigation into combinations of assessment tools or algorithms. Early studies of prediction models combining the results of clinical information such as previous obstetric history and cervical surgery, cervical length measurements and vaginal biomarkers have shown this approach to further enhance the identification of women and babies most likely to benefit from hospital admission and other interventions such as administration of antenatal corticosteroids and magnesium sulphate (Watson, Carter, Seed et al. 2017). There is opportunity for further investigation in this area, including which combination of predictive factors perform best, whether there is a role for a combination of vaginal biomarkers, and what the impact of these prediction models are on clinical practice.

There is also opportunity for synthesis of the new knowledge obtained from my study in individual patient data meta-analyses, like in the QUIDS Study, which aims to develop and

validate a decision support tool for the management of women with threatened preterm labour (Stock, Wotherspoon et al. 2018). Combining data increases statistical power, allows more meaningful subgroup analysis and improves generalisability of results.

Implementation of quantitative fFN at the study site provides an opportunity to compare management and pregnancy outcomes pre- and post-introduction of the quantitative fFN test. This will enable an assessment of the true impact of quantitative fFN on rates of hospital admission and other interventions for women with threatened preterm labour, validating the results from the Biomarkers for Preterm Birth Study which were based on hypothetical management according to clinical practice guidelines.

10.2 Theme 2: Specialised preterm birth clinics

10.2.1 Specialised preterm birth clinics: a systematic review

Aim

To assess current practice in specialised preterm birth clinics globally.

Summary of findings

In this systematic review I have assessed the reported practice in preterm birth clinics globally and shown significant variation in most aspects of care. Data from 39 clinics were combined; the majority of clinics were in the United Kingdom, but clinics in America, Germany, Italy and Australia were also identified. Whilst all clinics accepted referrals for women with a previous spontaneous preterm birth, the gestational age at prior early birth varied, as did additional clinical criteria for referral. Transvaginal cervical length scans were performed in all clinics, but the use of additional investigations such as urogenital swabs, urine culture and fFN varied. A range of interventions aimed at reducing the risk of spontaneous preterm birth were available, including cervical cerclage, intramuscular or vaginal progesterone and cervical pessary. There was variation in the primary management of women with a short cervix and also in the criteria used to define a short cervix. There was more consistency in the timing of first consultation, with most clinics planning to see women early in the second trimester, but there was heterogeneity in the timing of clinic discharge, ranging from 24 weeks up to 37 weeks or beyond. The majority of clinics determined the frequency of review according to clinical findings.

Implications for clinical practice

This is the first systematic review to assess practice in preterm birth clinics globally. Until recently no national or international guidelines were available to direct practice in these specialised clinics and care was often based on local expert opinion. Significant variation in practice has been identified in prior surveys in the United Kingdom, and confirmed in my systematic review. These findings support the need for development and implementation of preterm birth clinic consensus guidelines which may be incorporated into national prevention programmes. Consensus guidelines and preterm birth prevention programmes encourage best practice care, aiming to improve consistency and achieve equity in access and care for all women regardless of their location of residence, ethnicity or socioeconomic status.

Implications for future research

A limitation of my systematic review is the potential for publication bias. National surveys may provide a more systematic means of assessing practice, provided that high response rates are achieved. Surveys of practice in preterm birth clinics have been undertaken in the United Kingdom but are required in other localities to allow a more representative assessment of preterm birth practice worldwide. The recent introduction of a preterm birth guideline for commissioners and providers in the United Kingdom (UK Preterm Clinical Network 2019) is likely to improve consistency in care in the United Kingdom and may also have influence in other countries. Repeat surveys of practice can be undertaken to assess the impact of this guideline on clinical care.

Improving consistency in care in preterm birth clinics will also allow clinics to combine data in a more meaningful way and enable high-quality research into the effectiveness of interventions provided in these specialised clinics, as well as allow comparisons to be made between clinics. Networks of preterm birth clinics have been established and internet-based databases with minimal datasets are already available (Carter, Tribe et al. 2018). The combination of a consistent approach to care and a collaborative approach to data collection has great potential for the future evaluation of existing and new interventions to optimise the care of women at high risk of spontaneous preterm birth.

10.2.2 The experience and outcomes of a specialised preterm birth clinic in New Zealand

Aim

To assess the experience and outcomes from five years of practice in the first specialised preterm birth clinic in New Zealand.

Summary of findings

This observational study provides a detailed review of 345 women cared for in a specialised preterm birth clinic in Auckland, New Zealand over a five year period. The majority of women were seen following elective referral in pregnancy, with a smaller number seen after acute referral due to a short cervix, or for a pre-pregnancy or follow up review. Women seen in the preterm birth clinic were at high risk of spontaneous preterm birth, with many fulfilling multiple referral criteria and/or having multiple previous second trimester losses or early births. Just over two thirds of women referred electively in pregnancy had cervical surveillance as their primary management, and further treatment was avoided in most cases. Interventions such as cervical cerclage and vaginal progesterone were directed to those at greatest risk, who subsequently were most likely to deliver preterm. Despite being a high risk cohort, the majority of women referred electively achieved a term delivery with good outcomes for their babies. Most women who were referred acutely had an incidental finding of a short cervix detected at the fetal morphology scan. These women had high rates of intervention and despite this, most delivered early. Potential disparities in access to care by ethnicity and socio-economic status were identified, particularly for access to pre-conceptual care.

Implications for clinical practice

This study assesses practice in the first specialised preterm birth clinic in New Zealand. Preterm birth clinics provide individualised and coordinated care to asymptomatic women at high risk of spontaneous preterm birth. Whilst they are not currently common-place in Australasia, the more widespread introduction and development of preterm birth clinics is planned or in progress across New Zealand and Australia as part of national or state-wide preterm birth prevention programmes (Newnham & Morris 2019; Newnham, White et al. 2017). My study provides valuable information that can be used by clinicians and policy makers to inform the development

of these clinics, and has implications for resource and training needs. My study also provides local outcome data that can be used in patient counselling and clinical management.

The identification of potential disparities in access to care by ethnicity and socioeconomic status seen in women at high risk of spontaneous preterm birth in my study is relevant for clinical practice. Ethnic disparities in spontaneous preterm birth rates and outcomes for babies born preterm have already been identified as an issue in previous national review (Perinatal and Maternal Mortality Review Committee 2018). Inequities in access to care is likely to be a contributory factor and the findings from my study supports this. As Māori women have spontaneous preterm birth rates around twice that of non-Māori (Auckland District Health Board 2018a), improving equity in care for Māori women at high risk of spontaneous preterm birth will likely improve preterm birth rates nationally and should be prioritised. The findings from my study support the need for further research to identify effective strategies to improve access to care for all women at high risk of spontaneous preterm birth (described in further detail below).

Implications for future research

Further dedicated research is required to quantify disparities in access to pregnancy and pre-conceptual care by ethnicity, socio-economic status and location of residence for women at high risk of spontaneous preterm birth and to identify potential enablers and barriers to care. This information could be used in a future preterm birth prevention programme for New Zealand to achieve equity in access to care and in outcomes for all women and babies. This future research should be undertaken in both rural and urban areas to ensure appropriate geographical representation.

10.2.3 The psychological wellbeing of women cared for in a specialised preterm birth clinic

Aim

To report the prevalence of symptoms of anxiety and depression in women cared for in a specialised preterm birth clinic and to assess the potential impact of care on psychological wellbeing.

Summary of findings

This study assesses the psychological wellbeing of pregnant women at high risk of spontaneous preterm birth who are cared for in a specialised preterm birth clinic. High rates of psychological distress were identified in these high risk women, with 38% and 14% having significant symptoms of anxiety and depression, respectively, at the beginning of the second trimester. There were improvements in both mean anxiety and depression scores following the second visit to a specialised preterm birth clinic, compared to before the first visit, and a further improvement was seen in anxiety scores by clinic discharge at around 24 weeks of gestation. Rates of anxiety had halved to 19% by clinic discharge. Women identified care in the preterm birth clinic to be a significant factor in reducing pregnancy-related anxiety. General perceptions of care in a preterm birth clinic were also favourable and the majority would want to be seen again in another pregnancy.

Implications for clinical practice

My study is the first published study to assess the psychological wellbeing of women receiving care in a specialised preterm birth clinic. The new knowledge obtained from this novel study shows that preterm birth clinics are likely to have a role in reducing anxiety in women at high risk of spontaneous preterm birth. Whilst not the primary aim of these clinics, any improvement in psychological wellbeing confers an additional benefit. The results are reassuring as there is some evidence from prior studies that being labelled ‘high risk’ may increase anxiety, although other studies show women embrace this label in a positive way (O'Brien, Quenby et al. 2010; Simmons & Goldberg 2011). My study findings are consistent with the latter, and these results should provide reassurance to clinicians and policy makers.

The high rates of psychological distress identified in my study highlight the need for a heightened awareness of the presence of anxiety and depression in women at high risk of spontaneous preterm birth. Preterm birth clinics should ensure they have established referral pathways to access psychological assessment and support, or should incorporate these services into the clinic itself. The potential to reduce psychological distress and improve the recognition and management of anxiety and depression, provides preterm birth clinics with an additional opportunity to improve pregnancy outcomes and reduce maternal morbidity.

Implications for future research

It seems likely that advancing gestation also plays a role in improving pregnancy-related anxiety in these high risk women. This was not completely assessed in my study as we did not have access to a suitable comparator group at the study site. Future studies could include comparison to women with a similar risk profile who are not cared for in a preterm birth clinic, to assess the relative contributions of preterm birth clinic care and advancing gestation in improving psychological wellbeing.

Due to the high rates of psychological distress identified in my study and the recommendations provided, preterm birth clinics may choose to incorporate psychological support services into the package of care that they offer. This provides opportunity to measure the effect of such services, which is important given the associated costs and resources required. There is also opportunity for more detailed qualitative studies in this area to explore which aspects of preterm birth clinic care are the most beneficial for reducing anxiety, which sub-groups of women are the most likely to benefit and whether women perceive additional support services to be helpful.

10.3 Theme 3: Care when birth is expected at peri-viable gestations

10.3.1 Perinatal care for women and their babies who deliver at 23 and 24 weeks of gestation

Aim

To assess the antenatal counselling and perinatal care provided to mothers and their babies when birth occurs at 23 and 24 weeks of gestation.

Summary of findings

This study provides a detailed assessment of the antenatal counselling and perinatal care provided to mothers and their babies when birth occurs at the peri-viable gestational ages of 23 and 24 weeks in a single centre. All eligible cases were assessed over a two year period (n=23 pregnancies) at National Women's Health, Auckland City Hospital, a tertiary maternity hospital in New Zealand. My study shows that there is usually time for antenatal counselling and perinatal interventions when women are identified to be at very high risk for imminent birth at

peri-viable gestations. All women and families who were offered active intervention and resuscitation opted for this. Whilst rates of antenatal corticosteroid administration were high, there is opportunity to improve the use of magnesium sulphate for fetal neuroprotection. Documented plans for mode of delivery, intrapartum fetal monitoring, whether a caesarean section would be performed on fetal grounds, and for delayed cord clamping could also be improved.

Few babies are born at peri-viable gestational ages, yet these babies have high rates of perinatal mortality and morbidity (Ecker, Kaimal et al. 2016). The neonatal outcomes of babies in my study compare favourably with the published literature, however this may reflect differences in the populations included, timeframes assessed, and our small study number.

Implications for clinical practice

My study assesses practice in a single maternity hospital and therefore has direct relevance for clinical practice at the study site, but the general principles can also be applied to tertiary hospitals elsewhere. Birth at 23 and 24 weeks gestation is uncommon, and even in a tertiary hospital, many general obstetricians will have limited exposure. My study identifies areas for improvement in antenatal counselling and perinatal care when birth is expected at peri-viable gestational ages. As these babies have high rates of mortality and morbidity, improvements in provision of perinatal interventions such as administration of magnesium sulphate and delayed cord clamping are likely to have a significant influence on neonatal outcomes when active intervention is planned. Of equal importance is the need for improved awareness that women and their families have the choice of comfort care rather than active intervention when birth occurs at 23 or 24 weeks gestation. Learning points from my study can also be translated to later preterm gestations.

Local publication of my study in the *Australian and New Zealand Journal of Obstetrics and Gynaecology* (Dawes, Buksh et al. 2019) was well timed with the release of the first New Zealand consensus statement on the care of mothers and babies at peri-viable gestations (Newborn Clinical Network 2019). Not only is this likely to increase awareness and improve care at an individual clinician level, but it also provides hospital managers with an opportunity for education and use of implementation programmes to maximise uptake and improve clinical practice.

Implications for future research

Disparities by ethnicity and location of residence have been seen in both the rates of extremely early preterm birth in New Zealand as well as in whether active intervention is offered at peri-viable gestations (Perinatal and Maternal Mortality Review Committee 2018). This translates to disparities in neonatal outcome (Perinatal and Maternal Mortality Review Committee 2018). We were unable to complete a planned subgroup analysis by ethnicity and socio-economic status in my study due to small study numbers. A multi-centre study over a longer time period could assess potential disparities in antenatal counselling and perinatal care for women and babies born at peri-viable gestations, and should be undertaken.

Introduction of a New Zealand consensus statement for the care of mothers and babies at peri-viable gestations provides several opportunities for future research in this area. Hospitals throughout New Zealand should be encouraged to audit the care of babies born at peri-viable gestations. A comparison of perinatal care and outcomes pre- and post-release of the consensus statement can assess its impact. As mentioned previously, there are also opportunities for multi-faceted implementation programmes with research as an essential component to measure impact.

10.4 Overall conclusion

The six studies within this thesis collectively achieve the overall goal of exploring ways to optimise the care of women at high risk of spontaneous preterm birth. The findings of this thesis will be used in the development of a New Zealand-wide preterm birth prevention programme. Standardisation of care for women at risk of preterm birth and a targeted introduction of preterm birth clinics across New Zealand will form an integral part of this proposed national initiative which aims to address equity issues.

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