Prevention of preterm birth in women with prior cervical excision

Faye Platt

2021

A thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Master of Philosophy

Department of Women's and Children's health

Institute of Life Course and Medical Sciences

Supervisors

Dr Andrew Sharp

Dr Angharad Care

ABSTRACT

Background: Women with previous cervical surgery are at an increased risk of preterm birth (PTB) and this risk is present in all pregnancies thereafter. PTB remains the leading cause of neonatal morbidity and mortality. Interventions to prevent preterm birth are vaginal cerclage, vaginal progesterone and the Arabin pessary, indicated in women with cervical surgery with a mid-trimester cervical length <25mm between 16-24 weeks of gestation. It is unknown which intervention has the greatest efficacy in preventing PTB in this cohort.

Methods: This thesis systematically reviewed the literature surrounding the management of women with a previous LLETZ or knife cone biopsy. We performed searches within Scopus, Pubmed and Cinahl databases to identify any observational studies or randomised controlled trials comparing either progesterone, vaginal cerclage or Arabin pessary to a control or comparator group. Two independent review authors screened papers for inclusion and assessed risk of bias, cases of uncertainty were discussed with a third review author. The GRADE approach was used for quality assessment. A retrospective cohort study was conducted of all women with prior cervical surgery attending the specialist PTB prevention clinic at Liverpool Women's hospital between 2008-2020. Exclusions were made for women presenting more than once within the study period, missing data, transabdominal cerclage, radical trachelectomy and laser procedures. Data were analysed using univariable and multivariable generalised linear models in R (Version 3). Separate models were performed for women with and without a previous spontaneous preterm birth.

Results: We identified 6 studies eligible for inclusion in the systematic review. There was insufficient evidence to draw conclusions for progesterone or pessary. Studies demonstrated no evidence to support the use of cerclage in women with previous cervical surgery. Our cohort study identified 441 patients for analysis, which demonstrated no statistically significant association between vaginal cerclage or Arabin pessary and gestation time. Progesterone was associated with a decrease in gestation time (Est -3.15 (1.059); p-value 0.004) in women with a previous sPTB.

Conclusion: The systematic review yielded no studies comparing the efficacy of cerclage, pessary and progesterone to one another. Studies of cerclage found no additional benefit of its use in women with previous cervical surgery. These findings are supported by the findings of the retrospective cohort study. Vaginal cerclage, vaginal progesterone and the Arabin pessary, that are effective in other high-risk cohorts, do not present the same efficacy in women with previous cervical surgery.

ACKNOWLEDGEMENTS

This thesis would not have been possible without the support and encouragement of several staff members within the University of Liverpool.

Firstly, I'd like to thank my supervisors, Dr Andrew Sharp and Dr Angharad Care, for providing the opportunity to undertake this research, answering my many questions and offering ongoing guidance and expertise without which I would have undoubtedly fallen at the first hurdle.

I'd like to further extend my gratitude to Dr Richard Jackson, without whom the statistical analysis within this thesis would not have been possible. I'd also like to thank both Dr Kate Navaratnam for taking the time to impart her knowledge of systematic reviews and Siobhan Holt for confirming the suture materials used for those patients receiving a cerclage in our retrospective cohort study.

A special thank you to all of the patients attending the specialist preterm birth clinic at Liverpool Women's Hospital who consented to the use of their clinic data for research, without which I could not have undertaken a cohort study.

Finally, to my friends and family who continue to provide support and motivation in my attempt to complete this degree during a pandemic, I am enormously grateful.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

BPD – Bronchopulmonary dysplasia

CIN – Cervical intraepithelial neoplasia

CL – Cervical length

CST – Community state type

CVF – Cervicovaginal fluid

ECM – Extracellular matrix

fFN – Fetal fibronectin

HPV – Human papillomavirus

IM - Intramuscular

IPD – Individual participant data

IVH – Intraventricular haemorrhage

KCB – Knife cone biopsy

LCPUFA – Long-chain polyunsaturated fatty acid

LLETZ – Large loop excision of the transformation zone

LR – Likelihood ratio

NEC – Necrotising enterocolitis

NICE – National Institute for Health and Care Excellence

NICU – Neonatal intensive care unit

NPV – Negative predictive value

PAMG-1 – Placental alpha microglobulin – 1

PIGFBP-1 – Phosphorylated insulin-like growth factor binding protein-1

PPROM – Preterm prelabour rupture of membranes

PPV – Positive predictive value

PTB – Preterm birth

PTL – Preterm labour

QUiPP - Quantitative instrument for the prediction of preterm birth

RCT – Randomised controlled trial

RDS – Respiratory distress syndrome

ROP – Retinopathy of prematurity

sPTB – Spontaneous preterm birth

TVUSS – Transvaginal ultrasound scan

UK - United Kingdom

VP – Vaginal progesterone

17-OHPC – 17-α hydroxyprogesterone caproate

CHAPTER 1: INTRODUCTION

1.1 PRETERM BIRTH

Preterm birth (PTB) is defined as delivery of the child prior to 37 weeks of gestation. It affects around 10.6% of pregnancies, equating to approximately 15 million PTBs per year globally, though incidence differs per country[1]. It can be categorised into extreme preterm (<28 weeks), very preterm (28-32 weeks), moderate preterm (32-33+6 weeks) and late PTB (34-36+6 weeks)[2]. PTB can occur either following spontaneous labour or secondary to medical intervention (iatrogenic) for maternal factors such as placental compromise or fetal factors including intrauterine growth restriction and fetal distress[3]. Conversely, the aetiology of spontaneous preterm birth (sPTB) is multifactorial with age, ethnicity, BMI, smoking, socioeconomic status and number of fetuses all contributing to risk[4]. Previous history of PTB and prior excisional treatments of the cervix for cervical intraepithelial neoplasia (CIN) also confer an increased risk of PTB[5, 6]. In singletons, a previous sPTB is the best predictor of a subsequent PTB, and it is associated with a 5.6-fold increased risk of sPTB in future pregnancies[7].

Preterm delivery remains the principal cause of neonatal morbidity and mortality worldwide[8]. There is an inverse association between gestation at delivery and the occurrence of adverse neonatal outcomes[9], such as retinopathy of prematurity, sepsis, necrotising enterocolitis, bronchopulmonary dysplasia and intraventricular haemorrhage[10]. These conditions are associated with long-term morbidity including cognitive, hearing and visual impairments, especially in infants delivered between 30-34 weeks[11]. There is also a greater risk of severe cognitive impairment associated with earlier gestations at delivery[11]. PTB can indicate the need for a neonatal intensive care unit (NICU) admission and the requirement for further interventions such as ventilation, phototherapy, antibiotics and parenteral feeding. Length of hospital stay for preterm infants decreases with increasing gestational age at delivery. This highlights the importance of interventions to prolong pregnancy in high-risk groups to optimise neonatal outcomes, reduce the need for prolonged NICU admission and decrease the long-term health, social and economic burden resulting from the conditions associated with PTB.

1.2 THE CERVIX

The cervix is a mechanical structure which retains the fetus in utero during pregnancy, and acts as a barrier to infective organisms. The main components of the cervical stroma are

fibroblasts and smooth muscle cells that secrete extracellular matrix (ECM), largely composed of collagen, proteoglycans and elastic fibres. The mechanical strength of the cervix corresponds to the composition of the ECM, this changes throughout pregnancy and labour in response to levels of oestrogen and progesterone[12]. Maintenance of pregnancy requires a high progesterone and low oestrogen level, whereas cervical ripening for parturition occurs in response to a low progesterone and high oestrogen level[12]. Both oestrogen and progesterone levels are regulated by the expression of 17β-hydroxysteroid dehydrogenase type 2 in the endocervical epithelium[13]. The cervix remodels continuously and collagen becomes more disorganised with advancing gestation. This alters the role of the cervix allowing it to act as both a barrier to retain the fetus throughout pregnancy, and as a passage for delivery during labour[12]. CL decreases progressively from mid-pregnancy until delivery[14]. The downregulation of 17β-hydroxysteroid dehydrogenase type 2 results in a decrease in progesterone and increase in oestrogen concentration to create the ideal microenvironment for cervical ripening in preparation for parturition[13]. Should this process occur prematurely, CL may decrease below 20mm which is associated with an increased likelihood of PTB[2]. The National Institute for Health and Care Excellence (NICE) provides regular guidance updates for investigating and managing a variety of medical conditions. Their guidance on the management of PTB recommends mid-trimester ultrasound screening of CL in women at risk of PTB. NICE guidance uses CL <25mm as the threshold for offering preventative intervention, in line with the 10th percentile and a relative risk of PTB of 3.3[15, 16]. Mid-trimester CL screening in high-risk women has enabled the identification of cervical shortening at an earlier gestation and consequently the prediction and opportunity for intervention to prevent PTB.

1.3 CERVICAL INTRAEPITHELIAL NEOPLASIA

Cervical intraepithelial neoplasia (CIN) is a pre-malignant abnormal growth of squamous cells in the transformation zone of the cervix, graded from mild (CIN1) to severe (CIN3). Human papillomavirus (HPV) infection increases the risk of CIN, with subtypes 16 and 18 accounting for the majority of cases worldwide. Those at the greatest risk of HPV infection are sexually active women under 30[17]. The rates of HPV in the United Kingdom (UK) have significantly reduced following the introduction of the HPV vaccination programme in 2008. The HPV vaccine provides protection against the two most common subtypes, HPV 16 and 18, of which the prevalence has decreased from 8.2% to 1.6% in 16-18 year olds, as of 2016[18]. Progression of CIN to squamous carcinoma can occur though the likelihood has reduced as a result of the national cervical screening programme, allowing for early identification and excision of lesions. Lesions of the cervix alone, when untreated, are

thought to increase the risk of PTB in subsequent pregnancies and excisional treatments further increase that risk[19]. Notably, a 2009 study demonstrated the occurrence of sPTB in 11% of patients with untreated CIN3 relative to only 6% in the general population[20].

1.4 CERVICAL EXCISION

Treatment for moderate-severe CIN commonly involves cervical excision. These treatments allow for quick and effective intervention, often with precise margins, and the scope for histological analysis of removed cervical tissue post-excision. The main methods of excision are cold knife cone biopsy (KCB), large loop excision of the transformation zone (LLETZ) and radical trachelectomy. KCB and LLETZ are less invasive options than radical trachelectomy, which can be advantageous for women of child-bearing age[17]. However, all of these procedures carry their own risks of adverse effects. There is a significant association between excisional procedures of the cervix and the incidence of PTB, and 2.5% of UK PTBs per year are estimated to be a direct result of excisional procedures[21]. Cervical excision and incidental short CL are both independently associated with PTB[6], though studies and clinical guidance often group these two risk factors. The precise mechanism linking excisional treatments of the cervix to the risk of PTB is unknown. Theories include the presence of ascending vaginal infection and the weakening effects of cervical regeneration post-excision[22]. Excisional procedures of the cervix remove the glands that secrete components of the mucus plug, that normally acts as a chemical and physical barrier to infection[23]. Without the mucus plug, the risk of ascending infection is increased and as a result, so is the risk of PTB. An alternate theory suggests that following excision, the tissue rapidly regenerates, altering the collagen arrangement and weakening the quality of the regenerated tissue[24], resulting in an increased risk of PTB.

1.4.1 KNIFE CONE BIOPSY

KCB is a technique used in the treatment of CIN grades 2 or 3 (Figure 1), usually performed under general anaesthesia. The borders of cervical tissue to be excised are directed by colposcopy findings, allowing for clear margins. The procedure involves visualisation of the cervix using a right-angle retractor, followed by the excision of the cervix starting outside the transformation zone using an angled blade. Mayo scissors are then used to excise the base of the cone and a Kevorkian curette is used to remove the remaining endocervical canal[25]. KCB has been associated with perioperative infection risk, cervical stenosis, post-operative bleeding and the potential risk of PTB and perinatal mortality in subsequent pregnancies[26]. The depth of the cone is directly related to the risk of PTB, with greater depth conferring a higher risk[22]. A case control study demonstrated that risk of PTB increases linearly with depth of tissue removed beyond 9mm, although excision of less than 9mm of tissue represents no increased risk beyond that of the background population[27]. This leads to debate in the management of patients undergoing KCB in order to appropriately balance both their oncological and obstetric risks. Premature pre-labour rupture of membranes (PPROM) has also been linked to prior cold knife conisation of the cervix[28] and further studies have reported the increased risk of perinatal mortality associated with conisation[29].

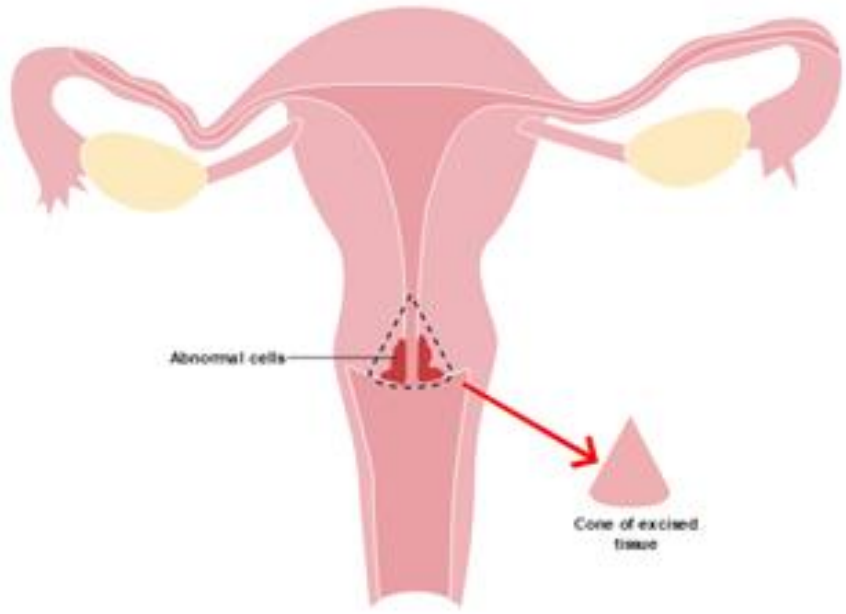

Figure 1: Knife cone biopsy

1.4.2 LARGE LOOP EXCISION OF THE TRANSFORMATION ZONE

Large loop excision of the transformation zone (LLETZ), also termed loop electrosurgical excision procedure (LEEP), involves the application of an electrical current through a wire loop electrode to produce a combined excisional and coagulation effect (Figure 2). The depth of tissue removed is typically less than that of a KCB and LLETZ procedures can be performed under local anaesthetic[26]. Though they are generally regarded as low risk of morbidity, studies have noted the presence of side effects including abdominal pain, vaginal bleeding and post-LLETZ cervical stenosis[30]. A 2013 Cochrane review comparing the effectiveness of surgical interventions for CIN, determined no statistically significant difference in the risk of vaginal bleeding, post-procedure cervical stenosis and residual disease between KCB and LLETZ procedures[17]. Similarly to cone biopsy, LLETZ has been linked to an increased risk of PTB, though many studies describe LLETZ as a safer alternative to KCB as it carries a lower risk of PTB[19] This is likely owed to the lesser volume of cervical tissue removed during a LLETZ procedure relative to that of a KCB. The depth of tissue excised during a LLETZ procedure directly corresponds to the risk of PTB, therefore it is logical that the greatest risk of PTB is more commonly seen following multiple LLETZ procedures as opposed to a single LLETZ[31]. Further to this, the risk of PTB applies not only to the first post-excisional pregnancy but to all subsequent pregnancies thereafter[32]. The interval from LLETZ procedure to pregnancy and its impact on PTB has been discussed in various studies and several studies have reported no significant difference in the incidence of PTB irrespective of the time interval between cervical excision and conception[27, 33, 34]. It can be concluded that the risk of PTB does not decrease with an increase in time interval from the procedure.

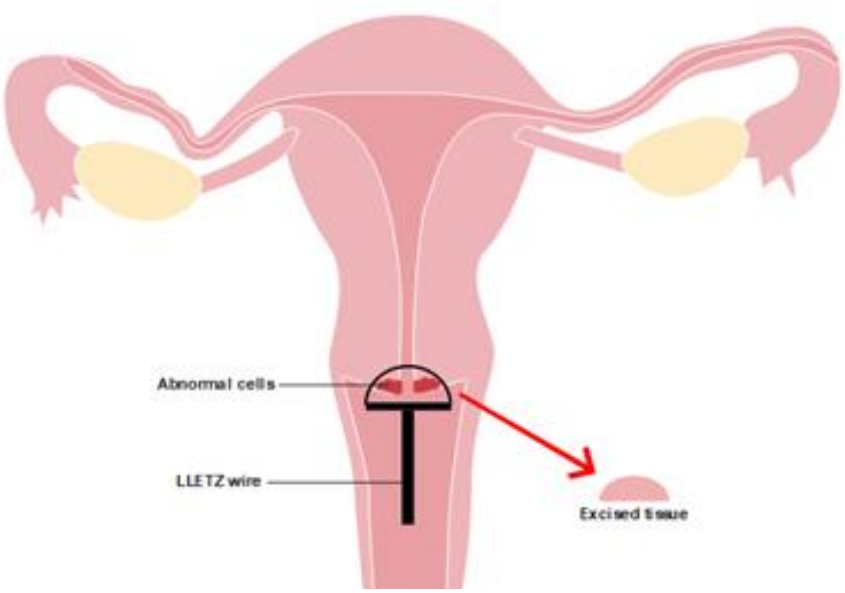

Figure 2: Large loop excision of the transformation zone

1.4.3 RADICAL TRACHELECTOMY

Radical trachelectomy involves the removal of the cervix, the superior portion of the vagina and the parametrium, and often incorporates the surrounding lymph nodes. This technique is more invasive than KCB and LLETZ procedures and is performed either vaginally or abdominally. The vaginal approach is composed of a laparoscopic phase to perform a pelvic lymphadenectomy followed by a vaginal phase. The abdominal approach involves more radical parametrial and paracervical resection than the vaginal approach. A cervico-isthmic cerclage is often placed at the end of the procedure[35]. Complications of the procedure include ureteral injuries, peritonitis and the formation of urinary tract fistulae[36]. Radical trachelectomy also increases the risk of PTB, threatened PTB, premature rupture of membranes and second trimester miscarriage in any subsequent pregnancies[35]. It has been hypothesised that the excisional procedure causes disruption to the mechanical structure of the cervix. This causes an increased susceptibility to ascending infection, and the resulting inflammatory processes can lead to PTB[37].

1.5 PREDICTING PRETERM BIRTH

Spontaneous preterm birth is multifactorial and the prediction of its occurrence is not always possible due to our lack of understanding of the pathophysiology. There are two main populations considered, asymptomatic and symptomatic, for which there are varying methods of PTB prediction. Those who are symptomatic present with threatened preterm labour including symptoms such as tightenings, abdominal pain, back pain, pelvic pressure and per vaginal bleeding or discharge. The most commonly used methods of PTB prediction in UK clinical practice are mid-trimester transvaginal ultrasound CL screening and quantitative fetal fibronectin (fFN). Other proposed methods of prediction include biomarkers, cervicovaginal fluid (CVF) acetate and the composition of the vaginal microbiome. Though several methods have been proposed, no single method alone has been effective in the prediction of sPTB. Therefore, the concomitant use of clinical presentation, biomarkers and CL screening is currently the most appropriate method of prediction. A newly released application, the quantitative instrument for the prediction of PTB (QUiPP) app considers the multifactorial nature of sPTB to calculate a percentage risk of sPTB. The ability to accurately predict the risk of sPTB during pregnancy not only provides a guide for management, avoiding the risk to health and cost-implications of unnecessary treatment, but can also serve as reassurance to low-risk women.

1.5.1 TRANSVAGINAL ULTRASOUND

Using transvaginal ultrasound to screen for CL requires the insertion of an ultrasound probe into the vaginal anterior fornix and the visualisation of the cervix in the sagittal plane (Figure 3)[38]. Serial CL screening using a transvaginal ultrasound scan (TVUSS) in the second trimester is a predictor of sPTB in high-risk women[39]. In symptomatic women over 30+0 weeks, CL screening is used to predict the likelihood of PTB within 48 hours where a CL<15mm indicates the need for treatment and a diagnosis of preterm labour (PTL)[40]. In asymptomatic women, a CL less than 25mm is considered an indication for intervention and many studies as well as NICE guidance favour this threshold[15, 16, 41]. This CL threshold corresponds to the 10th percentile at 24 weeks, and has a positive predictive value (PPV) of 17.8% and negative predictive value (NPV) of 97.4% for prediction of PTB <35 weeks in women with a previous PTB[42]. A 2001 study supported these findings and further recommended the use of the 25mm threshold for intervention[16]. In asymptomatic women with prior cervical surgery, mid-trimester CL <25mm has a PPV of 30% and a NPV of 95% in predicting sPTB <35 weeks[43].

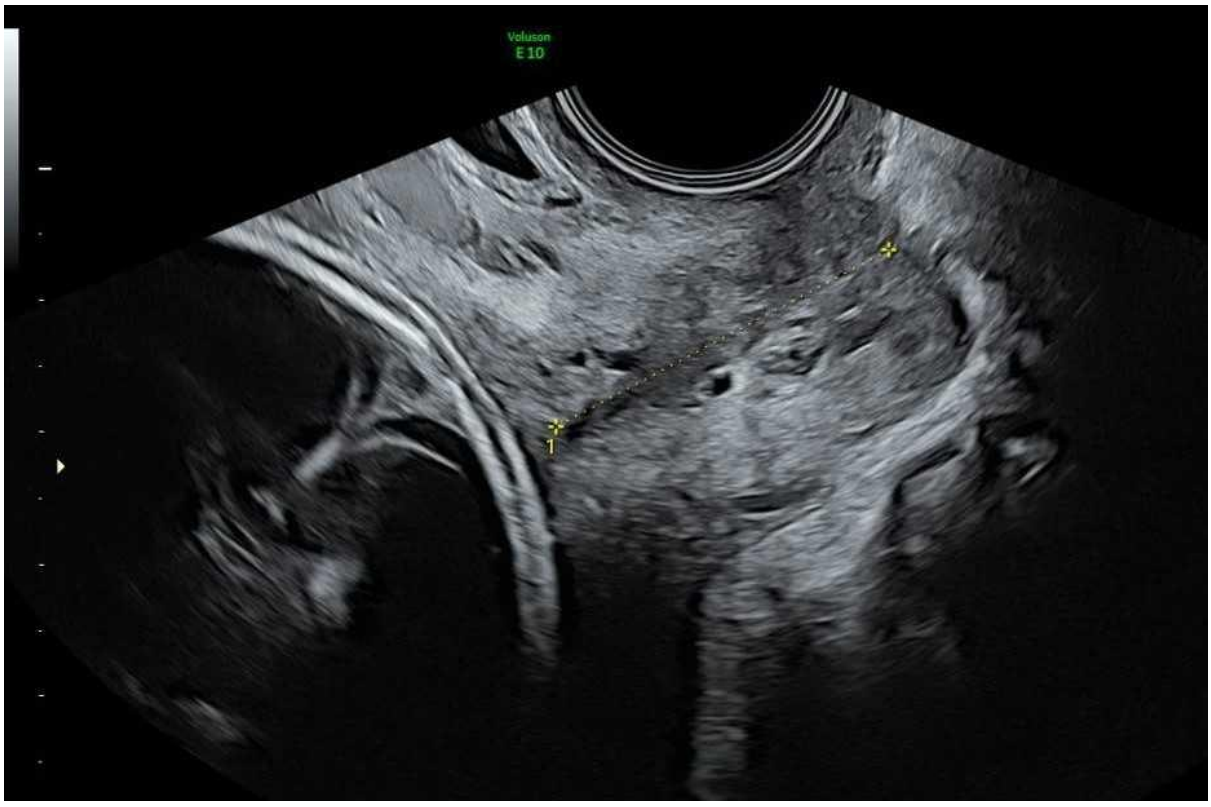

Figure 3: Normal cervical length measurement

Ultrasound-detectable markers that can indicate the need for intervention are i) funnelling of the cervix and ii) the presence of amniotic fluid sludge. These indicators are recommended for the screening of high-risk women in specialist PTB prevention clinics in the UK[44].

1.5.1.1 AMNIOTIC FLUID SLUDGE

Amniotic fluid sludge is hyperechogenic matter or cell debris near the internal os, composed of inflammatory cells from the placental microbiome or ascending infection and suggestive of an intra-amniotic infection (Figure 4)[39]. It is an independent risk factor for PTB in asymptomatic high-risk women and is associated with an earlier gestational age at delivery, lower birthweight, admission to the NICU and an increased risk of neonatal death[45]. In predicting PTB <28 weeks, the combination of CL <25mm and amniotic fluid sludge improves prediction over CL screening alone with odds ratios of 14.8 and 6.8 respectively[46]. Therefore, combining the two may allow for the identification of more PTBs[47].

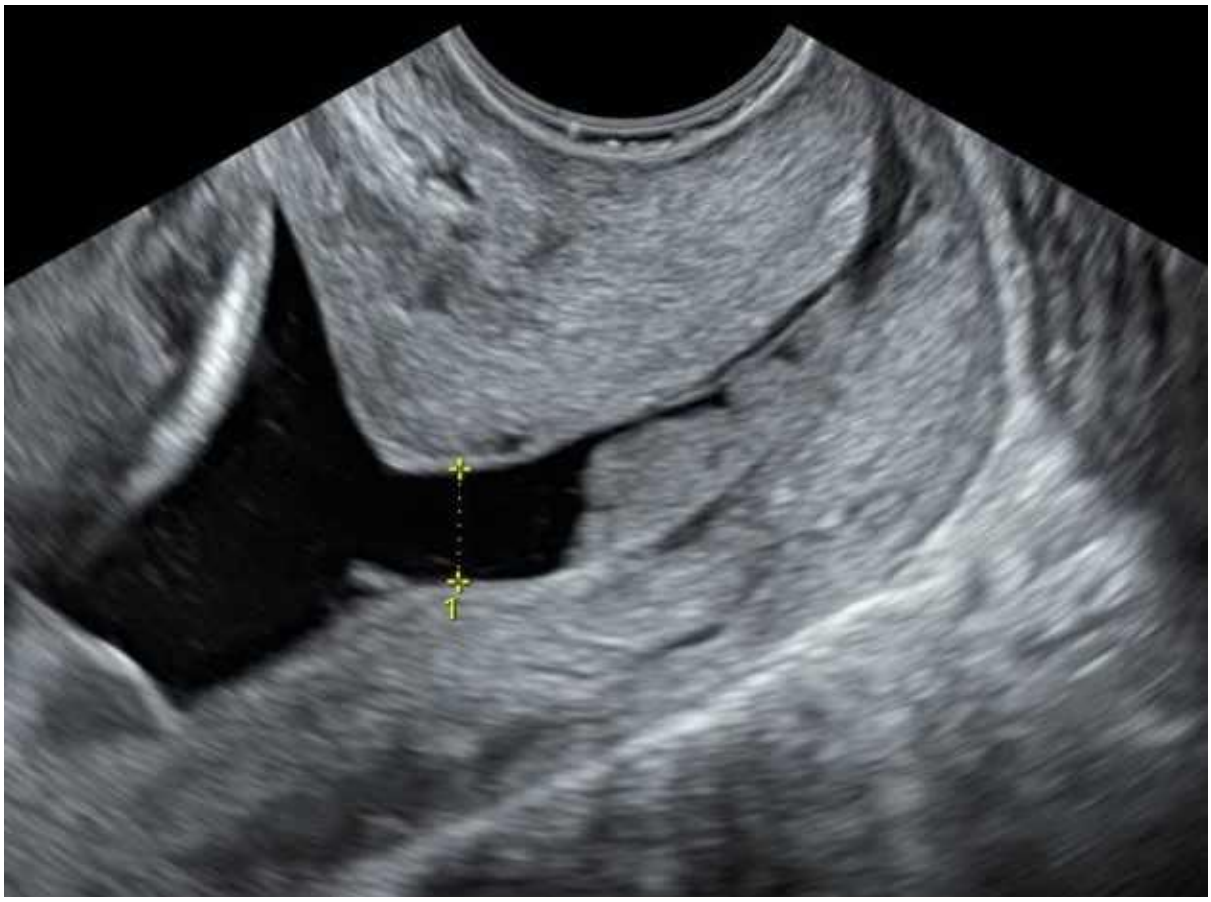

Figure 4: Amniotic fluid sludge

1.5.1.2 FUNNELLING

Funnelling of the cervix is dilation of the internal os allowing the protrusion of membranes into the endocervical canal producing either a U- or V-shape on TVUSS (Figure 5)[48]. Funnelling may be present spontaneously or can be assessed or further pronounced by the ultrasound operator applying fundal pressure and observing for a widening funnel-shape at the internal os. Care must be taken to avoid wrongly identifying a pseudo-funnel as a true funnel, where the lower uterine segment appears to form a funnel above a cervix of adequate length[49]. Studies present conflicting evidence as to whether it is an effective predictor of PTB. Some studies state funnelling is associated with an increased risk of sPTB in asymptomatic high-risk women[48], this is concluded in a 2018 systematic review[50]. Contradictory studies claim there to be no independent association of funnelling to PTB and therefore it provides no greater predictive advantage than that of CL screening alone[16, 51].

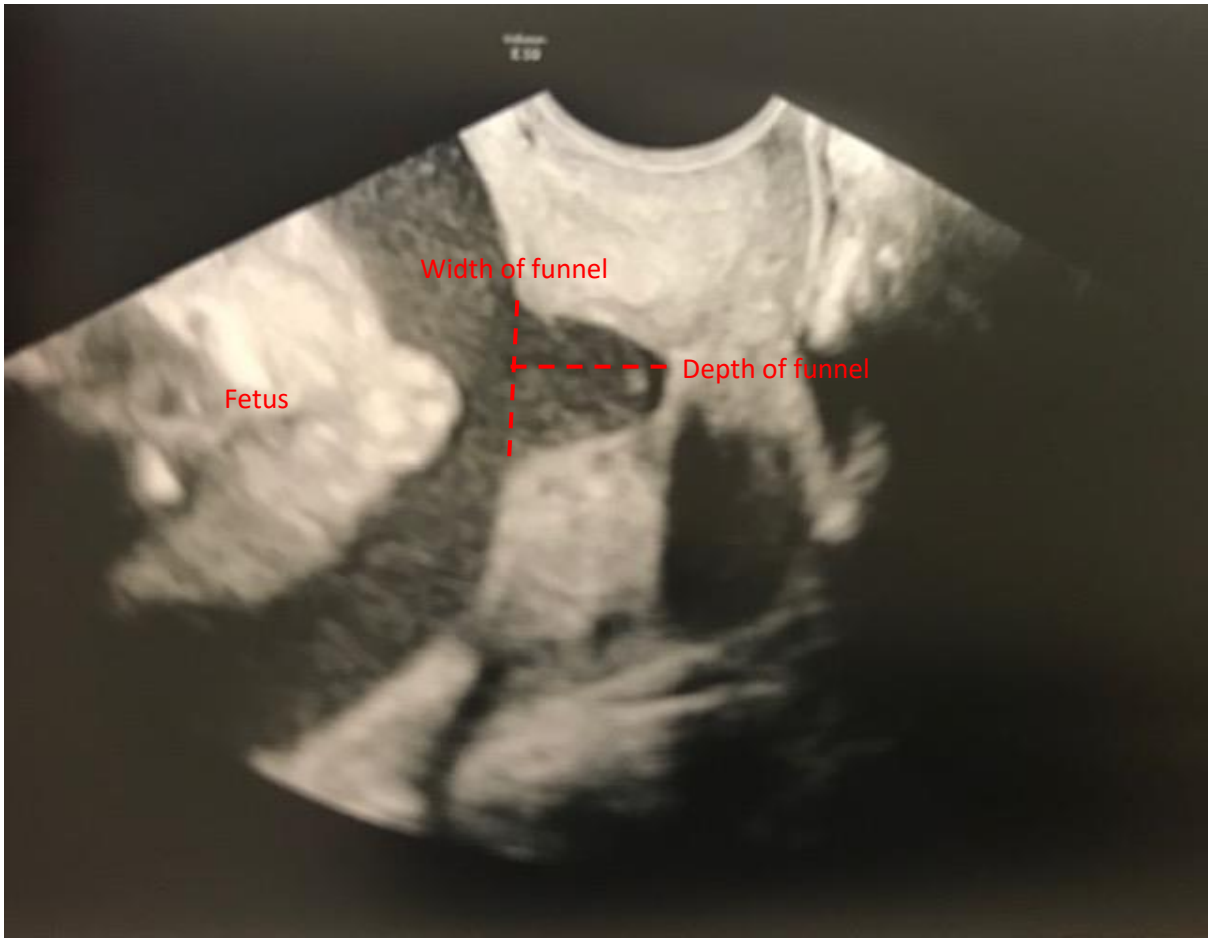

Figure 5: Ultrasound image of cervical funnelling

1.5.2 FETAL FIBRONECTIN

Fetal fibronectin is an ECM glycoprotein, released from between the decidua and chorion, present within the CVF until 18 weeks' gestation beyond which it is no longer detectable.

Presence of the glycoprotein in the CVF beyond 18 weeks is indicative of mechanical or inflammatory pathology associated with PTB. In symptomatic women over 30+0 weeks, where TVUSS is not available, fFN can be used to predict PTB within 48 hours with a threshold of 50ng/ml to diagnose PTL and offer treatment[40]. More recently the use of quantitative fFN (the absolute concentration of fFN), which allows for the use of multiple fFN thresholds, has been studied for the prediction of PTB within 7-14 days[52]. This method can be used for symptomatic women with cervical dilatation <3mm between 22+0 and 35+6 weeks and may allow for differing thresholds for offering treatment[53]. A study of asymptomatic high-risk women, including those with previous cervical surgery, demonstrated the benefit of multiple fFN thresholds[54]. Women with fFN <10 ng/mL could be considered low risk of PTB <34 weeks based on a high sensitivity and NPV, and a higher risk threshold of 500 ng/mL may be more appropriate with a positive likelihood ratio (LR) of 12[54]. In addition, the use of fFN alongside serial CL screening has potential to improve the predictive value over CL screening alone[39], though not all UK specialist clinics opt to use fFN alongside routine screening in high risk patients. However, the fFN value can be affected as a result of disruption to the cervix through sexual intercourse, digital examination or TVUSS[53]. In practice, fFN is used less frequently in asymptomatic women compared to symptomatic women, this may be due to the uncertainty surrounding the most appropriate management of this cohort.

1.5.3 QUiPP APP

The QUiPP app was designed by King's College London to calculate the risk of sPTB at various gestational ages in both symptomatic and asymptomatic women. The algorithm uses transvaginal ultrasound CL, patient history, uterine activity and quantitative fFN to calculate a percentage risk of delivery within 1, 2 and 4 weeks and the risk of sPTB <30, <34 and <37 weeks. The QUiPP app has been used in practice to communicate the risk of sPTB to patients and determine when hospitalisation may be necessary for high-risk women. A recent study of asymptomatic women at risk of PTB due to a either a previous PPROM, late miscarriage or sPTB, concluded that the applying the recommended >10% treatment threshold to the QUiPP app would double treatment rates in this cohort, many of which may be unnecessary interventions[55]. However, further studies may be required to determine the use of the QUiPP app for planning and appropriately timing preventative interventions in women with prior cervical surgery[56]. In addition to this, further studies would be useful to determine an appropriate treatment threshold for this cohort of women.

1.5.4 PHOSPHORYLATED INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-1

Phosphorylated insulin-like growth factor binding protein-1 (PIGFBP-1) is synthesised and secreted by the placenta into CVF in response to the onset of uterine contractions. As a result, it is a predictor of imminent PTB but its use is limited as a long-term predictor of PTB[52]. Actim partus is a clinical test using monoclonal antibodies to detect PIGFBP-1 in the CVF of symptomatic women after 22+0 weeks, however there is currently insufficient evidence to recommend its use in practice[53]. A study of PIGFBP-1 demonstrated an inferior PPV of 18.6% relative to 60% for placental alpha-microglobulin-1 (PAMG-1) for predicting PTB within 7 days in women with threatened PTL[57]. PIGFBP-1 also has low predictive accuracy for PTB prior to 34 and 37 weeks in asymptomatic women[58] and it does not meet the criteria for a clinical test to predict sPTB in this cohort[59].

1.5.5 PLACENTAL ALPHA-MICROGLOBULIN-1

Placental alpha-microglobulin-1 is a glycoprotein produced by the decidua and found in the amniotic fluid. The glycoprotein is present in CVF at the onset of labour, likely owed to either early contractions or the intra-amniotic inflammation that is more common during labour than throughout the earlier stages of pregnancy[60]. The increase in pressure associated with uterine contractions could bring about a leak of amniotic fluid through pre-existing pores in fetal membranes. Alternatively, inflammation may lead to the development of small perforations in fetal membranes, again allowing for the leak of amniotic fluid, detectable within the CVF. The Partosure test, which detects PAMG-1 in vaginal secretions, has recently been studied for its use in predicting PTB in symptomatic women with cervical dilation <3mm between 20+0 and 36+6 weeks of pregnancy[53]. PAMG-1 has demonstrated statistical significance in predicting preterm delivery within 48 hours, 7 days and 14 days of the test as well as the occurrence of sPTB prior to 35 weeks in women with a negative fFN[61]. A study of 383 women with intact membranes and cervical dilation <3cm between 20+0 and 36+6 weeks demonstrated a PPV of 60% and NPV of 97.7% for predicting sPTB within 7 days[57]. The Partosure test also offers the advantages of a quicker result turnaround than that of fFN and it is performed without the use of a speculum which increases both ease of testing and patient comfort[60]. However, due to insufficient evidence it is currently not recommended for use in UK clinical practice[53].

1.5.6 CERVICOVAGINAL FLUID ACETATE

Cervicovaginal fluid acetate is produced in large amounts in the vaginal microbiota and may be utilised in the prediction of PTB[52]. Studies reporting the effectiveness of acetate in

predicting PTB are limited, though some existing studies have considered its use for women symptomatic of PTL. In symptomatic cases, it has been reported that CVF acetate presents as good a predictive value as CL screening and fFN for onset of labour prior to 37 weeks or within 2 weeks of testing[62]. A combination of the three further enhances the prediction of PTB <37 weeks with a positive likelihood ratio (LR) of 5.0 and negative LR of 0.2[62]. Further studies are required to determine whether CVF acetate could be effective as a clinical test, though it is unlikely to be of use in a background population of asymptomatic women at high risk of PTB due to prior cervical excision. CVF acetate has other limitations including its use as a predictor of PTB when used early in pregnancy for those not at immediate risk.

1.5.7 VAGINAL MICROBIOME

The future of prediction of SPTB in asymptomatic women may include the use of the vaginal microbiome. It has potential as a predictor of PTB, though the practicalities of bacterial DNA sequencing are still being developed[52]. In a normal, healthy pregnancy only a few lactobacillus species, of which there are 5 community state types (CST), are expected within the vaginal microbiome. It has been observed that women who deliver preterm, have a lesser diversity in the vaginal microbiome between 15-20 weeks' gestation, relative to those who proceed to deliver at term. After 20 weeks, little difference can be found between women with term and preterm outcomes and therefore the utility of the vaginal microbiome as a predictor of PTB decreases beyond this point[63]. These findings are supported by another study that described the predominance of CST IV (diverse species) and an overall paucity of lactobacillus, in association with a second trimester short cervix and subsequent PTB[64]. This study collected samples predominantly in African-American women, on average 4 weeks later than a similar study by Kindinger *et al.*[65] This study found an over-representation of CST III (L.iners) at 16 weeks' gestation, in samples largely from Caucasian women that went on to deliver before 34 weeks[65]. This demonstrates the variability of the vaginal microbiome by ethnicity, and its further changeability throughout pregnancy.

1.6 PREVENTING PRETERM BIRTH

As sPTB is multifactorial in nature, there are several proposed mechanisms to prevent its occurrence. There is a large evidence base considering interventions in high risk women during pregnancy to prevent PTB. However, there is no consensus as to which is the most effective intervention[66]. In addition, these studies of high-risk cohorts are inclusive of women with prior sPTB, previous PPROM, previous mid-trimester loss, uterine anomalies, cervical surgery, cervical incompetence, short cervix and threatened PTL. Only a few studies include

an adequate sample size of cervical excision participants to perform subgroup analysis, however no such studies have attempted this. It is also not possible to extrapolate results for cervical surgery participants from other high-risk cohorts, as the mechanisms leading to PTB in these groups may differ leading to differential treatment effects. UK guidelines currently recommend the use of either cervical cerclage, vaginal progesterone (VP) or Arabin pessary to prevent PTB in women with prior cervical surgery[15]. Though there are some studies investigating the use of cerclage in this group, there are fewer investigating VP and the Arabin pessary. The lack of studies comparing the use of either VP of the Arabin pessary to a control group, and the comparison of these interventions to one another and cerclage, feeds into the uncertainty surrounding the management and optimisation of outcomes in these patients. Currently the evidence-base is unable to determine the most efficacious intervention or in which specific circumstances each may be most appropriate[67].

1.6.1 VAGINAL CERCLAGE

Vaginal cerclage is the most widely used method to prevent PTB in the UK[44], this may be due to the larger evidence base surrounding the use of cerclage over that of VP and the Arabin pessary. Current UK NICE guidance recommends the use of cerclage in women with prior LLETZ or cone biopsy and CL <25mm between 16 and 24 weeks of pregnancy[15]. This prophylactic cerclage acts mechanically, preventing the premature effacement of the cervix. Alternatively, a rescue cerclage can be sited in cases of threatened preterm labour to reverse dilation of the cervix and exposure of fetal membranes. The two main methods are Shirodkar and McDonald (Figure 6) with the option to use either monofilament such as nylon or a non-absorbable braided polyester suture. The McDonald technique involves the placement of a stitch at the cervicovaginal junction whereas a Shirodkar cerclage is placed more superiorly at the level of the cardinal ligaments, after reflection of the bladder. Both methods require regional anaesthesia as a minimum. The knot can be tied posteriorly to avoid bladder irritation or erosion caused by an anterior knot, though a posterior knot can present difficulties in removing the suture prior to delivery where the cervix may have migrated posteriorly. Insertion of a cerclage increases the risk of bacterial colonisation and in turn the risk of puerperal pyrexia. It is thought that monofilament confers a risk of bacterial colonisation though some have suggested it may be preferable to a braided cerclage in reducing the risk of PTB in patients with a short cervix[68]. Other risks associated with the insertion of a cerclage include causing uterine contractions, bleeding and infection which can result in either PTB or miscarriage[69]. Vaginal bleeding, an increase in vaginal discharge and abdominal pain may persist for up to 48 hours following the siting of a cerclage and a restriction on heavy lifting and/or sexual activity may be advised, though under normal

circumstances the literature does not support these recommendations[70]. Contraindications are inclusive of but not limited to signs of uterine infection, active vaginal bleeding and uterine contractions[15].

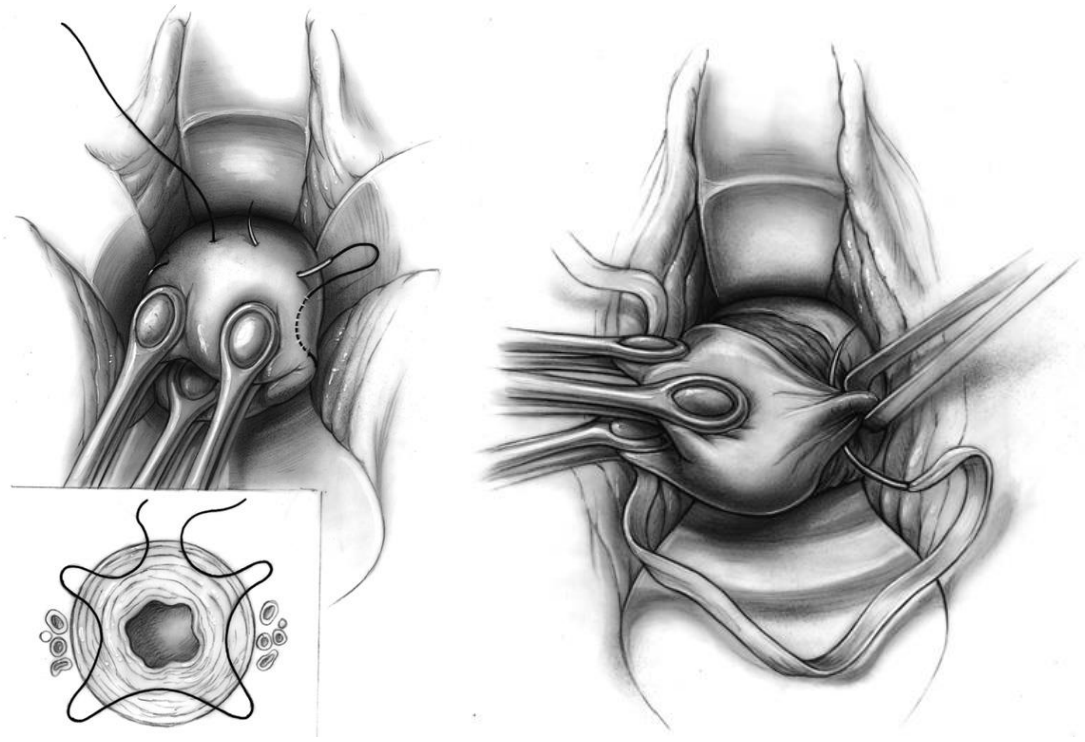

Figure 6: (a) McDonald cerclage technique[71] *(b) Shirodkar cerclage technique[71]*

The literature surrounding the use of cerclage in the treatment of high-risk singleton pregnancies is conflicting. A 2017 Cochrane review supported cerclage in women at high-risk of PTB, compared with expectant management. However, it stated that although data were limited for each clinical group, there was no evidence of effect of cerclage on short cervix indications[69]. Jarde *et al.*[72] determined cerclage did not significantly reduce PTB <34 weeks or <37 weeks in high-risk women compared to the control group, however subgroup analysis demonstrated a decreased risk of PTB <37 weeks in women with a short cervix. Both of these reviews considered studies with various individual criteria for the inclusion of high-risk participants. The definition of at-risk participants extended beyond prior excisional procedures to include; previous PTB, 2nd trimester loss or PPROM, physical examination or ultrasound-detected cervical changes, history of cervical cerclage and uterine malformations. Jarde *et al.*[72] included only one study of women with prior cervical surgery and therefore authors were unable to perform subgroup analysis. Though historically cerclage has been considered effective for women with prior cervical excision, other interventions may be more advantageous in this cohort.

1.6.2 VAGINAL PROGESTERONE

Progesterone is an inhibitor of the inflammatory process leading to PTB[73], a reduction in progesterone is responsible for inducing the cervical ripening in the onset of parturition[74]. Increasing local progesterone has been presented as one option to prevent the initiation of PTB by inhibiting the inflammatory process associated with PTB. VP causes a decrease in the proportion of decidual $CD8^{+}CD25^{+}Foxp3^{+}$ T cells, neutrophils and macrophages while increasing the proportion of CD4+ regulatory T cells, producing an anti-inflammatory microenvironment[75]. It is usually administered in the form of a vaginal pessary, inserted by the patient on a daily basis. Progesterone therapy can result in common side effects such as; irritation at the site of administration, headache, drowsiness, dizziness and oedema although these are usually mild[5]. A 2013 Cochrane review determined progesterone is effective in reducing PTB <34 and <28 weeks in women with a short cervix, though this included studies using either intramuscular (IM) or VP[76]. Similarly, a 2018 meta-analysis including 5 randomised controlled trials (RCT) comparing progesterone to placebo or no intervention, in singleton pregnancies with a mid-trimester short cervix, found VP significantly reduced the risk of PTB along with neonatal morbidity and mortality[77]. This is supported by a further meta-analysis demonstrating the ability of VP to reduce PTB <34, PTB <37 weeks and neonatal death[78]. In addition, the most recent review demonstrated the efficacy of progesterone in preventing PTB <34 weeks in asymptomatic high-risk women[79]. It was noted that the absolute risk reduction is most significant for women with a short cervix and therefore progesterone may present the greatest benefit in this group[79]. However, a large-scale multicentre randomised trial (OPPTIMUM study) demonstrated no benefit of VP in reducing the risk of PTB in high risk women due to either previous sPTB, previous 2nd trimester loss or a short cervix <25mm[80]. These findings are supported by the PROGRESS trial that also found no reduced risk of PTB or improved neonatal outcomes following the use of progesterone in women with a prior sPTB[81].

1.6.3 ARABIN PESSARY

The siting of an Arabin pessary in high-risk singleton pregnancies is a less invasive and often patient-favoured alternative to cerclage[82]. It is inserted longitudinally with the lubrication of antimicrobial cream or gel, unfolded within the vagina and pushed upwards towards the vaginal fornix to surround the cervix. Following the initial siting of the pessary, the adequacy of its placement is assessed along with CL at follow-up appointments. Removal takes place routinely at 37 weeks[83]. Although the exact mechanism is unknown, theories suggest the pessary contributes to a relief of pressure on the internal os due to an alteration in the weight distribution of the uterus, or alternatively, it acts as an added barrier

to infection[84]. The success of the Arabin pessary in preventing delivery before 34 weeks may also be due to an alteration in the uterocervical angle, which becomes more acute and results in a slight cervical elongation, sacralisation of the cervix and a reduction in funnelling[85]. This acts to reduce the contact of fetal membranes with the vagina. The most commonly reported side effect is a noticeable increase in white, non-offensive vaginal discharge[86]. Some patients report discomfort[87] and others may experience displacement of the pessary. A magnetic resonance imaging (MRI) observational study determined the rate of displacement of the pessary is notably higher in patients post-KCB than in other groups[85]. Despite these side effects, the Arabin pessary presents a cost-effective and non-invasive management option for preventing PTB, without the need for anaesthesia or repeated intervention. Two RCTs treating women with a short cervix at 20-24 weeks' gestation determined no greater efficacy of the Arabin pessary over expectant management in the prevention of sPTB <34 weeks gestation[87, 88]. These results were in contrast to another RCT vouching for the efficacy of the Arabin pessary in preventing sPTB <34 weeks gestation[89]. There are no studies comparing the efficacy of the Arabin pessary to either control or comparator groups specifically in women with a short cervix due to a prior excisional procedure. It is therefore difficult to draw conclusions as to the effectiveness of the pessary and how its performance compares to that of cerclage and VP in this group. Figure 7 shows the Arabin pessary.

Figure 7: Arabin pessary (a) inner diameter (b) outer diameter (c) lateral view[89]

1.6.4 TRANSABDOMINAL CERCLAGE

A transabdominal cerclage (TAC) is sited typically prior to pregnancy, though they can be sited during early pregnancy. They are recommended in cases of large excision, such as radical trachelectomy, where a significant portion of cervical stromal tissue has been removed, thus greatly impacting on the integrity of the cervix. A TAC can also be used in cases of significant anatomical defects or a prior failed transvaginal cerclage. In a similar approach to the Shirodkar cerclage technique, TAC involves the placement of the suture at the level of the internal os necessitating delivery via caesarean section. The open technique requires peritoneal entry and general anaesthesia resulting in a prolonged recovery time and increased maternal risk over that of vaginal cerclage techniques[5]. Alternatively, a TAC can be placed laparoscopically with the aim to reduce the risks and recovery time associated with open surgery while closely replicating the technique, without routine reflection of the bladder[90]. The suture may be sited in either the anteroposterior or posteroanterior direction, with an anterior knot causing potential bladder erosion but a posterior knot increasing the risk of adhesions in the pouch of Douglas. Most of the risks associated with the procedure are related to the cerclage itself, however the laparoscopic technique does provide additional risk of visceral and major blood vessel damage. Some complications associated with TAC, regardless of the technique used, include induction of PTB, intrauterine death, premature rupture of membranes, suture migration, uterine rupture and intrauterine growth restriction, though these are rare[91]. Although only some specialists currently site TACs laparoscopically, it is likely this technique will be the future of transabdominal cerclages. Figure 8 demonstrates the location of a cerclage resulting from each technique[90].

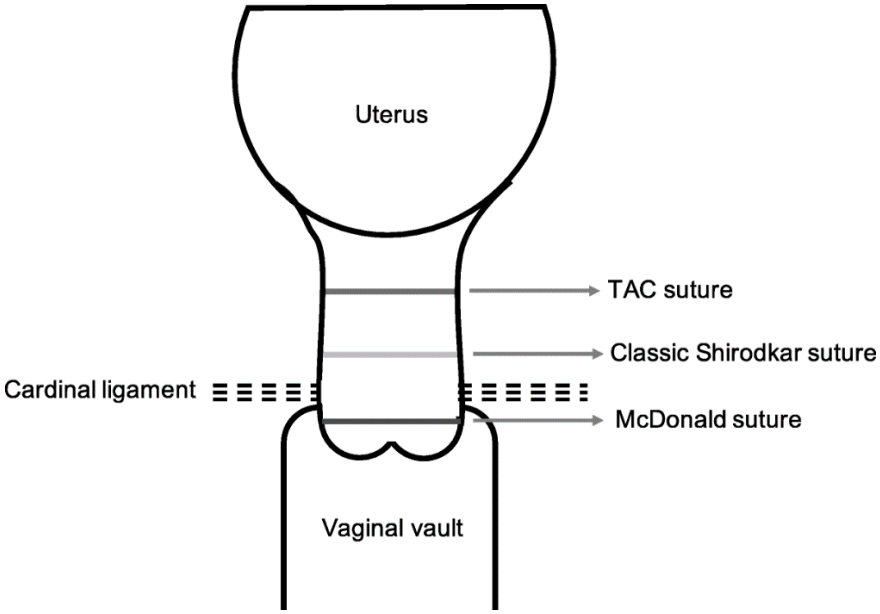

Figure 8: Cerclage suture locations

1.6.5 COMBINED THERAPIES

Interventions can be combined throughout pregnancy in a further attempt to prevent PTB. The use of an Arabin pessary concomitantly with VP has been studied in high risk pregnancies, including those with prior cervical surgery. Stricker *et al.*[92] suggested the potential benefit of combining pessary and progesterone, although the study presented no benefit in the reduction of PTB rate <34 weeks' gestation, it did demonstrate a shortening in the NICU stay following combined therapy compared to the use of VP alone. Nicolaides *et al.*[87] in their 2016 RCT also found no additional benefit in combining VP with an Arabin pessary for the prevention of sPTB. However, only women with CL<15mm received the combination whereas those in the comparison group had a CL of 15-25mm, this could have been a potential source of bias as a shorter CL confers a greater risk of PTB. Despite this, these findings were supported by those of another 2016 randomised open-label trial[93].

There are few studies detailing the outcomes resulting from the combination of an Arabin pessary and cerclage in women with prior conisation of the cervix. Wolnicki *et al.*[94] demonstrated no statistically significant benefit to this combination in prevention of sPTB <34 weeks' gestation, however neonatal outcomes including birthweight and shortened length of NICU stay were improved, though the small sample size and retrospective design may indicate the presence of confounders. These results are similar to those seen in the Stricker *et al.*[92] study of the Arabin pessary combined with VP and both studies present a case for the combination of interventions for the improvement of neonatal outcomes if not to prolong gestation at delivery.

In cases where progressive shortening is identified following VP administration in subsequent TVUSS assessment of CL, it may be necessary to site a cerclage. Or conversely in patients with a prior cerclage and further cervical shortening, VP may be required as an adjuvant preventative measure. In these patients, it must be determined whether VP is of further benefit once a cerclage has been sited or whether the combination of the two interventions is futile. Roman *et al.*[95] in a retrospective cohort study found a statistically significant increase in gestation of delivery following combined therapy relative to cerclage alone. Again, there are a lack of studies considering the use of both VP and cerclage prophylactically in women with prior excision of the cervix. Many of the existing studies either use different cohorts or inadequate sample sizes to draw conclusions. Larger prospective randomised trials are required to determine the potential benefits of this combination of interventions in preventing PTB.

Some publications have studied the use of a combination of all three interventions, cerclage, Arabin pessary and VP in order to determine whether increasing the number of interventions

confers a decrease in risk of PTB. One study demonstrated a similar efficacy of this combination of interventions, relative to groups receiving pessary and VP, cerclage and VP or VP alone, in reducing sPTB <37 weeks[96]. Therefore, the combination of all three interventions may increase the incidence of side effects and the cost of treatment in these patients, while providing no significant benefit to obstetric outcomes. A Jarde *et al.*[97] systematic review of studies using a variety of combinations of interventions found no determinable benefit nor risk for any combination. The use of multiple concurrent interventions to manage sPTB in women with prior excisional procedures is not widely studied and therefore it is difficult to draw conclusions from the available evidence. Further studies are required to determine the potential benefits of using multiple interventions during a single pregnancy.

1.6.6 17- ALPHA HYDROXYPROGESTERONE CAPROATE

Weekly IM injections of 17-α hydroxyprogesterone caproate (17-OHPC) have been studied as a potential preventative measure in women with a short cervix. The mechanism by which 17-OHPC impacts PTB is not well understood, but it does not appear to act as VP does to inhibit inflammatory processes[75]. The evidence surrounding the use of 17-OHPC is conflicting, though there is evidence for 17-OHPC reducing rates of PTB in women with prior sPTB[98], this has only recently been replicated in participants at risk due to a short cervix. A 2013 review by Romero *et al.*[74] concluded there is no additional benefit in using 17-OHPC to prevent PTB in women with a short cervix. This assertion has been supported by a 2015 RCT[99], though the study design included administering 17-OHPC at gestations later than recommended. No adverse maternal effects beyond mild injection site reactions, such as bruising and swelling, have been consistently reported following 17-OHPC use[100]. Overall the evidence is conflicting surrounding the use of 17-OHPC in women with a short CL and therefore it is not currently recommended in the NICE guidance. However, the 2021 EPPPIC review demonstrated the efficacy of 17-OHPC in reducing PTB <34 weeks in high risk women, and may have a greater impact in those with a short cervix[79]. These findings may present implications for future practice.

1.6.7 LIFESTYLE AND NUTRITION

Lifestyle changes can be key aids to reducing the risk of PTB. Maternal smoking is directly associated to the incidence of PTB[101], therefore stopping or significantly reducing cigarette consumption during pregnancy can further reduce the risk. Stress has also been widely linked to the occurrence of sPTB[102], and consequently recommendations including obtaining sick leave from work are occasionally advised. In cases of complications or threatened PTL,

historically bed rest was discussed with patients despite lacking evidence of its benefits. More recent studies have shown not only a lack of benefit to reduction in maternal activity but also the potential for both psychological and physiological adverse effects[103]. As a result, activity restriction is not recommended in clinical practice[104]. Several publications discuss coitus during pregnancy and the potential increased risk of sPTB. Studies have hypothesised this risk to; the cervical ripening properties of the natural prostaglandins found within sperm, female orgasm and its ability to stimulate uterine contractions, risk of infection especially following the siting of a cerclage, or in the case of short cervix, any direct mechanical force on the cervix that may contribute to further cervical instability[105]. Recommendations surrounding the restriction of sexual intercourse must be considered by clinicians on a case-by-case basis. However, in cases of significant cervical shortening, restriction is currently advised until further studies demonstrate safety data to the contrary[106]. In addition to lifestyle modifications, nutritional supplementation can be used to further reduce the risk of PTB in high risk women. A recent Cochrane systematic review found an 11% reduced risk of PTB <37 weeks and a 42% reduced risk of PTB <34 weeks when pregnant women received omega-3 long-chain polyunsaturated fatty acid (LCPUFA) supplements throughout pregnancy[107]. As a result, a minimum of 500mg daily omega-3 LCPUFA supplements are often recommended throughout pregnancy from 12 weeks, especially in women at increased risk of PTB. It is also possible to obtain an adequate amount of omega-3 LCPUFA from the diet, provided a substantial portion of oily fish is consumed per week.

1.7 CURRENT UK GUIDANCE

The current UK NHS guidance is outlined in the document entitled saving babies lives version 2[67], which describes the referral criteria, follow-up, screening and management of women at risk of PTB. It states, all women with a prior single LLETZ with >10mm depth of tissue removed, multiple LLETZ procedures or a single KCB are considered at intermediate risk of PTB and must be referred to a specialist clinic by 12 weeks' gestation. Transvaginal ultrasound screening of CL must take place a minimum of once between 18-22 weeks' and all women should receive follow-up at 24 weeks to determine whether they can safely be discharged back to routine antenatal care. Fetal fibronectin may be used as an adjunct to TVUSS for prediction of PTB risk in those specialist clinics that have the expertise to perform such tests[67]. NICE guidance supports the statements within saving babies lives and recommends preventative intervention, in the form of cerclage or VP, for women with a CL <25mm in mid-trimester TVUSS screening[15]. Saving Babies' Lives also states that discussions should be held with these patients, highlighting the current evidence for each

intervention, including progesterone, Arabin pessary and cerclage, and the potential risks of receiving no intervention[67].

1.8 SYSTEMATIC REVIEWS

Systematic reviews involve combining published, peer-reviewed evidence on a particular research topic, allowing for a clear and concise summary of the available evidence. Review methods including; search criteria, inclusion and exclusion criteria, PICO, risk of bias assessment and the techniques to be used in data synthesis and analysis must be pre-planned and documented in the form of a research protocol. The PRISMA-P statement details the required reporting items for a review protocol[108]. These protocols must then be submitted to PROSPERO, an international database for the registering of review protocols. The ability to search for registered reviews within PROSPERO prevents the unnecessary duplication of reviews and can help promote research collaboration and transparency throughout the review process[109]. The highest standard of systematic review is a Cochrane review, involving meticulous planning and highly structured format allowing for publication within the Cochrane database of systematic reviews. However, as Cochrane reviews include only RCTs, some subjects are not suitable for this type of review. When adequate standards for a systematic review are met, the conclusions can be used for decision-making. Particularly within healthcare, the findings of a systematic review can influence guidelines and directly impact clinical practice.

If adequate similarity and acceptable heterogeneity is achieved between the studies included in a systematic review, a meta-analysis can be performed to determine an overall effect size which increases the statistical power relative to a single study alone[110]. The strength of conclusions drawn from a meta-analysis is directly dependent on the quality of the included studies, for example a meta-analysis of well-conducted RCTs can produce a high level of evidence[111, 112]. However, the decision to undertake a meta-analysis must be taken with caution to avoid presenting misleading conclusions due to either low quality evidence or differing study designs[113]. Further to this, conclusions drawn from a review may be impacted by publication bias, where studies with positive findings are more likely to be published[114]. This highlights the importance of performing a GRADE assessment to consider the presence of publication bias and its potential impact on the conclusions of the review. Where studies are lacking, small in size or of inadequate study design, gaps in the literature can be highlighted, guiding future studies to address this[115]. A systematic review has been undertaken within a chapter of this thesis, to ascertain the availability and robustness of the evidence surrounding PTB prevention in women with prior conisation of the cervix.

1.9 RETROSPECTIVE COHORT STUDIES

Retrospective cohort studies consider a defined group of patients to look back at risk exposure, interventions and outcomes in order to draw conclusions. They are advantageous in studies of a particular exposure where the cohort may be limited in size, such as prior LLETZ or KCB of the cervix. However, due to the retrospective nature of data collection from medical records, several healthcare professionals may have been involved in the care of study participants. This may introduce some elements of inconsistency, for example in the recording of relevant risk factors or ultrasound screening of CL which is highly operator-dependent. Although an observational study design does not provide the same strength of evidence as an RCT, due to potential bias from covariates and confounding factors, they are often utilised in the study of PTB interventions. A recent randomised feasibility study determined inadequate power to perform a two-centre RCT on a cohort of women with a mid-trimester short cervix due to the small number of eligible participants[116]. Women with successful outcomes in prior pregnancies due to a particular intervention may wish to receive the same intervention in subsequent pregnancies and this would present difficulties in randomising patients to an intervention. Therefore, a retrospective cohort study design was undertaken within this thesis. The study aimed to address the lacking evidence surrounding the prevention of PTB in women with prior conisation of the cervix, particularly surrounding the use of VP and the Arabin pessary.

1.10 SUMMARY

Excisional procedures of the cervix represent a significant burden of sPTB annually. Optimising the management of these patients has the potential to significantly reduce consequent neonatal morbidity and mortality. The current literature surrounding excisional procedures of the cervix is growing but remains limited and it is unknown whether VP, cerclage or the Arabin pessary is most efficacious in preventing PTB in these women. The evidence used in clinical guidance and decision-making is based on either studies of women with a prior sPTB, short CL or high-risk cohorts with combinations of risk factors rather than women at increased risk of PTB due to prior cervical surgery. Further studies in this area are required to determine the optimal follow-up and management of these patients.

1.11 HYPOTHESIS AND AIMS

1.11.1 HYPOTHESIS

This thesis investigated the interventions used to prevent PTB by testing the following hypothesis:

(i) Excisional procedures of the cervix present an increased risk of PTB

(ii) Vaginal cerclage, VP and the Arabin pessary are all effective prophylactic interventions in the prevention of PTB in women with prior KCB or LLETZ of the cervix

(iii) VP or the Arabin pessary may demonstrate greater efficacy over cerclage in preventing PTB in this cohort of women

1.11.2 AIMS

The aims of this thesis were as follows:

(i) To conduct a systematic review to determine the current recommended intervention(s) to prevent PTB in women with prior excisional procedures of the cervix

(ii) To complete a retrospective cohort study, using single-centre clinic data, to establish the risk of PTB in women who have undergone prior KCB or LLETZ procedures

(iii) To synthesize the clinic data in order to determine which intervention presents the greatest efficacy in preventing PTB in this cohort of women

CHAPTER 2 – EFFICACY OF CERCLAGE, PROGESTERONE AND PESSARY IN PREVENTING PRETERM BIRTH IN WOMEN WITH PRIOR EXCISION OF THE CERVIX: A SYSTEMATIC REVIEW

2.1 BACKGROUND

Existing studies have demonstrated an increased risk of PTB in women with prior KCB or LLETZ procedures to the cervix. The majority of neonatal morbidity and mortality worldwide is a direct result of PTB[8]. KCB and LLETZ procedures are performed following the identification of cervical intraepithelial neoplasia grades 2 or 3 in women undergoing routine cervical screening. KCB is thought to confer a greater risk of PTB than LLETZ procedures[19], though some women may undergo several LLETZ procedures which further increases their risk due to the removal of a greater volume of cervical tissue[31]. The PTB risk applies to not only the first post-excision pregnancy but to all subsequent pregnancies[32] and therefore intervention to prevent PTB may be necessary in all future pregnancies for this cohort of women.

UK guidance, from the Saving Babies' Lives care bundle version 2, considers women with either a previous LLETZ >10mm in depth, multiple LLETZ procedures or a KCB as an intermediate risk of PTB[67]. It is advised that pregnant women meeting the above criteria should be referred to specialist PTB prevention clinics from 12 weeks' gestation and should receive transvaginal ultrasound screening of CL between 18-22 weeks' gestation[67]. Those women that are identified to have a CL <25mm on mid-trimester ultrasound screening are considered high risk and are offered intervention in the form of either VP, cerclage or Arabin pessary in an attempt to prevent the occurrence of PTB[15]. Some specialist PTB prevention clinics also use fetal fibronectin testing alongside CL screening to aid their risk assessment of these women.

A 2018 systematic review screened the guidelines of 16 developers globally, of which 8 endorsed the use of VP to prevent PTB in asymptomatic women with a CL <20mm on TVUSS prior to 24 weeks' gestation[117]. Table 1 details the referral, screening and management criteria for pregnant women with prior cervical surgery in various locations globally.

Table 1: Guidelines for prevention of PTB in high-risk pregnancies

Location	Criteria for screening/referral	Screening and gestation for TVUSS	Indication for intervention	Intervention type(s), dose	Additional info
UK[15, 67]	LLETZ >10mm depth 2 or more LLETZ Single KCB	18-22 weeks, Fetal fibronectin (where available)	CL <25mm	Cervical cerclage, Arabin pessary, vaginal progesterone 200mg nightly	Women given an intervention should remain under specialist clinic care until delivery and should undergo TVUSS of CL until 24 weeks.
Western Australia[118]	LLETZ >10mm depth 2 or more LLETZ Single KCB	16, 19 and 22 weeks	CL <25mm	Vaginal progesterone 200mg nightly	Continue treatment until 36 weeks' gestation. Women given an intervention receive weekly TVUSS until 23+6 weeks.
			CL <15mm	Cervical cerclage alone or in combination with vaginal progesterone 200mg nightly	
New Zealand[119]	LLETZ >10mm depth 2 or more LLETZ Single KCB	14-24 weeks	CL <25mm	Cervical cerclage	No indication for cerclage if prior KCB/LLETZ with a normal CL
Belgium[120]	None related to cervical surgery	14-24 weeks	Asymptomatic and CL <25mm	Vaginal progesterone 200mg once	"No beneficial or harmful effect of cerclage has been demonstrated in women with prior cervical surgery"
			Prior sPTB <32 weeks/recurrent 2nd trimester birth and CL <25mm	Consider cervical cerclage	
France[121]	None related to cervical surgery	16-24 weeks Fetal fibronectin	Asymptomatic CL<20mm	Vaginal progesterone	History-indicated cerclage is not recommended for women with a history of cervical surgery. Routine CL screening is not recommended.
Canada[122]	None related to cervical surgery	16-24 weeks	CL <25mm	Vaginal progesterone 200mg daily – this should also be offered to women as a "potentially superior" alternative to cerclage.	Continue treatment up to 34-36 weeks. Adding adjunct interventions i.e. cerclage/pessary to women already on progesterone is not recommended, with

					the exception of emergency cerclage.

A Cochrane review demonstrated the benefit of cerclage in managing high-risk singleton pregnancies, though authors were unable to draw conclusions for women with previous cervical surgery, and further stated that the question of whether cerclage is superior to other interventions remains unanswered[69]. Grabovac *et al.*[123] did not support the use of cerclage in preventing PTB for women with prior conisation of the cervix. Romero *et al.*[77] published a review supporting the use of VP to reduce the risk of PTB in women with a short mid-trimester CL. This is supported by the findings of the 2021 EPPPIC study published in the Lancet[79]. The evidence surrounding the use of the Arabin pessary is conflicting with one study supporting[89] and another disputing[87] its ability to prolong pregnancy in women with a CL <25mm. This can be seen to impact the high-risk pregnancy management guidelines globally, with only one of the locations, mentioned above, recommending the use of the Arabin pessary. Each of the aforementioned reviews considered the use of interventions to prevent PTB in different high-risk cohorts including women with a short cervix, previous PTB, and prior cervical surgery. In some cases, this has led to conflicting evidence. This highlights the need to consider these varying risk cohorts separately as we cannot assume all high-risk groups undergo the same mechanisms leading to PTB or demonstrate an equal response to interventions. However, despite the poor obstetric and subsequent neonatal outcomes associated with prior cervical surgery, there are a lack of reviews considering the prevention of PTB in a cohort of women with prior excisional procedures of the cervix in singleton pregnancies alone, specifically those receiving either pessary or progesterone. The results of large reviews with other risk groups, such as that of Alfirevic *et al.*[69] and Goya *et al.*[89], cannot be extrapolated to this cohort. There is also a lack of consideration for the differential risk groups within this cohort i.e. those receiving ultrasound-indicated treatment who are likely higher risk for PTB than those who do not develop a short cervix. This review aims to address this gap in the evidence-base.

2.2 Aims

The aim of this chapter is to identify studies that have analysed obstetric outcomes in singleton pregnant women with prior cervical surgery receiving either a cerclage, pessary or progesterone to prevent PTB. A secondary aim is to compare the efficacy of these interventions in this cohort of women.

2.3 METHODS

The systematic review protocol was registered on PROSPERO (CRD42021252327) accessed at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=252327.

2.3.1 SEARCH STRATEGY

Searches were conducted in February 2021 within Pubmed, Scopus and Medline databases. All search terms; “cervical surgery”, “cervical excision”, “LLETZ”, “LEEP”, “cone biopsy”, “conisation”, “conization”, “short cervix” and “high risk” were combined using the Boolean operator OR. A separate search was conducted using the same Boolean operator to combine the terms “cerclage”, “pessary”, “progesterone” and “17-OHPC”. The Boolean operator AND was then applied to combine the two separate searches. All articles were screened for the presence of these search terms within the title or abstract. Several synonyms have been used in publications to describe surgical procedures to the cervix. To ensure all possible terms were included, this was discussed with experts within research in obstetrics and gynaecology and pilot searches were carried out. The phrases “high risk” and “short cervix” were included to account for any studies that did not detail cervical surgery within the title or abstract but may have performed subgroup analysis for outcomes of interventions in this cohort. Restrictions for English language, human subjects and study type were applied. Restrictions were not made based on date of publication and therefore results include any relevant study published within or prior to February 2021.

2.3.2 ELIGIBILITY CRITERIA

Papers were screened for inclusion of participants with singleton pregnancies that had undergone prior KCB or LLETZ procedures and were treated with either vaginal cerclage (Shirodkar or McDonald), Arabin pessary, progesterone (vaginal, IM or oral) or a combination of these interventions during pregnancy. These interventions were compared to either a placebo, no intervention or another intervention. RCTs and observational studies (cohort and case-control) were included. Any reviews, editorials, books, letters and conference papers were excluded. We did not restrict searches based on date of publication. Although pessary and progesterone are more recent therapies, there has been little change in the management of high-risk patients using vaginal cerclage. Studies looking at outcomes in multiple pregnancies, women symptomatic of preterm labour and interventions of transabdominal cerclage or double (reinforcing) vaginal cerclage were excluded. Exclusions were also made for studies that did not report outcomes on gestational age at delivery or incidence of PTB.

2.3.3 STUDY SELECTION

Two independent reviewers (FP and AC) screened papers initially by title and abstract against pre-determined eligibility criterion. Full studies were then screened for eligibility of inclusion. Cases of uncertainty were discussed and disagreements between the two reviewers (FP and AC) were resolved by discussion and consensus with a third reviewer (AS).

2.3.4 DATA EXTRACTION

The following information was extracted from eligible studies by a single reviewer (FP), any cases of uncertainty were discussed with a second reviewer (AC). Authors were contacted for clarification of the cohort risk, indication for intervention and outcomes, where reviewers were unable to extract adequate detail from the study.

(i) Study design and data collection method
(ii) Population size and presence of PTB risk factors
(iii) Intervention type and comparator group
(iv) Obstetric outcomes
(v) Neonatal outcomes

The primary outcomes were PTB prior to 34 and 37 weeks. Secondary outcome measures included; PTB <32, <28 and <24 weeks, PPROM, onset and mode of delivery, livebirth/stillbirth, neonatal death, NICU admission, ventilatory support, use of surfactant, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, periventricular leukomalacia, sepsis, maternal mortality/harm and any side effects or adverse events as a result of the interventions[124].

2.3.5 RISK OF BIAS ASSESSMENT

Risk of bias and methodological quality of included studies was assessed by two separate reviewers (FP and AC) using a modified version of the Newcastle Ottawa quality assessment scale for cohort studies[125], as has been recommended previously by the Cochrane collaboration[126]. Under the comparability heading, participants with prior sPTB and those that developed a mid-trimester short cervix <25mm were considered to be at the greatest risk of confounding. Papers were assessed on their ability to alter inclusion criteria, exclude participants or adjust analysis of results to account for these factors. Two sections of the assessment were removed including demonstration that the outcome of interest was not present at the start of the study and demonstration that follow-up time was adequate. The outcomes of interest will not have been present at the time of intervention, as these were

carried out during pregnancy and follow-up cannot have occurred sooner than delivery, for which patients will likely have attended hospital. Therefore, the maximum score that could have been awarded using the modified Newcastle Ottawa tool was 7, indicating a low risk of bias.

2.3.6 GRADING OF EVIDENCE

Evidence was graded as either very low, low, moderate or high quality following the approach set out by the GRADE working group[127]. Grading of evidence was carried out by two independent reviewers (FP and AC). Each study was initially given a low grading due to the retrospective cohort study design, with the opportunity for upgrading following assessment based on risk of bias, inconsistency, indirectness of evidence and imprecision. As there were few studies included, formal assessment for the presence of publication bias was not carried out. An overall grade was determined for each of the following outcomes; PTB <34 weeks, PTB <37 weeks and neonatal mortality.

2.3.7 STATISTICAL ANALYSIS AND DATA SYNTHESIS

A narrative summary of the results of included studies, structured around the type of intervention, characteristics of the target population, the type of outcome and the content of the intervention was provided. I^2 was used to assess heterogeneity between studies where a result of <40% was considered acceptable. The odds ratios, 95% confidence intervals and relative risk were calculated for each of the main reported outcomes per study, using the Cochrane collaboration software Revman 5.4.1[128]. Data were presented as forest plots. Studies that reported outcomes for history-indicated cerclage and ultrasound-indicated cerclage were presented separately to account for the differing PTB risk in these two groups.

2.3.8 SUBGROUP ANALYSIS

Analysis of differential effects based on (i) previous LLETZ procedure and (ii) previous KCB and based on (iii) Ultrasound-indicated cerclage and (iv) history-indicated cerclage was planned.

2.4 RESULTS

2.4.1 STUDY SELECTION

Searches retrieved a total of 1793 results from 3 databases; Pubmed (*n* = 262), Scopus (*n* = 1283) and Cinahl (*n* = 248). Following removal of duplicates, 1582 articles remained for

screening by title and abstract. After exclusion based on title and abstract, 122 articles were screened by full-text leaving 6 articles for inclusion in the review. The reasons for exclusion of the 116 studies at full-text screening were; a lack of participants with cervical surgery (*n* = 61), a lack of subgroup analysis for cervical surgery participants (*n* = 50), a lack of comparator group (*n* = 1), transabdominal cerclage (*n* = 2), full-text not in English (*n* = 1) and case report (*n* = 1). Figure 9 is a PRISMA flowchart[129] summarising the study screening process.

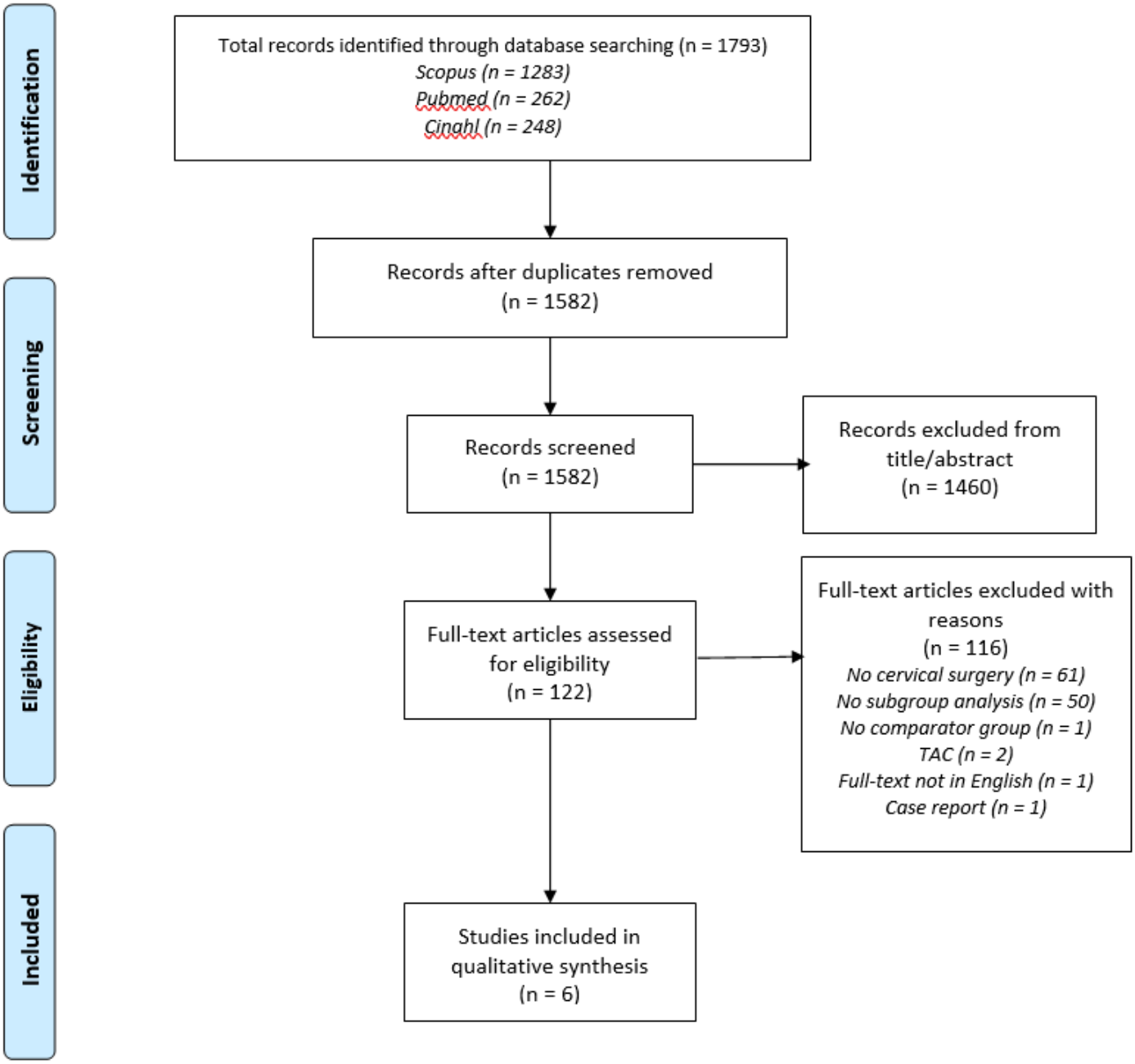

Figure 9: PRISMA flowchart of study screening

2.4.2 QUALITY OF INCLUDED STUDIES

All included studies were retrospective cohort studies and therefore risk of bias was assessed for each study using a modified version of the Newcastle Ottawa bias assessment tool for cohort studies. As per the modified tool, a score of 0-2 indicated a high risk, 3-5 a moderate risk and 6-7 a low risk of bias, with 7 being the highest achievable score. Two studies achieved a score of 7 having demonstrated an appropriate study methodology including adequate adjustments for the two major confounding factors. Three studies achieved the lowest recorded score of 5, having made no adjustments for the presence of confounders. A summary of the risk of bias assessment for each paper is presented in Table 2.

Table 2: Newcastle-Ottawa risk of bias assessment summary[125]

Author (date)	**Selection of participants (✵✵✵)**	**Comparability (✵✵)**	**Outcome (✵✵)**	**Newcastle-Ottawa score**	**Risk of bias**
Kindinger (2016)	✵✵✵	✵✵	✵✵	7	Low
Cho (2018)	✵✵✵	-	✵✵	5	Moderate
Rafaeli-Yehudai (2014)	✵✵✵	-	✵✵	5	Moderate
Shin (2010)	✵✵✵	✵✵	✵✵	7	Low
Nam (2010)	✵✵✵	-	✵✵	5	Moderate
Zeisler (1997)	✵✵✵	✵	✵✵	6	Low

2.4.3 GRADE ASSESSMENT

Table 3 summarises the GRADE assessment of the quality of evidence for each of the main reported outcome measures. The quality of evidence can vary between outcomes and therefore it is necessary to assess these individually. I^2 was used to assess inconsistency, this was high for each outcome indicating a strong likelihood of considerable heterogeneity within the studies. The quality of the included evidence on each outcome was considered very low. Due to the low quality of the included studies, the significant presence of heterogeneity and the slightly differing cohorts and criteria for intervention in each study, it was concluded it would be inappropriate to perform a meta-analysis of this data.

Table 3: GRADE assessment of key outcomes

Outcome	Study characteristics			Quality assessment					Importance
	Number of studies	**Study design**	**No. of participants**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Grade of evidence**	
PTB <34 weeks	3	Retrospective cohort	Cerclage: 18/145 No cerclage: 19/745	-1	-1	-1	-1	Very low	Critical
PTB <37 weeks	5	Retrospective cohort	Cerclage: 60/320 No cerclage: 117/1670	-1	-1	-1	-1	Very low	Critical
Neonatal mortality	1	Retrospective cohort	Cerclage: 0/25 No cerclage: 0/31	No change	N/A	-1	No change	Very low	Important

Table 4 summarises the reasoning for the ratings awarded under each domain per outcome.

Table 4: Reasons for downgrading/upgrading evidence as per GRADE

Outcome	Reason for grade awarded to each domain			
	Risk of bias	**Inconsistency**	**Indirectness**	**Imprecision**
PTB < 34 weeks	All 3 studies were retrospective cohort, 1 did not adequately adjust for confounders.	I^2 >90%	Mixture of indications for intervention, 1 history-indicated, 1 ultrasound-indicated and 1 a mix of both.	3 studies, all with wide confidence intervals and that of 2 studies crossed line of no effect.
PTB <37 weeks	All 5 studies were retrospective cohort, 4 did not adequately adjust for confounders.	I^2 >90%	Mixture of indications for cerclage.	5 studies, all with wide confidence intervals and that of 3 studies crossed the line of no effect.
Neonatal mortality	Retrospective cohort study with inadequate adjustment for confounders although adjusted for 2 major confounders.	Incalculable	Did not present data from subgroup analysis for this outcome despite mixed indications for cerclage.	Zero events so unable to calculate confidence intervals.

2.4.4 STUDY CHARACTERISTICS

All six of the included studies were retrospective cohort studies. Of the six included studies, one was from the UK, one from Austria, one from Israel and three from South Korea. All six examined the obstetric outcomes following insertion of a cerclage. Two studies included participants with a prior KCB, one study included participants with a prior LLETZ procedure, two studies included participants with either LLETZ or KCB and one study did not specify further beyond “conisation”. Despite contacting the corresponding author, we received no response and therefore did not establish the type of cervical surgery participants had undergone. The main technique used for cerclage was the McDonald technique, though three studies did not specify the exact technique used and one study included 3 participants that had Shirodkar cerclages. Only history-indicated cerclages were sited in one study and ultrasound-indicated cerclages alone were sited in one other study. Two studies had a mixture of indications for siting a cerclage, one of which performed subgroup analysis for those participants receiving an ultrasound-indicated cerclage. The remaining two papers did not explicitly specify the indication for cerclage for each participant. The characteristics of the included studies are summarised in Table 5.

Table 5: Characteristics of included studies

Study, study design	Country	Years of study	Type of conisation	Type of intervention (n)	Comparator (n)	Total population size	Indication for intervention	Outcomes assessed	Adjustment for confounders
Kindinger *et al.*[68] (2016), Retrospective cohort	UK	2004-2014	LLETZ, KCB	Cerclage (*n* = 98) Technique unspecified	No cerclage (*n* = 627)	725	All CL <25mm	PTB <37 weeks, PTB<34 weeks, NICU admission	Made exclusions for previous sPTB, mid-trimester miscarriage, uterine anomalies, pre-planned or history-indicated cervical cerclage
Cho *et al.*[130] (2018), Retrospective cohort	South Korea	2009-2013	Unspecified	Cerclage (*n* = 161) Technique unspecified	No cerclage (*n* = 914)	1075	Unspecified	PTB (gestation unspecified)	No identification of or adjustment for confounders
Rafaeli-Yehudai *et al.*[131] (2014), Retrospective cohort	Israel	1994-2011	KCB	Cerclage (*n* = 22) McDonald (*n* = 19) Shirodkar (*n* = 3)	No cerclage (*n* = 87)	109	History-indicated	PTB <34 weeks, mean gestation at delivery, PPROM, Mode of delivery, perinatal mortality	Multivariable logistic regression adjusting for – maternal age, PPROM, intrapartum fever and chorioamnionitis. Didn't report or control for previous sPTB
Shin *et al.*[132] (2010) Retrospective cohort	South Korea	2001-2008	LLETZ	McDonald cerclage (*n* = 25)	Expectant (*n* = 31)	56	CL <25mm (*n* = 12) Funnelling (*n* = 2) Unspecified/history-indicated (*n* = 11)	PTB <37, <34, <28 weeks, PPROM, mode of delivery, neonatal death, NICU admission, ventilatory support, NEC, ROP, IVH, PVL, RDS, BPD, sepsis	No significant difference in characteristics between study groups. Subgroup analysis for 19 patients with CL <25mm.
Nam *et al.*[133] (2010) Retrospective cohort	South Korea	1996-2009	LLETZ, KCB	Cerclage (*n* = 6) Technique unspecified	No cerclage (*n* = 59)	65	CL <25mm (*n* = 3) History-indicated (*n* = 1) Unspecified (*n* = 2)	Gestation at delivery	Univariate and multivariate analysis to determine relationship between potential confounders and PTB
Zeisler *et al.*[134] (1997) Retrospective cohort	Austria	1984-1990	KCB	McDonald cerclage (*n* = 30)	No cerclage (*n* = 39)	69	All history-indicated	PTB <37 weeks, PTB <33 weeks, mean pregnancy duration, PPROM, mode of delivery	Made exclusions for previous PTB, no adjustment for other potential confounders

2.4.5 RESULTS OF INCLUDED STUDIES

Of the included studies, three reported outcomes for the incidence of PTB <34 weeks, five reported outcomes for PTB <37 weeks and four reported outcomes for PPROM. Only two of the studies reported on neonatal outcomes. Shin *et al.*[132] was the only study to report outcomes on neonatal morbidity and mortality, for many of which we were unable to calculate an odds ratio (OR), relative risk (RR) or corresponding 95% confidence intervals (95% CI) due to a lack of events. Of the 1075 participants within the Cho *et al.*[130] study, 28 were multiple pregnancies for which authors did not perform subgroup analysis to account for the differential outcomes that may be seen in this group relative to singleton pregnancies. Table 6 contains a summary of the results of the included studies.

Table 6: Summary of results of included studies

Outcome	**Study**	**No. of participants**		**OR (95% CI)**	**RR**
		Cerclage	**No cerclage**		
PTB <34 weeks	Kindinger (2016)	6/98	8/627	**5.05 (1.71-14.87)**	**4.80**
	Rafaeli-Yehudai (2014)	7/22	5/87	**7.65 (2.14-27.33)**	**5.54**
	Shin (2010)	5/25	6/31	**1.04 (0.28-3.92)**	**1.03**
PTB <37 weeks	Kindinger (2016)	24/98	46/627	**4.10 (2.36-7.10)**	**3.34**
	Cho (2018)	17/161	39/914	**2.65 (1.46-4.81)**	**2.47**
	Shin (2010)	9/25	9/31	**1.38 (0.45-4.24)**	**1.24**
	Nam (2010)	3/6	15/59	**2.93 (0.53-16.12)**	**1.97**
	Zeisler (1997)	7/30	8/39	**1.18 (0.37-3.72)**	**1.14**
PTB <28 weeks	Shin (2010)	2/25	2/31	1.26 (0.16-9.65)	1.24
PPROM	Cho (2018)	10/161	22/914	2.69 (1.25-5.78)	2.58
	Rafaeli-Yehudai (2014)	3/22	17/87	0.65 (0.17-2.45)	0.70
	Shin (2010)	10/25	13/31	0.92 (0.32-2.70)	0.95
	Zeisler (1997)	4/30	6/39	0.85 (0.22-3.32)	0.87
Neonatal mortality	Shin (2010)	0/25	0/31	-	-
NICU admission	Kindinger (2016)	10/98	8/627	8.79 (3.38-22.88)	8.00
	Shin (2010)	4/25	7/31	0.65 (0.17-2.55)	0.71
Neonatal morbidity					
RDS	Shin (2010)	3/25	0/31	-	-
BPD	Shin (2010)	2/25	0/31	-	-
PVL	Shin (2010)	1/25	0/31	-	-
IVH	Shin (2010)	0/25	0/31	-	-
ROP	Shin (2010)	0/25	0/31	-	-
NEC	Shin (2010)	0/25	1/31	-	-
Sepsis	Shin (2010)	1/25	3/31	0.39 (0.04-3.99)	0.41
Ventilation	Shin (2010)	3/25	1/31	4.09 (0.4-42.01)	3.72

2.4.5.1 PTB <34 WEEKS

All three studies reporting on PTB <34 weeks demonstrate greater odds of the outcome occurring following the siting of a cerclage relative to participants that received no intervention. Two of these studies had wide confidence intervals and the remaining study had a confidence interval crossing the line of no effect, demonstrating a lack of certainty over these outcomes (Figure 10).

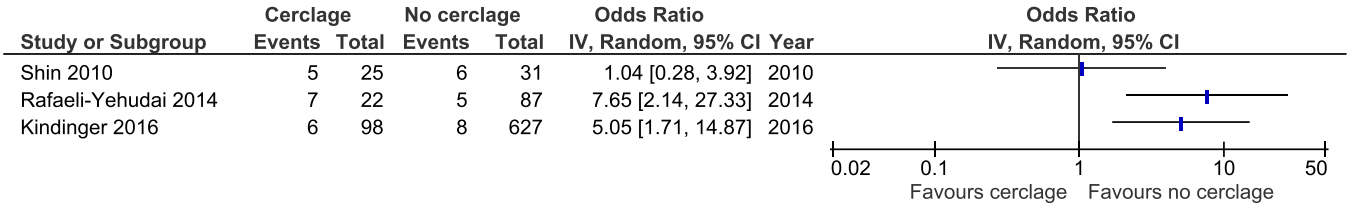

Figure 10: Forest plot without meta-analysis for studies reporting on PTB <34 weeks[128]

2.4.5.2 PTB <37 WEEKS

Five studies reported greater odds of PTB <37 weeks for participants receiving a cerclage relative to those that received no intervention. Again, three of the studies had confidence intervals crossing the line of no effect (Figure 11).

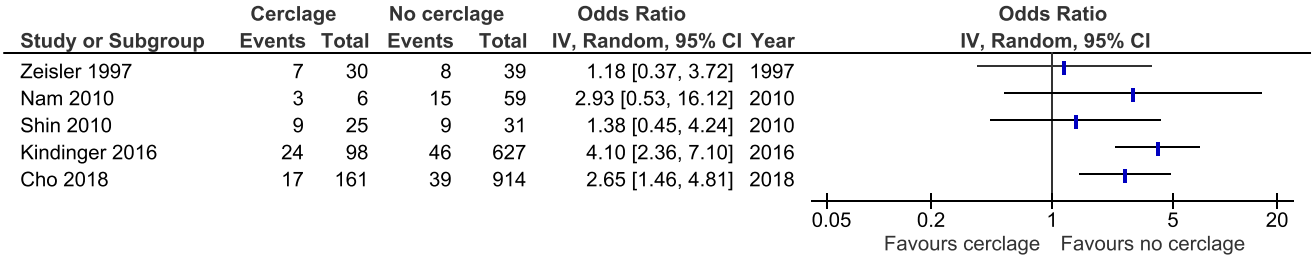

Figure 11: Forest plot without meta-analysis for studies reporting on PTB <37 weeks[128]

2.4.5.3 SECONDARY OUTCOMES

Cho *et al.*[130] demonstrated PPROM is more likely following intervention with cerclage (OR 2.69, 95% CI 1.25-5.78), however this was not supported by the 3 other studies reporting on this outcome, each demonstrating a decreased risk, though the confidence intervals crossed the line of no effect (Figure 12).

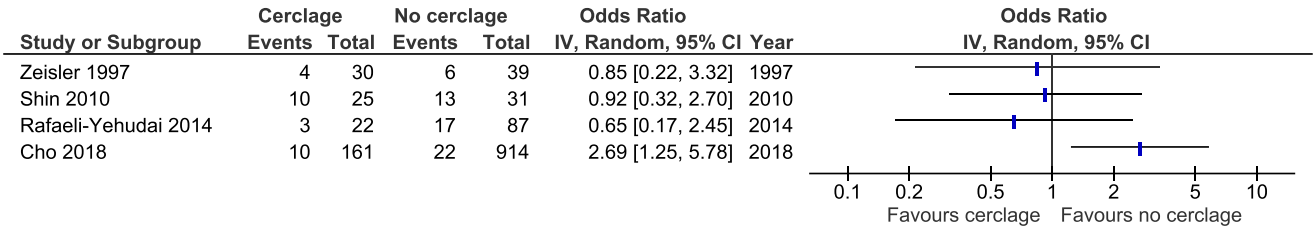

Figure 12: Forest plot without meta-analysis for studies reporting on PPROM[128]

Kindinger *et al*.[68] found increased odds of NICU admission following the siting of a cerclage (OR 8.79, 95% CI 3.38-22.88), however this finding is not supported by that of the Shin *et al.*[132] study (OR 0.65, 95% CI 0.17-2.55). Further to this, Shin *et al.*[132] reported extensively on adverse neonatal outcomes, of which there were few events including no neonatal mortality in either the intervention or comparator groups. Based on only four events between the two groups for each of sepsis and requirement for ventilation outcomes, it is difficult to draw useful conclusions from these results. Of the 6 included studies, none reported maternal adverse events, side effects as a result of the intervention or onset of delivery. Though 3 studies reported mode of delivery, we were unable to ascertain the cause of these modes and therefore this outcome lacks practical use without onset of delivery data.

2.4.5.4 ULTRASOUND-INDICATED CERCLAGE

Two studies reported outcomes on ultrasound-indicated cerclages, sited for a CL <25mm. A total of 98 out of 725 participants received a cerclage in the study by Kindinger *et al.*[68] as a result of a mid-trimester CL <25mm. This indicates that 13.5% of women with prior cervical surgery will develop a short cervix and require an intervention to prolong pregnancy. All women with a short CL received a cerclage and as a result we could not calculate odds ratios and confidence intervals for the Kindinger study. Shin *et al.*[132] performed subgroup analysis for 19 patients within the study cohort that had a short CL <25mm, two further participants developed funnelling and received a cerclage but these were not included in the subgroup analysis. Shin *et al.*[132] demonstrated a decreased likelihood of PTB <37 weeks in women with a cerclage relative to women that were not treated (RR 0.58, OR 0.44, 95% CI 0.06-3.24), though these results are based on only 6 events (Table 7).

Table 7: Primary outcomes for ultrasound-indicated cerclage

Outcome	Study	Number of participants	Odds of outcome with cerclage	OR (95% CI)	RR
PTB <34 weeks	Kindinger (2016)	6/98	0.06	-	-
PTB <37 weeks	Kindinger (2016)	24/98	0.24	-	-
	Shin (2010)	Cerclage: 3/12 No cerclage: 3/7	0.32	0.44 (0.06-3.24)	0.58

2.4.5.5 HISTORY-INDICATED CERCLAGE

All participants received a history-indicated cerclage in the Rafaeli-Yehudai *et al.*[131] and Zeisler *et al.*[134] studies contrast to only 11 of the participants within the Shin *et al.*[132] study. The studies indicate an increased risk of delivering prior to 37 weeks, following the siting of a history-indicated cerclage for prior cervical surgery. We were unable to calculate an odds ratio, 95% confidence interval or relative risk for the subgroup within the Shin *et al.*[132] study as the details for these participants were not recorded separately within the study. The confidence intervals are wide in the results of the Rafaeli-Yehudai *et al.*[131] study and cross the line of no effect in the Zeisler *et al.*[134] study (Table 8).

Table 8: Primary outcomes for history-indicated cerclage

Outcome	Study	Number of participants	Odds of outcome with cerclage	OR (95% CI)	RR
PTB <34 weeks	Rafaeli-Yehudai (2014)	Cerclage: 7/22 No cerclage: 5/87	0.32	5.05 (1.71-14.87)	4.80
PTB <37 weeks	Shin (2010)	Cerclage: 6/11	0.54	-	-
	Zeisler (1997)	Cerclage: 7/30 No cerclage: 8/39	0.23	1.18 (0.37-3.72)	1.14

2.5 DISCUSSION

This systematic review aimed to identify any studies of cerclage, pessary or progesterone to determine which intervention has the greatest efficacy in preventing PTB in women with singleton pregnancies and prior cervical surgery. The only published studies in this cohort focussed on cerclage and therefore we could not determine the comparative efficacy of progesterone and Arabin pessary in preventing PTB due to the paucity of evidence. In addition, the available evidence surrounding the use of cerclage in this cohort is of insufficient quality to draw conclusions. All studies reporting on the primary outcomes (*n* = 6) demonstrated an increased risk of PTB prior to both 34 and 37 weeks following the siting of a cerclage in asymptomatic women with a history of cervical surgery. However, this effect may be due to the identification of a high-risk subgroup of women that developed a short cervix and received an intervention relative to those that did not. These results must also be interpreted with caution due to the significant level of heterogeneity between studies and the very low-quality evidence as assessed using GRADE. In addition, 4/8 of the primary outcome confidence intervals crossed the line of no effect, indicating an uncertainty in the direction of these outcomes.

As aforementioned, women with previous cervical surgery that develop a mid-trimester CL <25mm, and subsequently receive a preventative intervention, are at a higher risk of PTB than those that do not experience cervical shortening and receive no intervention. Short mid-trimester CL may be the greatest indicator of PTB risk in women post-conisation[133] and therefore regardless of intervention, this cohort may still deliver at an earlier gestation than participants that do not develop a short cervix. Therefore, we cannot conclude that the occurrence of PTB is a direct result of the vaginal cerclage. Notwithstanding, the included studies are the best available evidence to determine the efficacy of cerclage in preventing PTB in women with prior LLETZ or KCB of the cervix. In any study of women with a short cervix, it would be unethical to offer the option of placebo or no intervention and therefore the best method of determining the efficacy of an intervention in future studies would be through direct comparison to another intervention.

The included studies varied in their indications for siting cerclages, with studies siting only history-indicated cerclages (*n = 2*), only ultrasound-indicated cerclages (*n = 1*), or a mixture (*n = 2*). As the risk of PTB between these groups differs, it is not possible to draw comparisons between these studies and this limited the generalisability of the findings from this review. However, our subgroup analysis for history-indicated cerclage may be useful to determine both the risk of delivering preterm and the efficacy of cerclage in women at intermediate risk. The overall rate of PTB <37 weeks in the untreated arm of the Zeisler *et*

al.[134] study is 20.5% which is greater than the background population rate of approximately 7.3% in the UK[135], demonstrating the increased risk in women with previous cervical surgery relative to the background population. Both the Zeisler *et al.*[134] and Rafaeli-Yehudai *et al.*[131] studies sited prophylactic cerclages. These studies provide a fairer comparison between the performance of cerclage versus no cerclage groups as the outcomes are not influenced by short CL and therefore participants are at a similar risk of PTB. Again, the findings indicate an increased risk of PTB in this cohort when managed with cerclage relative to no cerclage. It is more likely these results are linked to the cerclage, although bias due to confounding cannot be discounted due to the retrospective study designs. This increased PTB risk may be due to the bacterial colonisation and ascending infection associated with the siting of a cerclage[76]. Women with a prior KCB and no further indication should not be offered an intervention to prevent PTB, as is stated within several medical guidelines globally.

The results of cerclage studies may also be impacted by the suture material used. Kindinger *et al.*[68] aimed to determine the optimal suture material between braided and monofilament cerclage materials. Authors concluded that monofilament was the superior suture material and therefore this may have some influence on the performance of cerclage in studies considering the efficacy of vaginal cerclage. Currently, a large randomised clinical trial of cerclage materials (C-STICH), is due to publish findings and these may guide both future research and clinical practice in this area[136]. *The* Kindinger *et al.*[68] study also presents practical use as its methods closely replicated UK clinical practice and this gives an indication of the proportion of women (13.5%) with previous cervical surgery that would develop a short cervix and require an intervention to prolong pregnancy.

A recent study demonstrated parents highly value neonatal outcomes to assist in making healthcare decisions during pregnancy with 72% of parents valuing outcomes for offspring mortality and 68% favouring outcomes for neurodevelopmental morbidity and infection[124]. Only one of the included studies, Shin *et al.*[132] publishing a complete core set of neonatal outcomes, yet the study cohort was relatively small leading to a limited number of events for each outcome. As a result, it is not possible to draw conclusions on the impact of cerclage on neonatal outcomes. Although the majority of adverse neonatal outcomes may be owed to PTB, it is difficult to ascertain and predict any adverse long-term effects following an intervention to prevent PTB without these outcomes. This may also present further problems in counselling patients who value this information for decision-making.

There is only one published review comparing interventions in a cohort of women with previous cervical surgery. This review by Grabovac *et al.*[123] corroborated the findings of our review and authors did not support the use of cerclage for prevention of PTB. However, the

results face the same limitations as ours and may also be biased due to confounding factors, as reported by the review authors[123]. The review also included a random-effects meta-analysis of studies but reviewers did not perform subgroup analysis to account for the high-risk subgroup of women with a short cervix relative those without and therefore results may be misleading. Contrast to the results of this review, and based on a broad high-risk cohort, Alfirevic *et al.*[69] concluded cerclage is an effective intervention in prolonging pregnancy, though there was insufficient evidence for the subgroup of women with a short cervix alone. However, subgroup analysis for women with a short cervix in a review by Jarde *et al.*[72] demonstrated cerclage was effective in reducing PTB <37 weeks though results were not significant for prevention of PTB <34 weeks. Unfortunately, these results cannot be extrapolated to women with previous cervical surgery due to the uncertainty surrounding the mechanisms leading to PTB in various high-risk groups. This highlights the ongoing sparsity of evidence surrounding the management of this cohort of women and the further implications this has for clinical practice.

There are no published studies on the use of Arabin pessary or progesterone to prevent PTB in women with previous cervical surgery. As a result, we were unable to draw any conclusions for these interventions or determine how their efficacy compares to cerclage in this cohort. The evidence for the use of VP remains conflicting although the most recent review, EPPPIC[79], in congruence with a previous review by Romero *et al.*[77], demonstrated its efficacy in women with a short cervix. This is in contrast to the findings of the OPPTIMUM study[80] which did not support the use of progesterone in the same cohort. Again, studies of the Arabin pessary present contradictory evidence for women with a short cervix. Goya *et al.*[89] conducted the only study to support the use of the Arabin pessary in this cohort. Both Nicolaides *et al*.[87] and Hui *et al.*[88] found no additional benefit of the pessary over expectant management in women with a CL <25mm. There is an urgent need for further studies of these interventions to guide future practice for women with previous cervical surgery. A multi-centre randomised feasibility study should be conducted to determine whether this is a possibility and guide further studies.

2.5.1 Implications of the review

This systematic review did not identify any studies exclusively examining the effects of VP or Arabin pessary in this population. A Cochrane review of systematic reviews was unable to draw conclusions on the use of these interventions in high-risk women due to the paucity of evidence[137]. Future prospective studies, most favourably in the form of a multi-centre RCT, should be undertaken to determine the efficacy of these interventions and guide clinical practice for women with previous cervical surgery and a mid-trimester short cervix. This

review also demonstrated clear benefit from the use of cerclage in singleton pregnancies at high risk of PTB[137]. However, we are unsure as of yet, whether managing these women among a generic high-risk cohort would be appropriate or whether guidelines must be adjusted to account for the differing risk in women with prior cervical surgery. Further to this, it will be useful to ascertain whether the type of cervical surgery has any impact on the efficacy of the interventions in preventing PTB. Studies already suggest that a KCB more significantly increases the risk of PTB than LLETZ procedures due to the greater depth of tissue excised[19, 22]. Therefore, studies including subgroup analysis for KCB, single LLETZ and multiple LLETZ procedures within studies would be valuable in gaining insight into the impact on the efficacy of interventions.

Systematic reviews by Alfirevic *et al.*[69] *(2017)* and Grabovac *et al.*[123] (2019), both highlighted the need for more studies in this area. Yet there has been little advance in our knowledge of managing women with prior conisation of the cervix. There remains a need for further retrospective cohort studies and, where feasible, prospective studies to determine the efficacy of these interventions. A recent randomised-feasibility study described the challenges in performing an RCT of women with a short cervix in a single centre due to the low participant numbers in this group[116]. Therefore, the cohort of women with prior cervical surgery that develop a mid-trimester short cervix and require an intervention would be even smaller and likely present further challenges. Further to this, where patients have previously had positive pregnancy outcomes when treated with a particular intervention, they may wish to receive the same intervention in subsequent pregnancies and this may present difficulties in randomising participants to an intervention. Therefore, the best evidence will unlikely be in the form of a single-centre RCT although a multi-centre randomised-feasibility study may present more favourable findings.

2.5.2 LIMITATIONS

The studies included in this review consist of very low-grade evidence, as assessed using GRADE, and all of the included studies are retrospective cohort studies. Though some of these studies adjusted for the presence of major confounders, there is likely still bias as a result of confounding factors within and between each study. The exact population and indication for intervention differed between the studies and therefore it is difficult to draw exact comparisons between the outcomes of each study. This resulted in a limitation in performing a meta-analysis of the included studies and any conclusions drawn may still be limited due to confounding. We calculated odds ratios, confidence intervals and relative risks for the results of each study, but these may be misleading and must be interpreted with caution. We aimed to address a shortfall in reviews describing the efficacy of either the

Arabin pessary or progesterone to prevent PTB in women with prior cervical excision, but unfortunately studies are still lacking and therefore we could not address this within our review. As a result, we were also unable to determine the comparative efficacy of the three interventions we aimed to review.

2.6 CONCLUSION

The findings of this review indicate that women with prior cervical surgery that receive a cerclage during pregnancy are at increased risk of PTB prior to both 34- and 37-weeks relative to those that do not receive an intervention. This is likely due to the increased risk of PTB in women with a CL <25mm relative to those without cervical shortening. There is a lack of studies considering the management of women with prior cervical surgery during pregnancy. Further retrospective cohort studies comparing cerclage, pessary and progesterone to one another are required to determine the comparative efficacy of each in preventing PTB in women with prior cervical surgery. Prospective studies would also assist in determining the optimal management of this cohort, most favourably in the form of a multi-centre RCT.

CHAPTER 3 - CERCLAGE, PESSARY OR PROGESTERONE TO PREVENT PRETERM BIRTH IN WOMEN WITH PRIOR CERVICAL SURGERY

3.1 BACKGROUND

Women with prior cervical surgery, indicated following findings of moderate-severe cervical intraepithelial neoplasia, are at an increased risk of sPTB and this risk is present in all post-surgical pregnancies[32]. Following a KCB, the risk of PTB is greater in subsequent pregnancies relative to the risk following a LLETZ procedure[19], this may be owing to the greater volume of tissue excised during a KCB. However, collectively it is estimated that around 2.5% of UK PTBs per year are a result of surgical procedures to the cervix[21]. Theories suggest the PTB risk may be a result of a weakening in the mechanical strength of the cervix due to post-surgical regeneration producing an inferior quality of tissue[24]. Another theory suggests the removal of glands that secrete the cervical mucus plug leave the cervix vulnerable to ascending infection which further increases the risk of PTB[23]. Managing this risk is vital to prevent poor neonatal outcomes as PTB remains the leading cause of neonatal morbidity and mortality worldwide[8].

Preventative interventions in the form of either vaginal cerclage, VP or an Arabin pessary, are indicated following the findings of a mid-trimester CL <25mm[15, 67]. Cerclage has been used historically in the prevention of PTB in high-risk women but the results of various studies surrounding its efficacy remain contradictory. A review by Alfirevic *et al.*[69] concluded no benefit of cerclage for women with a short cervix but Jarde *et al.*[72] disputed these findings. The subgroup analysis within this review demonstrated efficacy of cerclage in reducing PTB <37 weeks in this cohort. Neither review was able to perform any analysis for women with prior cervical surgery. Similarly, the evidence surrounding the use of progesterone in asymptomatic high-risk women is conflicting with some studies demonstrating efficacy in prevention of PTB[76-78] and others disputing these findings[80, 81]. The 2021 EPPPIC study performed a large-scale individual participant meta-analysis and demonstrated the efficacy of progesterone in preventing PTB <34 weeks[79]. However, like all studies of both progesterone and the Arabin pessary, this study incorporated a broad high-risk cohort without subgroup analysis for participants with cervical surgery.

There remains no consensus as to which intervention offers the greatest efficacy in the prevention of PTB in women with prior cervical surgery. The systematic review conducted within this thesis, highlighted the need for further studies to determine the comparative efficacy of interventions to prevent PTB in women with prior cervical surgery. This is

supported by the findings of Grabovac *et al.*[123] and Alfirevic *et al.*[69] This retrospective cohort study aims to address the lack of evidence surrounding the use of cerclage, pessary and progesterone in this cohort of women.

3.2 METHODS

3.2.1 REFERRAL AND SCREENING

This is a retrospective cohort study of all women with prior cervical surgery attending the specialist PTB prevention clinic at Liverpool Women's Hospital (LWH) between 2008-2020. Patients are initially screened for risk factors associated with PTB at their first antenatal appointment with a midwife. Any women identified as high risk as defined by; previous KCB, single LLETZ >10mm depth, ≥2 previous LLETZ procedures, previous PPROM or sPTB before 34 weeks' gestation, are referred to the specialist PTB prevention clinic on booking their pregnancy. Some women may be referred to the clinic following an incidental finding of a short cervix during routine antenatal care screening or on symptomatic presentation to the maternity assessment unit. Gestational age is confirmed by the measurement of crown-rump length at the booking scan. The first attendance at the specialist PTB prevention clinic determines whether the patient has any further risk factors for PTB, and how these were managed in previous pregnancies. This appointment usually takes place around 16 weeks' gestation, though high-risk women planning for history-indicated cerclage will be seen from 12 weeks. Routine transvaginal ultrasound screening of CL for high risk women also typically takes place from around 16 weeks and continues up to 28-weeks' gestation. This includes the identification of a short cervix or the presence of any funnelling or cellular debris (amniotic fluid sludge) that may indicate an imminent risk of PTB. Patients return to follow-up appointments every 2-4 weeks, unless any significant cervical shortening has been identified between appointments or the patient becomes symptomatic, in which case they are seen more regularly, usually every 1 or 2 weeks. Patients can also attend more regularly if they are particularly anxious about the pregnancy outcome, and may have experienced significantly adverse outcomes in a previous pregnancy, usually with certain gestations providing anxiety triggers and increased reassurance is built into their care.

3.2.2 INTERVENTION

The LWH baseline for intervention, in line with the national guidelines, is a CL <25mm with or without the presence of funnelling or cell debris, though funnelling and sludge can indicate a more urgent requirement for intervention. Some women at a particularly high risk of PTB

may require intervention prior to CL screening, these patients can be seen as early as 10 weeks' gestation. In 2019, the LWH guidance changed to include the use of omega-3 dietary supplementation (Omacor) to aid the prevention of PTB<37 weeks, following a Cochrane evidence update[107]. This is offered at a dose of 2000mg once per day to all women aside from those already taking adequate supplements, such as those with a vegetarian diet. Should a patient require treatment to prevent PTB, the options of vaginal cerclage, VP and Arabin pessary are discussed. Patients who have had successful treatment with one of the interventions in a previous pregnancy will often receive the same intervention in subsequent pregnancies. If any one of these interventions fails and the patient experiences further cervical shortening between appointments, an additional preventative intervention may be added. Alternatively, should a patient struggle to tolerate a particular intervention due to side effects or otherwise, they may opt to switch to a different intervention. In cases of an extremely short cervix with funnelling, the siting of a vaginal cerclage is often the first-choice management. Similarly, patients presenting with a dilated cervix or bulging membranes may be deemed suitable to receive an emergency cerclage. Some patients attend clinic with a transabdominal cerclage sited prior to pregnancy often secondary to previous failed treatment or radical trachelectomy, these women are followed-up in an identical manner to those without a TAC. In cases of cervical shortening despite the placement of a TAC, patients can receive further intervention in the form of either progesterone or an Arabin pessary and where cervical dilation results in bulging membranes, a vaginal cerclage may be sited.

3.2.2.1 VAGINAL CERCLAGE

The McDonald technique for cerclage is used at LWH for those patients that require intervention and opt for a stitch. Regional anaesthesia is administered prior to the procedure. With the patient placed in the lithotomy position, using Allis' or Babcock's forceps, the cervix is gently pulled towards the vaginal opening[138]. Using a mayo needle, a monofilament or braided suture is inserted as superiorly as possible towards the level of the cervicovaginal junction. This is described as a purse-string suture as the internal os is closed by the tight stitch[138]. A handful of patients that are followed-up in the specialist PTB prevention clinic at LWH receive a Shirodkar cerclage, generally inserted in another centre prior to attending the LWH specialist PTB prevention clinic. The Shirodkar technique is more complex and requires the insertion of a suture more superiorly at the level of the cardinal ligaments, again under regional anaesthesia. Two incisions are made, one around the cervix at the level of the internal os and another posteriorly[139]. The anterior vaginal wall is opened and the bladder is reflected superiorly. Using either nylon or mersilene tape, a stitch is placed around

the cervix and a knot is tied anteriorly. The two incisions are then closed[139]. All patients undergo a TVUSS at each follow-up visit and this is used to assess both the position of the cerclage and any cervical shortening that may indicate a need for further intervention.

3.2.2.2 VAGINAL PROGESTERONE

Women that opt for treatment with VP are prescribed 200mg Cyclogest pessaries to insert once per night. In some cases, patients may already take progesterone 400mg as prescribed by the fertility clinic prior to referral to the specialist PTB prevention clinic and it is advised to reduce the progesterone dose to 200mg after the first specialist PTB prevention clinic appointment. On the prescription of VP pessaries, patients are informed of the insertion technique. It is recommended to insert the pessary at night while in either a squatting position or laid down. A lubricant gel can be used if the patient experiences any discomfort. Following insertion, patients should remain laid down for at least 30 minutes to avoid displacement. For this reason, inserting the pessary before going to bed is recommended.

3.2.2.3 ARABIN PESSARY

Patients that opt for an Arabin pessary have them sited by a trained specialist using the technique set-out by Arabin *et al.*[83] Prior to the siting of the pessary, a vaginal examination is performed to determine the cervical position and identify any potential obstructions such as anatomical abnormalities. The pessary is then compressed and, following the application of lubricant, inserted into the vagina towards the posterior fornix at a 45-degree angle. Once at the correct level, the pessary can be released to assume its position around the cervix. Following placement, the clinician then ensures a central position of the pessary by running the examining fingers around the cervix[82]. Incorrect siting of the pessary can result in displacement or discomfort to the patient and therefore the position is confirmed both on siting and at a follow-up appointment 1-2 weeks later. Following insertion, the pessary can be gently advanced more posteriorly to provide further angling of the cervix. At each specialist PTB prevention clinic follow-up appointment, the adequacy of the pessary's positioning is assessed and confirmed. Typically, this does not involve vaginal examination unless the patient is symptomatic[82]. Those that receive an Arabin pessary are informed at the time of its siting that should PPROM occur, they should attend the hospital and the pessary must be removed. The Arabin pessary is routinely removed at 37+0 weeks. Though it can be undertaken quickly, the procedure can cause discomfort and patients must be informed of this. The cervix is pushed upwards to allow for the insertion of the index finger over the inner ring of the pessary at 12 o'clock. Should this fail, the finger can be rotated

posteriorly, within the inner ring, to reach the 6 o'clock position and release the pessary. The application of downward traction posteriorly then anteriorly allows for the removal of the pessary. Alternatively, should both of the aforementioned manoeuvres fail, atraumatic scissors can be used to cut the pessary[82].

All women attending the specialist PTB prevention clinic at LWH, who went on to deliver between 2008-2020 were screened for inclusion in this retrospective cohort study. All data were extracted retrospectively from a database of continuous service evaluation collected prospectively. MEDITECH was used to collect the demographic data for each patient. Women with singleton pregnancies and prior history of either KCB, single LLETZ or multiple LLETZ procedures were included. Exclusions were made for duplicates, missing data, patients managed with transabdominal cerclage, multiple pregnancies, prior radical trachelectomy, laser procedures, and termination of pregnancy (TOP). Duplicates were defined as women who attended clinic for more than one pregnancy within the study period and these were identified based on hospital W numbers. The first pregnancy with specialist PTB prevention clinic involvement was retained and any subsequent pregnancies were excluded due to the increased likelihood of similar outcomes in future pregnancies. Patients with a transabdominal cerclage were excluded as this is most commonly sited prior to pregnancy as a primary preventative intervention. Multiple pregnancies and radical trachelectomy procedures constitute higher risk groups than singletons and women at risk due to LLETZ or KCB procedures respectively and therefore these were excluded. Laser procedures have not been performed within the trust for over 20 years and thus the data surrounding these procedures is less robust and lacks reliability. Any terminations were due to fetal abnormalities and therefore this alternate outcome would limit our ability to determine the pregnancy outcomes owed to the risk from previous cervical surgeries.

3.2.3 Statistical analysis

Initial analyses were performed to assess the association between demographic and clinical variables based on the treatment type. These were performed in IBM SPSS statistics version 26, using Chi-squared and one-way ANOVA tests as appropriate. The impact of clinical/demographic factors on each outcome were performed using univariable and multivariable generalised linear models. For continuous outcomes, such as birthweight and gestation time, identity link function and normal family were assumed. For the PPROM outcome, a logistic link and binomial family were assumed. Terms were included in the multivariable model using a backwards stepwise approach based on Akaike's Information Criterion. A p-value of 0.05 was used to determine statistical significance throughout.

Separate models were performed for those with and without a previous sPTB. All univariable and multivariable analyses were performed by Dr Richard Jackson in R (Version 3).

3.3 RESULTS

Of 1906 women attending the LWH specialist PTB prevention clinic, 607 met the inclusion criteria. Following exclusions, 441 cases were identified for analysis (Figure 13).

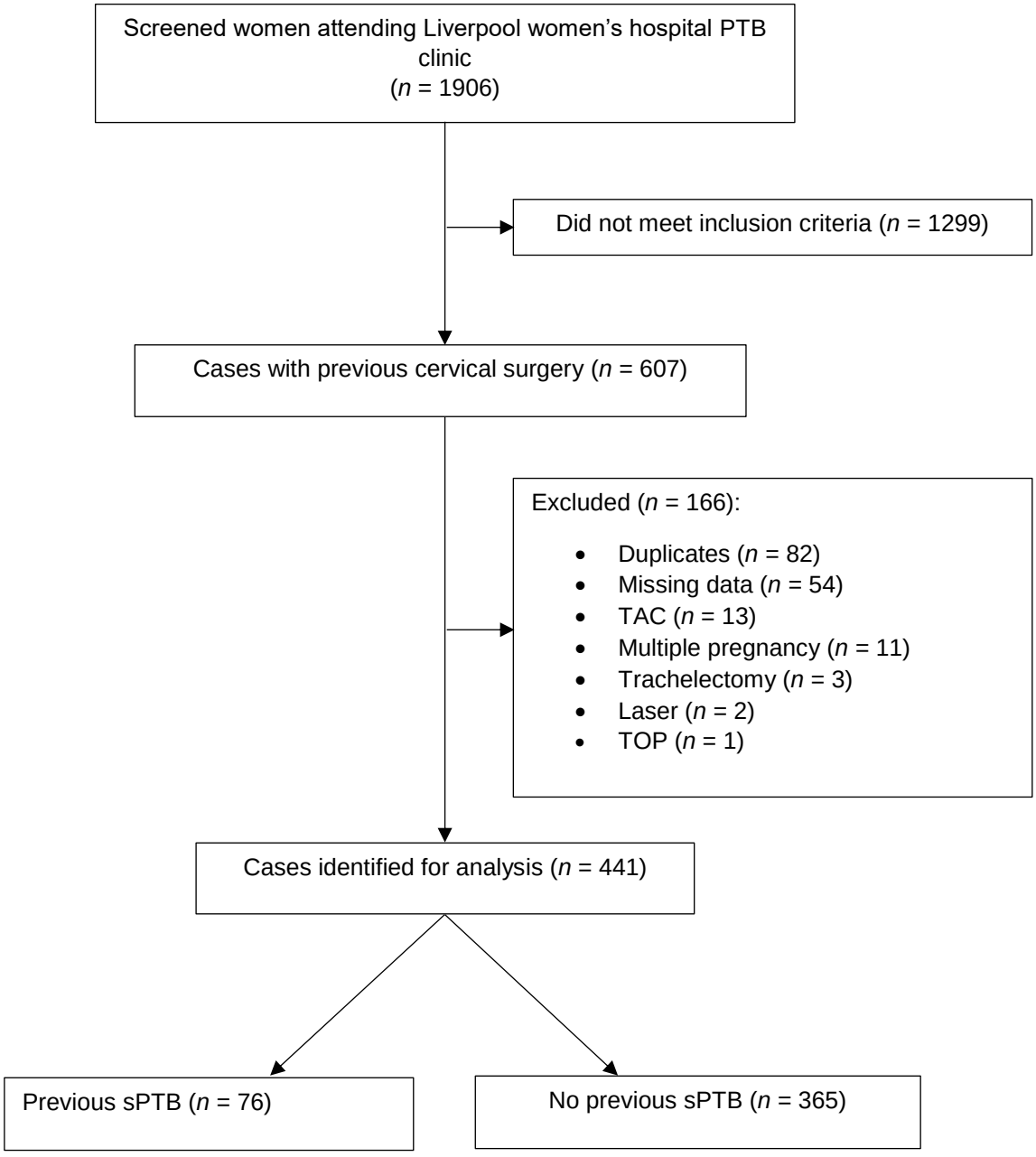

Figure 13: Cases identified for analysis following exclusions

3.3.1 STUDY POPULATION

Table 9 demonstrates the demographic characteristics of the included participants, separated based on whether the patient had a previous sPTB <37 weeks. History of cervical surgery is presented based on the most significant procedure and therefore where some participants have received both a KCB and LLETZ procedure, they have been included under the KCB heading. Four hundred and forty-one women with prior cervical surgery were included in the analysis, of which 365 had no previous sPTB and 76 had a previous sPTB. A total of 105 women delivered prior to 37 weeks constituting around half of the pregnancies in women with a previous sPTB and 18% of those without. Of the 105 women receiving treatment, 39% (*n = 41*) delivered before 37 weeks and 23% (*n = 24*) delivered prior to 34 weeks. Of the 18 cerclages, only 2 were monofilament sutures and the remaining 16 were braided.

Table 9: demographic characteristics of study participants by previous sPTB
Data are presented as n (%) or median (IQR)

Covariate	No previous sPTB	Previous sPTB	Total
Total	365	76	441
Height (cm)	165 (161, 169)	166 (162, 170)	165 (161, 169)
Weight (kg)	66 (60, 77)	67 (60, 75)	67 (60, 77)
BMI	24.2 (21.8, 28.3)	24.4 (22.1, 28.25)	24.3 (21.8, 28.35)
Ethnicity			
Caucasian	359 (98%)	72 (95%)	431 (98%)
Black	1 (0%)	3 (4%)	4 (1%)
Asian	2 (1%)	1 (1%)	3 (1%)
Mixed	2 (1%)	0 (0%)	2 (0%)
Other	1 (0%)	0 (0%)	1 (0%)
Smoker	86 (24%)	30 (39%)	116 (26%)
Age at EDD	32 (29, 35)	32.5 (29, 36)	32 (29, 36)
Previous cone biopsy	88 (24%)	7 (9%)	95 (23%)
Previous single LLETZ	132 (36%)	57 (75%)	189 (43%)
Previous multiple LLETZ	145 (40%)	12 (16%)	157 (36%)
Uterine abnormality	2 (1%)	1 (1%)	3 (1%)
Previous PPROM	25 (7%)	25 (33%)	50 (11%)
Previous late miscarriage (16-23 weeks)	10 (3%)	3 (4%)	13 (3%)
Gestation at intervention	20.4 (17.7, 24)	18.2 (16.5, 21.9)	20.1 (16.6, 23.6)
Received intervention	67 (18%)	38 (50%)	105 (24%)
Intervention			
None	298 (82%)	38 (50%)	336 (76%)
Vaginal Cerclage	13 (4%)	5 (7%)	18 (4%)
Progesterone	35 (10%)	22 (29%)	57 (13%)
Arabin pessary	32 (9%)	16 (21%)	48 (11%)
Shortest CL			
<15mm	37 (10%)	17 (22%)	54 (12%)

15-20mm	32 (9%)	12 (16%)	44 (10%)
20-25mm	61 (17%)	21 (28%)	82 (19%)
25-30mm	93 (25%)	14 (18%)	107 (24%)
30-35mm	72 (20%)	8 (11%)	80 (18%)
>35mm	70 (19%)	4 (5%)	74 (17%)
Omacor use	27 (7%)	8 (11%)	35 (8%)
Gestation at delivery			
<24 weeks	4 (1%)	1 (1%)	5 (1%)
<28 weeks	9 (2%)	4 (5%)	13 (3%)
<32 weeks	17 (5%)	12 (16%)	29 (7%)
<34 weeks	26 (7%)	21 (28%)	47 (11%)
<37 weeks	66 (18%)	39 (51%)	105 (24%)
Onset of labour			
Spontaneous	156 (43%)	47 (62%)	203 (46%)
Induced	138 (38%)	18 (24%)	156 (35%)
Pre-labour caesarean section	71 (19%)	11 (14%)	82 (19%)
Mode of delivery			
Vaginal	248 (68%)	56 (74%)	304 (69%)
C-section	117 (32%)	20 (26%)	137 (31%)
PPROM	21 (6%)	12 (16%)	33 (7%)
Late miscarriage (16-23 weeks)	1 (0%)	0 (0%)	1 (0%)
Livebirth	360 (99%)	75 (99%)	435 (99%)
Stillbirth	2 (1%)	1 (1%)	3 (1%)

Table 10 demonstrates the demographic characteristics and outcome variables based on the treatment received by each participant. Seventeen participants receiving more than one intervention during pregnancy were excluded. Any statistically significant differences are displayed in bold.

Table 10: Demographic characteristics of study participants by treatment received
Data are presented as n (%) or median (IQR)
† One-way ANOVA ‡ Chi-squared

Covariate	Cerclage	Pessary	Progesterone	No treatment	*p*
Total	10	38	41	336	
Height (cm)	165 (159, 168)	167 (163, 169)	166 (161, 170)	165 (161, 169)	0.634 †
Weight (kg)	70 (67, 81)	63 (60, 71)	70 (61, 80)	67 (60, 76)	0.424 †
BMI	27.1 (24.8, 31.0)	22.7 (21.4, 26.1)	24.5 (22.2, 29.8)	24.4 (22, 28.4)	0.201 †
Ethnicity					
Caucasian	10 (100%)	36 (95%)	41 (100%)	328 (98%)	0.452 ‡
Black	**0 (0%)**	**2 (5%)**	**0 (0%)**	**1 (0%)**	**0.006 ‡**
Asian	0 (0%)	0 (0%)	0 (0%)	4 (1%)	0.784 ‡
Mixed	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0.912 ‡
Other	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0.966 ‡
Smoker	**8 (73%)**	**9/37 (24%)**	**10/38 (26%)**	**86/335 (26%)**	**0.002 ‡**
Age at EDD	33 (29, 38)	31 (29, 35)	34 (31, 39)	32 (29, 35)	0.188 †
Previous cone biopsy	2 (20%)	7 (18%)	6 (15%)	76 (23%)	0.683 ‡
Previous single LLETZ	4 (40%)	18 (47%)	24 (59%)	135 (40%)	0.142 ‡
Previous multiple LLETZ	4 (40%)	13 (34%)	11 (27%)	125 (37%)	0.608 ‡
Uterine abnormality	0 (0%)	0 (0%)	0 (0%)	3 (1%)	0.849 ‡
Previous sPTB	**5 (50%)**	**11 (29%)**	**17 (42%)**	**38 (11%)**	**0.000 ‡**
Previous PPROM	**3 (30%)**	**7 (18%)**	**10 (24%)**	**28 (8%)**	**0.002 ‡**
Previous late miscarriage (16-23 weeks)	**4 (40%)**	**1 (3%)**	**0 (0%)**	**7 (2%)**	**0.000 ‡**
Gestation at intervention	**13.5 (12.5, 21.3)**	**19 (16, 23)**	**22 (17, 24.3)**	**-**	**0.000 †**
Shortest CL					
<15mm	**1 (10%)**	**21 (55%)**	**10 (24%)**	**5 (2%)**	**0.000 ‡**
15-20mm	**2 (20%)**	**8 (21%)**	**12 (29%)**	**13 (4%)**	**0.000 ‡**
20-25mm	**5 (50%)**	**8 (21%)**	**9 (22%)**	**44 (13%)**	**0.005 ‡**
25-30mm	**1 (10%)**	**1 (3%)**	**6 (15%)**	**99 (29%)**	**0.001 ‡**
30-35mm	**1 (10%)**	**0 (0%)**	**1 (2%)**	**91 (27%)**	**0.000 ‡**
>35mm	**0 (0%)**	**0 (0%)**	**3 (7%)**	**84 (25%)**	**0.000 ‡**
Omacor use	**2 (20%)**	**0 (0%)**	**9 (22%)**	**20 (6%)**	**0.000 ‡**
Gestation at delivery					
<24 weeks	0 (0%)	2 (5%)	1 (2%)	2 (1%)	0.068 ‡
<28 weeks	**0 (0%)**	**5 (12%)**	**2 (2%)**	**4 (1%)**	**0.000 ‡**
<32 weeks	**0 (0%)**	**6 (16%)**	**5 (12%)**	**15 (5%)**	**0.011 ‡**
<34 weeks	**1 (10%)**	**8 (21%)**	**9 (22%)**	**23 (7%)**	**0.001 ‡**
<37 weeks	**1 (10%)**	**13 (34%)**	**16 (39%)**	**64 (19%)**	**0.005 ‡**
Onset of labour					
Spontaneous	5 (50%)	23 (61%)	20 (49%)	146 (44%)	0.233 ‡
Induced	3 (30%)	8 (21%)	15 (37%)	125 (37%)	0.257 ‡
Pre-labour caesarean section	2 (20%)	7 (18%)	6 (15%)	65 (19%)	0.909 ‡
Mode of delivery					
Vaginal	5 (50%)	29 (76%)	27 (66%)	234 (70%)	0.410 ‡

C-section	5 (50%)	9 (24%)	14 (34%)	102 (30%)	0.410 ‡
PPROM	0 (0%)	5 (13%)	5 (12%)	19 (6%)	0.126 ‡
Late miscarriage (16-23 weeks)	0 (0%)	0 (0%)	0 (0%)	1/334 (0%)	0.966 ‡
Livebirth	10 (100%)	38 (100%)	40 (98%)	331 (99%)	0.798 ‡
Stillbirth	0 (0%)	0 (0%)	1 (2%)	2 (1%)	0.540‡

3.3.2 Univariable analysis

The results of the univariable analysis are included for each outcome in the table below (Table 11). Results are separated based on history of previous PTB. Gestation time is listed in weeks and birthweight in grams. Smoking refers to all current and past smokers. Results are presented in terms of model estimates (est) and standard error (se).

3.3.2.1 Previous spontaneous preterm birth

In women with prior cervical surgery and a previous sPTB, history of a single previous late miscarriage is significantly associated with a shortened gestation time of over 5 weeks (est: -5.07 (2.275); p-value 0.029) and, in turn, a lower birthweight can be seen (est: -980.96 (474.567); p-value 0.042). None of the 3 interventions, vaginal cerclage, progesterone or Arabin pessary demonstrated statistical significance against any of the outcome measures in these women. In addition, none of the other clinical or demographic factors were associated with any of the 3 clinical outcomes.

3.3.2.2 No previous spontaneous preterm birth

In women with cervical surgery and no previous sPTB, VP is associated with an increased risk of PPROM (est 2.17 (0.65); p-value 0.001). Below a CL of 35mm, the gestation time decreases with every 5mm decrease in CL. Vaginal cerclage reduces the gestation time by 3.5 weeks (est -3.45 (0.907); p-value <0.001), Arabin pessary by 2.5 weeks (est -2.52 (0.591); p-value <0.001) and progesterone by 1.5 weeks (est -1.51 (0.576); p-value 0.009). As expected, birthweight follows the same trend with cerclage having the greatest impact, followed by pessary then progesterone, on the reduction of birthweight. Women that received no intervention during pregnancy have a longer gestation time (est 1.67 (0.396); p-value <0.001) and therefore a higher birthweight (est 328.27 (88.705); p-value <0.001). Furthermore, omega-3 supplementation prolongs gestation by 3 weeks (est 3.1 (0.637); p-value <0.001).

Table 11: Univariable analysis of three clinical outcomes; PPROM, Birthweight (grams), Gestation time (weeks) in women with and without a previous sPTB
Data are presented as model estimates (est) and standard error (se) with associated p-values

	Previous sPTB						No previous sPTB					
	PPROM		Birthweight		Gestation time		PPROM		Birthweight		Gestation time	
Covariate	**est (se)**	**P**	**est (se)**	**P**	**est (se)**	**P**	**est (se)**	**P**	**est (se)**	**P**	**est (se)**	**P**
Height (cm)	-0.03 (0.048)	0.478	10.38 (14.547)	0.478	-0.03 (0.069)	0.658	0 (0.036)	0.984	5.45 (5.963)	0.361	-0.01 (0.027)	0.78
Weight (kg)	-0.02 (0.023)	0.381	6.51 (5.448)	0.236	0.01 (0.026)	0.797	0 (0.015)	0.957	7.11 (2.528)	0.005	0 (0.011)	0.779
BMI	-0.04 (0.062)	0.526	16.55 (16.151)	0.309	0.03 (0.077)	0.668	0 (0.042)	0.944	15.71 (6.934)	0.024	0 (0.031)	0.906
Smoking	0.08 (0.64)	0.898	-317.97 (193.743)	0.105	-0.6 (0.94)	0.529	0.94 (0.46)	0.042	-109.65 (88.584)	0.217	-0.22 (0.402)	0.59
Age at EDD	-0.06 (0.066)	0.325	24.33 (19.484)	0.216	0 (0.094)	0.979	-0.1 (0.055)	0.079	13.61 (9.049)	0.133	0.08 (0.041)	0.038
Single Cone biopsy	-16.01 (1495.296)	0.991	-1.47 (329.17)	0.996	0.53 (1.581)	0.738	-0.31 (0.57)	0.592	83.51 (88.516)	0.346	0.73 (0.401)	0.068
Multiple cone biopsy	-	-	-	-	-	-	-12.84 (1455.398)	0.993	611.25 (711.437)	0.391	2.12 (3.267)	0.518
No. of LLETZ 1	16.89 (2465.326)	0.995	-5.05 (335.411)	0.988	-0.36 (1.604)	0.821	0.36 (0.793)	0.653	-71.05 (120.323)	0.555	-0.49 (0.548)	0.37
No. of LLETZ 2	17.59 (2465.326)	0.994	97.14 (412.312)	0.814	-1.02 (1.936)	0.6	0.29 (0.809)	0.722	-9.9 (123.212)	0.936	-0.46 (0.558)	0.408
No. of LLETZ 3	0 (6972.994)	1	-589.86 (894.43)	0.512	-4.73 (4.28)	0.272	0.61 (1.267)	0.632	-159.24 (224.53)	0.479	-0.73 (1.031)	0.479
Uterine Abnormality	-13.91 (1455.398)	0.992	860.44 (828.158)	0.302	3.22 (3.999)	0.423	-12.78 (1029.121)	0.99	-146.55 (503.91)	0.771	0.8 (2.321)	0.731
Previous PPROM	0.45 (0.645)	0.483	-103.94 (205.421)	0.614	-0.88 (0.969)	0.368	0.38 (0.774)	0.619	-411.42 (145.834)	0.005	**-1.55 (0.673)**	**0.022**
Single previous late miscarriage	-15.94 (2284.102)	0.994	-980.96 (474.567)	0.042	**-5.07 (2.275)**	**0.029**	-14.8 (1318.727)	0.991	43 (254.538)	0.866	0.75 (1.106)	0.499

Multiple previous late miscarriages	-	-	-	-	-	-	-14.8 (3956.18)	0.997	80.5 (712.708)	0.91	0.38 (3.28)	0.907
No intervention	-0.34 (0.637)	0.597	86.99 (192.463)	0.653	0.49 (0.914)	0.59	-0.53 (0.48)	0.267	328.27 (88.705)	<0.001	**1.67 (0.396)**	**<0.001**
Received intervention	0.4 (0.637)	0.531	-137.68 (191.981)	0.476	-0.72 (0.911)	0.431	-0.49 (1.044)	0.638	68.97 (144.798)	0.634	-0.34 (0.654)	0.599
Vaginal Cerclage	-15.97 (1769.258)	0.993	185.76 (383.168)	0.629	1.47 (1.838)	0.425	0.86 (0.484)	0.075	-460.78 (95.721)	<0.001	**-1.95 (0.431)**	**<0.001**
Progesterone	0.25 (0.673)	0.716	-287.55 (210.973)	0.177	-1.85 (0.986)	0.064	2.17 (0.65)	0.001	-821.92 (195.987)	<0.001	**-3.45 (0.907)**	**<0.001**
Arabin pessary	0.77 (0.691)	0.263	-76.47 (233.835)	0.745	-0.33 (1.122)	0.769	1.19 (0.547)	0.03	-351.71 (130.432)	0.007	**-1.51 (0.576)**	**0.009**
Shortest CL (15-20 mm)	0.08 (0.878)	0.927	-301.12 (314.202)	0.341	-1.19 (1.469)	0.422	0.1 (0.768)	0.9	-578.42 (132.101)	<0.001	-2.52 (0.591)	<0.001
Shortest CL (20-25 mm)	-1.07 (0.938)	0.253	204.73 (264.916)	0.442	1.31 (1.272)	0.308	0.42 (0.719)	0.556	339.99 (166.46)	0.042	1.97 (0.757)	0.01
Shortest CL (25-30 mm)	-0.61 (0.954)	0.52	254.49 (293.051)	0.388	1.8 (1.407)	0.205	-0.85 (0.794)	0.284	681.62 (141.957)	<0.001	2.98 (0.653)	<0.001
Shortest CL (30-35 mm)	-0.77 (1.212)	0.527	309.92 (364.656)	0.398	2.11 (1.671)	0.211	-0.99 (0.736)	0.178	788.92 (133.002)	<0.001	3.03 (0.609)	<0.001
Shortest CL (>35 mm)	-16.39 (1978.09)	0.993	785.31 (451.239)	0.086	3.25 (2.166)	0.137	-1.03 (0.793)	0.196	705.62 (138.442)	<0.001	3.52 (0.634)	<0.001
Omacor	-0.3 (1.119)	0.788	470.98 (305.228)	0.127	2.27 (1.468)	0.126	-1.42 (0.892)	0.112	695.58 (139.149)	<0.001	**3.1 (0.637)**	**<0.001**

3.3.3 MULTIVARIABLE ANALYSIS

The results of the multivariable analyses are included for each outcome in the tables below.

3.3.3.1 PREVIOUS SPONTANEOUS PRETERM BIRTH

Table 12 shows the results of the multivariable analysis for each outcome in women with a previous sPTB. For this cohort, the estimated gestation at delivery is 36.31 weeks. For gestation time, the number of previous late miscarriages, progesterone and omacor all have a significant impact. The use of omacor supplementation prolongs gestation with an estimated increase of 4 weeks (est 4.03 (1.53); p-value 0.011), an increase in birthweight can also be seen (est 757.71 (326.18); p-value 0.023). It is the only variable with a positive impact on gestation time or birthweight in this subgroup. Intervention with progesterone is associated with a 3 week decrease in gestation time (est -3.15 (1.059); p-value 0.004). This effect can also be seen in women with a previous late miscarriage (est -4.6 (2.282); p-value -0.048). Given the relatively small data set, no factors were found to have a significant impact on PPROM. There is no impact of LLETZ in any model. Neither vaginal cerclage nor Arabin pessary had any significant effect on any outcome.

Table 12: Multivariable analysis of women with a previous sPTB

	BIRTHWEIGHT		**GESTATION TIME**	
	est (se)	**P**	**est (se)**	**P**
(Intercept)	2211.91 (504.897)	<0.001	36.31 (1.39)	<0.001
Weight (kg)	7.25 (5.229)	0.17	-	-
Smoking	-257.97 (189.789)	0.179	-	-
Single previous late miscarriage	-1017.96 (482.189)	0.039	**-4.6 (2.282)**	**0.048**
Progesterone	-552.86 (229.937)	0.019	**-3.15 (1.059)**	**0.004**
Omacor	757.71 (326.18)	0.023	**4.03 (1.54)**	**0.011**
No. of LLETZ 1	98.28 (321.267)	0.761	0.27 (1.508)	0.857
No. of LLETZ 2	294.8 (404.246)	0.468	0.31 (1.844)	0.868
No. of LLETZ 3	-388.12 (830.991)	0.642	-4.73 (3.933)	0.233

3.3.3.2 NO PREVIOUS SPONTANEOUS PRETERM BIRTH

Table 13 shows the results for each patient without a previous sPTB. The estimated gestation time is 33.62 (1.436) weeks in this cohort and this is shorter than that of women with a previous sPTB. Previous PPROM and CL both have a statistically significant impact on gestation time. Below 35mm, gestation time shortens for each 5mm decrease in CL. A history of PPROM decreases the gestation time by over a week (est -1.42 (0.681); p-value 0.037). Cerclage, pessary and progesterone demonstrated no statistically significant impact on gestation time or birthweight. However, cerclage is associated with an increased risk of PPROM (est 2.16 (0.723); OR 8.69 (2.104-35.869); p-value 0.003), although the wide confidence interval raises uncertainty surrounding the extent of this risk. For birthweight; smoking, age, number of previous PPROM and CL are all statistically significant. Again, there is no impact of LLETZ in any model.

Table 13: Multivariable analysis of women without a previous sPTB

	PPROM			BIRTHWEIGHT		GESTATION TIME	
	est (se)	**OR (95% CI)**	**P**	**est (se)**	**P**	**est (se)**	**P**
(Intercept)	-0.63 (1.908)	0.53 (0.013, 22.481)	0.743	2386.51 (217.581)	<0.001	33.62 (1.436)	<0.001
Smoking	0.8 (0.478)	2.22 (0.871, 5.675)	0.095	-150.91 (83.665)	0.072	-	-
Age at EDD	-0.1 (0.058)	0.91 (0.809, 1.018)	0.097	4.92 (2.445)	0.045	0.07 (0.04)	0.066
Single previous PPROM	-	-	-	-305.67 (145.026)	0.036	**-1.42 (0.681)**	**0.037**
Shortest CL (15 – 20 mm)	-	-	-	351.78 (164.361)	0.033	**2 (0.762)**	**0.009**
Shortest CL (20 – 25 mm)	-	-	-	665.95 (139.878)	<0.001	**2.84 (0.652)**	**<0.001**
Shortest CL (25 – 30 mm)	-	-	-	745.54 (131.954)	<0.001	**2.94 (0.61)**	**<0.001**
Shortest CL (30 – 35 mm)	-	-	-	644.95 (137.039)	<0.001	**3.37 (0.638)**	**<0.001**
Shortest CL (>35 mm)	-	-	-	645.59 (138.5)	<0.001	**3.16 (0.638)**	**<0.001**
Vaginal cerclage	**2.16 (0.723)**	**8.69 (2.104, 35.869)**	**0.003**	-	-	-	-
No. of LLETZ 1	0.55 (0.857)	1.74 (0.325, 9.341)	0.518	-69.59 (112.814)	0.538	0.28 (0.671)	0.676
No. of LLETZ 2	0.61 (0.882)	1.84 (0.326, 10.34)	0.491	-78.12 (114.004)	0.494	0.2 (0.732)	0.786
No. of LLETZ 3	0.1 (1.421)	1.1 (0.068, 17.844)	0.946	-88.77 (209.415)	0.672	0.49 (1.112)	0.657

3.4 DISCUSSION

This retrospective cohort study demonstrates the uncertainty surrounding PTB prevention in women with prior excisional procedures of the cervix. Women that do not require an intervention are lower risk and therefore have a prolonged gestation relative to women that receive an intervention. Current practice using either cerclage, pessary or progesterone confers no significant benefit in the prolonging of gestation time. Our analysis shows that progesterone may, in fact, be less effective than cerclage or pessary in this cohort. Our findings for cerclage are supported by both the systematic review undertaken within this thesis and the review by Grabovac *et al.*[123] The PECEP trial is the only multicentre randomised study to support the use of the Arabin pessary for short cervix indications[89]. However, this is not supported by our study or the findings of the RCTs by Nicolaides *et al.*[87] and Hui *et al.*[88] The differences in these results may be due to the inclusion of cervical surgery participants in our study and in the study by Nicolaides *et al.*[87] constituting 17% (*n* = 159/932) of the cohort, but the exclusion of these women from the PECEP trial. The OPPTIMUM study[80] demonstrated no efficacy of progesterone in women with a short cervix. Including women with prior cervical surgery within a broad risk cohort may have added to the heterogeneity of the study population and weakened the estimated overall benefit of progesterone in other high-risk groups. It is unclear precisely how many participants within this study had prior cervical surgery and therefore it is not possible to determine the extent of this impact on results. This highlights the need for women with prior cervical surgery to be studied as a separate cohort to women at high risk of PTB with a mid-trimester short cervix due to other indications. The 2021 EPPPIC study[79] included participant data from OPPTIMUM and supported the use of progesterone in women with a short cervix. This further supports the assertion that interventions may have varying efficacy in different risk cohorts.

Our understanding of the mechanisms leading to PTB is limited. The results of this study suggest that there may be differing mechanisms leading to cervical shortening and subsequent PTB in women with a mid-trimester short cervix following cervical surgery compared to other high-risk groups. This may explain the varying efficacy of interventions in different high-risk cohorts. Alternatively, the mechanisms by which the interventions prevent PTB may be impeded in women with cervical surgery due to the loss of cervical tissue. The pharmacodynamics of progesterone are not well understood in women with a short cervix. However, studies suggest that the administration of VP exerts only local anti-inflammatory effects and the impact on systemic progesterone concentration is limited[140]. Further studies are required to understand its precise mode of action and subsequently explain the varying

efficacy per cohort. In addition, the rates of Arabin pessary displacement are higher in women with prior cervical surgery, most significantly in those with a previous KCB[85], and this may reduce its effect in this group. If there is inadequate cervical tissue to correctly site the pessary or provide sufficient posterior angling of the cervix, this could reduce the efficacy of the pessary in preventing PTB.

Unfortunately, due to the limited cohort of participants that experienced PPROM, we were unable to draw many conclusions for this outcome. However, cerclage can be seen to cause an increased risk of PPROM. This may be due to the introduction of infection which, as with any surgical procedure, is a known risk associated with the siting of a cerclage[69]. Another key finding was the greater than 4-week reduction in gestation time in women with a previous late miscarriage. Women with a previous mid-trimester loss are a known risk group and present a high-risk subgroup in women with previous cervical surgery and a prior sPTB.

3.4.1 Implications for practice

Our findings do not support the use of vaginal cerclage, pessary or VP to prevent PTB in women with cervical surgery. A large-scale multicentre RCT is required to confirm these findings and inform future practice. Given the ongoing uncertainty surrounding the management of these women and the lack of an effective intervention, screening may also present little benefit. Women with prior cervical surgery that develop a mid-trimester CL <25mm are a higher risk cohort than those with surgery alone. The identification of these women, whilst unable to offer an effective intervention to prevent PTB, does not meet the Wilson and Jungner screening criteria[141]. Further to this, not only is screening costly, but it may induce patient anxiety and cause an increase in stress levels during pregnancy. This is an independent risk factor for sPTB[102]. This raises questions for future practice and the most appropriate follow-up and counselling of women with previous cervical surgery.

Our results support the findings of the latest Cochrane review[107] in supporting the use of omega-3 supplementation to prolong pregnancy. This effect can be seen in women with prior cervical surgery and a previous PTB and therefore we support the continued use of Omacor in these women.

3.4.2 Strengths and limitations

This study is the only study to compare the efficacy of interventions to prevent PTB in women with prior LLETZ or KCB of the cervix. Previously, several published retrospective cohort studies considered the use of vaginal cerclage in this cohort but, as of yet, no studies

have compared the efficacy to that of the Arabin pessary or VP. The results presented in this study are valuable in guiding future research.

The main limitation of this study is the retrospective design and the consequent risk of bias due to confounding. Despite stratification of data based on the most significant confounding factor, previous sPTB, there may still be presence of bias. Therefore, large multicentre RCTs are necessary in order to confirm our findings. A further limitation is the lack of neonatal outcomes due to our inability to obtain ethical approval, secondary to covid-related restrictions on new student projects, for the collection and use of neonatal outcomes and this limited our ability to present a complete core outcome set. Future studies should consider the impact of these interventions on neonatal outcomes. However, the most common cause of neonatal morbidity and mortality is PTB and therefore these outcomes are closely linked to gestation at delivery.

Suture material may affect the efficacy of cerclage in preventing PTB. A study by Kindinger *et al.*[68] found the use of a monofilament suture was more beneficial than a braided suture for women with cervical surgery. Our study included predominantly participants with braided sutures and this may have affected the overall efficacy of cerclage. Future studies should consider the cerclage material when studying its efficacy in women with prior cervical excisional procedures.

3.5 Conclusion

In women with previous cervical surgery, current interventions including vaginal cerclage, Arabin pessary and VP are ineffective in preventing PTB. Cerclage increases the risk of PPROM in women with cervical surgery and a previous sPTB. Large multicentre RCTs are required to confirm the findings of our study.

3.6 Ethical approval

Research ethics committee approval is in place for the collection and use of the specialist PTB prevention clinic data at LWH for continuous service evaluation.

3.7 Conflict of interests

The authors declare no conflicts of interest.

CHAPTER 4 - DISCUSSION

4.1 MAIN FINDINGS

The studies undertaken within this thesis have highlighted some of the key issues related to the management of women with prior cervical surgery. Firstly, there is a paucity of research which specifically determines the risk of PTB in a population with cervical surgery. Rather, most evidence for the management of this group comes from their inclusion in a mixed high-risk population with other conditions that predispose to PTB including previous PTB and short cervix indications. Only 6 published cohort studies have considered the use of cerclage and there are no studies considering the use of either pessary or progesterone in this cohort alone. Furthermore, there are no published studies comparing the efficacy of these interventions to one another in the prevention of sPTB for women with prior excisional surgery, nor are there any studies with a prospective design. The systematic review within chapter 2 demonstrates this lack of evidence and highlighted the urgent requirement for further research in this area.

In addition, our cohort study (chapter 3) demonstrated no statistically significant benefit of cerclage, pessary or progesterone in prolonging gestation in women with previous cervical surgery. Furthermore, cerclage can be seen to cause an increase in the risk of PPROM. In women with the additional risk of a previous sPTB, progesterone is associated with a decrease in gestation time to delivery. The studies within our systematic review did not support the use of cerclage for women with previous cervical surgery. Our study is the first to extend these findings to include pessary and progesterone and therefore caution should be taken in using these three interventions in women with previous cervical surgery. The findings of large studies with broad risk cohorts, including women with a short cervix or a previous sPTB, are the current basis for the use of these interventions. However, studies of this kind may overestimate the efficacy of these interventions in women with previous cervical surgery and we have demonstrated a lack of effect in this cohort. Further prospective studies are required to confirm our findings and inform future practice. Though a two-centre randomised-feasibility study demonstrated inadequate power to perform a multi-arm comparative RCT in this cohort[116], a larger multicentre trial comparing two treatments may be more appropriate to confirm our findings. A preceding pilot study may be necessary to confirm the feasibility of an RCT in this cohort.

It cannot be discounted that the results of chapter 3 may be in part due to the identification of a high-risk subgroup. Women that require treatment as a result of a mid-trimester short

cervix, are at a higher risk of sPTB than women that do not develop a short cervix[42] and therefore the apparent lack of effect of cerclage, pessary and progesterone in our study may reflect this. In addition, the results of published studies may have been impacted by the presence of participants with cervical surgery. This may have served to underestimate the effects of interventions in other high-risk cohorts where subgroup analysis had not been performed for women with prior excision of the cervix. This could provide an explanation for the discrepancies in the results of existing studies surrounding the use of cerclage, Arabin pessary and VP to prevent PTB. Up to now, all women with cervical surgery were managed following recommendations from large studies[69, 72, 76, 80, 89] considering broad high-risk cohorts including women with a previous sPTB and short cervix indications. However, our lack of understanding of the mechanisms leading to PTB limits our ability to extrapolate these results between risk groups. In addition, our results suggest that the mechanisms leading to PTB in separate risk cohorts differ and therefore the efficacy of interventions to prevent PTB in each group may also vary. As a result, future research in this area should stratify for the various risk factors of PTB either through exclusion or subgroup analysis within larger studies. This includes separating short cervix indications and participants with previous cervical surgery within studies.

Our cohort study highlights the rate of treatment 18% (*n* = 67/365), of which 34% (*n* = 23/67) delivered <37 weeks, in women with previous cervical surgery and no prior sPTB. This was greater than the 14% (*n* = 98/725) treatment rate and the 24% (*n* = 24/98) PTB rate in the Kindinger *et al.*[68] study whereby women with previous cervical surgery that developed a short cervix received a cerclage. Our cohort had a greater number of women developing a short cervix following cervical surgery and this may account for the differences in these rates. Both our cohort study and the study by Kindinger *et al.*[68] followed UK NICE guidance for the treatment of women at risk of PTB and therefore both provide an accurate representation of UK clinical practice. Both studies indicate a lack of effect of cerclage in preventing PTB in women with previous cervical surgery. From our cohort of women with cervical surgery and no previous sPTB, 82% (*n* = 298/365) of women received no treatment, of which 14% (*n* = 43/298) had a PTB <37 weeks. This is also greater than the UK background population PTB rate of 7.3%[135]. However, these rates demonstrate a multifaceted problem whereby not only are we failing to identify a proportion of high-risk women, the current interventions also do not appear effective in preventing its occurrence. In our cohort, the treatment rate increased to 50% (*n* = 38/76) with the additional risk factor of a previous sPTB, and of these women 37% (*n* = 14/38) went on to deliver spontaneously <37 weeks. Therefore, women with cervical surgery and previous sPTB are at a much greater risk of PTB than women with cervical surgery alone and these women may require more

regular follow-up. In addition, of the women with a previous sPTB that had a CL≥25mm and received no treatment, 21% (*n* = 5/24) had a PTB <37 weeks. Currently clinicians are guided to consider intervention in women from this cohort with a CL ≥25mm, as per NICE guidance[15]. However, it is unclear how many clinicians offer treatment in these situations and given we have demonstrated 21% of these women still deliver preterm, the guidance could be optimised to avoid undertreating these women.

4.1.1 Cerclage

Neither the systematic review nor the cohort study undertaken within this thesis support the use of cerclage for women with previous cervical surgery. These findings are congruent with that of the systematic review by Grabovac *et al.*[123] Not only did cerclage confer no significant benefit to the prolonging of pregnancy, we also demonstrated an increased risk of PPROM. This may be linked to the introduction of infection on siting the cerclage, a known risk of the procedure. The basis for the use of cerclage in women with prior cervical surgery is from studies including the Alfirevic *et al.*[69] Cochrane systematic review and the Jarde *et al.*[72] review. Alfirevic *et al.*[69] were unable to perform subgroup analysis for women with a short cervix but Jarde *et al.*[72] demonstrated the efficacy of cerclage in reducing PTB <34 weeks in this cohort. Neither study performed subgroup analysis for women with previous cervical surgery and therefore the current practice has been inferred by applying data from a generic high-risk cohort of women with a short cervix to women with a short cervix due to cervical surgery. All studies considering cerclage in women at risk of PTB due to cervical surgery alone are retrospective cohort study designs. As highlighted in our systematic review, these studies have found no benefit for the use of cerclage in this cohort although results may be biased due to confounding and impacted by the identification of the high-risk subgroup of women that develop a short cervix and require treatment.

One issue that must be addressed is the differential efficacy of a cerclage relative to the suture material used. Initial studies such as that of Kindinger *et al.*[68] suggest monofilament may be preferential to braided sutures in prolonging pregnancy in women with prior cervical surgery. Our cohort study had an insufficient population size with a cerclage to draw conclusions based on suture material. However, the majority of patients received a braided suture and therefore this may have had a direct impact on the efficacy of cerclage in preventing PTB in these women. Currently, the C-STICH trial[136] comparing cerclage suture materials is analysing the results of their RCT and the findings of this study will be useful in guiding both future research and future practice for managing high-risk women. In addition, cerclage technique is often debated in the literature. The McDonald technique involves the siting of the stitch at the cervicovaginal junction whereas using the Shirodkar technique, the

stitch is sited more superiorly at the level of the cardinal ligaments. Studies have suggested that the Shirodkar technique may be a more beneficial option to the McDonald technique for prolonging pregnancy in women with a short cervix[142, 143]. However, as of yet, there are no RCTs. This, again, may present a further consideration for future studies comparing the efficacy of interventions to prevent PTB. A protocol has been registered with PROSPERO, as of July 2020, for a systematic review and meta-analysis comparing the McDonald and Shirodkar cerclage techniques in women at risk of PTB[144]. The findings of this review may be utilised in the planning of future studies of cerclage.

4.1.2 Pessary

As discussed in chapter 2, there had been no studies of the Arabin pessary in women with previous cervical surgery and therefore the work presented here represents the first study of its kind. Similar to the findings of our cohort study for cerclage, the Arabin pessary also demonstrated no statistical significance in prolonging gestation time to delivery in women with previous cervical surgery. This is contradictory to the findings of the PECEP trial[89], that demonstrated the efficacy of the Arabin pessary in preventing PTB in women with a mid-trimester CL <25mm. However, studies of the Arabin pessary have historically presented conflicting results and the PECEP trial is the only large-scale study to support the use of the Arabin pessary in singleton pregnancies with a short cervix. Two further RCTs demonstrated no additional benefit of the Arabin pessary relative to expectant management in this group[87, 88]. The differences in these findings may be a result of differences in technique for the siting and confirmation of placement of the Arabin pessary. Equally, minor differences in the cohorts such as a varying number of participants that have experienced a previous spontaneous PTB may limit the strength of findings. We have also presented results to suggest the mechanism of PTB in women with a short cervix may vary to that of women with previous cervical surgery. This presents another potential confounder in the results of large randomised controlled studies that may not have accounted for the number of cervical surgery patients and this could further explain the conflicting results in studies.

The mechanism of action of the Arabin pessary is suggested to be linked to the posterior angling of the cervix that reduces the contact of fetal membranes with the vaginal canal in conjunction with a re-distribution in the weight of the uterus that relieves the pressure on the internal os[84]. It may also act as an added barrier to infection while providing some cervical elongation and a limitation on funnelling at the internal os[85]. However, in women with prior cervical surgery, specifically those with a KCB, the rate of cervical pessary displacement is greater and this may affect the overall efficacy of the pessary in this group[85]. Though the Arabin pessary may present a cost-effective and minimally invasive preventative intervention

for women in other high-risk groups, more consideration should be taken in women with previous cervical surgery.

4.1.3 PROGESTERONE

From the cohort study of LWH data, progesterone has no statistically significant impact on the gestation time of women with previous cervical surgery and no prior sPTB and is associated with a decrease in gestation time in women with a previous sPTB and cervical surgery. Studies suggest that the effect of progesterone is due to a local increase in progesterone concentration which inhibits the inflammatory process that causes PTB, there are limited effects on the systemic concentration of progesterone[140]. Our lack of understanding of the pharmacodynamics of progesterone limits our ability to explain the varying efficacy for PTB prevention seen in published studies of women with a short cervix and our cohort study of women with previous cervical surgery. The OPPTIMUM study[80] found no additional benefit of VP in women with a short cervix. However, the number of participants with cervical surgery are not detailed within the study results and therefore it is not possible to determine the extent of this impact on the overall results. The 2021 EPPPIC study incorporated the individual participant data (IPD) of several studies including OPPTIMUM[80] and supported the use of progesterone in women with a short cervix. This may be due to the inclusion of studies with a variety of risk cohorts such as previous sPTB, short cervix and IVF within the meta-analysis. Therefore, it is not inconceivable that progesterone may be effective in women at risk of PTB due to a previous sPTB or short cervix alone yet ineffective in those with previous cervical surgery. Future studies should consider these groups as separate cohorts either through subgroup analysis or exclusion and incorporation into stand-alone studies.

4.1.4 17-ALPHA HYDROXYPROGESTERONE CAPROATE

Progesterone in the form of IM 17-OHPC has not been studied for use in women with prior cervical surgery. However, in other high-risk cohorts there have been conflicting findings and as a result it is not currently recommended in UK guidance[15, 67]. The 2021 EPPPIC study concluded 17-OHPC was effective in reducing PTB <34 weeks and the impact may be greatest in women with a short cervix[79]. This is in contrast to the preceding findings of Winer *et al.*[99] in studying the same cohort. We have suggested there may be different mechanisms leading to PTB in women with a short cervix relative to women with previous cervical surgery. This is based on the findings of our cohort study compared to studies of short cervix cohorts[69, 72, 79, 89] demonstrating the differing efficacy of interventions in these groups. Therefore, IM 17-OHPC may be effective in women with a previous LLETZ or KCB despite

the study by Winer *et al.*[99] finding no benefit in a short cervix cohort. Our study also demonstrated the lack of statistically significant effect of VP on prolonging gestation in this group and the associated decrease in gestation time in women with a previous sPTB. However, previous studies have concluded the mechanism of action of 17-OHPC is likely different to that of VP due to the lack of local anti-inflammatory effect that can be seen with VP[75]. Given these findings, there remain questions over whether 17-OHPC could be effective in this cohort.

4.1.5 TRANSABDOMINAL CERCLAGE

One of the theories, explaining why women with previous cervical surgery are at an increased risk of PTB, describes a rapid regeneration of collagenous cervical tissue that is inferior in quality[24]. McDonald cerclages are likely sited within this inferior quality cervical tissue and this may increase the risk of cerclage failure due to the lacking integrity of the cervical tissue. One potential solution to this may be the use of a TAC in these women as these are generally sited more superiorly. The MAVRIC trial demonstrated the efficacy of TAC in preventing early PTB in women with a previous failed vaginal cerclage in a prior pregnancy[145]. The pregnancy outcomes were more favourable following a TAC than following a high or low vaginal cerclage[145]. Further studies would be required to determine the efficacy of TAC in women with previous cervical surgery alone. However, introducing TAC in this cohort would present several practical implications in terms of patient acceptability, cost and over-treatment of patients. A TAC is typically sited prophylactically and given our treatment rate in women with previous LLETZ or cone biopsy without a previous sPTB was 18% (*n* = 67/365), prophylactic intervention may be costly and lead to over-treatment of women in this cohort.

4.1.6 OMEGA-3 FATTY ACIDS

The use of omega-3 supplementation is recommended for women at risk of PTB as per the latest Cochrane review surrounding it's use[107]. Our retrospective cohort study supported these findings for the use of Omacor in women with previous cervical surgery. Our results demonstrate Omacor supplementation confers a significant lengthening in gestation time. This effect was not seen in any of the three interventions studied. This is the first time this has been demonstrated in a population of women with cervical surgery alone.

4.2 IMPLICATIONS FOR RESEARCH

Historically, women with previous cervical surgery have been studied alongside other cohorts of high-risk women, including women with a short cervix or a previous sPTB. However, this thesis has highlighted the need for women with previous cervical surgery to be studied as a separate cohort to other high-risk women. Our findings suggest that the aetiology of PTB in various risk groups may differ and this may directly impact the efficacy of interventions to prevent PTB. Therefore, future studies should separate all risk cohorts in order to determine the individual efficacy of interventions in those groups. This would also avoid the overestimation or underestimation of treatment effect that may occur when studying separate risk cohorts together. In addition, further prospective studies are required to confirm the findings of our studies. A multicentre RCT would present the highest quality evidence in order to confirm these findings and therefore undertaking a multi-centre randomised feasibility study would serve to inform future research.

4.3 IMPLICATIONS FOR PRACTICE

Given the ongoing uncertainty surrounding the optimal management of women with prior cervical excision and the retrospective study design within this thesis, it is not possible to make recommendations for clinical practice. However, the lack of statistically significant effect of cerclage, pessary and progesterone in prolonging gestation cannot be ignored. Caution should be used in treating women with cervical surgery as these interventions may be less effective than studies suggest for other risk groups. Further prospective studies in this area are necessary to confirm our findings and optimise the follow-up and management of women with cervical surgery.

4.4 STRENGTHS AND LIMITATIONS

This thesis is the first to establish the clinical problem we face in managing women with previous cervical surgery. There are no studies of the comparative efficacy of interventions to prevent PTB in these women and therefore management protocols are drawn from broad high-risk cohorts. Unfortunately, due to lacking evidence, the systematic review served only to demonstrate the gap in the evidence base and could not draw conclusions surrounding the most effective intervention to prevent PTB. Further to this, due to the timescale for undertaking this thesis, we were limited in choice of study design. A retrospective cohort

study does not present the highest quality of evidence. However, it would not have been feasible to perform either a prospective study of adequate population size or an RCT.

Due to the implications of Covid-19 and the subsequent change in university regulations regarding the seeking of ethical approval, we were unable to obtain ethical approval for the use of neonatal outcomes. In addition, LWH specialist PTB prevention clinic data did not consistently contain details of any side effects as a result of the interventions and as a result these were not included. This limited our ability to present a full core outcome set and therefore the cohort study is lacking some outcomes that may be considered important to both parents, when making decisions surrounding management options during pregnancy, and clinicians when counselling patients. However, we do not expect this to have made a difference to the principal findings of no benefit from different treatments in a cervical surgery cohort. We were further limited by the population demographics with 96% Caucasian patients. This limits the generalisability of our findings to other populations including those with a greater representation of Black ethnic groups as this is a significant risk factor for PTB[146].

4.5 Conclusion

There are currently no studies comparing the efficacy of interventions to prevent PTB in women with previous LLETZ or KCB of the cervix. Our study demonstrated around 18% of women with previous cervical surgery and no prior sPTB will develop a short cervix and require a preventative intervention during pregnancy. There is no statistically significant benefit of cerclage, Arabin pessary or VP in prolonging gestation time in this cohort. Progesterone is associated with a decrease in gestation time in women with previous cervical surgery and a previous PTB. As a result of the retrospective cohort study design, these results should be interpreted with caution due to potential bias due to confounding. Further prospective studies, preferably in the form of a multicentre RCT, are required to confirm our findings. Our results suggest that the aetiology of PTB or the mechanisms by which interventions prevent its occurrence in women with cervical surgery may differ to the mechanisms for those with a short cervix and other high-risk cohorts. Therefore, future studies should consider cervical surgery participants as a separate cohort to those at high risk of PTB due to other indications.

REFERENCES

1. Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health* 2019;7(1):e37-e46.
2. Nott JP, Bonney EA, Pickering JD, Simpson NAB. The structure and function of the cervix during pregnancy. *Translational Research in Anatomy* 2016;2:1-7.
3. Ananth CV, Vintzileos AM. Epidemiology of preterm birth and its clinical subtypes. *J Matern Fetal Neonatal Med* 2006;19(12):773-82.
4. Breslin N, Gyamfi-Bannerman C. Current Preterm Birth Prevention Strategies. *Clinics in Perinatology* 2020;47(4):705-17.
5. Jones EO, Liew ZQ, Rust OA. The Short Cervix: A Critical Analysis of Diagnosis and Treatment. *Obstetrics and Gynecology Clinics of North America* 2020;47(4):545-67.
6. Miller ES, Grobman WA. The association between cervical excisional procedures, midtrimester cervical length, and preterm birth. *Am J Obstet Gynecol* 2014;211(3):242.e1-4.
7. Laughon SK, Albert PS, Leishear K, Mendola P. The NICHD Consecutive Pregnancies Study: recurrent preterm delivery by subtype. *American Journal of Obstetrics and Gynecology* 2014;210(2):131.e1-.e8.
8. Kinney MV, Lawn JE, Howson CP, Belizan J. 15 Million preterm births annually: what has changed this year? *Reproductive health* 2012;9:28-.
9. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics* 2010;126(3):443-56.
10. Iacovidou N, Varsami M, Syggellou A. Neonatal outcome of preterm delivery. *Ann N Y Acad Sci* 2010;1205:130-4.
11. Marret S, Ancel PY, Marpeau L, Marchand L, Pierrat V, Larroque B, et al. Neonatal and 5-year outcomes after birth at 30-34 weeks of gestation. *Obstet Gynecol* 2007;110(1):72-80.
12. Mahendroo M. Cervical remodeling in term and preterm birth: insights from an animal model. *Reproduction* 2012;143(4):429-38.
13. Andersson S, Minjarez D, Yost NP, Word RA. Estrogen and Progesterone Metabolism in the Cervix during Pregnancy and Parturition. *The Journal of Clinical Endocrinology & Metabolism* 2008;93(6):2366-74.
14. Myers KM, Feltovich H, Mazza E, Vink J, Bajka M, Wapner RJ, et al. The mechanical role of the cervix in pregnancy. *Journal of Biomechanics* 2015;48(9):1511-23.

15. Excellence NIfHaC. *Prophylactic vaginal progesterone and prophylactic cervical cerclage* [NICE guideline]. 2019. https://www.nice.org.uk/guidance/ng25/chapter/Recommendations#prophylactic-vaginal-progesterone-and-prophylactic-cervical-cerclage (accessed 19/01 2021).
16. Owen J, Yost N, Berghella V, Thom E, Swain M, Dildy Iii GA, et al. Mid-trimester endovaginal sonography in women at high risk for spontaneous preterm birth. *Journal of the American Medical Association* 2001;286(11):1340-8.
17. Martin-Hirsch PPL, Paraskevaidis E, Bryant A, Dickinson HO. Surgery for cervical intraepithelial neoplasia. *Cochrane Database of Systematic Reviews* 2013;2013(12).
18. Mesher D, Panwar K, Thomas SL, Edmundson C, Choi YH, Beddows S, et al. The Impact of the National HPV Vaccination Program in England Using the Bivalent HPV Vaccine: Surveillance of Type-Specific HPV in Young Females, 2010–2016. *The Journal of Infectious Diseases* 2018;218(6):911-21.
19. Bruinsma FJ, Quinn MA. The risk of preterm birth following treatment for precancerous changes in the cervix: A systematic review and meta-analysis. *BJOG: An International Journal of Obstetrics and Gynaecology* 2011;118(9):1031-41.
20. Shanbhag S, Clark H, Timmaraju V, Bhattacharya S, Cruickshank M. Pregnancy outcome after treatment for cervical intraepithelial neoplasia. *Obstet Gynecol* 2009;114(4):727-35.
21. Wuntakal R, Castanon A, Landy R, Sasieni P. How many preterm births in England are due to excision of the cervical transformation zone? Nested case control study. *BMC Pregnancy Childbirth* 2015;15:232.
22. Mitra A, Kindinger L, Kalliala I, Smith JR, Paraskevaidis E, Bennett PR, et al. Obstetric complications after treatment of cervical intraepithelial neoplasia. *Br J Hosp Med (Lond)* 2016;77(8):C124-7.
23. Hein M, Valore EV, Helmig RB, Uldbjerg N, Ganz T. Antimicrobial factors in the cervical mucus plug. *Am J Obstet Gynecol* 2002;187(1):137-44.
24. Founta C, Arbyn M, Valasoulis G, Kyrgiou M, Tsili A, Martin-Hirsch P, et al. Proportion of excision and cervical healing after large loop excision of the transformation zone for cervical intraepithelial neoplasia. *Bjog* 2010;117(12):1468-74.
25. Cooper DB, Carugno J, Menefee GW. Conization Of Cervix. In: *StatPearls.* Treasure Island (FL): StatPearls Publishing

26. Bevis KS, Biggio JR. Cervical conization and the risk of preterm delivery. *American Journal of Obstetrics and Gynecology* 2011;205(1):19-27.

27. Castanon A, Landy R, Brocklehurst P, Evans H, Peebles D, Singh N, et al. Risk of preterm delivery with increasing depth of excision for cervical intraepithelial neoplasia in England: nested case-control study. *Bmj* 2014;349:g6223.
28. Klaritsch P, Reich O, Giuliani A, Tamussino K, Haas J, Winter R. Delivery outcome after cold-knife conization of the uterine cervix. *Gynecol Oncol* 2006;103(2):604-7.
29. Ortoft G, Henriksen T, Hansen E, Petersen L. After conisation of the cervix, the perinatal mortality as a result of preterm delivery increases in subsequent pregnancy. *Bjog* 2010;117(3):258-67.
30. Lindeque BG. Management of cervical premalignant lesions. *Best Practice and Research: Clinical Obstetrics and Gynaecology* 2005;19(4 SPEC. ISS.):545-61.
31. Noehr B, Jensen A, Frederiksen K, Tabor A, Kjaer SK. Depth of cervical cone removed by loop electrosurgical excision procedure and subsequent risk of spontaneous preterm delivery. *Obstetrics and Gynecology* 2009;114(6):1232-8.
32. Castañon A, Landy R, Brocklehurst P, Evans H, Peebles D, Singh N, et al. Is the increased risk of preterm birth following excision for cervical intraepithelial neoplasia restricted to the first birth post treatment? *Bjog* 2015;122(9):1191-9.
33. Khalid S, Dimitriou E, Conroy R, Paraskevaidis E, Kyrgiou M, Harrity C, et al. The thickness and volume of LLETZ specimens can predict the relative risk of pregnancy-related morbidity. *Bjog* 2012;119(6):685-91.
34. Anwar A, Igbenehi C, Lindow SW, Noor N, Musa S, Saha A. Pregnancy outcome after electrosurgical cervical cone biopsy using Fischer cone biopsy excisor. *J Matern Fetal Neonatal Med* 2016;29(3):477-81.
35. Dursun P, LeBlanc E, Nogueira MC. Radical vaginal trachelectomy (Dargent's operation): A critical review of the literature. *European Journal of Surgical Oncology (EJSO)* 2007;33(8):933-41.
36. Bentivegna E, Gouy S, Maulard A, Chargari C, Leary A, Morice P. Oncological outcomes after fertility-sparing surgery for cervical cancer: a systematic review. *Lancet Oncol* 2016;17(6):e240-e53.
37. Sanchez-Migallon A, Lago V, Matute L, Domingo S. Obstetric complications as a challenge after radical trachelectomy: a review of the literature. *J Obstet Gynaecol* 2019;39(7):885-8.
38. House M, McCabe R, Socrate S. Using imaging-based, three-dimensional models of the cervix and uterus for studies of cervical changes during pregnancy. *Clinical Anatomy* 2013;26(1):97-104.
39. Hughes K, Kane SC, Araujo Júnior E, Da Silva Costa F, Sheehan PM. Cervical length as a predictor for spontaneous preterm birth in high-risk singleton pregnancy: current knowledge. *Ultrasound in Obstetrics & Gynecology* 2016;48(1):7-15.

40. Excellence NIfHaC. *Diagnosing preterm labour for women with intact membranes* [NICE guideline]. 2019. https://www.nice.org.uk/guidance/ng25/chapter/Recommendations#diagnosing-preterm-labour-for-women-with-intact-membranes (accessed 26/04 2021).
41. Hatanaka AR, Mattar R, Kawanami TEN, França MS, Rolo LC, Nomura RMY, et al. Amniotic fluid "sludge" is an independent risk factor for preterm delivery. *Journal of Maternal-Fetal and Neonatal Medicine* 2016;29(1):120-5.
42. Iams JD, Goldenberg RL, Meis PJ, Mercer BM, Moawad A, Das A, et al. The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network. *N Engl J Med* 1996;334(9):567-72.
43. Berghella V, Pereira L, Gariepy A, Simonazzi G. Prior cone biopsy: Prediction of preterm birth by cervical ultrasound. *American Journal of Obstetrics and Gynecology* 2004;191(4):1393-7.
44. Sharp AN, Alfirevic Z. Provision and practice of specialist preterm labour clinics: a UK survey of practice. *BJOG: An International Journal of Obstetrics & Gynaecology* 2014;121(4):417-21.
45. Pergialiotis V, Bellos I, Antsaklis A, Loutradis D, Daskalakis G. Presence of amniotic fluid sludge and pregnancy outcomes: A systematic review. *Acta Obstet Gynecol Scand* 2020;99(11):1434-43.
46. Kusanovic JP, Espinoza J, Romero R, Gonçalves LF, Nien JK, Soto E, et al. Clinical significance of the presence of amniotic fluid ‘sludge’ in asymptomatic patients at high risk for spontaneous preterm delivery. *Ultrasound in Obstetrics & Gynecology* 2007;30(5):706-14.
47. Adanir I, Ozyuncu O, Gokmen Karasu AF, Onderoglu LS. Amniotic fluid "sludge"; prevalence and clinical significance of it in asymptomatic patients at high risk for spontaneous preterm delivery. *J Matern Fetal Neonatal Med* 2018;31(2):135-40.
48. Mancuso MS, Szychowski JM, Owen J, Hankins G, Iams JD, Sheffield JS, et al. Cervical funneling: effect on gestational length and ultrasound-indicated cerclage in high-risk women. *Am J Obstet Gynecol* 2010;203(3):259.e1-5.
49. Doyle N, Monga M. Role of ultrasound in screening patients at risk for preterm delivery. *Obstetrics and gynecology clinics of North America* 2004;31:125-39.
50. Ville Y, Rozenberg P. Predictors of preterm birth. *Best Practice and Research: Clinical Obstetrics and Gynaecology* 2018;52:23-32.
51. Saade GR, Thom EA, Grobman WA, Iams JD, Mercer BM, Reddy UM, et al. Cervical funneling or intra-amniotic debris and preterm birth in nulliparous women with

midtrimester cervical length less than 30 mm. *Ultrasound Obstet Gynecol* 2018;52(6):757-62.

52. Suff N, Story L, Shennan A. The prediction of preterm delivery: What is new? *Semin Fetal Neonatal Med* 2019;24(1):27-32.
53. Excellence NIfHaC. *Biomarker tests to help diagnose preterm labour in women with intact membranes* [NICE guideline]. 2018. https://www.nice.org.uk/guidance/dg33/resources/biomarker-tests-to-help-diagnose-preterm-labour-in-women-with-intact-membranes-pdf-1053749042629 (accessed 26/04 2021).
54. Abbott DS, Hezelgrave NL, Seed PT, Norman JE, David AL, Bennett PR, et al. Quantitative fetal fibronectin to predict preterm birth in asymptomatic women at high risk. *Obstet Gynecol* 2015;125(5):1168-76.
55. Goodfellow L, Care A, Sharp A, Ivandic J, Poljak B, Roberts D, et al. Effect of QUiPP prediction algorithm on treatment decisions in women with a previous preterm birth: a prospective cohort study. *Bjog* 2019;126(13):1569-75.
56. Watson HA, Seed PT, Carter J, Hezelgrave NL, Kuhrt K, Tribe RM, et al. Development and validation of predictive models for QUiPP App v.2: tool for predicting preterm birth in asymptomatic high-risk women. *Ultrasound Obstet Gynecol* 2020;55(3):348-56.
57. Nikolova T, Uotila J, Nikolova N, Bolotskikh VM, Borisova VY, Di Renzo GC. Prediction of spontaneous preterm delivery in women presenting with premature labor: a comparison of placenta alpha microglobulin-1, phosphorylated insulin-like growth factor binding protein-1, and cervical length. *Am J Obstet Gynecol* 2018;219(6):610.e1-.e9.
58. Conde-Agudelo A, Romero R. Cervical phosphorylated insulin-like growth factor binding protein-1 test for the prediction of preterm birth: A systematic review and metaanalysis. *American Journal of Obstetrics and Gynecology* 2016;214(1):57-73.
59. Conde-Agudelo A, Papageorghiou AT, Kennedy SH, Villar J. Novel biomarkers for the prediction of the spontaneous preterm birth phenotype: A systematic review and meta-analysis. *BJOG: An International Journal of Obstetrics and Gynaecology* 2011;118(9):1042-54.
60. Wing DA, Haeri S, Silber AC, Roth CK, Weiner CP, Echebiri NC, et al. Placental Alpha Microglobulin-1 Compared With Fetal Fibronectin to Predict Preterm Delivery in Symptomatic Women. *Obstet Gynecol* 2017;130(6):1183-91.
61. Lee SM, Romero R, Park JW, Kim SM, Park CW, Korzeniewski SJ, et al. The clinical significance of a positive Amnisure test in women with preterm labor and intact membranes. *J Matern Fetal Neonatal Med* 2012;25(9):1690-8.

62. Amabebe E, Reynolds S, Stern V, Stafford G, Paley M, Anumba DOC. Cervicovaginal fluid acetate: A metabolite marker of preterm birth in symptomatic pregnant women. *Frontiers in Medicine* 2016;3(OCT).
63. Haque MM, Merchant M, Kumar PN, Dutta A, Mande SS. First-trimester vaginal microbiome diversity: A potential indicator of preterm delivery risk. *Sci Rep* 2017;7(1):16145.
64. Gerson KD, McCarthy C, Elovitz MA, Ravel J, Sammel MD, Burris HH. Cervicovaginal microbial communities deficient in Lactobacillus species are associated with second trimester short cervix. *American Journal of Obstetrics and Gynecology* 2020;222(5):491.e1-.e8.
65. Kindinger LM, Bennett PR, Lee YS, Marchesi JR, Smith A, Cacciatore S, et al. The interaction between vaginal microbiota, cervical length, and vaginal progesterone treatment for preterm birth risk. *Microbiome* 2017;5(1):6.
66. Piccioni MG, Del Negro V, Bruno Vecchio RC, Faralli I, Savastano G, Galoppi P, et al. Is the Arabin Pessary really useful in preventing preterm birth? A review of literature. *J Gynecol Obstet Hum Reprod* 2020:101824.
67. England N. *Saving babies lives version two: A care bundle for reducing perinatal mortality* [NHS guideline]. 2019. https://www.england.nhs.uk/wp-content/uploads/2019/03/Saving-Babies-Lives-Care-Bundle-Version-Two-Updated-Final-Version.pdf (accessed 23/03 2021).
68. Kindinger LM, Kyrgiou M, MacIntyre DA, Cacciatore S, Yulia A, Cook J, et al. Preterm birth prevention post-conization: A model of cervical length screening with targeted cerclage. *PLoS ONE* 2016;11(11).
69. Alfirevic Z, Stampalija T, Medley N. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. *Cochrane Database Syst Rev* 2017;6(6):Cd008991.
70. Berghella V, Ludmir J, Simonazzi G, Owen J. Transvaginal cervical cerclage: evidence for perioperative management strategies. *American Journal of Obstetrics and Gynecology* 2013;209(3):181-92.
71. Ramin SM CS, Gilstrap LC, Cunningham F. *Operative obstetrics*. 2 ed. Philadelphia: McGraw-Hill Professional, 2002.
72. Jarde A, Lutsiv O, Park CK, Beyene J, Dodd JM, Barrett J, et al. Effectiveness of progesterone, cerclage and pessary for preventing preterm birth in singleton pregnancies: a systematic review and network meta-analysis. *Bjog* 2017;124(8):1176-89.
73. Di Tommaso M, Berghella V. Cervical length for the prediction and prevention of preterm birth. *Expert Review of Obstetrics and Gynecology* 2013;8(4):345-55.

74. Romero R, Yeo L, Miranda J, Hassan SS, Conde-Agudelo A, Chaiworapongsa T. A blueprint for the prevention of preterm birth: Vaginal progesterone in women with a short cervix. *Journal of Perinatal Medicine* 2013;41(1):27-44.
75. Furcron AE, Romero R, Plazyo O, Unkel R, Xu Y, Hassan SS, et al. Vaginal progesterone, but not 17α-hydroxyprogesterone caproate, has antiinflammatory effects at the murine maternal-fetal interface. *Am J Obstet Gynecol* 2015;213(6):846.e1-.e19.
76. Dodd JM, Jones L, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *Cochrane Database of Systematic Reviews* 2013(7).
77. Romero R, Conde-Agudelo A, Da Fonseca E, O'Brien JM, Cetingoz E, Creasy GW, et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. *Am J Obstet Gynecol* 2018;218(2):161-80.
78. Jarde A, Lutsiv O, Beyene J, McDonald SD. Vaginal progesterone, oral progesterone, 17-OHPC, cerclage, and pessary for preventing preterm birth in at-risk singleton pregnancies: an updated systematic review and network meta-analysis. *Bjog* 2019;126(5):556-67.
79. Stewart LA, Simmonds M, Duley L, Llewellyn A, Sharif S, Walker RAE, et al. Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials. *The Lancet* 2021;397(10280):1183-94.
80. Norman JE, Marlow N, Messow CM, Shennan A, Bennett PR, Thornton S, et al. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. *Lancet* 2016;387(10033):2106-16.
81. Crowther CA, Ashwood P, McPhee AJ, Flenady V, Tran T, Dodd JM, et al. Vaginal progesterone pessaries for pregnant women with a previous preterm birth to prevent neonatal respiratory distress syndrome (the PROGRESS Study): A multicentre, randomised, placebo-controlled trial. *PLoS Med* 2017;14(9):e1002390.
82. Ivandic J, Care A, Goodfellow L, Poljak B, Sharp A, Roberts D, et al. Cervical pessary for short cervix in high risk pregnant women: 5 years experience in a single centre. *The Journal of Maternal-Fetal & Neonatal Medicine* 2020;33(8):1370-6.
83. Arabin B, Alfirevic Z. Cervical pessaries for prevention of spontaneous preterm birth: past, present and future. *Ultrasound Obstet Gynecol* 2013;42(4):390-9.
84. Van Zijl MD, Koullali B, Mol BWJ, Pajkrt E, Oudijk MA. Prevention of preterm delivery: Current challenges and future prospects. *International Journal of Women's Health* 2016;8:633-45.

85. Cannie MM, Dobrescu O, Gucciardo L, Strizek B, Ziane S, Sakkas E, et al. Arabin cervical pessary in women at high risk of preterm birth: a magnetic resonance imaging observational follow-up study. *Ultrasound Obstet Gynecol* 2013;42(4):426-33.
86. Falcão V, Melo C, Matias A, Montenegro N. Cervical pessary for the prevention of preterm birth: Is it of any use? *Journal of Perinatal Medicine* 2017;45(1):21-7.
87. Nicolaides KH, Syngelaki A, Poon LC, Picciarelli G, Tul N, Zamprakou A, et al. A Randomized Trial of a Cervical Pessary to Prevent Preterm Singleton Birth. *N Engl J Med* 2016;374(11):1044-52.
88. Hui SY, Chor CM, Lau TK, Lao TT, Leung TY. Cerclage pessary for preventing preterm birth in women with a singleton pregnancy and a short cervix at 20 to 24 weeks: a randomized controlled trial. *Am J Perinatol* 2013;30(4):283-8.
89. Goya M, Pratcorona L, Merced C, Rodó C, Valle L, Romero A, et al. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. *Lancet* 2012;379(9828):1800-6.
90. Senarath S, Ades A, Nanayakkara P. Cervical Cerclage: A Review and Rethinking of Current Practice. *Obstetrical and Gynecological Survey* 2020;75(12):757-65.
91. Gibb D, Saridogan E. The role of transabdominal cervical cerclage techniques in maternity care. *The Obstetrician & Gynaecologist* 2016;18(2):117-25.
92. Stricker N, Timmesfeld N, Kyvernitakis I, Goerges J, Arabin B. Vaginal progesterone combined with cervical pessary: A chance for pregnancies at risk for preterm birth? *American Journal of Obstetrics and Gynecology* 2016;214(6):739.e1-.e10.
93. Karbasian N, Sheikh M, Pirjani R, Hazrati S, Tara F, Hantoushzadeh S. Combined treatment with cervical pessary and vaginal progesterone for the prevention of preterm birth: A randomized clinical trial. *J Obstet Gynaecol Res* 2016;42(12):1673-9.
94. Wolnicki BG, von Wedel F, Mouzakiti N, Al Naimi A, Herzeg A, Bahlmann F, et al. Combined treatment of McDonald cerclage and Arabin-pessary: a chance in the prevention of spontaneous preterm birth? *J Matern Fetal Neonatal Med* 2020;33(19):3249-57.
95. Roman AR, Da Silva Costa F, Araujo Júnior E, Sheehan PM. Rescue Adjuvant Vaginal Progesterone May Improve Outcomes in Cervical Cerclage Failure. *Geburtshilfe Frauenheilkd* 2018;78(8):785-90.
96. Shor S, Zimerman A, Maymon R, Kovo M, Wolf M, Wiener I, et al. Combined therapy with vaginal progesterone, Arabin cervical pessary and cervical cerclage to prevent preterm delivery in high-risk women. *J Matern Fetal Neonatal Med* 2019:1-5.
97. Jarde A, Lewis-Mikhael AM, Dodd JM, Barrett J, Saito S, Beyene J, et al. The More, the Better? Combining Interventions to Prevent Preterm Birth in Women at Risk: a

Systematic Review and Meta-Analysis. *Journal of Obstetrics and Gynaecology Canada* 2017;39(12):1192-202.

98. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003;348(24):2379-85.
99. Winer N, Bretelle F, Senat MV, Bohec C, Deruelle P, Perrotin F, et al. 17 alpha-hydroxyprogesterone caproate does not prolong pregnancy or reduce the rate of preterm birth in women at high risk for preterm delivery and a short cervix: A randomized controlled trial. *American Journal of Obstetrics and Gynecology* 2015;212(4):485.e1-.e10.
100. Manuck TA. 17-alpha hydroxyprogesterone caproate for preterm birth prevention: Where have we been, how did we get here, and where are we going? *Semin Perinatol* 2017;41(8):461-7.
101. Källén K. The impact of maternal smoking during pregnancy on delivery outcome. *European Journal of Public Health* 2001;11(3):329-33.
102. Latendresse G. The interaction between chronic stress and pregnancy: preterm birth from a biobehavioral perspective. *J Midwifery Womens Health* 2009;54(1):8-17.
103. McCarty-Singleton S, Sciscione AC. Maternal activity restriction in pregnancy and the prevention of preterm birth: an evidence-based review. *Clin Obstet Gynecol* 2014;57(3):616-27.
104. Walsh CA. Maternal activity restriction to reduce preterm birth: Time to put this fallacy to bed. *Aust N Z J Obstet Gynaecol* 2020;60(5):813-5.
105. MacPhedran SE. Sexual Activity Recommendations in High-Risk Pregnancies: What is the Evidence? *Sex Med Rev* 2018;6(3):343-57.
106. Goodfellow L, Care A, Alfirevic Z. Controversies in the prevention of spontaneous preterm birth in asymptomatic women: an evidence summary and expert opinion. *BJOG: An International Journal of Obstetrics & Gynaecology* 2021;128(2):177-94.
107. Middleton P, Gomersall JC, Gould JF, Shepherd E, Olsen SF, Makrides M. Omega-3 fatty acid addition during pregnancy. *Cochrane Database Syst Rev* 2018;11(11):Cd003402.
108. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4(1):1.
109. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ : British Medical Journal* 2015;349:g7647.

110. Pogue J, Yusuf S. Overcoming the limitations of current meta-analysis of randomised controlled trials. *Lancet* 1998;351(9095):47-52.
111. Guyatt GH, Haynes RB, Jaeschke RZ, Cook DJ, Green L, Naylor CD, et al. Users' Guides to the Medical Literature: XXV. Evidence-based medicine: principles for applying the Users' Guides to patient care. Evidence-Based Medicine Working Group. *Jama* 2000;284(10):1290-6.
112. Hadorn DC, Baker D, Hodges JS, Hicks N. Rating the quality of evidence for clinical practice guidelines. *Journal of Clinical Epidemiology* 1996;49(7):749-54.
113. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical Evidence of Bias: Dimensions of Methodological Quality Associated With Estimates of Treatment Effects in Controlled Trials. *JAMA* 1995;273(5):408-12.
114. Dickersin K, Min YI, Meinert CL. Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards. *Jama* 1992;267(3):374-8.
115. Anello C, Fleiss JL. Exploratory or analytic meta-analysis: Should we distinguish between them? *Journal of Clinical Epidemiology* 1995;48(1):109-16.
116. Care A, Jackson R, O'Brien E, Leigh S, Cornforth C, Haycox A, et al. Cervical cerclage, pessary, or vaginal progesterone in high-risk pregnant women with short cervix: a randomized feasibility study. *J Matern Fetal Neonatal Med* 2021;34(1):49-57.
117. Medley N, Poljak B, Mammarella S, Alfirevic Z. Clinical guidelines for prevention and management of preterm birth: a systematic review. *BJOG: An International Journal of Obstetrics and Gynaecology* 2018;125(11):1361-9.
118. Department of Health WA. *Preterm Birth Prevention: Moderate Risk Women* [Clinical guideline]. 2015. https://www.kemh.health.wa.gov.au/~/media/Files/Hospitals/WNHS/For%20health%20professionals/Clinical%20guidelines/OG/WNHS.OG.PretermBirthPrevention_ModRisk.pdf (accessed 25/03 2021).
119. group Mg. *Preterm labour/birth maternity guidelines*. 2021. http://edu.cdhb.health.nz/Hospitals-Services/Health-Professionals/maternity-care-guidelines/Documents/GLM0027-Preterm-Labour-Birth.pdf (accessed 25/03 2021).
120. (KCE) BHCKC. *Prevention of preterm birth in women at risk: selected topics* [Clinical practice report]. 2014. https://kce.fgov.be/sites/default/files/atoms/files/KCE_228_Preterm%20birth_Report.pdf (accessed 26/03 2021).
121. Sentilhes L, Sénat MV, Ancel PY, Azria E, Benoist G, Blanc J, et al. Prevention of spontaneous preterm birth: Guidelines for clinical practice from the French College of

Gynaecologists and Obstetricians (CNGOF). *Eur J Obstet Gynecol Reprod Biol* 2017;210:217-24.

122. Jain V, McDonald SD, Mundle WR, Farine D. Guideline No. 398: Progesterone for Prevention of Spontaneous Preterm Birth. *Journal of Obstetrics and Gynaecology Canada* 2020;42(6):806-12.
123. Grabovac M, Lewis-Mikhael AM, McDonald SD. Interventions to Try to Prevent Preterm Birth in Women With a History of Conization: A Systematic Review and Meta-analyses. *Journal of Obstetrics and Gynaecology Canada* 2019;41(1):76-88.e7.
124. van 't Hooft J, Duffy JMN, Daly M, Williamson PR, Meher S, Thom E, et al. A Core Outcome Set for Evaluation of Interventions to Prevent Preterm Birth. *Obstet Gynecol* 2016;127(1):49-58.
125. Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. . *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. 2011. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 25/02 2021).
126. Collaboration C. *Cochrane Handbook for Systematic Reviews of Interventions*. 2011. https://handbook-5-1.cochrane.org/chapter_13/13_5_2_3_tools_for_assessing_methodological_quality_or_risk_of.htm (accessed 07/06/2021 2021).
127. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;64(4):383-94.
128. Collaboration TC. Review Manager (RevMan) 5.4.1.: The Cochrane Collaboration; 2020.
129. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
130. Cho GJ, Ouh YT, Kim LY, Lee TS, Park GU, Ahn KH, et al. Cerclage is associated with the increased risk of preterm birth in women who had cervical conization. *BMC Pregnancy Childbirth* 2018;18(1):277.
131. Rafaeli-Yehudai T, Kessous R, Aricha-Tamir B, Sheiner E, Erez O, Meirovitz M, et al. The effect of cervical cerclage on pregnancy outcomes in women following conization. *J Matern Fetal Neonatal Med* 2014;27(15):1594-7.
132. Shin M-Y, Seo E-S, Choi S-J, Oh S-Y, Kim B-G, Bae D-S, et al. The role of prophylactic cerclage in preventing preterm delivery after electrosurgical conization. *Journal of gynecologic oncology* 2010;21(4):230-6.

133. Nam KH, Kwon JY, Kim YH, Park YW. Pregnancy outcome after cervical conization: Risk factors for preterm delivery and the efficacy of prophylactic cerclage. *Journal of Gynecologic Oncology* 2010;21(4):225-9.
134. Zeisler H, Joura EA, Bancher-Todesca D, Hanzal E, Gitsch G. Prophylactic cerclage in pregnancy: Effect in women with a history of conization. *Journal of Reproductive Medicine for the Obstetrician and Gynecologist* 1997;42(7):390-2.
135. Excellence NIfHaC. *Context* [NICE guideline]. 2019. https://www.nice.org.uk/guidance/ng25/chapter/context (accessed 07/06 2021).
136. group C-St. *Cerclage Suture Type for an Insufficient Cervix and its effect on Health outcomes (C-STICH)*. 2020. https://www.birmingham.ac.uk/documents/college-mds/trials/bctu/c-stich/cstich-protocol-v9.0-25-mar-2020.docx.pdf (accessed 07/06 2021).
137. Medley N, Vogel JP, Care A, Alfirevic Z. Interventions during pregnancy to prevent preterm birth: an overview of Cochrane systematic reviews. *Cochrane Database of Systematic Reviews* 2018(11).
138. McDonald IA. Suture of the cervix for inevitable miscarriage. *J Obstet Gynaecol Br Emp* 1957;64(3):346-50.
139. Simcox R, Shennan A. Cervical cerclage: A review. *International Journal of Surgery* 2007;5(3):205-9.
140. Boelig RC, Zuppa AF, Kraft WK, Caritis S. Pharmacokinetics of vaginal progesterone in pregnancy. *American Journal of Obstetrics and Gynecology* 2019;221(3):263.e1-.e7.
141. Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva; 1968. p. 163 pp.
142. Hume H, Rebarber A, Saltzman DH, Roman AS, Fox NS. Ultrasound-indicated cerclage: Shirodkar vs. McDonald. *J Matern Fetal Neonatal Med* 2012;25(12):2690-2.
143. Rodriguez PA, Fylstra D, Newman R, Nino JM. Shirodkar Cerclage is More Effective than McDonald for the Prevention of Preterm Birth [36N]. *Obstetrics & Gynecology* 2018;131.
144. Issah A, Diacci R, Williams KP, Aubin A-M, McAuliffe L, Phung J, et al. McDonald versus Shirodkar cerclage technique in women requiring a prophylactic cerclage: a systematic review and meta-analysis protocol. *Systematic Reviews* 2021;10(1):130.
145. Shennan A, Chandiramani M, Bennett P, David AL, Girling J, Ridout A, et al. MAVRIC: a multicenter randomized controlled trial of transabdominal vs transvaginal cervical cerclage. *Am J Obstet Gynecol* 2020;222(3):261.e1-.e9.
146. Goldenberg RL, Iams JD, Mercer BM, Meis PJ, Moawad AH, Copper RL, et al. The preterm prediction study: the value of new vs standard risk factors in predicting early

and all spontaneous preterm births. NICHD MFMU Network. *American Journal of Public Health* 1998;88(2):233-8.

Appendix 1 – Systematic review protocol submitted to PROSPERO

Efficacy of cerclage, progesterone and pessary in preventing preterm birth in women with prior excision of the cervix: a systematic review

Faye Platt, Angharad Care, Kate Navaratnam, Andrew Sharp

Citation

Faye Platt, Angharad Care, Kate Navaratnam, Andrew Sharp. Efficacy of cerclage, progesterone and pessary in preventing preterm birth in women with prior excision of the cervix: a systematic review. PROSPERO 2021 CRD42021252327 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021252327

Review question

What is the efficacy of cerclage, progesterone and pessary in preventing preterm birth in women with prior excision of the cervix?

Searches

A systematic search of PubMed, Scopus and CINAHL databases will be completed by FP using the following keywords; cervical surgery, cervical excision, LLETZ, LEEP, cone biopsy, conisation, conization, short cervix, high risk, cerclage, progesterone, 17-OHPC and pessary to search within study titles and abstracts.

Restrictions will be made for study type, English language and human studies.

Types of study to be included

Randomised controlled trials and observational studies (cohort and case-control) will be included in the review.

Any reviews, editorials, books, letters and conference papers will be excluded.

Condition or domain being studied

Existing evidence demonstrates an increased risk of preterm birth in women with prior knife cone biopsy or LLETZ procedures to the cervix. Preterm birth is the leading cause of neonatal morbidity and mortality worldwide. Intervention is indicated following findings of a short cervix on mid-trimester ultrasound screening. Current UK practice includes the use of either progesterone, cerclage or Arabin pessary to prevent preterm birth. A 2017 Cochrane review studied the use of cerclage for women with a short cervix but concluded there was insufficient evidence to compare the efficacy to that of progesterone or pessary. Grabovac et al reviewed interventions to prevent preterm birth in women with prior cervical surgery and singleton or multiple pregnancies. Due to lacking evidence, this review also could not draw conclusions for the use of progesterone or pessary. This systematic review aims to address this shortfall and serve as an update for the review conducted by Grabovac et al in 2017.

Participants/population

Women with singleton pregnancies that have undergone prior knife cone biopsy or LLETZ (large loop excision of the transformation zone) procedures will be included.
All studies reporting outcomes in only multiple pregnancies will be excluded.

Intervention(s), exposure(s)

Eligible treatments include vaginal cerclage, Arabin pessary, vaginal progesterone or intramuscular 17-alpha hydroxyprogesterone caproate used during pregnancy. Those that received a combination of different interventions will be reviewed as a separate treatment group.

Comparator(s)/control

• Comparison will be made to women that received another intervention.
• Comparison will be made to women that received no intervention.
• Comparison will be made to women that received placebo.

Main outcome(s)

Primary outcomes are preterm birth <34 and <37 weeks.

Additional outcome(s)

Secondary outcome measures include; preterm birth <32, <28 and <24 weeks, PPROM, onset and mode of delivery, livebirth/stillbirth, neonatal death, NICU admission, ventilatory support, use of surfactant, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, periventricular leukomalacia, sepsis, maternal mortality/harm, side effects and adverse events.

Data extraction (selection and coding)

The papers retrieved during the searches will be screened for inclusion by two independent reviewers using the pre-determined eligibility criteria.
Disagreements will be resolved by consensus with a third reviewer.
The first reviewer will complete data collection from studies that meet the eligibility criteria.

Risk of bias (quality) assessment

The risk of bias in each included study will be assessed using a modified version of the Newcastle-Ottawa Scale for assessing risk of bias by two different reviewers.
A sensitivity analysis will be performed for high quality trials.

Strategy for data synthesis

Aggregate random effects meta-analysis will be performed using RevMan 5.
Heterogeneity will be assessed using I^2, where a result of <40% will be considered acceptable.
If data are insufficient quality for analysis, we will provide a narrative summary of the results of included studies, structured around the type of intervention, the characteristics of the target population, the type of outcome and the content of the intervention.

Analysis of subgroups or subsets

If the included studies allow for subgroup analysis, we will assess differential effects based on:
1) Previous LLETZ procedure;
2) Previous cone biopsy;
3) Ultrasound-indicated interventions;
4) History-indicated interventions.

A sensitivity analysis will also be performed for high quality trials.

Appendix 2 – Search strategy used for systematic review

Pubmed

1. cervical surgery[Title/Abstract]
2. cervical excision[Title/Abstract]
3. lletz[Title/Abstract]
4. leep[Title/Abstract]
5. cone biopsy[Title/Abstract]
6. conisation[Title/Abstract]
7. conization[Title/Abstract]
8. short cervix[Title/Abstract]
9. high risk[Title/Abstract]
10. cerclage[Title/Abstract]
11. progesterone[Title/Abstract]
12. 17-OHPC[Title/Abstract]
13. pessary[Title/Abstract]
14. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
15. #10 OR #11 OR #12 OR #13
16. #14 AND #15 AND (clinical study[Filter] OR clinical trial[Filter] OR comparative study[Filter] OR controlled clinical trial[Filter] OR observational study[Filter] OR randomized controlled trial[Filter]) AND (humans[Filter]) AND (english[Filter])

Scopus

1. TITLE-ABS (cervical AND surgery)
2. TITLE-ABS (cervical AND excision)
3. TITLE-ABS (lletz)
4. TITLE-ABS (leep)
5. TITLE-ABS (cone AND biopsy)
6. TITLE-ABS (conisation)

7. TITLE-ABS (conization)

8. TITLE-ABS (short AND cervix)

9. TITLE-ABS (high AND risk)

10. TITLE-ABS (cerclage)

11. TITLE-ABS (progesterone)

12. TITLE-ABS (17-ohpc)

13. TITLE-ABS (pessary)

14. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

15. #10 OR #11 OR #12 OR #13

16. #14 AND #15 AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (EXACTKEYWORD , "Human") OR LIMIT-TO (EXACTKEYWORD , "Humans")) AND (LIMIT-TO (LANGUAGE , "English"))

Cinahl

S1. TI cervical surgery AND AB cervical surgery

S2. TI cervical excision AND AB cervical excision

S3. TI lletz AND AB lletz

S4. TI leep AND AB leep

S5. TI cone biopsy AND AB cone biopsy

S6. TI conisation AND AB conisation

S7. TI conization AND AB conization

S8. TI short cervix AND AB short cervix

S9. TI high risk AND AB high risk

S10. TI cerclage AND AB cerclage

S11. TI progesterone AND AB progesterone

S12. TI 17-ohpc AND AB 17-ohpc

S13. TI pessary AND AB pessary

S14. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9

S15. S10 OR S11 OR S12 OR S13

S16. S14 AND S15

Limiters - English Language, Human

Publication Type - Clinical Trial, Journal Article, Randomized Controlled Trial