Title: The Role Of The Obstetrician In The Prevention Of Retinopathy Of Prematurity

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Abstract (100-150 words)

This review underlines the important role that obstetricians play in the prevention of retinopathy of prematurity. Efforts predominately focus on predicting which pregnant women are at highest risk of preterm birth, instigating treatments to prevent pre-eclampsia, fetal growth restriction and maternal infection which could lead to iatrogenic or spontaneous preterm birth, and optimizing care when preterm birth is inevitable. More broadly, optimizing maternal health pre-conception through stopping smoking, improving diet, reducing obesity with its associated gestational diabetes, and treating hypertension may reduce preterm birth and other pregnancy complications. This is a message that all healthcare professionals including obstetricians, neonatologists and GPs, nursing and midwifery staff need to communicate all women and men who are contemplating having a baby.

Introduction

The obstetrician's role in preventing retinopathy of prematurity (ROP) centers around the accurate prediction and prevention of preterm birth (PTB). Defined as delivery before 37 completed weeks of gestation, PTB affects 7-15% of pregnancies worldwide[1]. Despite a significant increase in prematurity focused research over the last 20 years, the incidence of PTB remains largely unchanged, and persists as a global health concern. Given the linear correlation with early gestation age (GA) at birth and severity of ROP, prevention of PTB and low birth weight (LBW) is key. This review highlights the important pre-conception and antenatal measures that are important to optimise obstetric and neonatal outcome. We review the screening tools available for PTB prediction, including identification of maternal risk factors, antenatal sonographic assessment of the cervix and detection of biomarkers in the cervicovaginal fluid. We discuss the current measures available for spontaneous PTB prevention, such as cervical cerclage, vaginal progesterone and the cervical pessary, and iatrogenic PTB such as aspirin. Finally we consider the role the obstetrician plays in ameliorating additional modifiable risk factors for ROP, including LBW, antenatal infection, preterm prelabour rupture of membranes (PPROM) and multiple pregnancy[2,3].

Preconception care

An emerging area of intervention relevant for both women and men is pre-conception care, and the importance of 'getting fit for pregnancy'. Health before conception is strongly linked to pregnancy outcome and is crucial for health across generations[4]. A pre-conception diet high in fruit, vegetables, legumes, nuts and fish, and low in red and processed meat, up to 3 years pre-pregnancy, in addition to weight loss among obese women, appears to reduce the risk of PTB, hypertensive disease, gestational diabetes, macrosomia, and stillbirth in subsequent pregnancy[4]. Supplements are also important, particularly folic acid, iron and vitamin D to minimize adverse pregnancy outcomes including PTB and low birthweight[4]. In contrast, micronutrient supplements, dietary interventions and efforts to limit weight gain that are commenced *in* pregnancy, while able to correct important maternal nutrient deficiencies, are crucially not sufficient to alter or improve pregnancy outcomes or child health[4]. Lifestyle modifications such as smoking cessation and minimizing alcohol intake pre- and during pregnancy are also essential to reduce the risk of intrauterine growth restriction, LBW and fetal alcohol spectrum disorder respectively[4]. While not specifically associated with ROP, this emphasizes the unique window that the peri-conception period holds for health intervention.

Antenatal risk factors

Maternal and obstetric histories are central to estimating subsequent PTB risk. It is important that the following risk factors are highlighted early during antenatal care so that women may be monitored accordingly.

Previous obstetric history

A previous spontaneous PTB or late miscarriage (16-24 weeks gestation) is the single most important predictor of recurrent PTB[5]. These are associated with a 32% chance of a spontaneous PTB in subsequent pregnancy (relative risk [RR] 5.64, 95% confidence interval [CI], 5.3-6); and this risk increases with the number of prior preterm deliveries and the earlier the GA at prior birth[5].

Antenatal infection

Infection-induced inflammatory parturition pathways are thought to be the causal driver of around 40% of PTBs, and as many as 80% of early PTBs <28 weeks gestation[6,7]. LBW and preterm neonates are particularly susceptible to infection and when present in combination with infection, babies are at particular risk of ROP[2]. Ascending bacterial infection from the vagina into the uterine cavity is the most common source of intrauterine infection and inflammation leading to spontaneous PTB in singletons[8]. Bacterial vaginosis (BV) is the most common bacterial imbalance in the vagina, characterized by a depletion of Lactobacilli species and overgrowth of various anaerobic bacteria, including *Gardnerella vaginalis* and *Atopobium vaginae*[9]. BV is associated with adverse reproductive health outcomes including pelvic inflammatory disease[10], transmission of sexually transmitted infections[11,12], and in pregnancy is associated with a 2-fold increase in PTB[13]. In conjunction with this, subclinical vaginal dysbiosis is associated with an increased risk of subsequent PPROM[14], which in itself is an important risk factor for maternal sepsis, neonatal sepsis and ROP[14].

Multiple pregnancy

Multiple pregnancies account disproportionately for the incidence of PTB[15] and prematurity is the most common complication arising in twin pregnancies[16]. In 2013, 57% of multiple births delivered preterm, compared to only 7% of singleton pregnancies[16]. The underlying mechanism driving spontaneous PTB in multiple pregnancy is likely a combination the endocrine effects of increased corticotrophin-releasing hormone production from a larger placental mass[17], as well as the effect of uterine stretch upon contraction-associated and inflammatory mediators within the uterus[18]. Gynaecologists and reproductive medicine specialists therefore play a central role in preventing PTB and associated ROP by reducing the prevalence of multiple conceptions through Artificial Reproductive Techniques such as IVF, through promoting and practicing Single Embryo Transfer.

Uterine anomalies

Uterine anomalies, an umbrella term for unicornuate, bicornuate, septated uterus and uterus didelphys, are caused by a defective fusion of the mullerian ducts during embryogenesis. With a prevalence of about 2-4%, they remain largely unrecognised among reproductive age women until pregnancy conception[19]. Premature activation of uterine stretch due to a smaller intrauterine capacity is thought to drive PTB within this group[20].

Excisional cervical treatment

Pre-pregnancy excisional treatment methods for cervical intraepithelial neoplasia (cold knife conisation, laser conisation, and large loop excision of the transformation zone) are associated with an increased risk of adverse reproductive sequelae in subsequent pregnancy[21]. This includes a two-fold increased risk of PTB, LBW, PPROM, and perinatal mortality[21]. Hypotheses for PTB aetiology following cervical treatment include a mechanical weakness secondary to loss of cervical tissue, immunomodulation of parturition pathways relating to underlying HPV infection and a compromised barrier to ascending infection from the vagina[21,22]. Gynaecologists and colposcopists have a role in preventing PTB and associated ROP through less invasive treatment of pre-cancerous cervical lesions in women of reproductive age. They should also inform women who have had significant cervical tissue removed to undergo cervical length screening during pregnancy to aid timely interventions such as cervical cerclage[23].

Disorders of placentation

Abnormal placentation is a pathological feature present in about 30% of women with spontaneous PTB and is commonly associated with pre-eclampsia[8]. Among preterm babies, pre-eclampsia has been associated with an increased risk for severe ROP[24]. The vascular endothelial dysfunction that occurs at the uteroplacental interface increases the risk of PTB due to abnormal decidual haemostasis and propensity for thrombin formation[25,26]. Thrombin is a powerful uterotonic which stimulates premature myometrial contractility[25,26]. The placental ischaemia also induces the release of vasoactive and pro-inflammatory factors including VEGF and cytokines, which is thought to promote development of ROP in the preterm neonate[27].

Prediction of Preterm birth

Predictive tests for PTB are important, given the huge personal, economic, and health impacts of prematurity. The results may provide reassurance for women who are unlikely to deliver preterm. Women identified at higher risk of PTB can be offered timely interventions to prolong pregnancy, thereby reducing the risk of ROP. Predictive tests for PTB are frequently used in clinical practice to screen 1) asymptomatic women with established risk factors for PTB and 2) women presenting with symptoms of threatened preterm labour.

Ultrasound screening of cervical length

Cervical remodeling that occurs in preparation for labour is detectable at transvaginal ultrasound (TVUS) several weeks and months prior to the onset of labour symptoms by cervical length (CL) measurement. In asymptomatic women a shortened cervix, considered to be less than the 10th centile in the mid-second trimester (CL ≤25mm), differentiates those at risk of subsequent PTB from those likely to deliver a term[28,29]. The value of CL screening is in it's negative prediction; typically 90% with a CL over 25mm will deliver at term[30]. The positive predictive value of CL screening for PTB is largely dependent on thresholds of CL as well as the gestation at which screening takes place[28,31,32]. An inverse relationship exists between CL and risk of PTB where the shorter the cervix, the higher the risk of PTB; at 24 weeks a CL ≤25mm has a relative risk (RR) of 7 for PTB <37 weeks, while a CL≤13mm (below the 1st centile) increases this to RR of 14[28]. Gestational age at measurement impacts on screening accuracy as physiological shortening of the cervix occurs with advancing gestational age[28]. A short cervix detected early in the second trimester confers the greatest risk for subsequent PTB[31,32]. For example, the predicted probability of PTB <32 weeks is 55% for a CL of 10mm at 16 weeks, compared to 28% at 24 weeks[32]. Serial CL screening is therefore frequently implemented in clinical practice as it balances the low sensitivity of early screening, with improved sensitivity at the expense of specificity later on[31,32]. Serial screening also provides an additional assessment of rate of CL change over time[33]; the risk of PTB <35 weeks increases by 6% for each millimeter decline in length per week (OR 1.05, 95% CI 1.08-1.05)[32].

Measurement of CL has additional clinical utility in women presenting with symptoms of preterm labour. Knowledge of CL in pregnancy significantly reduces the rate of PTB <37 weeks in those with threatened preterm labour (RR 0.64; 95% CI 0.44–0.94)[34]. In the UK, a CL <15mm detected after 30 weeks is the recommended threshold for active management of threatened PTB[35].

Universal CL screening for the unselected pregnant population has been proposed by many. The argument against this is the low incidence of a short cervix among the healthy pregnant population. It is estimated the number of low risk pregnancies needed to screen is between 400 and 588 to avoid one PTB[36]. Once detected however, the number of women with a short cervix needed to treat to prevent one PTB is 7 to 13[36]. A recent systematic review and international consensus of PTB clinical guidelines concluded that universal screening is not cost-effective, has limited clinical utility and therefore is not recommended in routine practice[37]. Despite this in the US, as many as two thirds of institutions with Maternal Fetal Medicine Fellowship programs implement universal CL screening[38].

Fetal Fibronectin

In singleton pregnancy the bedside fetal Fibronectin (fFN) test is another useful predictor of PTB in women presenting with threatened preterm labour. fFN is a glycoprotein and biochemical marker that can be detected in a woman's cervicovaginal secretions throughout pregnancy[39]. In normal pregnancy fFN is present in the vagina up to the fusion of the chorionic membrane with the maternal decidua (at approximately 20 – 22 weeks of gestation). After this time the level of fFN falls to below 50ng/ml[39]. An abnormally elevated fFN level is thought to result from inflammatory or mechanical insult to the fetal membranes indicating separation of the chorion and the deciduas, and imminent delivery. Concentrations <50ng/ml detected between 23 and 35 weeks associate with high negative prediction (99%) for spontaneous PTB, and so when employed in clinical practice, symptomatic women are reassured that they will not deliver imminently and may be managed in an outpatient setting[40]. The positive predictive value of fFN has improved with the advent of quantitative testing[41,42]. When sampled between 22 and 28 weeks gestation, concentrations of fFN 50–199, 200–499, and >500 ng/mL are associated with rates of spontaneous PTB before 34 weeks of 15%, 34% and 48% respectively[42]. While this aides acute antenatal management of an individual, utility in population-based screening is limited as respective sensitivities are 47%, 29% and 9%[42].

Combination screening

A combination of CL and fFN testing improves predictive accuracy and risk stratification for PTB among high-risk asymptomatic women[43]. A model incorporating a history of spontaneous PTB or PPROM, quantitative fFN, and CL measurements, outperforms each screening tool in isolation. The model provides area under the receiver–operating-characteristic curves of 0.84 for PTB <34weeks, and 0.99 for delivery within 2 weeks. Furthermore this model is available for use in clinical practice as the QUiPP app[43].

Multiple pregnancy

As in singletons, CL screening in twins is largely influenced by GA at measurement and pre-determined thresholds of CL. The predictive accuracy of CL varies greatly in twins from that of singletons however. In twins, CL of 25mm at 18 weeks only provides 34% probability of birth <32 weeks, and 20% probability if taken at 24 weeks[44]. A shorter CL of 15mm at the same gestations (18 and 24 weeks) increases this probability to 70% and 49% respectively[44]. A long cervical length

(>25mm) also does not provide the same reassurance as it does in singletons[45], further limiting the clinical utility of CL screening.

Very little evidence exists for quantitative fFN in twins. Reports are predominantly retrospective, and describe only a binary threshold >50ng/ml to define a positive result[45-47]. Additionally, reports indicate only moderate test sensitivity (45%) and specificity (81%) for birth <34 weeks in asymptomatic twins, improving somewhat for birth within 7 days in symptomatic women (85% and 78% respectively)[45]. There is some suggestion that fFN may be used to risk stratify twins in the context of a short cervix however. Given a short CL ≤25mm with a positive fFN (≥50ng/ml), there is an 11-fold increased risk of PTB when compared to a short cervix alone[46]. Early indications also suggest that fFN out-performs CL measurement for the prediction of PPROM in twins[47].

Prevention of PTB

Interventions such as progesterone, cervical cerclage or an Arabin cervical pessary may be beneficial for asymptomatic women identified to be at risk of PTB. Immediate treatments for those symptomatic of PTB include tocolysis, antenatal corticosteroids and in-utero transfer to tertiary centers.

<u>Cerclage</u>

The cervical cerclage, a purse-string suture around the cervix, is traditionally considered the primary preventive intervention for PTB in singleton pregnancies (Fig. 1). Indications for a cerclage include women with a prior spontaneous PTB or late miscarriage where a short cervix (≤25mm) is identified before 24 weeks, or women with 3 or more spontaneous PTBs[48]. It is thought that a cerclage acts to provide structural reinforcement to a weak cervix, maintaining cervical length and supporting the endocervical mucus plug as a barrier to pathogens and ascending infection[49]. Although its mechanism of action is still not fully understood, insertion of a cerclage in a suitably high risk population, reduces the chance of spontaneous PTB <34 weeks by approximately 23% [RR 0.77, 95%CI 0.66-0.89][50]. Overall the number of cerclages needed to prevent one PTB <33 weeks is 25 (95% CI 12-300)[51]. Cerclage insertion has not shown to be associated with a reduction in neonatal morbidity (RR 0.80, 95%CI 0.55-1.18) or perinatal mortality however (RR 0.85, 95%CI 0.53-1.39)[50], and it is unclear whether it effectively reduces ROP. The procedure itself is also associated with a 2-fold increase in post-operative maternal pyrexia (RR 2.39, 95%CI 1.35-4.23)[50]. Despite this, the cerclage remains the mainstay of PTB prevention in current practice.

Progesterone

Vaginal progesterone, administered via daily suppository of 90-200mg from the early second trimester to 34-36 weeks gestation[52], has been focus of much debate regarding its effectiveness in PTB prevention. Progesterone's mode of action is thought to be via maintenance of myometrial quiescence via downstream anti-inflammatory signaling, as well as inhibition of premature cervical ripening[53]. When prescribed to singleton pregnancies with a short cervix (≤20mm) but without a prior spontaneous PTB, progesterone has been reported to reduce the risk of spontaneous PTB <33 weeks by up to 45%[54,55]. In contrast, given a higher threshold for a short cervix (<30mm), progesterone does not reduce neonatal morbidity or prematurity[56]. The findings of OPPTIMUM, the largest randomized controlled trial (RCT) comparing progesterone versus placebo among high risk pregnancies with a CL ≤25mm, concluded there was no reduction in the risk of PTB <34 weeks with progesterone administration[57]. Most recently, an individual patient data (IPD) metanalysis of 974 singletons pregnancies, including data from OPPTIMUM, stated that progesterone does reduce the risk of PTB given a mid-trimester short cervix ≤25mm with or without a previous PTB (RR, 0.62; 95% CI, 0.47-0.81), without any adverse effects on childhood neurodevelopment[52]. An additional reduction in composite neonatal morbidity (including respiratory distress syndrome (RDS), bronchopulmonary dysplasia, Grade III or IV intraventricular hemorrhage, periventricular leukomalacia, proven sepsis and necrotizing enterocolitis, but not specifically ROP) was described (RR, 0.57; 95% CI, 0.33–0.99)[52,58]. Following this, an indirect comparison meta-analysis of 769 women concluded comparable efficacy between progesterone and cervical cerclage for the prevention of PTB in those with cervical shortening (≤25mm) and a previous spontaneous PTB[59]. Progesterone's additional clinical benefit is the avoidance of surgical risks associated with cerclage insertion including vaginal bleeding, pyrexia and caesarean delivery[60]. The number of women with a short cervix needed to treat to prevent one spontaneous PTB <33weeks is estimated to be 12

(95% CI 8-23)[52]. This compares favourably to administration of antenatal corticosteroids to prevent RDS and neonatal death[61].

Cervical pessary

The Arabin cervical pessary is a flexible silicon ring, which is inserted around the cervix usually at around 18–22 weeks of gestation and removed at 37 weeks (Fig. 2). It aims to provide support through tilting the cervix posteriorly, in doing so shifting the uterocervical angle and the weight of the uterus onto the lower uterine segment[62]. The evidence for the cervical pessary's efficacy in PTB prevention consists of contradictory results from five RCTs among singleton pregnancies with a short cervix. A meta-analysis of these studies[63] concluded that the pessary does not reduce PTB or adverse neonatal outcome in women with a previous spontaneous PTB and a short cervix, although study heterogeneity was high. In another metanalysis comparing the pessary to progesterone and cerclage, the Arabin pessary was found to be ineffective at reducing PTB risk[64]. A subsequent RCT of 300 singletons, did however conclude that the pessary may provide some benefit in reducing the rate of delivery <34weeks in the context of a short cervix (≤25mm) without history of spontaneous PTB (RR 0.48, 95% CI 0.24-0.95)[65]. The intervention is now being tested against cerclage and progesterone in a three-way RCT called SuPPoRT for women found to have a short CL (Trial registry number ISRCTN13364447).

Multiple pregnancy

Twin conceptions with a prevalence of 1.5% of pregnancies, account for approximately 25% of PTBs[16], and therefore a disproportionate number of ROP cases[3]. Despite this there remains no effective intervention for the prevention of PTB. In twins, vaginal progesterone and the cervical cerclage have both been found to be ineffective[66]. Furthermore cerclage insertion is associated with a trend towards harm with increased perinatal death (RR 1.74, 95% CI 0.92–3.28) and adverse neonatal outcome in twins (RR 1.54, 95% CI 0.58–4.11)[67]. Evidence for use of the cervical pessary in twins is also conflicting. While the pessary does not reduce PTB in unselected twins pregnancies,[68,69] some data suggest the pessary may be beneficial in twins with a short cervix. A subgroup analysis of the ProTWIN study[69] reported a reduction in PTB <32 weeks for those with a

CL <38 mm (RR 0.41, 95% CI 0.22–0.76). In contrast however, Nicoladies et al[68] found no benefit among twin pregnancies with a shorter CL ≤25mm (RR 1.2, 95% CI 0.8–1.8). This was supported by a follow up meta-analysis which concluded that the pessary does not prevent PTB or improve perinatal outcome in twin pregnancies with or without a short cervix[70]. A further RCT trial, STOPPIT-2 aims to address this further and is currently recruiting (Trial registry number NCT02235181) [71].

Antenatal infection

Among pregnancies with PPROM, Erythromycin antibiotic treatment was associated with reduced PTB rates in the ORACLE I trial[72], in addition to a reduction in use of surfactant, neonatal oxygen dependence and major ultrasound cerebral abnormalities. The study did not report on ROP however. Caution was advised against the use of Co-amoxiclav which also prolonged pregnancy in the trial, but was associated with increased neonatal necrotising enterocolitis[72]. In an assessment of longer-term outcomes, neither erythromycin nor co-amoxiclav antibiotic improved childhood health compared to placebo however[73]. In the follow up ORACLE II study[74], antibiotics were not found to be beneficial for women in spontaneous preterm labour with intact membranes, as neither erythromycin or co-amoxiclav reduced neonatal mortality, RDS, or major cerebral abnormality[74]. Furthermore in a 7-year follow-up there was an increased incidence of cerebral palsy[75].

Currently there is no effective evidence to support 'screening and treating' vaginal infection in asymptomatic pregnant women with the aim of reducing rates of PTB. In particular, controversy surrounds antibiotic treatment of BV in pregnancy[76]. A meta-analysis of studies suggested some benefit of clindamycin for the treatment of BV prior to 22 weeks gestation, with reported reduction in rates of late PTB 34-37 weeks, but not PTB <33 weeks, LBW, NICU admissions, or maternal or neonatal infections[77]. Other studies largely indicate antenatal antibiotic treatment for BV does not effectively reduce PTB[13,76,78], and the current consensus is that there is little evidence for screening of BV in pregnancy, as it does not improve outcome[76].

Disorders of placentation

Over the last few decades the benefits of aspirin therapy for women at risk of fetal growth restriction, LBW and pre-eclampsia have been well established, and now form part of routine clinical practice for high risk pregnancies[79]. The ASPRE trial, a multicenter double-blind, placebo-controlled trial of 1776 singleton pregnancies, demonstrated that screening all pregnant women using an algorithm and treating high risk women with a higher dose of Aspirin (150mg) than is usually administered, substantially reduced the incidence of preterm pre-eclampsia (AOR 0.38; 95% CI 0.20-0.74)[80] and reduced small-for-gestational-age fetuses (weighing <10th centile) by 70% among babies born <32 weeks and by 40% in those born <37 weeks[81]. Given the association between LBW, prematurity and ROP this is likely to be a significant finding. To prevent fetal growth restriction, a large study-level and IPD meta-analysis confirmed that aspirin modestly reduces small-for-gestational-age pregnancy in women at high risk (RR 0.90, 95%CI 0.81-1.00) and that a dose of ≥100 mg should be recommended, and to start at or <16 weeks of gestation[82]. These findings support national clinical practice guidelines in the UK.

Optimising Delivery

Identification of pregnancies most likely to deliver preterm allows for timely and targeted antenatal preparation to optimize neonatal outcome.

Steroids

A course of corticosteroids is the single most important antenatal intervention in the event of an imminent preterm delivery. Associated with a significant reduction in neonatal mortality and morbidity, antenatal corticosteroids reduce the risk of ROP (OR 0.82, 95% CI 0.68-0.98) as well progression to severe ROP in preterm babies (OR 0.58, 95% CI 0.40-0.86)[83].

Magnesium sulphate

Magnesium sulphate is frequently prescribed antenatally when PTB <34 weeks is inevitable. Primarily for neuroprotection of the fetus, administered intravenously to the pregnant mother magnesium sulphate is associated with a reduction in cerebral palsy among preterm infants[84] There is no evidence that it prevents ROP or longer term blindness when administered for PTB[84], or for delivery in the context of PPROM[85] or fetal growth restriction however[86].

Mode of delivery

Evidence for the optimum mode of delivery for the preterm infant remains inconclusive. A Cochrane review of six trials and 122 women delivering either preterm or small babies, found no significant difference in the neonatal mortality or morbidity experienced among caesarean or vaginal births[87]. Conclusions were hampered by small sample sizes and recruitment difficulties among studies however, but it was noted that caesarean delivery was associated with an increase in serious morbidity for the mother (OR 6.4, 95% CI 1.5-27.9)[87]. In a more recent retrospective study of babies born ≤ 30 weeks gestation, while not reporting on the incidence of ROP, they reported that deliveries by caesarean were more likely to experience RDS (OR 1.79; 95% CI, 1.10–2.90), require intubation (OR 1.80; 95% CI 1.12–2.88), and have longer stays in NICU (70.0 ± 37.1 vs. 57.3 ± 40.1 days, $p = 0.02$)[88].

Delivery in tertiary care centre

A key determinant of neonatal morbidity following PTB is the availability of appropriately skilled neonatal staff and facilities within the delivering unit[89,90]. Delivery within a tertiary unit does not appear to significantly impact on rates of ROP or longer-term visual impairment (OR 0.76, 95% CI 0.58-3.67)[90], although ROP is an infrequently reported outcome among studies addressing the impact of birthplace on neonatal outcome. Nevertheless where PTB is imminent, it is prudent that in-utero transfer of the expectant mother to a unit with optimal neonatal facilities is arranged where necessary.

Discussion

This review underlines the important role of obstetrician in the prevention of ROP. Efforts predominately focus on predicting and preventing spontaneous PTB, as well as preventing fetal growth restriction, LBW and maternal infection. ROP is an infrequently reported outcome in obstetric trials, and so proxy outcomes described within this review included rates of spontaneous PTB and alternate neonatal morbidity. We have described how accurate prediction of pregnancies at highest risk of PTB is a major clinical challenge as no one screening test provides optimal performance. Clinicians therefore commonly elect to employ a combination of tests including of CL and fFN measurement in conjunction with discerning any pre-existing antenatal risk factors. Timely intervention for those at risk of spontaneous PTB is also important. The choice of intervention should therefore be patient-led and following an evidenced based discussion of the options based on the characteristics of the individual case.

Future work for the prediction and prevention of PTB may focus on a selection on biomarkers including vaginal microbiota[91-93]. There is some evidence that vaginal dysbiosis and *Lactobacillus iners* detected in the early second trimester of high risk pregnancies provides comparable screening performance (67% sensitivity and 71% specificity) to CL measurements for spontaneous PTB <34 weeks[94], as well as PPROM[14]. Application of vaginal microbiota testing is currently prohibited from clinical practice by the lack of a point of care test and the costly and lengthy processing times of 16S rRNA sequencing. More promising biomarkers for PTB prediction include phosphorylated insulin-like growth factor binding protein-1 (PIGFBP- 1) and placental alpha-macroglobulin-1 (PAMG-1). PIGFBP- 1 is synthesised in placental decidual cells and detectable in cervicovaginal fluid following disruption at the chorio-decidual junction when contractions occur[95]. The absence of PIGFBP- 1 has been demonstrated to have a high negative predictive value for PTB, however positive prediction is poor[95]. Like fFN, a quantitative version of this test may improve its potential for clinical utility. Placental alpha-macroglobulin-1 (PAMG-1), also synthesised in the decidua, was developed as a diagnostic test for rupture of amniotic membranes. Recently it has been demonstrated to be comparable to fFN for predicting PTB in women with intact membranes [96], and it likely to be the focus of future clinical trials.

Conclusion

The impact of obstetric practice on the prevention of retinopathy of prematurity is largely surmised through alternative outcomes and focuses predominantly the prediction and prevention of spontaneous PTB, its primary culprit. Measurement of CL and fFN helps to identify those at risk of PTB, while cerclage, progesterone, the cervical pessary and aspirin may be used to ameliorate this risk in specific populations. Diet and lifestyle modifications are important in the pre-conception period in addition to pregnancy in order to improve outcomes for the mother and offspring. More needs to be done in the plight against PTB however, and for the associated morbidities afflicted on the neonate.

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Figure 1. Cervical cerclage placement around the uterine cervix (A). The cerclage suture is inserted (B) and tied (C) in a purse-string fashion around the cervix

Figure 2. The Arabin cervical pessary (A), positioned in place around the cervix (B).

Table 1. Obstetric interventions to reduce the risk of retinopathy of prematurity and improve pregnancy outcome.

	Pathology	**Intervention**
Peri-conception	• All pregnancies	• Folic acid • Healthy diet
	• Iron deficiency	• Ferrous sulphate
	• Vitamin D deficiency	• Vitamin D
	• Obesity	• Weight loss
	• Smoking	• Smoking cessation
Antenatal	• Placental dysfunction • Fetal growth restriction • Hypertensive disease • Diabetes • Multiple pregnancy	• Aspirin 150mg (commenced from 16 weeks gestation)
	• Cervical shortening • Risk of spontaneous PTB	• Fetal fibronectin testing • Cervical cerclage • Vaginal progesterone • Cervical Pessary
	• PPROM • Vaginal infection	• Antibiotics
Labour and delivery	• PTB <34 weeks	• Maternity unit with appropriate neonatal facilities • Corticosteriods (with tocolysis) • Magnesium sulphate

PTB = preterm birth, PPROM = preterm prelabour rupture of membranes

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