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The Role of PTB Clinics: A Review of the Screening Methods, Interventions and Evidence for Preterm Birth Surveillance Clinics for High-Risk Asymptomatic Women

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Abstract

Context: Preterm birth accounts for significant neonatal mortality and morbidity as well as substantial health costs. As our understanding of aetiology and risk factors for preterm birth increases, predictive tools and prophylactic interventions have been developed to improve maternal and fetal outcomes. These are effective, but require surveillance of asymptomatic high-risk women, as well as ultrasound and surgical expertise. This has led to the development of preterm birth surveillance clinics (PSCs), which pool these resources together and have changed the focus of care from reactive to predictive and preventative management.

Methods: A literature review of the evidence surrounding the predictive tests (cervical length, fetal fibronectin, Actim Partus, Partosure) and prophylactic interventions (cerclage, progesterone, Arabin pessary, antibiotics, and steroids) for preterm birth to understand what preterm birth surveillance clinics do and how effective they are.

Results: Measuring cervical length and fetal fibronectin levels are two of the most accurate predictive tests preterm birth, especially when used in combination. Other predictive tools like Actim Partus and Partosure are effective for symptomatic women, but their role in surveillance of asymptomatic women is unclear. Cervical cerclage is effective in reducing preterm birth in women with previous losses, but the role of progesterone and pessaries remains debated. Steroids remain one of the most effective antenatal intervention, but they need to be administered within a tight timeframe in order to confer maximal benefit. The role of PSCs in predicting the timing of birth and targeting women at highest risk to appropriate interventions is therefore crucial in optimizing care and improving outcomes.

Conclusions: Nearly every step of management is still debated although many have a strong evidence-base and effective interventions do exist. The challenge is finding the optimal management pathway, and details of which populations benefit from which interventions need to be evaluated. While evidence continues to be collated, the poor outcomes of preterm birth and the multiple options available to reduce them justify preterm birth surveillance clinics being resourced.

Keywords: Preterm Birth, Predictive, Fetal Fibronectin, Cervical Length, Cervical Cerclage

1. Context

Defined as spontaneous or induced birth before 37+^{0}weeks' gestation, preterm birth (PTB) is responsible for significant perinatal morbidity and mortality. Preterm labour affects 11.1% of live births worldwide (1) and 7.6% of live births in England and Wales (2), but incidence is rising globally (3). PTB causes more than 3 million perinatal deaths a year (1) and causes increased risks of neurodevelopmental impairment, behavioural problems and respiratory diseases, which constitute significant health costs and decreased quality of life (4-6).

2. Methods

The primary research question our review is addressing is "what predictive tests and prophylactic interventions to preterm birth surveillance clinics use and what is the evidence behind them?" Our secondary question is "how effective are clinics at reducing preterm birth and improving outcomes for women and babies?"

The literature search focused on quantitative and qualitative papers on the incidence, practice and efficacy of preterm birth surveillance clinics for preterm birth prevention. It also included national guidelines (from the national institute for health and care excellence and the Royal College of obstetricians and gynaecologists). A search of EMBASE was undertaken by GV. The following keyword search terms were used: preterm birth, asymptomatic, high-risk, singleton gestation, predictive, fetal fibronectin, ultrasonic cervical length screening, cervical cerclage, ActimPartus, Partosure. The search was restricted to English language papers.

Eligible papers were those between 1995 and 2017. In addition, bibliographies of relevant papers were searched in order to identify papers missed by database search. 638 titles were identified by initial searches. These titles were assessed and 209 considered relevant to review. Following abstract review, 83 met inclusion criteria. Given the limited evidence on this subject, appraisal checklists were not used for further exclusion of studies, but the research methodology of each paper was critically appraised in the discussion.

3. Aetiology and Risk factors for PTB

In high-income countries, 30% - 35% of PTB are induced due to maternal or fetal disease like pre-eclampsia, intrauterine growth restriction or placental anomalies, where delivery is the safest option despite possible adverse consequences of prematurity (7). The other 65% - 70% of preterm births are spontaneous (sPTB). Causes of sPTB are not well established, but the current working model presents it as a complex multifactorial syndrome resulting from spontaneous labour with intact membranes (40% - 45%) or preterm premature rupture of membranes (P-PROM, 25% - 40%), which may be related (8, 9). These processes are triggered by infection, placental vascular pathology, uterine anomalies, cervical trauma, decidual senescence, progesterone imbalance, or stress (8).

Whilst aetiology is not fully understood, the following mechanisms are thought to play an important role. Inflammation from infection, trauma or vascular pathology causes synthesis of pro-inflammatory cytokines like IL-8, IL-1α and TNF-α. These stimulate production of prostaglandins, which cause uterine contractions, and matrix-degrading metalloproteinases, which can trigger P-PROM (3, 7, 8, 10, 11). Abnormal placentation causes haemorrhages, stimulating the production of the coagulation factor thrombin. This causes myometrial contractions and deteriorate the choriamniotic membrane extracellular matrix by stimulating synthesis of pro-inflammatory cytokines and metalloproteinases (11-13). Finally, disruption in progesterone levels secondary to functional progesterone deficiency or intra-uterine infections can also trigger labour (7). Progesterone usually maintainins uterine quiescence during pregnancy by inhibiting myometrial production of compounds that stimulate inflammation and contractions, including prostaglandins, oxytocin and cytokines (e.g. Il-1, IL-8 and CCL-2) (14, 15). Progesterone also inhibits TNF-α-induced apoptosis and matrix metalloproteinases-induced cervical ripening (16-19). If progesterone levels are altered however, these protective mechanisms are reversed and labour ensues (7). Much of the data comes from mice, rate and sheep models, but Shynlova et al. believe that the results are applicable to humans (14).

Several risk factors are well established, especially sources of inflammation, trauma or disruption to normal pregnancy. A previous PTB or late miscarriage is a widely recognized risk factor for PTB, which could be linked to many mechanisms (3). Systemic maternal infections, urinary tract or intra-uterine infections, bacterial vaginosis, and douching may all disrupt the maternal vaginal microbiome and are linked with the release of pro-inflammatory factors, which are linked to increased rates of sPTB (3, 8, 20, 21). Uterine and cervical weakness impair their ability to support mechanical stresses induced by full-term pregnancy. Mechanical weakness is thought to contribute to PTB in women with uterine anomalies, previous cervical surgery, more than 3 prior abortions, or an interpregnancy interval of less than 6 months (3, 22-24). Multiple pregnancies can also cause over-distention of the uterus and release of pro-inflammatory cytokines, leading to contractions and P-PROM (7). Domestic violence is also a risk factor for PTB, perhaps due to maternal stress, physical abdominal assault or sexual trauma (25). The presence of any one of these risk factors represents a “high-risk pregnancy” and is an indication for referral to a PTB surveillance clinic (PSC), so that the current pregnancy can be monitored and managed appropriately. These specialised units use predictive tools and interventions to monitor asymptomatic high-risk pregnancies in order to prevent and manage preterm labour (3, 8, 26, 27).

Other risk factors include low socioeconomic status, single marital status, lower maternal education, stress, drug and alcohol use, nutritional status, and black ethnicity. However, causative mechanisms and optimal interventions for them are not established and they are not in themselves sufficient to indicate referral (7, 8).

4. The role of Preterm Birth Surveillance Clinics

The development of specialized PTB clinics (PSCs) has occurred following growing understanding of risk factors, risk stratification techniques and prophylactic interventions for PTB. Treatments proven to improve outcomes exist (especially the advent of US-indicated cerclage in high-risk pregnancies), but they require surveillance of asymptomatic high-risk women, as well as ultrasound and surgical expertise (28, 29). This drive has changed the focus of care from reactive to predictive and preventative management (26, 27, 30). PSCs use tools (like cervical length and fetal fibronectin measurements) that are effective at predicting PTB to target women who can benefit from prophylactic interventions such as cerclage and progesterone administration, and thereby reduce PTB (31, 32).

Given the numerous and varied causes of PTB, identifying risk factors that are modifiable is crucial for management. Women may be referred to appropriate services such as stop-smoking services, substance misuse clinics, appropriate mental health services, and dieticians. Women who practice douching are advised to stop and patients at the extremes of BMI are counseled about the benefits of normal weight ranges. Victims of domestic violence are referred to social services and supported accordingly throughout their pregnancy and beyond (30).

However, many of these interventions can be coordinated with patients' routine maternity care, and the role of PSCs lies in monitoring women with non-modifiable risk factors, like previous PTB, cervical surgery, uterine anomaly, etc. (26). In recent years, a number of biomarkers have gained popularity for triaging various populations and indicating timely interventions when required (3).

4.1. Predicting PTB

4.1.1. Cervical Length

The cervix physiologically changes and shortens during normal labour, however these changes are highly predictive of PTB if they occur < 32 weeks spontaneously or after inflammation, haemorrhage, premature contractions, or uterine overdistension (27, 33). A short cervix identified by ultrasound is associated with increased risk of sPTB < 35 weeks in symptomatic and asymptomatic women with singleton and twin pregnancies (RR 3.3, 95% CI 2.1 - 5.9) (29, 33-36). Transvaginal ultrasound scans (TVUSS) are accurate, safe, well accepted, reliable, valid in low and high-risk women, and a systematic review concluded that cervical length (CL) < 25 mm between 16 - 24 weeks is the most reliable marker for PTB (33, 34).

Although ultrasound surveillance is subject to human error and inter-operator variability, PSCs may overcome this by allowing the concentration of resources in one unit and greater specialist training. Tracking cervical length allows PSCs to identify the population of women who will benefit most from specific interventions, especially cervical cerclage (36).

4.1.2. Fetal Fibronectin

Measureing fetal fibronectin (fFN) between 18 - 35 weeks' gestation can predict sPTB in symptomatic and asymptomatic women (37-40). fFN is a glycoprotein produced by cells between the chorion and decidua that is undetectable in the cervicovaginal fluid (CVF) after 18 weeks. Following inflammation, infection or disruption between fetal and maternal membranes, fFN leaks into the cervical fornix, and rising fFN concentrations in CVF predict imminent sPTB (38, 40, 41). fFN values have traditionally been assessed with a qualitative threshold of 50 ng/mL as a positive/negative indicator of risk (42). In asymptomatic high-risk women, fFN has a negative predictive value (NPV) of 98.6%, and as such values < 50 ng/mL are reassuring, whereas values $\geq$ 50 ng/mL can be used to target at-risk women for interventions (41).

Drawbacks of fFN include that results are affected by bleeding, cervical manipulation or intercourse within 48hours (56% false-positive rate in women who had sexual intercourse within 48hours versus 6% in controls, P < 0.001) (43). Qualitative fFN also has a low positive predictive value (PPV 13.6%), which can increase patient anxiety as most women with positive tests will not actually deliver preterm (44).

The advent of quantitative fFN measurements may overcome some of these issues. Increasing fFN values from < 10, 10 - 49, 50 - 199, 200 - 499, and $\geq$ 500 ng/mL are correlated to increased sPTB (2.7%, 11.0%, 14.9%, 33.9%, and 47.6% sPTB > 34 weeks, respectively) (41). Using a threshold of 200 ng/mL confers a PPV of 37.7% (95% CI 26.9 - 49.4) and NPV of 94.5% (95% CI 93.4 - 95.8), which means fewer false-positives than qualitative thresholds, with little effect on false-negatives (41). Using quantitative fFN value allows better discrimination between high- and low-risk women, and targeting their management more appropriately.

Several studies have found that using fFN measurements in combination with cervical length is a more reliable method of predicting PTB versus using either test alone because a positive fFN value enhances CL's predictive value (40, 45). In one observational study of high-risk asymptomatic women, < 1% (95% CI 0.1% - 3%) of fFN negative women delivered within a month of testing, despite having a cervix < 25 mm (46). Consequently, a negative fFN value is reassuring and can prevent unnecessary intervention despite shortening cervical length. When a short cervix (< 25 mm) was combined with a positive fFN value, 21% (95% CI 6% - 45%) of women delivered prematurely (46).

Therefore, combining predictive tests allows clinicians to re-classify women according to their risk and avoid prescribing interventions in patients who don't actually need them. Taking this into account, Kuhrt et al. developed a predictive model (QUIPP) based on previous risk factors, cervical length and quantitative fFN, which predicts risk of sPTB within 7 days, 4 weeks, and before 37 weeks. The QUIPP app translates these continuous variables into bespoke and clinically relevant predictions of PTB within meaningful timeframes (31).

4.1.3. Actim Partus

Actim Partus is a bedside test that predicts delivery within 48hours in women in preterm labour, but its use in screening asymptomatic women is debated (47-49).

The test qualitatively measures CVF levels of phIGFBP-1 (phosphorylated insulin-like growth factor binding protein). Similarly to fFN, the protein levels increase following placental-decidual disruption and can be detected before labour (47). phIGFBP-1 levels are as good as predicting delivery < 35 weeks in women having contractions as fFN (50), but are not affected by urine contamination or sexual intercourse within the previous 48hours, which gives it an advantage over fFN (51). However, its predictive value in high-risk asymptomatic women was poor (0% PPV and 70% NPV, versus 67% and 79% for fFN, respectively) (47). Its use in surveillance of asymptomatic high-risk women is therefore limited.

4.1.4. Partosure

Partsure is another bedside test that predicts sPTB within the next 7 days in women in preterm labour (sensitivity 80%, specificity 95%, NPV 96%, PPV 76%, n = 203) by measuring CVF levels of PAMG-1 (placental alpha macroglobulin), an amniotic fluid glycoprotein that can be present in CVF after degradation of fetal membranes and uterine contractions (52, 53). Its use in PSCs is contested because although it has higher PPV than fFN or CL < 25 mm in symptomatic women (76% versus 29% (n = 66) and 30% (n = 203), respectively, P < 0.01), there is no evidence for asymptomatic women (54). Furthermore, this study only measured fFN in 66 women and used qualitative fFN rather than quantitative measurements, while limits its accuracy (54). A prospective cohort study comparing the PartoSure versus maternal history and/or cervical length in high-risk asymptomatic women is ongoing and should shed light on this promising test (55).

Another limitation is that PartoSure only predicts risk for the next 7days, whereas fFN can predict the risk of any preterm delivery (38, 39, 41). This makes fFN far more valuable, as it allows better planning and is more useful for the patient (41). In addition, it can be used in asymptomatic women and as such is the most useful biomarker in predicting delivery in the setting of PSCs.

4.2. Preventing PTB

4.2.1. Cerclage

Cervical cerclage is a surgical procedure where a suture is placed around the cervix in order to prevent cervical dilatation and labour. Cerclage is indicated in cases of recurrent PTB, and short and/or dilated cervix (45, 46). The mechanisms by which stitches prevent PTB is unclear, but they may provide support to a weak cervix, maintain length and/or strengthen the endocervical mucus plug against ascending infections (56, 57). A Cochrane systematic review has shown that cerclage significantly reduces PTB rates versus no treatment (RR 0.80, 95% CI 0.69 - 0.95), but not perinatal deaths (RR 0.78, 95% CI 0.61 - 1.00). Additionally, cerclage caused increased maternal adverse effects (fever, vaginal discharge and bleeding) and C-sections (RR 1.19, 95% CI 1.01 - 1.40) (57). To avoid over-intervention, RCOG guidelines recommend that sutures should only be given in women with 3 or more previous PTB and/or late miscarriages, but not in women with incidental finding of a short cervix only (58).

There is some debate between using 15 or 25 mm as a lower threshold, as an RCT found that cerclage in women with CL < 25 mm reduced perinatal mortality, but that PTB was only reduced in women with CL < 15 mm (59). 2011 RCOG Guidelines recommend using 25 mm as an indication for treatment, but 41% of UK PSCs use 15 mm instead (26, 58).

Emergency 'rescue' cerclages can be performed in patients with a dilated cervix and exposed fetal membranes in order to stop preterm labour, however no RCTs exist and evidence is limited evidence (27). These cases often present as emergencies but may also be asymptomatic and only detected when patients have a CL scan in a PSC. An observational study found that rescue stitches increased gestational age by 8.8 weeks versus bed-rest alone, with a corresponding increase in neonatal survival (RR 0.09, 95% CI 0.01 - 0.76) (60). However, rescue stitches are not recommended in women with a stitch already in place, as reinforcement cerclages can increase chances of delivery versus expectant management (92% delivered < 32 weeks versus 42% in controls, P = 0.01) (61).

In women with previous surgery or extensive damage to the cervix prevents the placement of a stitch, or with previous failed cervical stitches, transabdominal cerclage (TAC) can be considered (62). This stitch is placed higher than the cervical suture, thereby giving better mechanical support. A study of women with histories of cervical insufficiency or defects (n = 101) showed that TACs were effective at increasing gestational age (7% (95% CI 2.9% - 13.9%) of births occurred < 32 weeks with TAC versus 76% (85% CI 70.2% - 81.1%) in controls). TACs also increased neonatal survival from 93.5% survival (95% CI 85.5% - 96.6%) versus 27.5% in controls (95% CI 22.5 - 33.8%) (62). A recently completed RCT has shown that TACs are more effective than cervical cerclage in decreasing PTB and late miscarriage rates in women with previous failed cerclage, however cervical stitches are preferred as first-line treatment because they are less invasive, carry fewer risks and are effective for the majority (27, 63).

The debate around indications for cerclage therefore remains controversial due to its limited evidence-base (41), and a review of PSCs found that only 45% (n = 22) of specialist clinics in England provided cerclage as primary treatment (26).

4.2.2. Progesterone

Progesterone may reduce PTB, probably due to its effects in controlling cervical ripening (11, 16). However, evidence surrounding its efficacy and potential long-term consequences are conflicting. A meta-analysis found that vaginal progesterone reduced sPTB $\leq$ 34 weeks (RR 0.64 versus placebo, 95% CI 0.45 - 0.90) and perinatal mortality (RR 0.50, 95% CI 0.33 - 0.75) in asymptomatic high-risk women (with previous sPTB or CL < 25 mm) (64). Contrastingly, the OPPTIMUM study (n = 1228) found that prophylactic progesterone was not associated with reduced risk of PTB (adjusted OR 0.86, 95% CI 0.61 - 1.22), and that childhood outcomes were not significantly different (mean difference in cognitive scores at 2 years old -0.48, 95% CI -2.77 - 1.81) (65). A subsequent meta-analysis (n = 974) of five trials including the OPPTIMUM study found that progesterone decreased the risk of PTB $\leq$ 34 weeks (RR 0.66, 95% CI 0.52 - 0.83) and had no adverse effects on neurodevelopmental outcomes (20). However, the study only included women with a short cervix (only 251 out of 1228 OPPTIMUM patients were included), and there remains uncertainty as to which populations benefit from progesterone.

The latest NICE guidelines recommend prescribing prophylactic progesterone in women with a history of sPTB with CL < 25 mm at 16 - 24 weeks (66). Nevertheless, only 18% of UK clinics use progesterone as a primary treatment (26), and the uncertainty surrounding its efficacy calls for further research, especially in long-term outcomes (20).

4.2.3. Arabin Pessary

The Arabin pessary is a flexible silicone ring that is inserted into the vagina to prevent sPTB in women with short cervixes (67). The mechanisms of action is debated, but it may be through mechanical support of the uterus, changing the uterocervical angle or by strengthening the cervical mucus plug, which is protective against infection (27, 67, 68).

Data on its efficacy is inconclusive as one multicentre RCT in Spain found that pessaries reduced sPTB < 34 weeks (OR versus controls 0.18, 95% CI 0.08 - 0.37) and improved neonatal mortality (OR 0.14, 95% CI 0.04 - 0.39) (69). Contrastingly, a single-centre RCT in China found that pessaries did not reduce sPTB < 34 weeks (9.4% of women with pessaries delivered < 34 weeks versus 5.5% of controls, P = 0.46) (70).

The effects of the Arabin pessary are thus unclear, nor is it known if it is more effective than progesterone or cerclage (56, 67). The UK-based SUPPORT trial is ongoing to compare the three treatments (71). A stronger evidence-base for pessaries may increase the use of this intervention (only 4% of UK PTB surveillance clinics use it as first line treatment), as they are less invasive and have fewer side effects than their alternatives (26, 67).

4.2.4. Antibiotics

Bacterial vaginosis has been linked to PTB, but treating it during pregnancy has conflicting evidence. Some studies have found antibiotics to worsen outcomes, with side effects severe enough to indicate changing or stopping treatment (RR 1.66, 95% CI 1.02 - 2.68) (72). Neonatal effects included increased risk of functional impairment, cerebral palsy and neonatal deaths when mothers received prophylactic antibiotics versus placebo (RR 1.57, 95% CI 1.03 - 2.40) (73). Some antibiotics showed increased risk of delivery < 37 weeks (RR with metronidazole versus placebo 1.6, 95% CI 1.05 - 2.4) (74). Antibiotics are therefore only recommended in women with P-PROM because they are effective in restoring vaginal flora73, but not as prophylaxis in high-risk asymptomatic women (66, 75, 76). A review of all UK PSCs reflects this, as no centres used antibiotics prophylactically. There was discrepancy in management of bacterial vaginosis however, as antibiotic use varied (45% used vaginal clindamycin, 15% oral clindamycin, 35% metronidazole) and 10% did not treat it (26).

4.3. Optimising Neonatal Outcomes

The use of antenatal corticosteroids (ACS) to improve neonatal outcomes in preterm infants is one of the most successful interventions for PTB. ACS accelerate fetal lung maturation and thereby decrease incidence of respiratory distress syndrome in neonates (RR versus placebo 0.66, 95% CI 0.43 - 0.69), cerebroventricular haemorrhage (RR 0.54, 95% CI 0.43 - 0.69), necrotising enterocolitis (RR 0.46, 95% CI 0.29 - 0.74) and combined fetal and neonatal death (RR 0.77, 95% CI 0.67 - 0.89) (77).

Whilst guidelines only recommend administering steroids to women in preterm labour, P-PROM or induced delivery and advise against repeat courses of ACS66, many clinicians opt to give prophylactic doses of ACS to asymptomatic women on the basis of perceived risk (e.g. previous sPTB at similar gestations). However, since most asymptomatic women admitted to hospital for prophylactic ACS will not go on to deliver before 30 weeks (52), the limitations of ACS deserve consideration. These include the narrow optimal timeframe and side effects like lower birthweight, impaired fetal growth, increased susceptibility to type II diabetes, and cardiovascular disease (77, 78). Additionally, ACS do not confer benefit when delivery occurs after 34 weeks (RR of combined fetal and neonatal death versus placebo 3.25, 95% CI 0.99 - 10.66) (77).

Furthermore, ACS are most beneficial when administered 48hours before delivery, but their benefit is lost after

7 days of administration (RR of combined fetal and neonatal death born within 48hours is 0.59, 95% CI 0.41 - 0.86, versus RR 0.81, 95% CI 0.60 - 1.09 in babies delivered within 1 - 7 days, and RR 1.42, 95% CI 0.91 - 2.23 in infants delivered after 7 days of administration) (77). If the patient does not deliver within 7 days but remains at risk of sPTB, the benefits of repeated doses of ACS is contested, as the improvement in lung function must be weighed against the increased risk of adverse effects associated with repeated doses (78).

Optimal timing is therefore crucial to confer maximal benefit and prevent harms of over-intervention (78). Predictive algorithms that calculate risk of delivery within 7 days are currently being developed and may play a greater role in guiding management in the future (31). What threshold should prompt interventions like ACS is still to be formally evaluated, but in the symptomatic population it appears as if a 5% - 10% risk of delivery within 7 days is sufficient for most clinicians (79).

Other antenatal interventions can be offered, including magnesium sulphate to improve neonatal outcomes and tocolytics to delay labour long enough to administer ACS (80, 81). However, since these are usually only given for women with contractions or in labour, they are usually prescribed on the labour ward rather than in PSCs, and so fall outside the scope of this article.

5. How Effective Are PTB Surveillance Clinics

A systematic review of all specialist PSCs in England (n = 22) found that protocols and care pathways vary greatly between centres, but involve surveillance assessment of CL (100%), fFN (32%), vaginal flora (59%), or a combination of or none of these (23%). Primary treatments of choice also vary between practices and include cerclage (45%), progesterone (18%), pessaries (4%), antibiotics for bacterial vaginosis (95%), or multiple therapies (22%) (26). The review concluded that this heterogeneity of care was concerning, as it reflects a lack of clear evidence and guidance on optimum care. It also makes it difficult to compare outcomes between clinics and thus assess their success in reducing PTB.

There should ideally be clear and decisive evidence before a clinic can be introduced, and a Cochrane review concluded that there was not enough evidence to show that PSCs reduced PTB30. However, this study found that standard outcomes measured varied so much between clinics that they did not have enough comparable results to provide statistical power to observe significant differences between groups. Moreover, the RCTs included were performed in the 1980s, when the screening tests used today were not available. Results from this review are therefore of limited use.

A more recent systematic review of PSCs had more mixed results. The observational studies showed that PSCs did reduce PTB < 37 weeks (no average RR given), but although the RCTs showed a trend of reduced PTB, none had clinically significant results. However, the trials were from 1985 - 1990, before interventions like fFN and CL were developed. The authors conclude that PSCs reduce PTB, adverse neonatal outcomes and increase net savings in cost of care, but that there was insufficient evidence to strongly refute or support their use (82). It could argued that very few clinics in other settings have been formally evaluated, and sufficient predictive tools and interventions exist to justify PSCs.

The conflicting conclusions on PSC efficacy stem from the fact that it is difficult to run RCTs in this setting, which are traditionally the highest level of evidence (82). However, it is nearly impossible to run RCTs looking at multiple interventions simultaneously, and defining which outcomes to equate to success is complex. Consequently, one could question whether RCTs are the best way of evaluating complex interventions like clinics. Oservational studies evaluating the most up-to-date predictive tests and management available should yield the most relevant and applicable results.

One such prospective cohort study found that screening high-risk asymptomatic women was effective at discriminating between women who required interventions from those who did not (32). The study found that, of all patients admitted to hospital from PSCs, over 33% delivered < 30 weeks, and 73% < 37 weeks. PSCs are therefore able to target interventions to women who would benefit most and prevent over-treatment of lower-risk women. These results, as well as growing evidence of the efficacy of varying interventions, justify providing intervention in women found to be at high-risk by PSCs.

One step to enabling higher-quality research would be for clinics to be transparent about their results and share data. The creation of the Preterm Clinical Network Database, which records detailed histories and clinical course of patients attending PSCs, is a step towards sharing results, enabling collaboration between researchers, and allowing direct comparison between clinics. If outcomes could be defined and classified, for example in a similar fashion as the Robson Criteria for C-sections or CROWN core outcomes in women and newborn health, evaluating the effect of PSCs would become more feasible.

6. Conclusion and Considerations for the Future

Specialized PTB surveillance clinics are a recent approach to managing asymptomatic women at high risk of

PTB, and consequently data about their techniques and efficacy is not yet clearly established (30). Many steps of management are still debated, although many have a strong evidence-base. Because of the complex interventions involved, conducting RCTs is challenging, but the growing pool of observational studies and meta-analyses will shed light on optimal care. There is a need for standardized outcome measures to enable clinics to regularly audit themsleves, so that fair comparisons may be drawn between them (83). Given their clustering of specialist skill and resources, PSCs foster an environment conducive to research, and further sharing of data will encourage innovation and self-improvement. These results will enable the medical community to clarify the true effectiveness of many treatments, as well as develop a standardized approach to gold-standard management (26, 82). The challenge is finding the optimal management pathway, and details of which populations benefit most from which interventions need to be evaluated. While evidence continues to be collated however, the poor outcomes of PTB and the multiple options available to reduce them do justify preterm birth surveillance clinics being resourced.

Footnote

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