CLINICAL GUIDELINES

MANAGEMENT OF PRETERM BIRTH

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INTRODUCTION

Preterm birth (PTB), defined as delivery before 37 weeks of gestation, remains a leading cause of perinatal morbidity and mortality worldwide. It is associated with increased risks of respiratory, neurological, and developmental complications in the neonatal period and beyond, as well as substantial emotional and financial burden for families and healthcare systems. In Singapore, despite declining overall birth rates and significant advances in obstetric and neonatal care, the national PTB rate has remained relatively unchanged over recent years. Between 2017 and 2023, the proportion of preterm deliveries has plateaued, with a premature birth rate of 8.2% reported in 2023, which is higher than that of neighbouring regions such as Hong Kong (6.5%) and China (6.9%). These trends highlight an important and persistent public health challenge.

Preterm birth is a heterogeneous condition with multifactorial aetiologies, including spontaneous preterm labour, preterm prelabour rupture of membranes, and iatrogenic preterm birth for maternal or fetal indications. Strategies to reduce PTB span the continuum of care from preconception and antenatal risk assessment to intrapartum management and postnatal follow-up. However, variation in clinical practice, evolving evidence, and differences in resource availability across institutions may contribute to inconsistent approaches in screening, prevention, diagnosis and management. A harmonised, evidence-based national framework is therefore essential to optimise care, reduce unwarranted variation, and improve outcomes for women and their babies in Singapore.

These national guidelines have been developed to provide clear, practical, and context-appropriate recommendations for the screening, prevention, diagnosis and management of spontaneous preterm birth. They synthesise current best evidence with expert consensus, while taking into account the local epidemiology, healthcare infrastructure, and multidisciplinary models of care.

AIM OF GUIDELINE

Target audience: The guidelines are intended for obstetricians, maternal–fetal medicine specialists, neonatologists, general practitioners, midwives, and other healthcare professionals involved in the care of pregnant women at risk of, or affected by, preterm birth.

Aims: By standardising practice and promoting timely, targeted interventions, these guidelines aim to reduce the burden of preterm birth in Singapore and to improve both short- and long-term outcomes for mothers and their children.

Commissioned by the College of Obstetricians and Gynaecologists, Singapore with use of the GRADE-ADOLOPMENT methodology (Adopt - Adapt - Develop).

STATEMENT OF INTENT

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve. The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

1. PRETERM BIRTH SCREENING STRATEGIES

The primary aim of preterm birth (PTB) screening is to facilitate early identification of women at increased risk of spontaneous PTB to allow effective preventive strategies, timely referral and appropriate surveillance. Screening should be applied along the continuum of care, from preconception, first antenatal visit and the mid-trimester detailed scan, and should be tailored according to individual risk factors of the pregnancy.

These screening recommendations apply to:

- Women with singleton or multiple pregnancies
- Women with past history and no past history of PTB
- Asymptomatic women (no signs and symptoms of preterm labour)
- All levels of care (primary, secondary and tertiary obstetric services) in both public and private sectors.

Clinical Risk Assessment

1.1 Timing of screening

A structured risk assessment for PTB should be performed:

- At **booking** (first antenatal visit)
- Reassessed at each key gestational milestone (e.g. 11-13 weeks, 18–22 weeks and 24 weeks)
- When new complications arise (e.g. threatened miscarriage, antepartum haemorrhage, diagnosis of multiple pregnancy)

1.2 Documentation of risk factors

Clinicians should specifically enquire about, and record, the following known reversible and irreversible risk factors for PTB.

Risk factors for preterm birth

1.2.1 Individuals at High Risk of Preterm Birth[1]

- Previous preterm birth or second trimester loss (14-34 weeks' gestation)[2]
- Previous preterm prelabour rupture of membranes (PPROM) less than 34 weeks
- Previous use of cerclage
- History of trachelectomy
- History of a previous full dilatation caesarean section
- Significant cervical excisional surgery i.e. large loop excision of the transformation zone (LLETZ) with an excision depth of greater than 1cm, more than one procedure or a cone biopsy.

Laser ablation is not associated with increased risk of preterm birth. **(Grade B, Level I+)**

1.3 Screening Recommendations

1.3.1 Infection-related screening

(i) Routine screening for asymptomatic bacterial vaginosis (BV) is not recommended. (Grade A, Level I++)

The United States Preventive Services Task Force (USPTF)[3] states with moderate certainty that screening asymptomatic pregnant persons who are not at increased risk of preterm delivery (i.e. those without a prior preterm birth) provides no net benefit in preventing preterm delivery and thus recommends against this practice **(Grade D)**. This position is supported by multiple randomized controlled trials (RCTs) and meta-analyses showing that treatment of asymptomatic BV in a general obstetric population does not reduce the incidence of preterm birth or related adverse outcomes.[4] **(Grade A, Level I++)**

Recent large trials, including the PREMEVA study[5] and the AuTop Randomized Clinical Trial[6], further confirm that screening and treating BV in low-risk pregnant women does not significantly reduce preterm birth rates, regardless of whether conventional or molecular diagnostic methods are used. International guidelines also advise against routine screening in low-risk populations.

(ii) Recommend screening for asymptomatic bacteriuria via mid-stream urine (MSU) culture at booking visit in patients with previous preterm birth. Following a positive urine culture, a repeat MSU culture to confirm clearance should be performed after antibiotics treatment. (Grade A, Level I++)

For low-risk patients, it is reasonable to offer MSU culture.

For screening of asymptomatic bacteriuria, MSU culture should be sent rather than urine full and microscopic examination (UFEME).[7-8]

A Cochrane study by Smaill FM et. al.[9] in 2019, involving 15 RCTs and over 2,000 women with confirmed asymptomatic bacteriuria in pregnancy showed that antibiotic treatment probably reduces pyelonephritis in pregnancy (RR, 0.24; 95% CI, 0.13–0.42; 12 trials, 2,017 women), but the certainty is rated low because the trials are old and methodologically weak. In addition, antibiotics may reduce

preterm birth (RR, 0.34; 95% CI, 0.13–0.88; 3 small trials, 327 women) and low birthweight (average RR, 0.64; 95% CI, 0.45–0.93; 6 trials, 1,437 babies), but evidence is limited and certainty is low.

Wang et al.[10] conducted a systematic review to assess the association between UTIs during pregnancy and the risk of PTB (**Grade B, Level 2++)**. The study included 30 studies, involving a total of 249,810 cases with 2,626,985 healthy controls. The meta-analysis revealed a significant positive association between UTIs during pregnancy and PTB occurrence (OR, 1.92; 95% CI, 1.62–2.27). A sub-group analysis showed significant association in both PTB-based (OR, 2.01; 95% CI, 1.58–2.56) and UTI-based studies (OR, 1.79; 95% CI, 1.42–2.26).

Schieve, L. A. et al.[11] conducted a retrospective cohort analysis with data from four hospitals with the largest obstetric populations in Chicago, between 1988 and 1989. In all, 25,746 women were included in this analysis; 1,988 (7.7%) were considered positive for antepartum urinary tract infection and constituted the exposure group. Elevated risks were observed for exposure to urinary tract infection and low birthweight (OR, 1.4; 95% CI, 1.2-1.6), prematurity (OR, 1.3; 95% CI, 1.1-1.4), preterm low birthweight (OR, 1.5; 95% CI, 1.2-1.7), premature labour (OR, 1.6; 95% CI, 1.4-1.8) and chorioamnionitis (OR, 1.4; 95% CI, 1.1-1.9) **(Grade B, Level II-III).**

(iii) Routine screening for periodontal disease is not recommended. (Grade A, Level I+)

There is no evidence that treatment of periodontal disease in pregnancy reduced the rate of preterm birth. **(Grade A, Level 1+)**

Two meta-analyses of RCTs were analysed. In the first meta-analysis by Uppal A et al.[12] in 2010, 10 RCTs met the inclusion criteria for preterm birth. The odds ratio of preterm birth in the treatment group was 0.589 (95% CI, 0.396-0.875). In the second meta-analysis by Iheozor-Ejiofor Z et al.[13] in 2017, there were 15 RCTs with 7,161 participants who had periodontitis (14 studies) or gingivitis (1 study). All the included studies were at high risk of bias mostly due to lack of blinding and imbalance in baseline characteristics of participants. The two main comparisons were: periodontal treatment versus no treatment during pregnancy and periodontal treatment versus alternative periodontal treatment. Eleven studies (n = 5671) compared periodontal treatment with no treatment during pregnancy. The meta-analysis shows no clear difference in preterm birth <37 weeks (RR, 0.87; 95% CI, 0.70-1.10; low-quality evidence) between periodontal treatment and no treatment. It is unclear whether periodontal treatment leads to a difference in preterm birth < 35 weeks (RR, 1.19; 95% CI, 0.81-1.76; 2 studies, 2,557 participants) and <32 weeks (RR, 1.35; 95% CI, 0.78-2.32; 3 studies, 2,755 participants). Four studies compared periodontal treatment with alternative periodontal treatment. It is unclear whether there is a difference in preterm birth <37 weeks and preterm birth <35 weeks, when different periodontal treatments are compared because the quality of evidence is very low.

Observational studies suggest that women with periodontal disease have an increased risk of preterm birth although current evidence are conflicting. **(Grade B, Level II)**

A prospective study by Offenbacher S et al.[14] on 1,020 pregnant women demonstrated 11.2% incidence of preterm birth among periodontally healthy women, compared with 28.6% in women with moderate-severe periodontal disease (adjusted RR, 1.6; 95% CI, 1.1-2.3). Antepartum moderate-severe periodontal disease was associated with an increased incidence of spontaneous preterm births (15.2% versus 24.9%, adjusted RR, 2.0; 95% CI, 1.2-3.2).

Nabet C et al.[15] conducted a case-control multi-centre study of singleton livebirths involving 1,108 women with preterm deliveries and 1,094 with deliveries at term (37 weeks and above) at six French maternity units in 2010. Localized periodontitis was identified in 129 (11.6%) cases and in 118 (10.8%) control women and generalized periodontitis in 148 (13.4%) and 118 (10.8%), respectively. A significant association was observed between generalized periodontitis and induced preterm birth for pre-eclampsia (adjusted OR, 2.46, 95% CI, 1.58-3.83). However, periodontitis was not associated with spontaneous preterm birth or preterm premature rupture of membranes or with the other causes.

1.3.2 Biomarker Screening

(i) Do not use fetal Fibronectin as a primary screening test due to its low positive predictive value (PPV). (Grade B, Level II+)

The presence of fetal Fibronectin in cervicovaginal secretions has been implicated as a risk factor for preterm birth.

Esplin MS et al.[16] conducted a prospective observational cohort study of nulliparous women with singleton pregnancies, from 8 clinical sites across the United States between October 2010 and May 2014. The study included 9,410 women – 474 (5.0%) had spontaneous preterm births, 335 (3.6%) had medically indicated preterm births, and 8601 (91.4%) had term births. Fetal fibronectin levels of 50 ng/mL or greater at 16 to 22 weeks identified 30 of 410 women (7.3%) with spontaneous preterm birth and 31 of 384 (8.1%) at 22 to 30 weeks.

1.3.3 Universal Cervical Length Screening in Asymptomatic Low-risk Singleton Pregnancies

Universal transvaginal cervical length screening at mid-trimester (18-22 weeks) should be recommended to all singleton pregnancies. (Grade A, Level I++)

Hessami K et al.[17] performed a systematic review and meta-analysis in 2,024 involving 8 studies, with a total of 447,864 patients, demonstrated that universal transvaginal ultrasound of cervical length (TVUS CL) was significantly associated with a lower risk of spontaneous preterm birth <32 weeks (OR, 0.84; 95% CI, 0.76−0.94, p=0.002), but did not significantly decrease spontaneous preterm birth rates <37 weeks (OR, 0.92; 95% CI, 0.84−1.01, p=0.07) and <34 weeks (OR, 0.87; 95% CI, 0.73−1.04, p=0.12) in the overall analysis. In women with singleton pregnancies without a prior spontaneous preterm birth, there was a significantly lower risk of spontaneous preterm birth <37 weeks (OR, 0.88; 95% CI, 0.79−0.97, p=0.01) and a trend towards lower spontaneous preterm birth <32 weeks (OR, 0.82;

95% CI, 0.66−1.01, p=0.06) when screened with TVUS CL compared with no screening. **(Grade B, Level II++)**

This recommendation is supported by evidence from a recent study published by Berghella V et al.[18] which demonstrated effective treatment to reduce spontaneous preterm birth for individuals with a singleton gestation, no prior spontaneous preterm birth and a short mid-trimester CL of ≤20.9mm before 24 weeks. **(Grade A, Level I++)**

Other organisations and societies such as FIGO (International Federation of Obstetrics and Gynaecology), RANZCOG (Royal Australian and New Zealand College of Obstetricians and Gynaecologists), ISUOG (International Society of Ultrasound in Obstetrics and Gynaecology) and SMFM (Society for Maternal-Fetal Medicine) recommend universal cervical length screening in asymptomatic low risk women.

However, the guideline committee recognise that implementing this recommendation will involve a significant change of infrastructure support and trained personnel. As such, the committee recommend that this guideline be allowed sufficient time and resources to be embedded into clinical practice.

1.3.4 Cervical Length Screening in Twin Pregnancies

Transvaginal cervical length screening at mid-trimester (18-22 weeks) may be considered in twin pregnancies. (Grade B, Level I+)

Hughes KM et al.[19] conducted a two-stage meta-analysis of individual participant data (IPD) involving thirteen studies. This study included dichorionic diamniotic (DCDA) and monochorionic diamniotic (MCDA) twin pregnancies but excluded monochorionic monoamniotic (MCMA) twins. Of 6,437 patients (4,839 with DCDA, 1,189 with MCDA, and 409 with unknown chorionicity), 2,889 experienced spontaneous preterm birth before 37 weeks, and 934 before 34 weeks. Individual participant data meta-analysis showed that for every 1mm increase in cervical length, spontaneous preterm birth <37 weeks decreased by 4% (HR, 0.96; 95% CI, 0.95-0.97) and <34 weeks by 6.8% (HR, 0.93; 95% CI, 0.92-0.95). No specific cervical length reliably predicts or excludes all spontaneous preterm birth as risk increases linearly with decreasing length. **(Grade B, Level I+)**

Khaikin, Y et al.[20] performed a cost-utility analysis using a decision-analytic model to compare the clinical and economical outcomes of three screening strategies: (1) no cervical length (CL) screening, (2) universal one-step CL screening at 18–20 weeks' gestation and (3) universal two-step CL screening at 18–20 and 20–22 weeks. The model focused on DCDA twin pregnancies without additional preterm birth risk factors, excluding miscarriage, prior preterm birth, monochorionic twins, higher-order pregnancies or those receiving prophylactic progesterone or cervical cerclage. The two-step screening strategy increased quality-adjusted life years and reduced lifetime costs; The one-step screening strategy also outperformed no screening.

Other international organisations such as ISUOG, RANZCOG, SOGC (Society of Obstetricians and Gynaecologists of Canada), and NICE (National Institute for Health and Care Excellence) recommend cervical length screening in twin pregnancies.

1.4 Definition of a short cervix

A short cervix is defined as cervical length of ≤25 mm measured by transvaginal ultrasound in the mid-trimester, typically between 16+0 to 24+0 weeks.

(i) Use transvaginal cervical length measurements performed according to standardized technique when TV CL results are used to guide treatment decisions (Grade C, Level II+)

There are 3 methods for sonographic cervical assessment – Transvaginal (TVUS), Transabdominal (TAUS), trans-perineal/trans-labial. Cervical length measured by TVUS is associated with better prediction of a PTB, hence considered as the gold standard by several obstetrics and gynaecology organizations, including American College of Obstetricians and Gynaecologists (ACOG), the World Association of Perinatal Medicine (WAPM), and ISUOG. Additionally, all RCTs that have demonstrated benefits of intervention in patients with a short cervix used the transvaginal approach and there are no society guidelines supporting the routine use of transabdominal ultrasound for CL screening.[21]

Transvaginal ultrasound cervical length measurements should be performed in a standardized way, preferably by operators who have been certified by a scientific body, such as The Fetal Medicine Foundation or the Perinatal Quality Foundation (CLEAR). **(GPP)**

Transvaginal ultrasound is safe and not affected by maternal obesity, the position of the cervix, or fetal parts' shadows, and it is reproducible across practitioners. A prospective study has shown that higher CL cut-offs would be needed for assessment by transabdominal sonography (≤36 mm) compared with TVS (≤25 mm), and TVUS would still be necessary in more than 60% of cases.

(ii) CL ≤25 mm can be used as a cut-off for the initiation of measures to prevent PTB in asymptomatic singleton pregnancies, irrespective of risk factors (GPP, Level I+).

As with any screening test, the selection of a cut-off value is a trade-off between sensitivity and screen-positive rate. A meta-analysis by Domin CM et al.[22] showed that a CL cut-off of 20 mm had a sensitivity of 22.1% for PTB <35 weeks, for a screen-positive rate of 1.8%; increasing the cut-off to 25 mm increased the sensitivity to 33.1%, at the cost of increasing the screen-positive rate to 4.1%.

The selection of an optimal cut-off is further hampered by the fact that CL can be part of a combined screening strategy, in which other factors may affect the estimation of risk. In practice, for more than 10 years, a cut-off of 25 mm has been used in the majority of interventional trials as the best option to predict PTB prior to 24 weeks' gestation.

2. ANTENATAL MANAGEMENT OF ASYMPTOMATIC WOMEN AT RISK OF PRETERM BIRTH

2.1 Recommendations for the asymptomatic Low Risk Singleton pregnancy (No prior spontaneous PTB or mid-trimester loss)

2.1.1 Vaginal progesterone for low risk women with short cervix

(i) Recommend vaginal progesterone for asymptomatic singleton pregnancies with TVCL ≤25 mm before 24 weeks to reduce preterm birth. (Grade A, Level I++)

The efficacy of vaginal progesterone in individuals with a sonographic diagnosis of a short cervix was demonstrated in 2 large, multicentre RCTs and by independent patient-level meta-analyses, including data from these trials and several other smaller trials.

Fonseca et al.[23] conducted a double-blinded trial that randomized participants to 200 mg micronized progesterone per vagina or placebo. Patients were randomized at 20 to 25 weeks of gestation and were treated from 24 to 34 weeks of gestation. A total of 413 participants with a CL of ≤15 mm were included in the trial. The incidence of delivery before 34 weeks of gestation was reduced to 19.2% in the group that received vaginal progesterone, compared with 34.4% in the placebo group (RR, 0.56; 95% CI, 0.36–0.86). Of the participants included in this study, 85% had no previous history of PTB. In a subgroup analysis of patients without a history of PTB, a similar reduction in PTB rate (<34 weeks of gestation) was noted in those with a short cervix (≤15 mm) who received progesterone (RR, 0.57; 95% CI, 0.35–0.93).

In the PREGNANT Trial, Hassan et al.[24] reported that the administration of vaginal progesterone gel (90 mg) to patients with a CL of 10 to 20 mm identified at 19+0 to 23+6 weeks of gestation resulted in a significant reduction in the rate of PTB at <33 (8.9% vs 16.1%; RR, 0.55; 95% CI, 0.33–0.92), <35 (RR, 0.62; 95% CI, 0.42–0.92), and <28 (RR, 0.50; 95% CI, 0.25–0.97) weeks of gestation. Moreover, the study demonstrated a neonatal benefit with a significant reduction in respiratory distress syndrome (RR, 0.39; 95% CI, 0.17–0.92). Only 16% of the study population had a history of previous PTB, and even after excluding these participants, there remained a significant benefit of progesterone in the setting of an isolated short cervix (RR, 0.50; 95% CI, 0.27-0.90).

An updated IPD meta-analysis by Romero et al.[25] published in 2025 incorporated data on a total of 966 singleton gestations with a CL of ≤25 mm (494 allocated to the vaginal progesterone group and 472 to the placebo group). This analysis reported a significant reduction in the risk of preterm birth <34 weeks (RR, 0.65; 95% CI, 0.51-0.82) and preterm birth <28 weeks (RR, 0.67; 95% CI, 0.45-0.98) and improved perinatal outcomes.

(ii) Vaginal progesterone regimen: Vaginal micronized progesterone 200 mg nightly (capsule or pessary or equivalent).

The optimal dosage of vaginal progesterone is not clear. The most studied formulations in literature are 200 mg micronized progesterone capsules and vaginal progesterone are 90 mg (8%) progesterone gel. Some studies have also been performed with 400 mg dose but there is uncertainty whether there is any benefit in the higher dose. At this time, there are insufficient data to recommend a specific formulation or dose for the treatment of a short cervix.

In twin pregnancies, subgroup analysis from a systematic review published in 2023 revealed that effect of vaginal progesterone on the risk of preterm birth <34 weeks of gestation did not significantly differ between women receiving 90-200 mg per day of vaginal progesterone compared with those receiving daily dose of 400 mg or 600 mg.[26] Consideration can be made for vaginal progesterone dose 200-400 mg daily in twin pregnancies.

Although most papers are studied with the use of vaginal progesterone, if patients are unable to tolerate vaginal progesterone, there might be some benefit in providing oral progesterone instead of no treatment although there are limited data available to support the use of oral progesterone for prevention of preterm labour.

(iii) When using vaginal progesterone, start treatment between 16+0 and 24+0 weeks of pregnancy and continue until at least 34 weeks. (GPP)

The timing of progesterone administration varied between the studies. However, most trials started treatment between 16+0 and 24+0 weeks.

There is currently no good quality evidence to ascertain optimal duration of treatment with vaginal progesterone and timing that progesterone should be stopped. The recommendation to continue until at least 34 weeks is based on NICE Preterm Labour and Birth recommendations[1], which is also based on their committee's opinion.

(iv) Consider repeat TV CL every 1-2 weeks until 24 weeks to detect further cervical shortening. (GPP)

(v) Do not use 17-OHPC (including compounded formulations) for the treatment of a short cervix. (Grade B, Level I)

ACOG[27] and SMFM[28] advise against the use of 17-OHPC due to its lack of efficacy with its FDA approval withdrawn in April 2023.

2.1.2 Role of Cerclage for low risk women with short cervix

(i) Cervical cerclage should be considered in women with a short cervix with TV CL ≤15.9 mm. Cervical cerclage may be offered in women with TV CL 16.0 mm - 20.9 mm.

Thresholds for cervical cerclage has been variously proposed to be 10 mm to 20 mm. Cervical cerclage can be considered in women whose cervix shortens to <10 mm despite being on vaginal progesterone[29] **(Grade C, Level II+)**. Subgroup analyses of studies suggest that women with no prior spontaneous PTB, but a very short cervix (<10 mm) may benefit from cerclage and typically involves shared decision-making with a specialist.

A recent systematic review and IPD meta-analyses study published by Berghella V et al.[18] evaluated the efficacy of cervical cerclage in preventing preterm birth in asymptomatic pregnancies with a short cervix and without prior spontaneous preterm birth. The study included 6 trials with 507 singleton gestations without prior spontaneous preterm birth and short mid-trimester TV CL ≤25.9 mm. The study concluded that for women with a singleton pregnancy, no history of spontaneous PTB, and a TV CL ≤20.9 mm before 24 weeks, cerclage was associated with a 25% reduced risk of preterm birth <37 weeks (RR, 0.75; 95% CI, 0.56-0.99) but this was not significant for preterm birth <35 weeks. Cerclage was also associated with a significantly longer latency from randomization to delivery (p=0.049). There was no benefit to cerclage for patients with TV CL 21.0 - 25.9 mm in the second trimester overall. **(Grade A, Level I++)**

Given this result, for pregnant individuals with singleton gestations, no prior spontaneous PTB and a TV CL ≤15.9 mm before 24 weeks, cerclage insertion should be considered. For those with a TV CL of 16 mm - 20.9 mm, the guideline committee has reviewed the available literature and recommends that given current evidence does not suggest one treatment over the other, either vaginal progesterone or cerclage may be offered, after shared discussion and decision-making with the patient.

Following placement of a cerclage for short cervical length, further CL measurements are not recommended, as no further therapy has been shown to change outcome.

Current evidence are conflicting regarding the use of progesterone after cerclage. Management options with regards to the use of progesterone could include no further use of progesterone, to continued use of progesterone post-cerclage. It is unclear given the current lack of evidence whether either option is superior.

A systematic review and meta-analysis by Aubin et al. concluded that combined treatment of cervical cerclage and vaginal progesterone could potentially result in a greater reduction in preterm birth than in single therapy.[30] However, a retrospective cohort review of 451 participants published in 2023 found that adjunct progesterone does not decrease the preterm delivery rate and may in fact cause harm by decreasing latency from cerclage to delivery.[31]

2.1.3 Role of Cervical pessaries for low risk women with short cervix

(i) Current evidence does not support the use of cervical pessaries to prevent PTB in asymptomatic patients with CL ≤25 mm outside research protocols. (Grade B, Level I+)

Two major RCTs have been published, with conflicting results. The Pesario Cervical para Evitar Prematuridad (PECEP) trial[32] studied 385 patients with CL ≤25 mm and reported a significant reduction in PTB <34 weeks in the group of patients treated with a pessary (6% vs 27%), while the largest multicentre pessary trial of 932 patients with a short cervix did not report a significant difference in the incidence of PTB between treatment and control groups (12% vs 11%).

A systematic review and meta-analysis of six RCTs (1,982 women) by Conde-Agudelo A et al.[33] comparing cervical pessary with standard care or alternative interventions in asymptomatic women at high risk for PTB also failed to show differences in the rates of PTB <37, <34, <32 and <28 weeks and the rates of adverse perinatal outcome. The Pessary Plus Progesterone to Prevent Preterm Birth (P5) RCT (936 women)[34] also failed to demonstrate effectiveness of cervical pessary in addition to vaginal progesterone in decreasing rates of neonatal morbidity or mortality in asymptomatic pregnant women with incidental short cervix.

2.2 Recommendations for the asymptomatic High Risk Singleton pregnancy

2.2.1 Vaginal progesterone for the High Risk women

(i) Consider prophylactic vaginal progesterone for women who are at high risk for preterm birth.

(ii) For women with short cervix and high risk for preterm birth, offer a choice of prophylactic vaginal progesterone or prophylactic cervical cerclage using shared-decision making. (Grade A, Level I++)

The EPPPIC IPD meta-analysis[35], which included mostly women with previous spontaneous PTB or a short cervix, demonstrated a statistically significant 22% reduction in PTB <34 weeks in women who used vaginal progesterone compared to placebo.

Progesterone should be offered as an equal option with cervical cerclage as there is no evidence to determine which of these options is more effective. As the treatment options are very different (regular use of vaginal progesterone pessaries throughout pregnancy, compared with a single operative procedure), the choice of treatment should be made after discussion of the risks and benefits of the two treatments with the patient.[36] **(GPP)**

Follow-up CL measurements should be considered after initiation of progesterone, as women with shortening cervix despite progesterone treatment may benefit from cervical cerclage.[37] (Grade C, Level II+)

A meta-analysis including data from four RCTs indicated that an ultrasound-indicated cerclage for a cervical length ≤25 mm in women who had had one or more spontaneous mid-trimester losses or preterm births reduced the incidence of birth before 35 weeks (RR, 0.57; 95% CI, 0.33–0.99) in women who had a previous second-trimester loss, and RR, 0.61; 95% CI, 0.4–0.92 in women with a previous preterm birth before 36 weeks of gestation.

2.3 Role of cervical cerclage in pregnancies

Types of Cerclage based on Indication (adapted from Royal College of Obstetricians and Gynaecologists (RCOG) Cervical Cerclage Green-top Guidelines 2022)[37]:

History-indicated cerclage	**Offer** if ≥3 prior spontaneous PTB/ second-trimester losses OR those with classic history of cervical incompetence (painless cervical dilatation in the absence of labour or abruptio placenta).
Ultrasound-indicated cerclage	In patients with a pregnancy undergoing TV CL measurement with a shortened cervix. (See above)
Physical examination-indicated (emergency / rescue) cerclage	For painless cervical dilation with visible membranes in the 2nd trimester, an "emergency" cerclage can prolong pregnancy by ~4–5 weeks on average vs expectant care, though neonatal benefit data are limited. Counsel on limitations of cerclage and exclusion of infection prior to placement of emergency cerclage.

2.4 Transabdominal Cerclage (TAC)

2.4.1 In women with a previous unsuccessful transvaginal cerclage, insertion of a transabdominal cerclage may be discussed and considered in a specialist centre. (Grade A, Level I+)

The MAVRIC Trial[38], a multicentre RCT of transabdominal vs transvaginal cervical cerclage, concluded that TAC is superior to low vaginal cerclage in the reduction of risk of early preterm birth and fetal loss in women with previous failed vaginal cerclage. High vaginal cerclage does not confer this benefit. The numbers needed to treat are sufficiently low to justify transabdominal surgery and caesarean delivery required in this select cohort.

Patients should be adequately counselled regarding the risks and benefits of transabdominal and transvaginal approaches and informed consent should be taken prior to the procedure.

2.4.2 Transabdominal cerclage can be performed pre-conceptually or in early pregnancy. Pre-conceptual procedures may be more effective and are not associated with sub-fertility. (GPP)

2.5 Antenatal Management of Twin Pregnancies

Twin pregnancies are at a significantly higher risk of preterm delivery than singletons, with more than half likely to deliver before 37 weeks and 15% prior to 34 weeks. Despite the proven benefits of

progesterone and cerclage placement in preventing preterm delivery in high-risk singletons, these treatments have not shown similar effects in twin pregnancies and current evidence is conflicting. **(Grade B, Level I++)**

(i) Vaginal progesterone in twin pregnancies without other risk factors is not recommended. (Grade A, Level I++)

The 'Early vaginal progesterone for the preVention of spontaneous prEterm birth iN TwinS' (EVENTS) multicentre trial[39] tested the hypothesis that a higher dose of vaginal progesterone (600 mg per day) started earlier (between 11 and 14 weeks) in unselected multiple pregnancy would reduce the incidence of PTB <34 weeks. Of note, there were no differences between the treatment and placebo groups.

(ii) Prophylactic use of vaginal progesterone may be considered in twin pregnancies with CL ≤25 mm (Grade C, Level II+)

An updated IPD meta-analysis published by Romero R et al.[40] in 2022 reported that vaginal progesterone significantly reduced PTB before 33 weeks in twin pregnancies with a second-trimester CL ≤ 25 mm (RR, 0.60; 95% CI, 0.38–0.95). A reduction in composite neonatal morbidity and mortality was also observed. However, these findings were based on a relatively small sample size (n = 95).

Overall, vaginal progesterone may confer potential benefit in twin pregnancies with a short cervix ≤25 mm, although the current evidence base remains limited. Further adequately powered RCT are required to confirm these findings.

(iii) The insertion of a history-indicated cerclage in women with multiple pregnancies is not routinely recommended. (Grade B, Level I++). Current evidence are conflicting regarding the role for ultrasound-indicated cerclage in twin pregnancies with an asymptomatic mid-pregnancy short cervix.

Evidence of history-indicated cervical cerclage in women with multiple pregnancies is lacking and therefore not routinely recommended. A retrospective matched case control study by Rottenstreich et al.[41] published in 2019 showed some positive effect on pregnancy and neonatal outcomes for history-indicated cerclage performed in the first trimester, as compared with expectant management, in women with a twin pregnancy.

A recent systematic review and meta-analysis from Lissa van Gils et al.[42] suggested cerclage may benefit women with a twin pregnancy with an asymptomatic mid-pregnancy short cervix ≤25 mm and especially in women with CL ≤15 mm, by reducing preterm birth and improving neonatal outcomes. However, there is need for well-powered RCTs to support these findings before introducing cerclage insertion into routine clinical practice for these women. As such, further evaluation and discussion should be undertaken with a MFM specialist or senior obstetrician and through a multidisciplinary team approach. **(Grade A, level I+)**

(iv) Consider emergency or physical examination-indicated cerclage in twin pregnancies with asymptomatic cervical dilation <24 weeks (Grade C, Level I+)

An RCT investigating the efficacy of a combination of physical examination-indicated cerclage, indomethacin and antibiotics, in a group of asymptomatic twin pregnancies with cervical dilation between 1 and 5 cm before 24 weeks, was interrupted prematurely due to the significant decrease in PTB at all gestational ages, a 50% decrease in PTB <28 weeks and a 78% reduction in perinatal mortality.[43]

2.6 Antenatal Management of Patient with Congenital Uterine Anomalies

(i) Effectiveness of pre-pregnancy surgical treatment of non-obstructive uterine anomalies to improve reproductive outcomes, especially if they are incidentally diagnosed, is unproven and debatable.

The BJOG Scientific Impact Paper No. 62 for Reproductive Implications and Management of Congenital Uterine Anomalies advised that the usefulness of cervical length surveillance in these cases is uncertain. In addition, the role of cervical cerclage in uterine anomalies is uncertain.[44]

Vaginal progesterone is not recommended for preventing preterm birth in women with congenital uterine anomalies (CUAs) because there is no evidence supporting its effectiveness for this specific condition.

3. MANAGEMENT OF SYMPTOMATIC WOMEN AT RISK OF PRETERM BIRTH

3.1 Antenatal Corticosteroids

A course of antenatal corticosteroids administered before preterm birth decreases perinatal and neonatal mortality as well as respiratory distress syndrome. (Grade A – Level I++)

A Cochrane systematic review, including 27 studies with 11,272 women and 11,925 babies, demonstrated high certainty of the benefits of antenatal corticosteroids for neonates, with no increase in adverse maternal outcomes. These benefits include a reduction in perinatal death (RR, 0.85, 95% CI, 0.77–0.93), neonatal death (RR, 0.78, 95% CI, 0.70–0.87), respiratory distress syndrome (RR, 0.71, 95% CI, 0.65–0.78), intraventricular haemorrhage (RR, 0.58, 95% CI, 0.45– 0.75), and developmental delay in childhood (RR, 0.51, 95% CI, 0.27–0.97). Simultaneously, there is no increase in maternal adverse outcomes, including maternal death (RR, 1.12, 95% CI, 0.36-3.89), chorioamnionitis (RR, 0.86, 95% CI, 0.69-1.08), and endometritis (RR, 1.14, 95% CI, 0.82-1.58).[45]

Refer to the Singapore Antenatal Steroids Clinical Practice Guideline (CPG) Development Group for dosing and timing of administration.

3.2 Purpose of Tocolysis in Preterm Labour

The aim of tocolysis is to reduce the risk of preterm delivery within 48 hours of initiating treatment to facilitate the concurrent administration of corticosteroids, thereby promoting fetal lung maturity. (GPP, Level IV)

Inhibition of preterm labour is contraindicated if delivery is in the best interest of the mother and/or the fetus. Medical therapy should be discontinued if labour progresses. (GPP, Level IV)

Tocolysis should not be used if the maternal or fetal risks of delaying delivery or the risks from tocolytic drugs are greater than the risks of preterm birth, for example:

- Intrauterine fetal demise
- Lethal fetal anomaly
- Non-reassuring fetal status
- Severe preeclampsia or eclampsia
- Maternal bleeding with hemodynamic instability
- Chorioamnionitis

Adapted from ACOG[46]

3.3 Tocolytic Agents

Recommend tocolytics to women between 24+0 weeks to 33+6 weeks of pregnancy who have intact membranes and are in suspected or diagnosed preterm labour. (GPP, Level IV)

NICE, ACOG, and WHO recommend tocolytics for women under 34 weeks of pregnancy experiencing preterm labour with intact membranes.[1,46-47] The purpose of tocolytics is to prolong pregnancy, enabling the administration of corticosteroids, initiation of antibiotics, or facilitating in-utero transfer.

Nifedipine as the first-line tocolytic agent. (Grade A – Level I++)

A network meta-analysis conducted on tocolytic therapy by the Cochrane review, which included 112 trials, demonstrated that nifedipine effectively delays preterm birth by 48 hours (RR, 1.16, 95% CI. 1.07-1.24), delaying preterm birth by 7 days (RR, 1.15, 95% CI, 1.04-1.27), and prolonging pregnancy duration by approximately 5 days, with a range from 0.1 to 9.2 days.[48]

Nonetheless, there exists a potential risk of discontinuing nifedipine therapy owing to adverse effects (RR, 2.96, 95% CI, 1.23-7.11). Headache constitutes the most prevalent adverse effect (RR, 2.59, 95% CI, 1.39-4.83). Furthermore, the medication may exert minimal or no influence on the risk of palpitations (RR, 1.40, 95% CI, 0.62-3.1) or nausea and vomiting (RR, 0.67, 95% CI, 0.39-1.15).[48]

The use of nifedipine for more than 48 hours should be reviewed on a case-by-case basis, with careful consideration of its benefits relative to potential adverse effects. (Grade A – Level I+)

An IPD meta-analysis, encompassing 6 RCTs and involving data from 787 patients (n = 390 for nifedipine over 48 hours; n = 397 for placebo or no treatment), demonstrated that nifedipine maintenance tocolysis is not associated with improved perinatal outcomes or pregnancy prolongation.[49]

FIGO and WHO recommend nifedipine use for two to 7 days, whichever comes first, to assist in completing antenatal corticosteroids or arranging in-utero transfer.[47,50]

If nifedipine is contraindicated, consider oxytocin receptor antagonist or betamimetics. (Grade A – Level I++)

A network meta-analysis conducted by the Cochrane review, which included 112 trials, demonstrated that oxytocin receptor antagonists are likely to delay preterm birth by 48 hours (RR, 1.13, 95% CI, 1.05-1.22), by 7 days (RR, 1.18, 95% CI, 1.07-1.30), and extend pregnancy by approximately 10 days, with a range from 2.4 to 16.7 days. Furthermore, oxytocin receptor antagonists generally cause fewer adverse effects than alternative tocolytic agents. The likelihood of treatment discontinuation due to side effects remains low and their use is unlikely to increase the risk of symptoms such as palpitations, headaches, nausea, vomiting, tachycardia, hypotension, or dyspnoea.[48]

Betamimetics increase the likelihood of delaying birth by 48 hours (RR, 1.12, 95% CI, 1.05-1.20) and by 7 days (RR, 1.14, 95% CI, 1.03-1.25). However, they carry a significant risk of treatment discontinuation due to side effects (RR, 14.44, 95% CI, 6.11-34.11), with about 892 out of every 1,000 women stopping the medication because of side effects compared to those not taking it. The side effects include palpitations, headache, nausea or vomiting, tachycardia, and dyspnea.[48]

Oxytocin receptor antagonists or betamimetics can be considered as alternatives; if nifedipine is contraindicated, the clinician should exercise judgment based on cost, side-effect profile, and availability. Nevertheless, it is advisable to undertake careful monitoring for potential adverse effects associated with betamimetic therapy.

3.4 Role of Magnesium Sulfate

Intravenous magnesium sulfate reduces the risk of preterm-related cerebral palsy. (Grade A – Level I++)

A 2024 update of the Cochrane review presents high-certainty evidence of a 29% reduction in the risk of cerebral palsy up to 2 years' corrected age (RR, 0.71, 95% CI, 0.57-0.89). This includes a decreased likelihood of mild (RR, 0.73, 95% CI, 0.53-1.00) and moderate-to-severe cerebral palsy (RR, 0.69, 95% CI, 0.50-0.95). There is also potential to reduce severe intraventricular haemorrhage (grades 3 or 4) (RR, 0.76, 95% CI, 0.60-0.98). Nonetheless, no significant difference was observed in major neurodevelopmental disability (RR, 1.09, 95% CI, 0.83-1.44) or in improving gross motor dysfunction (RR, 0.88, 95% CI, 0.72-1.07) up to two years' corrected age.[51]

Recommend intravenous magnesium sulfate for neuroprotection of the baby to women between 24+0 weeks and 31+6 weeks of pregnancy who are imminent birth. (GPP, Level IV)

Discuss intravenous magnesium sulfate for neuroprotection of the baby to women between 32+0 weeks and 33+6 weeks of pregnancy who are imminent birth. (GPP, Level IV)

There is no consensus on the upper gestational age for administering magnesium sulfate for fetal neuroprotection. Most international guidelines[52], including ACOG and WHO, recommend that the upper limit of gestation be 32 weeks, with NICE guideline suggesting considering administering up to 34 weeks.

Give a 4 g intravenous bolus of magnesium sulfate over 15 minutes, followed by an intravenous infusion of 1 g per hour until the birth or for 24 hours (whichever is sooner). (GPP, Level IV)

There is no demonstrated benefit in administering repeated doses of magnesium sulfate for fetal neuroprotection following an initial course. (Grade A – Level I++)

Current evidence does not strongly support giving a second course of magnesium sulfate for fetal neuroprotection after an initial treatment. There is no proven additional benefit from repeated magnesium sulfate if delivery does not happen within 24 hours of starting treatment, but it only leads to adverse effects related to the treatment.[51]

Monitor women for clinical signs of magnesium toxicity at least every 4 hours by recording pulse, blood pressure, respiratory rate, and deep tendon (e.g., patellar) reflexes. (GPP, Level IV)

If a woman shows signs of renal dysfunction or oliguria, check the magnesium level and reduce the magnesium sulfate dose by half or stop if there are concerning signs of toxicity. (GPP, Level IV)

There is no increased risk of severe maternal outcome, including death, cardiac arrest or respiratory arrest, related to magnesium treatment. However, there is a higher chance of stopping therapy due to adverse effects related to magnesium sulfate (RR, 3.21, 95% CI, 1.88-5.48), including nausea or vomiting (RR, 3.99, 95% CI, 2.05-7.74), flushing (RR, 7.13, 95% CI, 4.28-11.86), tachycardia (RR, 1.53, 95% CI, 1.03-2.29), hypotension (RR, 1.70, 95% CI, 1.29-2.25), sweating (RR, 6.12, 95% CI, 2.86-13.10), or dizziness (RR, 3.16, 95% CI, 1.50-6.68).[51]

3.5 Antibiotic use

Do not routinely offer antibiotics to women in threatened preterm labour with intact membranes who do not show clear signs of infection. (Grade A – Level I++)

The ORACLE II trial indicates that antibiotics should not be routinely given to women in spontaneous preterm labour unless there is clear evidence of clinical infection.[53] This finding is reinforced by a meta-analysis of fourteen RCTS involving 7,837 women, comparing antibiotic use to placebo or no treatment in cases of preterm labour with intact membranes. The analysis showed no evidence that antibiotics

decrease perinatal mortality, extend pregnancy duration, or lower the incidence of respiratory distress syndrome, neonatal sepsis, or neonatal intensive care admissions.[54]

Offer intrapartum antibiotics to women with:

- **established preterm labour**
- **Group B streptococcus colonisation in current pregnancy**
- **history of a previous baby with an invasive group B streptococcal infection**
- **clinical diagnosis of chorioamnionitis**

(GPP, Level IV)

3.6 Diagnostic Tests for Preterm Labour

Consider offering PAMG-1 or phIGFBP-1 to symptomatic women with suspected preterm labour to rule out preterm delivery within the next 7 days. (Grade B, Level II++)

Biomarkers should not be used in isolation to diagnose preterm labour, and results must be interpreted in the context of the overall clinical presentation. (GPP, Level IV)

There are three biomarker tests available on the market, namely placental alpha microglobulin-1 (PAMG-1), fetal fibronectin (fFN), and phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1).

A meta-analysis conducted in 2018 demonstrated that the positive predictive value (PPV) of PAMG-1 was markedly higher than that of phIGFBP-1 or fFN for predicting spontaneous preterm birth within seven days of testing among women with signs and symptoms of preterm labour. Other diagnostic accuracy measures did not differ between the three biomarker tests.[55]

The table below shows the pooled sensitivity, pooled specificity, pooled positive predictive value (PPV), and pooled negative predictive value (NPV) for PAMG-1, fFN, and phIGFBP-1.

Biomarkers	**Pooled Sensitivity (95% CI)**	**Pooled Specificity (95% CI)**	**Pooled PPV (95% CI)**	**Pooled NPV (95% CI)**
PAMG-1	0.76 (0.57–0.89)	0.97 (0.95–0.98)	0.76 (0.69–0.84)	0.97 (0.94–0.99)
fFN	0.58 (0.47–0.68)	0.84 (0.81–0.87)	0.34 (0.29–0.39)	0.93 (0.92–0.95)
phIGFBP-1	0.93 (0.88–0.96)	0.76 (0.70–0.80)	0.35 (0.31–0.40)	0.99 (0.98–0.99)

A Diagnostics Assessment Report produced in 2018 by the Peninsula Technology Assessment Group (PenTAG), adapted for use in the NICE guideline, yields similar results.[1,56]

Biomarkers	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)
PAMG-1	0.83 (0.61–0.94)	0.95 (0.89–0.98)
fFN	0.75 (0.69–0.80)	0.79 (0.76–0.83)
phIGFBP-1	0.77 (0.68–0.83)	0.81 (0.76–0.85)

Overall, despite demonstrating high negative predictive values, all three tests exhibit limited positive predictive value.

Due to commercial reasons, fFN has been withdrawn from the market since November 2025.

4. MANAGEMENT OF WOMEN WITH PRETERM PRELABOUR RUPTURE OF MEMBRANES

4.1 Antenatal Corticosteroids

A course of antenatal corticosteroids administered before preterm birth decreases perinatal and neonatal mortality as well as respiratory distress syndrome. (Grade A – Level I++)

Refer to the Singapore Antenatal Steroids CPG Development Group for dosing and timing of administration.

4.2 Tocolytic Agents

Routine tocolysis in women with preterm prelabour rupture of membranes is not recommended. (Grade A – Level I++)

A Cochrane review found that for women with PPROM before 34 weeks, there was a significantly increased risk of chorioamnionitis in women who received tocolysis (RR, 0.87, 95% CI, 1.02-3.14), while there is no benefit in prolonging latency (mean difference 79.22 hours; 95% CI, -27.56-186.01) and no difference in births within 48 hours (RR, 0.59; 95% CI, 0.34-1.00) compared to no tocolysis.[57]

4.3 Antibiotic Use

Recommend oral antibiotics to women with preterm prelabour rupture of membranes. (Grade A – Level I++)

A 2013 Cochrane Review, which included 22 trials involving 6,872 women and newborns, demonstrated that the prophylactic use of antibiotics following PPROM significantly reduced the incidence of chorioamnionitis (RR, 0.66; 95% CI, 0.46–0.96), early delivery within 48 hours (RR, 0.71; 95% CI, 0.58–0.87), and delivery within 7 days of randomization (RR, 0.79; 95% CI, 0.71–0.89). Additionally, there was a reduction in neonatal infection (RR, 0.67; 95% CI, 0.52–0.85), use of surfactant (RR, 0.83; 95% CI, 0.72–0.96), oxygen therapy (RR, 0.88; 95% CI, 0.81–0.96), and abnormal cerebral ultrasound scans

prior to hospital discharge (RR, 0.81; 95% CI, 0.68–0.98). However, no statistically significant reduction in perinatal mortality was observed.[58]

Erythromycin is recommended to prolong pregnancy in women experiencing preterm prelabour rupture of membranes. (Grade A – Level I+)

NICE[1] and RCOG Green-top Guideline No. 73[59] recommended that the patient be administered oral erythromycin 250 mg four times daily for 10 days or until the woman enters established labour, whichever occurs first. This recommendation is based on the findings of the ORACLE 1 trial.[60]

A systematic review and meta-analysis comparing azithromycin with erythromycin in women with PPROM included 5 retrospective cohort studies involving 1,289 women. The latency period was similar between the two regimens (6.7 vs 6.6 days; mean difference 0.07 days; 95% CI, 0.45-0.60). However, azithromycin was associated with a lower rate of clinical chorioamnionitis (OR, 0.53; 95% CI, 0.39–0.71; median prevalence 14% vs 25%). Neonatal outcomes, including respiratory distress syndrome, neonatal sepsis, birth weight, Apgar scores, and neonatal death, were similar between groups.[61]

The optimal azithromycin regimen remains uncertain.[64,65] Reported regimens include either a single 1 g oral dose or 500 mg daily for 5–7 days, often combined with a beta-lactam antibiotic[62-63], although evidence supporting the optimal dosing strategy remains limited.

4.4 Group B Streptococcus Screening

Patients with PPROM should be screened for Group B Streptococcus (GBS). (GPP, level IV)

Antibiotic susceptibility testing should be performed on GBS isolates when a penicillin allergy is reported. (GPP, level IV)

When a woman presents with PPROM, a combined vaginal–rectal swab for GBS culture should be obtained at initial presentation. If a penicillin allergy is reported, this should be clearly indicated on the laboratory requisition to ensure appropriate antibiotic susceptibility testing of any GBS isolates.[64]

GBS prophylaxis should be initiated in addition to erythromycin for PPROM and continued for at least 48 hours. (GPP, level IV)

In the absence of a reported Penicillin allergy, it is recommended to administer Intravenous Benzylpenicillin at a dose of 5 million units, followed by 2.5 million units every four hours, or alternatively, Intravenous Ampicillin at 2 grams, followed by 1 gram every four hours.

In the event that a Penicillin allergy is reported, consider administering intravenous Clindamycin 900 mg every 8 hours, provided the GBS is susceptible to Clindamycin, or alternatively, intravenous Vancomycin 1 gram every 12 hours if the GBS exhibits resistance to Clindamycin GBS.[64]

GBS prophylaxis should be continued until delivery if the woman goes into active labour. (GPP, level IV)

If the woman does not go into active labour, GBS prophylaxis should be discontinued. (GPP, level IV)

A retrospective study suggests that a short course (approximately 3 days) of antibiotic prophylaxis is adequate for eradicating GBS colonization in women with PPROM receiving antimicrobial therapy.[65] Therefore, prolonged intravenous GBS prophylaxis beyond 48 hours in the absence of active labour may not be required.

4.5 Time of delivery

If PPROM happens before 34 weeks 0 days, it should be managed expectantly if there is no maternal or fetal contraindication. (Grade A – Level I++)

A subgroup analysis conducted in the 2017 Cochrane review, including 12 RCTs, concluded that expectant management is not associated with an increased risk of neonatal infection RR, 1.6; 95% CI, 0.74-3.5 or maternal chorioamnionitis RR, 0.77;95% CI, 0.45-1.30 compared with immediate delivery when PPROM occurs before 34 weeks.[66]

If PPROM happens after 34+0 weeks, either expectant management or delivery may be considered appropriate. However, the decision should involve a careful evaluation of the potential benefits and risks from both maternal and neonatal perspectives. (Grade A – Level I++)

Offer induction of labour to the woman by 37 weeks who opts for expectant management if the onset of labour has not happened. (GPP – Level IV)

A subgroup analysis in the 2017 Cochrane review[66], comprising 12 RCTs, demonstrated a reduced risk of chorioamnionitis (RR, 0.26; 95% CI, 0.12–0.57) with immediate delivery. Conversely, it indicated an increased risk of neonatal respiratory distress syndrome (RR, 1.45; 95% CI, 1.10–1.90) when compared to the expectant management group in cases of PPROM occurring after 34 weeks.

A meta-analysis of IPD conducted in 2018[67], which included the 3 largest RCTs—PROMOXIL, PPROMEXIL-2, and PPROMT—concluded that both immediate delivery and expectant management resulted in comparable rates of the composite adverse neonatal outcomes. Specifically, among cases of preterm premature rupture of membranes (PPROM) between 34- and 37-weeks' gestation, immediate delivery was associated with a reduced risk of antepartum haemorrhage and chorioamnionitis. However, it was also associated with an increased risk of neonatal respiratory distress syndrome (RR, 1.47, 95% CI, 1.10–1.97) and neonatal intensive care unit admission (RR, 1.17, 95% CI, 1.11–1.23).

Discuss induction of labour if PPROM happens after 34+0 weeks and the patient is known to be a GBS carrier. (GPP – Level IV)

Recommend delivery if there is clinical suspicion of chorioamnionitis or maternal or fetal compromise, regardless of gestational weeks. (GPP – Level IV)

A subgroup analysis of the PPROMT trial revealed that immediate delivery did not confer a benefit to women in whom Group B Streptococcus was isolated from the genital tract, as neonatal sepsis demonstrated no significant difference between immediate delivery and expectant management. (3.6% versus 3.8%, RR, 0.9, 95% CI, 0.2-4.5).[68]

This differs from the secondary analysis of the PPROMEXIL trials, which revealed a significantly higher risk of early-onset neonatal sepsis, with 15.2% in the expectant management group compared to 1.8% in the immediate delivery group, yielding an odds ratio of 0.10 (95% CI, 0.01-0.84) among women with PPROM and GBS colonization. Therefore, early intervention may be preferable.[69]

The RCOG recommends that it might be beneficial to expedite delivery if a woman is identified as a known GBS carrier and has reached more than 34 weeks of gestation.[70]

4.6 Cerclage in-situ

The decision whether to remove or retain cerclage in cases of preterm premature rupture of membranes (PPROM) between 24 and 34 weeks of gestation with no signs of infection or preterm labour should balance the prematurity related risks with those of complications of infections. Thus, the decision should be made carefully in consultation with an experienced senior obstetrician who has expertise in managing patients with cerclage. (GPP – Level IV)

Consider removal of cerclage in cases of preterm premature rupture of membranes (PPROM) occurring prior to 24 weeks of gestation or after 34 weeks, as delaying suture removal probably offers no significant advantage (Grade C – Level 1-)

There are no adequately powered prospective studies to guide the management of women with PPROM who have a cervical cerclage in situ. A multicentre RCT was conducted to evaluate women who underwent cerclage placement prior to 24 weeks of gestation in singleton or twin pregnancies, with subsequent rupture of membranes occurring between 22 and 33 weeks of gestation, and to randomize these women to either retention or removal of the cerclage. The study found no statistically significant differences in latency prolongation, infection incidence, or composite neonatal outcomes. However, the trial was terminated early because of insufficient statistical power, and the interim analysis did not demonstrate a significant difference between management strategies.[71]

A meta-analysis that included 5 retrospective cohort studies and 1 RCT, involving 169 women undergoing immediate removal and 208 women undergoing delayed removal, demonstrated that immediate removal was significantly associated with a decreased incidence of chorioamnionitis (OR,

0.57, 95% CI, 0.34–0.96; p = 0.03) and a lower incidence of Apgar scores below 7 at five minutes (OR, 0.22, 95% CI, 0.08–0.56; p = 0.002). However, it was associated with a reduced incidence of pregnancy prolongation exceeding 48 hours (OR, 0.15, 95% CI, 0.07–0.31; p<0.0001), as well as a decreased incidence of pregnancy prolongation exceeding 7 days (OR, 0.30, 95% CI, 0.11–0.83; p=0.02).[72]

Evidence is insufficient to support a definitive recommendation regarding removal or retention of a cervical cerclage after PPROM; therefore, either approach may be reasonable. Management should be individualized, taking into account the competing risks of prematurity and intrauterine infection. The decision should be made carefully in consultation with an experienced senior obstetrician who has expertise in managing patients with cerclage.

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