Controversies in the prevention of spontaneous preterm birth in asymptomatic women: an evidence summary and expert opinion

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Accepted 13 August 2020. Published Online 11 November 2020.

This article includes Author Insights, a video abstract available at https://vimeo.com/rcog/authorinsights16544.

Preterm birth prevention is multifaceted and produces many nuanced questions. This review addresses six important clinical questions about preterm birth prevention as voted for by members of the UK Preterm Clinical Network. The questions cover the following areas: preterm birth prevention in ‘low-risk’ populations; screening for asymptomatic genital tract infection in women at high risk of preterm birth; cervical length screening with cerclage or vaginal pessary in situ; cervical shortening whilst using progesterone; use of vaginal progesterone in combination with cervical cerclage; and optimal advice about intercourse for women at high risk of preterm birth.

Keywords Cerclage, cervical shortening, genital tract infection, pessary, preterm birth prevention, progesterone.

Please cite this paper as: Goodfellow L, Care A, Alfirevic Z. Controversies in the prevention of spontaneous preterm birth in asymptomatic women: an evidence summary and expert opinion. BJOG 2021;128:177–194.

Background

Preterm birth (PTB), with its associated infant mortality and morbidity, is recognised as an important public health problem. The World Health Organization set a goal of a 50% reduction in mortality related to PTB in resource-poor countries from 2010 to 2025. This is a crucial effort towards achieving the Sustainable Development Goal of ending preventable newborn and child deaths by 2030. The UK Department of Health has committed to reducing the PTB rate from 8% to 6% by 2025; however, a postal survey of all UK maternity units in 2017 found that only 31% were providing specialist PTB prevention clinics. Since then, NHS England has published the Saving Babies Lives Version II Care Bundle recommending that every maternity provider has a designated clinician with an interest in PTB prevention and access to transvaginal ultrasound assessment of the cervix.

Active participation of many more UK obstetricians in PTB prevention activities has highlighted areas of uncertainty in clinical practice. In January 2020, the authors conducted an email survey of clinicians in the UK Preterm Clinical Network, who identified 24 ‘important clinical questions’ related to PTB prevention (Appendix S1). In this review, we have summarised the available evidence and provide an interpretation of the implications on clinical practice and research for the top six questions. As multiple pregnancies pose a distinct clinical challenge, the focus of this review is on singleton pregnancies. The authors have also produced a video abstract to introduce the themes of the paper (Video S1).

How can we reduce the risk of spontaneous preterm birth in the ‘low-risk’ population?

Approximately two-thirds of PTBs occur in women considered to be at low risk, and therefore even a modest reduction in PTB could have a large population effect. As a multifactorial disease, PTB prevention requires the modification of multiple risk factors. We have attempted to summarise potentially modifiable risk factors for PTB in the ‘low-risk’ population in Tables 1–4, along with suggested risk-reducing measures and, where available, evidence for...
| Risk factor                          | OR or RR of PTB (<37 weeks of gestation, unless specified) | Risk-reducing interventions                                                                 | Effect of intervention                                                                 |
|-------------------------------------|-----------------------------------------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Maternal age under 20 years         | aOR 2.12 (95% CI 1.06–4.25) for birth at <32 weeks       | (i) Contraceptive services for young women                                                   | (i and ii) Not formally assessed but theoretical delay in childbearing until lower risk age |
|                                     | aOR 5.06 (95% CI 1.23–20.7) for birth at <28 weeks      | (ii) Support and advice about optimal timing of childbearing                                | (iii) Teenage antenatal clinics may reduce PTB (OR 0.40, 95% CI 0.25–0.6), but uncertain benefit |
|                                     |                                                           | (iii) Specialist antenatal services for younger women                                        |                                                                                        |
|                                     |                                                           | (iv) Postnatal contraception for teenage mothers                                            |                                                                                        |
| Domestic violence                    | OR 1.91 (95% CI 1.6–2.29)                                | (i) Screening for intimate partner violence                                                 | (i) Screening increased the identification of victims (OR 2.95, 95% CI 1.79–4.87, moderate quality evidence) |
|                                     |                                                           | (ii) Brief advocacy                                                                         | (ii) Cochrane review concluded that there is uncertainty of benefit, but may provide small short-term benefits and reduce abuse in pregnancy |
| Stress                              | OR 1.98 (95% CI 0.91–4.31)                               | Access to clinical psychologist                                                             | Uncertain                                                                             |
| Recreational drug use               | Any drug abuse, aRR 1.6 (95% CI 1.5–1.6) (aRR 1.1–1.9)  | (i) Reduce drug abuse within society                                                        | (i) Reduction in drug abuse in society potentially removes risk to pregnant women      |
|                                     |                                                           | (ii) Specialist antenatal services                                                          | (ii) Women with drug abuse and no antenatal care are at higher risk of PTB (OR 12.05, 95% CI 8.99–16.16) |
| Unwanted pregnancy                  | OR 1.50 (95% CI 1.41–1.61)                              | Use tools such as London Measure of Unplanned Pregnancy to focus family planning resources  | Uncertain                                                                             |
| Social deprivation                  | OR 1.5 (95% CI 1.2–1.9) in most vs least deprived       | (i) Political measures to reduce societal inequality                                        | (i) Uncertain                                                                         |
|                                     |                                                           | (ii) Enhanced antenatal care to areas with greater social deprivation                      | (ii) Individual studies show an improvement in PTB rate but insufficient evidence to recommend a particular programme |
| Maternal education                  | RR 1.48 (95% CI 1.29–1.69) for low education vs medium or high education | (i) Improve education for girls worldwide                                                  | Uncertain                                                                             |
|                                     |                                                           | (ii) Targeted antenatal care for women with low maternal education                         |                                                                                        |
| Surgical uterine evacuation         | OR 1.44 (95% CI 1.09–1.90)                              | Offer medical management of miscarriage and termination of pregnancy, and cervical preparation prior to surgical uterine evacuation | In 1980–1983, termination of pregnancy was associated with PTB (aOR 1.12, 95% CI 1.09–1.16), but risk has progressively declined and is no longer apparent in 2000–2003 (aOR 0.98, 95% CI 0.91–1.05) |
| Perception of racial discrimination | RR 1.4 (95% CI 1.0–2.0), but uncertain                   | (i) Reduce prejudice and discrimination within society                                     | Uncertain                                                                             |
the effect of risk-reducing measures on PTB rates. More often than not, the available evidence does not differentiate between spontaneous and medically indicated PTB, as they have common risk factors such as chronic vascular disease and social deprivation. Indeed, a previous spontaneous preterm birth (sPTB) increases the risk of a medically indicated PTB in a subsequent pregnancy (OR 2.5, 95% CI 1.9–3.3).9 Nevertheless, in Tables 1–4 we have focused on modifiable risk factors for sPTB. The table is most suited to high-income healthcare systems, but where information is available for low-income settings, this is included.

The optimal PTB prevention strategy for a population will depend on the risks faced by that population. For example, Table 1 shows that a maternal age of <20 years is a strong risk factor for PTB before 32 weeks of gestation (aOR 2.12, 95% CI 1.06–4.25).10 The UK teenage conception rate fell by 63% between 1999 and 2018, to 0.17% of births in 2016/17 were to women aged 15–17 years.11 Therefore, any new interventions focused on teenage pregnancy in the UK are likely to have little benefit on population-level PTB rates.

Conversely, the rate of high body mass index (BMI) is increasing in the UK: 8.7% of all births in 2016/17 were to mothers with a BMI of ≥ 35 kg/m².12 BMIs of 35–40 have an aOR for PTB of 1.33 (95% CI 1.12–1.57).13 UK clinicians looking to reduce PTB rates within their population could consider reviewing the 2012 UK Health Technology Assessment that estimated dietary interventions in pregnant women with a high BMI could reduce the risk of PTB by 32% (RR 0.68, 95% CI 0.48–0.96).14

As described in Table 2, observational studies consistently show that dietary patterns associated with high intakes of vegetables, fruits, wholegrains, low-fat dairy and lean protein foods have a lower risk of PTB (OR 0.79, 95% CI 0.68–0.91) for the top compared with the bottom tercile of ‘healthy food’ intake.15 Modification of dietary patterns for women at low risk of PTB is difficult, however. A 2005 randomised controlled trial (RCT) of dietary modification in pregnancy only recruited 13% of the 2238 invited participants, and of those, 10% (n = 14) did not complete the study despite the support of a study dietician and research team.16 This study did show a reduction in PTB (RR 0.10, 95% CI 0.01–0.77), but since 2005 no further RCTs in dietary interventions for PTB prevention have been performed.17 This could be because of the difficulty in recruiting and maintaining motivation for alterations in dietary habits that are often deeply rooted.

An alternative strategy is to focus on individual nutrients by modifying a small part of the diet, or introducing a supplement, as described in Table 2. Omega 3 supplementations is of particular interest because the 2018 Cochrane
Table 2. Areas of nutrition associated with preterm birth (PTB) and effect of modification of risk factor on PTB rate

| Risk factor | OR or RR of PTB (<37 weeks of gestation, unless specified) | Risk-reducing interventions | Effect of intervention |
|-------------|----------------------------------------------------------|-----------------------------|------------------------|
| Dietary pattern with high intake of vegetables, fruits, wholegrains, low-fat dairy and lean protein foods | OR 0.79 (95% CI 0.68–0.91) for top compared with bottom tertile of ‘healthy foods’ intake\(^{15}\) | Dietary advice with support from dietician | RR 0.10 (95% CI 0.01–0.77),\(^{16}\) but uncertain\(^{141}\) |
| Omega 3 intake | aOR at <34 weeks 10.27 (95% CI 6.8–15.79) in lowest vs highest three quintiles of EPA + DHA\(^{142}\) | Omega 3 supplementation | RR 0.89 birth at <37 weeks (95% CI 0.81–0.97)\(^{17}\) Subsequent RCT showed no overall benefit, however.\(^{18}\) Benefit may be limited to women with low baseline omega 3.\(^{143}\) |
| Maternal anaemia | RR 1.56 (95% CI 1.25–1.95)\(^{144}\) | Iron supplementation | Uncertain benefit for PTB,\(^{145}\) but recommended in UK practice\(^{146}\) |
| Fish intake | RR 0.87 (95% CI 0.82–0.92) for eating fish 1–2 times/week, compared with less than once/week\(^{147}\) | Dietary advice with support from dietician | No specific RCT of intake of fish on risk of PTB. Presumed placement in lower risk category by increase in fish intake |
| Dietary selenium intake | Increased dietary selenium associated with reduced risk of PTB. Hazard ratio per SD 0.92 of selenium intake (95% CI 0.87–0.98)\(^{148}\) | Dietary advice with support from dietician | No specific RCT on intake of selenium. Presumed placement in lower risk category by increase in selenium intake |
| Zinc intake | No significant difference in baseline status and birth at <37 or <32 weeks\(^{149}\) | Zinc supplementation | RR 0.86 birth at <37 weeks (95% CI 0.76–0.97)\(^{150}\) |
| Multiple micronutrient supplementation | Expert opinion that multiple micronutrient deficiency is associated with poor infant and maternal health\(^{151}\) | Multiple micronutrient supplementation | Probably a slight reduction in PTBs (RR 0.95, 95% CI 0.90–1.01, 18 trials, 91 425 participants; moderate-quality evidence)\(^{152}\) |
| Vitamin D intake | Deficiency (serum 25-OHD at <50nmol/L) OR 1.25 birth at <37 weeks (95% CI 1.13–1.38)\(^{153}\) | Vitamin D supplementation | Little or no difference in risk of PTB (RR 0.66, 95% CI 0.34–1.30, 7 trials, 1640 women, low-certainty evidence)\(^{154}\) |
| Low body mass index | Low BMI adjusted RR of PTB 1.21 (95% CI 1.14–1.28)\(^{155}\) | (i) Interventions to increase weight gain in pregnancy (ii) Interventions to normalise weight prior to pregnancy | (i) No association found between pattern of gestational weight gain and risk of PTB\(^{156}\) (ii) Weight loss or unchanged between pregnancies in underweight women was associated with an increased risk of recurrent PTB in underweight women (aOR 1.67, 95% CI 1.07–2.60)\(^{157}\) |
| High body mass index | BMI 35–40 aOR 1.33 (95% CI 1.12–1.57) BMI >40 aOR 1.83 (95% CI 1.62–2.07)\(^{13}\) | (i) Dietary interventions during pregnancy (ii) Lifestyle weight management interventions during pregnancy (iii) Weight loss programmes prior to pregnancy | (i) Dietary interventions reduced risk of PTB (RR 0.68, 95% CI 0.48–0.96; 4 studies, 1474 women)\(^{14}\) (ii) Lifestyle weight management options might reduce risk of PTB (RR 0.76, 95% CI 0.56–1.02, 11 studies, 2198 women)\(^{14}\) (iii) Theoretical allocation to lower risk category if able to normalise weight pre-pregnancy |
review showed an overall reduction in PTB (RR 0.89 for birth at <37 weeks of gestation, 95% CI 0.81–0.97). At the time of publication of the Cochrane review, Makrides et al. were performing a large confirmatory RCT of omega 3 supplementation in Australia. A total of 5544 pregnancies were randomised and, surprisingly, found no difference in PTB rates. The same team went on to perform an exploratory analysis testing long-chain omega 3 status using blood stored from trial participants prior to randomisation. Although omega 3 supplementation significantly reduced the risk of early PTB among women with low omega 3 status, supplementing women with a high baseline omega 3 status increased their risk of early PTB, accounting for the overall null effect within the original study. This suggests that caution should be applied to any recommendations for routine dietary supplementation, unless the baseline nutrient status of the population (and ideally the individual) is understood.

Until recently most interventions have tackled single risk factors, with understandably modest results. It may be that ‘packages’ of PTB prevention care are better able to tackle this complex issue. In Western Australia, a ‘comprehensive PTB prevention programme’ was launched in 2014 called ‘Thewholeninemonths’. This care bundle had three components, some of which were relevant to the low-risk population: (i) a clinician education programme, including preconception care, smoking cessation, cervical length screening as part of the mid-trimester scan and the judicious use of fertility treatments; (ii) a public engagement campaign highlighting the importance of PTB and ways to prevent it; and (iii) access to a specialist PTB prevention clinic. Following the introduction of this programme the PTB rate reduced from 7.5% in 2013 to 6.9% in 2015. As the PTB rate had previously been rising, and in 2015 it was the lowest for 6 years, this led the authors to conclude that the programme had significantly lowered the rate of PTB.

Midwifery-led continuity of carer models of antenatal care could also be viewed as packages that appear to reduce the risk of PTB (average RR 0.76, 95% CI 0.64–0.91). The mechanism by which the reduction in PTB is achieved is poorly understood, however, and warrants further scrutiny.

Cervical length screening for women at low risk of PTB is appealing because of the analogous programmes for women at high risk of PTB; however, with the multifactorial nature of PTB, such universal screening would, at best, reduce the rate of PTB in the UK from 7.4% to 7.0%. Despite such a small absolute reduction, economic analyses from the USA and Ireland suggest that this would be a cost-effective strategy. In the UK, however, a 2014 external review for the UK National Screening Committee concluded that universal cervical length screening for PTB prevention did not meet the screening criteria, in particular because of uncertainty about an agreed cervical length to trigger intervention and a lack of randomised controlled trial evidence to show a reduction in morbidity or mortality. There also concerns about the potential harms of ‘over medicalisation’ of approximately 70% of women who screen ‘positive’ but would be destined to give birth at term without any intervention (false positives).

Many modifiable risk factors for PTB described in Tables 1–4 co-occur, for example social deprivation, maternal stress, unemployment, domestic violence and poor diet. Data from the USA show that increasing income inequality was associated with PTB. This could support the introduction of enhanced antenatal care programmes for socially disadvantaged and vulnerable women. These programmes can only have a modest impact upon a family’s life, however. Recently, awareness has increased of PTB as a public health issue, both in terms of public health interventions that can optimise pre-pregnancy and pregnancy health and in terms of the perpetuation of the cycle of deprivation if PTBs reoccur over generations. Clinicians may need to engage as advocates with policymakers and successive governments to bring about changes with more profound societal impact.

**Should we offer an assessment of vaginal flora in asymptomatic women at high risk of preterm birth when they first present to a preterm birth prevention clinic?**

The uncertainty with regards to the assessment of vaginal flora in asymptomatic women at high risk of PTB is demonstrated by a 2012–13 survey of UK PTB prevention clinics that found a 59%/41% split in the practice of offering an assessment of vaginal flora or not.

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The interest in the link between vaginal microbiota and PTB has been renewed by the use of 16S ribosomal RNA (16S rRNA) sequencing of the whole vaginal microbiota, including bacteria not amenable to traditional culture methods.35–37 Lactobacillus crispatus has been found to be protective for PTB in some populations.38,39 These studies have struggled with low reproducibility, however,40,41 explained by ‘differences in every technical aspect of study design’.39 More importantly, these new testing methods cannot yet be applied clinically, because the analysis pipeline takes about 3 months.

The assessment of vaginal microbiota that is available to most clinicians in high-resource settings is the high vaginal swab (HVS). In the UK, Public Health England
recommend that all HVSs in pregnancy are tested for: Staphylococcus aureus, Lancefield group A, B, C and G streptococci, yeasts and Trichomonas.42 Local laboratories tend to develop their own pathways based on their demographics, however, and may not offer all of these tests or may offer additional tests.

Screening and treatment for lower genital tract infection showed a reduction in PTB in the general pregnant population in a 2015 Cochrane review.43 This was based on a single study by Kiss et al., in which only 3% of women had had a previous PTB.44 The predominant infections screened and treated for within this study were bacterial vaginosis (prevalence 7%) and Candida (prevalence 13%).

In order to further assess the benefits of screening and treating for asymptomatic vaginal candidiasis in the general population, the results from Kiss et al. were combined with those from Roberts et al.45 in a metanalysis, and showed a reduction in PTB risk (RR = 0.36, 95% CI = 0.17–0.75) in

| Risk factor                  | OR or RR of PTB (<37 weeks of gestation, unless specified) | Risk-reducing interventions                                                                 | Effect of intervention                                                                 |
|------------------------------|----------------------------------------------------------|------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| **Bacterial vaginosis**      | OR 2.19 (95% CI 1.54–3.12)150                            | (i) Screening and treatment for bacterial vaginosis within a programme of screening for infections in pregnancy  
(ii) Screening and treatment only for bacterial vaginosis | (a) RR of 0.55 for PTB (95% CI 0.41–0.75, 2058 participants, moderate-quality evidence).43 No evidence of benefit in low-income settings173  
(ii) RCT in low-risk pregnancies showed no difference in PTB risk with treatment of bacterial vaginosis (RR 1.10, 95% CI 0.53–2.29)159 |
| **Chlamydia trachomatis**   | OR 2.28 (95% CI 1.64–3.16)174                            | Screening and treatment for Chlamydia trachomatis                                                                                                   | Treatment under 20 weeks of gestation associated with lower risk of PTB compared with treatment after 20 weeks (RR 0.54, 95% CI 0.37–0.80).175 Risk of PTB with infection in Australia in 2001–12 similar to background rate, attributed to treatment.176 No evidence of superiority of particular treatment177 |
| **Asymptomatic bacteriuria** | OR 2.10 (95% CI 1.56–2.85)178                            | Antibiotics for asymptomatic bacteriuria                                                                                                             | May be associated with a reduction in PTB (RR 0.34; 95% CI 0.13–0.88; 2 studies, 327 women, low-certainty evidence)179  
Single study in women at low risk for PTB showed no benefit in treatment for birth at <34 weeks (risk 2.5% in treated vs 1.0% in untreated, risk difference –1.5%, 95% CI –15.3 to 18.5).180 |
| **Periodontal disease in pregnancy** | OR 2.04–4.19181                                         | Periodontal treatment during pregnancy                                                                                                               | Reduction in risk of PTB (OR 0.65, 95% CI 0.45–0.93),182 but uncertain183 |
| **Trichomonas vaginalis**   | OR 1.42 (95% CI 1.15–1.75)184                            | Screening and treatment for Trichomonas vaginalis                                                                                                    | RCT found increased risk of PTB with metronidazole treatment in USA (RR 1.8, 95% CI 1.2–2.7).185  
Subsequent Cochrane review found no benefit of treatment186 |
| **Vaginal candidiasis**      | No increased risk in cohort studies47,48                | (i) Screening and treatment for vaginal candidiasis within a programme of screening for infections in pregnancy  
(ii) Screening and treatment only for vaginal candidiasis                                                                                           | (i) RR of 0.55 for PTB (95% CI 0.41–0.75; 2058 participants, moderate-quality evidence)43  
(ii) Pilot study showed non-significant trend towards prevention of PTB (RR 0.33, 95% CI 0.04–3.03)45 |
the general population. As vaginal candidiasis is common in pregnancy (prevalence 13%), and not associated with PTB in observational studies, the 2019 British Association for Sexual Health and HIV national guideline on management of vulvovaginal candidiasis summarised the above as insufficient evidence to justify treatment for PTB prevention, and called for well-designed studies in this area. The specific situation of women at high risk of PTB was not considered.

The main motivation for offering an HVS for PTB prevention is often to test for bacterial vaginosis (BV), a condition that has long been associated with PTB. In the UK, however, the National Institute for Health and Care Excellence (NICE) recommends not screening asymptomatic women for BV in pregnancy, and recommends discussion with a woman’s obstetrician about treatment if asymptomatic BV is detected. This is largely based on the 2013 Cochrane review of antibiotics for BV in pregnancy which showed no definitive evidence of a reduction in the risk of preterm labour before 37 weeks of gestation both in the general population (average RR 0.88, 95% CI 0.71–1.09) and in women with a previous PTB (average RR 0.78, 95% CI 0.42–1.48).

In 2018 Subtil et al. published the PREMEVA study, which confirmed that systematic screening and subsequent treatment for BV in French women with low-risk pregnancies does not reduce the risk of late miscarriage or spontaneous PTB at <32 weeks of gestation. Interestingly, although women at low risk of PTB were randomised to single-course clindamycin, triple-course clindamycin, spaced 1 month apart, or placebo, the placebo arm was considered to be unethical for women with a history of PTB. This decision was, undoubtedly, informed by a previously published meta-analysis showing a benefit of clindamycin treatment (RR 0.60, 95% CI 0.42–0.86, P < 0.001, n = 2346), particularly if initiated prior to 22 weeks of gestation.

The number of women with previous PTB in the PREMAVA study was relatively low (n = 236), with only five miscarriages and PTBs at <32 weeks of gestation (4.4%) in the single-course arm compared with eight (6.0%) in the single-course arm (RR 0.67, 95% CI 0.23–2.00, P = 0.47). These results are inconclusive; such wide confidence intervals imply that a future adequately powered study could show that triple-course clindamycin therapy reduces the risk of very early PTB by more than 50%, but may also show no benefit at all, not only when compared with single-course therapy but also when compared with a placebo.

Preterm birth (PTB) is an emotive topic, and women who have experienced it, and the clinicians who look after these women, often feel that some form of intervention is mandatory. It is important to be mindful of the potential for harm, however. Brown et al., who used 16S rRNA sequencing to assess the vaginal microbiota, demonstrated that in 10/16 (62.5%) participants with ‘healthy’ (Lactobacillus-dominated) vaginal microbiota prior to preterm prelabour rupture of membranes (PPROM), erythromycin treatment was associated with a ‘worsening’ of the vaginal microbiota (Lactobacillus depletion). Conversely, six participants who had an ‘unhealthy’ (Lactobacillus-depleted) vaginal microbiota prior to PPROM had an improvement in their vaginal microbiota with erythromycin treatment. The ‘unhealthy’ vaginal microorganisms that were depleted in Lactobacillus after PPROM were then associated with higher rates of chorioamnionitis, funisitis and early-onset neonatal sepsis. The authors suggested that there is an urgent need to develop patient-specific therapy or selective antibiotics. We agree, and add that there is also an urgent need to develop clinically applicable tests of the vaginal microbiota that can be used to evaluate more targeted therapies.

Colonisation with group B streptococcus (GBS) causes parental anxiety as a result of the well-publicised increased risk of early-onset neonatal GBS disease. Maternal vaginal colonisation during pregnancy with GBS has a weak association with PTB (RR 1.21, 95% CI 0.99–1.48, P = 0.061, n = 216 132). This is in contrast to the established increased prevalence of GBS at the time of preterm delivery. To our knowledge, however, the effect of treatment of GBS on risk of PTB has not been evaluated recently, although this did rank highly in a recent research prioritisation project. An programme of GBS vaccine development is currently underway and the effect upon PTB risk will be an interesting end point.

We recommend that clinicians discuss the quality and testing capacity of their local laboratories to make informed decisions about whether to offer vaginal swabs in asymptomatic women at high risk of PTB. If testing is to be offered, we recommend that this is performed prior to 22 weeks of gestation and includes an assessment for and treatment of BV and vaginal candidiasis.

Should we perform cervical length measurements once a cervical cerclage or pessary has been placed?

It is recognised that both a shorter cervical length (CL) after initial cerclage placement (<25 mm) and progressive cervical shortening after cerclage placement are associated with a higher risk of PTB. Effective interventions for progressive cervical shortening are currently lacking. The American College of Obstetricians advise against performing CL measurements after placement of a cervical cerclage. In two small retrospective studies of progressive cervical shortening with cerclage in situ, the placement of a reinforcing cerclage was associated with a higher risk of

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PTB than expectant management, but only a total of 49 women were included in these two studies.

Small studies have evaluated the ability of ultrasound examination after cerclage placement to prognosticate for the continuing risk of PTB. A cerclage placed within the distal 10 mm of a closed cervix or the absence of cervical elongation after cerclage were highlighted as predictors of PTB and could be used to determine the frequency of follow-up.

Within trials of cervical pessary, Goya et al. performed monthly cervical assessments after the placement of a cervical pessary but no details of interventions based on this assessment are given. Nicolaides et al. randomised women with a cervix of <25 mm to cervical pessary or expectant management, and women subsequently had 4-weekly cervical assessment until 34 weeks of gestation, with supplemental vaginal progesterone for all women with a CL of ≤15 mm. This approach showed no difference in PTB at <34 weeks of gestation (OR 1.12, 95% CI 0.75–1.69).

Within our own practice we offer follow-up after the placement of a cervical pessary, usually up to 28 weeks of gestation. In our case series of 129 patients treated with cervical pessary, four women had prolapse of fetal membranes treated with cerclage and five women had further significant cervical shortening, treated either with additional progesterone (n = 3) or with cerclage (n = 2). Of the women requiring cerclage after pessary placement, two had a subsequent term birth, one woman had a late PTB (34 weeks 3 days versus 27 weeks 5 days, P = 0.0001). This result is consistent with a planned subgroup analysis of five RCTs comparing cerclage with no treatment, focusing on women with a CL of <10 mm. This subgroup had a lower rate of PTB at <35 weeks of gestation in women with a cerclage (39.5% versus 58.0%, RR 0.62, 95% CI 0.47–0.81).

In most PTB prevention clinics, once treatment for short cervix with vaginal progesterone (VP) commences, a follow-up appointment will be arranged 2–4 weeks later to confirm treatment compliance and provide reassurance that VP has ‘arrested’ further cervical shortening. Further cervical shortening, sometimes labelled as ‘treatment failure’, does call for a revised management plan. One option, proposed by Shennan et al., is the use of fetal fibronectin (fFN) to quantify the risk, and possibly avoid further treatment if the overall risk is low. If the risk is high, however, or testing is not available, most clinicians faced with very short cervix in women already using VP will contemplate a change of treatment plan.

A review of 310 pregnant women treated with VP for an incidental short cervix identified 75 women (24%) in whom, despite VP treatment, CL shortened progressively to below 10 mm; 48% of them had a cerclage and continued with VP and 52% continued with VP alone. The decision to perform additional cervical cerclage was based solely on individual physician preference. The mean gestational age at delivery was significantly greater for women with cerclage (34 weeks 3 days versus 27 weeks 5 days, P = 0.0001). This result is consistent with a planned subgroup analysis of five RCTs comparing cerclage with no treatment, focusing on women with a CL of <10 mm. This subgroup had a lower rate of PTB at <35 weeks of gestation in women with a cerclage (39.5% versus 58.0%, RR 0.68, 95% CI 0.47–0.98, 126 participants).

If a ‘mechanical’ therapy like cerclage is indeed complimentary to VP, this raises the possibility that the cervical pessary should be considered as an alternative ‘mechanical’ therapy in women with progressive shortening on VP. Although there are currently no studies of cervical pessary as a secondary therapy in progressive cervical shortening, some groups have started to evaluate a combination of pessary and VP. Stricker et al. did not find a reduction in PTB rates in a pre- and post-intervention study from a PTB prevention clinic. They compared their standard treatment of pessary alone for women with a short cervix (<10th percentile, n = 53) at risk of PTB with treatment after 2011, when vaginal progesterone 200 mg was given as an adjunctive therapy to treatment with pessary (n = 53). Delivery at <34 weeks of gestation occurred in 32% of women with pessary plus VP and in 24.5% of women treated with pessary alone. This finding is consistent with the RCT previously described by Nicolaides et al. comparing pessary with expectant management. Of 935 women randomised, 423 (45%) received additional VP for a CL of <15 mm at randomisation: 204 women in the pessary arm (pessary plus VP) and 219 women in the expectant arm, demonstrating a significant risk reduction in PTB at <33 weeks of gestation with vaginal progesterone (RR 0.62, 95% CI 0.47–0.81).

What should we do if the cervix shortens in women at high risk of preterm birth who are already using vaginal progesterone?

Consideration of vaginal progesterone as a first-line prophylaxis against PTB is recommended by NICE for women with either a short cervix of ≤25 mm or a history of PTB at 16–34 weeks of gestation. A systematic review and meta-analysis of individual patient data of five high-quality RCTs, including 974 women, using a CL cut-off of ≤25 mm, demonstrated a significant risk reduction in PTB at <33 weeks of gestation with vaginal progesterone (RR 0.62, 95% CI 0.47–0.81).

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management arm (VP alone). Spontaneous delivery at <34 weeks of gestation occurred in 12.0% of women in the pessary arm and in 10.8% of women in the expectant management arm (OR 1.12, 95% CI 0.75–1.69). Therefore, to date, no additional benefit of using pessary with VP has been demonstrated.

We suggest that it is reasonable to offer cervical cerclage to women with singleton pregnancies, where progressive cervical shortening (<10 mm) occurs while using VP for PTB prevention; however, it should be noted that the evidence underpinning this recommendation ‘should be considered tentative’ and this should be an area of future research focus. This assumes that there are no contraindications to cervical cerclage insertion, such as vaginal bleeding or suspected or confirmed uterine infection.

**Should we offer vaginal progesterone in addition to cerclage for preterm birth prevention?**

It is tempting to contemplate that if ‘mechanical’ and medical therapy for PTB prevention are complementary, then optimal risk reduction may be achieved by dual therapy from the outset. However, this strategy is not currently endorsed in the UK by NICE.69

In 2017, Jarde et al. performed a systematic review and meta-analysis of combining interventions to prevent PTB. They identified six studies assessing the impact of progesterone in addition to either cerclage or pessary for PTB prevention in singletons. No differences in PTB at <37 weeks of gestation were found when comparing combined cerclage and progesterone with cerclage alone (RR 1.04, 95% CI 0.71–2.42, 310 women). The noteworthy small number of women available for this analysis could be explained by the continuous questioning of efficacy, safety and optimal route of progesterone for PTB prevention. It could now be time to reconsider combination therapy because most recent individual patient data meta-analyses and network meta-analyses have confirmed the effectiveness of progesterone on PTB prevention for high-risk singleton pregnancies.77,78 The exception to these is the recently published PROLONG trial of intramuscular progesterone that showed no benefit in PTB prevention,79 and is too recent to be included in these analyses. The participants in the PROLONG trial were of a lower risk profile, and potentially not those who would also be undergoing a cervical cerclage.80

At present, the C-Stitch trial is recruiting women to an RCT comparing cervical cerclage material.81 The target recruitment is 2050 women, and data will be collected about concurrent progesterone use. This will be a rich source of data about the use of progesterone with cerclage and should shed more light on this under-analysed question. In the meantime, and given that preterm labour is best described as a pathological condition with multiple aetiologies,82 it may be difficult to justify denying progesterone treatment to women at high risk of PTB because clinicians feel that cervical cerclage may be beneficial.

**What is the best advice to give women at high risk for spontaneous preterm birth on intercourse?**

Women with pregnancies complicated by short cervix or a history of PTB are frequently counselled to restrict sexual activity or abstain from intercourse completely. This is largely based on the hypothetical risks of oxytocin release following orgasm leading to uterine contractions,83 physical contact with the cervix releasing endogenous prostaglandins or from the direct effect of prostaglandins in semen.84 Levels of oxytocin release and threshold levels of oxytocin for uterine contraction, even in women who deliver at term, are poorly understood, however.85 Sexual activity has also been shown to alter the vaginal microbiota,86 although whether this in turn impacts upon the PTB risk is uncertain.

A Cochrane review in 2001 concluded that the role of sexual intercourse as a method of induction of labour at term is uncertain.88 More recent studies concurred in finding no evidence that intercourse causes cervical ripening or reduces time to delivery in term patients.89–91

Historical studies found that coitus in mid or late pregnancy, with or without orgasm, did not increase the risk of PTB.92–96 Women with a history of PTB were excluded from these studies.

The term ‘high-risk pregnancy’, even when used exclusively for sPTB, incorporates several different clinical populations. The highest risk includes previous history of sPTB or PROM, short cervix, with or without previous excisional surgery, and women with PPROM in the index pregnancy.

With regards to women with a previous sPTB or PPROM, Yost et al. performed a secondary analysis of a blinded observational study of 165 women with a prior sPTB at <32 weeks of gestation.97 Women who reported infrequent sexual intercourse during early pregnancy had an incidence of recurrent sPTB at <37 weeks of gestation of 28%, compared with 38% in women who reported some intercourse. This difference was not statistically significant (P = 0.35). Analysis of the data makes the assumption that sexual activity in early pregnancy reflects subsequent activity throughout pregnancy, which is uncertain. In the absence of further research, however, it indicates that sexual activity may not have a large impact upon the risk of recurrent PTB and need not be discouraged if women have a normal cervical length. It is possible that women at high risk of PTB who are comfortable having intercourse have lower anxiety levels or increased closeness to their partner,
which could have a positive influence on their pregnancy outcome. As there is insufficient data to tease apart these factors, it is reasonable to personalise recommendations to expectant mothers based on a consideration of their unique pregnancy history and a discussion of the patient’s and partner’s concerns.

There are two studies that have investigated the safety of sexual activity in women with a short cervix (without previous PTB). First, Grobman et al. performed a secondary analysis of an RCT of 17-alpha hydroxyprogesterone caproate (OHPC) on 657 primiparous women with a CL of <30 mm.

Women were asked weekly if they had been placed on pelvic rest (prohibition of sexual activity), work rest or non-work rest. As these types of rest were often not mutually exclusive, they were analysed as a single 'activity restriction' group. This makes it hard to pull out the specific effects for the 217 women (33.6%) on pelvic rest, and it is not clear what the sexual practices of the control group were. The results showed that PTB at <37 weeks of gestation was significantly more common among women placed on any activity restriction (37% compared with 17%, \( P < 0.001, \) OR 2.91, 95% CI 2.0–4.21). This is consistent with moderate levels of physical activity being protective of PTB in the general population, as described in Table 3, and could be promising in support of sexual activity in women with a short cervix. It is likely that women who were instructed to reduce activity had clinical features that made their doctors more worried about their chance of PTB, however, and this result is not entirely related to physical activity. More recently, Saccone et al. performed a secondary analysis of an RCT of cervical pessary in singleton pregnancies with short cervix of \( \leq 25 \) mm without a prior sPTB. This time women were not prescribed any restriction in activity. For an analysis of the effect of sexual intercourse on PTB, 50 women (16.7%) who had sexual intercourse on \( \geq 1 \) day a week were included in the sexual intercourse group and 250 women (83.3%) who reported sexual intercourse on <1 day a week were included in the no sexual intercourse group. PTB at <37 weeks of gestation occurred in 10 women (20.0%) in the sexual intercourse group and in 78 women (31.2%) in the no sexual intercourse group (aOR 0.55, 95% CI 0.26–0.94). It is encouraging that these data are complimentary to the results from Grobman et al., and suggests that we should avoid advising against intercourse for women who have a short cervix without prior PTB.

Unfortunately, the authors could not find a study of sexual activity in women with a history of sPTB and a short cervix. MacPhedran et al. performed a comprehensive review of the literature and have provided recommendations based on a priori PTB risks. They advise restrictions of sexual activity in this population based on the lack of data and unknown risks of prostaglandin in semen or oxytocin levels following orgasm. The authors of this review are inclined to agree until further safety data are available. We encourage consideration of the potential beneficial effect of intimacy on the mother’s wellbeing, but feel it is prudent to advise restrictions on sexual intercourse, particularly if the cervical length is especially short, for example under 15 mm.

In women with PPROM in the index pregnancy, there is evidence for a strong relationship between time of first vaginal examination following rupture of membranes and delivery or maternal infection as a result of presumed ascending infection. The authors feel that it is safest to assume that penetrative intercourse would provide the same risk and that sexual activity should be discontinued.

Further research is needed to make validated recommendations on sexual activity in women with previous PTB; however, the practical and logistical difficulties in conducting a well-designed clinical trial may mean that this evidence may never become available and recommendations are currently based on expert opinion of currently available data.

### Research priorities

The prediction and prevention of labour before term was voted as the top research priority in PTB in two large UK research priority-setting projects involving service users and healthcare professionals. All 24 of the areas of uncertainty identified by members of the preterm clinical

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**Box • Summary of research questions**

- What effect will implementing known or suggested risk-reducing interventions for the prevention of preterm birth have on current population rates of preterm birth?
- How should we best develop and implement a package of preterm birth prevention that maximises the impact in a given population?
- What is the optimal cervical length to trigger preterm birth prevention treatment in women at low risk of preterm birth?
- What are the benefits and harms of cervical length screening in the low-risk population?
- Does screening and treating for bacterial vaginosis, vaginal candidiasis and group B streptococcus in a population at high risk for preterm birth reduce the risk of preterm birth?
- What are the most effective antibiotics for treating bacterial vaginosis in women at high risk of preterm birth, and what impact do the antibiotics have on the vaginal microbiota as a whole?
- What are the optimal treatments and treatment thresholds for women with progressive cervical length shortening if already using vaginal progesterone?
- Should we be combining known treatments for short cervix to improve preterm birth prevention; if so, what are the most effective regimens and for which populations?
- What is the best advice to give women at high risk for spontaneous preterm birth on intercourse?
- What effect does intercourse have on maternal physiology in women at high risk for spontaneous preterm birth?
network (Appendix S1) are more nuanced questions, with the same overarching aim as the research priority-setting projects.\textsuperscript{104,105} We felt that it would be valuable to highlight key research areas from the areas of controversy and our evidence summary on the top six questions (Box 1). We hope that this will help to identify areas of uncertainty and future research directions.

**Concluding remarks**

Our attempt to summarise the most recent evidence on the effectiveness and safety of various PTB prevention strategies highlights the complexity of such critical appraisal in a rapidly evolving field. Deciding on what are important clinical questions is highly subjective and depends on many factors, including the populations and healthcare systems of interest. Even when such prioritisation exercises are performed in an unbiased way, the reviewers are faced with publication bias, favouring positive results, the selective reporting of outcomes and the failure to evaluate harm; all of these issues have been well documented, including various strategies to tackle them.\textsuperscript{106}

We also wish to highlight the ever-growing concerns related to the (un)trustworthiness of the published evidence.\textsuperscript{107} Methodologically weak and sometimes even fabricated studies should not be given false credibility by including them in a ‘tsunami’ of various meta-analyses of equally dubious quality. We must call for more stringent assessments of trustworthiness, including a formal assessment of study protocols, data feasibility and, in particular, completeness of individual patient data. Evidence from high-quality, trustworthy clinical research should be complemented with prospectively collected real-life data that go well beyond Hospital Episode Statistics data and are designed to capture clinically important outcomes related to the various innovative, but also harmful, practices that we keep hearing about. The UK Preterm Clinical Network Database could be such an initiative;\textsuperscript{108} however, the efforts needed to establish and, even more importantly, maintain such a database should not be underestimated and must be recognised by funders and policymakers.

We look forward to future reviews that will benefit from formal assessments of research trustworthiness and include robust outcome data from large national prospective audits of good clinical practice.

**Disclosure of interests**

AC and ZA received a grant from the Wellbeing of Women charity to establish the Harris-Wellbeing Research Centre, University of Liverpool. This provided study support costs to AC and LG. Completed disclosure of interest forms are available to view online as supporting information.

**Contribution to authorship**

ZA conceived the idea for the analysis. LG and AC reviewed the literature and wrote the article. ZA reviewed and edited the article.

**Details of ethics approval**

Not applicable for this summary of evidence.

**Funding**

Study support costs for AC and LG were provided by a charitable donation that funded the Harris-Wellbeing Research Centre, University of Liverpool. No additional funding was used.

**Acknowledgements**

We would like to thank Mrs Tracy Ricketts for administrative support for the Harris-Wellbeing Research Centre.

**Supporting Information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Appendix S1.** Survey response questions.

**Video S1.** Author Insights.

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