

# 2020 surveillance of preterm labour and birth (NG25)

## Surveillance proposal

We will not update the guideline on [preterm labour and birth](#) (NG25).

### *Reasons for the proposal*

New evidence and information identified during surveillance was considered not to have an impact on current guideline recommendations. Overall, the new evidence is either considered outside of the scope of this guideline or is deemed insufficient in volume or quality to impact on the recommendations.

The main areas that were identified were:

### **The efficacy of progesterone**

The guideline recommendations on the clinical effectiveness of prophylactic progesterone on the prevention of preterm labour were updated in 2019. The review considered all current evidence and concluded that progesterone is safe and effective to use to prevent preterm labour. No evidence was found through the surveillance review to contradict current recommendations. Three randomised controlled trials (RCTs) were considered during the surveillance review. One of these did not fully complete. One RCT suggested that there was no difference between the 2 groups when using progesterone and the results of 1 RCT indicated that progesterone could decrease preterm birth when combined with other treatments such as indomethacin and treatment of bacterial vaginosis.

### **Identifying women at high risk for premature labour (including the use of transvaginal ultrasound scans)**

Topic experts suggested that more information should be given regarding screening for women at high risk of premature labour to align with other guidelines in this area, such as [NHS England Saving Babies' Lives](#).

Identifying women at high risk for premature labour is outside the scope of this

guideline and is also considered further by the [National Screening Committee](#). Therefore the guideline will not be updated to include this area.

### **Diagnostic testing for women under 30 weeks' gestation**

One topic expert believed that diagnostic testing should be considered for women under 30 weeks gestation and the [UK Preterm Clinical Guidelines](#) suggest that fetal fibronectin testing should be used from 18 weeks gestation. However NICE guideline [DG33](#) and 1 Cochrane review found insufficient evidence to support the use of fetal fibronectin for diagnosing preterm labour. During the development of NG25 it was noted that a 'treat all' approach for women under 30 weeks' gestation was more cost effective than diagnostic testing. No evidence was found to contradict this recommendation and therefore no update of current recommendations is needed.

### **Delivery (including mode of delivery, timing of delivery for women with preterm prelabour rupture of membranes (P-PROM) and delayed cord clamping)**

No evidence was found regarding mode of birth for women in preterm labour. Intelligence was given from a stakeholder to suggest that caesarean section should not be considered first before vaginal breech delivery, however the reasons for this were not given. NG25 only recommends considering caesarean section for women presenting in suspected, diagnosed or established preterm labour between 26 and 36 weeks of pregnancy with breech presentation and therefore no amendment to the guideline is needed.

One topic expert requested further information around when women with P-PROM should deliver. Evidence was found from a limited number of studies regarding the impact on neonatal outcomes of immediate or expectant management of delivery and therefore it is suggested that this guideline is not updated at this time.

Intelligence was given which suggested that delayed cord clamping should have a firmer recommendation within the guideline. There is now a much larger amount of evidence to support the current recommendations that delayed cord clamping is more beneficial to the preterm child than immediate

cord clamping. The current recommendation is for at least 30 seconds but no longer than 3 minutes. No studies were found that compared delayed clamping of 30 seconds with delayed clamping of 3 minutes or under and therefore it is suggested that the current recommendations do not require any amendments at this time.

### **The effectiveness of tocolysis and nifedipine**

Two stakeholders did not consider tocolysis nor specifically the drug nifedipine to be effective at improving neonatal outcomes in women in preterm labour. The [UK Preterm Clinical Guidelines](#) also do not consider tocolysis to be effective. Seven RCTs were found which considered the use of nifedipine. No studies were found that stated that nifedipine was ineffective and nifedipine was considered the safest drug when compared with ritodrine and magnesium sulfate.

Due to the lack of evidence to contradict the current recommendations and new evidence found that supports the current recommendation that tocolytics and nifedipine should be considered in women with suspected preterm labour, there will be no impact to the guideline at this time.

### **Repeat courses of maternal corticosteroids**

One updated Cochrane review was considered during surveillance which concluded that repeat courses of maternal corticosteroids were safe and effective for women in suspected preterm labour. This review had already been considered in the original guideline development and a recommendation of “do not routinely offer repeat courses of maternal corticosteroids” was created. Although NICE have identified no further evidence in this area, it would be useful to understand whether clinicians believe this recommendation is still acceptable in practice. Therefore, NICE is asking stakeholders to specifically comment on their implementation of this recommendation in practice.

During this consultation NICE is also asking for comment on whether there are any gaps in the guideline that haven't been addressed and that should be considered.

For further details and a summary of all evidence identified in surveillance, see the [summary of evidence from surveillance](#).

## **Overview of 2020 surveillance methods**

NICE's surveillance team checked whether recommendations in [preterm labour and birth](#) (NG25) remain up to date.

The surveillance process consisted of:

- Feedback from topic experts via a questionnaire.
- A search for new or updated Cochrane reviews and national policy.
- Consideration of evidence from previous surveillance.
- Examining related NICE guidance and quality standards and NIHR signals.
- A search for ongoing research.
- Examining the NICE event tracker for relevant ongoing and published events.
- Literature searches to identify relevant evidence.
- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.
- Consulting on the proposal with stakeholders (this document).

For further details about the process and the possible update proposals that are available, see [ensuring that published guidelines are current and accurate](#) in developing NICE guidelines: the manual.

### ***Evidence considered in surveillance***

#### **Search and selection strategy**

We searched for new evidence related to the whole guideline.

We found 46 studies published between 1 January 2015 and 31 October 2019.

We also included:

- 1 relevant study from a total of 7 identified by topic experts

From all sources, we considered 47 studies to be relevant to the guideline.

See the [summary of evidence from surveillance](#) for details of all evidence considered, and references.

### ***Selecting relevant studies***

We searched for RCTs and systematic reviews, however due to the large amount of studies identified, only RCTs with sample sizes of 50 and over, and only Cochrane reviews were included.

### ***Ongoing research***

We checked for relevant ongoing research; of the ongoing studies identified, 7 studies were assessed as having the potential to change recommendations. Therefore, we plan to regularly check whether these studies have published results and evaluate the impact of the results on current recommendations as quickly as possible. These studies are:

- [Evaluating hormone treatments for women at increased risk for preterm birth](#)
- [The safety of out-patient compared with in-patient treatment in women with preterm prelabour rupture of the membranes \(PPROM\) prior to 34 weeks of gestation](#)
- [C-STICH2: Rescue cervical stitching to prevent miscarriage and premature birth](#)
- [The EQUIPTT Study: Evaluation whether clinicians using the QUIPP app make more appropriate management decisions for women who arrive to hospital thinking they may be in preterm labour](#)
- [Can a test of preterm labour \(quantitative fetal fibronectin\) help diagnosis and clinical decision making?](#)

- [Early compared to delayed umbilical cord clamping in very small prematurely born babies: A study to know which one is better for infant health](#)
- [Stitch, progesterone or pessary: a randomised controlled trial](#)

## ***Intelligence gathered during surveillance***

### **Views of topic experts**

We considered the views of topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. For this surveillance review, topic experts completed a questionnaire about developments in evidence, policy and services related to the guideline.

We received 4 questionnaire responses: from a midwife; a maternal-fetal medicine and obstetrics specialist; a labour ward and delivery education lead; and an obstetrics specialist. Two felt that the guideline should be updated and 2 did not express an opinion.

Areas raised in topic expert feedback included:

- Identifying women at high risk for premature labour which is outside of the scope for this guideline.
- The gestational age for giving magnesium sulfate, fetal steroids and tocolytics. Only one study was found regarding the use of magnesium sulfate which had similar effects on fetal neuroprotection regardless of gestational age and therefore supported NICE's recommendations.
- The efficacy of progesterone. Please see "[Reasons for the proposal](#)" section.
- Techniques for cervical cerclage (including suture material). No evidence was found in this area.

## **Views of stakeholders**

Stakeholders are consulted on all surveillance reviews except if the whole guideline will be updated and replaced. Because this surveillance proposal is to not update the guideline, we are consulting with stakeholders.

See [ensuring that published guidelines are current and accurate](#) in developing NICE guidelines: the manual for more details on our consultation processes.

## ***Equalities***

No equalities issues were identified during the surveillance process.

## ***Overall proposal***

After considering all evidence and other intelligence and the impact on current recommendations, we decided that no update is necessary.

# 2020 surveillance of preterm labour and birth (2015) NICE guideline NG25 – summary of evidence

## Overview

Studies identified in searches are summarised from the information presented in their abstracts.

Feedback from topic experts was considered alongside the evidence to reach a view on the need to update each section of the guideline.

Evidence from previous surveillance for this topic was also considered.

### [1.1 Information and support](#)

#### ***Surveillance proposal***

No new information was identified at any surveillance review.

This section of the guideline should not be updated.

### [1.2 Prophylactic vaginal progesterone and prophylactic cervical cerclage](#)

#### ***Surveillance proposal***

This section of the guideline should not be updated.

#### **Prophylactic vaginal progesterone**

##### **Previous surveillance**

An exceptional surveillance review was conducted in January 2017 considering the OPPTIMUM study on vaginal progesterone prophylaxis compared with placebo for the delay of preterm labour and birth. The results of this study suggested that progesterone had no significant effect on the primary obstetric outcome, neonatal outcome or the childhood outcome and it was recommended that the guideline should be updated. A meta-analysis was conducted for the update and the combined evidence suggested that

progesterone was effective in reducing the risk of preterm birth. The guideline recommendations [1.2.1](#) and [1.2.2](#) were updated to amend the population groups who could benefit from progesterone.

### **2020 surveillance summary**

Three randomised controlled trials (RCTs) were found during the surveillance review which were published after the update of the guideline and which considered the use of progesterone in women at risk of preterm labour.

An RCT (1) of 95 women with singleton gestation and a short cervix <25mm were randomised to 3 groups to receive either dydrogesterone, 17-hydroxyprogesterone or oral/vaginal micronised progesterone (VP) with cerclage for the prevention of preterm birth. Women (15-24 weeks gestation) at risk of preterm delivery had a significantly decreased rate of preterm birth when they received combination therapy with VP, indomethacin and treatment of bacterial vaginosis with the subsequent use of VP until 36 weeks together with cervical length monitoring.

Another RCT (2) comparing IM 17-hydroxyprogesterone with standard care in 105 women (20-31 weeks gestation) with a short cervix and a history of preterm labour was halted early due to a lack of efficacy with 17-hydroxyprogesterone.

An RCT (3) compared vaginal progesterone suppository with no vaginal progesterone suppository in 200 pregnant women (24-34 gestational weeks) at risk of preterm labour who had already been treated with magnesium sulfate and corticosteroid. There were no significant differences between the 2 groups in terms of preventing preterm delivery.

### **Intelligence gathering**

The [National Screening Committee](#) (NSC) currently state that “there is not enough evidence to be sure that vaginal progesterone is an effective treatment for preventing preterm labour or that it reduces the most severe outcomes for the baby”. This information was published in 2015, prior to the update of NG25, and therefore does not consider the most recent evidence in

this area. The NSC report was due for review in 2017/18 and the update is anticipated Spring 2020.

One ongoing study was found regarding the use of progesterone in women at risk of preterm labour. A [meta-analysis](#) is evaluating the benefits and harms of progesterone in its different forms, doses, routes of administration and timing when used for the prevention of preterm birth. This study is due to publish in April 2020. It will be tracked by NICE and the results will be assessed for impact on publication when available.

### **Impact statement**

This section of the guideline was updated in 2019. New evidence published after the search cut-off date for the guideline was considered in this surveillance review.

The current guideline recommends the use of progesterone, as consideration of the evidence found its use to be safe and effective. Evidence and the committee's discussion of the evidence is published in the [August 2019: Evidence Review](#).

Three RCTs were considered during the surveillance review. One of these did not fully complete. One RCT suggested that there was no difference between the 2 groups when using progesterone and the results of 1 RCT indicated that progesterone could decrease preterm birth when combined with other treatments such as indomethacin and treatment of bacterial vaginosis.

The NSC report is not in alignment with NICE's current recommendation, however their report is due to be updated and may consider more recent evidence.

There is no new evidence identified through the surveillance review that conflicts with NICE's recent decision to recommend the use of progesterone. None of the RCTs found noted any safety or efficacy concerns with the use of progesterone for this indication and 1 RCT supports the view that progesterone can help delay preterm labour. As such the guideline will not be updated at this time.

## **Prophylactic cervical cerclage**

### **2020 surveillance summary**

During the surveillance review 1 Cochrane review and 1 RCT were found which considered cervical cerclage.

A Cochrane review (n = 15 RCTs) (4) considered the safety and efficacy of cervical cerclage in women at high risk of pregnancy loss. Women, who were assessed at 37, 34 and 28 completed weeks of gestation and had received cerclage, were significantly less likely to have preterm births compared to control groups who had received either no treatment or an alternative intervention. It was also stated in the study that cervical cerclage can reduce the risk of perinatal death, compared to no cervical cerclage, however the confidence interval for this result crossed the line of no effect.

An RCT (5) compared transabdominal cervical cerclage, high vaginal cervical cerclage and low vaginal cervical cerclage in women (n = 111 at 14 weeks gestation or prior to conception) with a history of failed cerclage. Rates of preterm birth were significantly lower in the transabdominal cerclage group compared to the low vaginal cerclage group. There were no significant differences between the high and low vaginal cerclage groups in terms of preterm birth.

### **Intelligence gathering**

NICE guideline [IPG639](#) Laparoscopic cerclage for cervical incompetence to prevent late miscarriage or preterm birth supports the use of this procedure with standard arrangements. The [scope](#) of NG25 states that laparoscopic cerclage will not be covered by the guideline, however this procedure is linked to NG25 through the [Preterm labour and birth pathway](#).

### **Impact statement**

NICE considered new evidence that has published since the recommendations were updated in 2019. The new evidence indicates that cervical cerclage is effective at preventing preterm delivery. One RCT states that transabdominal cerclage is the most successful form. One NICE

Interventional Procedures guideline recommends the use of laparoscopic cerclage for cervical incompetence to prevent preterm birth.

NG25 recommends prophylactic cervical cerclage for women between 16-24 weeks pregnant however the method of cervical cerclage is not specified. Transabdominal cerclage, high vaginal cerclage, low vaginal cerclage and laparoscopic cerclage were not considered during the development of NG25 and laparoscopic cerclage was outside of the scope.

No new evidence was found to contradict the current recommendations and not enough evidence regarding the use of transabdominal cerclage was discovered. Therefore, due to a lack of evidence and intelligence found, and because no contradiction to the current recommendations was made, no impact on the guideline is expected at this time.

### **[1.3 Diagnosing preterm prelabour rupture of membranes \(P-PROM\)](#)**

#### ***Surveillance proposal***

No new information was identified at any surveillance review.

This section of the guideline should not be updated.

### **[1.4 Antenatal prophylactic antibiotics for women with P-PROM](#)**

#### ***Surveillance proposal***

This section of the guideline should not be updated.

#### **2020 surveillance summary**

No relevant evidence was identified.

#### **Intelligence gathering**

An [ongoing study](#) is looking at the safety of out-patient compared with in-patient treatment in the form of intravenous antibiotics in women with P-PROM prior to 34 weeks of gestation. This study is due to publish in

December 2020 and will be tracked by NICE and assessed for impact on publication.

### **Impact statement**

No new evidence was identified that will have an impact on the recommendations at this time.

Ongoing research has been identified in this area so NICE will track this study and consider any impact of the results on guideline recommendations when available.

## **1.5 Identifying infection in women with P-PROM**

### ***Surveillance proposal***

No new information was identified at any surveillance review.

This section of the guideline should not be updated.

## **1.6 'Rescue' cervical cerclage**

### ***Surveillance proposal***

This section of the guideline should not be updated.

### **2020 surveillance summary**

An RCT (6) compared emergency cervical cerclage combined with progesterone with progesterone alone in 100 women in early labour at 24-28 weeks. Pregnancy was significantly prolonged in the rescue cerclage plus progesterone group in addition to significant increases in fetal gestational age, heavier gestational weight and lower rates of caesarean deliveries compared to the progesterone alone group.

### **Intelligence gathering**

An [ongoing study](#) is looking at rescue cervical stitching to prevent miscarriage and premature birth. The study is due to publish in June 2025 and will be tracked by NICE and assessed for impact on publication.

## **Impact statement**

NG25 currently recommends considering rescue cervical cerclage in women between 16 and 27 weeks of pregnancy if the cervix is dilated and the membranes are exposed but not unruptured. At the time of guideline development, the committee did not consider the option of giving the combination of progesterone and cerclage and was aware that usual clinical practice is to use one or the other. One RCT identified through the surveillance review indicated that women who received rescue cerclage plus progesterone had significant pregnancy prolongation.

There is not enough evidence to confirm that rescue cerclage combined with progesterone significantly prolongs pregnancy and no evidence was identified through the surveillance review that conflicts with the current recommendations therefore there will be no impact to the guideline at this time.

## **[1.7 Diagnosing preterm labour for women with intact membranes](#)**

### ***Surveillance proposal***

This section of the guideline should not be updated.

### **2020 surveillance summary**

A Cochrane review (n = 13 RCTs) (7) considered the effectiveness of a home uterine activity monitor which aimed to detect increased contraction frequency and therefore potentially begin early intervention with tocolytic drugs to inhibit labour. There were no significant differences between any groups when sensitivity analyses using only trials at low risk of bias were used, however when risk of bias was not considered, women using the home uterine monitoring were significantly less likely to experience preterm birth at less than 34 weeks.

One Cochrane review (n = 6 RCTs) (8) considered the effectiveness of management based on knowledge of fetal fibronectin testing results. No significant results were found for the outcome of preventing preterm birth.

## **Intelligence gathering**

During consultation on the updated NG25 guideline in 2019, 1 stakeholder commented that clinicians should use preterm predictors under 30 weeks gestation. Risk assessments are outside of the scope for this guideline. Another stakeholder also suggested that NICE should offer diagnostic tests such as fetal fibronectin to women under 30 weeks gestation instead of treating all women with suspected preterm labour. The stakeholder believed that this 'treat all' approach leads to unnecessary hospital admissions, unnecessary interventions, in utero transfers and bed blocking.

### ***Treat all approach***

The [UK Preterm Clinical Guidelines](#) (2019) suggest that a treat all approach is not easy to implement and may not be cost effective and recommend that additional use of quantitative fetal fibronectin in asymptomatic women from 18 weeks gestation can be considered where centres have this expertise. This information was taken from a [prospective study](#) which considered the combined use of fetal fibronectin and transvaginal ultrasound measurement of cervical length in asymptomatic high risk women (n=147), however this study did not meet the inclusion criteria for this surveillance review which only considered RCTs.

### ***Fetal fibronectin testing***

During consultation on the updated guideline in 2019 a stakeholder made a comment that, in practice, transvaginal ultrasound scans (to determine cervical length) have limited availability and suggested that fetal fibronectin testing would be more useful in determining which women need to be transferred or need further clinical intervention. However, NICE guideline [DG33](#) Biomarker tests to help diagnose preterm labour in women with intact membranes states that "there is currently insufficient evidence to recommend the routine adoption of the Rapid Fetal Fibronectin (fFN) 10Q Cassette Kit to help diagnose preterm labour in women with intact membranes".

### ***Transvaginal ultrasound scans***

Another stakeholder asked for clarification as to whether transvaginal ultrasound scans should be carried out to all women at high risk of preterm birth. The stakeholder also queried what the best method of measuring cervical length was, whether it was a single measurement or an average of 3 measurements.

NICE's implementation team contacted 8 midwives/obstetricians in September 2017 and asked them about their use of transvaginal ultrasound scanning for cervical length. All responded to say that the use of this within their units was rare however the reasons for this were not given.

[NHS England Saving Babies' Lives](#) gives information around when cervical length scans should be performed. This guideline states that women with high risk factors should have a scan between 18 and 22 weeks. High risk factors for considering when to scan are considered by the NICE NG25 [evidence review 2019](#) to be: history of preterm birth; short cervix; uterine malformations; previous cervical surgery; P-PROM; midtrimester bleeding; and positive fetal fibronectin test.

Two ongoing studies were considered. NICE will track the studies and will assess their impact on the guideline recommendations on publication:

- An [ongoing study](#) is looking at the use of an application for clinicians to make more appropriate management decisions for women who arrive to hospital thinking they may be in preterm labour. This study is due to publish in June 2021.
- An [ongoing study](#) is looking at whether a test of preterm labour (quantitative fetal fibronectin) can help aid diagnosis and clinical decision making. It is not known when the results of this study will publish.

### **Impact statement**

NICE considered new evidence and intelligence regarding the 'treat all' approach for women at risk of preterm labour, diagnostic testing, and transvaginal ultrasound scanning for cervical length measurement.

### ***Treat all approach***

At the time of guideline development, it was noted that the additional costs of 'treat all' are worth the reduction in adverse outcomes at lower gestational ages. The committee felt that there was not a sufficiently large impact on the diagnostic accuracy threshold to justify using a diagnostic test at gestational age lower than 30 weeks. NG25 therefore recommends not offering diagnostic testing to women under 30 weeks gestation and that tocolysis and maternal corticosteroids is the most cost effective option for all women at this point.

Due to a lack of evidence to state that diagnostic tests would be more cost effective than a treat all approach for women less than 30 weeks gestation, no impact on the guideline is anticipated at this time.

### ***Diagnostic testing***

There is conflicting information regarding diagnostic testing for preterm labour. One stakeholder believed that diagnostic testing should be considered for women under 30 weeks gestation and the UK Preterm Clinical Guidelines suggest that fetal fibronectin testing should be used from 18 weeks gestation. However NICE guideline DG33 and 1 Cochrane review found insufficient evidence to support the use of fetal fibronectin for diagnosing preterm labour.

NG25 recommends a speculum examination (followed by a digital vaginal examination if necessary) to diagnose preterm labour. NG25 also recommends transvaginal ultrasound measurements of cervical length to confirm determined likelihood of birth within 48 hours for women over 30 weeks who are in preterm labour. NG25 recommends fetal fibronectin testing to determine likelihood of birth within 48 hours if transvaginal ultrasound measurement of cervical length is not available or acceptable in women over 30 weeks who are in preterm labour.

Due to a lack of evidence regarding the effectiveness of diagnostic testing for all women at any gestational age, and evidence within NG25 which confirms that a treat all approach without the need for diagnostic testing for women

under 30 weeks pregnant is cost effective (see below), no impact on the guideline is anticipated at this time.

### ***Transvaginal ultrasound scans (TVUs)***

No new evidence was found but intelligence was given regarding the lack of availability and clinical use of TVUs. At the time of guideline development, the committee noted that transvaginal ultrasound scanning is not available across the NHS because of limitations of equipment or expertise, and that investment in technology and training may be required for its universal implementation in the NHS. Two years after the publication of NG25 it was noted that at 8 obstetric units transvaginal ultrasound scanning was rarely being used, however the reasons behind this were not given. It is noted by stakeholders that the use of TVUs is uncommon in clinical practice.

Topic experts requested further information in the guideline on when and how to use TVUs. Further information on this may be provided by the NSC in their anticipated update in Spring 2020. No evidence was found during the surveillance review regarding how best to measure cervical length when using TVUs, however NG25 acknowledges that training is necessary to be able to undertake these actions adequately. No evidence was found regarding when to perform TVUs, and risk assessment interventions are outside of the scope for this guideline. NG25 recommendation 1.7.4 recommends using TVUs in women over 30 weeks gestation for diagnosing preterm labour.

The new evidence and intelligence found do not contradict the advice to use TVUs in clinical practice as a diagnostic tool for preterm birth and therefore no impact on the guideline is expected at this time.

## **1.8 Tocolysis**

### ***Surveillance proposal***

This section of the guideline should not be updated.

## **2020 surveillance summary**

### ***Nifedipine***

Seven RCTs were found evaluating nifedipine tocolysis for prevention of preterm labour.

One RCT (9) compared oral nifedipine and IV atosiban in women (n=503 at 25-34 weeks pregnant) at risk of preterm labour. There were no significant differences between the groups in delaying delivery by 48 hours. The economic analysis of this RCT (10) found there were lower costs associated with the use of nifedipine and there were no significant differences between the groups in terms of adverse perinatal outcomes.

In 1 RCT (11) women (n = 73, between 24-34 weeks) with symptoms of preterm labour, a shortened cervix but a negative fetal fibronectin test received either nifedipine (80mg a day) or placebo. The results did not show any significant differences between the 2 groups in terms of delivery within 7 days.

An RCT (12) compared nifedipine and ritodrine in 60 women between 24 and 36 weeks at risk of preterm labour. Maternal adverse effects were significantly higher in the ritodrine group however there were no significant differences in fetomaternal blood flow, fetal mortality, maternal morbidity or time to delivery between the groups.

An RCT (13) compared intravenous magnesium sulfate and oral nifedipine in 220 women between 32 and 34 weeks pregnant at risk of preterm labour. There were no significant differences regarding preventing preterm delivery or with neonatal outcomes. There were significant differences in minor adverse effects with the magnesium group having more maternal side effects than the nifedipine group.

One RCT (14) compared oral nifedipine combined with vaginally administered sildenafil citrate with nifedipine alone in 239 women (weeks' gestation unknown) with threatened preterm labour. Women who received nifedipine combined with sildenafil citrate were significantly more likely to have a

delayed birth and fewer admissions to neonatal intensive care units as well as increased neonatal birthweight compared to the women who received nifedipine alone.

An RCT (15) compared nifedipine with a placebo in 206 women (weeks gestation unknown) with threatened preterm labour. Women delivered significantly sooner in the placebo group compared to the nifedipine group, confirming that the nifedipine group was more successful at reaching the outcome of prolonging pregnancy.

An RCT (16) compared nifedipine plus placebo with indomethacin plus placebo and a combination of nifedipine plus indomethacin. The outcome was prohibiting preterm uterine contractions in 147 pregnant women (26-34 weeks). The combination group was significantly more successful at prohibiting preterm contraction compared to the other groups during 3 time stages: within the first 2 hours of receiving the intervention; 48 hours after the intervention; and 7 days after the intervention.

### ***Ethanol***

A Cochrane review (17) (RCT = 12) considered the efficacy of ethanol infusion in stopping preterm labour, preventing preterm birth and the impact on neonatal outcomes. No evidence was found to indicate ethanol was an effective tocolytic compared to placebo or other tocolytic drugs.

### ***Competitive inhibitors of cyclooxygenase (COX) Inhibitors***

A Cochrane review (18) (RCT = 20) considered the effect of COX inhibitors administered as a tocolytic agent to women in preterm labour on maternal and neonatal outcomes compared with placebo, no intervention or other tocolytics. There was a significant reduction in preterm birth in the group that received indomethacin. There were no significant differences in morbidity or mortality between the groups. COX inhibitors were associated with significantly fewer maternal adverse effects compared with betamimetics and with magnesium sulfate. However, due to the small numbers and limited quality of the data there was no clear benefit shown for COX inhibitors compared to the comparators.

### ***Atosiban***

In an RCT (19) women (n = 70) who had become pregnant through assisted reproductive technology and were at risk of preterm labour received either atosiban or ritodrine. Atosiban was significantly more successful at extending gestational age by 48 hours compared with ritodrine however both groups were effective at extending gestational age by 7 days. The perinatal mortality rate and prevalence of neonatal asyphxia was significantly lower in the atosiban group compared to ritodrine. Maternal adverse effects were also significantly lower in the atosiban group compared to the ritodrine group.

### ***Retosiban***

An RCT (20) compared IV retosiban with a placebo in 64 women with spontaneous preterm labour. There was a significant delay to delivery in the intervention group compared to the control. There were no differences in maternal or neonatal adverse effects between the groups.

### ***Magnesium sulfate***

A Cochrane review (21) (RCT = 3) considered the safety and efficacy of alternative magnesium sulfate regimens when used as single agent tocolytic therapy during pregnancy. There was insufficient conclusive evidence to make any conclusion on the use of magnesium sulfate for this indication.

### **Intelligence gathering**

One stakeholder wrote to NICE after the guideline was originally published and suggested that NICE reconsider the effectiveness of tocolysis and of nifedipine during preterm labour. It was suggested that NICE consider 2 studies ([Roos 2015](#) and [de Heus 2009](#)) however these were not RCTs and 1 was also outside the required date period for the surveillance review and therefore they were not included. One topic expert suggested that the threshold of viability for giving treatments such as tocolytics and steroids may change post ongoing discussions that are arising from the publication of the [Precept Trial](#).

The [UK Preterm Clinical Guidelines](#) (2019) recommend not using tocolysis for women at risk of imminent preterm birth to improve neonatal outcomes and state that there is no evidence that maintenance tocolysis is beneficial.

### **Impact statement**

NG25 recommends considering tocolysis in women between 24 and 25 weeks who have intact membranes and are in suspected preterm labour and offering tocolysis to women between 26 and 33 weeks who have intact membranes and are in suspected or diagnosed labour. For both recommendations the drug suggested is nifedipine.

NICE considered new evidence and intelligence regarding the use of tocolysis in women at risk of preterm labour.

### ***Nifedipine***

Seven RCTs were found which considered the use of nifedipine. Four out of the 7 RCTs showed no significant differences regarding delaying preterm delivery or improvement on relevant health outcomes when nifedipine was compared with atosiban, ritodrine, magnesium sulfate or placebo. One RCT showed that nifedipine on its own significantly prolonged pregnancy when compared with placebo. Two RCTs showed that nifedipine in combination with another drug such as sildenafil citrate or indomethacin significantly delayed preterm birth compared to nifedipine alone or indomethacin alone. No studies were found that stated that nifedipine was ineffective and nifedipine was considered the safest drug when compared with ritodrine and magnesium sulfate.

Two stakeholders did not consider tocolysis nor the drug nifedipine to be effective at improving neonatal outcomes in women in preterm labour. The [UK Preterm Clinical Guidelines](#) also do not consider tocolysis to be effective.

At the time of guideline development the committee noted that the evidence showed that calcium channel blockers had the highest probability of being the best medicine for reducing respiratory distress syndrome and were more effective for this outcome than the other tocolytics used in the network meta-

analysis. It was noted that the majority of evidence on calcium blockers was derived from trials which included nifedipine. Given that nifedipine is the most widely used calcium blocker in clinical practice and nicardipine (the other calcium blocker included in the trials that were reviewed) is associated with significant side effects, the committee recommended the use of nifedipine for tocolysis. The economic model also found that calcium channel blockers were the most cost effective treatment for women of all gestational ages.

There was no evidence found regarding maintenance tocolysis in this group and little evidence regarding the importance of weeks gestation when using tocolysis. At the time of guideline development, the committee felt that although dosage, mode of administration and timing of treatment may influence the effectiveness of different tocolytics interventions, it was considered unlikely for this factor to change the direction of relative effect for the different interventions.

Due to the lack of evidence to contradict the current recommendations and new evidence found that supports the current recommendation that tocolytics and nifedipine should be considered in women with suspected preterm labour, there will be no impact to the guideline at this time.

Evidence was also found regarding the use of ethanol, COX inhibitors, atosiban, retosiban and magnesium sulfate for tocolysis for women at risk of preterm labour. The studies found stated there was no clear benefit shown for the use of ethanol, COX inhibitors, retosiban or magnesium sulfate.

### ***Ethanol***

At the time of guideline development, the committee stated that although ethanol was 1 of the first agents used as a tocolytic, it would no longer be considered a therapeutic option even if found to be effective for neonatal outcomes because of known maternal side effects. No evidence was found during the surveillance review to contradict this opinion.

### ***COX Inhibitors***

At the time of guideline development, the committee stated that although prostaglandin inhibitors were found to be the most beneficial treatment in terms of delaying birth by more than 48 hours and for increasing estimated gestational age, and the second most effective treatment for reducing perinatal mortality, they were not found to improve other outcomes such as neonatal mortality, respiratory distress syndrome and neonatal sepsis in all of which they scored very low in the ranking of best treatments. The committee was also aware of other harms thought to be associated with prostaglandin inhibitors, such as premature closure of the ductus arteriosus. Therefore, the committee did not consider them as a tocolytic option for women in suspected or diagnosed preterm labour. No evidence was found during the surveillance review to contradict this opinion.

### ***Atosiban***

At the time of guideline development, the committee stated that the use of oxytocin receptor blockers for reduction of maternal side effects and for increasing gestational age had to be balanced against its poor efficacy in reducing intraventricular haemorrhage and respiratory distress syndrome and its modest effect on perinatal mortality. Therefore, the committee decided that this should not be the first option of tocolytic treatment. No evidence was found during the surveillance review to contradict this opinion.

### ***Retosiban***

Retosiban was not considered during the development of NG25 and no further intelligence was found during the surveillance review to suggest it should be considered in the guideline.

### ***Magnesium sulfate***

There was little evidence in the full [NICE guideline](#) regarding magnesium sulfate being used for tocolysis and no further intelligence was found during the surveillance review.

New evidence found during the surveillance review supports the current recommendation that tocolytics and nifedipine should be considered in women

with suspected preterm labour and there will be no impact to the guideline at this time.

## **1.9 Maternal corticosteroids**

### ***Surveillance proposal***

This section of the guideline should not be updated.

### **2020 surveillance summary**

During the surveillance review 2 Cochrane reviews were found which related to corticosteroids in preterm labour. One review looked at single courses and 1 looked at repeat doses. Both of these reviews were updates of previous reviews which had been used in the development of NG25. Their conclusions had not altered.

A Cochrane review (22) (RCT = 30) considered the effect of a single course of corticosteroids administered to the mother (gestational week unknown) prior to anticipated preterm birth on the outcomes of fetal, neonatal and maternal morbidity and mortality. There was a significant reduction in perinatal death, neonatal death and respiratory distress syndrome in the group that were treated with corticosteroids compared with the group who received placebo or no treatment.

A Cochrane review (23) (RCT = 10) considered the safety and efficacy of repeat doses of prenatal corticosteroids in women (gestational week unknown) who had received a single course 7 or more days previously but were still at risk of preterm birth. There was a significant decrease in number of infants experiencing respiratory distress syndrome and serious infant outcome in the repeat corticosteroid group compared to those who did not receive a repeat corticosteroid treatment. It was suggested that treatment with repeat dose of corticosteroid was associated with a reduction in mean birthweight however at early childhood follow up there were no significant differences between infants that had been exposed to prenatal corticosteroids compared with those not exposed. There were no significant adverse effects

reported. The evidence found supported the use of repeat dose prenatal corticosteroids.

The original review protocol for NG25 considered the following outcomes: maternal mortality and adverse events as well as neonatal and child mortality; need for mechanical ventilation; bronchopulmonary dysplasia/chronic lung disease; intraventricular haemorrhage; neonatal sepsis and neurodevelopment disability.

### **Intelligence gathering**

During consultation on the update of the guideline in 2019, 1 stakeholder suggested that NICE should consider the timing of administering fetal steroids. The stakeholder stated that steroids provide benefit as early as 6 hours after being given and are of minimal benefit after 7 days.

The [UK Preterm Clinical Guidelines](#) (2019) suggest that the timing and appropriate administration of steroid doses is important as steroid doses can be associated with a reduction in the birthweight of the infant.

One topic expert suggested that the gestational age for giving corticosteroids had changed since the initial publication of the guideline following on from the [Precept Trial](#).

### **Impact statement**

NICE considered updated evidence on single and repeat courses of maternal corticosteroids. Both Cochrane reviews showed significant differences in outcomes of neonatal and maternal health when single use corticosteroids or repeat courses of corticosteroids were used.

NG25 recommends, for women who are in suspected or established preterm labour, discussing corticosteroids at 23 weeks pregnant, offering corticosteroids between 24 and 33 weeks pregnant and considering corticosteroids between 34 and 35 weeks pregnant. One Cochrane review confirmed these current recommendations. NG25 does not recommend how long to continue giving corticosteroids.

At the time of guideline development the committee concluded that there was insufficient evidence of benefit to support a recommendation that courses of steroids should be repeated routinely, but that this should not rule out the judicious use of repeat courses of corticosteroids in circumstances where clinical judgement suggested that it might be beneficial given the lack of clear evidence that such practice would cause harm. As such the committee developed the following recommendation of: “do not routinely offer repeat courses of maternal corticosteroids but take into account: the interval since the end of the last course; gestational age; the likelihood of birth within 48 hours”.

Evidence was found regarding repeat courses of corticosteroids. A Cochrane review concluded that repeat courses were safe and effective, however this was an update of a review which had already been considered during the original development of the guideline, the conclusions of which had not altered. The current recommendations are permissive to use repeat courses of corticosteroids if clinical judgement believes this is needed and therefore, due to the lack of evidence regarding all other potential outcomes that may be influenced by repeat courses of corticosteroids it is suggested there is no impact on the guideline at this time.

Intelligence was given regarding the importance of when fetal steroids should be administered.

During the development of NG25 the guideline development committee noted the lack of available evidence on which to judge the optimal timing of administration of corticosteroids in relation to the time of birth and particularly the ‘latest point’ at which the drug could most effectively be given. The committee acknowledged that this had not been prioritised as an aim of the review but, taking account of the drug’s pharmacological mechanism of action, the committee suspected that any benefits would be likely to be transferred even if there was only a limited amount of time (such as less than 24–48 hours) between administration and time of birth. However, the committee could not make any recommendations to this effect.

Intelligence raised that there are no recommendations regarding the timing for when corticosteroids should be administered, the gestational age for taking corticosteroids or appropriate administration for corticosteroids however no evidence was found in this area through the surveillance review, therefore no impact on the guideline is expected at this time.

## **1.10 Magnesium sulfate for neuroprotection**

### ***Surveillance proposal***

This section of the guideline should not be updated.

### **2020 surveillance summary**

The [Precept Trial](#) was suggested by a topic expert for consideration during this surveillance review. This individual participant data meta-analysis aimed to assess the effects of antenatal magnesium sulfate on women at risk of preterm birth compared to not receiving magnesium sulfate. The outcome was fetal neuroprotection. There was a significant reduction in the risk of death and of cerebral palsy within the magnesium sulfate treatment group compared with the no treatment group.

### **Intelligence gathering**

One topic expert suggested that the gestational age for giving magnesium currently recommended in the guideline should be reconsidered following on from the [Precept Trial](#).

### **Impact statement**

NICE considered new evidence and intelligence regarding the use of magnesium sulfate for neuroprotection. Intelligence gathered suggested that the gestational age for giving magnesium sulfate should be reconsidered following publication of more recent evidence. The Precept Trial noted that antenatal magnesium is effective at preventing cerebral palsy and has similar effects regardless of gestational age.

NG25 recommends offering magnesium sulfate to women between 24 and 29 weeks who are in established preterm labour or having a planned preterm

birth within 24 hours. It recommends considering magnesium sulfate for women between 30 and 33 weeks who are in established preterm labour or having a planned preterm birth within 24 hours.

Evidence found from the surveillance review does not contradict the current recommendations and therefore there will be no impact on the guideline at this time.

### **1.11 Intrapartum antibiotics**

#### ***Surveillance proposal***

This section of the guideline should not be updated.

This section of the guideline is fully covered by [CG149](#) Neonatal infection (early onset): antibiotics for prevention and treatment and no information regarding the recommendations in this guideline was identified at this surveillance review.

### **1.12 Fetal monitoring**

#### ***Surveillance proposal***

This section of the guideline should not be updated. An editorial amendment will be made to reference NICE guideline NG121 to ensure that NG25 considers women with known or suspected immune thrombocytopenic purpura and sepsis or suspected sepsis.

#### ***Monitoring options: cardiotocography (CTG) and intermittent auscultation (IA)***

#### **2020 surveillance summary**

No relevant evidence was identified.

#### **Intelligence gathering**

The [BAPM Perinatal Management of Extreme Preterm Birth Before 27 weeks of Gestation](#) (2019) Guidelines do not recommend continuous fetal heart rate monitoring below 26 weeks of gestation.

NICE guideline [NG133](#) Hypertension in pregnancy: diagnosis and management recommendation [1.6.12](#) states that in women who need additional fetal monitoring, carry out CTG only if clinically indicated. This population of women are not necessarily at risk of preterm labour, they are presenting with hypertensive disorders or pre-existing hypertension or are at risk of developing hypertensive disorders – therefore the recommendation is not necessarily applicable to NG25.

### **Impact statement**

No evidence was found regarding CTG and IA during the surveillance review.

Intelligence was gathered in the form of 1 guideline which suggests that fetal heart rate monitoring should not occur before 26 weeks. Another guideline recommends that fetal heart rate monitoring should only be considered in special circumstances.

NG25 recommendation [1.12.5](#) suggests clinicians offer women in established preterm labour but with no other risk factors a choice of fetal heart rate monitoring using either CTG using external ultrasound or IA. NG25 also suggests that fetal monitoring should be used alongside NICE guideline [CG190](#) Intrapartum care for healthy women and babies however these recommendations are not written for women in preterm labour or at risk of preterm labour.

During guideline development the committee stated that despite the paucity of research evidence relating to the method of fetal heart monitoring in preterm labour, the committee felt it was nevertheless important to monitor fetal heart rate by some means during preterm labour. The committee agreed that women should be fully consulted before performing continuous fetal heart rate monitoring and that it was important to inform women of the lack of evidence of benefit of CTG versus IA prior to offering monitoring. As such recommendation [1.12.2](#) states that senior obstetrician should be involved in discussions regarding monitoring the fetal heart rate for women who are between 23 and 25 weeks pregnant and recommendation [1.12.4](#) recommends

explaining to the woman that there is an absence of evidence that using CTG improves the outcomes of preterm labour.

The intelligence found through the surveillance review does not contradict NG25, which recommends the use of fetal monitoring, CTG and IA with caution. No new evidence was found, therefore no impact on the guideline is expected at this time.

### ***Fetal blood sampling***

#### **2020 surveillance summary**

No relevant evidence was identified.

#### **Intelligence gathering**

NICE guideline [NG121](#) Intrapartum care for women with existing medical conditions or obstetric complications and their babies makes recommendations around fetal blood sampling which are not included in NG25. [NG121](#) recommendation [1.6.5](#) states do not use fetal blood sampling for women with known or suspected immune thrombocytopenic purpura. Recommendations [1.13.20](#) and [1.13.21](#) also suggest considering sepsis or suspected sepsis before performing any fetal blood sampling.

#### **Impact statement**

No evidence was found during the surveillance review for this section of the guideline, however recommendations from another NICE guideline were considered and were found to be important to the recommendations in NG25.

NG25 recommends reading NICE guideline [CG190](#) Intrapartum care for healthy women and babies alongside this recommendation but does not include [NG121](#) in this list. The recommendations from NG121 are not considered in NG25 however they may be relevant for this population.

It is therefore suggested that NG25 is editorially amended to ensure that it is used alongside [NG121](#) in order to consider the recommendations around women with known or suspected immune thrombocytopenic purpura and sepsis or suspected sepsis.

## 1.13 Mode of birth

### ***Surveillance proposal***

This section of the guideline should not be updated.

### **2020 surveillance summary**

No evidence was found regarding the best mode of birth for preterm babies, however evidence was found regarding the timing of delivery for preterm babies with and without P-PROM.

A Cochrane review (24) (RCT = 1) considered the effects of immediate versus deferred delivery of preterm babies with suspected fetal compromise on neonatal, maternal and long-term outcomes. The median difference between immediate delivery and deferred delivery was 4 days. There were no significant differences in perinatal mortality, or death and disability at or after 2 years of age. There was a significant difference in the immediate delivery group where more babies were ventilated for more than 24 hours compared to the deferred delivery group. Women were significantly more likely to have caesarean deliveries in the immediate delivery group.

During the surveillance review, 1 Cochrane review and 3 RCTs were found which considered timing of delivery in women with P-PROM.

A Cochrane review (25) (RCTs = 12) considered the effects of planned early birth (immediate intervention within 24 hours) compared with expectant management (no immediate intervention within 24 hours) for women with P-PROM between 24 and 37 weeks gestation. There was a significant difference in levels of respiratory distress syndrome, prevalence of caesarean section, neonatal death, ventilation need and admission to neonatal intensive care with the early birth group having a higher rate of incidence compared to the expectant management. The review concluded that expectant management with careful monitoring is associated with better outcomes for mother and baby.

An RCT (26) compared intentional early delivery with expectant management in 360 women with P-PROM. There were no significant differences between

the 2 groups regarding the outcome of improved neonatal and maternal health however the study was underpowered to confirm any conclusions.

An RCT (27) compared the costs to the healthcare system of immediate birth with expectant management in 1,835 women with P-PROM. There were no significant differences in costs between the 2 groups.

An RCT (28) compared immediate birth in 1839 women with P-PROM to expectant management with the outcome of reducing neonatal infection. Neonates born in the immediate delivery group had significantly increased rates of respiratory distress and spent more time in intensive care compared to the expectant management group. Women in the immediate delivery group had significantly lower rates of haemorrhage, fever and use of antibiotics and were more likely to have caesarean deliveries.

### **Intelligence gathering**

During consultation on the guideline update in 2019, 1 stakeholder suggested that NICE should consider vaginal delivery as well as caesarean section for women in diagnosed or established preterm labour whose baby is breech.

NICE guideline [CG132](#) Caesarean Section (CS) recommendation [1.2.3.1](#) suggests that preterm birth is associated with higher neonatal morbidity and mortality, however the effect of planned CS in improving these outcomes remain uncertain and therefore CS should not routinely be offered outside a research context.

Another stakeholder suggested that NICE should consider when women with P-PROM should deliver.

NICE guideline [CG70](#) Inducing labour recommendation [1.2.2.1](#) states that if a woman has preterm prelabour rupture of membranes induction of labour should not be carried out before 34 weeks unless there are additional obstetric indications (for example infection or fetal compromise). [CG70](#) recommendation [1.2.2.2](#) states that if a woman has preterm prelabour rupture

of membranes after 34 weeks, the maternity team should discuss certain factors with her before a decision is made about whether to induce labour.

An [ongoing study](#) is looking at the feasibility and design of a trial to determine the optimal mode of delivery in women presenting in preterm labour or with planned preterm delivery. It is due to publish in October 2022.

### **Impact statement**

NICE considered new evidence and intelligence regarding the timing of birth and new intelligence regarding the mode of birth.

No evidence was found regarding mode of birth for women in preterm labour. Intelligence was given from a stakeholder to suggest that caesarean section should not be considered first before vaginal breech delivery, however the reasons for this were not given. NG25 only recommends considering caesarean section for women presenting in suspected, diagnosed or established preterm labour between 26 and 36 weeks of pregnancy with breech presentation. NICE guideline [CG132](#) Caesarean section suggested that caesarean sections did not improve the outcomes for preterm birth, however this was not in breech delivery incidences.

Evidence around the timing of preterm birth was considered and for women with fetal compromise, deferred delivery showed significant differences in neonatal health outcomes in 1 Cochrane review. For women who had P-PRM, 1 Cochrane review and 1 RCT stated that there were significant benefits with deferred expectant management, compared to immediate delivery. Two RCTs showed no significant differences between immediate and expectant delivery and 1 RCT showed benefits to the neonate with 1 method and to the mother in another method.

There are no recommendations in NG25 regarding the timing of birth of preterm infants with suspected fetal compromise and with P-PRM. The benefits of immediate or deferred birth were not considered in the review protocol for NG25. There is only evidence from a limited number of studies regarding the impact on neonatal outcomes of expectant management of

delivery and therefore it is suggested that this guideline is not updated at this time.

### **1.14 Timing of cord clamping for preterm babies (born vaginally or by caesarean section)**

#### ***Surveillance proposal***

This section of the guideline should not be updated.

#### **2020 surveillance summary**

Two Cochrane reviews and 13 RCTs were found that considered cord clamping and care in preterm babies.

One Cochrane review (29) (RCT = 1) considered the efficacy and safety of respiratory support provided during delayed cord clamping (60 seconds after birth) compared with no respiratory support during placental transfusion (delayed cord clamping/milking or stripping). There were no significant results reported for any of the outcomes.

A Cochrane review (30) (RCT = 40) compared 4 scenarios:

- Delayed cord clamping compared to early cord clamping both with immediate neonatal aftercare.
- Delayed cord clamping with immediate neonatal aftercare with cord intact compared with early cord clamping with immediate neonatal aftercare after cord clamping.
- Delayed cord clamping with immediate neonatal aftercare with cord intact compared with umbilical cord milking.
- Umbilical cord milking with early cord clamping compared with immediate neonatal aftercare after cord clamping.

Delayed cord clamping (which was usually 30-60 seconds after birth) significantly reduced the number of neonatal deaths compared to early cord clamping (under 30 seconds) and significantly reduced the rates of intraventricular haemorrhage. Delayed cord clamping with immediate neonatal aftercare with the cord intact also significantly reduced the number of

neonatal deaths compared with early cord clamping. There were no other statistically significant results.

### ***Cord milking***

An RCT (31) compared umbilical cord milking with immediate clamping in 73 preterm infants with the outcome of improving systemic blood flow and neonatal outcomes. Haemoglobin levels were significantly higher in the umbilical cord milking group compared with the immediate clamping group.

An RCT (32) compared delayed umbilical cord clamping (60 seconds) and umbilical cord milking in 204 preterm infants. There were no significant differences in terms of neonatal outcomes between the 2 groups.

An RCT (33) compared intact umbilical cord milking with immediate cord clamping in 102 preterm infants who had P-PROM with the aim of reducing infection. The neonates in the intact umbilical cord milking group had significantly higher haematocrit levels and received fewer blood transfusions compared with the immediate cord clamping group. There were no significant differences between the 2 groups in terms of neonatal outcomes such as neonatal infection.

### ***Early and delayed cord clamping***

An RCT (34) (n=1497) compared outcomes of fetuses who were born preterm and either received immediate cord clamping <10 seconds after birth or delayed cord clamping >60 seconds. There were no significant differences between the 2 groups in terms of neonatal health outcomes.

An RCT (35) (n=266) compared delayed cord clamping (>60 seconds) with immediate cord clamping (<60 seconds) in very preterm infants. There were no significant differences between the 2 groups in terms of superior vena cava flow.

An RCT (36) (n=276) compared delayed cord clamping (after 120 seconds) and immediate neonatal care with the cord intact to early cord clamping (within 20 seconds) and immediate neonatal care after clamping in preterm

babies. There were no significant differences between the 2 groups in terms of neonatal health outcomes.

Two RCTs (37 and 38) (n=86 and n=100) considered the effectiveness of delayed cord clamping (120 seconds after birth) compared to immediate cord clamping in preterm neonates on the level of haematocrit. Neonates in the delayed cord clamping group had significantly higher haematocrit levels in both studies than those in the immediate cord clamping group. In 1 RCT the levels of serum ferritin were also higher in the delayed cord clamping group

An RCT (39) (n=67) compared delayed cord clamping (30 seconds) with cord stripping, with delayed cord clamping without cord stripping in preterm neonates. Infants with gestational ages of 28 weeks or more had significantly higher haematocrit levels in the without cord stripping group than they did in with cord stripping group. There were no other significant differences between the 2 groups in terms of the primary outcome of initial fetal haematocrit.

An RCT (40) (n=100) compared delayed cord clamping (by 120 seconds) with early cord clamping (less than 30 seconds) in infants born before 34 weeks with the outcome of rates of hyperbilirubinemia and polycythaemia. Levels of haematocrit were significantly higher in the delayed cord clamping compared to the early cord clamping group. There were no significant adverse effects.

An RCT (41) (n=120) compared delayed cord clamping (between 30 and 60 seconds) and immediate cord clamping (within 20 seconds) in preterm neonates. There were significant benefits to delayed cord clamping on neurobehavioural outcomes compared with the immediate cord clamping.

An RCT (42) (n=218) compared deferred cord clamping ( $\geq 120$  seconds) and immediate neonatal care with cord intact with immediate cord clamping ( $\leq 20$  seconds) and immediate neonatal care in preterm infants with the aim of improved neurodevelopmental outcomes at the age of 2. There were significantly higher rates of death and adverse neurodevelopment outcomes in the immediate cord clamping group compared to the deferred cord clamping group.

An RCT (43) (n=208) compared delayed cord clamping (30-45 seconds) with immediate cord clamping (<10 seconds) in preterm infants. There were no significant differences in rates of intraventricular haemorrhage (IVH) or late onset sepsis between the groups. The risk of IVH was significantly doubled in women who had P-PROM.

### **Intelligence gathering**

During the consultation on the updated guideline in 2019, 1 stakeholder suggested that delayed clamping should be enforced in all deliveries irrespective of other prerogatives due to the publication of the [Mercer study \(summarised above\)](#).

An [ongoing study](#) is looking at early compared to delayed umbilical cord clamping in very small prematurely born babies to determine the impact on infant health. It is due to publish in October 2021 and NICE will track the study and assess it for impact on publication.

### **Impact statement**

NICE considered new evidence regarding timing of cord clamping.

Three RCTs considered the effects of cord milking compared to immediate or delayed cord clamping. When cord milking was compared to delayed cord clamping there were no significant differences in terms of neonatal outcomes. When cord milking was compared to immediate clamping there were significantly higher levels of haemoglobin in the infants in the cord milking group.

One Cochrane review stated that delayed cord clamping (30-60 seconds) had significant benefits to neonatal outcomes compared to early cord clamping. Ten RCTs compared delayed cord clamping to immediate cord clamping. Six indicated significant benefits of delayed cord clamping with 4 of these recommending waiting for 2 minutes, and the others suggesting between 30-60 seconds. The other 4 RCTs showed no differences between the 2 groups with 1 study showing a difference only in the subgroup of women who had P-PROM.

Intelligence was given which suggested that delayed cord clamping should have a firmer recommendation within the guideline.

During the development of NG25 the committee suggested that there was limited evidence available in this area and therefore they did not feel confident about making strong recommendations for practice regarding the timing of cord clamping. They noted there was some evidence in favour of delayed cord clamping and no evidence of harm was associated with it. As such the committee recommended clamping the cord as soon as possible or consider milking the cord if the baby needs to be moved away from the mother for resuscitation or there is significant maternal bleeding. If mother and baby are stable then clinicians should wait at least 30 seconds but no longer than 3 minutes before clamping the cord.

There is now a much larger amount of evidence regarding this intervention to support the recommendations that delayed cord clamping is more beneficial to the preterm child than immediate cord clamping. No studies were found that confirmed a specific time frame for delayed clamping that would be most beneficial for the health of the newborn. Therefore it is suggested that the current recommendations do not require any amendments and therefore there will be no impact on the guideline at this time.

## **Areas not currently covered in the guideline**

In surveillance, evidence was identified for areas not covered by the guideline. This new evidence has been considered for possible addition as a new section of the guideline.

### ***Surveillance proposal***

#### ***Sealant post P-PROM***

This section should not be added.

#### **2020 surveillance summary**

A Cochrane review (44) (RCT = 2) considered the effectiveness of different forms of sealing techniques following P-PROM compared to standard care

(including no sealant), on maternal and neonatal outcomes. In 1 study cervical adapter (mechanical sealing) was compared with standard care and there were no significant differences between the 2 groups. In the other study, oral immunological membrane sealant was compared to standard care and there was a significant reduction in preterm birth and neonatal death in the intervention group, however the evidence was considered low quality. No specific information regarding gestational age was given.

### **Intelligence gathering**

No relevant intelligence was identified.

### **Impact statement**

NICE considered new evidence regarding sealing techniques following P-PRM. There was limited and low quality evidence to suggest that sealing techniques following P-PRM can be effective.

NG25 makes no recommendations for sealing techniques for this population group.

Due to the limited evidence in this area there is no expected impact on the guideline at this time.

### ***Cervical pessaries***

This section should not be added.

### **2020 surveillance summary**

During the surveillance review 2 RCTs were found that considered the use of Arabin pessaries for preterm labour.

An RCT (45) considered the effectiveness of cervical pessaries in women at risk of preterm labour. Women (n=130) 24-34 weeks pregnant with a short or intermediate cervical length and a positive fetal fibronectin test received either a pessary or no treatment. There were no significant differences between the

2 groups in terms of reducing the rate of preterm birth, however this trial was ceased early.

An RCT (46) compared cervical pessaries with standard care in 357 pregnant women with threatened preterm labour and a short cervix. Spontaneous preterm birth under 37 weeks and preterm rupture of membranes were significantly less frequent in the cervical pessary group compared to standard care. There was no difference in the rate of spontaneous preterm birth under 34 weeks.

### **Intelligence gathering**

One stakeholder suggested that NICE should consider the use of Arabin pessaries or create research recommendations around their use.

Two ongoing studies were considered:

An [ongoing study](#) is looking at prevention of preterm birth and comparing the Arabin pessary, cervical cerclage or vaginal progesterone pessary to see which is the most effective. It is not known when this study is due to publish.

An [ongoing study](#) is looking at the effectiveness of cervical stitching, vaginal progesterone or Arabin pessary in preventing preterm birth in women with 1 baby and a short cervix. The study is due to publish in July 2022. NICE will track this study and will assess its impact on the guideline recommendations on publication.

### **Impact statement**

Arabin pessaries are recommended in the [UK Preterm Clinical Guidelines](#) (2019) as an alternative to prophylactic cervical cerclage or progesterone in women who have had a history of spontaneous preterm birth or midtrimester loss between 16+<sup>0</sup> and 34+<sup>0</sup> weeks of pregnancy and in whom a transvaginal scan reveals a cervix of less than 25 mm.

NICE guideline [NG137](#) on Twin and Triplet pregnancies recommendation [1.5.2](#) states do not offer Arabin pessaries routinely to prevent spontaneous

preterm birth in women with a twin or triplet pregnancy. There are no recommendations for its use in singleton pregnancy, however.

NICE considered new evidence and intelligence regarding cervical pessaries. Two RCTs were considered with 1 suggesting that cervical pessaries significantly reduced preterm birth under 37 weeks. Intelligence was gathered that suggested Arabin pessaries should be considered for use in women at risk of preterm labour.

Cervical pessaries were not considered during the development of NG25.

As only 1 RCT is showing evidence of efficacy it is suggested that there is not enough high-quality evidence at this time and therefore there will be no impact on the guideline.

### ***In utero transfer***

This section should not be added.

### **2020 surveillance summary**

No relevant evidence was identified

### **Intelligence gathering**

[UK Preterm Clinical Guidelines](#) (2019) recommend in utero transfer to settings with level 3 neonatal intensive care units. In utero transfer is when a mother is moved to another hospital before the baby is born. It is noted that “it is now a priority NHS England recommendation for local maternity services to take action to ensure that all women <27 weeks are delivered in centres with a neonatal intensive care unit (NICU)”.

The [BAPM Perinatal Management of Extreme Preterm Birth Before 27 weeks of Gestation](#) (2019) Guidelines state that “In utero transfer to a maternity facility co-located with a NICU should be considered at the earliest opportunity when active management is planned”.

The [National Neonatal Audit Programme](#) also suggests that outcomes are improved if premature babies are cared for in a NICU from birth.

### **Impact statement**

No evidence was found regarding in utero transfer however intelligence was gathered from guidelines and audit programmes which specify the importance of in utero transfer to settings with NICU for the improved outcome of the baby. It is stated that this is an NHS England prioritised recommendation.

NG25 mentions transferring to another unit for the benefit of neonatal care in recommendation 1.8.1 when it suggests that clinicians consider the availability of neonatal care (need to transfer to another unit) when making their decision around the use of tocolysis.

The full [NICE guideline](#) states that it is possible that some units would not be able to treat all the women recommended for treatment, particularly if 'treat all' was considered optimal, and this would necessitate the transfer of a proportion of women to alternative units.

The full [NICE guideline](#) also states that optimal diagnosis can facilitate transfer to a place where appropriate neonatal intensive care can be provided, a strategy known to improve rates of survival for the baby.

The [scope](#) for NG25 states that in current practice optimising outcomes for babies likely to deliver preterm includes transfer to a centre with appropriate neonatal facilities. Although it is noted in the scope that there is variation in both the use of this approach in the UK and the diagnostic criteria applied to determine transfer there is very little in the guideline to clarify this situation.

In utero transfer to hospitals with appropriate care is important for the safety and wellbeing of mother and child, however it is not a 1 service fits all requirement and relies on clinician consideration. NG25 already mentions that clinicians should make this assessment in recommendation 1.8.1 and the British Association of Perinatal Medicine (BAPM) guideline gives advice in this area, therefore this guideline does not need an update at this time.

## Research recommendations

### 1. [Prophylactic vaginal progesterone](#)

Does progesterone reduce the risk of preterm birth in women who have risk factors for preterm birth, but do not have a short cervix (cervical length of more than 25 mm)?

#### ***Summary of findings***

No studies were found which specifically stated that the population group they considered had a cervical length measurement that was greater than 25mm. Evidence regarding the use of progesterone in women at risk of preterm labour was found however the characteristics of the population in the studies were not fully confirmed and no evidence was found to suggest an update would be needed within this section.

### 2. [Prophylactic vaginal progesterone](#)

Does progesterone reduce the risk of preterm birth in women who have a short cervix (cervical length of 25 mm or less), but do not have other risk factors for preterm birth?

#### ***Summary of findings***

No studies were found which specifically stated that the population group they considered had a cervical length measurement that was less than 25mm but had no other risk factors for preterm birth. Evidence regarding the use of progesterone in women at risk of preterm labour was found however the characteristics of the population in the studies were not fully confirmed and no evidence was found to suggest an update would be needed within this section.

### 3. [Prophylactic vaginal progesterone](#)

At what gestation should treatment with prophylactic vaginal progesterone for the prevention of preterm birth be started and stopped?

### **Summary of findings**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

#### 4. [Prophylactic vaginal progesterone and prophylactic cervical cerclage](#)

What is the clinical effectiveness of prophylactic cervical cerclage alone compared with prophylactic vaginal progesterone alone and with both strategies together for preventing preterm birth in women with a short cervix and a history of spontaneous preterm birth?

### **Summary of findings**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

#### 5. [Identifying infection in women with preterm prelabour rupture of membranes \(P-PROM\)](#)

What is the diagnostic accuracy of serial C-reactive protein testing to identify chorioamnionitis in women with P-PROM?

### **Summary of findings**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

#### 6. ['Rescue' cervical cerclage](#)

What is the clinical effectiveness of 'rescue' cerclage in improving outcomes for women at risk of preterm birth?

### **Summary of findings**

The new evidence shows emergency cervical cerclage combined with progesterone in early labour at 24-28 weeks was more effective than progesterone alone in prolonging pregnancy. There were significant increases in fetal gestational age, heavier gestational weight and lower rates of caesarean deliveries compared to the progesterone alone group, however the evidence to confirm that rescue cerclage combined with progesterone

significantly prolongs pregnancy is currently insufficient in volume and therefore no update is recommended.

7. [Magnesium sulfate for neuroprotection](#)

What is the clinical effectiveness of a bolus plus infusion of magnesium sulfate compared with a bolus alone for preventing neurodevelopmental injury in babies born preterm?

***Summary of findings***

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

8. Is intermittent auscultation or electronic fetal monitoring effective in the preterm fetus?

***Summary of findings***

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

9. Is there any advantage to preterm babies from delayed versus early cord clamping, or cord milking?

***Summary of findings***

The new evidence shows that delayed clamping is more beneficial to preterm babies than early cord clamping, however there is no further information on what time frame would be most beneficial when delaying. Therefore no updated is recommended.

## References

1. Pustotina O (2018) Effectiveness of dydrogesterone, 17-OH progesterone and micronized progesterone in prevention of preterm birth in women with a short cervix. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians* 31(14):1830–8
2. Winer N, Bretelle F, Senat M-V, Bohec C, Deruelle P, Perrotin F, et al. (2015) 17 alpha-hydroxyprogesterone caproate does not prolong pregnancy or reduce the rate of preterm birth in women at high risk for preterm delivery and a short cervix: a randomized controlled trial. *American journal of obstetrics and gynecology* 212(4):485e1-485e10
3. Lalooha F, Movahed F, Chegini V, Pakniat H, Takaloo F (2019) The effect of vaginal progesterone suppository on prevention of preterm delivery. *Scientific journal of kurdistan university of medical sciences* 24(2):111–8
4. Alfirevic Z, Stampalija T, Medley N (2017) Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. *Cochrane Database of Systematic Reviews* (6)
5. Shennan A, Chandiramani M, Bennett P, David AL, Girling J, Ridout A, et al. (2019) MAVRIC: A Multicentre Randomised Controlled Trial of Transabdominal Versus Transvaginal Cervical Cerclage. *American journal of obstetrics and gynecology*
6. Ragab A, Mesbah Y (2015) To do or not to do emergency cervical cerclage (a rescue stitch) at 24-28 weeks gestation in addition to progesterone for patients coming early in labor? A prospective randomized trial for efficacy and safety. *Archives of gynecology and obstetrics* 292(6):1255–60

7. Urquhart C, Currell R, Harlow F, Callow L (2017) Home uterine monitoring for detecting preterm labour. *Cochrane Database of Systematic Reviews* (2)
8. Berghella V, Saccone G (2019) Fetal fibronectin testing for reducing the risk of preterm birth. *Cochrane Database of Systematic Reviews* (7)
9. van Vliet EOG, Nijman TAJ, Schuit E, Heida KY, Opmeer BC, Kok M, et al. (2016) Nifedipine versus atosiban for threatened preterm birth (APOSTEL III): a multicentre, randomised controlled trial. *Lancet* (London, England) 387(10033):2117–24
10. Nijman T, van Baaren GJ, van Vliet E, Kok M, Gyselaers W, Porath MM, et al. (2019) Cost effectiveness of nifedipine compared with atosiban in the treatment of threatened preterm birth (APOSTEL III trial). *BJOG : an international journal of obstetrics and gynaecology* 126(7):875–83
11. Vis JY, van Baaren G-J, Wilms FF, Oudijk MA, Kwee A, Porath MM, et al. (2015) Randomized comparison of nifedipine and placebo in fibronectin-negative women with symptoms of preterm labor and a short cervix (APOSTEL-I Trial). *American journal of perinatology* 32(5):451–60
12. Baykal BO, Avcioglu SN (2015) Comparison of effects of nifedipine and ritodrine on maternal and fetal blood flow patterns in preterm labor. *Journal of the turkish german gynecology association* 16(2):80–5
13. Khooshideh M, Rahmati J, Teimoori B (2017) Nifedipine versus magnesium sulfate for treatment of preterm labor: comparison of efficacy and adverse effects in a randomized controlled trial. *Shiraz e medical journal* 18(6)
14. Maher MA, Sayyed TM, El-Khadry SW (2019) Nifedipine alone or combined with sildenafil citrate for management of threatened preterm labour: a randomised trial. *BJOG : an international journal of obstetrics and gynaecology* 126(6):729–35

15. Songthamwat S, Na Nan C, Songthamwat M (2018) Effectiveness of nifedipine in threatened preterm labor: A randomized trial. *International Journal of Women's Health* 10:317–23
16. Kashanian M, Shirvani S, Sheikhansari N, Javanmanesh F (2019) A comparative study on the efficacy of nifedipine and indomethacin for prevention of preterm birth as monotherapy and combination therapy: a randomized clinical trial. *Journal of Maternal-Fetal and Neonatal Medicine*
17. Haas DM, Morgan AM, Deans SJ, Schubert FP (2015) Ethanol for preventing preterm birth in threatened preterm labor. *Cochrane Database of Systematic Reviews* (11)
18. Reinebrant HE, Pileggi Castro C, Romero CLT, dos Santos RAN, Kumar S, Souza JP, et al. (2015) Cyclooxygenase (COX) inhibitors for treating preterm labour. *Cochrane Database of Systematic Reviews* (6)
19. Xu Y-J, Ran L-M, Zhai S-S, Luo X-H, Zhang Y-Y, Zhou Z-Y, et al. (2016) Evaluation of the efficacy of atosiban in pregnant women with threatened preterm labor associated with assisted reproductive technology. *European review for medical and pharmacological sciences* 20(9):1881–7
20. Thornton S, Miller H, Valenzuela G, Snidow J, Stier B, Fossler MJ, et al. (2015) Treatment of spontaneous preterm labour with atosiban: a phase 2 proof-of-concept study. *British journal of clinical pharmacology* 80(4):740–9
21. McNamara HC, Crowther CA, Brown J (2015) Different treatment regimens of magnesium sulphate for tocolysis in women in preterm labour. *Cochrane Database of Systematic Reviews* (12)
22. Roberts D, Brown J, Medley N, Dalziel SR (2017) Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database of Systematic Reviews* (3)

23. Crowther CA, McKinlay CJD, Middleton P, Harding JE (2015) Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. *Cochrane Database of Systematic Reviews* (7)
24. Stock SJ, Bricker L, Norman JE, West HM (2016) Immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes. *Cochrane Database of Systematic Reviews* (7)
25. Bond DM, Middleton P, Levett KM, van der Ham DP, Crowther CA, Buchanan SL, et al. (2017) Planned early birth versus expectant management for women with preterm prelabour rupture of membranes prior to 37 weeks' gestation for improving pregnancy outcome. *Cochrane Database of Systematic Reviews* (3)
26. Pasquier J-C, Claris O, Rabilloud M, Ecochard R, Picaud J-C, Moret S, et al. (2019) Intentional early delivery versus expectant management for preterm premature rupture of membranes at 28-32 weeks' gestation: A multicentre randomized controlled trial (MICADO STUDY). *European journal of obstetrics, gynecology, and reproductive biology* 233:30–7
27. Lain SJ, Roberts CL, Bond DM, Smith J, Morris JM (2017) An economic evaluation of planned immediate versus delayed birth for preterm prelabour rupture of membranes: findings from the PPRoMT randomised controlled trial. *BJOG : an international journal of obstetrics and gynaecology* 124(4):623–30
28. Morris JM, Roberts CL, Bowen JR, Patterson JA, Bond DM, Algert CS, et al. (2016) Immediate delivery compared with expectant management after preterm pre-labour rupture of the membranes close to term (PPRoMT trial): a randomised controlled trial. *Lancet (London, England)* 387(10017):444–52
29. Meyer MP, Nevill E, Wong MM (2018) Provision of respiratory support compared to no respiratory support before cord clamping for preterm infants. *Cochrane Database of Systematic Reviews* (3)

30. Rabe H, Gyte GM, Diaz-Rossello JL, Duley L (2019) Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. The Cochrane database of systematic reviews 9:cd003248
31. El-Naggar W, Simpson D, Hussain A, Armson A, Dodds L, Warren A, et al. (2019) Cord milking versus immediate clamping in preterm infants: a randomised controlled trial. Archives of disease in childhood. Fetal and neonatal edition 104(2):f145–50
32. Shirk SK, Manolis SA, Lambers DS, Smith KL (2019) Delayed clamping vs milking of umbilical cord in preterm infants: a randomized controlled trial. American journal of obstetrics and gynecology 220(5):482e1-482e8
33. Li J, Yu B, Wang W, Luo D, Dai Q-L, Gan X-Q (2018) Does intact umbilical cord milking increase infection rates in preterm infants with premature prolonged rupture of membranes?. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians :1–7
34. Tarnow-Mordi W, Morris J, Kirby A, Robledo K, Askie L, Brown R, et al. (2017) Delayed versus Immediate Cord Clamping in Preterm Infants. The New England journal of medicine 377(25):2445–55
35. Popat H, Robledo KP, Sebastian L, Evans N, Gill A, Kluckow M, et al. (2016) Effect of Delayed Cord Clamping on Systemic Blood Flow: A Randomized Controlled Trial. The Journal of pediatrics 178:81–86e2
36. Duley L, Dorling J, Pushpa-Rajah A, Oddie SJ, Yoxall CW, Schoonakker B, et al. (2018) Randomised trial of cord clamping and initial stabilisation at very preterm birth. Archives of disease in childhood. Fetal and neonatal edition 103(1):f6–14
37. Salae R, Tanprasertkul C, Somprasit C, Bhamarapratana K,

- Suwannarurk K (2016) Efficacy of Delayed versus Immediate Cord Clamping in Late Preterm Newborns following Normal Labor: A Randomized Control Trial. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet* 99suppl4:159–65
38. Ranjit T, Nesargi S, Rao PNS, Sahoo JP, Ashok C, Chandrakala BS, et al. (2015) Effect of early versus delayed cord clamping on hematological status of preterm infants at 6 wk of age. *Indian journal of pediatrics* 82(1):29–34
  39. Krueger MS, Eyal FG, Peevy KJ, Hamm CR, Whitehurst RM, Lewis DF (2015) Delayed cord clamping with and without cord stripping: a prospective randomized trial of preterm neonates. *American journal of obstetrics and gynecology* 212(3):394e1-5
  40. Rana A, Agarwal K, Ramji S, Gandhi G, Sahu L (2018) Safety of delayed umbilical cord clamping in preterm neonates of less than 34 weeks of gestation: a randomized controlled trial. *Obstetrics & gynecology science* 61(6):655–61
  41. Datta V, Kumar A, Yadav R (2017) A Randomized Controlled Trial to Evaluate the Role of Brief Delay in Cord Clamping in Preterm Neonates (34-36 weeks) on Short-term Neurobehavioural Outcome. *Journal of tropical pediatrics*
  42. Armstrong-Buisseret L, Powers K, Dorling J, Bradshaw L, Johnson S, Mitchell E, et al. (2019) Randomised trial of cord clamping at very preterm birth: outcomes at 2 years. *Archives of disease in childhood. Fetal and neonatal edition*
  43. Mercer JS, Erickson-Owens DA, Vohr BR, Tucker RJ, Parker AB, Oh W, et al. (2016) Effects of Placental Transfusion on Neonatal and 18 Month Outcomes in Preterm Infants: A Randomized Controlled Trial. *The Journal of pediatrics* 168:50–5e1
  44. Crowley AE, Grivell RM, Dodd JM (2016) Sealing procedures for

preterm prelabour rupture of membranes. Cochrane Database of Systematic Reviews (7)

45. Hermans FJR, Schuit E, Bekker MN, Woiski M, de Boer MA, Sueters M, et al. (2018) Cervical Pessary After Arrested Preterm Labor: A Randomized Controlled Trial. *Obstetrics and gynecology* 132(3):741–9
46. Pratcorona L, Goya M, Merced C, Rodo C, Llurba E, Higuera T, et al. (2018) Cervical pessary to reduce preterm birth <34 weeks of gestation after an episode of preterm labor and a short cervix: a randomized controlled trial. *American journal of obstetrics and gynecology* 219(1):99e1-99e16

© NICE 2020. All rights reserved. Subject to [Notice of rights](#).