NICE National Institute for Health and Care Excellence

2022 exceptional surveillance of preterm labour and birth (NICE guideline NG25)

Surveillance report

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Contents

Surveillance decision

We will update the NICE guideline on preterm labour and birth. The update will focus on 2 topic areas:

- Diagnosing preterm labour for women with intact membranes
- Timing of cord clamping for preterm babies.

Each of these topic areas is discussed below in turn.

Methods

The exceptional surveillance process consisted of:

- Considering new evidence being tracked by NICE as it publishes and assessing it for an impact on the guideline.
- Considering relevant information from the 2020 full surveillance review of the guideline.
- Considering the evidence used to develop the guideline in 2015.
- Feedback from the Multiple Obstetric Guidelines Update Committee.
- Examining related NICE guidance and quality standards.
- Examining the NICE event tracker for relevant ongoing and published events.
- A search for ongoing research.
- Assessing the new evidence and intelligence against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.

We decided that full updated literature searches were not needed because the information we had from the new published evidence was enough to establish whether an update to the guideline was needed.

For further details about the process and the possible update decisions that are available,

see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Diagnosing preterm labour for women with intact membranes

Reasons for the exceptional review

New evidence has emerged since the guideline was developed which related to diagnosing preterm labour in women with intact membranes. Feedback from the 2022 update of the NICE guideline also highlighted the QUantitative Innovation in Predicting Preterm birth app (QUiPP app) as an important development.

Information considered in this exceptional surveillance review

There have been 2 studies published which relate to how to predict preterm labour in women with intact membranes with symptoms of threatened preterm labour as well as asymptomatic high-risk women.

QUiPP app

The EQUIPTT study was a multicentre cluster randomised controlled trial (cluster-RCT) involving 13 maternity units in the UK that recruited 1,872 pregnant women between 23+0 and 34+6 weeks' gestation with symptoms of preterm labour. It evaluated use of the QUiPP app which aims to support clinical decision-making about women in threatened preterm labour by combining quantitative fetal fibronectin values, cervical length, and significant preterm birth risk factors to create an individualised percentage risk of delivery, compared with conventional management of threatened preterm labour. The QUiPP app calculates risk for both symptomatic and asymptomatic women. In asymptomatic high-risk women, the app requires input of data on previous cervical surgery, previous preterm birth, previous late miscarriage, number of fetuses, gestation of test, together with shortest cervical length measurement and/or fetal fibronectin result. In symptomatic women the app requires input of data on symptoms of suggestive abnormality or premature uterine activity, previous cervical surgery, previous preterm birth, previous P-PROM, number of fetuses, gestation test, together with shortest cervical length measurement and/or fetal fibronectin result.

The study failed to demonstrate a positive finding for the primary outcome, which was a composite of the number of unnecessary admission or discharge decisions, unnecessary in utero transfer and ex utero transfers (odds ratio [OR] 0.97, 95% confidence interval [CI] 0.66 to 1.42). The authors considered that the failure to reach the primary outcome could have been related to the unexpected low event rate in the control arm, which was similar to that anticipated as a result of the intervention, and potentially also related to clinicians in the control arm not following national guidance on conventional management but incorporating aspects of the QUiPP app available to them, such as the use of fetal fibronectin.

The authors also noted a number of limitations of the study including the fact that the expectation of a 25% unnecessary admission rate may have been incorrect as unnecessary admission at control sites was only 10.8%. There was also a disproportionately higher level of women from the tertiary hospitals compared to smaller units with less established women's health academic departments. However, the 2 most research-active tertiary maternity units were both randomised to control.

A previous publication of the QUiPP App v2 using data from 3 cohort studies, had already demonstrated that the app could provide individualised risk of delivery based on 3 algorithms: cervical length, quantitative fetal fibronectin or both tests combined, taking into account further risk factors, such as twins pregnancy (Watson et al. 2020). The authors concluded that all 3 algorithms demonstrated high accuracy for the prediction of spontaneous preterm birth at less than 30, 34 and 37 weeks' gestation and within 1, 2 and 4 weeks of testing, with areas under the curve (AUCs) between 0.75 and 0.90 for the use of fetal fibronectin and cervical length combined plus risk factors, between 0.68 and 0.90 for fetal fibronectin plus risk factors, and between 0.71 and 0.87 for cervical length plus risk factors. The authors deemed this would enable use of the QUiPP app in situations where either fetal fibronectin or cervical length measurement was not available.

Overall, the authors concluded that the QUiPP app is a safe and accurate method for identifying women most likely to benefit from preterm labour and birth interventions. The app has now been recommended by NHS England and the British Association of Perinatal Medicine.

QUIDS

The QUIDS study was comprised of 5 parts:

- A qualitative study on symptoms of preterm labour to establish the decisional needs of pregnant women and their caregivers.
- An individual participant data (IPD) meta-analysis of existing studies to develop a prognostic model for spontaneous preterm birth within 7 days in women with symptoms of preterm labour based on quantitative fetal fibronectin and clinical risk factors.
- An external validation of the prognostic model in a prospective cohort study across 26 UK centres including pregnant women at 22+0 to 34+6 weeks gestation with signs and symptoms of preterm labour.
- A model based economic evaluation comparing the prognostic model with qualitative fetal fibronectin, and quantitative fetal fibronectin with cervical length measurement, in terms of cost per quality adjusted life year (QALY) gained.
- And finally, a qualitative assessment of the acceptability of quantitative fetal fibronectin. The QUIDS prognostic model itself included quantitative fetal fibronectin, smoking, ethnicity, nulliparity and multiple pregnancy.

The IPD meta-analysis included 1,783 women and 139 events of spontaneous preterm birth within 7 days (event rate 7.8%). The prognostic model that was developed included quantitative fetal fibronectin, smoking, ethnicity, nulliparity and multiple pregnancy and was externally validated in a cohort of 2,837 women, with 83 events of spontaneous preterm birth within 7 days (event rate 2.93%), with an AUC of 0.89 (95% CI 0.84 to 0.93). The economic analysis found that the prognostic model was cost-effective compared with using qualitative fetal fibronectin at a threshold for hospital admission and treatment of greater than or equal to 2% risk of preterm birth within 7 days.

The parsimonious prognostic model based on quantitative fibronectin and 4 clinical predictors (smoking, ethnicity, nulliparity, multiple pregnancy) was calibrated for the UK population and had an AUC of 0.89 (95% CI 0.84 to 0.93). The prognostic model including fetal fibronectin and clinical risks factors was found to be cost-effective compared with fetal fibronectin alone, with an additional cost of £3 per 0.0015 QALY gain, resulting in an incremental cost effectiveness ratio (ICER) of £2,000 per QALY.

The authors concluded that the prognostic model including fetal fibronectin and clinical risks factors was clinically effective and cost-effective at predicting spontaneous preterm birth within 7 days of test (at a willingness to pay of £54 per quality adjusted life-day [QALD] which is equivalent to a threshold of £20,000/QALY). They stated that the

prognostic model will be embedded in electronic maternity records and a mobile telephone application, enabling ongoing data collection for further refinement and validation of the model.

Information considered when developing the guideline

There was no evidence of the QUiPP app or QUIDS decision tool during guideline development in 2015.

The committee considered evidence for various diagnostics and concluded that measuring cervical length using transvaginal ultrasound is the most accurate way to predict preterm labour when used alone for women over 30 weeks in pregnancy. Fibronectin was also useful if cervical length measurement was not available or not acceptable but not as good a diagnostic tool as cervical length. The committee noted the importance of false positives and false negatives and the associated harm with either missing women at risk of preterm birth who are deprived of the benefits of treatment or identifying wrongly that women are at risk of preterm birth resulting in unnecessary management. They acknowledged the need for women to understand different diagnostic testing options, including their associated benefits and harms, and the interpretation of the results to guide possible subsequent management strategies.

Information considered in previous surveillance of this guideline

There was no evidence of the QUiPP app or QUIDS in the 2020 surveillance of the guideline. However, both studies were identified as important to track and added to the NICE event tracker at that time.

Multiple Obstetric Guidelines Update Committee feedback

Committee feedback highlighted this as an important area of the guideline, with the potential to improve both maternal and neonatal outcomes. They explained that QUiPP was already used in clinical practice and noted the stakeholder feedback highlighting QUiPP as an important development. The guideline would therefore benefit from an update related to new prognostic models to predict preterm delivery. The committee also highlighted that the risk factors which identify women as higher risk of preterm birth and trigger referral to a preterm birth clinic and/or assessment of risks of preterm birth using a prognostic tool such as QUiPP or QUIDS need updating.

Other relevant NICE guidance

NICE's diagnostics guidance on biomarker tests to help diagnose preterm labour in women with intact membranes found that there is currently insufficient evidence to recommend the routine adoption of Actim Partus and PartoSure to help diagnose preterm labour in women with intact membranes when transvaginal ultrasound measurement of cervical length is not available or not acceptable. There is also currently insufficient evidence to recommend the routine adoption of the Rapid fetal fibronectin (fFN) 10Q Cassette Kit (using thresholds other than 50 nanograms/millilitre [ng/ml] to guide clinical management) to help diagnose preterm labour in women with intact membranes when transvaginal ultrasound measurement of cervical length is not available or not acceptable.

NICE's quality standard on preterm labour and birth does not cover QUiPP, QUIDS or fetal fibronectin testing.

The UK National Screening Committee (NSC)

Th UK NSC do not currently recommend a population screening programme for preterm birth in low risk asymptomatic pregnant women. This was because the UK NSC Preterm Birth Screening (2020) concluded that the screening tests currently available (fetal fibronectin, cervical length measurement, tests for bacterial vaginosis, or uterine contraction home measurement) to predict preterm birth in women without symptoms at population screening level were not reliable enough. Therefore, UK NSC does not recommend using these tests for population screening programmes.

Furthermore, the committee deemed that it was uncertain that treating women identified by screening as having a higher chance of preterm birth would reduce their risk of having a premature baby. The next review is due in 2023 to 2024.

Equalities

The committee highlighted that women's knowledge of the risk factors of preterm birth was likely to impact on their understanding of when and where to seek care for suspected preterm birth. For example, women who knew the risk factors are more likely to understand that level 3 services provide the whole range of medical neonatal intensive care necessary for preterm babies, particularly those babies under 27 weeks. The availability of level 3 services in some rural areas may also make accessing care difficult, particularly for women without transport.

Overall impact on the guideline

There is new evidence which found that QUiPP and QUIDs may be beneficial in predicting preterm birth in women with intact membranes with symptoms of threatened preterm labour as well as asymptomatic high-risk women. The obstetrics committee agreed this was an important finding that needed to be considered. They also explained it would be important to understand what risk factors should trigger use of these prognostic tests. We will therefore update the section on diagnosing preterm labour for women with intact membranes in the NICE guideline. However, screening programmes for low risk asymptomatic women will not be considered as this is the remit of the UK NSC, which currently does not recommend routine screening for preterm birth.

Timing of cord clamping

Reasons for the exceptional review

New evidence has published since the guideline was developed. Feedback from the committee during the 2022 update of the NICE guideline relating to corticosteroids also highlighted cord clamping as an important area for update.

Information considered in this exceptional surveillance review

There has been a recent randomised control trial (RCT; n=1,531 infants, 75% singleton births) comparing clamping the umbilical cord less than 10 seconds after birth versus at least 60 seconds after birth in very preterm infants (less than 30 weeks gestation; Robledo et al. 2022). The primary outcome was death or major disability (cerebral palsy, severe visual loss, deafness requiring a hearing aid or cochlear implants, major language or speech problems, or cognitive delay).

The study found:

- Death or major disability was statistically significantly lower in the delayed cord clamping group versus immediate clamping (risk ratio [RR] 0.83, 95% CI 0.72 to 0.95).
- Death was statistically significantly lower in the delayed cord clamping group versus immediate clamping (RR 0.70, 95% CI 0.52 to 0.95).

- Among those who survived, major disability at 2 years was not statistically significant (RR 0.88, 95% CI 0.74 to 1.04).

The study concluded that clamping the umbilical cord at least 60 seconds after birth reduced the risk of death or major disability by 17% at 2 years, which reflects a 30% reduction in relative mortality with no difference in major disability (cerebral palsy, severe visual loss, deafness requiring a hearing aid or cochlear implants, major language or speech problems, or cognitive delay).

The trial authors noted the following limitations. The staff and parents were not blinded to the intervention and assessments of outcome, but researchers who assessed disability were unaware of randomised groups and death is not prone to observer bias. Cord clamping occurred before 60 seconds in 26% of infants assigned to delayed clamping, which mainly reflected clinical concerns for the baby. The authors also did not record heart rate or time to first breath or to regular breathing.

There is also an ongoing study of delayed cord clamping versus cord milking, but this is not due to complete until June 2024 (PREMOD2FU; NCT03476980). This trial will be added to the NICE event tracker so that its results can be assessed for impact on the guideline when available.

Information considered when developing the guideline

Recommendation 1.14.2, which recommends waiting at least 30 seconds but not longer than 3 minutes to clamp the cord, was developed in 2015 and based on evidence from 1 Cochrane review and 3 RCTs (Rabe et al. 2012, March and de Veciana 2011, Elimian et al. 2014, Ranjit et al. 2015). The committee discussion noted that the majority of the studies defined delayed cord clamping as being between 30 and 60 seconds after birth. In some studies, the cord was clamped after a longer interval (up to 180 seconds after birth). The committee felt that in clinical practice, delayed cord clamping is generally conducted within the 30 to 60 second time limit and although they felt the same benefits might be seen at other timings, they decided that the recommendations should reflect the 30 to 60 second interval.

Given that there was limited evidence available in this area, the committee did not feel confident about making strong recommendations for practice regarding the timing of cord clamping. They noted there is some evidence in favour of delayed cord clamping and no evidence of harm associated with it. The committee identified that an advantage of

delayed cord clamping, not addressed by any of the studies in the evidence base, is that placental transfusion allows newborn infants to continue to receive oxygen by the placenta as long as the cord is pulsing. In babies born with fetal distress, it is believed that the passage of blood in the first minute can contribute to a better resuscitation. Leaving the cord intact does not necessarily preclude other actions being taken for the benefit of the baby simultaneously, for example giving oxygen. Given this, the committee agreed that in most cases, clamping should not take place before 30 seconds after the birth of the baby, and that in situations where speed is of the essence, cord milking should be considered a reasonable alternative to delayed clamping. The committee also noted that in nearly all studies the baby was kept below the level of the placenta in order to help blood flow. However, the committee was aware that a recent trial in term babies had cast doubt on the assumption that the position of the baby in relation to the uterus is important but noted that this has not been tested in preterm babies, so no further conclusions could be made.

Information considered in previous surveillance of this guideline

The 2020 surveillance of the guideline found 2 Cochrane reviews (Meyer et al. 2018, Rabe et al. 2019) and 14 RCTs (El-Naggar et al. 2019, Shirk et al. 2019, Li et al. 2018, Katheria et al. 2019, Tarnow-Mordi et al 2017, Popat et al. 2016, Duley et al. 2018, Salae et al. 2016, Ranjit et al. 2015, Krueger et al. 2015, Rana et al. 2018, Datta et al. 2017, Armstrong-Buisseret et al 2019, Mercer et al. 2016) related to this area. One Cochrane review found that delayed cord clamping (30 to 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 to 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 preterm prelabour rupture of membranes (P-PROM). Intelligence was also received which suggested that delayed cord clamping should have a firmer recommendation within the guideline. However, the guideline was not deemed to be impacted by the new evidence as none of the studies gave a specific time frame for delayed clamping that would be most beneficial for the health of the newborn.

The previous surveillance review had also found 4 studies related to cord milking, see the 2020 surveillance of the guideline for further details.

Multiple Obstetric Guidelines Update Committee feedback

Committee feedback highlighted this as an important area of the guideline, with the potential to improve neonatal outcomes. Stakeholder feedback had raised issues with the minimum timing of cord clamping, which the committee considered a safety risk. As such, this section of the guideline was edited to reflect the committee's experience in this area. However, the committee considered it would be worth updating the evidence reviews related to this section of the guideline to consider both the minimum and maximum time for cord clamping. They noted both the new evidence found during this surveillance review and previous 2020 surveillance and considered there was likely to be sufficient evidence to warrant an update.

Other relevant NICE guidance

NICE's quality standard on preterm labour and birth does not cover timing of cord clamping.

The NICE guideline on intrapartum care for healthy women and babies provides advice on timing of cord clamping for term babies but not preterm babies. The guideline is currently being updated and is due to publish in December 2022. The scope of the update does not include preterm labour.

Equalities

No equalities issues were identified during the surveillance process.

Overall impact on the guideline

There is new evidence which found that clamping the umbilical cord at least 60 seconds after birth reduced the risk of death or major disability at 2 years. Previous surveillance and evidence considered during guideline development also indicated a body of evidence in favour of delayed cord clamping, but this was unable to identify a specific time for cord clamping. The obstetrics committee agreed this was an important finding that needed to be considered. As such, the section on cord clamping will be updated.

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