UK National Screening Committee

UK National Screening Committee (UK NSC)

Screening for preterm birth in asymptomatic, low-risk women

Date: 28 October 2020

Contents

Aim

1. To ask the UK National Screening Committee (UK NSC) to make a recommendation, based on the evidence presented in this document, whether or not screening for preterm birth in asymptomatic, low-risk women meets the UK NSC criteria for a systematic population screening programme.

Current Recommendation

2. The UK National Screening Committee (NSC) does not currently recommend systematic population screening of asymptomatic low risk pregnant women for risk of preterm labour and birth. This recommendation was made on the basis of the last evidence review on the topic, published in 2015.

3. Prior to the last evidence review, a 2009 Health Technology Assessment (HTA) had investigated the accuracy of screening tests to predict risk of preterm labour and effectiveness of prophylactic/therapeutic interventions for asymptomatic women. Optimal LR+ (where a positive screening result would mean the condition is likely) was found for fetal fibronectin (fFN) testing and cervical length (CL) measurement, while optimal LR- (where a negative result would give reassurance that the condition is unlikely) was found for home monitoring of uterine contractions and amniotic fluid C-reactive protein (CRP) measurement. There was a trade-off between sensitivity and specificity, and none of the tests demonstrated a high LR+ in combination with a low LR-. Regarding intervention to prevent preterm birth prophylactic treatment, the HTA generally found poor quality of evidence, but potential for vaginal progesterone, cervical cerclage and antibiotics for bacterial vaginosis to reduce risk of preterm birth.

4. The 2015 UK NSC evidence review looked for evidence published up to 2013. Most evidence was available on CL measurement, but this was not found to be a reliable enough screening test. Questions remained over the timing of the test, and the lack of a standardised 'normal' measure making it difficult to establish what is 'abnormal'. The review also found that there was very limited evidence on screening for bacterial vaginosis, and absent evidence on fFN testing, detection of uterine contractions or amniotic fluid CRP measurement. Regarding treatment, the 2015 review found some trials indicating that vaginal progesterone and cervical cerclage may reduce risk in low-/mixed-risk populations, but the overall body of evidence was small.

Evidence Summary

5. The 2020 evidence summary was undertaken by Bazian, in accordance with the triennial review process.

6. The 2020 evidence summary addresses questions relating to:

    a. The diagnostic measurement of the following for CL measurement; cervicovaginal fFN; tests for bacterial vaginosis; and uterine contraction (by home monitoring device) to predict preterm labour, birth or associated morbidity/mortality: (Criteria 4 and 5)

    b. The effectiveness of available treatments such as progesterone; cervical cerclage; cervical pessary; antibiotics for bacterial vaginosis; and probiotics, for the prevention of preterm labour, birth or associated morbidity/mortality: (Criterion 9)

7. The conclusion of the 2020 evidence summary is that the volume, quality and direction of evidence published since January 2013 and September 2019 is not sufficient to change the current UK NSC recommendation on systematic screening for preterm birth in asymptomatic, low-risk women. This recommendation is made for the following reasons:

    a. Screening tests:

        - Similar to the last UK NSC evidence review and 2009 HTA, this evidence indicates that fFN testing and CL measurement are not useful to predict preterm birth in asymptomatic low-risk women. A balance of high sensitivity and specificity is not achieved. Testing at different cut-offs and/or gestations to achieve optimal (though still inadequate) sensitivity results in poorer specificity with the majority of screen-positives being false. This evidence update did not identify studies looking at screening for bacterial vaginosis or home monitoring for uterine contractions as screening tests.

- **Criteria 4 is not met**

b. Interventions:

- Vaginal progesterone: Vaginal progesterone was associated with a modest reduction in the risk of preterm birth at all gestations <36 weeks. There was no effect on overall preterm birth <37 weeks. There was also limited assessment of spontaneous preterm birth specifically (excluding medically-indicated). These findings on progesterone are essentially unchanged from the 2015 UK NSC evidence review, which was based on most of the same evidence.

- Cervical pessary: It is uncertain whether cervical pessary may benefit women with short cervix. Only a single trial was available at the 2015 UK NSC evidence review (which found a benefit). Four RCTs have since been published comparing with expectant management and one RCT comparing pessary with progesterone. The results are conflicting, with some finding a benefit of pessary and others not. The effect on risk of associated neonatal morbidity or mortality was also inconsistent across studies. However, even the trials finding a benefit showed little consistency in their findings or study populations, some of which included low-risk women only, while others included those with existing risk factors for preterm birth. All trials were, however, unanimous in finding that pessary increased reports of vaginal discharge, though the prevalence and risk increase was again inconsistent across studies. There was minimal other assessment of tolerability or acceptability which may be beneficial.

- Cervical cerclage: As with the conclusions of the 2015 UK NSC review, the latest systematic review on cervical cerclage found that it had no effect on the risk of preterm birth or associated neonatal morbidity in otherwise low-risk women with short cervix. There was also no effect on any neonatal outcomes reported. Trials to date have also performed limited assessment of maternal adverse effects or acceptability of cerclage.

- Bacterial vaginosis: One large, high-quality trial in otherwise low-risk women with bacterial vaginosis found that oral clindamycin (single or triple course) had no effect on risk of preterm birth or associated neonatal morbidity. It did, however, increase the risk of gastrointestinal adverse effects, though the prevalence of side effects was still low at 3% among treated women. There was no evidence available on the standard UK treatment of oral metronidazole. This evidence is consistent with evidence

included in the 2015 UK NSC evidence review, which found that antibiotics (any) for bacterial vaginosis had no effect on preterm birth risk. There were no studies on probiotics.

- None of the identified evidence on any intervention assessed whether treating women with short cervix or bacterial vaginosis who went on to have full term birth (that is false positives) was associated with any negative effects, such as psychological outcomes.

♦ **Criterion 9 not met**

Consultation

8. A three month consultation was hosted on the UK NSC website. Direct emails were sent to 14 stakeholder organisations. *Annex A*

9. Two consultation responses were received. One by the National Guideline Alliance, on behalf of the NICE Antenatal care guideline committee to indicate that it had noted the UK NSC's recommendations and reviews and had no comments. A second set of comments by the British Maternal and Fetal Medicine Society (BMFM) which supported the overall recommendation that routine screening for preterm labour in asymptomatic women but noted that the society strongly believes and recommend that where there is an incidental finding of short cervix in these women, appropriate interventions should be offered. *Annex B*

    a. Also, the BMFM provided comments on some technical points which were evaluated by the reviewers, such as:

        - Exclusion of studies looking at evaluating quantitative fFN and combining this with CL

Response: this evidence summary reviewed the evidence published since 2013 on screening tests of cervical length (CL) measure, fFN, tests for bacterial vaginosis and uterine contraction. Tests could be assessed alone or in combination, using any cut-off, and performed at any gestational age, on single or multiple occasions and fFN may have been qualitative or quantitative. The only restriction to inclusion was to study population, who were required to be asymptomatic, low-risk women. The identified US cohort by Esplin et al assessed both CL and fFN on the same cohort. The study publication primarily assessed their accuracy as isolated tests, but did report that the combination of both CL and fFN measures did not improve upon CL alone (giving the same area under the curve of 0.67, as stated in the review).

- Adding reference to the NICE guidance for Antenatal Care in the bacterial vaginosis section and Saving Babies Lives Care

Bundle version 2, Appendix F in relation to in incidental finding of short cervix.

Response: The NICE recommendation on MSU was noted when reviewing the NICE guidance for this rapid evidence review. However, the NICE recommendations on testing for UTI were not stated as it was not being included as one of the screening tests scoped for assessment. The 4 tests selected (CL, fFN, bacterial vaginosis testing, and home monitoring for uterine contractions) were informed by the prior 2015 NSC external evidence review, which was previously informed by the 2009 Honest et al HTA. As noted on page 14, 'Future studies may also wish to explore whether other screening tests used as an alternative to, or in combination with CL or fFN testing (for example, measuring cervical consistency or cervical incompetence) may have potential as screening tests and demonstrate improved test performance.

In relation to the reference to Appendix F of Saving Babies Lives Care Bundle version 2 the review outlines verbatim the recommendations in NICE 2015 guidance on selective or targeted screening by CL for asymptomatic women with existing risk factors for preterm birth, and the indications for prophylactic progesterone or cervical cerclage. Appendix F appears in agreement with this recommendation, this appendix tabulates risk assessment and management for at-risk women giving specific recommendations. Overall the appendix does not seem to be giving clear recommendations covering the use of screening/surveillance for women without existing risk factors.

Recommendation

10. The Committee is asked to approve the following recommendation:

Systematic population screening programme for preterm birth in asymptomatic, low-risk women is not recommended in the UK.

Criteria (only include criteria included in the review)	Met/Not Met
Section 1 - Criteria for appraising the viability, effectiveness and appropriateness of a screening programme	
The Test	
4. There should be a simple, safe, precise and validated screening test.	**Not Met**
The Intervention	
9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.	**Not Met**

Annex A

List of organisations contacted:

1) Association for Improvements in the Maternity Services
2) The Birth Trauma Association
3) BLISS
4) British Association of Perinatal Medicine
5) British Maternal & Fetal Medicine Society
6) Faculty of Public Health
7) National Childbirth Trust
8) PHE ANNB Screening Programmes
9) Royal College of General Practitioners
10) Royal College of Midwives
11) Royal College of Obstetricians and Gynaecologists
12) Royal College of Physicians
13) Royal College of Physicians and Surgeons of Glasgow
14) Royal College of Physicians of Edinburgh

UK National Screening Committee

Annex B

Stakeholder comments:

Name:	(Maija Kallioinen on behalf of) NICE Antenatal care guideline committee	**Email address:**	xxxx xxxx
Organisation (if appropriate):	National Guideline Alliance, part of RCOG (guideline developer)		
Role:	Guideline lead		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes ~~**No**~~

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
General	General	The NICE Antenatal care guideline committee has noted these recommendations and reviews and have no comments.

Please return to the UK NSC Evidence Team at screening.evidence@nhs.net by 23 October 2020

NSC UK National Screening Committee

UK National Screening Committee

Screening for preterm birth in asymptomatic, low-risk women
Consultation comments pro-forma

Name:	Dr Surabhi Nanda (in consultation with Preterm Birth Experts across UK)	**Email address:**	XXXX XXXX
Organisation (if appropriate):	British Maternal and Fetal Medicine Society		
Role:	**Fetal Medicine Representative**		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
72 Second Paragraph	**Fetal fibronectin (fFN) measurement**	The recommendation should not be limited solely to qualitative fibronectin. Future screening should consider evaluating the established quantitative Fetal fibronectin and combining this with cervical length. These could be incorporated into decision aid tools and other biomarkers

		theories about the role of infection in adverse pregnancy outcomes, but again, the confidence in the effect is limited given the low certainty of the evidence." We agree with exclusion of MSU as a screening test, but we recommend that it is worth referencing to the NICE evaluation in the document for completeness.
Overall Comments from Preterm Birth Experts		We support the overall recommendation that routine screening for preterm labour in asymptomatic women, but we strongly believe and recommend that where there is an incidental finding of short cervix in these women, appropriate interventions should be offered. The screening would improve with the use of quantitative fibronectin (instead of qualitative), and more so with addition of cervical length.

Please return to the UK NSC Evidence Team at screening.evidence@nhs.net by 23 October 2020