Paper 11_UK NSC_27022019

UK National Screening Committee

NIPT systematic review:
Microarray based NIPT
NIPT in twins and higher order multiple pregnancies

27 February 2019

Aim

1. To ask the UK National Screening Committee (UK NSC) to note two modifications to the Fetal Anomaly Screening Programme (FASP) evaluative roll out of non-invasive prenatal testing (NIPT). The modifications are to include:

- microarray based NIPT as an option for NHS Trusts engaged in the evaluative roll out
- twins, and higher order multiple pregnancies, in the evaluative roll out

Background

2. The UK NSC recommended the use of NIPT in the FASP screening pathway for T21, T18 and T13 in January 2016. The recommendation was made on the basis of a systematic review of test accuracy and estimate of cost consequences undertaken by Warwick University in 2015.

It was recommended that:

- the test should be offered contingently, on the basis of a combined test threshold ≥1:150
- women in this group should be recalled following the combined test result for further discussion of the range of options available at that point, and that
- the strategy should be explored in an evaluative roll out

This strategy was considered an ethical and proportionate use of NIPT by the Nuffield Council on Bioethics following a process of stakeholder engagement. The evaluative roll out is planned to last for three years after which the UK NSC will be asked to make a recommendation on whether NIPT should be included in the FASP trisomy screening pathway. Preparations for the evaluative roll out are currently ongoing.

Microarray based NIPT

3. The search strategy for the 2015 Warwick University systematic review was directed towards any type of NIPT. All the included approaches to NIPT relied on next generation sequencing to quantify cell free DNA (cfDNA).

During the preparation for the evaluative roll out UK NSC advice was sought on NIPT based on a different, microarray, approach to DNA quantitation. One study of this approach had been considered for inclusion in the 2015 systematic review. However, although the index test met the review's inclusion criteria, the study was excluded because of uneven application of the reference standard.

A systematic review of microarray based NIPT for T21, T18 and T13 was commissioned from Warwick University in 2018 which has been circulated with the papers for this meeting. This reports

test values which are consistent with sequencing based NIPT but highlights the limited evidence base from which the estimates are drawn.

The document development process included discussion on the way in which microarray based NIPT should be characterised in relation to sequencing based approaches. This involved correspondence with Roche / Ariosa, direct discussion with the review team's independent laboratory adviser and direct discussion with the FASP laboratory adviser. The consensus was that, from the perspective of an evaluation of test accuracy, this change to the quantitation method represented a relatively minor modification to the testing process. This is an important consideration in terms of both the review's rationale for recommending the use of microarray based NIPT and the action required of the UK NSC.

A further point was discussed at the UK NSC's Fetal, Maternal and Child Health Reference Group (FMCH). It was noted that a patent case had distinguished between microarray and sequencing approaches as significantly different technologies. However, legal advice from two sources had confirmed that the judgement in the patent case did not prevent microarray and sequencing technologies being grouped together in a systematic review of test accuracy.

Action

4. The UK NSC is asked to note:

- that microarray based NIPT for T21, T18 and T13 will be included as an option for Trusts engaged in the evaluative roll out of contingent testing
- that the work on microarray based NIPT draws attention to NIPT as a rapidly changing field and that the Warwick University review has made recommendations which might help address this.

NIPT in twins and higher order multiple pregnancies

5. The previous Warwick University review found a very low volume of studies reporting the performance of NIPT for T21, T18 and T13 in twins and higher order multiple pregnancies. The studies were evaluated as a subgroup analysis of the main meta-analysis. However, the volume of studies was a key limiting factor in the review. The use of NIPT in twins was not recommended because of insufficient evidence. To enable reconsideration of this issue, Warwick University were commissioned to provide an updated analysis of the evidence.

In terms of performance values for T21, T18 and T13, the 2018 updated review estimates that the sensitivity of NIPT is lower in twins than in singletons, but that the specificity is comparable. However, the review also highlights the limitations of the evidence base which persist despite an increase in the volume of studies. Due to these limitations, the review concludes that test performance in twins is uncertain.

Discussion at the recent FMCH meeting considered that, despite the review's uncertainty, NIPT should be offered to women with twin and higher order multiple pregnancies in the evaluative roll out of NIPT. The Reference Group also considered that FASP should be asked to develop a statement in this area to guide practice.

A number of factors need to be considered:

i. the evaluative roll out would provide an opportunity to monitor and report on the use of the test in this small but important subgroup of the pregnant population. Because the evaluative roll out is based on a recall strategy there would be an opportunity for an appropriate level of discussion of the issues relating to these clinically complex pregnancies;

ii. the limitations associated with the evidence base relating to NIPT in twins are shared by those relating to the combined test which is currently recommended for use in twins by the UK NSC and NICE. For example a 2014 systematic review exploring the performance of the combined test for T21 was only able to include five studies with a total of 12, 794 twin fetuses (6,397 pregnancies) and 69 cases of T21. All five studies used different thresholds to define screen positive and negative and none used the currently recommended cut off used in UK practice. The second trimester quadruple test is even less well served by primary studies;

iii. based on what is reported, the test values for NIPT appear generally higher than both the combined test and the quadruple test. For example the updated Warwick University review estimated NIPT point estimates of 97.5% and 99.93% respectively for sensitivity and specificity for T21. Depending on zygosity, the sensitivity of the quadruple test has been estimated to be between 60% and 80% and the specificity between 90% and 97%. The higher values were estimated in the minority of monozygotic twins. Similarly, the largest study in the above mentioned systematic review of combined test performance for T21 in twins reported sensitivity and specificity values of 90% and 94.1% in dizygotic twins. In monozygotic twins the values were 100% and 95.4% respectively;

iv. previous recommendations in twins, for example on the use of the second trimester quadruple test, have been based on a limited level of expert stakeholder engagement rather than public consultation which is UK NSC practice for major modifications.

Action

6. The UK NSC is asked to note the FASP flowchart adding twins to the planned algorithm for the roll out, which is included in the meeting paper bundle for consideration, and that FASP will develop a supporting statement to accompany the flowchart. The experience of this approach will be reported back to UK NSC on completion of the evaluation.