Genetic testing for fetal chromosome abnormalities

A US multicentre observational study found that non-invasive genetic prenatal testing was more accurate than standard prenatal screening at identifying fetuses with chromosome abnormalities.

Overview: Aneuploid chromosome disorders occur when a developing fetus has too many or too few chromosomes in its cells. Down’s syndrome is characterised by 3 instead of 2 copies of chromosome 21 (trisomy 21), and Edwards’ syndrome by 1 extra copy of chromosome 18 (trisomy 18).

Pregnant women are screened for Down’s syndrome with a blood test to measure the levels of several hormones and an ultrasound scan to measure the thickness of the nuchal translucency (a pocket of fluid) at the back of the fetus’s neck (NHS Choices 2013). Edwards’ syndrome is usually detected at the 18–20 week ultrasound scan or at the test for Down’s syndrome (NHS Choices 2014). If these tests indicate a high risk, definitive diagnosis with genetic tests on invasively collected samples (chorionic villus sampling or amniocentesis) is offered.

An alternative approach to screening for these abnormalities is sequencing cell-free DNA (cfDNA) testing. cfDNA is fetal DNA that circulates freely in the maternal blood stream. Several studies have suggested that cfDNA testing can accurately detect fetal chromosome abnormalities in high-risk women (Palomaki et al. 2012, Sehnert et al. 2011). However, the effectiveness of this test in a general obstetric population is not yet clear.

Current advice: NICE guidance on antenatal care recommends that all pregnant women should be offered screening for Down’s syndrome between 11 weeks 0 days and 13 weeks 6 days gestation. The screen for Down’s syndrome should comprise the ‘combined test’: nuchal translucency screening and biochemical tests for beta-human chorionic gonadotrophin and pregnancy-associated plasma protein-A.

For women who book screening later in pregnancy, the most clinically and cost-effective serum screening test should be offered between 15 weeks 0 days and 20 weeks 0 days. Either the triple test (human chorionic gonadotrophin, unconjugated estriol and alpha-fetoprotein) or quadruple test (as per triple test plus inhibin A) should be offered.

The NICE Pathway on antenatal care brings together all related NICE guidance and associated products on the subject in a set of interactive topic-based diagrams.
New evidence: Bianchi et al. (2014) conducted a multicentre observational study comparing cfDNA prenatal testing against standard prenatal screening for identifying aneuploid chromosome disorders in a general obstetric population.

Women with singleton pregnancies in their first or second trimester were recruited from 21 medical centres in 14 US states. All participants had planned to undergo or had completed standard prenatal screening tests, such as human chorionic gonadotrophin and unconjugated estriol (with or without first-trimester measurement of nuchal translucency). Blood samples were collected at enrolment and analysed using massively parallel sequencing of cfDNA. The data from the standard prenatal tests and the cfDNA tests were analysed by blinded study personnel for trisomy 21 (Down’s syndrome) and trisomy 18 (Edwards’ syndrome). All patients were followed up for pregnancy outcomes and categorised as affected or not affected for trisomies 21 and 18.

A total of 2052 women were enrolled; 1909 (93%) women were screened for trisomy 21 and 1905 (93%) for trisomy 18. cfDNA testing returned fewer false positives than standard prenatal screening for trisomy 21 (0.3% versus 3.6%, p<0.001) and trisomy 18 (0.2% versus 0.6%, p=0.03). When the data for trisomy 21 and trisomy 18 were combined, the false positive rates were 0.5% for cfDNA screening and 4.2% for standard prenatal screening. This difference means that 89% fewer women would have required an invasive procedure to confirm a positive screening result if all pregnant women had undergone cfDNA testing as the primary screening method, and all women with positive results had undergone an invasive procedure.

Limitations of this evidence include the relatively small number of true positive results (5 cases of trisomy 21 and 2 cases of trisomy 18), which limited the authors’ ability to determine test sensitivity. In addition, pregnancy outcomes were determined mainly by clinical examinations, and nearly 1% of cfDNA tests did not provide results. The study was supported by Illumina, the company that provided the cfDNA testing.

Commentary: “This study adds further evidence to suggest that the performance of non-invasive prenatal testing for aneuploidy is likely to be good in all women as well as in the high-risk group. However, in addition to the relatively small sample size, a major drawback of this study is the fact that Downs’ syndrome screening and cfDNA testing was not done at the same time, with non-invasive prenatal testing being done later in pregnancy and often in the third trimester.

“In the UK, the target gestation for Down’s syndrome screening is 11–13 weeks (that is, in the first trimester). Non-invasive prenatal testing for aneuploidy can be done from 10–11 weeks, at which point the amount of cfDNA is usually sufficient. Data on the performance of non-invasive prenatal testing in a large number of ‘all risk’ women at this stage of pregnancy is what is really required. In addition, we know that the proportion of cfDNA increases with gestation, and thus performance may be improved at later gestations.

“As it stands, this study alone does not deliver sufficient evidence to influence current practice in the UK, where we need to understand the overall costs and benefits of cfDNA testing. This will require knowledge of any potential influence of cfDNA testing on overall uptake of Down’s syndrome screening and any subsequent invasive diagnostic testing, as well as test performance in all risk women in early pregnancy.” – Professor Lyn Chitty, GOSHCC Professor of Genetics and Fetal Medicine, UCL Institute of Child Health, Great Ormond Street Hospital NHS Foundation Trust and University College London Hospitals NHS Foundation Trust, London

Study sponsorship: Illumina.
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