Antenatal screening for Down's syndrome

First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS)

NJ Wald[1*]
J Walters[1]
C Rodeck[2]
L Chitty[2]
AK Hackshaw[1]
AM Mackinson[1,2]

[1] Department of Environmental and Preventive Medicine, Wolfson Institute of Preventive Medicine, Bart's and the London School of Medicine and Dentistry, UK
[2] Department of Obstetrics and Gynaecology, University College and Middlesex School of Medicine, University College London, UK

[*] Corresponding author

Executive summary

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Executive summary

Objectives

To identify the most effective, safe and cost-effective method of antenatal screening for Down's syndrome using nuchal translucency (NT), maternal serum and urine markers in the first and second trimesters of pregnancy, and maternal age in various combinations.

Design

A prospective study of women who booked for their antenatal care at about 8–14 weeks of gestation, with follow-up to identify pregnancies with Down's syndrome ascertained through second trimester screening or at birth.

Setting

Twenty-five maternity units (24 in the UK and one in Austria) offering second trimester Down's syndrome serum screening that agreed to collect observational data in the first trimester.

Participants

The results were based on 47,053 singleton pregnancies, including 101 pregnancies with Down's syndrome.

Measurements and tests

NT measurements were included if obtained between 9 and 13 weeks of pregnancy; serum and urine samples were also taken and stored. Another pair of serum and urine samples was collected in the second trimester and included if obtained between 14 and 20 weeks. Urine and serum samples from each affected pregnancy and five matched controls were tested for:

serum:

- alphafetoprotein (AFP)
- total human chorionic gonadotrophin (hCG)
- unconjugated oestriol (uE_3)
- pregnancy associated plasma protein A (PAPP-A)
- free β-hCG
- dimeric inhibin-A.

urine:

- invasive trophoblast antigen (ITA)
- β-core fragment
- total hCG
- free β-hCG.

The matching criteria were gestation (using an ultrasound crown–rump length or biparietal diameter measurement), duration of storage, and centre. Screening performance of the individual markers and combinations of markers together with maternal age was assessed using standard methods. In addition pairs of first and second trimester serum samples from 600 controls were tested to secure a larger set in which screening performance could be determined using distribution parameters based on dates (time since first day of the last menstrual period).

Main outcome measures

The following were determined for different combinations of markers:

- efficacy (by assessing screening performance, focusing on the false-positive rate (FPR) for an 85% detection rate (DR))
- safety (focusing on the number of fetal losses due to amniocentesis (or chorionic villus sampling) in 100,000 women screened)
- cost-effectiveness (focusing on the cost of screening 100,000 women and the cost per Down's syndrome pregnancy diagnosed).

Results

Efficacy (screening performance)

The false-positive rates for an 85% detection rate for the main screening tests are shown in the following table, in decreasing order of screening performance:

Test (all include maternal age)	Measurements	FPR for 85% DR (%)	95% confidence interval (%)
Integrated test	NT and PAPP-A at 10 completed weeks AFP, uE_3, free β-hCG and inhibin-A at 14–20 completed weeks	1.2 (1.3[a])	1.0 to 1.4 (1.2–1.4[a])
Serum integrated test	Integrated test without NT. PAPP-A at 10 completed weeks	2.7 (4.9[a])	2.4 to 3.0 (4.4–5.4[a])
Combined test	NT, free β-hCG and PAPP-A at 10 completed weeks	6.1 (6.0[a])	5.6 to 6.5 (5.5 to 6.5[a])
Quadruple test	AFP, uE_3, free β-hCG, inhibin-A at 14–20 completed weeks	6.2	5.8 to 6.6
Triple test	AFP, uE_3, free β-hCG at 14–20 completed weeks	9.3	8.8 to 9.8
Double test	AFP and free β-hCG at 14–20 completed weeks	13.1	12.5 to 13.7
NT measurement	NT at 12–13 completed weeks	20.0	18.6 to 21.4

[a] *NT and/or serum measurements at 12 completed weeks of pregnancy*

With the serum integrated test, 10 weeks is the preferred time in pregnancy for the PAPP-A measurement. For the integrated test and the combined test, the timing of the measurement of the first trimester markers is less critical.

Safety

The lower false-positive rate with the integrated test compared with other tests means that at an 85% detection rate there would be nine diagnostic procedure-related unaffected fetal losses per 100,000 women screened compared with 44 using the combined test or 45 with the quadruple test.

Cost-effectiveness

Screening using the integrated test is less costly than might be expected because the extra screening costs tend to be offset by savings in the cost of diagnosis arising from the low false-positive rate. It was estimated that to achieve an 85% detection rate the cost to the UK NHS would be £15,300 per Down's syndrome pregnancy detected. The corresponding cost using the second trimester quadruple test would be £16,800 and using the first trimester combined test it would be £19,000.

Conclusions

Implications for healthcare

The results showed that screening performance in the first trimester of pregnancy was virtually the same as that in the second trimester, and in either it was much less effective than integrating screening measurements from both trimesters into a single test. In applying these results to screening practice several conclusions can be drawn. The following tests offer the most effective and safe method of screening:

- overall: the integrated test
- if an NT measurement is not available: the serum integrated test
- for women who do not attend for antenatal care until the second trimester of pregnancy: the quadruple test
- for women who choose to have a screening test in the first trimester: the combined test.

At a constant detection rate, the cost-effectiveness of these four tests is broadly similar, any extra screening costs tending to be offset by fewer diagnostic costs. The evidence presented in this report does not support retaining the double test, the triple test, or NT measurements on their own (with or without maternal age) because each would lead to many more women having invasive diagnostic tests, without increasing the proportion of Down's syndrome pregnancies detected.

Publication

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NHS R&D HTA Programme

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Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme continues to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

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The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

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The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

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