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Review

Executive summary

Antenatal screening for Down's syndrome

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Health Technology Assessment
NHS R&D HTA Programme

Executive summary

Background

Over the past 15 years there have been notable advances in antenatal screening for Down's syndrome. First serum α-fetoprotein (AFP) and later human chorionic gonadotrophin (hCG) and unconjugated oestriol (uE_3), together with maternal age, have been widely used in screening for Down's syndrome, with a detection rate of about 70% for a 5% false-positive rate. More recently inhibin A has been added as a fourth serum marker.

Objectives

- To summarise the expected performance of serum and ultrasound makers for Down's syndrome.
- To evaluate the effectiveness, safety and cost-effectiveness of the different methods of antenatal screening and diagnosis.
- To review current screening practice for Down's syndrome in Britain.
- To specify the most appropriate method of Down's syndrome screening and identify areas for further research.

Methods

The literature on antenatal screening for Down's syndrome was reviewed.

Results

Principles of antenatal screening for Down's syndrome

Methods of screening need to be fully evaluated before being introduced into routine clinical practice. This includes choosing markers for which there is sufficient scientific evidence of efficacy, quantifying performance and establishing methods of monitoring performance. Screening services need to be well integrated and managed.

Serum markers at 15–22 weeks of pregnancy

Screening performance varies according to the choice of markers used and whether ultrasound is used to estimate gestational age. When the latter is used in combination with maternal age, the detection rate for a 5% false-positive rate is estimated to be 59% for the double test (AFP and hCG), 69% for the triple test (AFP, hCG, uE_3) and 76% for the quadruple test (AFP, hCG, uE_3, inhibin A).

Urinary markers and foetal cells in maternal blood

Urinary β-core hCG has been shown to be raised in Down's syndrome pregnancies. Urinary total oestriol and free β-hCG may also be of value but it would be premature to introduce them into screening practice.

Foetal cells can be identified in maternal circulation and techniques such as fluorescent *in situ* hybridisation can be used to identify Down's syndrome. However, this does not have the performance, simplicity or economy needed to replace existing methods.

Demonstration projects

Several demonstration projects using triple and double tests have been conducted, in which screening uptake was about 80% with screen positive rates of about 5–6%. Approximately 80% of women with positive results had an invasive diagnostic test, and about 90% of those found to have a pregnancy with Down's syndrome chose to have a termination.

Ultrasound markers at 15–22 weeks of pregnancy

There are a number of ultrasound markers of Down's syndrome at 15–22 weeks, of which nuchal fold thickness is the most discriminatory on its own, but not discriminatory enough for screening. The markers could be used in combination with the serum markers but no studies assessing this have been completed to date.

Serum and ultrasound screening at 10–14 weeks of pregnancy

The serum markers pregnancy-associated plasma protein-A (PAPP-A) and free β-hCG, combined with maternal age have an estimated detection rate of 62% for a 5% false-positive rate.

Nuchal translucency is a useful marker of Down's syndrome. There are differing estimates of screening performance and some are subject to bias. Further studies are needed to quantify the performance of this test alone and in combination with biochemical markers. There is also a need to compare the performance of such screening with screening at 15–22 weeks to determine which has the greater efficacy and which is the most cost-effective.

Methods of antenatal diagnosis

The standard method of antenatal diagnosis is amniocentesis at about 15 weeks of pregnancy followed by karyotyping of cultured cells from the

amniotic fluid. The excess foetal loss attributed to amniocentesis is approximately 0.9%.

Before 15 weeks of pregnancy, transabdominal chorionic villus sampling (CVS), although less accurate than mid-trimester amniocentesis, seems to be the diagnostic method of choice.

Cost-effectiveness of serum screening

In general, serum screening is more cost-effective than screening based on maternal age alone at detection rates of about 50% or greater. As the number of screening markers increases, the cost per pregnancy screened increases but, if an extra marker is sufficiently discriminatory, the cost per Down's syndrome birth avoided may decline. For example, the estimated cost per pregnancy screened and the cost per Down's syndrome birth avoided is: £8.90 and £25,600 for the double test; £9.60 and £22,700 for the triple test, and £11.60 and £23,100 for the quadruple test.

Safety

Screening leads to women having an invasive diagnostic procedure that can result in foetal loss. As screening performance improves, the number of unaffected foetal losses per Down's syndrome birth avoided declines by 24%, from 0.59 (double test) to 0.45 (quadruple test).

Psychosocial aspects

Several studies have shown that the anxiety associated with screening is short lived and can be minimised by the provision of clear and simple information before screening, together with counselling for women with positive results.

Health professionals often do not have adequate knowledge of serum screening and therefore have difficulty in reporting screening results to women.

Quality assurance and monitoring

Quality assurance and monitoring should be an integral part of a screening service. It is currently not possible to tell whether screening centres undertake epidemiological monitoring and service audit satisfactorily.

Current screening practice

Serum screening for Down's syndrome has been widely introduced into practice and has enabled a substantially higher proportion of pregnancies to be identified without materially increasing the proportion of women requiring an invasive diagnostic procedure. Although the screening approach, using multiple markers concurrently, was novel, it has been introduced reasonably effectively using statistical methodology that has been accepted and empirically validated. There is also an active research programme being conducted alongside the clinical service. In spite of the achievements, a number of problems were identified – incomplete coverage of screening, inconsistent practice and a lack of overall direction. The introduction of alternative methods of screening has led to multiple stepwise screening in an uncoordinated manner which is confusing to staff and patients. Some research findings have been introduced into practice before being fully evaluated.

Conclusions

Implications for policy

The evidence indicates that screening using the triple test with maternal age is more effective, safe and cost-effective than the double test. The performance of the quadruple test including inhibin A appears somewhat better.

There is substantial variation in screening services for Down's syndrome throughout the UK. This needs to be rectified. The authors recommend that policy makers should ensure overall direction, with a written policy, specified funding and line responsibility, while preserving local commitment.

The authors suggest the establishment of local screening units (covering 15,000 births per year – about three to four maternity units) which would have full responsibility for their service. These would each have a dedicated screening coordinator who would work together with a screening consultant.

Inequity of access to the service and the current multiple, stepwise uncoordinated screening of Down's syndrome should be addressed. The tendency to offer more than one method of screening to the same women at different stages of pregnancy should be avoided.

There is evidence that better staff education and training is needed so that patients are adequately informed about screening and its implications.

Implications for research

Serum markers and nuchal translucency have been shown to be effective in screening for Down's syndrome in the first trimester. However, this needs further evaluation in carefully monitored pilot screening programmes before a decision is made to introduce first trimester screening into general routine practice.

Other research areas include the study of urinary markers and foetal cells in maternal blood.

Publication

Wald NJ, Kennard A, Hackshaw A, McGuire A. Antenatal screening for Down's syndrome. *Health Technol Assessment* 1998; **2**(1).

NHS R&D HTA Programme

The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Population Screening Panel.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members 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 England, policy options in this area are to be considered by the National Screening Committee, chaired by the Chief Medical Officer, who will take into account the views expressed here, further available evidence and other relevant considerations.

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