

Prenatal Screening for Down's Syndrome

Guidelines	Level of Evidence	References
Early in pregnancy, all women should receive appropriate written information concerning available screening (including potential risks and benefits, the difference between screening and diagnostic testing and possible costs to women).	II IV	15 4-6
The offer of screening for Down's Syndrome should be made available to all pregnant women, irrespective of age.	III IV	16 3
Pre-screening counselling must be given by appropriately trained staff and should be specific to the age of each woman.	III IV	8,9 11
If after counselling women choose to proceed with screening tests for Down's Syndrome;		
i. Screening should include accurate pregnancy dating by ultrasound, preferably in the first trimester.	IV	3
ii. Screening should be by either second trimester biochemistry or by nuchal translucency (alone or in combination with first or second trimester biochemistry).	III	12-14
iii. Women should be notified of their screening result, irrespective of the risk, in a format that they understand.	II	23
iv. Women who have an increased risk of Down's Syndrome should be offered further counselling and diagnostic testing within 72 hours or as soon as possible.	IV	3
Good Practice Notes		
The quality of counselling is of primary importance in any screening program. Education programs should be introduced for all practitioners and include training in techniques of non-directive counselling. If a woman chooses screening she should be offered single-step screening rather than sequential testing.	III	12
Nuchal translucency screening should be performed at 11-14 weeks gestation by suitably trained operators and the risks derived in conjunction with gestation and maternal age.	IV	3

Aim

The aim of these guidelines is to assist midwives and doctors to counsel women enabling them to make informed choices regarding prenatal testing for Down's Syndrome.

Evidence

Down's Syndrome is the single most common cause of severe intellectual disability in our community, with a birth prevalence of approximately one in 650 births in Victoria^{1,2}. The major risk factor for having a baby with Down's Syndrome is advanced maternal age. Accordingly, as the average age of the pregnant population continues to increase, so does the birth prevalence of Down's Syndrome. The only primary prevention for Down's Syndrome is to encourage women to have their children at a younger age. There are features of Down's Syndrome pregnancies that allow their detection in early pregnancy through screening and diagnosis.

Such testing is voluntary and offered to give information to the woman, and her partner, about her pregnancy on which a decision can be based concerning further care of that pregnancy³. However, there is considerable evidence that the general population has a poor understanding of both Down's Syndrome itself and the available tests for Down's Syndrome^{4,5}. There is also evidence from the UK (Level IV) that midwives and doctors working in an antenatal setting may have a limited knowledge about screening,^{6,7} highlighting the need for professional development in this area. This is particularly important because many women find screening a negative experience^{8,9}, often because of a poor understanding of the issues and because of inadequate or inappropriate initial counselling. Such studies indicate harm may be done if counselling is only undertaken after testing. Prior to the offer of any testing therefore, women should be given accurate and balanced information about Down's Syndrome and the available tests. The provision of such information should be seen as fundamental to quality antenatal care.³ The midwives and doctors who offer prenatal testing should be conversant with the issues and with appropriate counselling techniques.

For women who wish to proceed with Down's Syndrome testing in pregnancy there are two types of test: screening tests and diagnostic tests. There are key features of these tests that differ.

Screening tests **cannot** diagnose fetal Down's Syndrome. They can only identify a group of women who are at higher risk of having a baby with Down's Syndrome to whom a diagnostic test can be offered. Diagnostic tests give a fetal karyotype, defining whether this is normal or not and will identify Down's Syndrome and other chromosomal abnormalities.

Screening tests are **non-invasive**. They have no associated risks of miscarriage nor harm to the fetus. Diagnostic tests are **invasive** and have an associated increased risk of miscarriage of approximately 0.5-1.0 per cent¹⁰. As discussed above, testing may be associated with heightened parental anxiety, particularly if performed without appropriate counselling^{8,9}.

Over the last 20 years there have been several significant developments in Down's Syndrome screening. Traditionally, in Victoria screening has been based upon maternal age. This is based upon the recognised association between maternal age and the risk of having a baby with Down's Syndrome¹¹. Usually, a 'cut-off' age of 35-37 is used to identify the 'higher risk' women who are offered diagnostic testing (see below). Such screening identifies approximately 30 per cent of Down's Syndrome pregnancies (the 'detection rate') by performing diagnostic testing on five per cent of pregnant women. The number of diagnostic tests done is usually termed the 'screen positive rate' indicating the number of women required to be tested to give the detection rate.

However, it is also known that various feto-placental products measurable in the mother's blood at 14-20 weeks are present in different levels in Down's Syndrome pregnancies compared with normal pregnancy. By combining the measurement of a number of these products with maternal age the accuracy of screening can be improved. This approach to screening is known as 'second trimester maternal serum screening'. The most commonly used combinations are often called the 'triple test' (AFP, unconjugated oestriol, β hCG) or the 'quadruple test' (the triple test plus inhibin-A). In contrast to maternal age based screening, second trimester serum screening has a detection rate of 75 per cent for the same 5 per cent screen positive rate¹². More recently, maternal serum screening that can be offered as early as 9-10 weeks of pregnancy has been developed. This blood test, known as first trimester serum screening (β hCG and PAPP-A), offers a 60 per cent detection rate for a five per cent screen positive rate¹³.

It is also possible to screen for Down's Syndrome using ultrasound. The first reports of ultrasound based screening for Down's Syndrome were derived from the 18-20 week mid-trimester ultrasound examination. However, while there are a number of structural anomalies that are more common in fetuses with Down's Syndrome it has been estimated that, at best, the mid-trimester scan will detect only 40-45 per cent of Down's Syndrome fetuses. This is significantly poorer than maternal serum screening. However, it was recognised recently that a measurement made on ultrasound examination at 11-14 weeks' gestation, known as nuchal translucency, is a useful screening test for Down's Syndrome. While appropriate training is critical to the usefulness of this test, when performed

by suitably trained operators nuchal translucency can offer a detection rate of approximately 75 per cent for a five per cent false positive rate and when added to serum screening detection rates approaching 90 per cent **may** be possible¹⁴. Confirmation of these preliminary results are awaited from trials that are currently underway. Nonetheless, it is clear that diagnostic testing offered upon the basis of maternal age **alone**, which remains common practice in Victoria, is neither equitable, effective nor cost-beneficial in comparison with serum and/or ultrasound screening offered to the entire pregnant population¹⁵.

Importantly, maternal age is a key component of all screening tests. The performance of any screening test is therefore related to the woman's age. For example, while the overall detection rate of a test may be 70 per cent, for a five per cent screen positive rate, in younger women (<25 years old) the detection rate will be approximately 30 per cent with a very low screen positive rate (one per cent) while in older women (>40 years old) the detection rate will be very high, >90 per cent, with a correspondingly high screen positive rate (50 per cent). It is therefore important that women are counselled using screening performances relevant to women of their age.

Midwives and doctors providing counselling for Down's Syndrome testing also need to recognise that the majority of women who are screen positive ('at higher risk') do not have a baby with Down's Syndrome. Only one in 40 of those women who are screen positive actually have a Down's Syndrome fetus. Since a screen positive result engenders heightened anxiety in women, most of whom have a normal baby, many women find screening a negative experience^{9,10}. However, this anxiety normalises after a normal diagnostic test result. In addition, that screening can identify 70-90 per cent of Down's Syndrome pregnancies indicates that 10-30 per cent will remain undetected. Typically, approximately 1 in 2500-8000 women who are screen negative or 'low risk' will have a Down's Syndrome baby. There is evidence that women who choose to have screening and who had such a false negative result adjust to their Down's Syndrome baby less well than those who chose not to have screening at all¹⁵.

Last, health care providers should be aware that screening can be optimised (highest detection rates and lowest screen positive rates) by accurate gestational dating³, ideally with ultrasound, by avoiding multi-step screening (that is, having a series of separate screening tests),^{16,17} and by resisting the provision of diagnostic testing on the basis of maternal age alone¹⁸.

In contrast to screening tests, diagnostic testing is invasive and has associated risks of miscarriage. The two diagnostic tests available are chorion villus sampling (CVS) and amniocentesis. These are commonly undertaken at 10-14 weeks of pregnancy

and after 15 weeks, respectively. While early studies suggested that CVS may be associated with a higher pregnancy loss rate than amniocentesis this appears to be specific for transcervical CVS only^{10,19}. The risks of miscarriage related to amniocentesis and transabdominal CVS are approximately one per cent for both^{10,20}, with higher risks evident when the indication for diagnosis was an abnormal screening test result²¹. However, the most effective method of diagnostic testing is amniocentesis because it is more likely to yield a sample for karyotyping than CVS is and the sample is more likely to be informative. In only 0.8 per cent of procedures a sample is not obtained from an amniocentesis compared to 1.3 per cent for transabdominal CVS²². Of the samples obtained, an uninformative result arises in 0.6 per cent of amniocenteses and one per cent of transabdominal CVSs²².

Methods of Search and Appraisal

Numerous strategies were used to develop guidelines from evidence. However, the process for developing these guidelines differed from the other guidelines.

I. Search on defined questions (February 2001)

The Centre for Clinical Effectiveness began search and appraisal for the following questions:

1. Is universal first trimester ultrasound scanning better than a universal second trimester scanning at detecting major fetal anomalies (neural tube defects, anencephaly, cardiac and renal anomalies)?
2. Is universal first trimester ultrasound scanning better than universal second trimester scanning at accurately dating pregnancies and outcomes associated with accurate dating (induction rates for post-term pregnancy)?
3. In pregnant women does routine universal second trimester ultrasound scanning compare favourably to selective (that is, clinically indicated) second trimester ultrasound scanning on these outcomes - detection of fetal abnormalities, incidence of pre-term delivery, perinatal mortality and morbidity, and maternal perceptions?
4. In pregnant women, does routine universal MSS combined with directed detailed fetal anomaly ultrasound scanning detect more fetal neural tube defects than second trimester ultrasound scanning alone (at 18-20 weeks)?

The Centre was unable to appraise the literature in the given time frame. Instead they sent the key citations to the lead person for appraisal. Of particular interest was the report commissioned by the National Health Service Research and Development Health Technology Assessment Program (NHS RandD HTA Program) published in 1998. Associate Professor Euan Wallace, as lead person for this set of guidelines, is also the lead

investigator of a current prospective study evaluating Down's Syndrome screening practices. On the advice of the steering group and reviewers he refocused the draft guidelines on research surrounding the routine offer of screening:

5. Should all women be offered Down's Syndrome screening tests? If so, how, when and by whom?

There were 4 Level I, 4 Level II, 5 Level III and 10 Level IV studies/documents retrieved to address this question.

II. Consultation with Experts and External Reviewers to Identify Evidence and Practice Wisdom.

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