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Prenatal screening for Down's syndrome

It is important to emphasise that the decision to have any form of screening should be an informed one. Some people may decide against having diagnostic testing or even screening for Down's syndrome when offered the choice. It is important that appropriate information, counselling and support accompanies testing and screening.

Down's syndrome pre-screening discussion

Women should be given information regarding Down's syndrome screening at their first appointment with a healthcare professional.^[1] This should include:

- Balanced and accurate information about Down's syndrome.
- The fact that screening does not give a definite diagnosis.
- An explanation of the risk score obtained following screening.
- The screening pathway and next steps for screen-positive and screen-negative results, including information about the decisions that need to be made at each step and their consequences.
- Information about amniocentesis and chorionic villus sampling.

Be aware that parents may be ambivalent around the benefits of screening; whilst acknowledging the advantages of knowing a diagnosis before delivery, they also may have concern for screening creating a less diverse population that has fewer support mechanisms for people with Down's syndrome.^[2]

Down's syndrome pre-screening probability

The risk of Down's syndrome varies with maternal age:^[3]

- 1:1,500 at 20 years.

- 1:800 at 30 years.
- 1:270 at 35 years.
- 1:100 at 40 years.
- >1:50 at 45 years and over.

The risk also increases after a previously affected pregnancy:

- With regular trisomy 21, the recurrence risk is 0.75% at 12 weeks; 0.42% during the middle trimester and 0.34% at term.^[4]
- Following trisomy due to a translocation, the recurrence risk is dependent on the type of translocation and which partner carries the translocation.
- People with Down's syndrome rarely have children. Of maternal offspring, less than half have Down's syndrome.

Down's syndrome screening

- All women, regardless of age, are offered screening for Down's syndrome. There is at present some variation in the type and timing of the screening tests used in England, Northern Ireland, Scotland and Wales.^[5]
- The aim of this screening programme is to identify those women at a higher risk of having a baby with Down's syndrome and to offer them diagnostic testing using either chorionic villus sampling (if less than 13 weeks of gestation) or amniocentesis (if beyond 15 weeks of gestation). These procedures carry a risk of miscarriage (0.5-1% excess miscarriage risk for amniocentesis; 1-2% for chorionic villus sampling).
- Women found to be carrying a baby with Down's syndrome will be offered expert counselling and support, they may be offered a termination of pregnancy or they may choose to continue with the affected pregnancy with support.
- The challenge of a prenatal screening programme is to identify women in whom a risk of Down's syndrome is sufficiently high to justify such an invasive test and to minimise the risk of miscarrying a healthy baby.

Down's syndrome screening methods

- There are two methods of screening for Down's syndrome: serum screening and ultrasound screening (nuchal translucency). These can be used in combination (the combined test):^[6]
 - The blood sample can be taken from the mother between 10 weeks and 14 weeks + 1 day of pregnancy.
 - The ultrasound scan can be carried out between 11 weeks + 2 days and 14 weeks + 1 day of pregnancy.
- The serum screen measures free beta human chorionic gonadotrophin (beta-hCG) and pregnancy-associated plasma protein A (PAPP-A) (see 'Serum markers for Down's syndrome', below).
- If a woman books later in pregnancy (when nuchal translucency is not as accurate, or if it is not technically possible to measure it) the quadruple test can be taken between 14 + 2 to 20 + 0 weeks of gestation. This measures free beta-hCG, alpha fetoprotein (AFP), inhibin-A and unconjugated estriol (uE3) (see 'Serum markers for Down's syndrome', below). It is less accurate than the combined test.
- Once a screening test has been performed, the chance of the fetus having Down's syndrome is calculated using software that takes into account maternal factors such as age, weight and family origin, along with gestation of the pregnancy.
- The screening test is positive if this probability is equal to, or greater than, a nationally agreed cut-off level.
- The current cut-off level in England is a 1 in 150 chance (that the pregnant woman is carrying a baby with Down's syndrome). These women are then offered diagnostic testing.^[6]

Serum markers for Down's syndrome^[7]

These include:

- **PAPP-A:** produced by placental syncytiotrophoblasts; levels reduced in pregnancies affected by Down's syndrome.
- **Beta-hCG:** produced by placental syncytiotrophoblasts; raised levels in pregnancies affected by Down's syndrome.

- **AFP:** produced by fetal yolk sac and liver; reduced levels in pregnancies affected by Down's syndrome.
- **uE3:** produced by placenta and fetal adrenals; reduced levels in pregnancies affected by Down's syndrome.
- **Inhibin-A:** produced by placenta; raised levels in pregnancies affected by Down's syndrome.

Factors affecting the test

Adjustments are required to take account of the following factors:

- Serum marker levels tend to be decreased in heavier women and increased in lighter women.
- AFP, free beta-hCG and hCG levels, and PAPP-A levels are higher in Afro-Caribbean women than in Caucasian women.
- Free beta-hCG and hCG levels tend to be about 10% higher and uE3 and PAPP-A levels about 10% lower in women who have become pregnant as a result of IVF compared with non-IVF pregnancies
- AFP and uE3 levels tend to be low in women with insulin-dependent diabetes mellitus.
- PAPP-A, free beta-hCG and hCG levels tend to be about 20% lower and inhibin levels about 60% higher in women who smoke.
- The serum marker levels are raised in twin pregnancies. Screening in twin pregnancies poses a difficulty because of the possibility that one fetus may be affected and the other may not.
- Previous affected pregnancies: if a previous pregnancy with Down's syndrome or open neural tube defect is reported, the result will be classified as 'screen-positive' regardless of the level of the screening markers, so that further testing can be discussed with the woman.
- Vaginal bleeding immediately before taking the second blood sample can affect the screening result by increasing the maternal serum AFP level.

If a woman has been screened for Down's syndrome or open neural tube defects in a previous pregnancy, the levels of the screening markers in that pregnancy can be used to adjust the marker levels in the current pregnancy. A woman with a false positive result in one pregnancy is likely to have a false positive result again in a subsequent pregnancy.

Nuchal translucency scanning^[8]

- Fetal nuchal translucency (FNT) screening uses ultrasound to measure the size of the nuchal pad at the nape of the fetal neck. It should be performed between 11 weeks + 2 days and 14 weeks + 1 day.
- Increased nuchal translucency reflects fetal heart failure; it is typically seen in any serious anomaly of the heart and great arteries and strongly associated with a chromosomal abnormality. In one study, 84% of karyotypically proven trisomy 21 fetuses had a nuchal translucency >3 mm at 10–13 weeks of gestation (as did 4.5% of chromosomally normal fetuses).
- The greater the extent of FNT, the greater the risk of abnormality and adverse pregnancy outcome.
- It is a straightforward test but will have a 20% false positive rate (FPR) if the thresholds are set to detect 85% (if used alone and maternal age adjusted).
- Adding nasal bone screening during the same examination may increase sensitivity further and reduce the FPR.^[9] ^[10] One study concluded that an absent nasal bone should be considered as a highly predictive marker of Down's syndrome.^[11]
- Specific standards have been set for nuchal translucency measurement.^[12]

The evidence base for the screening tests

A key study in Down's syndrome screening was the Serum Urine and Ultrasound Screening Study (SURUSS).^[13] ^[14] It compared the different prenatal screening tests available for Down's syndrome. It was a prospective study of about 47,000 singleton pregnancies conducted in 25 maternity units. It concluded that:

- **The integrated test** offers the most effective and safe method of screening for women who attend in the first trimester.
- **The quadruple test** is the best test for women who first present in the second trimester.

The screening policy has been subject to several reviews, which have altered the recommendations for the national programme.^[12] Screening within the NHS must be cost-effective, easy to deliver and achieve the agreed targets.

There are a number of considerations given to recommending a screening test which is simple and practical to implement, is workable in the NHS, has lower service delivery risks, is acceptable to women, achieves the agreed standard and is also cost-effective compared to others.

The Integrated and Serum Integrated tests require women to have two serum tests on different appointments for the risk result to be generated. Failing to attend the second appointment renders the test invalid and so there is a responsibility for busy healthcare professionals (usually a midwife) to trace defaulters and ensure they complete the screening cycle. There is a risk that the completion of the test will not occur and data cannot be correlated from one attendance to another. There is also a greater chance that results will not be accurate because of the differing variables involved and that screening follow-up and closure of the screening on those women who change postcodes during the two appointments may not be achieved.

The result of the test is provided later in the pregnancy, limiting the timeframe for decision making. Equally, the more complex the process, the more likely it is that clinical errors will occur. Costs incurred from all strategies have been assessed, providing evidence that the combined test is more cost-effective whilst still delivering to the set standard.

The National Institute for Health and Care Excellence (NICE) guidelines for antenatal care have also looked at all available evidence for Down's syndrome screening. NICE found that:^[15]

- The combined test has a higher detection rate and lower FPR when compared with other screening tests.

- It is cost-effective and results in the fewest losses of normal fetuses after invasive diagnosis.
- There are concerns regarding the practicality of this test. Up to 25% of women fail to attend for the second component of the test.
- There is also evidence that women prefer a one-stage test.

This led NICE to the conclusion that the combined test should be the screening test offered to women in the first trimester. This has good diagnostic accuracy for Down's syndrome and other chromosomal abnormalities.

Down's syndrome screening in multiple pregnancy^[16]

- Around 2% of pregnancies affected by Down's syndrome are twins.
- If the twins are dizygotic, the risk of Down's syndrome for each baby individually is the same as for a single baby (around 1 in 800 pregnancies).
- If the twins are monozygotic, the risk to both of having Down's syndrome is also around 1 in 800.
- Serum markers are affected by the presence of more than one baby.
- Recent studies have shown that a combination of nuchal translucency scanning and serum screening may be beneficial in the risk assessment of Down's syndrome for twin pregnancies.^[17] ^[18]

The future of Down's syndrome screening

The examination of fetal cells in the maternal circulation for prenatal diagnosis is currently being evaluated and may reduce the need for invasive tests such as chorionic villus sampling (CVS) and amniocentesis.^[19]

Further reading

- [Zbucka-Kretowska M, Niemira M, Paczkowska-Abdulsalam M, et al](#); Prenatal circulating microRNA signatures of foetal Down syndrome. Sci Rep. 2019 Feb 20;9(1):2394. doi: 10.1038/s41598-018-35876-5.
- [Long S, O'Leary P, Lobo R, et al](#); Women's Understanding and Attitudes towards Down Syndrome and Other Genetic Conditions in the Context of Prenatal Screening. J Genet Couns. 2018 Jun;27(3):647-655. doi: 10.1007/s10897-017-0167-7. Epub 2017 Oct 24.

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