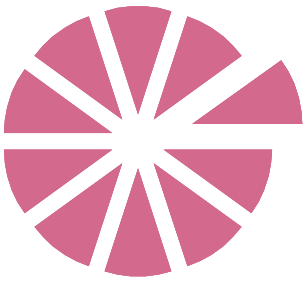


Antenatal Screening

FIRST TRIMESTER ANTENATAL SCREENING FOR DOWN'S SYNDROME

THE COMBINED TEST

Information for Health Professionals

Antenatal Screening

SUMMARY

- Antenatal screening identifies women with an increased risk of having a pregnancy with Down's syndrome so that they can be offered a diagnostic test.

- The Combined test is a method of screening involving the measurement of two substances in the maternal serum (serum markers) and an ultrasound scan measurement. The serum markers are Pregnancy Associated Plasma Protein-A (PAPP-A) and the free ß-subunit of human chorionic gonadotrophin (free ß-hCG). The ultrasound marker is the nuchal translucency (NT).

- The three markers are used together with the woman's age to estimate the risk of having a pregnancy with Down's syndrome. Women with a risk of 1 in 250 or greater are interpreted as screen-positive and offered further tests. About 1 in 33 of all women screened will fall into the screen-positive group, and about 1 in 35 women with screen-positive results will have an affected pregnancy.

- The Combined test identifies about 4 out of 5 women who have pregnancies with Down's syndrome.

Women considering whether to be screened need appropriate information to help them decide what to do. This leaflet is designed to assist Health Professionals provide the necessary information.

CONTENTS

DOWN'S SYNDROME (TRISOMY 21)

Down's syndrome is the most common cause of severe learning disability in children. In the absence of antenatal screening, about 1 in 700 babies born would be affected.

People with Down's syndrome have varying degrees of learning disability, but most often the disability is severe. Some people will lead semi-independent lives while others will be completely dependent. About 50% of Down's syndrome pregnancies will miscarry between conception and term, but nine out of ten affected babies who reach term will survive their first year. About one-third of babies with Down's syndrome are born with a serious heart defect. The average life expectancy of a person with Down's syndrome is now about 60 years, although most will develop pathological changes in the brain associated with Alzheimer's disease after the age of 40.

THE MARKERS USED IN THE COMBINED TEST

Pregnancy Associated Plasma Protein-A (PAPP-A) and the free ß-subunit of human chorionic gonadotrophin (free ß-hCG) both originate from the placenta. Nuchal translucency (NT) is the thickness of the fluid filled space under the skin at the back of the fetal neck.

THE TIMING OF THE COMBINED TEST

The test can be performed between 10 and 13 completed weeks of pregnancy. An ultrasound scan is performed to estimate the gestational age of the pregnancy and to obtain the nuchal translucency measurement. A 10ml sample of clotted blood is required at the time of the ultrasound scan.

INTERPRETATION OF THE COMBINED TEST

The test categorises women into two groups according to their risk of having an affected pregnancy. Those who fall into the high risk group are interpreted as screen-positive and the remainder are interpreted as screen-negative.

If the risk of an affected pregnancy, using maternal age together with the levels of PAPP-A, free β-hCG and the nuchal translucency measurement, is estimated to be 1 in 250 or greater then the result is **screen-positive**.

About 1 in 33 women screened will have a screen-positive result. Most of these women will **not** have affected pregnancies.

A **screen-negative** result means that the risk of a pregnancy with Down's syndrome is not high. It does not exclude the possibility of an affected pregnancy.

ACTION FOLLOWING A SCREEN-POSITIVE RESULT

If the result is screen-positive for Down's syndrome then diagnostic tests such as chorionic villus sampling or amniocentesis should be offered.

REPORTING OF RESULTS

The results of the test are usually ready within one day of receipt of the blood sample and will be sent to the doctor who ordered the test. Screen-positive results are telephoned and faxed directly to the doctor.

PERFORMANCE OF THE TEST

The **detection rate** of the test (the proportion of women with Down's syndrome pregnancies who have screen-positive results) is 81%.

The **false positive rate** of the test (the proportion of women with unaffected pregnancies who have screen-positive results) is about 3%.

Among women with a screen-positive result, one will have an affected pregnancy for every 34 that do not, i.e. the Odds of Being Affected given a Positive Result (OAPR) are 1:34.

CALCULATION OF THE RISK OF DOWN'S SYNDROME

Maternal Age

The risk of having a term pregnancy with Down's syndrome increases with maternal age as shown in Table 1 opposite. It is known as the maternal age-specific risk and is the background risk of Down's syndrome used when interpreting a screening result.

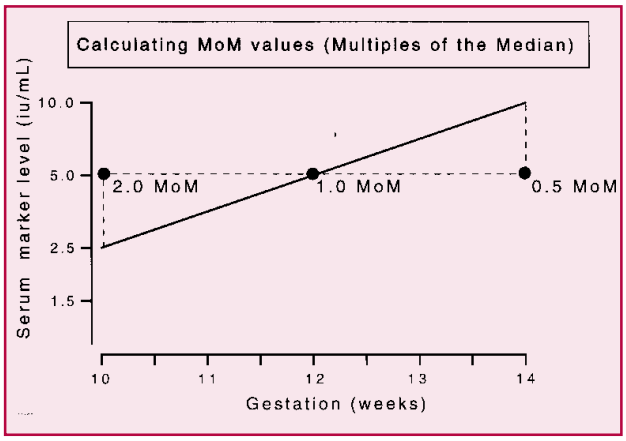
Table 1

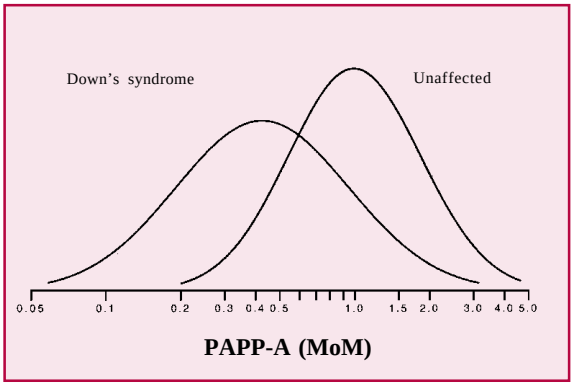
Maternal age at EDD*	Risk of Down's syndrome	Maternal age at EDD*	Risk of Down's syndrome	Maternal age at EDD*	Risk of Down's syndrome
under 25	1:1500	33	1:570	42	1:65
25	1:1350	34	1:470	43	1:50
26	1:1300	35	1:380	44	1:35
27	1:1200	36	1:310	45	1:30
28	1:1100	37	1:240	46	1:20
29	1:1000	38	1:190	47	1:15
30	1:910	39	1:150	48	1:11
31	1:800	40	1:110	49	1:8
32	1:680	41	1:85	50	1:6

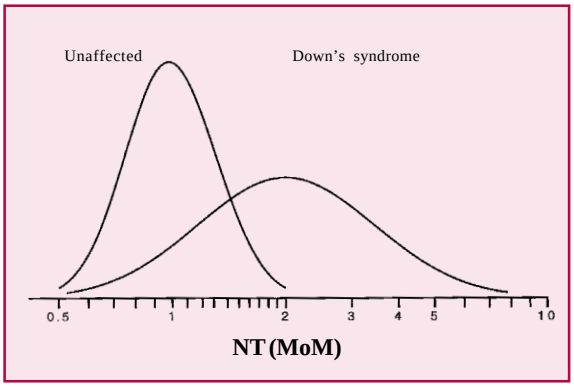
*EDD = expected date of delivery

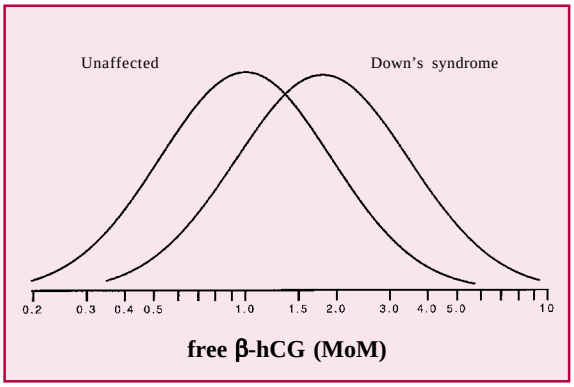
The three markers

The first trimester maternal serum PAPP-A level is, on average, low in Down's syndrome pregnancies (about half that of unaffected pregnancies), the free β-hCG level is, on average, high (about double that of unaffected pregnancies) and the nuchal translucency measurement is, on average, high (about double that of unaffected pregnancies). The concentrations of the three markers vary with gestational age (PAPP-A and nuchal translucency increase, free β-hCG decreases). To take account of this variation, the concentration of each marker is expressed as a multiple of the median for unaffected pregnancies of the same gestational age (MoM). In the diagram the median marker level is 2.5 iu/mL at 10 weeks, 5 iu/mL at 12 weeks and 10 iu/mL at 14 weeks. If a woman is found to have 5 iu/mL at 10 weeks her level is twice the median (5/2.5) or 2.0 MoM. Similarly if the level is 5 iu/mL at 14 weeks this is half the median (5/10) or 0.5 MoM.









Risk of Down's syndrome in relation to marker levels

The graphs on this page show the overlapping relative frequency distributions of PAPP-A, nuchal translucency and free β-hCG in affected and unaffected pregnancies from 10 to 13 completed weeks. The points of intersection are the values at which the risk of Down's syndrome is the same as the background risk in the population. Values of free β-hCG and nuchal translucency above each point of intersection increase the risk of Down's syndrome above the background risk while values below each point of intersection decrease the risk. The points of intersection are 1.5 MoM for nuchal translucency and 1.35 MoM for free β-hCG. For PAPP-A values *below* the point of intersection increase the risk of Down's syndrome above the background risk while values *above* decrease the risk. The point of intersection is 0.6 MoM.

FACTORS AFFECTING THE TEST

Maternal weight and ethnic group

Serum marker levels tend to be decreased in heavier women, and increased in lighter women. Free β-hCG levels tend to be higher in Afro-Caribbean women than in Caucasian women. Appropriate adjustments of the MoM values are made for weight and ethnic group.

Twins

PAPP-A and free β-hCG levels are raised in twin pregnancies. Screening in twin pregnancies poses a special problem because of the presence of two fetuses, and the possibility that one may be affected and one may not. There is reasonable reluctance to act on a positive screening result and perform a CVS or an amniocentesis on a twin pregnancy or consider a termination of an unaffected co-twin in the event of a positive diagnosis. Twin pregnancies may therefore be seen as an indication to avoid screening.

Previous affected pregnancies

If a previous pregnancy with Down's syndrome is reported, the result will be classified as 'screen-positive' regardless of the woman's individual marker levels or her individual risk which will still be calculated taking into account both the marker levels and the previous history.

DIAGNOSTIC TESTS

Chorionic Villus Sampling (CVS)

A CVS is performed at about 11 to 14 weeks of pregnancy and a result is usually available within 10 days. Under ultrasound guidance and using a local anaesthetic, a sample of placental tissue is collected either using a needle inserted through the abdominal wall or with a fine forceps passed through the cervix. Cells from the sample can be used to diagnose Down's syndrome. There is a small risk of miscarriage (about 1%) associated with the procedure.

Amniocentesis

An amniocentesis is performed at about 16 weeks of pregnancy and a result is usually ready in 2 weeks. Under ultrasound guidance a sample of amniotic fluid is collected using a needle inserted through the abdominal wall. Cells from the sample can be used to diagnose Down's syndrome. The risk of miscarriage is similar to that associated with a CVS (about 0.5-1%).

EFFECT OF MATERNAL AGE ON SCREENING PERFORMANCE

An older woman is more likely to have a screen-positive result than a younger woman as she starts with a higher age-specific risk of Down's syndrome. For this reason, the test is more likely to detect a Down's syndrome pregnancy in an older woman than in a younger woman. Table 2 below shows, using a 1 in 250 cut-off, according to age, the probability of a screen-positive result and the proportion of Down's syndrome pregnancies detected. Whatever the woman's age, the best estimate of her risk of having an affected pregnancy is obtained using her age in conjunction with her marker values.

Table 2

Maternal age group (years)	Probability of a screen-positive result	Proportion of Down's syndrome pregnancies detected (%)
Under 25	1 in 80	70%
25-29	1 in 60	72%
30-34	1 in 35	77%
35-39	1 in 15	85%
40-44	1 in 5	93%
45 and over	greater than 1 in 2	98%
All	1 in 33	81%

OTHER DOWN'S SYNDROME SCREENING TESTS

Table 3 on the opposite page shows, for a 5% false-positive rate (FPR), the detection rate (DR) and odds of being affected given a positive result (OAPR), for different methods of screening for Down's syndrome in the second trimester of pregnancy. Estimates of performance are established and corroborated by different studies.

Table 4 shows, for a 5% false-positive rate the detection rate and OAPR for first trimester screening methods and the integrated test.

Table 3

Method of screening	Timing of Test (weeks)	Using an ultrasound scan to estimate gestational age	
		DR	OAPR
Maternal age		30%	1:130
Maternal age and AFP	14-22	40%	1:95
Double test[a] (using free ß-hCG)	14-22	62%	1:62
Triple test[b] (using free ß-hCG)	14-22	71%	1:54
Quadruple test[c] (using free ß-hCG)	14-22	78%	1:49

[a] Maternal age with AFP + hCG (total or free ß-hCG)
[b] Maternal age with AFP + uE_3 + hCG (total or free ß-hCG)
[c] Maternal age with AFP + uE_3 + inhibin + hCG (total or free ß-hCG)

Table 4

Method of screening	Timing of Test (weeks)	Using an ultrasound scan to estimate gestational age	
		DR	OAPR
PAPP-A free ß-hCG and maternal age	10-13	62%	1:62
Nuchal translucency and maternal age	10-13	72%	1:53
The Combined test[d]	10-13	85%	1:45
The Integrated test	10-13 then 14-22	95%	1:40

[d] Maternal age with PAPP-A + free β-hCG + Nuchal translucency

PATIENT INFORMATION

Points to remember when discussing the screening test with a woman considering whether to be screened:

- Invite an explicit decision on whether to be screened.
- Determine the woman's knowledge of Down's syndrome and whether more information is needed.
- The test does not give a definite answer – it divides women into a higher risk group (screen-positive) and a lower risk group (screen-negative) only.
- On average 1 in 33 women screened will have a screen-positive result and they will be offered a CVS or amniocentesis, both of which carry a risk of miscarriage. Most women with a screen-positive result will **not** have affected pregnancies.
- The chance of having a screen-positive result increases with age. Informing an older woman of this in advance may reduce her anxiety on hearing that she has a screen-positive result.
- The test will not detect all pregnancies with Down's syndrome.
- In the few pregnancies in which Down's syndrome is diagnosed, the woman will be offered a termination of pregnancy.

OTHER SCREENING APPROACHES

Patients should know that the Integrated test provides better screening performance by using information in the first and second trimester of pregnancy to provide a single result and risk assessment. It is also able to offer screening for open neural tube defects, which the Combined test is not able to provide. The Integrated test is a more effective test because it has a higher detection rate for a lower fasle positive rate. The detection rate of the Integrated test is 85% for a 1% false positive rate, while the detection rate of the Combined test is 81% for a 3% false positive rate. This means less women are offered an invasive diagnostic procedure and more Down's syndrome pregnancies are detected using the Integrated test. This test is also useful for women who may have a separate screening test in the first and second trimester as it avoids the dilemna of having two tests with different results.

REFERENCES

Wald NJ, George L, Smith D, Densem JW, Petterson K. On behalf of the International Prenatal Screening Research Group. Serum screening for Down's syndrome between 8 and 14 weeks of pregnancy. *BR J Obstet Gynaecol* 1996;**103**:407-12

Wald NJ, Hackshaw AK. Combining ultrasound and biochemistry in first trimester screening for Down's syndrome. *Prenat Diagn* 1997;**17**:821-829

Pandya PP, Kondylios A, Hilbert L, Snijders RJM, Nicolaides KH. Chromosomal defects and outcome in 1,015 fetuses with increased nuchal transluncey. *Ultrasound Obstet Gynecol* 1995;**5**:15-19

RCOG. Screening for Down's syndrome in the First Timester. Ed Grudzinskas J, Ward R. RCOG press. June 1997.

Report of the RCOG Working Party on biochemical markers and the detection of Down's syndrome. RCOG press. July 1993.

USEFUL TELEPHONE NUMBERS

Down's Syndrome Association 020 8682 4001

Antenatal Results and Choices (ARC) 020 7631 0285

For further information about where you can obtain the Combined test, please contact:

Antenatal Screening
Centre for Environmental and Preventive Medicine
Wolfson Institute of Preventive Medicine
Barts and The London, Queen Mary's
School of Medicine and Dentistry
Charterhouse Square
London
EC1M6BQ

Telephone: 020 7882 6293/4
e-mail: a.n.screening@qmul.ac.uk

or find us at: www.smd.qmul.ac.uk/wolfson/epm/screening

The Wolfson Institute of Preventive Medicine is a leader in the discovery, introduction and development of antenatal screening methods. It is committed to improving the efficacy and safety of screening. We use information collected as part of our screening programme, including measurements on stored blood samples, to audit our screening programme and ensure that it is meeting our expected quality standards. Such information may also be used to help discover and validate new tests that improve the quality of screening services.