

Screening for Down's syndrome, Edwards' syndrome and Patau's syndrome in twin pregnancies

1. Introduction to twins and screening

Twin pregnancies account for 1.6% of all pregnancies in the UK. In order for women to be able to make a fully informed decision about entering the screening pathway they need to understand the stages in the pathway prior to deciding whether to have screening or further tests. Decision making for women around the offer of screening for these conditions in a twin pregnancy is more complicated than in singleton pregnancies. Invasive testing in a twin pregnancy carries a higher risk of miscarriage than a singleton pregnancy and there are risks associated with selective termination if that is the decision taken if one fetus has one of the conditions screened for.

N.B Screening for Down's syndrome, Edwards' syndrome and Patau's syndrome is not offered in triplets or higher multiple pregnancies.

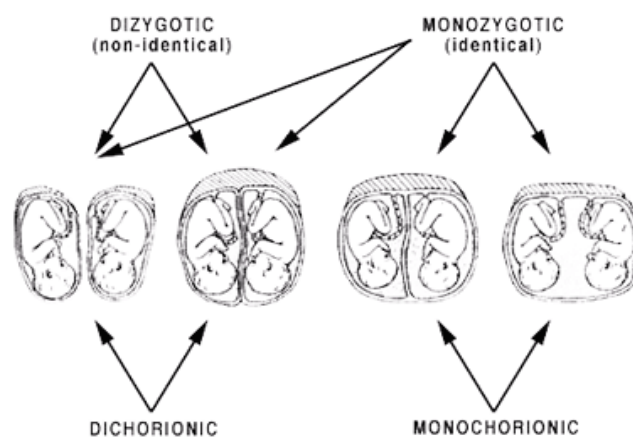
The accuracy of the combined test and the risks associated with invasive testing will be different for:

- dizygotic twins (70% of all twin pregnancies) - arise from two separate eggs that are fertilised by separate sperm and are non-identical
- monozygotic twins (30% of all twin pregnancies) - occur when a single fertilised egg later divides into two embryos. These twins usually share the same genetic material (are identical).

Diagram 1

Lambda λ sign = dichorionic

T sign = monochorionicⁱ



Monochorionic twins are almost always monozygotic (identical).

Dichorionic twins in most cases (around 90%) are dizygotic and are therefore usually non-identical. However around 10% of dichorionic twins are identical (monozygotic).

2. Ultrasound Measurements in a Twin Pregnancy

The largest of the two crown rump length (CRL) measurements is used for estimation of gestational age for the purpose of standardizing the biochemical measurements. For combined testing in twins, both should have a CRL of 45mm or more and the larger CRL should be not be greater than 84mm. ie if one twin has a CRL of more than 84mm screening cannot be performed.

3. Tests available in a twin pregnancy-NHS Wales

Combined screening (offered between 11⁺²-14⁺¹ weeks). With a higher chance result, the woman would be offered:

- No further testing
- NIPT, or,
- Invasive testing (CVS, if between 11⁺⁰ -13⁺⁶ weeks gestation) and amniocentesis (>15 weeks gestation)

4. Tests not available for twins in Wales

Quadruple screening is not offered to women with twin pregnancies. This is because this test does not perform well in twins with a detection rate of only 40-50% for a 3% screen positive rate.

NIPT cannot be offered if this pregnancy was initially a twin pregnancy (e.g. if a second fetal pole or pregnancy sac has been seen on scan). This is because the free fetal DNA may still be present in the maternal blood from the demised twin potentially giving an inaccurate result.

5. Combined testing in monochorionic twins

5.1 Accuracy

The sensitivity of a test means how good the test is at identifying those who do have the condition in question. The sensitivity of combined screening in monochorionic twins is comparable to or better than in singleton pregnancies. The specificity means how good a test is at identifying those who do not have the condition. The specificity of combined screening in monochorionic twins is slightly lower than in singleton pregnancies.

5.2 Calculation of chance using nuchal translucency (NT) and biochemistry

The prior chance in screening takes into account maternal age. Other factors such as, smoking status, and ethnicity, affect the marker levels (free Beta hCG and PAPP-A) and are adjusted for as part of the analysis. The analysis also takes into account whether it is a singleton or twin pregnancy, and whether it is a monozygotic twin pregnancy.ⁱⁱ

The chance of the fetus having one of the conditions being screened for is calculated using the mean of the two NT measurements.

If either twin has a CRL of greater than 84.0mm a combined screening test cannot be offered.

If the CRL and NT measurement can only be obtained for one twin the laboratory will provide a result based on that measurement and the result will state that this will be less accurate for the pregnancy than if the two measurements were available.

5.3 Result

The result of combined screening in a monochorionic twin pregnancy will be:

- A chance of Down's syndrome 1:xxx for **the pregnancy** and
- A chance of Edwards'/ Patau's syndrome 1:xxx for **the pregnancy**

5.4 Invasive procedures in monochorionic twins

Monochorionic twins will almost always have the same karyotype, but it is not impossible to have a chromosomal change in one twin, and not the other.

An invasive test in a twin pregnancy carries an increased risk of miscarriage of around 2%.

6. Combined testing in dichorionic twin pregnancies

6.1 Accuracy

The sensitivity of combined screening in dichorionic twins, how good the test is at identifying fetuses that do have the condition, is comparable to or better than in singleton pregnancies. The specificity, how good the test is at identifying fetuses that do not have the condition, is slightly lower than in singleton pregnancies.

If dichorionic twins are monozygotic (around 10% of cases of dichorionic twins), the accuracy of the chance result for these women will be affected. This is because the biochemistry calculation will have made the assumption that the twins are non-identical based on the chorionicity. This will affect the accuracy of the result for the woman who has a monozygotic twin pregnancy that is dichorionic.

There is no way of telling zygosity unless the twins have different genders, which cannot be defined on scan at this gestation.

6.2 Calculation of chance using NT and biochemistry

The chance of a dichorionic twin pregnancy having one of the conditions being screened for is higher than for a singleton pregnancy as each fetus has the same chance as a singleton pregnancy and there are two fetuses. This means that the calculation of chance for the pregnancy needs to be adjusted. Therefore, the prior chance, which takes into account things such as maternal age, and other factors such as smoking status etc, is adjusted for the type of twin pregnancy.ⁱⁱⁱ.

The chance of each fetus having one of the conditions being screened for is calculated using the NT measurements for each fetus in a dichorionic twin pregnancy, as it is assumed they will be non-identical twins.

The calculation of the chance of a pregnancy having one of the conditions being screened for will also be adjusted because of the increase in the expected amount of the biochemical markers for twin pregnancies. This will be affected by the chorionicity of the twins.

If either twin has a CRL of greater than 84.0mm combined screening test cannot be offered.

If the CRL and NT measurement can only be obtained for **one** twin the laboratory will provide a result based on that measurement and the result will state that this will only be accurate for the twin that was measured.

6.3 Result

The result of combined screening in a dichorionic twin pregnancy will be:

- A chance of Down's syndrome 1:xxx for **each twin**
- A chance of Edwards'/ Patau's syndrome 1:xxx for **each twin**

7. Higher chance screening results

Women with a higher chance screening result in a twin pregnancy should have a face to face appointment with the health board nominated professional for screening in a twin pregnancy.

The woman should have a full discussion about the result and her options for:

- No further testing, and ongoing multi professional care planning and support
- NIPT, benefits and limitations,
- Invasive testing; benefits and harms; and options if a condition is diagnosed. This should include information about risk of miscarriage and risks of selective termination of pregnancy in a dichorionic twin pregnancy.

8. NIPT

NIPT is a further screening test offered as a contingent test for a higher chance combined test result in a twin pregnancy. NIPT involves a maternal blood sample which analyses the total cell free DNA (cfDNA). Maternal blood contains both placental and maternal DNA. It works by comparing the amount of genetic material aligned to chromosome 13, 18 and 21 in comparison to other chromosomes to see if they are over represented. If more chromosome 13, 18 or 21 are detected, a high chance is reported.

NIPT within the screening programme will look for Down's syndrome, Edwards' syndrome and Patau's syndrome; it will not detect other chromosomal conditions or detect fetal sex.

NIPT is reported as:

- low chance - for this cohort of women, no further testing will be offered
- high chance - women will be offered invasive testing for a definitive diagnosis

8.1 Accuracy of NIPT

Warwick 2016^{iv} showed the accuracy of NIPT in a singleton pregnancy as:

- a sensitivity of between 93-97%, which in practice allows us to answer the question "For a fetus with the condition, what is the chance the mother will have a high chance test result?"
- a positive predictive (PPV) value of between 84-91%, which allows us to answer the question "If the mother's test comes back high chance, what is the chance that the fetus will have the condition?"
- a negative predictive value of 99.8-99.9% which allows us to answer the question "If the mother has a low chance result, what is the chance that the fetus will not have the condition?"

NIPT may be less accurate in a twin pregnancy.

The most common reason for a false positive result is due to confined placental mosaicism (CPM). Around 2% of samples taken will not give a result and in this case, an amniocentesis will be offered if the woman wants a definite result.

8.2 Results of NIPT

Results for NIPT take around 10 calendar days from sample draw to results reporting to the health board.

A low chance NIPT result report in a twin pregnancy will state:

Conclusion: NIPT result - Low chance of trisomy 13, 18 and 21 in both twins.

Non-invasive prenatal testing (NIPT) showed a low chance for trisomy 13, 18 and 21. Both twins in the current pregnancy are therefore considered to be at low chance of having Patau syndrome, Edwards syndrome or Down syndrome.

An example of a high chance NIPT report in a twin pregnancy will state:

*Conclusion: NIPT result - High chance of (*trisomy 21). One or both twins are at high chance of having Down syndrome –OFFER OF INVASIVE DIAGNOSTIC TESTING RECOMMENDED*

*Non-invasive prenatal testing (NIPT) showed a high chance of (*trisomy 21). One or both twins in the current pregnancy is therefore considered to be at high chance of having Down syndrome.*

This test is a screening test only, and therefore false positive and false negative results can occur. It is recommended that confirmation of the diagnosis should be offered for both twins by invasive testing.

Non-invasive prenatal testing (NIPT) showed a low chance for trisomy 13 and 18 for both twins.

*A similar report would be generated for a report with a high chance result for either trisomy 18, or trisomy 13

9. Invasive procedures

An invasive test in a twin pregnancy carries an increased risk of miscarriage around 2% as there will need to be two samples of either amniotic fluid or chorionic villi collected.

If the woman chooses an invasive procedure this must be performed in a unit where the obstetrician can perform a selective termination of pregnancy if required. This is to enable the twins to be identified at the time that the invasive procedure is performed. This will reduce the risk of termination of the twin not found to have one of the conditions, if the woman chooses to have a selective termination.

10. Risks associated with selective termination of pregnancy

In a twin pregnancy where one fetus has one of the conditions and the other fetus does not, the woman may decide to have a selective termination of the fetus with the condition.

The risk of miscarriage of the twin without the condition and below 25 weeks gestation following a selective termination is around 9% higher than in a continuing twin pregnancy. In pregnancies following selective termination the birth of fetuses is earlier than for continuing twin pregnancies^v ^{vi}

There is a risk of neurodevelopmental morbidity for the surviving twin. This risk is 2% in dichorionic twins and 26% in monochorionic twins ^{vii}.

There is a very small risk that the twin without the condition could be terminated by the health professional carrying out the procedure.

Crib sheet for Health Board nominated professional for discussing this screening

Discuss:

- Screening is a choice and the woman can decide to change her mind at any point in the pathway and will be supported in all of her decisions.
- Type of twins identified on scan if known.
- Screening is more complicated in twin pregnancies.
- Options for women who have a higher chance combined screening test:
 - No further testing
 - NIPT
 - Invasive testing
- NIPT is a further screening test, but not diagnostic. The accuracy of NIPT in a twin pregnancy is likely to be slightly lower than in a singleton pregnancy.
- NIPT takes around 10 calendar days to get a result. A result will be issued for the pregnancy and not for each twin.
- Around 2% of samples taken will not get a result and in these cases, an invasive test will be offered if the woman wants a definite diagnosis.
- A low chance NIPT result-no further testing will be offered
- A high chance NIPT result, or no result obtained from the NIPT-an invasive procedure will be offered if the woman wants a definite result.
- The risk of miscarriage from an invasive procedure is around double the risk for a singleton pregnancy.
- Options following an invasive procedure with a diagnosis of Down's syndrome, Edwards' syndrome or Patau's syndrome.

Specific information if a monochorionic twin pregnancy:

- These are much less common and as the twins are very likely to be identical, it is likely that:
 - both fetuses will have one of the conditions screened for, or
 - both fetuses will not have one of the conditions screened for.
- The "chance" result for the combined test will be for the pregnancy having either Down's syndrome or Edwards'/ Patau's syndrome.
- If only one twin could be measured then a less accurate result for the pregnancy will be issued if the woman wishes to continue on the screening pathway.

- If the combined test cannot be obtained, quadruple testing is not offered in Wales.
- If the combined test result is higher chance for Down's syndrome or Edwards'/Patau's syndromes the options are:
 - No further testing
 - NIPT
 - Invasive procedure– either CVS or amniocentesis – dependant on gestation and maternal choice.
- The risk of miscarriage from the invasive procedure should be discussed.
- If the invasive procedure shows that the fetuses have one of the conditions, the woman should understand that in most cases she will be offered a termination of the pregnancy for both twins.

Specific information if a dichorionic twin pregnancy:

- These are the most common type of twins and as the twins are likely to be non identical, therefore each fetus could either:
 - Have one of the conditions being screened for
 - Not have one of the conditions being screened for
- The chance result for the combined test will be for each fetus having either Down's syndrome or Edwards'/ Patau's syndrome.
- If only one fetus could be measured, and the woman wishes to continue on the screening pathway then a result will be issued for only one fetus.
- The combined test is slightly less accurate in dichorionic twins because a small number of dichorionic twins are identical but the test assumes they are all non identical.
- If the combined test cannot be obtained quad testing is not offered in Wales.
- If the combined test result is higher chance for Down's syndrome or Edwards'/Patau's syndromes the options are:
 - No further testing
 - NIPT
 - Invasive procedure– either CVS or amniocentesis – dependant on gestation and maternal choice.
- If an invasive test diagnoses one fetus having one of the conditions and the other fetus not having any of the conditions, the woman may decide to have a selective termination of the fetus diagnosed with the condition. In this instance the invasive procedure should be performed by the person who will also perform the selective termination of pregnancy.
- The risk of miscarriage from the invasive procedure should be discussed.
- If the invasive procedure identifies that one fetus has Down's syndrome, Edwards' syndrome or Patau's syndrome, the woman should understand that in most cases she will be offered a termination of the fetus with the condition and that this can carry risks for the fetus who has not been diagnosed with the conditions and these should be explained.

ⁱ Multiple Births Foundation Accessed from:
<http://www.multiplebirths.org.uk/identical.asp>

ⁱⁱ Cuckle H, Wilson C. "Twins - Risk per fetus or per pregnancy." Down's Screening News 13:1:8, 2006.

ⁱⁱⁱ Cuckle H, Wilson C. "Twins - Risk per fetus or per pregnancy." Down's Screening News 13:1:8, 2006.

^{iv} Warwick (2016) Accuracy of non-invasive prenatal testing using cell-free DNA for detection of Down, Edwards and Patau syndromes: a systematic review and meta-analysis. BMJ Open, 6 (1)

^v Mheen, L. et al (2015) Pregnancy outcome after fetal reduction in women with a dichorionic twin pregnancy. Human Reproduction, Vol.30, No.8 pp. 1807–1812

^{vi} Wimalasundera, RC. (2010) Selective reduction and termination of multiple pregnancies. Seminars in Fetal & Neonatal Medicine 15 (2010) 327-335

^{vii} Mackie, F, Morris, RK & Kilby, M 2016, 'Fetal brain injury in survivors of twin pregnancies complicated by demise of one twin: A review' Twin Research and Human Genetics, vol 19, no. 03, pp. 262-267. DOI:10.1017/thg.2016.39