The Quadruple Test For Antenatal Screening

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Prenatal diagnostic tests aim to detect genetic diseases and congenital anomalies of the foetus prior to delivery. These results provide options to parents: an opportunity to plan for the birth of an affected child, or a choice to terminate a pregnancy as the disease burden for the affected individual and the family can be significant. Down syndrome is the most common aneuploidy and may be clinically associated with heart defects, cognitive disabilities, and other sequelae.

Currently, among prenatal screening tests, NIPS (non-invasive prenatal screening) or cell-free foetal DNA analysis have the highest diagnostic performance, with a sensitivity of more than 99% and a false-positive rate of < 1%. However, screening with NIPS is expensive, limiting its use in developing counties with scarce resources. In South Africa, (although increasing) not all medical aids pay for these tests and most require an abnormal first or second trimester screening test before agreeing to funding. At Lancet laboratories the triple test is currently available for second trimester screening. This will be replaced by the quadruple test.

Pre-test counselling

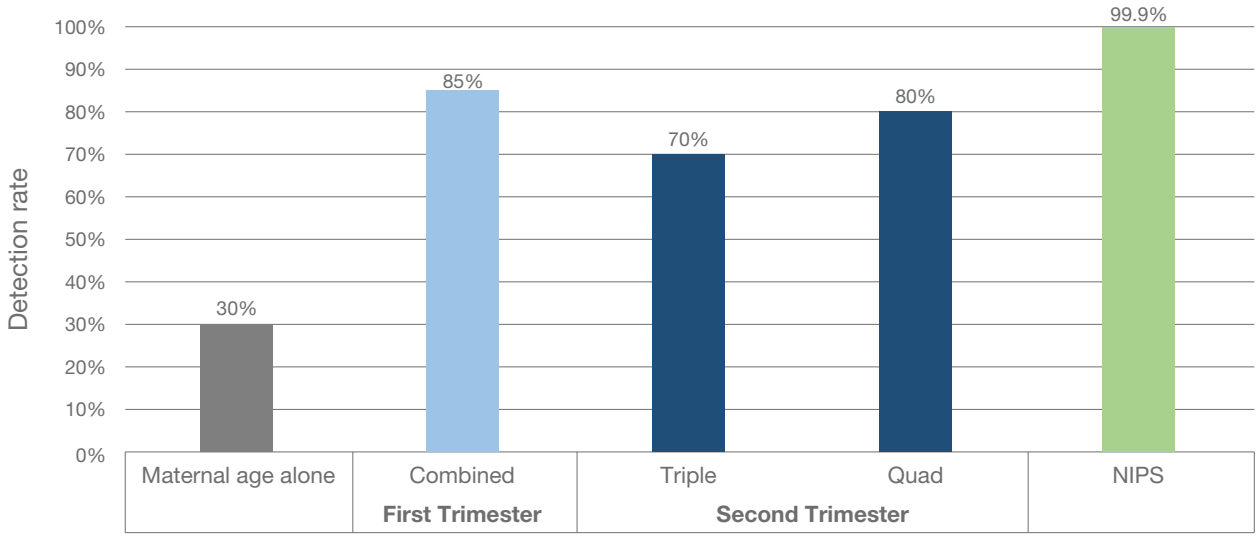
It is strongly recommended that ALL patients and their partners have pre-test counselling. This aims to provide couples with comprehensive information that allows them to make informed, preference-based test choices. Current guidelines advise that all women should be offered aneuploidy screening, preferably in early pregnancy. Lancet Laboratories offers genetic counselling if required. Patients can email genetics@lancet.co.za for an appointment with the clinical geneticist.

The choice of screening test in the second trimester

The triple test evaluates three maternal serum markers: Alpha-foetoprotein (AFP), Unconjugated oestriol (uE3) and Human chorionic gonadotropin (HCG). The quadruple test includes the analyte Dimeric Inhibin A (DIA). Maternal serum AFP and uE3 levels are on average, reduced by 25 – 30%, and HCG and DIA are on average twice as high in pregnancies affected by Down syndrome compared to unaffected pregnancies.

The quadruple test is performed between 15 to 20 weeks and 6 days of pregnancy on a maternal blood sample. It reports risk for Down syndrome, neural tube defects (NTD) and trisomy 18. The quadruple test is superior to the triple test as it has a higher detection rate for Down syndrome. Integrated tests for screening will not initially be offered.

Figure 1. Performance of maternal age and screening options for Down syndrome



The bar graphs describe approximate detection rates attained at a fixed 5% false-positive rate for each of the screening tests. The chart was modified from Reference 1 to indicate screening tests offered by Lancet Laboratories.

- A combined test refers to a first trimester test based on ultrasound and maternal serum measurements: Nuchal translucency (NT), free beta HCG and PAPP-A, together with maternal age.
- The performance of the NIPS was added for comparative purposes.

Management of screening results

1. **LOW-RISK CATEGORY**
   This indicates that the foetus is at low- risk for Down syndrome (as defined by the specific laboratory cut-off), trisomy 18 and NTD. A low-risk result does NOT exclude the possibility that an affected foetus may require further investigations. The clinician should interpret the screening result in conjunction with clinical history (e.g. family history, previous delivery of an affected baby), radiological features and other elements of the pregnancy (e.g. recurrent vaginal bleeding). If there is still uncertainty, further options are available. These include definitive laboratory testing, NIPS, referral to a foetal medicine unit or specialist or high-resolution ultrasound scans.

2. **HIGH-RISK CATEGORY**
   A high- risk result indicates that the fetus is at increased risk for Down syndrome (and sometimes other conditions). After obtaining a high-risk screening result, it is helpful for the parents to consult with a genetic counselor. This will enable them to access and assimilate information regarding diagnostic and management options, including details about the natural history and features of the specific condition. Women who have a high-risk screen may choose secondary screening (e.g. NIPS) or a diagnostic procedure (e.g. amniocentesis for karyotyping).

Prenatal care and course of pregnancy in cases of down syndrome

Ongoing pregnancies with fetal trisomy are at increased risk for foetal demise.

- For Down syndrome, it is estimated that the risk of foetal demise between chorionic villus sampling and delivery is up to 30 - 50%, between diagnostic amniocentesis and delivery is up to 30 %, and between 24 weeks gestation and delivery is 7,4 %, excluding electively terminated pregnancies. Many of these losses are related to severe structural anomalies and the effect of trisomy 21 on placental function. In comparison, the risk of foetal demise was 0.4 % in a reference population of singleton pregnancies without anomalies or Down syndrome.
- For trisomy 18, spontaneous loss is estimated to occur before birth in 70 % of foetuses alive at 12 weeks of gestation and 65 % of those alive at 18 weeks. A high proportion (33%) are stillborn.

Prenatal, intrapartum, and postpartum care are provided according to usual obstetric standards. Ultrasound examination at 18 to 22 weeks is the optimum time to evaluate the foetus for congenital anomalies associated with Down syndrome. In a systematic review of 24 American studies (1995 to 2011) that reported data for pregnancies with definitive prenatal diagnosis of Down syndrome and subsequent pregnancy termination, the weighted mean termination rate was 67% (range 61 to 93 %).

Conclusion

Pretest counselling followed by prenatal screening tests for foetal anomalies are recommended to all pregnant women worldwide. The widespread implementation of prenatal screening programmes combined with prenatal diagnosis and pregnancy termination has substantially reduced the number of Down syndrome births.

The quadruple test replaces the triple test as the screening test during the second trimester of pregnancy. This is supplemented by analysis of test results and guidance to referring doctors by a team of dedicated pathologists with expertise in foetal medicine laboratory tests.

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