

Challenges and Controversies in Prenatal Genetic Screening in the South African Context

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Abstract

Prenatal genetic screening is an integral part of general antenatal care and is regarded as standard of care for all pregnant women. All pregnant women < 20 weeks gestation should be offered some form of genetic screening and this should be discussed in an extensive pre-test counselling session. Late screening (after 20 weeks) may also be offered but will be limited by management options. Cell-free DNA testing has added another dimension to the landscape of prenatal screening but has to be appropriately used for the correct indication. Interpretation of risk for Down's syndrome is a critical component of the screening process. A guideline would be to regard screening risks in absolute terms as there is no provision made to interpret risk in relative risk terms. An important safeguard to overcome the "relative risk" conundrum would be to inform all patients during pre-test counselling of an intermediate risk category generally between 1:300-1:1000 where cfDNA testing may be considered, at the parents' own discretion. If the screening risk is <1:1000, no further testing is advised as this risk is deemed very low. A screening risk for Down's syndrome >1:300 will be deemed high risk, as is presently the case.

In counselling expecting parents concerning prenatal screening for chromosomal abnormalities e.g. Down's syndrome (T21), the key principle is that it should be voluntary, should be easily understood with clear and complete information that allows patients to make informed, preference-based screening and diagnostic testing decisions.¹

The approach should be able to empower expecting parents to understand the limitations and consequences of prenatal screening, and balance this with the issues involved in raising a child with a chromosomal anomaly or termination of pregnancy. Written information of prenatal screening and diagnosis is desirable to ensure

that they have a clear understanding about all the relevant issues.

During prenatal visits some of the aspects relating to prenatal screening that should be discussed^{2,3} include an explanation of the differences between a screening test and diagnostic test, the potential consequences of prenatal screening, what constitutes a high risk, low risk and intermediate low risk result, a description of the performance of available screening and diagnostic tests, the option of diagnostic testing instead of screening, the procedure related risks of diagnostic testing, information about the length of time necessary to obtain results from screening and diagnostic testing, the implication of having a child with Down's syndrome, the detection of chromosomal anomalies other than Down's syndrome and the implications of having a child with one of these other anomalies, information about the option of continuing

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the pregnancy, pregnancy and delivery management, paediatric care and resources for families with an affected child and information about the option of termination of pregnancy. All of this should be documented in the woman's medical record.

The next question is who are candidates for prenatal screening and diagnostic testing? The American College of Obstetrics and Gynaecologists (ACOG) recommends that all women should be offered some form of prenatal screening before 20 weeks of gestation^{2,4} and that would be in keeping with the practice in the South African context although locally it is often still offered at gestations beyond 20 but before 24 weeks. The question of testing for Down's syndrome post 24 weeks in the context of no major physical anomaly on sonography would be the individual couple's decision, as most fetal centres in this country would not offer a fetocide procedure and interruption of pregnancy in the event of an abnormal result in this scenario. The parents however could still request testing to prepare for the arrival of a child with special needs. ACOG also recommends that all women should have the option of a diagnostic/invasive test regardless of age.^{2,4} This has not been the general practice in the South African context with limited resources and cost constraints, where invasive testing has traditionally been offered to women presenting with a "high risk" result following one or more of a variety of screening tests, including ultrasound assessments, blood tests and maternal age, parental chromosomal rearrangements or past history of a fetus or infant with Down's syndrome.

There are multiple options of screening tests and the type of screening offered or chosen is often dependent on the availability of expertise for high level screening scans, laboratory access, types of biochemical aneuploidy screens available locally and importantly, especially in the South African context, cost. Generally the most accessible and therefore most widely used approach is assessment of maternal serum levels of specific biochemical markers associated with Down's syndrome, with or without assessment of specific ultrasound markers.⁵ The ultrasound assessment could be a first trimester scan using nuchal translucency and nasal bone (and other chromosomal markers like absent A wave in the ductus venosus or tricuspid regurgitation, if the expertise is there) performed by an operator accredited by the Fetal Medicine Foundation, which in combination with biochemistry will have a sensitivity of 85-90% for a 5% false positive rate for T21 (at a risk cut-off of 1:300) or could be a genetic sonogram performed by an accredited operator between 18-23 weeks gestation (with a sensitivity in the region of 75% for a false positive rate of approximately 10% when using a specific risk calculation algorithm). This approach may also detect other less common disorders like T13 and 18

and certain structural anomalies. A "super screening" test with very high detection rates for Down's syndrome by measuring cell free DNA in maternal blood is also available⁶ but, mainly due to cost, is currently not recommended as initial screening in women at low risk for fetal aneuploidy and is in most countries reserved for pregnant women above a certain risk threshold after conventional screening. This would be appropriate in the South African context too.

Management of Screening Results

Screen negative test result:

A screen negative result means that the fetus is at low risk for Down's syndrome and Edward's syndrome (trisomy 18 or T18) as defined by the specific laboratory cut-off (e.g. <1:300). It does not exclude the possibility of Down's syndrome or trisomy 18 or the possibility of a chromosomal anomaly not targeted by the screening test but detectable with diagnostic testing.⁷ It is not appropriate to tell women with a low risk result that the test is "normal" or "negative" as they may interpret this to mean their baby has a definitely normal karyotype. However the detection rate of the specific test should be clearly spelt out to the parents (e.g. the combined 11-14 week screen has an 85-90% detection rate for a 5% false positive rate whilst the second trimester biochemical triple test has a 60% detection rate for a 5% false positive rate⁸) and the pre- and post-test results for Down's syndrome and T18 provided in the report should be discussed as well. Generally after a low risk result further testing for Down's syndrome or trisomy 18 is not recommended.

Screen positive test result:

A screen positive result means that the fetus is at increased risk for Down's syndrome as defined by the specific laboratory cut-off (e.g. >1:300). The parents need to be counselled in detail about the pre- and post-test result and it needs to be explained that a high risk result does not mean the fetus definitely has the chromosomal anomaly as false positive results occur with all screening tests. Testing may be escalated to either a cfDNA test or invasive/diagnostic test, depending on how high the risk is and on which of the markers is contributing to the high risk. If, for example, the high T21 risk emanates from an elevated nuchal translucency on the sonogram or if the overall risk is very high say >1:10 (this cut-off could vary from unit to unit) the counselling would be directed towards doing an invasive test rather than cfDNA test whilst if the risk is positive but above 1:10 to 1:300 for example (this again could vary from unit to unit) and if the risk is mainly emanating from abnormal biochemistry rather than a strong sonographic marker the counselling would be more directed to cfDNA rather

than an invasive test. CfDNA could also be offered in a high risk patient where the risk is emanating from a soft marker with a low likelihood ratio in the context of a positive biochemical screen. The general principle is that if the likelihood is very high for one of the common trisomies or a genetic condition other than Down's syndrome, the counselling should be directed towards invasive testing rather than cfDNA, because a positive result on the cfDNA test will still need to be confirmed with an invasive/diagnostic test, or cfDNA may be false negative for rarer karyotype abnormalities. Another option would be that the patient can be offered a genetic sonogram by a fetal medicine specialist to re-calculate the risk based on additional information obtained during the expert scan to assist the patient in deciding for or against invasive testing⁹ if the result of such an adjustment is that the risk is now deemed low. The sensitivity of this type of risk adjustment using ultrasound is 78-85% for Down's syndrome.

It is also important to note that detection rates and false positive rates vary significantly with maternal age but there are scant publications in this area.^{10,11} It is for example not appropriate to counsel a 20 year old that the test will identify 60% of cases when for her the detection rate is closer to 40% or to counsel a 40 year old that the false positive rate is 5% while it is in fact 40%, due to the difference in prevalence of the condition at 20 years and 40 years, as risks increase with advancing age. Using the 2nd trimester triple test approach, Reynolds et al¹¹ showed that detection and false positive rates increased from 44% and 3% at 16 years, to 56% and 6% at 30 years to 91% and 40% at 40 years. As with 2nd trimester screening, detection rates and false positive rates with combined screening in the first trimester vary with maternal age from 77% and 1.9% at 15 years, to 84% and 4% at 30 years to 96% and 34% at 40 years.¹¹ Since the odds of a positive result vary with maternal age, this information may be useful in the process of counselling women before screening, as well as when an increased risk result is obtained in both the first or second trimester screening.

The controversial question of how to interpret "a screen negative result" (whether in absolute risk terms or relative risk terms) is important and has implications and ramifications especially for the busy generalist. For example if the background T21 risk in a 22 year old patient is 1:1200 and the screen result reveals a risk of 1:400, in absolute terms she still screens low risk for T21 but in relative risk she in fact has a 3-fold increase in her risk – does this now change her risk to a high risk status for which she needs to be offered escalated testing? A literature survey of this controversial question shows that present screening tests do not make provision for the interpretation of relative risk as most of the studies dealing with genetic screening

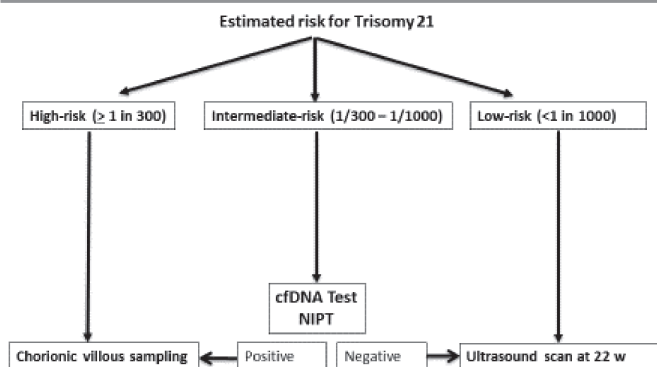
are population-based studies^{4,5,12,13} and risk cut-offs are based on a balance between high detection rates and low false positive rates with most statistical risk cut-offs set at 1:250-1:300, giving detection rates for T21 between 60 and 90% for a particular false positive rate between 3 and 5%, depending on the type of screening test. The busy generalist may not have in-depth knowledge of risk, sensitivity and specificity rates of all the different genetic screening tests and may therefore interpret every low risk result as low risk. In the context of an a-priori risk that was substantially lower than the post-test risk, one can actually not advise the clinician what relative risk increase should trigger escalation to further testing as there is no provision for this type of risk interpretation in the literature. It would thus be a subjective interpretation. On this basis one could expect that there should be no legal ramifications in the event of a low risk but false negative result when the relative risk was increased by the screening test, as long as proper counselling was provided pre-test. In reality however, the legal question pertaining to absolute versus relative risk could be open to interpretation in a litigated case depending on the opinion of the expert witness and how the court receives it, which could impact on the outcome of the claim. Therefore some guidelines are essential. This question would have been very difficult in the pre-cfDNA test era as the clinician would need to justify an invasive test in what would be a low risk result but a perceived "high" relative risk, and there is no good data for this. In the era of cfDNA testing this problem can easily be resolved by creating a category of "intermediate" risk from between 1:300 to 1:1000, for which cfDNA testing can be offered. This option should become part of the routine pre-test counselling. Thus to obviate this controversy of interpretation of absolute versus relative risk, it could be advocated to the generalist as a guideline to include in the pre-test counselling an additional category of "intermediate risk" from 1:300-1:1000 where parents will be given the option of cfDNA, with the parents themselves ultimately deciding whether they want to exercise this option or not.

Conclusions

Prenatal genetic screening is an integral part of general antenatal care and is regarded as standard of care for all pregnant women. All pregnant women < 20 weeks gestation should be offered some form of genetic screening and this should be discussed in an extensive pre-test counselling session. Late screening (after 20 weeks) may also be offered but will be limited by management options. Cell-free DNA testing has added another dimension to the landscape of prenatal screening but it has to be appropriately used for the correct indication, should not be mis-used, and most importantly should be

regarded as complementary and not exclusive to current screening methods. Interpretation of risk for Down's syndrome is a critical component of the screening process. A guideline would be to regard screening risks in absolute terms as there is no provision made to interpret risk in relative risk terms. An important safeguard to overcome the "relative risk" conundrum would be to inform all patients during pre-test counselling of an intermediate risk category generally between 1:300-1:1000 where cfDNA testing may be considered, at the parents' own discretion (Fig 1). If the screening risk is <1:1000, no further testing is advised as this risk is deemed very low. The concept of offering cfDNA testing to an "intermediate risk" group is not new and some fetal units internationally are already following this protocol.

Figure 1: General Management Algorithm in Managing T21 Risks using Combined Risk Assessment at the First Trimester Scan



Modified from Nicolaides, *Advances in MFM* 2013, London

All positive or high risk cfDNA test results will need to be confirmed with an invasive test.

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