



Prenatal Screening for Foetal Down Syndrome

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 March 2009.

Introduction

Down syndrome is the most frequent chromosomal disorder among live-born children, with an expected prevalence of 1/600-800 live births. Conventionally, prenatal testing (screening or invasive) for Down syndrome has been offered to women aged 35 or above because they are at a higher risk than younger women. However, the detection rate is as low as 30% while the rate of invasive testing can be as high as 30%. Recently, the American College of Obstetrics and Gynecology (ACOG) recommends that all pregnant women, regardless of their age, be offered screening for Down syndrome.¹ This approach can detect 85% of Down syndrome at an invasive testing rate of 5%.

Several studies were performed on the isolation and analysis of maternal plasma foetal nucleated cells,² total cell-free DNA,³ foetal DNA⁴, and placental expressed mRNA,⁵ and have found that it is feasible to detect foetal trisomy 21 non-invasively. However, these new non-invasive genetic based approaches have not been applied in clinical practice yet and are beyond the scope of this review. This article will discuss the various Down syndrome screening tests which are available in Hong Kong (Table 1). The timing, sensitivities and false positive rate of these tests vary.

It is a complex decision-making process for an individual woman to choose one out of these screening tests. An appropriate non-directional counselling is required to help women make an informed decision.

Aged 35 or Above

Conventionally, women aged 35 or above are offered an option of invasive procedure including chorionic villus sampling or amniocentesis. However, these procedures are invasive and associated with 0.5 to 1% miscarriage rate. More and more women in Hong Kong choose to start a family later in recent years. This approach will mean that over 20% of pregnant women in Hong Kong will have to undergo an invasive procedure. Therefore, the current approach is to offer these women an option of a screening test which can detect around 85% of Down syndrome fetuses at a false positive rate of around 5%. If the screening test shows a negative result,

an invasive test can be avoided. Women need to understand that screening test may miss a small proportion of fetuses with Down syndrome. In 2007, in a teaching hospital where screening test was offered as an alternative to direct invasive tests, 68% of women aged 35 or above preferred some form of screening test.⁶

Age Below 35

Although advanced maternal age is a risk factor for Down syndrome, 70% of the children with Down syndrome are born to women below 35. Therefore, these women should also be offered a screening test. Although the test itself is noninvasive, a woman will have to make the decision on an invasive test if the result of the test turns out to be positive. Adequate pre-test counselling is essential.

Other Risk Factors

If a woman has a previously affected child, or either one of the couple carries balanced structural rearrangements of chromosome 21, she is at high risk of carrying a foetus with Down syndrome. A direct invasive test is recommended for these women. Other family history of Down syndrome, unless associated with a translocation involving chromosome 21, is usually not associated with a significantly increased risk to warrant direct invasive tests.

Which Screening Test?

Second Trimester

In the Hong Kong Hospital Authority (HA), second trimester screening test in the form of double markers (hCG and alpha-foetal protein) between 15 and 20 weeks' gestation has been offered to women aged 35 or above. The sensitivity is 63% at 5% false positive rate. First trimester nuchal translucency measurements (NT) were available in some HA hospitals in addition to the second trimester serum markers. The sensitivity of this two staged integrated testing is 85% at 5% false positive rate.⁷ The sensitivity of second trimester serum test can



be increased by using triple markers (adding Oestriol) or using quadruple markers (adding oestriol and Inhibin A).⁸ These are available in some private laboratories in Hong Kong. It is important to note that all serum markers vary with gestational age (some increase with gestational age and some decrease with gestational age) and need to be converted to MoM (multiple of median) according to gestational age. Therefore, ultrasound determination of the gestational age will improve the performance of these tests.

Second trimester screening allows spontaneous fetal loss to occur and thus reduces the likelihood of electively terminating a pregnancy that was destined to be spontaneously miscarried. However, if fetal aneuploidy is found, termination of pregnancy may have to be performed after 16 to 18 weeks' gestation.

First Trimester

For a woman who wants to know their Down syndrome risk early, first trimester screening based on NT (between 11-13^{6/7} weeks gestation) and maternal serum PAPP-A and free-beta hCG can be offered.⁹ The maternal blood test can be done on the same day of the NT or slightly earlier. The main advantage of first trimester over second trimester screening is that it allows earlier prenatal diagnosis (provided that chorionic villus sampling is available) and thus earlier pregnancy termination if aneuploidy is detected. However, approximately 9% of all Down syndrome fetuses viable in the first trimester are lost spontaneously before the second trimester,¹⁰ and thus early detection may lead to some unnecessary invasive diagnostic and pregnancy termination procedures. Fetal nuchal translucency (NT) increases with crown-rump length (CRL), and so it is important to take gestational age into account.¹⁰ The NT measurement is converted into MoM (multiple of median) or delta-NT (difference from the median) for the gestational age based on CRL for risk calculation. Strict guidelines of technique of measuring NT has been well documented.^{11,12}

Two Stage Tests:

Integrated First and Second Trimester Test:

For women who want to choose a more sensitive screening or to reduce the false positive rate (thus reducing the risk of procedure related fetal loss), a two staged integrated first and second trimester test, combining NT and all the first and second trimester serum markers, can theoretically achieve a detection rate of around 90% with a false positive rate of around 2%.⁸ However, the risk estimate will only be available after the second trimester test is completed. Furthermore, some women may miss the second part of the screening test.

Step-wise Sequential Screening:

This means women undergo a first trimester screening first and if the result is positive, an early invasive procedure will be offered. If the first trimester result is negative, a second trimester screening is done. The risk calculation is then based on combining the first and second trimester markers, not on the second trimester

markers alone. This approach will increase the detection rate at the expense of a slight increase in the false positive rate.¹³

Contingent Sequential Screening:

This means women undergo a first trimester screening first. Based on this result, they are classified into three risk categories: high, intermediate and low risk. Only those at high risk will be offered definitive diagnosis by CVS; those determined to be at low risk will have no further screening and those at intermediate risk will go on to the second trimester screening test.¹⁴ It was calculated that for an overall false positive rate of 5%, 94% Down syndrome detection rates can be achieved, with 70% of the cases detected in the first trimester, and only 15% of women requiring a second trimester test.¹⁴

The principles of sequential contingent screening can be applied to a two-stage test, all completed in the first trimester. Instead of waiting for a second trimester serum test, women with intermediate risk can be offered further first-trimester ultrasound assessment for presence or absence of the foetal nasal bone, increased resistance to flow in the ductus venosus and for tricuspid regurgitation. Patients with a positive secondary ultrasound marker will be offered CVS, whereas those with absence of these markers will be considered screened negative. This approach can still identify more than 90% of affected foetuses while reducing the false positive rate to 2-3%.¹⁵ However, ultrasound assessment of these markers is technically demanding. This approach cannot be widely applied

Genetic Sonogram

The genetic sonogram is a systematic algorithm combining multiple individual ultrasound markers during the second trimester to improve Down syndrome risk assessment. Markers include major structural malformations, shortened humerus or femur, and other anatomic findings such as increased nuchal skin thickness, pyelectasis, echogenic intracardiac focus, hypoplastic fifth digit, sandal gap toe, echogenic bowel and widened iliac angle.¹⁶ The absence of any marker on a second trimester scan conveys a 60-80% reduction in prior risk of Down syndrome based on advanced maternal age or serum screen risk. On the other hand, risk is adjusted in the presence of multiple sonographic markers by multiplying age-related risk by the product of the respective ultrasound markers' likelihood ratios. Although this concept was applied in high risk referral populations¹⁷, a large meta-analysis concluded that sonographic markers are not of practical value in the low-risk population probably due to the variability in obtaining and interpreting these markers, operator experience, sonographic equipment and quality control.¹⁸ Therefore, a genetic sonogram is not recommended as the primary screening method for foetal Down syndrome. Its use is mainly for women who want to reduce the need of invasive tests following a positive integrated test or second trimester serum test. Furthermore, most of these studies were performed on Caucasian subjects. Ethnic variations in these markers, such as the humerus length and prevalence of echogenic intracardiac focus in normal foetuses must be



taken into consideration. Caution is needed when applying these markers to the Asian population.

Multiple Pregnancy

NT measurement which is foetus-specific, seems to be a promising method of screening in these women.¹⁹ The addition of maternal serum analytes may improve the sensitivity of first trimester screening. A 80% detection rate of Down syndrome for a 5% false positive rate using NT and first trimester serum makers has been reported.²⁰ However, a large discordance between the NT in a pair of monochorionic twins is more likely to be an early sign of twin-twin transfusion, rather than a risk of chromosomal aneuploidy.

Pregnancies Conceived After Assisted Reproduction Technology

It seems that there is a significant impact of assisted reproduction technology (ART) on second, but not first, trimester markers and the screen positive rates. Therefore, an appropriate adjustment in the second trimester screening protocol should be considered to reduce the unnecessary anxiety and miscarriage related to invasive diagnostic tests.²¹

Conclusions

The first trimester combined test performs at least as well as the traditional second trimester quadruple screen and 12 weeks appears to be the optimal time for screening if anomaly scan is performed as well. This is recommended for women who want early screening and diagnosis. For women who want a higher detection rate or to reduce the risk of procedure related loss, the integrated or contingent sequential screening can be offered, provided that they accept the possibility that the screening may not be completed until the second trimester. For women who first seek antenatal care after 14 weeks of gestation, second trimester serum screening can be offered. Where available and affordable, quadruple test performs better than triple or double test.

Table 1 Down syndrome risk assessment approaches in Hong Kong

<p>A. First trimester screening</p> <ol style="list-style-type: none"> 1. Combination of nuchal translucency (NT) + Pregnancy associated plasma protein-A (PAPP-A) and free β-Human chorionic gonadotrophin (free β-hCG) 2. Individual risk-oriented two-stage screening for Down syndrome: First trimester test (NT + PAPP-A + free β-hCG) + diagnostic test (if high risk), further ultrasound assessment of fetal nasal bone, ductus venous, and triscupid regurgitation (if intermediate risk), or nothing (if low risk).
<p>B. Second trimester screening</p> <ol style="list-style-type: none"> 1. Double screen: maternal serum alpha-fetoprotein (MSAFP), hCG, 2. Genetic sonogram: multiple ultrasound markers 3. Extended sonogram: serum screen + ultrasound markers
<p>C. First and second trimester screening</p> <p>(i) Integrative (nondisclosure of first trimester results)</p> <ol style="list-style-type: none"> 1. Integrated (NT, PAPP-A, double screen)
<p>(ii) Sequential first and second trimester screening (disclosure of first trimester results)</p> <ol style="list-style-type: none"> 1. Step-wise: first trimester test + diagnostic test (if positive) or second trimester test (if negative); final risk estimate incorporates both test results 3. Contingent: first trimester + diagnostic test (if high risk), second trimester test (if intermediate risk) or nothing (if low risk)

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