Singapore Journal of Obstetrics and Gynaecology
2006; 37(1): 19-26

Review Article

First Trimester Screening For Down Syndrome

TL Tan, TYT Tan

INTRODUCTION

Down syndrome (DS) or trisomy 21 is the commonest fetal chromosomal disorder, occurring in one in every 700 live births.[1] This was first described by Dr John Langdon Down in 1866 when he noted that there was a group of patients characterized by deficiency in skin elasticity, giving the appearance of being too large for the body, having a flat face, small nose and eyes that often slanted upwards and outwards, the so-called Mongolian features. DS is also characterized by mental retardation and other medical problems such as cardiac abnormalities. It is the most common genetic cause of severe learning disabilities in children.

The diagnosis of Down syndrome in the fetal period requires invasive testing, commonly by amniocentesis and chorionic villous sampling (CVS). These procedures are carried out to procure fetal cells that are required for karyotyping. However, these invasive tests are not without risks. Amniocentesis carries a 0.5-1% risk of fetal loss when done during 15-20 weeks of gestation. CVS, on the other hand, affords an earlier diagnosis as it could be performed after 10 weeks of gestation and is associated with a procedure-related loss rate of about 1%. As such invasive diagnostic procedures are associated with a small risk of miscarriage, these procedures are generally reserved for patients screened to be high risk for DS.

TL Tan
Medical Student
National University of Singapore

TYT Tan
Consultant
Department of Maternal Fetal Medicine
KK Women's and Children's Hospital
Correspondence to:

Dr Tony Tan
Department of Maternal Fetal Medicine
KK Women's and Children's Hospital
100 Bukit Timah Road
Singapore 229899
Email: Tony.Tan.YT@kkh.com.

Screening allows pregnant women of all ages to be evaluated for the risk of DS, with those who are high risk being offered diagnostic tests. Since June 2004, the Premier First Trimester Screening (FTS) Programme in KK Women's and Children's Hospital (KKH) has been implemented to screen patients at 11 to 13^{+6} weeks gestation for DS. The method utilizes maternal age, ultrasound scan to measure nuchal translucency and nasal bone and/or maternal serum screening either in the first or second trimesters to determine the risk of DS.

ULTRASOUND ASSESSMENT

Ultrasound assessment is made in the following 3 aspects:
(a) Nuchal translucency (NT) measurement
(b) Presence or absence of nasal bone
(c) Presence or absence of other structural abnormalities

NT measurement

NT refers to the sonographic appearance of fluid behind the fetal neck and back in the first trimester of pregnancy.[2] During the first trimester, the term translucency is used regardless of whether it appears septated or clear, and whether the fluid appears confined to the neck or it envelops the whole fetus. The size of the NT increases with gestational age as well as crown-rump length (CRL).[3] After 14 weeks gestation, the NT becomes less visible due to increase echogenicity of the subcutaneous tissue4 and also because it becomes technically more difficult to obtain a picture of the fetus in a horizontal position. A NT measurement higher than the 95th percentile increases the likelihood of a fetal chromosomal abnormality.[5]

Technique of NT measurement

In 95% of patients, nuchal translucency can be measured successfully by transabdominal ultrasound, however, in the other 5%, it may be necessary to perform transvaginal sonography to supplement the findings.

The appropriate time for measurement of NT is when the fetal CRL is 45 to 84 mm, corresponding to

gestational age of 11 to 13^{+6} weeks. The success rate for taking a measurement at this gestation is 98–100%, falling to 90% at 14 weeks. Measurements should be taken with the fetus in the neutral position. When the fetal neck is hyperextended, the measurement can be increased by up to 0.6mm and when the neck is flexed, the measurement can be decreased by up to 0.4mm.[6]

For a correct measurement, care must be taken to distinguish between fetal skin and amnion because both structures appear as thin membranes at this gestation. This is achieved by waiting for spontaneous fetal movement away from the amniotic membrane; alternatively, the fetus is bounced off the amnion by asking the mother to cough and/or by tapping the maternal abdomen.

The maximum thickness of the translucency between the skin of the fetus and the tissue overlying the cervical spine should be taken. The crossbar of the caliper should be placed such that it is hardly visible as it merges with the white line of the border, care should be taken that it is not in the nuchal fluid. During the scan, more than one measurement should be taken. These are strict guidelines recommended by Fetal Medicine Foundation (FMF) in the correct technique of NT measurement.[7]

The effect of training and accreditation

Appropriate training and accreditation ensures a high standard of clinical practice and better detection rates. Because the measurements of NT are to the nearest tenths of millimeters, inter-operator variability can cause measurements to be inaccurate and thus, detection rates to fall.[8,9]

Accredited sonographers recognized by FMF have undergone stringent training and have met standards that satisfy FMF standards. They are also required to regularly submit to the FMF their NT measurements and representative images for audit. Monni et al reported that after modifying their technique of measuring NT by following the guidelines established by the FMF, detection rate of trisomy 21 improved from 30% to 84%.[10]

Possible causes of increased NT in DS

The exact aetiology of increased NT is not well known. However, evidence from ultrasonographic and postmortem studies show that possible causes of increased NT include cardiac failure, abnormalities in the extracellular matrix of the thickened nuchal skin and abnormal lymphatic development.

Nasal Bone

The nasal bone of the fetus can be visualized using ultrasound by the 10th weeks.[11] At 11-14 weeks, it is absent or hypoechogenic when compared to the overlying nasal skin in 60-70% of DS fetuses. This could be due to the delay in ossification of the nasal bone in DS fetuses.[12] Thus it can be used as an additional marker for DS during the first trimester.[13-15] A more in-depth discussion on the role of nasal bone in screening for DS written by Zuzarte et al has been published in the previous issue of KK Hospital Review.

Structural abnormalities

Some structural abnormalities (e.g. exomphalos) detected in the fetus at $11\text{-}13^{+6}$ weeks gestation may also increase the risk of DS and other chromosomal abnormalities.

MATERNAL SERUM SCREENING (MSS)

First Trimester MSS

Biochemical markers used to screen for DS in the first trimester are maternal serum free beta human chorionic gonadotropin (b-hCG)[16-18] and pregnancy associated plasma protein A (PAPP-A).[17,18] During normal pregnancies, the maternal serum levels of free b-hCG decrease while PAPP-A increase with gestation.

In DS pregnancies, free b-hCG levels and PAPP-A levels are comparatively higher and lower respectively.[18] As gestation progresses, the difference between levels of free b-hCG found in normal pregnancies and the high levels of b-hCG found in DS increases.[17] The pathophysiology for increased hCG levels remains unknown. It is postulated that an increase in b-hCG promoter activity in DS-derived fibroblasts increases transcription of the beta chains.[16] The mechanism of reduction of PAPP-A in DS is similarly uncertain. PAPP-A is produced in the primarily in the placenta and secondary in the deciduas. A general decrease in trophoblastic function may account for this decrease in fetal chromosomal abnormalities.[19]

The detection rate using PAPP-A alone is about 40% and, in combination with maternal age, the detection increases to about 50%.[20] When maternal age, PAPP-A and free b-hCG are used, the detection rate is 60% - 70% for a 5% false positive rate.[21-23]

Second Trimester MSS

In KKH, the second trimester MSS programme utilises AFP and b-hCG levels for the screening of DS. In studies done in Asian population, second trimester MSS detection rates are 48% - 56%, at a false positive rate of 3% - 6%.[24-27] This compares favorably with first trimester maternal serum screening.

Table 1. Detection Rates of Various Down syndrome Screening Programmes

Test	Detection rates	False Positive Rate
Maternal Age (>= 35yrs at birth)	30%	5%
Maternal age and 2nd trimester MSS (b-hCG, AFP, uE3)	60 - 73%	4 - 8%
Maternal age and 2nd trimester screening scan	60 - 80%	4 - 12%
Maternal age, 2nd trimester MSS and 2nd trimester screening ultrasound	75-90%	10% - 15%
Maternal age and 1st trimester MSS (b-hCG & PAPP-A)	60% - 70%	5%
Maternal age and 1st trimester NT	73% - 82%	5%
Maternal age, 1st trimester NT & NB	90% - 92%	5%
Maternal age, 1st trimester NT & 1st trimester MSS	90%	5%
Maternal age, 1st trimester NT & NB & 1st trimester MSS	97%	5%
Maternal age, 1st trimester NT and trimester MSS	95% 90%	7.2%, 5%

WHY SCREEN FOR DOWN SYNDROME DURING THE FIRST TRIMESTER?

The 11-13+6 weeks gestation presents a window of opportunity for the measurement of one of the best markers for DS which is the NT. It also allows invasive diagnostic test to be performed earlier in pregnancy if one is screened positive. When screened negative, it allows the couple to be reassured earlier as well. NT increase can be transient and may not be seen after 14 weeks of gestation. The decrease in echogenicity of the tissue after 14 weeks may play a role. The fetus also tends to assume a vertical position after 14 weeks and thus makes NT measurement more difficult to visualize.

Screening during the first trimester also allows the patient option of termination of pregnancy during the first trimester as opposed to second trimester. Second-trimester fetal aneuploidy screening by either biochemical or sonographic markers implies late decisions and eventually late pregnancy termination, with possibly more detrimental effects on psychological and physical maternal health.[28]

Informed patients are aware that women at any age may give birth to a child with DS. They show a preference to go for screening at the first trimester, provided the test is sensitive and has a low false positive rate.[29,30] Seventy-six percent of women who participated in a study, preferred screening to have been in the first trimester, mainly because of the easier termination of pregnancy and/or the earlier reassurance provided.[31]

Screening during the first trimester is more cost effective. A first trimester screening approach that used NT measurement and MSS was evaluated against second trimester maternal serum triple screening. Screening sensitivities and screen-positive rates were 91% and 5% for the first trimester approach and 70% and 7.5% for the second trimester approach, respectively. The costs of fetal DS, live-born DS cost, and total costs (screening plus live-born costs) were calculated for each screening program. Resultsshowed that first trimester screening was associated with lower screening and live-born DS costs versus second trimester serum screening. Total DS screening costs were 29.1% lower with first trimester screening. This showed that first trimester screening for fetal DS was more cost-effective than universal second trimester MSS in the setting reported.[32]

A Point of Contention for Some

Some clinicians do not endorse screening during the first trimester because they believe that DS fetuses detected during screening early in the pregnancy were more severely affected fetuses, and thus screening during the first trimester would only detect DS fetuses that were destined to miscarry.

Dunstan and Nix provided a statistical methodology to calculate rates in which first trimester screening had to achieve to be better that the respective second trimester detection based on a major study done by Morris in 1999[33]. Detection rates for screening programs during the second trimester range from 60%-75%, thus first trimester detection rates would have to be 64%-75% in order to better a second trimester detection rate of 60%, and 78%-86% in order to better a second trimester detection rate of 75%.[33]

In a study of over 100 DS fetuses diagnosed in the first trimester, the parents chose to continue with the pregnancy in 5 cases, whereas in the other 103 cases they opted for termination.[34] DS was also diagnosed in one of the fetuses in a twin pregnancy where the parents decided against fetocide. Thus making the total number of DS fetuses in this study to be 6. In 5 of the 6 fetuses, the translucency resolved, and at the second-trimester scan the nuchal-fold thickness was normal. All 6 trisomy 21 babies were born alive. This data suggest that increased nuchal translucency detected in FTS does not necessarily identify those destined to die in utero.[34] Very few would opt to continue their pregnancy when DS is diagnosed, thus few studies are done on this aspect.

EFFECTIVENESS OF SCREENING

Comparison of screening strategies for DS shows that FTS in various combinations is the best strategy in terms of detection rates.[8-10,21,22,26-28,35-42]

First trimester screening in advanced maternal age FTS has been shown to decrease the rate of invasive testing in high risk women (>35 years of age).[43] Studies show that false-positive rates increased with maternal age from 6.6-18% at 35 years to about 50-60% at 40 to 41 and 100% in women over 41. It was shown that screening in this high risk group did not compromise the detection of trisomy 21 and was able to reduce invasive testing by 94% at 35 years down to 50% at 40 to 41 years.[44] Thus it is economically more sensible to screen first, but more importantly fewer fetal loses would occur. This point is substantiated by other studies using different screening techniques.45-47

Birth Prevalence of Down syndrome

Studies both overseas and locally have seen a drop in the birth prevalence of DS that probably results from the implementation of DS screening policies.

In a study looking at the years 1993-1998, the livebirth prevalence of DS in Singapore has fallen over the years from 1.17/1000 livebirths in 1993 to 0.89/1000 livebirths in 1998 due to antenatal diagnosis and selective termination48. This is due to increased awareness as well as increased willingness towards screening.

An evaluation was done in France on the effectiveness of screening policy implemented in 1996. The livebirth prevalence of DS decreased from 1 in 950 in 1990 to 1 in 1500 in 2000-2001. This decrease was observed from 1994 onwards but has proved stronger since 1996, in spite of the observed increase in the total prevalence partly explained by changes in the maternal age distribution.[49] This proves the effectiveness of screening for DS.

OTHER POSSIBLE FIRST TRIMESTER MARKERS

(A) Ductus Venosus (DV) Doppler studies
(B) Tricuspid regurgitation
(C) Fetal Heart Rate
(D) Urine Tests
(E) Maternal serum superoxide dismutase (SOD)
(F) Fetal ear length and shape

(A) Ductus venosus Doppler studies

The DV is a unique shunt that carries well-oxygenated blood from the umbilical vein through the inferior atrial inlet on its way across the foramen ovale. Blood flow in the DV of fetuses with chromosome defects may be abnormal due to cardiac failure, superior mediastinal compression, abnormal development of lymphatic system or altered composition in the subcutaneous tissue.[50] The association between increased NT and cardiac failure is based on the demonstration that a high proportion of chromosomally normal and abnormal fetuses with increased NT have abnormalities of the heart or great vessels.[51,52] DV flow may be absent or reversed during atrial contraction (i.e. absent or reversed “a” wave) in 90.5% of chromosomally abnormal fetuses.[53] Assessment of DV blood flow in high risk pregnancies may result in reduced need for invasive testing.

(B) Tricuspid regurgitation

Tricuspid regurgitation (TR) at 11 to 13^{+6} weeks gestation was present in 8.5% of chromosomally normal fetuses, in 65% of trisomy 21, in 53% of trisomy 18 or 13, and in 22% of other chromosomal defects.[54] The prevalence of tricuspid regurgitation however also increases with the presence of a cardiac defect and with fetal NT thickness. Experienced fetal echocardiographers performed these examinations. Likelihood ratios have been derived by the Fetal Medicine Foundation and have recently been incorporated into their software. Both examinations of DV and TR require the use of the Doppler function in the ultrasound machines, hence limiting its use to practitioners with better equipped ultrasound machines and trained in the use of Doppler and echocardiography.

(C) Fetal Heart Rate (FHR)

The FHR was measured at 10-14 weeks of gestation of 1,061 chromosomally abnormal fetuses and compared with 25,000 normal pregnancies. Only 10% of DS fetuses had FHR above the 95th centile of normal range.[55] This association with DS was independent of the association of thickened NT and DS.[56,57]

(D) Urine Tests

Using urinary beta core human chorionic gonadotropin fragment as a marker for DS, studies showed variable results with detection rates ranging from 20 to > 80%.[58,59] This wide range was due to differences in storage. It was important for fresh urine to be used in order to obtain a reliable result. The results of a 3 year prospective study done in 1999 revealed that the detection rate of Down using beta core fragment alone was 65%, when it was coupledwith maternal age, it was 66%.[59] However, in combination with NT, urine beta core hCG gave only an additional detection rate of 2%.[60]

(E) Maternal serum superoxide dismutase (SOD)

Superoxide dismutase (SOD: EC1.15.1.1) has been shown to increase in DS subjects and in amniotic fluid from DS affected pregnancies. This increase could be possibly due to triplicate set of genes coding for SOD in DS. In order to verify a possible increase of maternal serum SOD in

DS affected pregnancies and its possible contribution as a potential marker, the serum enzyme activity was retrospectively measured in samples from normal and DS affected pregnancies. The maternal serum SOD activity in the DS group (3.12+/-0.73 U/ml) was significantly higher ($p<0.001$) than in the control one (2.20+/-0.7 U/ml). The addition of SOD appeared to be capable of improving the sensitivity of detection.[61] However it is noted that in this study that the number of subjects were too few for the results to be statistically significant.

(F) Ear Length

Studies have shown that measuring the fetal ear length during the second trimester could be used as a marker for DS. The mean ear length and measured-to-expected ear length ratios were significantly lower in the affected group as compared to the normal one. A measured-to-expected ear length ratio of less than 0.8 was 75.0% sensitive and 98.8% specific in detecting Down syndrome fetuses, and resulted in an 8.5% positive predictive value in the general population.[62]

A study[62] done measuring ear length during the first trimester, in the DS fetuses the median ear length was significantly below the normal mean for crown-rump length by 0.45 mm ($p = 0.013$) but it was below the percentile of the normal range in only two (6.3%) of the cases. However the degree of deviation from normal is too small for this measurement to be useful in screening for DS.

CONCLUSION

FTS has been shown to have better detection rates (up to 97%) than second trimester screening strategies and has other added advantages such as facilitation, costs and earlier information. The prospect of inclusion of future markers, such as ductus venosus flow, look promising, and could be added to current forms of testing to further increase detection rates.

With improved education of DS and better awareness of screening, the rates of live births with DS can be reduced further.

REFERENCES

1. *Thein MM, Koh D, Tan KL, et al. Descriptive profile of birth defects among livebirths in Singapore. Teratology 1992; 46(3):277-84.*

2. *Haak MC, van Vugt JM. Pathophysiology of increased nuchal translucency: a review of the literature. Hum Reprod Update 2003; 9(2):175-84.*

3. *Pajkrt E, Bilardo CM, Van Lith JM, Mol BW, Bleker OP. Nuchal translucency measurement in normal fetuses. Obstet Gynecol 1995; 86(6):994-7.*

4. *Roberts LJ, Bewley S, Mackinson AM, Rodeck CH. First trimester fetal nuchal translucency: problems with screening the general population. 1. Br J Obstet Gynaecol 1995; 102(5):381-5.*

5. *Jauniaux E, Gavrill P, Khun P, Kurdi W, Hyett J, Nicolaides KH. Fetal heart rate and umbilico-placental Doppler flow velocity waveforms in early pregnancies with a chromosomal abnormality and/or an increased nuchal translucency thickness. Hum Reprod 1996; 11(2):435-9.*

6. *Whitlow BJ, Chatzipapas IK, Economides DL. The effect of fetal neck position on nuchal translucency measurement. Br J Obstet Gynaecol 1998; 105(8):872-6.*

7. *Broussin B, Sarramon MF. [Nuchal translucency: technical measurement and value]. J Radiol 2002; 83(12 Pt 2):1891-8.*

8. *Bewley S, Roberts LJ, Mackinson AM, Rodeck CH. First trimester fetal nuchal translucency: problems with screening the general population. 2. Br J Obstet Gynaecol 1995; 102(5):386-8.*

9. *Kornman LH, Morssink LP, Beekhuis JR, De Wolf BT, Heringa MP, Mantingh A. Nuchal translucency cannot be used as a screening test for chromosomal*

abnormalities in the first trimester of pregnancy in a routine ultrasound practice. Prenat Diagn 1996; 16(9):797-805.

10. *Bindra R, Heath V, Nicolaides KH. Screening for chromosomal defects by fetal nuchal translucency at 11 to 14 weeks. Clin Obstet Gynecol 2002; 45(3):661-70; discussion 730-2.*

11. *Kanellopoulos V, Katsetos C, Economides DL. Examination of fetal nasal bone and repeatability of measurement in early pregnancy. Ultrasound Obstet Gynecol 2003; 22(2):131-4.*

12. *Larose C, Massoc P, Hillion Y, Bernard JP, Ville Y. Comparison of fetal nasal bone assessment by ultrasound at 11-14 weeks and by postmortem X-ray in trisomy 21: a prospective observational study. Ultrasound Obstet Gynecol 2003; 22(1):27-30.*

13. *Odibo AO, Sehdev HM, Dunn L, McDonald R, Macones GA. The association between fetal nasal bone hypoplasia and aneuploidy. Obstet Gynecol 2004; 104(6):1229-33.*

14. *Orlandi F, Bilardo CM, Campogrande M, et al. Measurement of nasal bone length at 11-14 weeks of pregnancy and its potential role in Down syndrome risk assessment. Ultrasound Obstet Gynecol 2003; 22(1): 36-9.*

15. *Otano L, Aiello H, Igarzabal L, Matayoshi T, Gadow EC. Association between •rst trimester absence of fetal nasal bone on ultrasound and Down syndrome. Prenat Diagn 2002; 22(10):930-2.*

16. *Goshen R, Gonik B, Ariel I, Weiss Y, de-Groot N, Hochberg A. High levels of maternal serum human chorionic gonadotropin in Down syndrome pregnancies: the possible role of a transcription factor on chromosome 21. Fetal Diagn Ther 1999; 14(2):106-11.*

17. *Cuckle HS, van Lith JM. Appropriate biochemical parameters in •rst-trimester screening for Down syndrome. Prenat Diagn 1999; 19(6):505-12.*

18. *Newby D, Aitken DA, Crossley JA, Howatson AG, Macri JN, Connor JM. Biochemical markers of trisomy 21 and the pathophysiology of Down's syndrome pregnancies. Prenat Diagn 1997; 17(10):941-51.*

19. *Brambati B, Macintosh MC, Teisner B, et al. Low maternal serum levels of pregnancy associated plasma protein A (PAPP-A) in the •rst trimester in association with abnormal fetal karyotype. Br J Obstet Gynaecol 1993; 100(4):324-6.*

20. *Spencer K, Souter V, Tul N, Snijders R, Nicolaides KH. A screening program for trisomy 21 at 10-14 weeks using fetal nuchal translucency, maternal serum free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol 1999; 13(4):231-7.*

21. *Haddow JE, Palomaki GE, Knight GJ, Williams J, Miller WA, Johnson A. Screening of maternal serum for fetal Down's syndrome in the •rst trimester. N Engl J Med 1998; 338(14):955-61.*

22. *Krantz DA, Larsen JW, Buchanan PD, Macri JN. First-trimester Down syndrome screening: free beta-human chorionic gonadotropin and pregnancy-associated plasma protein A. Am J Obstet Gynecol 1996; 174(2): 612-6.*

23. *Wald NJ, Kennard A, Smith D. First trimester biochemical screening for Down's syndrome. Ann Med 1994; 26(1):23-9.*

24. *Jou HJ, Shyu MK, Chen SM, Shih JC, Hsu JJ, Hsieh FJ. Maternal serum screening for Down syndrome by using alpha-fetoprotein and human chorionic gonadotropin in an asian population. a prospective study. Fetal Diagn Ther 2000; 15(2):108-11.*

25. *Lam YH, Ghosh A, Tang MH, et al. Second-trimester maternal serum alpha-fetoprotein and human chorionic gonadotrophin screening for Down's syndrome in Hong Kong. Prenat Diagn 1998; 18(6):585-89.*

26. *Hsu JJ, Hsieh TT, Hsieh FJ. Down syndrome screening in an Asian population using alpha-fetoprotein and free beta-hCG: a report of the Taiwan Down Syndrome Screening Group. Obstet Gynecol 1996; 87(6):943-7.*

27. *Cuckle H. Established markers in second trimester maternal serum. Early Hum Dev 1996; 47 Suppl:S27-9.*

28. *Brambati B, Cislaghi C, Tului L, et al. First-trimester Down's syndrome screening using nuchal translucency: a prospective study in patients undergoing chorionic villus sampling. Ultrasound Obstet Gynecol 1995; 5(1): 9-14.*

29. *Chasen ST, Skupski DW, McCullough LB, Chervenak FA. Prenatal informed consent for sonogram: the time for first-trimester nuchal translucency has come. J Ultrasound Med 2001; 20(11):1147-52.*

30. *Mulvey S, Wallace EM. Women's knowledge of and attitudes to first and second trimester screening for Down's syndrome. Bjog 2000; 107(10):1302-5.*

31. *Kornman LH, Wortelboer MJ, Beekhuis JR, Morssink LP, Mantingh A. Women's opinions and the implications of first- versus second-trimester screening for fetal Down's syndrome. Prenat Diagn 1997; 17(11):1011-8.*

32. *Cusick W, Buchanan P, Hallahan TW, Krantz DA, Larsen JW, Jr., Macri JN. Combined first-trimester versus second-trimester serum screening for Down syndrome: a cost analysis. Am J Obstet Gynecol 2003; 188(3): 745-51.*

33. *Spencer K. What is the true fetal loss rate in pregnancies affected by trisomy 21 and how does this influence whether first trimester detection rates are superior to*

those in the second trimester? Prenat Diagn 2001; 21(9):788-9.

34. *Pandya PP, Snijders RJ, Johnson S, Nicolaides KH. Natural history of trisomy 21 fetuses with increased nuchal translucency thickness. Ultrasound Obstet Gynecol 1995; 5(6):381-3.*

35. *Cuckle H. Time for total shift to •rst-trimester screening for Down's syndrome. Lancet 2001; 358(9294):1658-9.*

36. *Chew S, Anandakumar C, Ratnam SS. Maternal serum markers for Down's syndrome pregnancies. Singapore Med J 1995; 36(4):417-23.*

37. *Spencer K, Aitken DA, Crossley JA, et al. First trimesterbiochemical screening for trisomy 21: the role of free beta hCG, alpha fetoprotein and pregnancy associated plasma protein A. Ann Clin Biochem 1994; 31 (Pt 5):447-54.*

38. *Schuchter K, Hafner E, Stangl G, Ogris E, Philipp K. Sequential screening for trisomy 21 by nuchal translucency measurement in the first trimester and maternal serum biochemistry in the second trimester in a low-risk population. Ultrasound Obstet Gynecol 2001; 18(1):23-5.*

39. *Nicolaides KH. Screening for chromosomal defects. Ultrasound Obstet Gynecol 2003; 21(4):313-21.*

40. *Mul NA, ten Velden GH. Prenatal study of trisomy 21: triple test more e•cient than age criterion. Ned Tijdschr Geneeskd 1996; 140(41):2032-5.*

41. *Conde-Agudelo A, Kafury-Goeta AC. Triple-marker test as screening for Down syndrome: a meta-analysis. Obstet Gynecol Surv 1998; 53(6):369-76.*

42. *Audibert F, Dommergues M, Benattar C, Taieb J, Thalabard JC, Frydman R. Screening for Down syndrome using first-trimester ultrasound and second-trimester maternal serum markers in a low-risk population: a prospective longitudinal study. Ultrasound Obstet Gynecol 2001; 18(1):26-31.*

43. *Zoppi MA, Ibba RM, Putzolu M, Floris M, Monni G. Nuchal translucency and the acceptance of invasive prenatal chromosomal diagnosis in women aged 35 and older. Obstet Gynecol 2001; 97(6):916-20.*

44. *Centini G, Rosignoli L, Scarinci R, et al. Re-evaluation of risk for Down syndrome by means of the combined test in pregnant women of 35 years or more. Prenat Diagn 2005; 25(2):133-6.*

45. *Muller F, Thalabard JC, Ngo S, Dommergues M. Detection and false-positive rates of maternal serum markers for Down syndrome screening according to maternal age in women over 35 years of age. A study of the agreement of eight dedicated software packages. Prenat Diagn 2002; 22(5):350-3.*

46. *Dommergues M, Audibert F, Benattar C, Champagne C, Gomel V, Frydman R. Is routine amniocentesis for advanced maternal age still indicated? Fetal Diagn Ther 2001; 16(6):372-7.*

47. *Wald NJ, Watt HC, Hackshaw AK. Integrated screening for Down's syndrome on the basis of tests performed during the •rst and second trimesters. N Engl J Med 1999; 341(7):461-7.*

48. *Lai FM, Woo BH, Tan KH, et al. Birth prevalence of Down syndrome in Singapore from 1993 to 1998. Singapore Med J 2002; 43(2):070-6.*

49. *Goujard J. [Are there any changes in Down syndrome prevalence in France following the implementation of the measurement of nuchal translucency and maternal serum screening?]. Gynecol Obstet Fertil 2004; 32(6):496-501.*

50. *Souka AP, Snijders RJ, Novakov A, Soares W, Nicolaides KH. Defects and syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10-14 weeks of gestation. Ultrasound Obstet Gynecol 1998; 11(6):391-400.*

51. *Hyett J, Moscoso G, Nicolaides K. Abnormalities of the heart and great arteries in •rst trimester chromosomally abnormal fetuses. Am J Med Genet 1997; 69(2):207-16.*

52. *Hyett J, Moscoso G, Papapanagiotou G, Perdu M, Nicolaides KH. Abnormalities of the heart and great arteries in chromosomally normal fetuses with increased nuchal translucency thickness at 11-13 weeks of gestation. Ultrasound Obstet Gynecol 1996; 7(4): 245-50.*

53. *Matias A, Gomes C, Flack N, Montenegro N, Nicolaides KH. Screening for chromosomal abnormalities at 10-14 weeks: the role of ductus venosus blood •ow. Ultrasound Obstet Gynecol 1998; 12(6):380-4.*

54. *Faiola S, Tsoi E, Huggon IC, Allan LD, Nicolaides KH. Likelihood ratio for trisomy 21 in fetuses with tricuspid regurgitation at the 11 to 13+6-week scan. Ultrasound Obstet Gynecol 2005; 26(1):22-7.*

55. *Liao AW, Snijders R, Geerts L, Spencer K, Nicolaides KH. Fetal heart rate in chromosomally abnormal fetuses. Ultrasound Obstet Gynecol 2000; 16(7):610-3.*

56. *Hyett JA, Noble PL, Snijders RJ, Montenegro N, Nicolaides KH. Fetal heart rate in trisomy 21 and other chromosomal abnormalities at 10-14 weeks of gestation. Ultrasound Obstet Gynecol 1996; 7(4):239-44.*

57. *Zoppi MA, Ibba RM, Putzolu M, Floris M, Monni G. First trimester umbilical artery pulsatility index in fetuses presenting enlarged nuchal translucency. Prenat Diagn 2000; 20(9):701-4.*

58. *Cuckle HS, Iles RK, Chard T. Urinary beta-core human chorionic gonadotrophin: a new approach to Down's syndrome screening. Prenat Diagn 1994; 14(10):953-8.*

59. *Cole LA, Rinne KM, Mahajan SM, et al. Urinary screening tests for fetal Down syndrome: I. Fresh beta-core fragment. Prenat Diagn 1999; 19(4):340-50.*

60. *Spencer K, Noble P, Snijders RJ, Nicolaides KH. First-trimester urine free beta hCG, beta core, and total oestriol in pregnancies a•ected by Down's syndrome: implications for first-trimester screening with nuchal translucency and serum free beta hCG. Prenat Diagn 1997; 17(6):525-38.*

61. *Ognibene A, Ciuti R, Tozzi P, Messeri G. Maternal serum superoxide dismutase (SOD): a possible marker for screening Down syndrome affected pregnancies. Prenat Diagn 1999; 19(11):1058-60.*

62. *Awwad JT, Azar GB, Karam KS, Nicolaides KH. Ear length: a potential sonographic marker for Down syndrome. Int J Gynaecol Obstet 1994; 44(3):233-8.*

Editorial Note: First Trimester Screening (including NT measurement) for Down Syndrome has better detection rates than Second Trimester Screening. The obstetrician need to be cognizant of this when patient presents early for antenatal care in the first trimester.

Reprinted from KK Hospital Review: Special Issue on Antenatal Screening. May 2006; 9(01) with permission from Editor.

.

O&G History in Photo: Low Risk Labour Ward KKH 1985. Six patients in a room.
Courtesy of Professor Ingemar Ingemarsson, Sweden.