

Importance of first trimester scan – 3 of 4 Screening for chromosomal defects

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Introduction

Pregnant women are routinely scanned in the first trimester in order to confirm viability, assess the gestational age and for systematic assessment of twin pregnancies^{1,2}. It has become apparent that most of the chromosomal and structural problems can be screened in the early pregnancy. Screening is a process of identifying apparently healthy people who may be at increased risk of a disease or condition. The traditional method of screening for trisomy 21 was based on maternal age. This method increased the rate of invasive tests among pregnant women with a detection of less than half of the fetuses with trisomy 21. This is because the majority of affected fetuses come from the younger age group³. It has been realized that effective screening for major aneuploidies can also be provided in the first trimester by combining first trimester scan and serum biochemistry³.

Risk calculation

Interpretation of screening result is complicated as it does not give a figure and instead it gives a probability. If the screening test shows the risk of the fetus having trisomy 21 is lower than the recommended local cut-off level for risk, this is known as having a low-risk result. However, a low-risk result does not exclude the possibility of having a baby with trisomy 21. Aneuploidy risk calculation starts on with the background risk of a woman which depends on her age and the gestational age. The patient specific risk is calculated by multiplying the background risk by series of likelihood ratios derived from the screening tests. The likelihood ratio for each test is calculated by dividing the percentage of chromosomally abnormal fetuses by the percentage of normal fetuses with the same result. Each time when

the new test results are added for the screening, the background risk will be changed according to the new test and this new risk will become the background risk for the next test. If the tests are dependent on each other then more sophisticated techniques, involving multivariate statistics, can be used to calculate the combined likelihood ratio.

Maternal age

Most of the chromosomal aneuploidies increase with maternal age as a consequence of non-disjunction at the meiosis. Incidence of aneuploidies decreases with gestational age because about 30% and 80% of affected fetuses with trisomy 21 and trisomy 18/13 respectively die between the 12th and 40th week of pregnancy (Table 1). Incidence of Turner syndrome is unrelated to maternal age with the prevalence of 1 in 1500 at 12 weeks and 1 in 4000 at 40 weeks. Antenatally diagnosed Turner syndrome fetuses carry very poor prognosis with the rate of fetal death between the 12th and 40th week is about 80%.

Table 1. Maternal age and risk of major chromosomal aneuploidies

Maternal age (years)	Trisomy 21 40 weeks	Trisomy 18 40 weeks	Trisomy 13 40 weeks
20	1/1527	1/18013	1/42423
25	1/1352	1/15951	1/37567
30	1/895	1/10554	1/24856
31	1/776	1/9160	1/21573
32	1/659	1/7775	1/18311
33	1/547	1/6458	1/15209
34	1/446	1/5256	1/12380
35	1/356	1/4202	1/9876
36	1/280	1/3307	1/7788
37	1/218	1/2569	1/6050
38	1/167	1/1974	1/4650
39	1/128	1/1505	1/3544
40	1/97	1/1139	1/2683
41	1/73	1/858	1/2020
42	1/55	1/644	1/1516
43	1/41	1/481	1/1134
44	1/30	1/359	1/846

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First trimester ultrasound markers of chromosomal aneuploidy

Nuchal translucency (NT)

Nuchal translucency is the collection of fluid under the skin behind the fetal neck which can be demonstrated ultrasonically. The incidence of chromosomal abnormalities is related to the size of the NT³. The NT can be best visualized between 11⁺⁰-13⁺⁶ weeks' gestation when the optimum fetal crown-rump length (CRL) is between 45 mm and 84 mm. The rationale for this optimum time window is based on availability of the diagnostics tests and reliability of the scan findings. The success rate for taking a measurement decreases after 13 weeks because the fetus becomes vertical making it more difficult to obtain the appropriate image, therefore the NT is more reliable before 13⁺⁶ weeks gestation. During the second trimester, the translucency usually resolves and, in a few cases, it can be transformed into either nuchal edema or cystic hygroma.

All NT measurements in a true screening setting should fulfill the quality standards as sub optimum measurement either under or over estimate the risk of chromosomal aneuploidy. The optimum criteria for NT measurement as follows³ (Figure 1):

- The magnification of the image should be such that the fetal head and upper thorax occupy the whole screen.
- A mid sagittal section of the fetus must be obtained.
- The fetus should be in a neutral position, with the head in line with the spine. When the fetal neck is hyper extended the measurement can be falsely



Figure 1. Mid sagittal (median) view of the fetus. Calipers demonstrate the nuchal translucency.

increased and when the neck is flexed, the measurement can be falsely decreased.

- Care must be taken to distinguish between fetal skin and amnion.

The NT thickness in euploid fetuses increases with fetal CRL and in 75-80% of trisomy 21 fetuses the NT thickness is above the 95th centile of the normal range³. In a fetus with a given CRL, every NT measurement represents a likelihood ratio. The larger the NT, the higher the likelihood ratio becomes and therefore the higher the new risk. In contrast, the smaller the NT measurement, the smaller the likelihood ratio becomes and therefore the lower the new risk. In other words a woman at age of 44 can have a low risk result if the NT is thin.

Complementary ultrasound markers of chromosomal aneuploidy

New first trimester ultrasound markers have been introduced in order to improve the diagnostic accuracy of trisomy 21 screening⁴⁻⁷. However, none of these markers are superior to NT. Combination of NT / serum biochemistry and these markers reduce the false positive rate whilst improving the detection rate slightly (Table 2).

First trimester biochemical markers of chromosomal aneuploidies

Trisomic pregnancies are associated with altered maternal serum concentrations of various fetoplacental products. These placental products can be measured and used to assess the risk of chromosomal aneuploidies. Sensitivity of these biochemical markers vary according to the gestation (Figure 2).

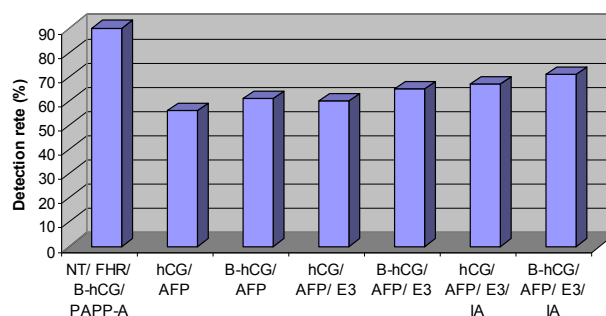


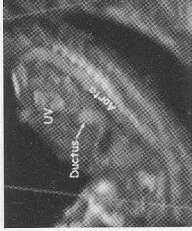
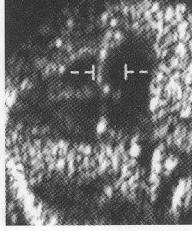


Figure 2. Detection rates of aneuploidies by various biochemical markers³ - tests containing AFP E3, IA are routinely done in second trimester (NT - nuchal translucency, FHR - fetal heart rate, hCG - human chorionic gonadotrophins, PAPP-A - pregnancy associated plasma protein A, AFP - alpha-feto protein, E3 - Estriole, IA - inhibin A)

Table 2. Complementary ultrasound markers of chromosomal aneuploidy during first trimester

Other first trimester ultrasound markers of chromosomal aneuploidy

Technique	Detection rate for Trisomy 21	Image
<p>Absent nasal bone⁴</p> <p>Mid-sagittal plane of the fetal face</p> <ul style="list-style-type: none"> ■ The echogenic tip of the nose and rectangular shape of the palate anteriorly ■ The translucent diencephalon in the centre ■ The nuchal membrane posterior 	65%	
<p>Facial angle⁶</p> <p>(The mean facial angle decreases with CRL from 84° at CRL 45 mm to 76° at CRL of 84 mm)</p> <p>Mid-sagittal plane of the fetal face</p> <ul style="list-style-type: none"> ■ The echogenic tip of the nose and rectangular shape of the palate anteriorly ■ The translucent diencephalon in the center ■ The nuchal membrane posterior 	45%	
<p>Ductus venosus flow⁴</p> <ul style="list-style-type: none"> ■ Positive or absent (normal) ■ Reversed (abnormal) <p>The magnification of the image should be such that the fetal thorax and abdomen occupy the whole screen</p> <ul style="list-style-type: none"> ■ A right ventral mid-sagittal view of the fetal trunk should be obtained ■ Colour flow mapping should be used to demonstrate the umbilical vein, ductus venosus and fetal heart 	65%	
<p>Tricuspid flow⁷</p> <p>Tricuspid regurgitation</p> <p>The magnification of the image should be such that the fetal thorax occupies the whole screen</p> <ul style="list-style-type: none"> ■ An apical four-chamber view of the fetal heart should be obtained ■ The pulsed Doppler sample should be large (2.0-3.0 mm) and positioned across the tricuspid valve ■ The insonation angle to the direction of flow should be less than 30 degrees from the direction of the inter-ventricular septum 	55%	

(Pictures courtesy of www.fetalmedicine.com)

Free β -hCG and PAPP-A

In trisomy 21 pregnancies maternal serum free β -hCG is about twice as high and PAPP-A is reduced to about half compared to chromosomally normal pregnancies (Figure 3). Detection rate of trisomy 21 by maternal age and serum free β -hCG and PAPP-A is 65% with false positive rate of 5%³. However, the measured concentration of free β -hCG and PAPP-A is influenced by the machine and reagents used, gestational age, maternal weight, ethnicity, smoking status and method of conception. Therefore, it is necessary to make adjustments in the measured free β -hCG and PAPP-A. Each measured level is first converted to a multiple of the expected normal median (MoM) specific to a pregnancy of the same gestation, maternal weight, smoking status, ethnicity and method of conception³.

Combined screening

Combination of maternal age, gestation, NT and serum free β -hCG and PAPP-A during first trimester will give the best detection rate for the trisomy 21 with the detection rate of 90% for a false positive rate of 3%⁸. In contrast, screening in the second trimester by maternal age and various combinations of total or free β -hCG, AFP, uE3 and Inhibin A can only identify 56-

71% of trisomy 21 pregnancies for a false positive rate of 5%⁹ (Figure 2).

Increased NT without underlying aneuploidy

Increased fetal NT without an aneuploidy can be associated with various fetal structural and genetic disorders¹⁰⁻¹¹. Underlying mechanism for the collection of fluid under the skin of the fetal neck could be due to:

- Cardiac defects / dysfunction
- Venous congestion in the head and neck
- Altered composition of the extracellular matrix
- Failure of lymphatic drainage
- Fetal anaemia
- Fetal hypoproteinaemia
- Fetal infection

It has been postulated that in 100 fetuses with NT of 3.5 - 4.4 mm diagnosed at 12 weeks 20 would have a chromosomal abnormality and 80 would be euploid. In the 80 euploid fetuses there would be 2 (2.5%) that would die in the subsequent few weeks and in an additional 8 of them (10%) there would be a major defect. The remaining 70 euploid fetuses with no major defects would be live born and healthy^{10,11} (Figure 4).

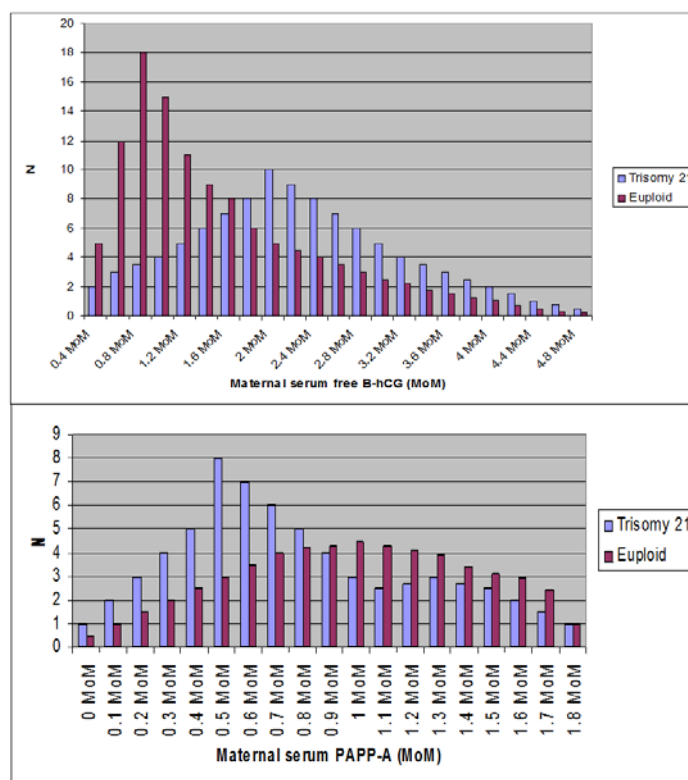


Figure 3. Distribution of serum beta-hCG (top) and PAPP-A in trisomy 21 and euploid fetuses. ((hCG - human chorionic gonadotrophins, PAPP-A - Pregnancy associated plasma protein A). (www.fetalmedicinefoundation.com)

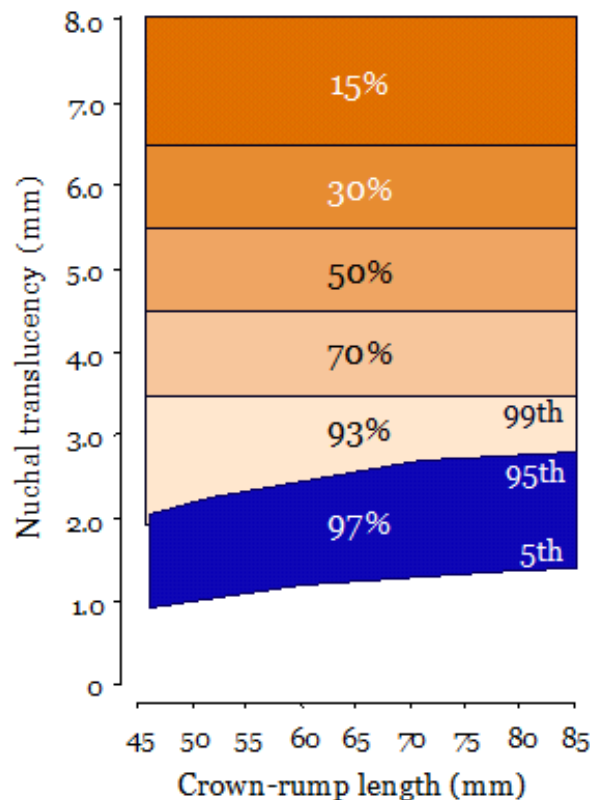


Figure 4. Healthy live bone rate with increasing NT.
(www.fetalmedicine.com)

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