

Nuchal Translucency Measurement in First Trimester Down Syndrome Screening

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Summary

- ✓ **Approximately three in every four fetuses with Down syndrome have increased nuchal translucency (NT), which is a larger than normal build-up of fluid at the back of the neck.**
- ✓ **The ultrasound measurement of NT between 11 and 14 weeks' gestation, in combination with the mother's age and the levels of placental biochemical markers in her blood, can be used to detect approximately 84% of fetuses with Down syndrome.**
- ✓ **The accuracy of NT measurement is affected by fetal position, measurement technique, the type of risk-calculation software used, and the sonographer's experience and technical expertise.**
- ✓ **A rigorous standardization and quality-assurance system for NT measurement is needed before any test using NT ultrasound is offered universally. The cost of establishing such a program is unknown.**

The Technology

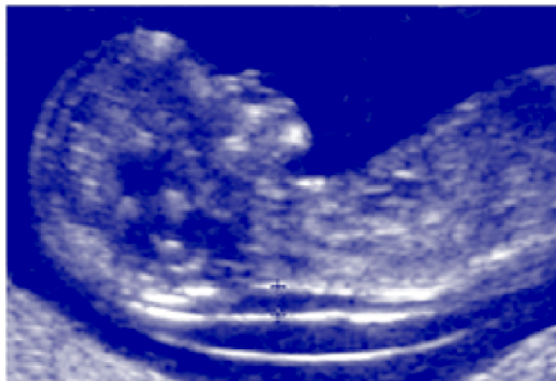
The human embryo receives 22 autosomal chromosomes and one sex chromosome (X or Y)

from each parent. Sometimes, the embryo receives three copies of a chromosome instead of two (a condition known as trisomy). The most common of these conditions is trisomy 21, also known as Down syndrome, which affects one in 700 babies.^{1,2}

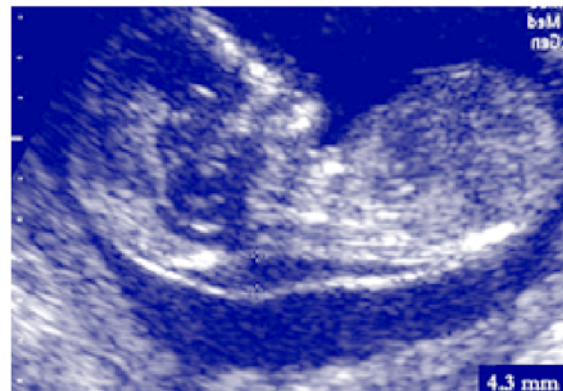
Although the severity of problems varies between individuals, Down syndrome is usually associated with specific facial features, cognitive disability, heart defects, gastrointestinal and musculoskeletal abnormalities, impaired vision and hearing, and thyroid problems.^{1,2}

During the first trimester of pregnancy (0 to 14 weeks), a small amount of fluid (edema) collects under the skin at the back of the fetal neck (nuchal area) until it is eventually drained away by the maturing lymph system.³⁻⁷ This edema, which is visible on an ultrasound scan as a translucent space behind the fetal neck until 14 weeks' gestation, is called the nuchal translucency (NT) (Figure 1). Approximately 75% of fetuses with Down syndrome have a larger than normal NT, as do many fetuses with other forms of trisomy.⁸

NT has been used since the 1990s to assist with the identification of fetuses with Down syndrome.^{3,4} It is measured using ultrasound between 11 weeks and 13 weeks 6 days of gestation, when the fetus is between 45 mm and 84 mm long from crown to rump (sitting height).^{8,9} Normal NT thickness generally ranges from 1.2 mm to 1.9 mm (at crown



12 week fetus with normal NT



Trisomy 21 fetus with increased NT

Image courtesy of Fetal Medicine
Foundation Canada

to rump lengths of 45 mm and 84 mm respectively).⁶ NT thickness is usually used as part of the “combined test,” which includes measurements of placental biochemical markers, free beta-human chorionic gonadotrophin (hCG), and pregnancy associated plasma protein-A (PAPP-A) in the mother’s blood.^{6,9-11} This screening test can be used to detect 84% (95% confidence interval, 80% to 87%) of fetuses with Down syndrome at a fixed false-positive rate of 5% (5 in 100 healthy babies will be incorrectly classified as having Down syndrome).^{1,3,4,12,13} The combined test only identifies individuals at a higher risk of having a fetus with Down syndrome (or trisomy 13 or 18). Further diagnostic testing is needed to confirm the screening test result.¹⁴

Regulatory Status

An error of 0.5 mm in an NT measurement can reduce Down syndrome detection rates from 82% to 67%. It takes at least 80 scans for a sonographer to achieve accurate, reproducible results.^{8,15,16}

Consequently, the Fetal Medicine Foundation (FMF) in the UK (FMF UK) and the US-based Maternal-Fetal Medicine Foundation, which runs the Nuchal Translucency Quality Review Program, established guidelines for measuring NT thickness.^{17,18} Both organizations provide training, credentialing, and ongoing quality assurance.

In Canada, Fetal Medicine International, now known as Fetal Medicine Foundation Canada (FMF Canada), offers theory courses, practical training, and image audits for NT measurement, under the auspices of FMF UK.¹⁹ More than 2,000 Canadians have completed the course through FMF Canada. While such accreditation is not mandatory for sonographers conducting NT measurements in Canada, it is recommended by the Society of Obstetricians and Gynaecologists of Canada (SOGC).²⁰

All pregnant women in Canada are offered an ultrasound scan between 18 and 20 weeks’ gestation to screen for major anatomic abnormalities, but first trimester screening with the combined test is not routinely performed.^{14,20} Early in 2007, the American College of Obstetricians and Gynecologists and SOGC recommended that all pregnant women should be offered non-invasive first trimester screening for Down syndrome, regardless of age.^{20,21}

Patient Group

A chromosomal defect can occur in any pregnancy. The known risk factors are advanced maternal age and the previous birth of an affected child.^{1,2} Although the percentage of babies born to Canadian mothers aged between 30 and 39 years has risen from 21.5% in 1980 to 41.2% in 1995, the prevalence of Down syndrome has remained stable at 13.2 per 10,000 births.² This is likely due to fewer babies with Down syndrome being born to mothers who are >35 years old because of increased screening and access to pregnancy termination.^{1,2}

Current Practice

Chorionic villus sampling (CVS) and amniocentesis are used to diagnose fetuses with Down syndrome and other chromosome abnormalities. CVS is conducted in the first trimester, between weeks 10 and 14, and amniocentesis is conducted after 15.5 weeks’ gestation. In amniocentesis and transabdominal CVS, a thin needle is inserted through the abdomen to obtain a sample of amniotic fluid or placental tissue, which usually has the same chromosomes as the fetus. In transcervical CVS, a placental tissue sample is obtained by inserting a catheter through the cervix.^{8,14} Amniocentesis carries a 0.5% risk of miscarriage, while the risk for CVS is 1.5%. In Canada, until 2007, invasive testing for chromosomal abnormalities was only offered when a woman’s risk of having a fetus with Down syndrome exceeded the procedure-related risk.²⁰

The aim of using non-invasive screening is to reduce the number of women undergoing invasive testing.¹⁴ The triple test, which is usually performed in the second trimester between weeks 15 and 18, is the most commonly used screening technique in North America. A risk estimate is calculated on the basis of maternal age and the measurement of three substances in the mother’s blood: hCG, alpha fetoprotein (AFP), and unconjugated estriol. The triple test detects between 60% and 70% of all Down syndrome cases at a false-positive rate of 5%.¹⁴ The addition of another marker, the hormone inhibin A, forms the basis of the quad screen, which can identify 75% of cases at a 5% false-positive rate.^{14,20} Women who screen positive on a triple or quad

screen are usually offered invasive testing to confirm the fetal chromosome profile (karyotype).

The triple test and quad screen fail to detect >20% of Down syndrome cases and are performed in the second trimester, when pregnancy termination is riskier.³ The combined test has a 16% to 25% higher detection rate (1% to 5% false-positive rate) than that of second-trimester tests, with the added advantage of an earlier result.^{1,3,4,12,13} This allows parents to take more time to decide whether to undergo invasive testing. If the diagnosis of Down syndrome is confirmed by fetal chromosome analysis, the parents have the option of early pregnancy termination or more time to prepare for the delivery of a baby with Down syndrome.

The Evidence

Some factors that can affect the accuracy of an NT measurement have been formally assessed.

Delta-NT versus NT-MoM Method

Determining what constitutes an abnormally large NT involves the calculation of the delta value: the difference between the NT measurement and the normal median NT thickness for that gestational age. Another method, known as multiples of the median (MoM), is used for results taken from blood tests. The concentration is divided by the age-specific median value of the biochemical marker in unaffected pregnancies.^{8,9,20} There is controversy about whether NT measurements can be treated similarly to biochemical data and converted to MoM values. A study of 128,030 unaffected and 428 Down syndrome pregnancies tested this conversion.²² While the NT-MoM and delta-NT methods provided similar overall detection rates, the former overestimated the risk at 11 weeks and considerably underestimated it at 13 weeks.

Image Size

A prospective case series study assessed the effect of using different ultrasound image sizes to measure NT thickness.²³ In 120 scans, the images were adjusted so that the head and neck view of the fetus occupied 60%, 100%, or 200% of the screen. A mean variation of 29% in the NT measurement occurred when the magnification was changed from 60% to 200%. The 100% image size produced a

MoM that was closest to the ideal of 1.0. Another study by the same group assessed the effect of image size on individual risk estimates for 350 pregnant women.²⁴ The NT measurement was, on average, 8% lower using the 200% image, compared to 100%, likely because the borders of the NT were more blurry and more difficult to delineate on a larger image. This resulted in a 55% reduction in the number of women testing positive for a fetus with Down syndrome. However, neither study assessed the effect of image size on the detection rate, and certain adjustments recommended by the FMF UK for decreasing the blurriness of ultrasound screen images were not made.²⁴

Fetal Position

A case series study of 85 fetuses found that their position in the uterus – face down versus face up – had no effect on the NT measurement.²⁵ Another case series study reported that NT measurements were greater when the fetal neck was extended and lower when the neck was flexed, compared to the neutral position.²⁶ NT measurements that were made when the neck was neutral had the highest reproducibility.

Calliper Placement

The most common methods of positioning the measurement callipers on the ultrasound image are on-to-on (both callipers placed on the inside edge of the white lines bordering the NT) and on-to-out (one calliper placed on the inside edge of a white line and the other placed on the outside edge of the opposite white line). A study comparing these two methods in 282 fetuses found a mean difference in measurements of 0.95 mm (standard deviation 0.14 mm). The effect of these differences on risk assessments was not evaluated.²⁷

Software

The algorithms and software that are used to calculate risk profiles have an influence on the results. A case series study of 94 pregnant women showed marked disparities between numerical risk estimates that were derived from two software packages, FMF software and Wallac-Perkin-Elmer software, which are commonly used to calculate the risk of Down syndrome.²⁸ Statistically significant differences in reported likelihood ratios occurred for biochemical markers ($p=0.01$), NT measurements

($p < 0.0001$), and both parameters combined ($p = 0.003$). This study did not assess the effect of these discrepancies on the detection rate.

Training

The NT thickness was measured in 161 fetuses by different pairs of sonographers from a pool of five who were experienced in NT ultrasound and four who were not.²⁹ The measure of agreement between operators varied from 0.83 to 0.95 for the five experienced sonographers and from 0.47 to 0.83 for the others (1.0 represents complete agreement). The values ranged from 0.74 to 0.95 for pairs of experienced sonographers. One pair of inexperienced sonographers scored 0.51.

Another study assessed NT measurements and blood test results from 15,013 pregnancies. These data were obtained by 264 obstetricians, one of whom was an FMF trainee.¹⁰ The screen-positive rate for the trainee was 4.4%, compared to 3% for the others. NT measurements were underestimated by the untrained obstetricians, particularly in the lower range of values, with a consequent higher number of negative screening results. The effect of these results on individual risk estimates was not reported. A later study conducted by the same group had similar results.³⁰

Adverse Effects

Ultrasound scanning, which has been used in pregnant women for >40 years, is considered to be safe.^{8,14,31} The risks associated with NT measurement relate to the consequences of a false-positive result, which can lead to unnecessary invasive testing, possible termination of pregnancy, and psychological stress. A false-negative result can give misleading reassurance. The other disadvantage of first trimester testing is that, although the information can be useful for subsequent genetic counselling, in some cases it may be clinically unnecessary, given that up to 30% of fetuses with Down syndrome are spontaneously aborted.^{8,14,31}

Administration and Cost

First trimester screening with the combined test is more cost-effective than second-trimester testing.³²⁻³⁴ Appropriate training, experience, and adherence to a standard and reproducible technique are essential for

the NT measurement to be a reliable screening tool. This requires a national credentialing and training program and an ongoing quality management process that incorporates feedback.^{4,7} No studies have evaluated the administrative challenges or costs associated with establishing such a program, which may substantially affect the cost-effectiveness of tests based on NT ultrasound.

Concurrent Developments

Automated rapid immunoassay techniques that measure PAPP-A and hCG within 30 minutes have recently been developed. This enables the establishment of one-stop clinics for the assessment of risk, known as OSCAR, where prospective parents can receive the blood test and NT measurement results during one office visit. The Down syndrome detection rate for OSCAR is 92%.^{8,35}

Ultrasound examination of the fetal nose is being explored as another potential indicator of trisomy because, in most fetuses with Down syndrome, the nasal bone is underdeveloped.⁸ A promising experimental technique involves extracting fetal or placental nucleic acids from maternal blood and examining them for chromosomal abnormalities.^{36,37}

Rate of Technology Diffusion

A fetal ultrasound examination performed between 18 and 20 weeks' gestation is an established practice in Canada, and the technology is widespread. The main factor determining the uptake of the combined test is the availability of appropriately trained sonographers.³ Also, despite recommendations by professional societies that all women be offered first trimester screening, regardless of age, younger women may not undergo testing because of the perception that they are at low risk.^{20,38}

Implementation Issues

The evidence shows that the accuracy of an NT measurement is affected by the fetal position; measurement technique; type of risk-calculation software used; and sonographer's training, experience, and technical expertise. The effect of these variables on risk estimates that are partly based on NT thickness is unknown. Measurement variations may be remedied if NT ultrasound

screening is subject to the same rigorous standardization and quality assurance that are applied to laboratory measurements.⁷ Ongoing audits are essential given that, over time, trained sonographers tend to develop incorrect techniques that can only be changed by extensive personal feedback.^{15,39}

The SOGC's guidelines state that the combined test should only be provided as part of a comprehensive program that includes genetic counselling, access to more invasive diagnostic testing for mothers with a positive-screen result, and appropriately trained sonographers who adhere to standard techniques and are subject to routine performance audits.^{20,21} Such a program is needed before any test using NT ultrasound is offered universally.

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