# Nuchal translucency screening

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**Change is a concept that is difficult to accept unless there is a change for the better.**

John Down, a London physician, wrote a paper in 1866 entitled, 'An ethnic classification of idiots'. In his paper, he noted in the group who had what we now call Down syndrome…'the skin has a slightly yellowish tinge and is deficient in elasticity, giving the appearance of being too big for the body'.

Clinicians have known for many years that if they have delivered a fetus with hydrops, there is a high association with aneuploidy. They have also noted, often with despair, that when a baby was delivered with a chromosome anomaly, such as Trisomy 21 or Trisomy 18, that many of the mothers were in fact young.Often at peri-natal meetings, the comment would be made that this was a most unusual occurrence, because generally, aneuploidy was associated with older mothers.

It was recognised early in the 20th century, that older mothers were at an increased risk for having a baby with Trisomy 21. The concept of non-dysjunction in Down syndrome was developed by Waardenburg in 1932. When amniocentesis was first introduced, it was targeted at the older patient, as these patients individually were at a higher risk of aneuploidy. In most states in Australia, the amniocentesis/CVS was offered to patients aged 35 years or beyond.

There were two reasons for this strategy. One was that the risk of miscarriage from amniocentesis was at least equal to the risk of finding a fetus with aneuploidy. The second reason was that the number of women aged 35 or over delivering a baby was about 5 per cent of the total obstetric population. Thus, if antenatal testing were offered to this group, it could be predicted as to how many women would require invasive testing. In Queensland in the 1970s, chromosome analysis was done by the State Health Laboratory. They set the age for testing at 37 years or greater, primarily based on the estimate of the number of patient tests that the laboratory could handle each year. As the number of private laboratories offering chromosome analysis has increased, the age at which testing is offered has been reduced to 35.

This strategy of testing women over 35 years of age has failed. The number of women now having babies later in life has increased. Now, more than 15 per cent of pregnancies are in women who are over 35 years. This number continues to grow. Within a few years, 20 per cent of the obstetric population will be age 35 years or more. If we look at the number of women who have a baby with Down syndrome, 70 per cent of these women will be under 35 and will have not traditionally been offered any testing. Only 30 per cent of women who have a baby with Down syndrome are over 35. So by increasing the number of invasive tests each year from 5 per cent of the population to more than 15 per cent, we are still missing 70 per cent of the women who have a baby with Down syndrome. This does not take into account other Trisomies, including Trisomy 13 and Trisomy 18.

With this failure to detect a fetus with a chromosome anomaly by using maternal age, the idea slowly evolved that it would make more sense to look at the fetus to see if there are any characteristics or markers that could be identified, which then may give a better idea as to whether the fetus, regardless of the mother's age, was at high or low risk for having Trisomy 21. This strategy would also appeal to women who were older and did not wish to automatically submit themselves to an invasive test. Many of these older women were quite keen to have a non-invasive assessment. If the fetus was assessed as being at low risk of aneuploidy, they would elect not to proceed with invasive testing. For younger woman, if it were seen that her fetus was at a higher risk for having Trisomy 21, she might be more willing to submit to invasive testing. With the evolution of nuchal translucency screening, the idea was not only to improve the sensitivity for detection of Trisomy 21, but also to reduce the number of invasive tests. By using age alone, with almost 20 per cent of the population being 35 years or older at the time of pregnancy, there would be a huge amount of laboratory work required to undertake karyotyping.

Dr Kypros Nicholaides published the first clinical trial of nuchal translucency screening in 1996. He recruited 100,000 patients across the United Kingdom who were scanned between 11 weeks and 14 weeks. All of the operators in the trial had been trained for the nuchal translucency assessment process. Rigid criteria were laid down: the CRL had to be between 45mm and 85mm; the view of the fetus had to be large and mid-sagittal; the embryonic membrane had to be distinguished from the skin of the fetus; and the definition of measurement had to be precise. Multiple measurements were to be taken and the largest measurement was the one that was used for the calculation of risk.

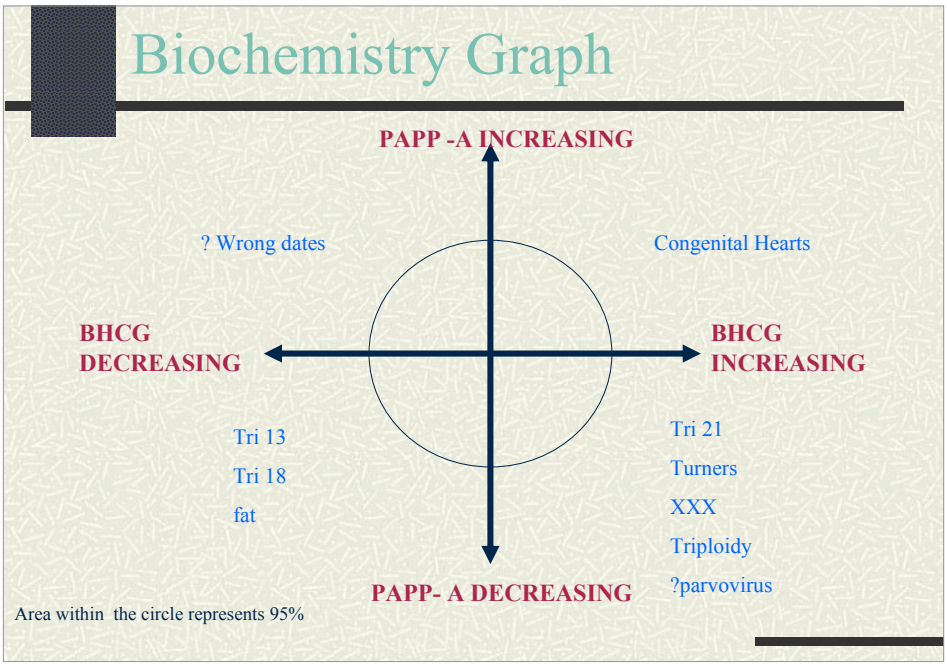
Of the 100,000 patients, 326 had a fetus with Trisomy 21. 70 per cent of these fetuses with Trisomy 21 had a nuchal translucency measurement which was greater than the 95th centile. However, disappointingly, 30 per cent of fetuses with Trisomy 21 had a normal neck thickness below the 95th centile. This then gave the test a 70 per cent sensitivity which compared more than favourably with using the age-based assessment as to who should have invasive testing. The sensitivity of age-based testing is 30 per cent.

Biochemistry had been traditionally offered as a second trimester screening using serum levels of AFP, oestriol and total HCG. The sensitivity of second trimester biochemistry is in the region of 65 per cent. Thus, a search began for biochemical markers which could be useful in the first trimester. Two markers, beta HCG and PAPP-A, were found to have a different distribution of values for gestational age in the Down syndrome population compared to the normal population.

Total HCG is released spontaneously from the placenta. Left to stand at room temperature, it will unwind to form two chains, the alpha chain and the beta chain. The unwinding process is facilitated by a co-factor, Pregnancy Associated Plasma Protein-A (PAPP-A). The PAPP-A is consumed in the unwinding process. In a normal pregnancy, as the pregnancy advances, the amount of beta

HCG increases and the amount of PAPP-A decreases. In the Down syndrome pregnancy, for reasons unknown the unwinding process is accelerated, thus resulting in a high beta HCG and a low PAPP-A.

**Diagram 1.**
Distribution for the Down syndrome, Trisomy 13 and Trisomy 18 groups.




The above diagram shows the distribution for the Down syndrome group and the Trisomy 13 and Trisomy 18 group. Patients who are obese have a higher uptake of hormones into the adipose tissue, thus giving a much lower than expected level of beta HCG and PAPP-A. The hormones are sequestrated in the maternal fat. The software package that is used for the assessment of risk will make an adjustment automatically for maternal obesity, when the maternal weight is entered into the program.

Using first trimester biochemistry alone, the sensitivity for detection of Trisomy 21 would be 70 per cent. Once again then, 30 per cent of patients with a fetus with Trisomy 21 would be missed, as they would be placed in the low-risk group.

Combining the two techniques of nuchal translucency and first trimester biochemistry, the sensitivity rises to 90 per cent. This represents the best test we have for identifying patients who should have an invasive test regardless of maternal age. The false positive rate of 5 per cent is at an acceptable level.

*'First trimester testing should become the accepted method for assessment as to who should have an invasive test for chromosome analysis.'*

The dividing line between high-risk and low-risk results is set as a statistical line – it places the top 5 per cent of results as a high-risk group for aneuploidy. From a practical point, this group corresponds to a risk of greater than 1:300. It is often misinterpreted that the division between high-risk and low-risk is related to the risk of miscarriage associated with invasive testing. It is traditionally thought that a miscarriage rate of 1:200 is associated with amniocentesis. With larger studies and more clinical experience, the risk of miscarriage with amniocentesis is probably much lower than 1:200.

First trimester testing then should become the accepted method for assessment as to who should have an invasive test for chromosome analysis. Since commencing nuchal translucency screening in my practice in 1996, I have found that the average age for a patient to have a baby with Trisomy 21 is 31 years old. This means that half of the population with a fetus with Trisomy 21 are 31 years or under. The youngest patient we have had who had a fetus with Trisomy 21 was 17 years old. This patient would have had an age-based risk of Trisomy 21 of 1:1450. After her nuchal translucency test, she was shifted into the high-risk group of 1:70. Invasive testing confirmed that the fetus did have Trisomy 21.

One of the greatest difficulties I have is convincing my colleagues of the value of nuchal translucency and biochemistry testing. One of my friends, who remains a sceptic about the validity of nuchal translucency screening, considers it no better than going to the bookmaker in terms of obtaining odds. My pleas to him of the poor sensitivity for using age as the determining factor as to who should have invasive testing seem to have fallen on deaf ears.

Several times each year, I am asked to give an opinion on cases where Trisomy 21 has been missed. Invariably, no first trimester screen was undertaken in these patients. Instead, the second trimester ultrasound was relied upon as the bench mark for high-risk or low-risk for aneuploidy. It has been shown in many studies that the sensitivity of second trimester ultrasound for Trisomy 21 is between 30 per cent and 50 per cent. In the patients where the diagnosis is not made, they are generally obese, they have multiple striae on the abdomen and may have had abdominal surgical procedures. As well, this is complicated by the fact that often the fetus is in the wrong position for a good assessment and the fetus may not roll into a position where it can be better assessed. These are the patients in whom the diagnosis of the AV canal is most often missed.

Research continues to progress with new ways of increasing sensitivity of first trimester assessment. John Down, when he wrote his paper in 1866, made the observation that 'the nose is small' in people who have Trisomy 21. In 2001, Kypros Nicholaides added the presence or absence of the nasal bone as part of the first trimester assessment. He contends that for a 1 per cent false positive rate, sensitivity of 90 per cent can be obtained by combining first trimester ultrasound, biochemistry and the presence or absence of a nasal bone. If one was to accept a 5 per cent false positive rate, Dr Nicholaides contends that the sensitivity would be 100 per cent. No one else has been able to achieve this degree of sensitivity.

Other parameters that are being reviewed for inclusion into first trimester testing are tricuspid regurgitation and an abnormal ductus venosus pattern. The overall aim of first trimester testing then would be to increase the sensitivity to as near to 100 per cent as possible. However with more and more steps in the assessment process being required, the test will inevitably take longer and longer to perform, and require a higher degree of training for the ultrasound staff. It does become an issue of diminishing returns. In most instances, the biochemistry is automated and the ultrasound assessment can be done in less than 15 minutes. With the addition of more and more steps in the screening protocol, the less enthusiastic the operators may well become.

As time has progressed, we have had an opportunity to look at the high-risk group of patients more closely. At first, it was thought that the high-risk group would just need a chromosome analysis. If the chromosomes were normal, the patient could be reassured and the antenatal care could continue as normal. However, in the high-risk patient, when the chromosomes returned as normal, this is 'good news' but it is also 'bad news'. If the increased risk was brought about by an increase in the nuchal translucency, there is approximately a 5 per cent to 10 per cent chance that there is another underlying structural problem which has accounted for the increase in nuchal translucency. As each year progresses, the list of syndromes and structural anomalies associated with an increased nuchal translucency grows. From a practical point of view, the main associations with increased nuchal translucency and structural anomalies would be:

- cardiac lesions;
- diaphragmatic hernia;
- congenital cystic adenomatoid malformation; and
- broncho pulmonary sequestration.

In the patient who has a high risk for aneuploidy on first trimester screening because of a thick neck, and the fetus has normal chromosomes, a targeted tertiary fetal cardiac ultrasound should be undertaken. Looking at biochemistry, a low PAPP-A of less than 0.2 multiples of the median can be a marker for a bad pregnancy outcome. This would include hypertensive disease, intrauterine growth restriction, pre-term labor and antepartum haemorrhage.

On the other hand, in the patient who has a low risk assessment with first trimester ultrasound, the pregnancy outcome would be better than initially predicted. The risk of congenital anomalies is reduced and the risk of IUGR, PET and so on is also reduced.

With improvement in the resolution of ultrasound, the early assessment of fetal anatomy can now also be a real possibility. Anomalies such as acrania or anencephaly may be quite easily appreciated in the first trimester assessment. Even a hypoplastic left heart may be appreciated on first trimester assessment. The diagnosis of multiple pregnancy can be made early. Determination of the chorionicity of the pregnancy is easier in early pregnancy than it would be in the second trimester. The non-viable pregnancy will be identified as well.

Looking at first trimester assessment of anatomy, one must be careful of the diagnosis of an omphalocoele in a fetus. As you will recall from embryology, the small bowel growth occurs within the cord substance. There may be a physiological delay in return of the herniated cord into the abdominal cavity. However, if the diagnosis of an omphalocoele is made at 11 to 12 weeks, it would be prudent to review the patient by the end of the twelfth week before making the diagnosis of an omphalocoele.

The nuchal translucency risk for Trisomy 21, therefore the adjusted risk for the patient, is often helpful with the management of the second trimester ultrasound. We are all familiar with the reporting of 'minor markers' in the second trimester scan when the report contains comments such as, 'This can be associated with a chromosome anomaly'. In most of these instances, all we are doing is increasing the anxiety of the patient.

Certain anomalies that are seen in the second trimester scan can have a significant increase in the risk for aneuploidy. These would include:

- absence of the fetal nasal bone (representing an increase in the risk of aneuploidy by 50 times);
- increase in the nuchal fold (increasing the risk of aneuploidy by 15 times); and
- a cardiac lesion (increasing the risk of aneuploidy by ten times).

The nuchal fold assessment is totally different from the assessment of nuchal translucency. The nuchal fold is a view of the head taken in the axial plane where the measurement is made from the outer edge of the occipital bone to the outer margin of the skin and should be less than 6mm. Unlike nuchal translucency, the nuchal fold is not graded, it is just reported as normal or abnormal.

Minor markers would be familiar to you in second trimester scan reports. These would include:

- the intracardiae;
- the echogenic intracardiac focus;
- renal pelvic dilatation; and
- choroid plexus cysts.

Probably at least 20 per cent of the pregnant population would have one or more of these markers. The echogenic intracardiac focus is of particular note in that it is found in 5 to 10 per cent of Caucasians, but has been found in 25 per cent of Asians. The minor markers can increase the likelihood ratio for aneuploidy, but the significance of these markers is hotly debated. The Australian Association of Gynaecological Ultrasonologists has recently made a statement that if a minor marker is seen in isolation, the significance of the marker can be ignored. The likelihood ratio for renal pylactesis increasing the risk for aneuploidy has been reported in some cases as low as 1.0 – not increasing the risk at all. The echogenic intracardiac focus may increase the risk by only 1.1 times.

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In conclusion, I would have to say that I was a sceptic when nuchal translucency was first introduced in 1996. I was unsure how something as simple as measurement of nuchal translucency and biochemistry could give such a high sensitivity for Trisomy 21 and other chromosome anomalies. With the passage of time, I have become a 'true believer'. I think that nuchal translucency assessment has been the greatest advance in obstetrics in the last ten years. It is a great help to know the nuchal translucency results when commencing a morphology scan. If the minor markers for aneuploidy are seen in the second trimester scan, these can be interpreted more objectively than if one does not have this first trimester information.

Presently, I think that all patients should be offered first trimester screening. Using age alone, the sensitivity for detecting Down syndrome is 30 per cent. Using nuchal translucency, the sensitivity is 90 per cent.

We are at an exciting time in terms of where we go from here. With the new linear array technology, a complete karyotype of the fetus can be done from a very small sample of amniotic fluid. 1 to 2 mls of amniotic fluid taken with a 25 gauge needle may give us a complete karyotype. One would expect that the miscarriage rate using such a small needle would be very low. This may become a much more commonly requested test by the patient. Perhaps that is where the future lies.

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# Informed financial consent

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**In case you were unaware, there is currently a Federal initiative to have all surgical patients obtain informed financial consent (IFC) before elective surgery.**

Apparently, this had its origins in the Australian Health Minister requiring an operation in Sydney, after which he received an unexpectedly high out-of-pocket bill.

The latest consumer survey, taken in November and December 2006, measured the level of informed financial consent for privately insured patients. The survey showed an improvement in the surprise gap rate since the same survey in 2004 (16 per cent versus 21 per cent). The survey, carried out by Ipsos Australia, was distributed to 10,000 patients who had recently made a claim from their health fund for treatment as a private patient in a private or a public hospital. There were 4,596 respondents.

Anaesthetists, tests, pathology, radiology, ultrasound, x-ray and specialist's or surgeon's assistants accounted for more than two thirds (67 per cent) of all episodes where informed financial consent was not provided. These providers are characterised by lower levels of direct patient contact and, to a degree, lack of knowing what precise services will be required in the hospital (tests for example).

Federal Government wants this percentage to be higher or else they are threatening to introduce mandatory legislation allowing Medicare benefits to be withheld. The exact level at which the government will be happy is not exactly known, but 90 per cent seems to be an often repeated figure (versus 84 per cent in the last survey).

An agreement has been made between the government and the Australian Medical Association to promote IFC with particular specialist groups via a funded education campaign (*Let's talk about fees*) and to conduct a follow-up survey. The government acknowledged that the results of the 2006 survey were encouraging but not yet sufficient to avoid mandating IFC. The government's final position will be decided when it receives the findings of the 2007 survey.

I always thought that I did a reasonable job in letting my surgical patients know before their surgery what my fees were and when they were required to be settled. However, just recently things went wrong. I used to give my patients a handout explaining what the total fee was, and as a courtesy, what their rebates would be from their fund, Medicare and the remaining out-of-pocket costs. One particular patient mistook the rebate amount from Medicare as hers to keep and managed to get Medicare to issue the rebate amount to herself, subsequently refusing to pass this on to my practice. Several gentle reminder letters went unanswered and then a 'please explain' letter came from the Health Complaints Commission (HCC) as to why my secretary was unfairly harassing the patient. Several months later, several letters later, and numerous secretarial hours later, the HCC exonerated my practice and issued a 'please pay' letter to the patient. The HCC did tell me that my pre-operative handout was not legally binding as the patient did not sign it with a witness. I have to now acknowledge that the HCC has done something useful and constructive for my practice.

The moral of this story is that I now issue the patient pre-operatively with an estimation of my fees and request them to sign and have the form witnessed. Exact details of how to contact the anaesthetist and the surgical assistant are also included.

(Nuchal translucency screening - references continued)

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