The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

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NUCHAL TRANSLUCENCY

ultrasound, education and monitoring program

NTUEMP Newsletter

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Welcome to this Edition of the NTUEMP newsletter. We wanted to provide updates on several aspects of first trimester screening as this scan continues to develop from the 'NT scan' to include assessment of a broader range of potential obstetric complications.

DUCTUS VENOSUS ASSESSMENT IN THE FIRST TRIMESTER

Dr Lynne Brothers

The ductus venosus (DV) is a fetal vessel connecting the umbilical vein to the inferior vena cava. The shape and contour enables optimal transfer of oxygen and nutrients towards the right atrium. The flow velocity profile is typically forward throughout the cardiac cycle. Given the close position to the heart, the waveform reflects cardiac afterload, cardiac contractility, compliance and vascular information.

The DV waveform can be obtained during the 11-13 week scan. Particular care should be taken to follow the recommended guidelines for waveform acquisition, and to obtain the Doppler trace whilst the fetus is quiescent.

Waveform analysis can be performed in 2 ways:

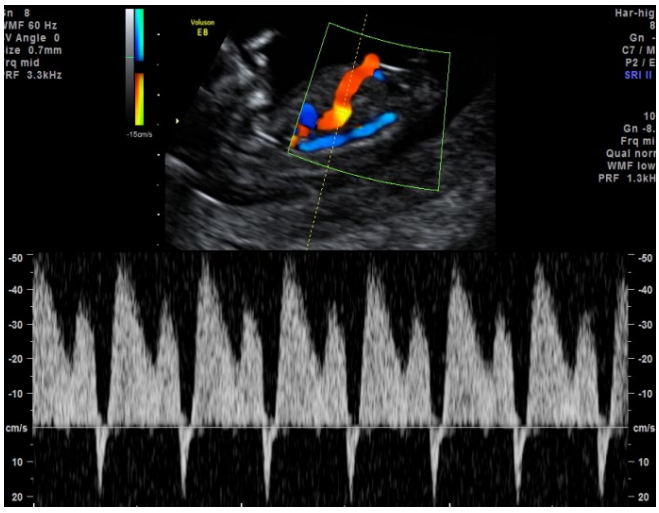
1.The pulsatility index (PIV) can be used as a continuous variable in estimation of patient specific risks for pregnancy complications.

2. The waveform can be assessed subjectively and regarded as normal if the A-wave (atrial contraction) is positive or regarded as abnormal when the A-wave is absent or reversed.

Addition of the DV PIV to first trimester risk assessment improves the sensitivity of cFTS for Trisomy 21 from 90% to 95%. It is most useful as a second line screen to modify risk in the intermediate risk group of 1:51-1:1000. (approximately 16% of the population) The DV maybe abnormal in 3% of euploid fetuses with normal outcome.

Targeted cardiac assessment of fetuses with a reversed A-wave will improve early detection of cardiac abnormalities by approximately 50%.

Adverse pregnancy outcomes such as fetal growth restriction have also been reported to be associated with A-wave reversal or absence. Additional growth scans in the third trimester can be considered.



1. Assessment of the ductus venosus showing a reversed 'A' wave.

REVIEW CUT OFF POINTS FOR HIGH-RISK PREGNANCIES

Dr Edward O'Mahony

Advances in prenatal screening and diagnosis have raised questions regarding the clinical utility of combined first trimester screening and nuchal translucency measurement compared to that provided by cfDNA screening.

In a Victorian population-based study of 103,319 combined first trimester screening tests linked to prenatal diagnostic tests from 2014-2015, the prevalence of chromosomal abnormalities was 0.4%.[1] 25% of these chromosomal abnormalities would not be detectable by cfDNA screening.

Up to 90% of atypical abnormalities could be detected by offering diagnostic testing to women who, at cFTS, were found to have a high-risk screen result for T21 (>1/100), a low PAPPA (<0.2 MoM) or BHCG (<0.2MoM) or high BHCG (≥5.0 MoM) or with other abnormal ultrasound features.

In a population-based study of 193,638 pregnancies, using these outlier risk parameters increased detection for all chromosomal abnormalities but also increased the screen positive rate from 4.4% to 4.8%.[2]

In a contingent screening model, each patient has routine first-stage screening (NT + biochemistry) which produces a risk result. The ability of the second-stage screening to alter that risk is contingent upon the result of the first-stage screening. If the first-stage risk result is very high (>/=1/100), the patient is offered diagnostic testing directly. If the risk is very low, any further screening will not alter the first-stage risk result. If the risk falls into a borderline category (1 in 101 to 1 in 1000), cfDNA screening can be offered as the second-stage test due to its higher sensitivity (>99% for trisomy 21, >97% for trisomy 18, 99% for trisomy 13) and lower false positive rate (<1%).

Contingent screening that offers women with a cFTS risk of >/=1/100 an invasive test and women with a risk from 1/100-1/1000 a cfDNA test significantly reduces the false positive rate compared with offering invasive testing to all women with a risk of >/=1/300.

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2. Vogel I, Tabor A, Ekelund C, Lou S, Hyett J, Petersen OB, The Danish Fetal Medicine Study Group, and the Danish Cytogenetic Study Group. Population-based screening for trisomies and atypical chromosomal abnormalities: improving efficacy using the combined first trimester screening algorithm as well as individual risk parameters. Fetal Diagn Ther 2019;45: 424-429. doi: 10.1159/000492152. Epub 2018 Sep 10. PMID: 30199859

SCREENING FOR SCA (SEX CHROMOSOME ANEUPLOIDIES)

Dr Debbie Nisbet

Screening for SCA (sex chromosome aneuploidies) increases the false positive rate of NIPT. In a study of 5,267 singleton pregnancies the screen positive rate increased from 1.2% to 2.3% with the inclusion of SCA screening in NIPT. Following a positive screening result the odds of being affected is lower for SCA than for autosomal trisomies; for monosomy X in particular the odds of being affected were just 20% in this study. After receiving a high risk NIPT result 65.5% of those with a high risk for SCA underwent invasive testing, and 85% of cases high risk for other aneuploidies underwent invasive

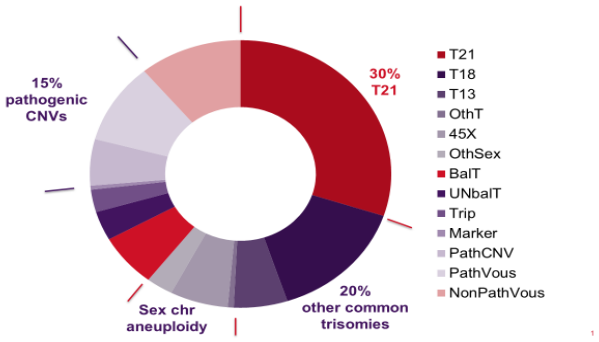
testing. High risk SCA results may cause significant anxiety and counselling can be complex. Pre-test counselling prior to inclusion of SCA in the NIPT panel is required.[1]

The positive predictive value (PPV) – the probability of being affected when the screening result is positive – is consistently low for monosomy X (MX) at under 30%. It has been proposed that X inactivation, which increases with advancing age in female somatic cells, results in increasing false positive NIPT results for MX. In this study of 52,499 NIPT samples, the PPV for monosomy X was 26%; there were 96 cases screen positive for MX with a known outcome.

There was a trend toward an increase in false positive results with increasing maternal age however this did not reach statistical significance. This result does not support including pre-test counselling about a higher false positive rate for women of advanced maternal age. In this study the likelihood of a false positive MX result increased significantly if there were no ultrasound features of MX, and with reducing PAPP-A levels.

CVS was more commonly performed if there were structural anomalies identified. If the ultrasound was normal, amniocentesis was preferred because of the risk of confined placental mosaicism. In the group undergoing CVS or in whom products of conception were evaluated (after spontaneous demise or after TOP for hydrops) 56% of cases were true positives (versus 16% undergoing amniocentesis or postnatal testing). [2]

Figure: The range of chromosome abnormalities detected by microarray (adapted from Wapner *et al*. NEJM 2012)



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1. Kornman L, Palma-Dias R, Nisbet D, Scott F, Menezes M, da Silva Costa F, McLennan A. Non-invasive prenatal testing for sex chromosome aneuploidy in routine clinical practice. Fetal Diagn Ther. 2018;44(2):85-90.

2. Sandow R, Scott FP, Schluter PJ, Rolnik DL, Menezes M, Nisbet D, McLennan AC. Increasing maternal age is not a significant cause of false positive results for Monosomy X in non-invasive prenatal testing. Prenatal Diagnosis. July 2020 PMID: 28873375 DOI: 10.1159/000479460

SCREENING FOR SPINA BIFIDA IN THE FIRST TRIMESTER

Dr Kristy Milward

Recognition of highly sensitive cranial signs (the lemon-shaped head and banana-shaped cerebellum) for open neural tube defects has permitted diagnosis of most cases at the 18-20-week scan, without a need for preliminary biochemical screening. As fetal aneuploidy screening has moved to the first trimester, we have an opportunity to assess fetal anatomy at this earlier gestation with the prospect of being able to diagnose open spina bifida significantly earlier.

In 2009, Chaoui et al. reported the 'Intracranial Translucency', an anechoic linear structure representing the 4th ventricle, visible in healthy fetuses at 11-14 weeks gestation. This translucent space was absent in four fetuses with open spina bifida1. Several potential sonographic

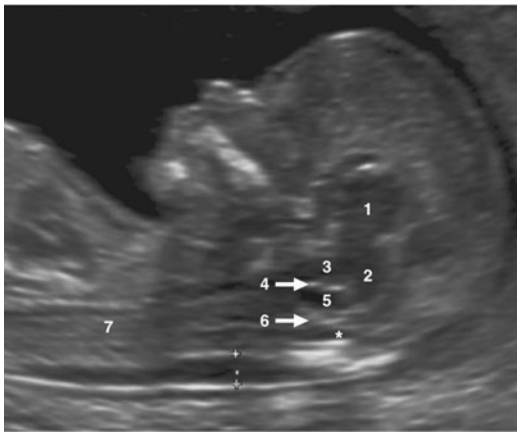
markers have since been reported for first trimester screening for open spina bifida, including:

- Intracranial Translucency – absent or small.[1,2]
- Cisterna Magna – absent or small.[2,3]
- Brainstem thickness - > 95th centile.[4]
- Posterior shift of the brainstem – through subjective assessment, or as a BS/BSOB ratio.[3,4,5]
- Absence of the choroid plexus of the 4th ventricle.[6]
- The Crash sign – posterior displacement of the mesencephalon to meet the occipital bone, viewed in the axial plane.[7]
- Dry brain sign – increased size of the choroid plexus of the lateral ventricles, relative to the head.[8]

As the midline longitudinal plane of the fetus is already obtained routinely for the assessment of the nuchal translucency and nasal bone, advocates of longitudinal markers for spina bifida screening argue that this provides the easiest mode of screening, without adding significantly to the requirements of a first trimester anatomical assessment. Authors of pattern-recognition markers, such as the crash sign, consider that screening methods that do not require specific measurements to be taken will be faster and easier to implement.

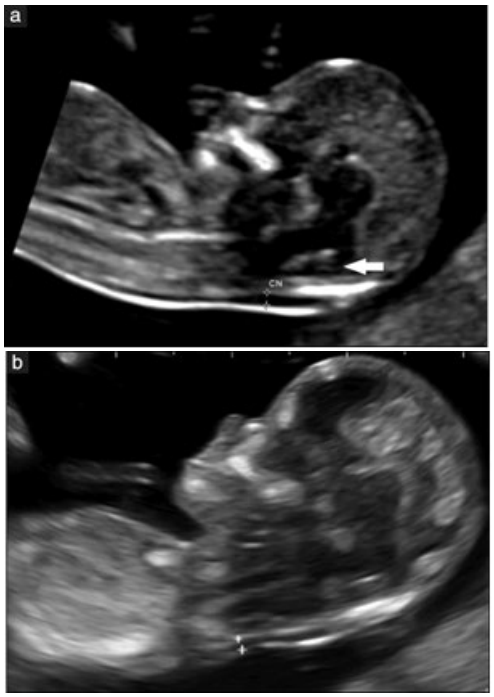
Due to the infrequent occurrence of spina bifida, most published studies are based on retrospective case reviews. A prospective longitudinal study from Chen et al. in 2017 found 11 affected fetuses from a study population of 16,164 fetuses (1 in 1,470). Using posterior fossa markers assessed in the longitudinal plane they found that a small cisterna magna had the highest sensitivity for detecting open spina bifida (73%). A small IT had a lower sensitivity. BS thickness and BS/BSOB ratio were not found to be useful.[2]

Whilst more research is required to determine the sensitivity, specificity and false positive rates for these markers, this shows the potential of adapting routine screening for structural anomalies to the first trimester. It is important to recognise that screening for uncommon anomalies will have an impact on patient anxiety related to false positives. The finding of an abnormal marker should prompt a more careful examination of the fetal spine, with consideration of early review (around 15 to 16 weeks) if no neural tube abnormality is identified immediately.



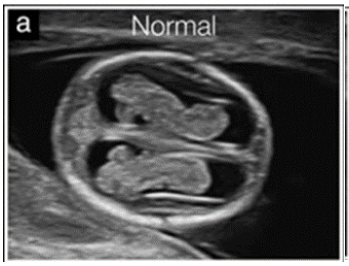
2 Normal mid sagittal fetal brain

1.Thalamus 2. Midbrain 3. Brainstem 4. Posterior wall of brainstem 5. Fourth ventricle 6. Choroid plexus of fourth ventricle 7. Posterior spine * Cisterna magna

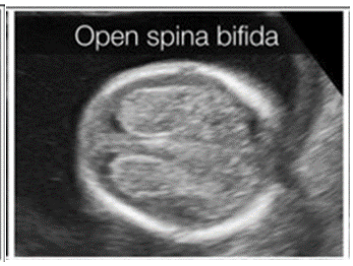


3 Mid sagittal brains in fetuses with open spina bifida

Images from UOG, Vol. 42, Issue: 4, Pages: 416-420, First published: 14 March 2013, DOI: (10.1002/uog.12463), courtesy of F. Dhombres

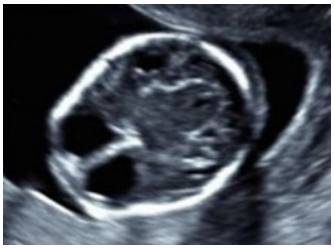


4.Normal appearance of the choroid plexus

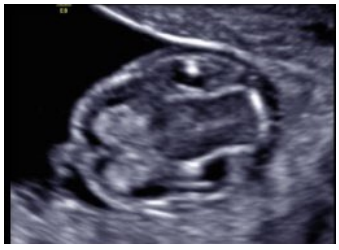


5. 'Dry brain in a fetus with open spina bifida

Images from UOG, Vol: 55, Issue: 1, Pages: 81-86, First published: 27 September 2019, DOI: (10.1002/uog.20856), courtesy of R. Chaoui



5. Normal axial appearance of the fetal mid-brain



6.'Crash sign' in a fetus with open spina bifida

Images from Ultrasound in Obstetrics & Gynecology, Volume: 54, Issue: 6, Pages: 740-745, First published: 11 April 2019, DOI: (10.1002/uog.20285), courtesy of F. Ushakov

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