Authors' reply

We thank the authors for an insightful dissection of current standard practice, in particular with reference to first trimester screening (FTS) for foetal aneuploidy,[1] and their own work documenting the peformance of the theoretical addition of nasal bone assessment in a mathematical model of aneuploidy screening.[2] We agree also that the three restructured hospitals and most private hospitals in Singapore have methodically adopted the FTS as a standard of care; in the National University Hospital FTS testing began in January 2004. Over the last decade, FTS has systematically replaced either traditional screening based on maternal age alone or the triple test, and rightfully so. In fact, back in 2009, when the test was still being rolled out in the UK, senior academics lobbied for its implementation on the grounds that babies were "*dying completely unnecessarily*".[3] To be congratulated, the clinicians in our hospitals were quickly aware of the then new test that had an increased accuracy, leading to a lower risk of miscarriage, and the adoption across hospitals was smooth.

But there are problems. Ultrasonography in general, and nuchal translucency (NT) and nasal bone measurements in particular are sometimes challenging and always operator dependent.[4] We have often seen NT scans performed that do not meet the Fetal Medicine Foundation criteria; scans performed both locally and abroad. This is because of the considerable intra- and interobserver variability.[5] In contrast, the coefficient of variation of laboratory assays are usually much lower, e.g. the variability between assessing anaemia by examining conjunctival pallor and the laboratory estimation of the haemoglobin level in the patient's blood.

Finally, this paper was meant to examine the patient's perception of risk and to offer informed choices in the prenatal testing for foetal aneuploidy. While additional benefits such as identifying cardiac defects in the foetus may be a bonus, using NT measurement is a poor screening method for even major congenital heart diseases.[6,7] The NHS informs patients that the false-negative rate of the NT scan is 30%,[8] while the Wolfson Institute of Preventive Medicine informs its clients that the combined test has a false-negative rate of 16%.[9] In contrast, in a recent large-scale 11,105-patient, 49-medical centres multicentre study, noninvasive prenatal testing using cell-free foetal DNA in maternal plasma, the sensitivity and specificity for the detection of trisomies 21 and 18 were 100% and 99.96%, respectively, and there were no false-negative cases.[10] The authors of this same paper[10] anticipated a 98% reduction of invasive prenatal diagnostic procedures if such a test were introduced into routine clinical practice. It is important to allow patients to know the detection rate, false-positive rate and also the false-negative rate, so that patients can make informed choices in their own prenatal care.

Yours sincerely,

Mahesh Choolani, Arijit Biswas

Department of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore. mahesh_a_choolani@nuhs.edu.sg

References

1. Nicolaides KH. Screening for fetal aneuploidies at 11 to 13 weeks. Prenat Diagn 2011; 31:7-15.
2. Yeo GS, Lai FM, Wei X, et al. Validation of first trimester screening for trisomy 21 in Singapore with reference to performance of nasal bone. Fetal Diagn Ther 2012; 32:166-70.
3. Campbell D. NHS failure on Down's screening kills healthy babies: Missed target means only one in three hospitals offer pregnant women the best test, admits screening chief. Denis Campbell, Health correspondent. In: The Guardian, 16 May 2009 [online]. Available at: www.guardian.co.uk/society/2009/may/16/health-nhs. Accessed December 12, 2012.
4. Crossley JA, Aitken DA, Cameron AD, McBride E, Connor JM. Combined ultrasound and biochemical screening for Down's syndrome in the first trimester: a Scottish multicentre study. BJOG 2002; 109:667-76.
5. Senat MV, Bernard JP, Boulvain M, Ville Y. Intra- and interoperator variability in fetal nasal bone assessment at 11-14 weeks of gestation. Ultrasound Obstet Gynecol 2003; 22:138-41.
6. Jouannic JM, Thieulin AC, Bonnet D, et al. Measurement of nuchal translucency for prenatal screening of congenital heart defects: a population-based evaluation. Prenat Diagn 2011; 31:1264-9.
7. Westin M, Saltvedt S, Bergman G, et al. Is measurement of nuchal translucency thickness a useful screening tool for heart defects? A study of 16,383 fetuses. Ultrasound Obstet Gynecol 2006; 27:632-9.
8. NHS. Diagnosing Down's syndrome. In: Down's syndrome – Diagnosis [online]. Available at: www.nhs.uk/Conditions/Downs-syndrome/Pages/Diagnosis.aspx. Accessed December 12, 2012.
9. Barts and The London School of Medicine and Dentistry. The Combined Test. In: Antenatal Screening Services. Available at: www.wolfson.qmul.ac.uk/epm/screening/combined.html. Accessed December 12, 2012.
10. Dan S, Wang W, Ren J, et al. Clinical application of massively parallel sequencing-based prenatal noninvasive fetal trisomy test for trisomies 21 and 18 in 11,105 pregnancies with mixed risk factors. Prenat Diagn 2012; 32:1225-32.