LETTERS TO THE EDITOR

Nuchal translucency and gestational age

Professor Wald and his team (Wald et al., 2004) have remodelled the already modelled SURUSS data (Wald et al., 2003a) to claim, firstly, that their results are now similar to those of the multicentre study co-ordinated by the Fetal Medicine Foundation (Snijders et al., 1998), and, secondly, that the gestation of choice for nuchal translucency (NT) measurement is 10 weeks. The latest modelling exercise was apparently prompted by the study of Spencer et al. (2003a). However, the multiple of the median (MoM) approach used by Professor Wald for the analysis of the NT data is the same as the one shown by Spencer et al. (2003a) to be inappropriate. Furthermore, in SURUSS, there were 101 fetuses with trisomy 21 but NT was measured in only 85 (Wald et al., 2003a). At 10 weeks, there were six trisomy 21 fetuses and the NT was below the 95th centile in all the cases. In the analysis, which now claims a 73% detection rate, for a 5% false-positive rate, the data from only three of the six cases were used.

We summarise the results of the study by Spencer et al. (2003a). In screening for trisomy 21 by NT, patient-specific risks are derived by multiplying the a priori maternal age and gestation-related risk by a likelihood ratio, which depends on the difference in fetal NT measurement from the expected normal median for the same fetal crown-rump length (delta value). In screening using maternal serum–biochemical markers, a different approach has been used to take into account the gestation-related change in marker levels. This method involves converting the measured concentration into a multiple of the median of unaffected pregnancies at the same gestation. The study of Spencer et al. (2003a), involving analysis of data from 128 030 unaffected and 428 trisomy 21 pregnancies, demonstrated that the delta NT approach provides accurate patient-specific risks. In contrast, the traditional MoM approach was found to be inappropriate for this purpose because none of the three basic assumptions that underpin this method are valid. Firstly, in the unaffected population, the distributions of NT MoM and log10 (NT MoM) were not Gaussian; secondly, the SDs did not remain constant with gestation; and thirdly, the median NT MoM in the trisomy 21 pregnancies was not a constant proportion of the median for unaffected pregnancies. The NT MoM approach resulted in women being given an overestimate of risk for trisomy 11 weeks and a considerable underestimate of risk at 13 weeks (Spencer et al., 2003a). The non-Gaussian nature of Log10 (NT MoM) still persists for gestation specified by week or by day, so the calculation of detection rates and false-positive rates on the basis of this assumption needs to be carefully verified. In screening for trisomy 21 by fetal NT, the likelihood ratio associated with delta NT is effectively constant for gestations between 10 and 13+6 weeks (Spencer et al., 2003a).

Professor Wald’s letter also presents the effect of the remodelled data of SURUSS on the performance of the integrated test. However, there are concerns about both the first- and the second-trimester biochemical components of this test. Firstly, Professor Wald’s claim that 10 weeks is the best gestation for starting the process of screening is essentially based on the good performance of PAPP-A. However, in SURUSS, the data on PAPP-A from 10 weeks were combined with those at 9 weeks, which would exaggerate the importance of this metabolite. In particular, the contribution of samples from 9 weeks was 16% for the unaffected pregnancies and 40% for the trisomy 21 pregnancies (Wald et al., 2003a). Secondly, in SURUSS, the predicted detection rates, for a 5% false-positive rate, were 71% for the double test, 77% for the triple test and 83% for the quadruple test (Wald et al., 2003a). These detection rates are substantially higher than the respective rates of 61, 66 and 75% reported by the same authors in their prospective screening studies (Wald et al., 2003b). Thirdly, Spencer et al. (2002; 2003b) have demonstrated temporal changes in maternal serum–biochemical markers of trisomy 21 across both the first and second trimesters of pregnancy. Consequently, calculation of accurate patient-specific risks requires a variable median–separation model (Spencer et al. 2003b), rather than the conventional constant median–separation model proposed by Wald et al. (1988). Fourthly, there are major concerns on the robustness of the inhibin A assay.

In 1992, we selected 10 weeks as the earliest gestation for measurement of NT (Nicolaides et al., 1992) because screening necessitates the availability of a diagnostic test and chorionic villous sampling before 10 weeks may be associated with transverse limb–reduction defects (Firth et al., 1991). We subsequently changed the minimum gestation to 11 weeks because it was realised that at this gestation, but not at 10 weeks, many major fetal abnormalities, such as anencephaly, cardiac defects, obstructive uropathy, exomphalos and some cases of spina bifida, can also be diagnosed at the NT scan. Advances in fetal medicine should not be reversed by remodelling of modelled detection rates for trisomy 21.

Nicolaides KH1, Heath V1, Spencer K2 and Nix ABJ3

1Fetal Medicine Foundation, London
2Clinical Biochemistry Department, Harold Wood Hospital, Essex
3Department of Epidemiology, Statistics and Public Health, University of Wales, Cardiff

DOI: 10.1002/pd.888
REFERENCE


REFERENCE

834 LETTERS TO THE EDITOR

Response to Nicolaides

Sir,

We are grateful for the opportunity to respond to the comments from Professor Nicolaides.

1. Modelling. All analyses based on a combination of screening markers are necessarily based on modelling. It is needed to estimate a woman’s risk of having an affected pregnancy and to estimate screening performance. An advantage of modelling is that information across several weeks is used to estimate screening performance at any one week; it takes account of the changes in the screening markers from week to week as well as their values at each week. It is good practice to regularly review and improve such models by using additional relevant information. This is what we did (Wald et al., 2004a) by taking account of new evidence, showing a statistically significant decline in median NT MoM values in Down syndrome pregnancies with increasing gestational age.

2. Comparison of screening performance in the first trimester from SURUSS and the Fetal Medicine Foundation (FMF). In the SURUSS report, we pointed out (Results, Screening Performances of Markers Individually) that using NT and maternal age yielded 73% for 5% (Nicolaides et al., 1998). In our revised analysis, taking account of the decline in the median separation of NT MoMs between affected and unaffected pregnancies (Wald et al., 2004a), the estimate at 11 weeks of pregnancy from SURUSS was 73% for a 5% false-positive rate (69% at 12 weeks and 63% at 13 weeks). Whatever the methodological differences between SURUSS and the FMF results, it is noteworthy that the two estimates are as close as they are.

3. Preferred gestational age in the first trimester for the measurement of screening markers. Nicolaides and his colleagues are correct in saying that there are few data at 10 weeks on NT in affected pregnancies. We pointed this out (Wald et al., 2004), and for this reason focussed on 11 weeks in presenting the results of screening using first-trimester markers. In the SURUSS report (Wald et al., 2003a), we did not say that the gestation of choice for NT measurement was 10 weeks. The original analysis took account of the declining standard deviation of NT with gestational age in unaffected pregnancies, which explains the previously reported improvement at 12 to 13 weeks compared with 10 and 11 weeks (Wald et al., 2003a). With the subsequent recognition that NT MoMs in Down syndrome pregnancies decline with gestation, it emerged that screening performance of NT measurement at 10 to 11 weeks is better than at 12 and 13 weeks; the effect of the decline in NT MoMs in Down syndrome pregnancies outweighs the reduction in the standard deviation in unaffected pregnancies (Wald et al., 2004b).

4. Nuchal translucency expressed as multiples of the median. Three reasons are given by Nicolaides and his colleagues against the use of NT MoMs but, in our view, none are valid: (1) it is stated that NT MoMs are not Gaussian. After log transformation, NT is Gaussian over most of the range of values and is only somewhat skewed at high MoM values, and this can be allowed for by using appropriate truncation limits. The fit to a Gaussian model is remarkably good, as is shown in Figure 7 of their article (Spencer et al., 2003a, corrected in a subsequent letter Spencer et al., 2003b). (2) Standard deviations do not remain constant with gestation. This is correct, but not relevant. The model can, and does, allow for this (Wald et al., 2003a). (3) Median NT MoM in trisomy 21 pregnancies declines with gestation. This is the point of our letter (Wald et al., 2004a) and can be allowed for in the model.

Copyright © 2004 John Wiley & Sons, Ltd.