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The effect of nuchal translucency measurement on second-trimester biochemical screening for Down's syndrome

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ABSTRACT

In this study we examined the effect of introducing first-trimester nuchal translucency measurement on the second-trimester maternal serum screening for trisomy 21. The detection rate, false-positive rate, likelihood ratio and positive predictive value of the double marker test before and after introduction of nuchal translucency measurement were determined. The detection rate of nuchal translucency screening for trisomy 21 was 83% (5/6) with a 1.3% false-positive rate, a 63.8 likelihood ratio and a positive predictive value of 22.7%. After the introduction of nuchal translucency measurement, the likelihood ratio for a positive result and positive predictive value of the biochemical screening decreased from 9.1 to 5 and 2.7% to 0.45%, respectively. Our results show that nuchal translucency measurement is not only an effective method of first-trimester screening for Down's syndrome but also has implications for the likelihood ratio and positive predictive value of second-trimester biochemical screening. Since the biochemical test is now applied to a population with a decreased risk of trisomy 21, a positive test will be less likely to indicate Down's syndrome than when nuchal translucency measurement was not applied.

INTRODUCTION

Screening for Down's syndrome in the UK has usually been performed during the second trimester by maternal serum biochemistry. However, during the last 4 years, nuchal translucency measurement in the first trimester has been proposed as an alternative[1,2]. The benefits of first-trimester screening are early reassurance for the mother, and physically and emotionally less traumatic termination of pregnancy when required. First-trimester nuchal translucency measurement has been shown to be an effective screening method for chromosomal abnormalities[1–5]. However, many obstetric units have been reluctant to introduce this screening method to replace traditional second-trimester screening because high-risk women have usually been studied and extrapolating these results to a low-risk population may not be appropriate. The aim of this study was to assess the effect of introducing nuchal translucency measurement on second-trimester biochemical screening for Down's syndrome in a low-risk population.

METHODS

Since April 1993, we have offered prenatal diagnosis for Down's syndrome to all our obstetric patients at the Royal Free Hospital by maternal serum screening with α-fetoprotein and free β-human chorionic gonadotropin (free β-hCG) after counselling by midwives. A dating scan is performed prior to biochemical testing by either research fellows or ultrasonographers, as this has been shown to have a significant impact on the risk calculation, improves the detection rate and reduces the false-positive rate[6]. Our hospital is situated in an area of London which has an older childbearing population than the national average (9.4% aged ≥ 37 years vs. 5.4%, respectively). In 1994, 17% of our obstetric population were older than 34 years and in 1995, this increased to 17.6% (the UK national figure is 9.6%).

We developed reference ranges of nuchal translucency measurement with crown–rump length in a low-risk population[7]. Since 1995, all patients undergoing first-trimester scanning have been counselled and offered nuchal translucency screening. When the nuchal translucency measurement is more than the 99th centile, irrespective of maternal age, invasive testing by chorionic villus biopsy is offered. The rest of the patients (including those who do not attend for nuchal translucency measurement) are offered mid-trimester biochemical screening, which has remained the official screening policy of the unit. The α-fetoprotein and

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free β-hCG multiples of the median (MoM) were used to adjust the age-related risk for trisomy 21. Nuchal translucency measurements are performed in mid-sagittal view with the fetal neck extended, by clinical research fellows at 10–13 weeks' gestation[8]. Transabdominal sonography is performed first and the transvaginal route is used when the transabdominal route is unsuccessful in obtaining a measurement (8% of cases).

The results of the chromosomal analysis were obtained from the cytogenetic laboratory. Details of neonatal outcome were obtained from the maternity records and neonatal computerized database.

Detection rates, false-positive rates, likelihood ratios – together with 95% confidence intervals (CI) – and positive predictive values for the double marker test before and after introduction of nuchal translucency screening and for nuchal translucency measurement itself were determined.

RESULTS

In 1994, 2540 patients opted to have screening for trisomy 21 by the double marker test. The detection rate for Down's syndrome was 87.5% (seven out of eight) with a 9.6% (244/2532) false-positive rate, a 9.1 (95% CI, 6.8–12.1) likelihood ratio for a positive result and a positive predictive value of 2.7% (Table 1). In 1995, nuchal translucency measurements were attempted and performed in 1302 pregnancies (100% success rate) at 10–13 weeks' gestation and detected five out of six affected fetuses (detection rate 83%), with a 1.3% (17/1296) false-positive rate, likelihood ratio of 63.8 (95% CI, 35.1–115) and a 22.7% positive predictive value. The five affected fetuses underwent termination of pregnancy. Biochemical testing was declined in the sixth pregnancy; no abnormality was seen during the second-trimester scan and trisomy 21 was diagnosed postnatally. In the same year, biochemical screening was carried out in 2236 pregnancies and one out of two affected fetuses were detected, for a detection rate of 50%, false-positive rate of 10% (223/2234), likelihood ratio for positive test of 5 (95% CI, 1.25–20.1) and a positive predictive value of 0.45% (Table 1).

Ninety karyotypes were obtained for positive biochemical screening in 1994. However, in 1995, 124 karyotypes were obtained, with 14 chorionic villus biopsies for positive screening by nuchal translucency and 110 amniocenteses for positive maternal serum biochemistry.

There was a tendency for the likelihood ratio for positive biochemical results to decrease after nuchal translucency measurements were introduced. However, the confidence interval was wide, since only two fetuses undergoing biochemical screening after introduction of nuchal translucency screening were affected. Since the odds of trisomy 21 need to be 1/250 or more to justify invasive testing, we calculated the necessary likelihood ratio required by biochemical screening in order to raise the post-test odds to this level. According to the use of Bayes' theorem, the post-test odds equals the product of the pre-test odds and the likelihood ratio. Therefore, for a given pre-test odds based on the prevalence of trisomy 21 in our study, and the requirement for the post-test odds to be 1/250, the required likelihood ratio for a positive test result can be calculated[9]. Before nuchal translucency screening was introduced, the overall odds of trisomy 21 in the population were 8/2532 (1/316.5); therefore a likelihood ratio of 1.26 was required to raise the odds to 1/250. After nuchal translucency screening was introduced, the overall odds of trisomy 21 in the population were 2/2234 (1/1117); therefore the likelihood ratio needed to be 4.5 for similar odds. Our observed results suggest that the likelihood ratio for a positive result on biochemical screening after nuchal translucency measurement is still compatible with this requirement.

DISCUSSION

The present study shows that nuchal translucency measurement is not only an effective method of first-trimester screening for Down's syndrome, but also has implications on the likelihood ratio, positive predictive value and cost-effectiveness of second-trimester biochemical screening. Since the majority of pregnancies with trisomy 21 will be detected by nuchal translucency measurement and terminated during the first trimester, the mid-trimester biochemical test will be applied to a population with a decreased risk of trisomy 21 and a positive test will be less likely to indicate Down's syndrome than when nuchal translucency measurement was not applied. However, our study has some limitations. First, the number of affected fetuses was small. Second, not all the pregnant patients were referred for nuchal translucency measurement and, last, it is impossible to assess how many of the affected pregnancies detected by nuchal translucency measurement and terminated would have continued to the second trimester and have been detected by biochemical screening.

We have shown that the positive predictive value of biochemical screening has fallen from 2.7% to 0.45% after

Table 1 Down's syndrome cases at the Royal Free Hospital

		Nuchal translucency				*Biochemical screening*			
Period	*Total**	*Detection rate*	*False-positive rate*	*Likelihood ratio*	*Positive predictive value*	*Detection rate*	*False-positive rate*	*Likelihood ratio*	*Positive predictive value*
1 April 1994 to 31 March 1995	12	—	—	—	—	87.5% (7/8)	9.6%	9.1 (95% CI 6.8–12.1)	2.7%
1 April 1995 to 31 March 1996	10	83% (5/6)	1.3%	63.8 (95% CI 35.1–115)	22.7%	50% (1/2)	10%	5.0 (95% CI 1.25–20.1)	0.45%

*Total number of cases of trisomy 21 in the population

the introduction of nuchal translucency measurement. This is not surprising since, in the latter case, a lower-risk population was undergoing biochemical screening and positive predictive value is well known to depend on prevalence[10]. This emphasizes that the odds of Down's syndrome will need to be multiplied more heavily by the result of biochemistry in a population that has already undergone nuchal translucency screening.

The association of increased nuchal translucency and Down's syndrome in fetuses during the first trimester of pregnancy has been well documented[1,11]. However, its usefulness as a screening test for Down's syndrome in the general population has been disputed[12,13]. Roberts and colleagues[12] claimed poor reproducibility of nuchal translucency measurement, which would adversely affect its sensitivity and specificity as a screening test. An 18% failure rate in obtaining a measurement was reported in the same study, with the commonest reasons given by the ultrasonographers being unfavorable fetal position and maternal obesity. However, in our experience, these problems were overcome by the use of transvaginal ultrasound. Using the transabdominal and/or the transvaginal route, researchers and more recently ultrasonographers found that the success rate of nuchal translucency measurement was 100% in our center.

Conflicting results regarding the sensitivity and specificity of nuchal translucency thickness as a screening test for chromosomal abnormalities have been reported. At 10–13 weeks' gestation, a nuchal translucency measurement of 3 mm is associated with a four-fold increase, and measurements of > 3 mm with a 29-fold increase in the maternal age-related risk for fetal trisomies[3]. Combining maternal age and fetal nuchal translucency thickness at 10–13 weeks' gestation has been predicted to give a detection rate of at least 85% with a false-positive rate of 5%, which compares favorably with second-trimester biochemical screening[2]. However, Haddow and Palomaki[14] reported that nuchal translucency measurements in the first trimester are less discriminatory than biochemical screening tests in the second trimester. With measurement of nuchal translucency in 2318 unaffected and 30 trisomy 21 fetuses in 11 centers and the use of a screening cut-off level of 3 mm, 53% of the Down's syndrome pregnancies were identified with a 30% false-positive rate. With the use of the 95th centile for each center as the screening cut-off level, 33% of the Down's syndrome cases were detected with a 6% false-positive rate. Considering that nuchal translucency measurement increases with gestation, a single cut-off value of 3 mm is incorrect and may explain the high false-positive rate reported in the above study[7].

Even if nuchal translucency measurement is introduced into routine clinical practice, there will still be a place for second-trimester biochemical testing. Although second-trimester biochemical screening can be affected by many variables, e.g. maternal height, ethnic origin, weight and gestational age[6], it is easy to perform, does not require additional training of personnel and has a wider gestational window when it can be performed (14–20 weeks) in comparison to nuchal translucency screening (11–14 weeks). Therefore, it will remain the method of screening in patients who initially attend late in pregnancy. However, it has been demonstrated than an ultrasound examination for correct dating of gestation is required prior to maternal serum biochemistry to avoid the need to revise the estimate of gestational age after a woman has been screened and found to be positive[6]. Training is essential prior to implementation of nuchal translucency testing, but experienced sonographers will need to perform only 80–100 supervised scans before they can achieve repeatable measurements[8]. Ultrasonographic detection of many other fetal malformations in the first trimester in a low-risk population has recently been described[15]. In addition, increased nuchal translucency in karyotypically normal fetuses in the first trimester may be the consequence of congenital heart disease[16,17]. Therefore, the first-trimester scan promises to become the most important scan performed in pregnancy for the detection of fetal malformations.

The effect of introducing nuchal translucency measurement on the second-trimester biochemical screening for trisomy 21 has not been assessed before. As nuchal translucency thickness and maternal serum α-fetoprotein and free β-hCG are independent variables (S. M. Verdin and colleagues, submitted for publication), it is possible to combine these in estimating an individual risk for each pregnancy and keeping the false-positive rate to a minimum. Using both tests in conjunction may increase the overall detection rate. However, it may also increase the number of pregnancies exposed to invasive prenatal testing, with a potential increase in pregnancy loss due to these procedures. In this pilot study, there was an increase in the number of invasive procedures performed for screen-positive patients with no increase in the detection rate, because the biochemical results were not adjusted by the nuchal translucency measurements. Therefore, the interpretation of biochemical screening was suboptimal. The other potential problem of sequential screening includes difficulties with counselling when faced with conflicting results.

First-trimester biochemical screening has been shown to be as effective as second-trimester testing[18,19]. Recent studies have shown that an improved estimate of risk for fetal trisomies at 10–13 weeks' gestation can be achieved by combining data on maternal age, nuchal translucency measurement, maternal serum total or free β-hCG or pregnancy-associated placental protein A[20–22]. The optimal way of delivering screening for Down's syndrome is by providing the patient with a single individual risk by a combination of nuchal translucency measurement and maternal serum screening. However, large prospective studies are required to assess the feasibility and efficacy of introducing this new approach in routine maternity units.

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