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A comparison of the impact of screen-positive results obtained from ultrasound and biochemical screening for Down syndrome in the first trimester: a pilot study

Martin J. N. Weinans[1]*, Loes Kooij[2], Moira A. Müller[3], Katia M. Bilardo[3], Jan M. M. van Lith[3] and Tjeerd Tymstra[2]

[1]*Antenatal Diagnosis Unit, Department of Obstetrics and Gynaecology, University Hospital Groningen, The Netherlands*
[2]*Department of Health Sciences, Faculty of Medicine, University of Groningen, The Netherlands*
[3]*Department of Obstetrics and Gynaecology, Academic Medical Centre, Amsterdam, The Netherlands*

Objective To compare the experiences of women who received a screen-positive test result for Down syndrome after nuchal translucency screening or after biochemical screening in the first trimester of pregnancy in the Netherlands.

Method Semi-quantitative questionnaires were sent to 40 women with a screen-positive test result for Down syndrome in the first trimester of pregnancy: 20 had undergone nuchal translucency screening (NT group) and 20 had undergone serum screening (PAPP-A and free beta-hCG) (SS group). In all the cases, chorionic villus sampling (CVS) had not revealed any chromosomal abnormalities.

Results The major reason for undergoing the screening test in both groups of women was to be more reassured about the health of the baby. In the NT group, 5 out of the 20 women stated that they had suddenly been confronted with the NT measurement during the ultrasound examination without even being asked, or had been caught by surprise about the possibility. Together with two other women, they felt that at that stage they had been insufficiently informed about what the test meant. In the SS group, two women also held this opinion. In 10 out of the 20 women in the SS group, the positive-screening result had caused (a great deal of) anxiety. In the NT group, this proportion was as high as 18 out of the 20. Six of the women in the NT group mentioned that 'seeing the baby' had been an important factor in their decision to undergo CVS. Even after a favourable result of CVS, a proportion of the pregnant women were still feeling anxious about the health of their baby (5 women in the SS group and 12 in the NT group). Nevertheless, a large proportion of the women in both groups was pleased that they had undergone the screening test. Only a few of them stated that they would not choose the same screening test again in a future pregnancy.

Conclusions An unfavourable screening result after NT screening appeared to have a greater impact than an unfavourable result after serum screening. This might partly be explained by the ultrasound examination *visualising* the increased risk during NT screening. An additional important role may have been played by the fact that an abnormal NT screening result implies an increased risk of other disorders besides Down syndrome, which the women should be informed about beforehand. Several factors place special demands on the counselling prior to NT screening. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS: Down syndrome; first trimester; nuchal translucency; biochemical screening; questionnaires

INTRODUCTION

A major development in prenatal screening for Down syndrome over the past few years is the shift in time from the second trimester to the first trimester. Large studies have shown that the results of first-trimester screening for Down syndrome on the basis of maternal serum markers or fetal nuchal translucency measurement in combination with maternal age are at least comparable to those of second-trimester serum screening (Haddow *et al*., 1998; Snijders *et al*., 1998). Consequently, first-trimester screening is now being applied routinely on a large scale in western Europe. In the Netherlands, women also prefer early screening (Kornman *et al*., 1997; De Graaf *et al*., 2002). However, the Netherlands holds a unique position compared to other western countries as far as screening for Down syndrome is concerned; in 1996, the *Population Screening Act* was passed containing limitations for mass screening regarding permission for its execution. Only women aged 36 years and older are permitted to undergo screening for Down syndrome, a group for whom prenatal diagnosis was already available. Pregnant women of younger than 36 years are not offered screening unless they specifically ask for it. In practice, this means that screening is only offered to a small minority of all pregnant women. Owing to the dismissive policy of the Dutch government, strong regional differences have developed in the Netherlands regarding screening for Down syndrome, particularly first-trimester screening. In some regions, such as the northern provinces of the

*Correspondence to: Martin J. N. Weinans, Antenatal Diagnosis Unit, Department of Obstetrics and Gynaecology, University Hospital Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands. E-mail: martinweinans@planet.nl

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Netherlands, it has been possible for women to undergo first-trimester serum screening based on PAPP-A, free beta-hCG and maternal age since the end of 1999. In the *Amsterdam* region, first-trimester screening can be conducted on the basis of nuchal translucency measurement and maternal age.

There are differences between biochemical serum screening and ultrasound screening by means of nuchal translucency measurement. In the case of biochemical screening, the pregnant woman undergoes a simple blood test and hears the result a few days later. This result sometimes implies an increased risk, but it is just a series of numbers on a piece of paper. However, in the case of nuchal translucency measurement, the baby is visualised by ultrasound and sometimes 'something abnormal' is seen. Theoretically, this is also just a statistically increased risk, but the *visualisation* of the increased NT gives a different perception of this risk. Our hypothesis was that this can lead to different reactions of the women involved. In order to gain insight into the differences in reaction, we performed a study on two groups of pregnant women who had received a screen-positive test result for Down syndrome. To our knowledge, this is the first report comparing these two screening tests for their impact on women.

MATERIALS AND METHODS

Semi-quantitative questionnaires were sent to two groups of women: one to women in the *Amsterdam region* who had undergone NT screening during their first trimester of pregnancy (NT group; $n = 20$) and one to women in the *Northern provinces region* who had undergone serum screening during their first trimester of pregnancy (SS group; $n = 20$). In both groups, screening had indicated that there was an increased risk for Down syndrome. The result of the screening test was given as a numerical value. Supplementary chorionic villus sampling(CVS) had not detected any chromosomal abnormalities. The questionnaires were sent when the women had reached 20 to 32 weeks of pregnancy.

Two slightly different questionnaires were developed for the two groups of women. They were based on questionnaires that had been used in previous studies in the Northern provinces region (Kornman *et al.*, 1997; Weinans *et al.*, 2000) and on interviews with three women who described their experience after receiving an unfavourable NT screening result during pregnancy. The questionnaires comprised three parts: the period prior to screening, the screening result and the period before and after CVS. At the end of the questionnaires, the women were invited to describe their own personal experience with the prenatal screening.

Two medical centres participated in the study: Amsterdam Medical Centre (AMC, Amsterdam region) and University Hospital Groningen (UHG, Northern provinces region). The results of the screen-positive tests were given with the addition of the numerical value. At both centres, recruitment continued until 20 fully completed questionnaires had been returned by each group. Statistical testing of differences between the groups was done using Fisher's exact test.

Nuchal translucency (NT) group

At the AMC, women were recruited who had undergone CVS on the grounds of a screen-positive NT measurement result. Fifteen out of the 20 NT measurements had been conducted at other hospitals in the Amsterdam region. These women had subsequently been referred to the AMC for CVS. The women who had undergone NT screening at the AMC were either from the prenatal diagnosis outpatient clinic or they had been receiving routine obstetrical care at the AMC. NT screening was performed according to the guidelines of the Fetal Medicine Foundation. Women were offered second-trimester ultrasound examination if the NT was more than 3 mm because of an increased risk of other structural abnormalities. This ultrasound examination was conducted at the AMC. The questionnaire was sent to these women after the second ultrasound examination, provided that no fetal abnormalities had been found. In the study period, first-trimester serum screening was not available at the AMC.

Serum screening (SS) group

At the UHG, women were recruited who had undergone CVS on the grounds of a first-trimester screen-positive serum result. Thirteen out of the 20 women had been referred to the UHG for CVS by their general practitioner, midwife or gynaecologist from another hospital, after the unfavourable result of the serum screening test had been discussed with them. The remaining women were from the UHG prenatal diagnosis outpatient clinic. Maternal serum PAPP-A and free beta-hCG were measured between 9 and 11 completed weeks of pregnancy with a fluoroimmunoassay (AutoDELFIA PAPP-A and Free hCGß kit; Wallac Oy, Turku, Finland). In the study period, NT ultrasound screening was not available at the UHG.

RESULTS

Some background characteristics of the respondents are shown in Table 1. There are statistically significant differences between the groups for maternal age (Fisher's exact test, $p = 0.004$) and for the number of women aged 36 years or older ($p = 0.0006$). In the NT group, 14 out of the 20 women, and in the SS group, 3 out of the 20 women were younger than 36 years.

The women were asked to give the reasons why they had participated in Down syndrome screening. In the two groups, the major reason in over half of the respondents was to obtain more reassurance about the health of the baby. Slightly less than half of the SS group said that the reason was to help them decide whether to undergo invasive testing. In the NT group, 5 out of the 20 women had been unpleasantly surprised by the finding of an

Table 1—Background characteristics of the respondents

	NT group	SS group
Response (%)	20/29 (69)	20/28 (71)
Mean maternal age (range)*	33.4 (25–41)	36.8 (30–43)
Number of women ≥36 years†	6/20	17/20
Completed high school (%)	13/20 (65)	10/20 (50)
Primigravida (%)	10/20 (50)	4/20 (20)

Statistical significance using Fisher's exact test. * $P < 0.004$, † $P < 0.0006$.

increased NT, or they had suddenly been confronted with the news without being asked beforehand. Four other women in the NT group mentioned that one of their reasons to choose for NT measurement was that they would undergo any available test during pregnancy. In response to the question of whether they had been adequately informed about the screening test at the time this was done, seven respondents in the NT group and two respondents in the SS group gave the answer: no (Fisher's exact test, not significant).

The women were also asked whether the screening test had made them anxious. In the NT group, 18 out of the 20 respondents had been (very) anxious about the result of the screening test, compared to only half of the respondents in the SS group. This difference is statistically significant (Fisher's exact test, $p = 0.008$). The two women in the NT group who had not been (very) anxious were both younger than 36 years. In the SS group, one out of the three women younger than 36 years was represented in the group of 10 (very) anxious respondents. We also asked whether the ultrasound images had influenced their decision to undergo further invasive tests. In the NT group, 6 out of the 20 women reported that 'seeing the baby' during the ultrasound examination had influenced their decision to have CVS. Table 2 shows that despite the favourable result of CVS, 12 out of the 20 women in the NT group versus 5 out of the 20 in the SS group were still anxious about the health of their baby when they filled in the questionnaire, a statistically significant difference (Fisher's exact test, $p = 0.032$). For example, 6 out of the 20 women in the NT group remarked: 'I still keep wondering why there was more fluid in the neck than normal'. At the end of the questionnaire, there was room for the women to provide additional information in their own words. Various respondents in both groups described the distressing, emotional period that they had gone through and their satisfaction about the support from health-care professionals. One of the women who underwent serum screening wrote: 'It was quite something the result of the blood test and the CVS. I had assumed that the result of the blood test would be OK. Luckily the person who rang me on the telephone was really friendly and calm. Although my husband and I had already talked about it and we knew exactly what we wanted, I still found it very difficult emotionally. Especially the CVS. Having to wait for the result was pretty awful too. You start thinking all sorts of things. All in all I wasn't able to enjoy my pregnancy during that period. I was pleased that the midwife did an ultrasound examination the day after the CVS to see whether everything was alright with the baby'. Also, in the NT group, several women described their experience with the test in their own words. One of the respondents wrote: 'We feel that we were treated without delay and in a very pleasant manner and that we were kept well-informed about the result of the CVS. The counselling was also fine, the explanations about all sorts of things. The emotional side was properly taken care of. We are very happy now. The fluid has disappeared and after all the measurements, everything seems to be the correct size'. However, another respondent was still suffering from anxiety. She wrote: 'The extensive ultrasound examinations at 20 and 25 weeks have left us feeling very positive and reassured. But we are still wondering why the neck fold was thickened at the first measurement and no one can give us an answer'. Another respondent wrote: 'Although I probably know far more about the health of my unborn baby than many other pregnant women, the care-free feeling of pregnancy has disappeared'.

The last question asked the women's opinions about the screening tests. Table 3 shows that the large majority of respondents in the two groups were pleased that they had undergone the screening test and would have another screening test for Down syndrome during a subsequent pregnancy. Similarly, the majority of women in the two groups expressed that in their opinion a screening test for Down syndrome should be offered to all pregnant women in the Netherlands.

DISCUSSION

In order to gain more insight into the extent to which the screening method influences pregnant women's reactions, we compared the experience of women who have received a false-positive result after either first trimester biochemical or ultrasound screening for Down syndrome. The most noticeable result was that a significantly higher number of respondents in the NT group

Table 2—Are you presently feeling anxious about the health of your baby, despite the favourable CVS result?

	NT group			SS group		
	All	(<36 years)	(≥36 years)	All	(<36 years)	(≥36 years)
No, I am not feeling anxious	8	6	2	15	2	13
Yes, I am feeling anxious	11	7	4	5	1	4
Yes, I am feeling very anxious	1	1	—	—	—	—
	$n = 20$	14	6	20	(3)	(17)

Table 3—Opinions about the screening test

(a)-I am pleased that I had the screening test

	NT group ($n = 20$)	SS group ($n = 20$)
I totally agree	9	11
I agree	7	6
Do not agree/do not disagree	2	1
I disagree	2	2
I totally disagree	—	—

(b)-In a future pregnancy, I would choose the same screening test

	NT group ($n = 20$)	SS group ($n = 20$)
I totally agree	11	13
I agree	5	5
Do not agree/do not disagree	1	1
I disagree	3	1
I totally disagree	—	—

(c)-Do you think that the screening test should be offered to all pregnant women?

	NT group ($n = 20$)	SS group ($n = 20$)
No	4	6
Yes	16	14

were feeling anxious to some degree about the health of their baby than the respondents in the SS group at the time of filling in the questionnaire. Thus, as we have measured, the impact of a screen-positive test result for Down syndrome after NT measurement appeared to be greater than that after biochemical screening.

This pilot study had important limitations concerning the study design. We compared two groups of women who differed in age and place of residence (different geographical regions, where they also received their care). In a randomised controlled trial, these difficulties could have been overcome, but we were unable to conduct such a study design in view of the present Dutch practice. Another limitation was the small sample size; we received responses from two groups of only 20 women. Also, we used semi-quantitative questionnaires that did not include any standardised measures. Owing to the small sample size, higher-powered studies are needed to see whether ultrasound screening is indeed associated with a larger number of negative consequences. When comparing the background characteristics of the two groups, the significant difference in the number of women aged 36 years or older was probably even more relevant than the difference in mean maternal age. In the SS group, the large majority of women were 36 years of age or older and were therefore eligible for prenatal screening according to current Dutch regulations. To a certain extent, they knew that they had an increased risk of DS because of their age. In the NT group, the majority (14 out of the 20) did not have an age indication for prenatal screening. Thus, it may very well be that the younger women were more surprised by a screen-positive result. By analysing the distributions of anxious and non-anxious respondents in the younger women and those aged 36 years or older, we attempted to unravel age from the mode of screening as a cause of distress. On the basis of our very small numbers, we could not see a trend towards younger women being more anxious than older women.

A possible explanation for the higher level of anxiety we found in the NT group is related to visualisation of the anomaly causing the increased risk. It is clearly apparent that for a pregnant woman, the image of her child with an increased amount of fluid in the neck at the time of the screening means much more than receiving a figure as an abnormal serum screening result. In the present study, 6 out of the 20 women in the NT group reported that their decision to undergo CVS had been influenced by the ultrasound images.

Another important difference between the two screening methods is that biochemical screening only screens for Down syndrome, whereas NT measurement not only screens for Down syndrome and other chromosomal abnormalities but also for cardiovascular defects and for a wide range of structural defects and rare genetic syndromes (Nicolaides *et al*., 2002). In women who have a screen-positive NT measurement and a favourable subsequent CVS result, the story may not always end there, because in the group of women with a NT value of larger than 3 mm, a structural or genetic abnormality may be detected at further extensive ultrasound (Bilardo *et al*., 1998; Souka *et al*., 2001; Bilardo, 2001; Senat *et al*., 2002). If the second-trimester ultrasound examination does not reveal any abnormalities, then the risk of underlying fetal abnormalities decreases to about 2% (Hyett, 2002). The fact that an increased NT measurement implies an increased risk of other disorders besides Down syndrome puts greater emphasis on the counselling prior to ultrasound screening compared to biochemical screening, also based on the knowledge that counselling for biochemical screening often falls short of the mark (Green, 1994; Gekas *et al*., 1999; Williams *et al*., 2002). The persistent anxious feeling about the health of the baby of women with a screen-positive NT result might be partly reduced by giving them supplementary psychological support, for example, by offering them an ultrasound and a consultation, once the karyotype is known.

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