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The attitude of women toward current and future possibilities of diagnostic testing in maternal blood using fetal DNA

Loes Kooij^{1*}, Tjeerd Tymstra¹ and Paul van den Berg²

¹Department of Health Sciences, University Medical Centre Groningen, The Netherlands

²Department of Obstetrics and Gynecology, University Medical Centre, Groningen, The Netherlands

Objective To determine the opinions of women about the new developments in the field of noninvasive prenatal diagnosis (NIPD).

Method Prospective study using questionnaires in two groups of women: women visiting the University Medical Centre Groningen and the Martini Hospital Groningen for the routine fetal anomaly ultrasound scan at 20 weeks' gestation and female medical master students.

Results Both groups consider NIPD an important asset in the reliable diagnosis of fetal aneuploidy and gender-determined genetic disorders, with the exception of disorders manifesting themselves later in life. There is a negative response as to its application for family balancing. Eighty-two percent of the pregnant women and 79% of the medical students responded positively to the question whether they consider NIPD an important asset in prenatal care. The statement that it is an asset because it enables pregnant women to bear an 'optimal child' is strongly rejected by both groups.

Conclusions NIPD paves the way for screening on a large scale. Our survey shows that women feel positive about these new possibilities, but find it hard to fully realize the consequences and new choices they will be confronted with. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS: noninvasive prenatal diagnosis; Down syndrome; fetal DNA; maternal blood; opinion

INTRODUCTION

There are several methods for the detection of aneuploidy in the fetus during pregnancy. Invasive procedures such as amniocentesis and chorionic villus sampling have been available since the 1970s. These techniques are considered to be highly accurate but involve a 0.5–2% risk of fetal loss. For that reason they are mainly recommended to women with a greater risk for having a pregnancy affected by Down syndrome. The chance of a miscarriage is absent with the noninvasive risk-assessment tests that have been developed in the last two decades. They do not result in certainty, however, but only in an individual risk assessment. At present the test of maternal serum screening at 9 to 14 weeks' gestation, in combination with nuchal translucency screening between 11 and 14 weeks and maternal age, renders up to a 90% accurate assessment of Down syndrome, with a 5% false-positive rate (Spencer *et al.*, 2003).

A new development is the possibility to isolate fetal nucleic acids from maternal blood. It has been known since 1997 that during pregnancy fetal DNA is present in a pregnant woman's blood (Lo *et al.*, 1997). Recently Lo showed that fetal mRNA transcripts can be used to diagnose fetal aneuploidy (Lo *et al.*, 2007). Currently researchers worldwide are trying to develop techniques

that are to result in accurate testing for fetal aneuploidy (Dhallan *et al.*, 2007). It is quite possible that these tests can already be applied in the first trimester of pregnancy.

By means of this new technology fetal screening for Down syndrome will probably become available on a large scale in the next decade, just as a routine screening service. The test is relatively simple—a blood sample of the pregnant woman will do—and the diagnose can be given with a high certainty in the first trimester of pregnancy (Dhallan *et al.*, 2007).

Not only does the test offer new possibilities for the detection of Down syndrome and other chromosomal defects but it also indicates gender-related disorders. Early fetal gender determination by means of noninvasive prenatal diagnosis (NIPD) is already being practiced clinically. Prenatal applications have been laid down for myotone dystrophy (Amicucci *et al.*, 2000), cystic fibrosis (Gonzales-Gonzales *et al.*, 2002) and Huntington disease (Gonzales-Gonzales *et al.*, 2003). Also in case of congenital disorders occurring later in life, e.g. breast cancer, early determination of gender could be important. Additionally there is the possibility of determination of gender for nonmedical reasons, although this is not generally accepted. The number of congenital disorders that can be detected via NIPD will significantly increase in the future. The application of these diagnostic tools is therefore expected to become ever more popular.

The question remains what women's opinions are as to this development and its applications. How do they feel about the existing possibilities and new developments in

*Correspondence to: Loes Kooij, Department of Health Sciences, University Medical Centre Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands. E-mail: halkooij@xs4all.nl

the field of prenatal diagnostics and screening? What do they consider positive and where do they draw a line? To find out we have taken a survey of women's attitudes toward current and future testing possibilities.

MATERIALS AND METHODS

To procure the information a questionnaire was submitted to two groups of respondents: pregnant women and women for whom the wish to have children is not (yet) an issue at present. For the first group, women were approached who made use of the routine fetal anomaly ultrasound scan at 20 weeks' gestation at the University Medical Centre Groningen and the Martini Hospital in Groningen. Only women with a negative scan (low-risk women) were given the questionnaire with the request to fill it out and return it within 2 weeks ($n = 100$). The second group consisted of female master students studying at the Medical School of the University Groningen ($n = 100$). On the basis of a difference of 20%, alpha 0.05 and 80% power, $n = 100$ was concluded to be a sufficient sample size.

The study was approved by the Medical Ethic Committee of the University Medical Centre Groningen.

The questionnaire consisted of four parts. Each part contained a 'textbox' in which the propositions listed further down were briefly clarified. The first part dealt with the present condition around the testing for Down syndrome. In the textbox the correlation between the age of the pregnant woman and the chance of having Down syndrome was mentioned, followed by a description of the available diagnostic possibilities. The main advantages and disadvantages of the available tests on the basis of concrete risk and detection percentages were also mentioned. Subsequently a number of statements about this were presented.

The second part dealt with the situation in the future. In the textbox is explained that DNA of the child is present in the blood of the mother and that in future it is to be expected that by a blood sample taken from her at an early stage of her pregnancy the diagnosis of Down syndrome can be made with a high certainty. In that case amniocentesis and chorionic villus sampling would become unnecessary. Subsequently we included a number of statements about this diagnostic option.

In the third part the subject was extended to the application of NIPD for gender determination. Statements were presented on the basis of three situations. The first situation related to gender determination in the case of congenital genetic disorders, in this case the disease of Duchenne. Apart from describing the development of the disease, we also mentioned that it only occurs in males, explaining that further invasive procedures to determine the presence of this affliction would only be necessary in the case of a male fetus. A second situation concerned gender determination for genetic disorders manifesting themselves later in life. We indicated prevalence and risk percentage in the case of genetic breast cancer and that further invasive procedures would only be necessary in the case of a female fetus, since male carriers

rarely develop breast cancer. In the third situation we focused on 'gender determination for nonmedical reasons'. It was stated that parents may simply be curious as to the gender of their child, but parents may also have a strong preference for one gender over the other. The need for family balancing and the risk of sex selection were also mentioned.

The last part of the questionnaire concerned the application of NIPD as a screening tool for congenital disorders in a wider sense. Prior to the statements the following information was included in the textbox: 'The majority of children are born healthy, but a small percentage (2–3%) is born with a congenital disorder. At the moment, prenatal diagnosis is restricted to pregnant women with a greater risk of a child suffering from a congenital disorder. In the near future NIPD will make it possible for all pregnant women to be noninvasively screened early in their pregnancy'. We also mentioned that the number of genetic disorders detectable via NIPD will continue to rise. Finally respondents were confronted with the fact that due to modern diagnostics a pregnant woman's choice as to whether or not terminate her pregnancy will be made at an ever earlier stage in pregnancy. This was formulated as follows: 'In a number of cases pregnancy would have resulted in an early miscarriage. Early miscarriages are relatively frequent: at least one in ten pregnancies ends in an early miscarriage. Its cause is usually a defect in the fetus. This means that without early detection a considerable number of pregnancies would have ended in a natural way and the choice as to whether or not to terminate pregnancy would not have presented itself'.

Questionnaires were handed out until 100 fully completed questionnaires had been returned by each group. The questionnaire was based on a questionnaire used in a previous study (Weinans *et al.*, 2000). Data were analyzed by the Statistical Package for Social Sciences (SPSS/Windows). Five-point Likert scales were limited to three categories to avoid small cells. The responses to the propositions of the two groups were analyzed to determine if there were any significant differences between them. The difference in age and education was also evaluated. Statistical testing of differences between the groups was done using Chi-square distribution.

RESULTS

General

Some background characteristics of the respondents are shown in Table 1. As expected the pregnant women are significantly older than the female medical students (average age 32.0 vs 21.6).

Testing for Down syndrome: now and in the future

The results in Table 2 show that a majority of the respondents are critical of offering invasive prenatal tests

Table 1—Socio demographic characteristics

	Pregnant women (<i>n</i> = 100)	Female medical students (<i>n</i> = 100)
Age:		
Mean age (range)	32.0 (19–43)	21.6 (20–37)
SD	4.9	2.3
Level of education:		
Low	3	—
Medium	31	—
High	65	100
Missing	1	—

on a general basis. Only 11% of the students agree with the statement that chorionic villus and amniocentesis should be supplied to all pregnant women, regardless of age. Forty-five percent of the pregnant women agree ($p < 0.05$). A general offer of noninvasive screening tests is given a more positive rating by both groups. Three quarters of the pregnant women agree with the statement that the blood test in combination with nuchal translucency screening should be offered to all pregnant women versus 63% of the students.

The attitudes of the respondents differ toward a general offer of NIPD. Eighty-one percent of the pregnant women support the statement that NIPD should be offered to all pregnant women in order to detect Down syndrome in an early stage of pregnancy. Forty-nine percent of the students agree to this statement ($p < 0.05$). Both groups largely support the statement that NIPD is an important asset in prenatal screening for Down syndrome.

NIPD within the framework of gender determination

Table 3 shows to what extent the respondents support offering NIPD within the framework of gender determination. Pregnant women as well as students show massive support for the statement that NIPD is an important asset in prenatal screening for gender-determined congenital disorders. The respondents are less positive about NIPD for congenital disorders occurring later in life. Forty-eight percent of the pregnant women support the proposition that NIPD is an important asset within prenatal screening for congenital breast cancer. Only 17% of the students support this proposition ($p < 0.05$). The statement that NIPD may only be used for gender determination if there are medical reasons to do so and not for family balancing is supported by a majority of respondents in both groups.

NIPD: wider use

The respondents' attitudes toward the use of NIPD as part of testing fetal abnormalities are listed in Table 4. The statement that DNA screening in an early stage of pregnancy may be considered a significant asset, because it enables every pregnant woman to bear a healthy child, is strongly rejected by the pregnant women as well as the students. On the other hand, the majority of both groups of respondents agree with the statement that NIPD is a significant asset in the present prenatal care. Forty-one percent of the pregnant women and 37% of the students agree that the advantage of timely detection counterbalances the disadvantage of a possibly unnecessary choice to terminate a pregnancy. This in spite of the fact that a number of the pregnancies with an affected fetus would have ended in a miscarriage anyway.

Table 2—Attitudes of women toward statements about prenatal tests for Down syndrome

	Pregnant women (<i>n</i> = 100)	Female medical students (<i>n</i> = 100)
I think that amniocentesis and chorionic villus sampling should be offered to all pregnant women regardless of their age		
Agree	45	11
Disagree	44	83
Neither agree nor disagree	11	6
I think that screening tests (blood test in combination with nuchal translucency screening) should be offered to all pregnant women regardless of their age		
Agree	74	63
Disagree	18	27
Neither agree nor disagree	8	10
I think that in the future NIPD should be offered to all pregnant women in order to get 100% accuracy as to the presence Down syndrome		
Agree	81	49
Disagree	14	36
Neither agree nor disagree	5	15
I consider NIPD an important asset in screening for Down syndrome		
Agree	92	89
Disagree	2	4
Neither agree nor disagree	6	7

Table 3—Attitudes of women toward statements about NIPD for gender

	Pregnant women (n = 100)	Female medical students (n = 100)
I consider NIPD in an early stage of pregnancy an important asset in prenatal diagnosis of gender-determined congenital disorders		
Agree	90	85
Disagree	2	4
Neither agree nor disagree	8	11
NIPD is an important asset within prenatal screening for congenital breast cancer		
Agree	48	17
Disagree	26	53
Neither agree nor disagree	26	30
In my opinion NIPD should only be used for gender determination for medical reasons, not for family balancing		
Agree	84	92
Disagree	9	5
Neither agree nor disagree	7	3

Table 4—Attitudes of women toward statements about NIPD to screen for congenital defects

	Pregnant women (n = 100)	Female medical students (n = 100)
I consider NIPD in an early stage of pregnancy a great asset, because it enables every pregnant woman to bear a healthy child		
Agree	30	13
Disagree	38	66
Neither agree nor disagree	32	21
NIPD is an important asset in present prenatal care		
Agree	82	79
Disagree	5	7
Neither agree nor disagree	13	14
In my opinion, the advantage of timely detection counterbalances the disadvantage of a possibly unnecessary choice to terminate a pregnancy		
Agree	41	37
Disagree	25	36
Neither agree nor disagree	34	27

DISCUSSION

Modern biotechnology offers more and more possibilities for an early detection of abnormalities. Compared with the present methods for the detection of Down syndrome NIPD has advantages: no risk for miscarriage and a high sensitivity. When a reliable test becomes available, it will be possible to routinely screen all pregnant women. This is progress, but it also means that there will be changes in the choices that are made in screening for Down syndrome. In the case of invasive testing, the choice is far-reaching and not without risk and therefore made consciously. 'Our survey shows that a minority of the women think that invasive tests should be offered to all pregnant women, regardless of their age'. This corresponds with the present restrained policy in the Netherlands of availability of invasive testing only for women who are considered to be at increased risk.

The risk-assessment tests are noninvasive and there is no chance of miscarriage, thus facilitating the choice. On the downside there remains the fact that these tests do not result in a full accuracy. NIPD is not only simple and risk-free to carry out but it also supplies direct

certainty in an early stage of pregnancy. In spite of these advantages our respondents do not agree about making this test generally available: a majority of the pregnant women support a general availability of NIPD, whereas the students are far more reluctant. In previous research it was also shown that female medical students are less positive about offering testing (Kooij *et al.*, 2005). An explanation might be that they are more aware of the negative effects. Both groups agree, however, that NIPD is an important asset in prenatal screening for Down syndrome. Therefore we may expect to see a substantial rise in participation in prenatal screening.

NIPD can also be used for the diagnosis of many other congenital disorders. A general availability of NIPD will therefore have far-reaching consequences and the situation in the field of prenatal diagnosis will change drastically. Our survey shows that women support the use of NIPD for gender determination in connection with gender-related genetic disorders. In the case of genetic disorders manifesting themselves later in life attitudes are more critical. An explanation for this might be that people have to deal with choices and responsibilities that they have no longer a clear view of. Gender determination for nonmedical reasons is clearly rejected.

Every pregnancy carries a chance of a child with a congenital defect. NIPD makes early detection possible. It is estimated that at least one in ten and possibly even 25–30 or 40% of pregnancies end in an early miscarriage; usually as a result of an abnormality in the fetus. These defects are detected earlier and earlier and as a result there is a surge in pathology, which now is partly filtered out by evolution. Early detection also means that in an early stage of their pregnancy women have to decide whether or not to terminate it. In a number of cases a choice would not have been necessary, because the pregnancy would have resulted in a miscarriage anyway. From our survey it is clear that for more than one-third of the respondents this is not seem to be as a reason not to subject to the tests (Table 4).

A general availability of NIPD may result in fewer births of children with a congenital defect. When directly confronted with this, the respondents became hesitant. Only a small number of respondents consider it an asset that NIPD enables the birth of a healthy child. This shows that people do not always seem to realize all consequences of screening. No doubt NIPD will be the future and paves the way for screening on a large scale. Our survey shows that women feel positive about these new possibilities but find it hard to fully realize the consequences and new choices women will be confronted with. In addition to the technical aspects, it is now time to evaluate its psychosocial aspect and end-users' acceptance. This study belongs to this

category and can be considered as a first step to a wider discussion.

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