CHAPTER 5

Non-invasive prenatal screening for trisomy 21: what women want and are willing to pay

ABSTRACT

OBJECTIVE

To investigate the attitude among pregnant women regarding non-invasive prenatal testing (NIPT) for detecting trisomy 21 (T21) and to quantify their willingness to pay for NIPT.

METHODS

A questionnaire was administered to pregnant women who received counselling for first-trimester combined test (FCT) in two hospitals and nine midwife practices in the Netherlands.

RESULTS

A total of 147 women completed the questionnaire, yielding a response rate of 43%. If NIPT for detecting T21 were available, 81% stated they would choose to have this test, and 57% of women who elected not to undergo FCT in their current pregnancy would perform NIPT if available. Willingness to pay for NIPT was correlated with age and income, but not education level. The price that participants were willing to pay for NIPT was similar to the current price for FCT.

CONCLUSION

The pregnant women in our study had a positive attitude regarding NIPT for T21, and more than half of the women who rejected prenatal screening would receive NIPT if available.

PRACTICE IMPLICATIONS

Due to the elimination of iatrogenic miscarriage, caregivers should be aware that informed decision-making can change with respect to prenatal screening with the introduction of NIPT.

INTRODUCTION

Non-invasive prenatal testing (NIPT) can use cell-free foetal DNA circulating in Maternal blood to detect chromosomal trisomy, and NIPT was recently introduced into clinical practice. NIPT has both high sensitivity and high specificity.[1] In the Netherlands, first-trimester combined test (FCT) is currently offered to all pregnant women as part of a national antenatal screening programme that is based on the "informed choice" principle, meaning that the individual's decision is voluntary and made with full understanding of the circumstances, including all expected benefits, burdens, risks and available alternatives. Invasive testing using chorion villus sampling (CVS) or amniocentesis is offered when the risk of trisomy is ≥1:200. In the Netherlands, approximately 25% of women elect to receive FCT, which is low compared to other countries, and women over the age of 36 have the right to request CVS and/or amniocentesis. Decision-making regarding prenatal screening includes pre-paring for the next step, which is an invasive procedure in the event of increased risk of trisomy 21 (T21, or Down syndrome). At this stage, the decision requires balancing the probability of having a child with T21 against the risk of a procedure-related (iatrogenic) miscarriage. The most frequently cited reason for screening is to gain both knowledge regarding the health of the foetus and reassurance.[2] The principal reasons for declining screening include unfavourable characteristics of the screening test, ethical and/or religious objections, post-testing anxiety or uncertainty, and risks associated with invasive testing.[2] These arguments suggest that if a near 100% accurate, non-invasive test for foetal trisomy were available, women may make different choices regarding prenatal screening. Depending on cost and/or availability, NIPT may eventually replace current screening methods. Although nearly everyone in the Netherlands has medical insurance, the cost of FCT (approximately €150) is only reimbursed for women ≥36 years of age. We therefore asked whether – and how much – women would be willing to pay for NIPT for T21 with risk-free diagnostic certainty. The price that women are willing to pay might also reflect how women value the test's risk-free diagnostic certainty.

MATERIALS AND METHODS

Data were obtained from questionnaires that were completed by pregnant women. Information regarding prenatal screening for T21 was provided in accordance with current guidelines. The questionnaires were distributed by midwives and doctors following patient counselling for prenatal screening within the patient's first trimester. Questionnaires were distributed to all women in their first trimester, independent of their expressed interest regarding prenatal screening. The women were recruited from August 2011 through December 2011 from two hospitals and seven midwife practices in two regions (Leiden and Amsterdam) in the Netherlands. All questionnaires were treated anonymously (no name or address was listed

on either the questionnaire or the envelope). The questionnaires were returned to one central hospital in pre-paid envelopes. In total, 340 women were invited to participate. Background information regarding NIPT was provided, followed by questions designed to determine the participant's attitude towards NIPT. NIPT for T21 was described as a safe test with high (nearly 100%) diagnostic accuracy. The first part of the questionnaire addressed women's attitudes towards receiving information regarding prenatal screening and the reason(s) they might accept or decline prenatal screening in their current pregnancy. The participants were asked to indicate whether they would prefer NIPT replacing screening and/or invasive testing. Content analysis was used. The visual analogue scale (VAS) was used; the VAS is a graphic tool with a 100-mm horizontal line; the left end is labelled "very uncertain", and the right end is labelled "very certain". The participants were instructed to indicate the point on the scale that corresponds best with their feelings regarding the question.[3] Willingness to pay (WTP) was assessed using a payment card, consisting of a list of nine costs ranging from €50 to €500. For each amount, the women were asked to indicate whether they would be willing to pay this amount for non-invasive screening for trisomy 21. If they indicated a willingness to pay more than €500, they were asked to indicate the maximum amount they would be willing to pay.[4-6] The last part of the questionnaire included sociodemographic questions regarding age, education level, religious preference and household income. Education level was determined by asking respondents to indicate their highest completed level of education. Religious preference was determined by asking respondents to describe themselves as belonging to one of the following eight categories: no religion, Catholic, Protestant, other Christian, Islamic, Hindu, Humanist, or Other (specify). Income was determined by asking the respondents to indicate the range corresponding with their monthly net household income. The following hypotheses regarding the relationship between the aforementioned sociodemographic factors and WTP were tested:

- Higher-income respondents have a higher WTP.
- Highly educated respondents have a higher WTP.
- Older participants have a higher WTP.
- Religious participants have a lower WTP.

The questionnaires were developed and pre-tested in both healthcare workers and pregnant women (n=10/group) to determine the clarity of information, and several questions and answers were then optimised based on this pre-test. The Dutch legislation does not require informed consent for a prospective study using questionnaires if the results are handled anonymously. Data were analysed using SPSS 17.0. 2.1.

Participants

Table 1 shows the demographics of the participants. The mean age of the participants was 32.9 years, which is older than the average age of pregnant women in the Netherlands (31 years).[7]

The percentage of women <36 (68.7%) and ≥36 years of age (31.3%) was consistent with the age distribution of pregnant women in the Netherlands.[8] Relatively few participants had a low level of education and/or low income.

RESULTS

In total, 340 women were given a questionnaire and invited to participate in the study, and 147 women (43%) completed and returned the questionnaire. In total, 79 respondents (54%) opted for FCT in their current pregnancy, 7 respondents (5%) opted for an invasive procedure (all of whom were ≥36 years of age), and 61 respondents (42%) rejected prenatal screening, including 5 respondents who also declined information regarding the availability of prenatal screening. Forty-eight respondents (33%) were recruited by the two hospitals, and the remaining 99 participants (67%) were recruited by their midwife. The reasons stated (via an open-text field) for choosing screening were "we want to obtain knowledge regarding the baby's health" (41%); "'I have a higher risk for having a T21 baby because of my age" (24%); "we want reassurance" (5%); "if we receive a diagnosis of T21, we will terminate the pregnancy" (8%); "preparing for a possible child with Down syndrome" (4%); "if the child has T21, I do not want to burden my other children with the care of this child" (4%); and "I received screening during a previous pregnancy" (1%); 13% did not provide a reason. The reasons for declining prenatal screening (indicating more than one reason was possible) included (n = 61) "not wanting to gain knowledge regarding T21 (15%); "I do not want to perform an invasive follow-up test" (23%); "I am opposed to terminating a pregnancy" (33%); "women felt that their risk of having a T21 child was too low to warrant testing" (41%); unfavourable features of the test (46%); and "I cannot or do not want to pay for FCT" (10%). All 86 participants who opted for FCT in their current pregnancy expressed a positive attitude towards NIPT. Among the respondents who did not receive prenatal screening, 57% (n=35) said that they would choose NIPT if available. Finally, 26 participants who did not opt for FCT in their current pregnancy would also not opt for NIPT if available. As noted above, 121 of the 147 participants (82%) expressed an interest in performing NIPT, and 89 participants (61%) were interested in NIPT only as a replacement for invasive procedures or screening. A few respondents (6.4%) preferred to receive FCT before NIPT in order to have an additional ultrasound in their first trimester. Thirty-two women (22%) specifically stated in an open-text field that they would prefer NIPT as a replacement screen. The following arguments were stated: "easier and more efficient"; "why do you need a risk assessment when you get certainty with NIPT?"; "the result will be available earlier in the pregnancy"; and "less time living with uncertainty". Of the women who were recruited in a hospital, 94% had a positive attitude towards NIPT, compared with 77% of women recruited by their midwife (p=0.011).

Participants were asked to indicate on a VAS scale their certainty with respect to accepting or declining NIPT if it were available. Among the participants with a positive attitude regarding NIPT, the median score was 95.0 (range: 10–100), indicating high certainty for accepting NIPT. Among the participants with a negative attitude towards NIPT, the median score was 97.5 (range: 0–100), indicating that this group was also highly certain about rejecting NIPT. The mean price that participants were willing to pay for NIPT was €169 (median: €150; range: €0–1000). Three of the 121 participants (2%) were willing to pay €1000 for the NIPT test for T21. Table 2 shows the relationship between willingness to pay and age, income, education level and religious preference for the 121 participants with a positive attitude towards NIPT. We found no significant correlation between willingness to pay and either education or religious preference. However, as we hypothesised, willingness to pay correlated significantly with both income (p<0.001) and age (p=0.049). Interestingly, women age 36 and older were willing to pay more for NIPT (mean WTP: €218) than women <36 years of age (mean WTP: €185).

DISCUSSION AND CONCLUSIONS

Discussion

This study is the first in which pregnant women were asked in the first trimester whether they would opt for NIPT if it were available. The timing of the questioning regarding a sensitive topic such as FCT is extremely important, as confronting a pregnant woman regarding the uncertainty of her baby's health could change her opinion of FCT. If available, the vast majority (81%) of women in our study indicated that they would choose to undergo NIPT. This positive attitude towards NIPT is consistent with a study published by Kooij et al., who studied both pregnant women (past the first trimester) and not-pregnant students (82 and 79%, respectively, had a positive attitude towards NIPT)[9], and with a study published by Tischler et al., who studied women in their third trimester (72% of whom had a positive attitude towards NIPT).[10] An intriguing and novel finding of our study was that more than half (57%) of the women who rejected prenatal screening in the current system would elect to have NIPT if it was available. This suggests that more than half of the women rejected FCT because of unfavourable test characteristics and/or to avoid undergoing an invasive test. The question of whether to accept or decline NIPT became more relevant with the recent introduction of commercially available NIPT in the United States.[11] Moreover, in several European countries, NIPT is offered as a commercially available alternative to invasive procedures in high-risk pregnancies. Interestingly, the women surveyed in our study were positive regarding the introduction of NIPT in general, but were even more positive regarding the introduction of NIPT as a screening tool. The reasons cited included reduced anxiety and uncertainty because

of the one-step method and higher diagnostic accuracy compared with current FCT methods. The willingness to pay for NIPT revealed information regarding how women value NIPT for detecting trisomy 21 and the test's risk-free diagnostic certainty. The mean amount that women were willing to pay was slightly higher than the current average cost of FCT (which is €150), and some women were prepared to pay much more. The range of willingness to pay was wide (€0–1000), and this could be a reflection of the study population's diversity and/or personal preferences. Interestingly, consistent with our hypotheses, willingness to pay was correlated with both age and income, but it was not related to the level of education. However, in contrast with our hypothesis, WTP was not associated with religion. Analysing willingness to pay is often subject to criticism. For example, the method used to estimate WTP is a common source of criticism. The advantages and disadvantages of the payment card as used in this study compared with other methods to estimate WTP have been widely discussed; however, it is a commonly accepted tool. Another criticism of the WTP method is that hypothetical answers are obtained based on a hypothetical survey situation, and these answers may differ from answers given in a real-life situation, causing a so-called "hypothetical bias". In general, hypothetical willingness to pay overestimates one's actual willingness to pay.[12] Therefore, the current WTP estimates might be an overestimation of actual WTP. The strength of this study is that the participants were asked at the same time in their pregnancy as they would have to decide about NIPT, if available. In addition, this study included both women who declined prenatal screening and women who opted for prenatal screening. Although several previous studies examined the attitudes of pregnant women, they included high-risk women only or failed to obtain sufficient information from participants who refused prenatal screening.[10-13] Although Kooij et al. studied a low-risk group, they did not mention whether the women received prenatal screening or an invasive procedure.[9] Our study was limited by the relatively small sample size, a low response rate, and an underrepresentation of women with lower education and lower income levels. The difference in opinion between the participants and the non-responders are not known. The patients might have been influenced by the attitude of the healthcare provider while handling the questionnaire. The difference between the national FCT compliance rate and the response rate in our study population may be explained by the circumstance that women who receive FCT are more willing to complete a questionnaire regarding FCT than women who refuse FCT. Furthermore, the women in this study were slightly older than the average age of pregnant women in the Netherlands; older pregnant women are generally more aware of the risks and are more interested in prenatal testing. This study may have also included a selection bias. First, participating midwives and doctors may have felt that less-educated women would be less interested in completing the questionnaire; in their first trimester, these women are particularly sensitive to receiving an overload of information regarding pregnancy and prenatal screening in a single visit.[14] Second, only women who could read Dutch were invited to participate in the study. Several publications

have addressed the roles of ethnic and socio-economic differences in the decision to receive screening.[15-18] Although the reasons why certain groups do not opt for screening are unclear, Dormandy et al. suggested that ethnic inequalities regarding access to prenatal testing might play a role.[14] This so-called "health gap" could arise from the relative complexity of the multi marker FCT. Importantly, this "health gap" might be reduced when the NIPT – which is relatively easy to explain to patients – is introduced. Our study did not investigate these issues, and future studies should examine the difference in attitude towards NIPT between lower and higher education levels and various ethnic groups. Finally, our study was performed in the Netherlands, and similar studies conducted in other countries could yield different results. Although many other countries appear to have higher screening uptake, most countries (particularly Denmark) lack reliable nationwide data.

Conclusions

The majority of pregnant women in our study expressed a positive attitude towards NIPT and indicated that they would request NIPT if available. Importantly, more than half of the women who rejected prenatal screening in the current system would opt for NIPT if available. A prospective study to determine the practicality of NIPT in the general population is needed. The price that women <36 years of age are willing to pay for NIPT is similar to what they currently pay for prenatal screening. Healthcare workers should be aware that if prenatal costs are not reimbursed, the uptake rate will be dependent on income. Clearly, the answers given in a questionnaire are a stated preference, and although they can approximate the preferences of pregnant women, they might not predict their actual preference in real-life situations.

Practical implications

The reasons stated by pregnant women for receiving or declining prenatal screening were quite similar to those described by Van den Berg et al.[19] Not unexpectedly, the lack of a risk of procedure-related miscarriage was the most important reason for a woman to opt for NIPT. As noted by several groups regarding the current prenatal screening programme, because of insufficient knowledge, women do not generally make an informed choice, despite receiving counselling.[19,20] We agree with other groups that although NIPT differs from other tests, patients should still receive counselling after NIPT becomes available in order to discuss potential decision-making and the consequences of knowing whether the foetus has trisomy 21.[10,21] The finding that approximately half of pregnant women reject FCT in the current system because of unfavourable test features must be taken into account by policy makers, laboratories and insurance companies when preparing to introduce NIPT into existing screening programmes.

Variables	*Participants (n=147)*	*%*
Age		
Mean age (range)	32.9 (21 - 44)	
SD	4.6	
Low (<36 years)	101	68.7
High(≥36 years)	46	31.3
Level of education		
Low	13	8.8
Medium	15	10.2
High	57	38.8
Academic	62	42.2
Religious affiliation		
Religous	46	31.3
Not religious	100	68.0
Missing	1	0.7
Income household per month (euro)		
<1500	2	1.4
1500-3000	28	19.0
>3000	101	68.7
Missing	16	10.9

Table 1. *Sociodemographic characteristics*

Variables	*N (total)*	*Mean (Euro)*	*p*
Age (years)			
<36	77	185	0.049
≥36	44	218	
Income euro/month			
<1500	2	no information	<0.001
1500-3000	21	145	
3000-5000	64	190	
>5000	23	304	
Education			
Low	6	183	NS
Medium	12	125	
High	49	196	
Academic	54	217	
Religion			
Religious	31	229	NS
Not religious	89	187	
Unknown	1	150	

Table 2. *Variations of the maximum willingness-to-pay for NIPT in women with a positive attitude*

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