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CHAPTER 4.

PRESENT TO FUTURE: WHAT THE REASONS FOR DECLINING FIRST TRIMESTER COMBINED TESTING TELL US ABOUT ACCEPTING OR DECLINING CELL-FREE DNA TESTING

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Currently, uptake rates for first-trimester combined screening (FCT) for fetal trisomy differ widely across countries, with a relatively low uptake in the Netherlands.(1) By using circulating cell-free DNA (cfDNA) in the plasma of pregnant women, it is now possible to screen for foetal aneuploidies with a higher sensitivity and specificity. If non-invasive prenatal screening using cfDNA were to be introduced as a first-tier test, uptake rates are expected to increase when compared to the uptake of FCT.(2-5) Despite its many advantages, there are concerns of routinised or uncritical use of cfDNA testing,(3-5) possibly undermining the aim of prenatal screening, which is to provide autonomous reproductive choices.(6)

Reasons for accepting or declining FCT include attitudes towards Down syndrome (DS), attitudes towards termination of pregnancy (TOP) and adverse test characteristics of FCT.(7;8) The question arises as to whether reasons specified for declining prenatal screening remain unchanged when FCT is replaced by cfDNA testing. The aim of this study was thus to explore women's reasons for declining FCT and how these relate to accepting or declining future (hypothetical) use of cfDNA testing.

We combined (unpublished) data of a quantitative survey and a qualitative focus group study with pregnant women in the Netherlands. Data were collected shortly before implementation of cfDNA in the Netherlands and each study questioned reasons for using prenatal screening.(2;9) Data from the quantitative study provided us with a general classification of women declining FCT and their intentions to use cfDNA testing, while the qualitative data were used to deepen and illustrate the analyses. By using knowledge on decision-making regarding FCT and the relation with hypothetical intentions to use cfDNA testing, we intended to postulate on the future of prenatal testing.

The quantitative study comprised an online questionnaire, placed on the website of the 'Nine Months Fair' (annual event for Dutch pregnant women) January-March 2014. 381 questionnaires were included for analysis. The questionnaire described the prenatal screening programme in the Netherlands with FCT, and a brief description on the cfDNA test (test procedure, conditions tested for, timing and follow-up),(2) followed by questions on whether women had used FCT in a previous or current pregnancy, and if not, why not: *'In this pregnancy, have you decided to take the FCT?' (answer options 'Yes'; 'No, but I am planning to do so'; 'No, but I did in an earlier pregnancy'; 'No'), and 'What is the main reason for not taking the FCT?'* (ten answer options, see Table 1). Only women who reported specific reasons for declining FCT were included for further analysis (n=239). Hypothetical interest in cfDNA testing was measured by a single item: *'If cfDNA testing was available in the Netherlands, would you choose this test in this or a subsequent pregnancy?' (answer options: 'most certainly'; 'probably'; 'maybe, maybe not'; 'probably not'; 'most certainly not').*(2) Based on this question, women were grouped into three categories: "Would accept cfDNA testing", "Unsure about cfDNA testing" and "Would decline cfDNA testing". Data were

analysed using SPSS version 20 for Windows (IBM Statistics for Windows, IBM, NY, USA).

The qualitative study consisted of five focus groups (n=46) including women who declined FCT (n=22). Women were recruited from five community midwife practices in the Utrecht region of the Netherlands. The focus groups were conducted during July 2012-January 2013. Participants received written information on FCT prior to the focus groups (including the national FCT leaflet).(9) cfDNA testing was mentioned in every group as an option for reducing unfavourable test characteristics and brief oral information on the test was given (a hypothetical non-invasive maternal blood test using foetal DNA, giving results on DS with high accuracy). Qualitative data were content analysed using NVivo (QSR International Pty Ltd. Version 10, 2012).

In the questionnaire study, women who reported reasons for declining FCT (n=239) were mainly Dutch (92%) and more than half were highly educated (defined as high vocational training and university) (52%). Mean age was 28 (SD 4, range 18-40). Of these women, 32% would accept cfDNA testing, 29% were unsure and 39% would decline cfDNA testing. Of the women in the focus groups who declined FCT (n=22) the majority were Dutch (91%) and highly educated (77%). Mean age was 30 (range 23-35). Four women would accept cfDNA testing, four were unsure and 14 would decline cfDNA testing.

Women's main reasons for declining FCT and the percentage of women intending to use cfDNA testing are presented in Table 1. 'FCT gives only a risk estimation' was the reason most frequently mentioned (55%) for declining FCT. Most women stating this reason were likely to use cfDNA testing if available (42%), as would most women (39%) who stated they declined FCT because 'I do not want to have invasive follow-up testing because of the risk of a miscarriage'. Qualitative data showed that, when considering FCT, some women weighed the wish for information about their unborn child against the fear of losing their pregnancy. A 'no-risk' test, like cfDNA testing, eliminates the latter disadvantage and therefore would make them decide to have this test to gain information about their child's health.

'What if you have a miscarriage because you wanted to know if everything was OK [...]. But if it was really a 'no-risk', with a yes or no answer, I would probably participate' [#F903, decline FCT, accept cfDNA testing]

Of the women who did not want to have FCT because they 'would never terminate their pregnancy' or 'don't think DS is a severe handicap', the majority would also decline cfDNA testing (63% and 70%, respectively). For these women, TOP is not an option, and thus they see no reason to participate in screening.

'For me it's important that a child can have a happy life...from what I hear, children with DS can have a very happy life[...] therefore I don't think DS is a reason to terminate my pregnancy' [#F904, decline FCT, decline cfDNA testing]

However, 17% of women who stated 'I would never terminate my pregnancy' would accept *cfDNA testing* (Table 1). For these women, *cfDNA testing* may be used to prepare for a child with DS.

'The reason for declining the test [FCT] is that we would never want to terminate a pregnancy[...] The only reason for us to take a test would be to prepare ourselves for the birth of a child with special needs' [#F501, decline FCT, accept cfDNA testing]

For women stating the reason 'Fear of regretting testing when I get confronted with a decision regarding TOP' intended use of *cfDNA testing* was equally distributed (36% would accept, 36% were unsure, and 28% would decline *cfDNA testing*). Apparently, difficulties and dilemmas in decision-making will remain, regardless of the test offered.

'If you receive a high-risk [FCT] result, your problems increase even more...then you have to decide on taking an invasive test, with even higher [miscarriage] risks...and then you have to decide if you want to terminate your pregnancy [...] and then you end up with a decision which is impossible to make' [F#903, decline FCT, accept cfDNA testing]

'The choice is actually not a choice. Terminating my pregnancy is not an option, I would feel guilty for the rest of my life' [#F901, decline FCT, decline cfDNA testing]

Table 1. Reasons for declining FCT and the percentage of women intending to use cfDNA testing within each different reason

Reasons for declining FCT n=239^a	Would ACCEPT cfDNA testing n=77 n (%)	UNSURE about cfDNA testing n=69 n (%)	Would DECLINE cfDNA testing n=93 n (%)
FCT gives only a risk estimation (n=132)	56 (42)	40 (30)	36 (27)
I would never terminate my pregnancy (n=93)	16 (17)	18 (19)	59 (63)
I do not want to have invasive follow-up testing (chorionic villus sampling, amniocentesis) because of the risk of a miscarriage (n=89)	35 (39)	24 (27)	30 (34)
Because of the low risk of having a child with Down syndrome (n=88)	32 (36)	29 (33)	27 (31)
Fear of regretting testing when I get confronted with a decision regarding termination of pregnancy (n=47)	17 (36)	17 (36)	13 (28)
I think one should let nature take its course and therefore not take the test (n=38)	3 (8)	12 (32)	23 (61)
I don't think Down syndrome is a severe handicap (n=30)	2 (7)	7 (23)	21 (70)
I have to pay for the test myself (n=23)	16 (70)	2 (9)	5 (22)
My midwife/gynaecologist advised against testing (n=7)	4 (57)	1 (14)	2 (29)
My partner does not want it (n=5)	0 (0)	4 (80)	1 (20)

^a Five respondents had taken non-invasive prenatal testing and had therefore not taken first-trimester combined testing.

Multiple responses possible.

FCT: First-trimester combined test.

cfDNA: cell-free DNA

In this study we found a clear distinction in decisive reasons cited for declining FCT. Moreover, women who declined due to attitudes towards DS and TOP more often intended to decline cfDNA testing as well. Women who decline FCT for test-related reasons more often intended to accept cfDNA testing. For some women, DS is perceived as a condition which is acceptable and not a reason for TOP.(7;8) These women prefer not to be screened for conditions that are acceptable to them or without an acceptable treatment. It is unlikely that the availability of cfDNA testing will change their opinion. Of the women declining FCT for attitudes towards DS and TOP, 17% intended to accept cfDNA testing, indicating a hypothetical wish to prepare for the birth of a child with special needs. A reliable and safe test fulfils this need and probably more women will use cfDNA testing to prepare for the birth of a child with a disability, instead of terminating their pregnancy, as was suggested earlier.(2;4) Declining FCT because of 'fear of regretting testing when getting confronted with a decision regarding TOP' was equally distributed when considering the use of cfDNA testing. This may indicate that women considering screening, currently are aware of decisions they might get confronted with, and acknowledge the attached difficulties and dilemmas. When considering use of cfDNA testing, this awareness hypothetically remains the same, suggesting that cfDNA testing may not be viewed by Dutch women as a routine choice. While technical improvements of prenatal tests will make some decisions easier, ethical dilemmas remain essentially the same. Pre-test counselling is essential and should be personalized and provide sufficient information to promote informed and autonomous decision-making.(10) Additionally, cfDNA testing needs to be implemented in a way that women do not feel pressured to take the test. Furthermore, it is expected that an increasing number of women will prepare for the birth of a child with DS using cfDNA testing, and will benefit from post-test counselling and support in preparation.

Limitations of our study are that both studies were not executed at the same time and without the intention to be combined. Both studies asked about actual behaviour and motives regarding FCT. Future intentions to use cfDNA testing were asked which may not reflect actual use. Future research on potential routinisation when cfDNA testing becomes available as a first-tier test should be undertaken.

In conclusion, women declining FCT for reasons relating to DS and TOP are more likely to decline cfDNA testing as well, while women declining for test-related reasons are more likely to accept the 'safer' cfDNA testing. With the introduction of cfDNA testing, based on these results we anticipate no need to fear its uncritical use, provided that women have the opportunity to reflect on their personal values. Therefore, cfDNA testing should not be offered as a routine part of a comprehensive screening procedure, but should be presented in a context which facilitates autonomous reproductive choice.

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