Preferences for prenatal testing among pregnant women, partners and health professionals

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ABSTRACT

INTRODUCTION: Cell-free DNA testing (cfDNA testing) in maternal plasma has recently been implemented in Danish healthcare. Prior to that we wanted to evaluate the preferences among pregnant women, partners and health professionals regarding cfDNA testing compared with invasive prenatal diagnostics.

METHODS: Responders were recruited at public hospitals in the Central and North Denmark Regions. Stated preferences for prenatal testing were obtained through an online questionnaire incorporating a discrete choice experiment. Test choices differed according to attributes such as risk of miscarriage (none or small) and genetic information provided by the test; simple (Down syndrome only) or comprehensive (chromosomal abnormalities beyond Down syndrome).

RESULTS: No risk of miscarriage was the key attribute affecting the preferences of women (n = 315) and partners (n = 102). However, women with experiences of invasive testing placed more emphasis on comprehensive genetic information and less on risk of miscarriage compared with other women. Likewise, foetal medicine experts, obstetricians and sonographers (n = 57) had a greater preference for comprehensive genetic information than midwives who were not directly involved in counselling for prenatal testing (n = 48).

CONCLUSIONS: As safety seems to affect the majority of pregnant couples' choice behaviour, thorough pre-test counselling by trained health professionals is of paramount importance.

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Analysis of cell-free DNA (cfDNA) in maternal plasma, also known as non-invasive prenatal testing, has been validated in multiple international clinical trials as an alternative screening tool for foetal trisomy 21, 18 and 13 [1-3]. For these common trisomies, cfDNA testing yields a higher detection rate, a lower false-positive rate and a higher positive predictive value than combined first-trimester screening (cFTS); moreover, it is risk-free compared with invasive prenatal diagnosis, which has been linked to a low risk of miscarriage [4]. At this point in time, however, molecular karyotyping on invasive samples is superior to cfDNA testing with respect to detection of atypical chromosomal abnormalities [5, 6].

Since September 2015, prenatal molecular karyotyping has been used in the Central Denmark Region as a primary genomic diagnostic tool on invasive samples from high-risk pregnancies (> 1:300) of foetal trisomy 21 after cFTS [7]. Over time, cfDNA testing has been implemented in different regions in various groups of pregnant women [8]. In January 2017, The Danish Health Authority issued a standardised national strategy stipulating that cfDNA testing should be offered solely as an alternative to invasive diagnostics for women at high risk after cFTS [9]. Recently, the expected view of follow-up testing with cfDNA testing as an alternative to invasive testing has been studied among women in a different region in Denmark. The study showed that women had a positive attitude towards cfDNA testing [10]. Neither Danish partners, health professionals' or the actual national uptake of cfDNA testing in Denmark has been explored- In several countries, the views of pregnant women and health professionals on prenatal testing have been studied [11-15]. Hill et al studied the preferences of pregnant women and health professionals (n = 3,911) in nine countries [12], including Denmark, and concluded that marked differences exist between countries.

We wished to explore preferences for prenatal tests among Danish stakeholders with the objective of comparing cfDNA testing with invasive diagnosis. A sub-set of these data has been published previously as part of Hill et al's international study [12]. Here we report the complete Danish data set, which includes additional questions, partner preferences and an in-depth analysis of results relevant for the implementation of cfDNA testing in Denmark.

METHODS

The questionnaire was adapted from the questionnaire used in Hill et al's study [11] and was translated directly from English into Danish by the Danish authors. The Danish version was piloted in pregnant couples (n = 10) and in health professionals (n = 10).

ORIGINAL ARTICLE

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TABLE 1

Demographic data on the women, their partners and health professionals[a].

	Women (n = 315)	Partners (n = 102, ♂: 101, ♀: 1)	Health professionals (n = 111)
Age, median, yrs (IQR)	31 (27-34)	31 (28-34)	-
Danish ethnicity, %	94.6	95.1	-
Qualification, %			
Higher education	82.2	76.5	-
Trained as health professional at any qualified level	32.4	-	-
Invasive test in pregnancy, %	7.9	-	-
Fertility treatment in current pregnancy, %	11.4	9.8	-
Gestation, %[b]			
≤ 11 wks	15.9	11.8	-
12-22 wks	50.8	65.7	-
> 22 wks	32.4	22.5	-
Have had or will have screening in this pregnancy, %[c]	94.6	81.4	-
Which statement best matches why you have chosen DS screening, %			
So that I can plan and prepare for the possibility of having a child with DS	15.8	11.0	-
To help me/my partner make a decision with respect to termination of pregnancy	57.9	74.4	-
I would want as much information about the baby as possible	14.5	7.3	-
Because my partner and family would want me to	0.7	-	-
Because my/my partner´s doctor suggested it	0.0	0.0	-
Because it is part of the routine prenatal care that women would want in pregnancy	7.7	6.1	
Other	2.7	1.2	-
Do not know	0.7	0.0	-
Age, mean, yrs (IQR)	-	-	43.3 (35-50)
Gender, n (%)			
Female	-	-	106 (95.5)
Male	-	-	5 (4.5)
Profession, n (%)			
HPs1:			
Foetal medicine, expert/obstetrician	-	-	23 (20.7)
Sonographer: midwife or nurse	-	-	34 (30.6)
HPs2:			
Midwife	-	-	48 (43.2)
General practitioner	-	-	5 (4.5)
Other	-	-	1 (0.9)
In profession, n (%)			
< 5 yrs	-	-	48 (43.2)
6-15 yrs	-	-	45 (40.5)
16-25 yrs	-	-	11 (9.9)

DS = Down syndrome; HPs1 = health professionals, group 1; HPs2 = health professionals, group 2; IQR = interquartile ranges.
a) The response rates were: 39.2%, 318/811 (women), 31.4%, 106/338 (partners) and 50.6%, 118/233 (health professionals).
b) Totals may not add to 100% due to "Do not know" responses.
c) 2.2% of women and 15.7% of partners do not know if they have had or will have a screening.

Recruitment

Pregnant women and partners attending prenatal care were recruited from foetal medicine units at seven hospitals in the Central and North Denmark Regions, the midwifery practice at Aarhus University Hospital and six general practitioners. Pregnant women were recruited whether or not they had attended cFTS and independently of the results of their cFTS. All questionnaires were filled in electronically using the internet-based online service SurveyXact from February 2014 to June 2015. Respondents were given the option of providing their email address so that they could be entered into a prize draw to win DKK 500 (about £ 50) gift voucher. Health professionals were recruited by email and once through a national meeting.

Discrete choice experiment

Before filling in the questionnaire, participants were given information on prenatal test attributes. Ten hypothetical choice sets constructed as discrete choice experiments (DCE) were generated from four attributes that varied at different levels (**Figure 1**). Participants were asked to choose between two tests, A or B, or a neither option. Women and partners were asked to provide their answers without any clinical context. The health professionals were asked, which test they would prefer to offer to women who were at high risk after cFTS. One choice set with a clearly superior option was included to check if participants were paying attention to the phrasing of the questions, and participants who did not answer this question as expected were excluded from the analysis. For further information on the DCE design, we refer to the international study [12].
A conditional logit regression model was used to analyse the DCE preference data in Stata 10.0 (StataCorp USA) [11].

Structured questions and demographics

Three structured questions included: ranking of prenatal test attributes, a direct choice between cfDNA testing and invasive diagnosis, and trading of no miscarriage risk for comprehensive genetic information. The last question was added by the Danish research team. Additional questions for women and partners included demographic characteristics for subgroup comparisons.

Trial registration: This study was registered with the Danish Data Protection Agency (1-16-02-586-13/2007-58-0010).

RESULTS

A total of 543 participants completed the questionnaire. Participants were excluded if they had not filled in the DCE question with the superior option as expected (n = 15). Hence, a total of 315 women, 102 partners and 111 health professionals were included in the study (**Table 1**). The health professionals were divided into two groups; HPs1: foetal medicine experts and sonographers who discussed options for Down's syndrome screening and diagnostic testing with pregnant women on a daily

basis; and HPs2: midwives providing prenatal care but who were not involved in prenatal screening.

The DCE results from the ten choice sets are presented in **Table 2**. Comparison of the coefficients for no miscarriage risk show that women and partners placed a significantly greater emphasis on this attribute than both groups of health professionals, whereas both HPs1 and HPs2 placed a significantly greater emphasis on accuracy than the women and partners. HPs1 had the greatest coefficient for comprehensive information. A total of 72% of the participants considered more than one attribute when choosing between tests. Of the 28% who always chose a test choice based on one attribute only, 113/146 based their choice on no miscarriage risk.

Subgroup comparison between women showed that women with experiences of high-risk cFTS screening results and invasive testing placed more emphasis on comprehensive genetic information and less on no miscarriage risk than women who had no such experience. Coefficients between the two groups were 0.55 versus 0.12 ($p < 0.05$) for comprehensive genetic information and 1.22 versus 1.64 ($p < 0.05$) for no miscarriage risk. Women who had undergone fertility treatment also had a stronger preference for comprehensive genetic information than women who had conceived naturally (0.56 versus 0.10; $p < 0.05$). Women who were healthcare professionals placed less emphasis on having no risk of miscarriage than other women (coefficients: 1.41 versus 1.70; $p < 0.05$). No other subgroup comparison within the groups of women and partners showed significant results, including comparisons based on age, number of children, level of qualification and gestational age.

The results on ranking of prenatal test attributes showed that the majority of both women and partners ranked no risk of miscarriage as their first priority, whereas the majority of all health professionals ranked a high level of accuracy as the most important attribute. Comprehensive genetic information was ranked as the highest priority among 25% (95% confidence interval (CI): 13-36%) of HPs1; this was significantly higher than among HPs2 (8%; 95% CI: 0.5-16%) and women (14%; 95% CI:10-18%) ($p < 0.05$), but not partners (18%; 95% CI: 10-25%).

FIGURE 1

An example of one of the ten discrete choice sets in the choice experiment. The information given about the test attributes and levels was as follows. Accuracy: the test can identify 95%, 99%, 100% of the foetuses with Down syndrome. Time (result available): at 10, 12 and 16 wks of pregnancy. Risk of miscarriage: a blood sample has no risk of miscarriage, whereas chorionic villus sampling and amniocentesis carry a small (1%) risk of miscarriage. Genetic information: "simple" means information on Down syndrome only, "comprehensive" means information on Down syndrome as well as rare conditions that may cause learning disability, developmental delay or other health problems. In some cases, it can be difficult to predict what problems, if any, the child may have. The 1% risk of miscarriage was chosen to enable comparison with the study by Hill et al [11].

	A	B
Accuracy, %	99	100
Time, wks	10	12
Risk of miscarriage	Small (1%)	No risk
Genetic information	Comprehensive	Simple

Which test would you prefer? (women)/Which test do you think your pregnant partner should choose? (partner)/Which test would you prefer to offer to a woman at high-risk of foetal aneuploidy? (health professionals)

O A
O B
O Neither

TABLE 2

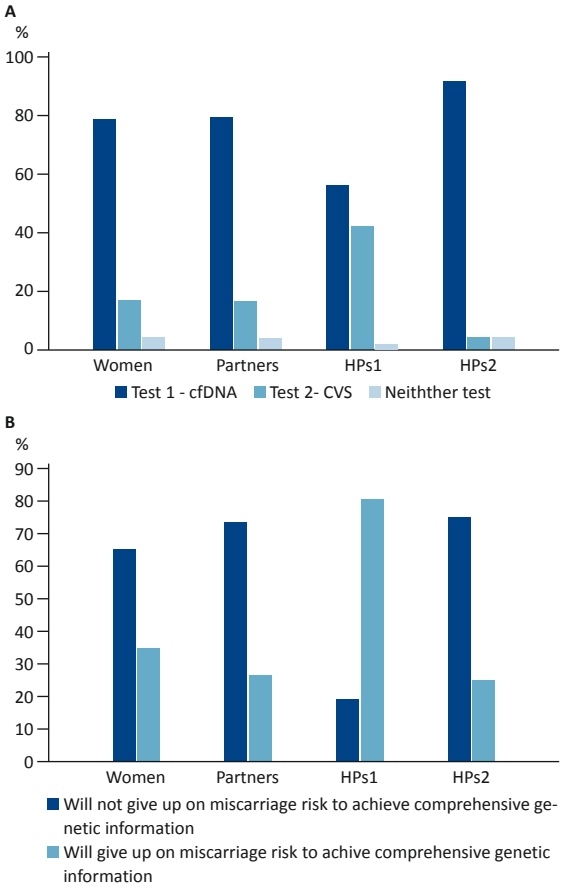
Conditional logit analysis regression results of the discrete choice experiment sets[a].

	Coefficient (95% confidence interval)				Difference, p-value					
Attribute	women (n = 315)	partners (n = 102)	HPs1 (n = 57)	HPs2 (n = 48)	W/P	W/HPs1	W/HPs2	P/HPs1	P/HPs2	HPs1/HPs2
Accuracy	0.213 (0.183-0.243)	0.208 (0.149-0.266)	0.302 (0.233-0.371)	0.328 (0.249-0.407)	ns	< 0.05	< 0.05	< 0.05	< 0.05	ns
Time of result	–0.194 (–0.217–-0.174)	–0.158 (–0.201–-0.117)	–0.228 (–0.283–-0.174)	–0.233 (–0.295–-0.172)	ns	ns	ns	< 0.05	ns	ns
No miscarriage risk	1.594 (1.478-1.711)	2.017 (1.787-2.248)	0.542 (0.297-0.787)	0.965 (0.686-1.244)	< 0.05	< 0.001	< 0.001	< 0.001	< 0.001	< 0.05
Full information	0.155 (0.051-0.258)	0.197 (0.001-0.394)	0.914 (0.667-1.162)	–0.763 (–1.039–-0.486)	ns	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

HPs1 = health professionals, group 1; HPs2 = health professionals, group 2; ns = non-significant; P = partners; W = women. a) In the regression analysis, the sign (+ or –) of the coefficients indicates the direction of the preference for each attribute. Positive coefficients for accuracy, comprehensive information and no miscarriage risk were anticipated as we expected participants to prefer tests with higher accuracy, more information and greater safety. Negative coefficients for the timing attribute refer to a preference for a test conducted early in pregnancy. The positive coefficients imply that women, partners and health professionals all placed an emphasis on an accurate and safe test. Negative coefficients for the timing of results indicate that all participants preferred a test conducted early in pregnancy. Women, partners and health professionals performing sonography (HPs1) also emphasised a test with comprehensive genetic information. Midwives (HPs2) preferred tests with simple genetic information.

FIGURE 2

Comparison of two structured questions. **A.** Combined first trimester screening risk unknown. Results relating to a direct choice between Test 1, blood test which will provide simple genetic information, and Test 2, CVS which will provide comprehensive genetic information, but implies a low risk of miscarriage. **B.** Combined first trimester screening risk unknown to women and partners; information on high-risk pregnancy to health professionals. Results concerning the participants' willingness to trade no miscarriage risk for comprehensive genetic information.



cfDNA = cell-free DNA testing; cFTS = combined 1st trimester screening; CVS = chorionic villus sampling; HPs1 = health professionals, group 1 (foetal medicine experts, obstetricians and sonographers); HPs2 = health professionals, group 2 (midwives who do not discuss prenatal screening with pregnant women).

Figure 2A shows results from the direct choice between Test 1 (resembling cfDNA testing) and Test 2 (resembling invasive testing) for a pregnant woman who has not undergone cFTS. The majority of all groups would prefer cfDNA testing instead of invasive testing even though a significantly smaller proportion of HPs1 than HPs2, women and partners would choose Test 1.

Figure 2B shows results for the participants' willingness to trade no miscarriage risk for comprehensive genetic information; the health professionals were told before they should trade that they needed make a choice for a pregnant woman at high risk after cFTS. The women were not informed of any high risk. Despite this, a total of 35% of the women were willing to trade. Their most frequent choice of chosen miscarriage risk was 1%. Significant differences were found as more HPs1 were willing to trade no miscarriage risk to get comprehensive genetic information compared with women, their partners and HPs2 ($p = 0.000$ (χ^2-test). The majority of women showed consistency in their answers and would either choose Test 1 and would not be willing to trade no miscarriage risk for comprehensive genetic information or choose Test 2 and would be willing to accept a miscarriage risk to get comprehensive genetic information. Eighty women (27%) had inconsistent answers regarding the direct choice between Test 1 and Test 2 and the question regarding willingness to trade safety for comprehensive genetic information. These 80 women were compared with the women with similar age, number of children, educational level and gestational age; no significant differences were found; however, we observed a trend towards a lower gestational age among the 80 women with inconsistent answers (week < 12, 24% compared with 15%; $p = 0.059$).

DISCUSSION

This article is the first to evaluate preferences of Danish pregnant women, partners and health professionals for prenatal screening with cfDNA testing as an alternative prenatal testing tool. No miscarriage risk has a high priority in decision-making of women although, when asked to directly trade-off miscarriage risk and type of information, 35% are willing to accept a miscarriage risk of 1% to get comprehensive genetic information.

Limitations

The stated preferences might not reflect actual real-life decisions as the majority of respondents have not experienced getting a high-risk cFTS result. Furthermore, the questionnaire generates quantitative data and we do not know the reasons behind the respondents' preferences. Furthermore, the majority of women and partners in this study are well educated and born in Denmark. Women with less education and from other ethnic groups may have different preferences [13]. Another limitation is the translation from English into Danish, since differences in the precise understanding of central words could have an impact on the results.

Women's and partners' preferences

The inclusion of partner preferences is a major strength of this study as very few studies investigating views on cfDNA testing include partner preferences [16, 17]. We have shown that the majority of pregnant women and their partners accept the offer of prenatal screening and share similar relative values to the test attributes. How-

ever, a significant difference was seen between their stated reasons for choosing prenatal screening (Table 1). Thus, 98% of pregnant couples in Denmark choose to terminate a trisomy 21-pregnancy [18, 19]. Women who chose another reason for having cFTS screening may already have decided whether or not to terminate the pregnancy if affected. Another explanation why partners seem more willing to terminate the pregnancy may be that they are more aware of the possible implications of cFTS or that they are less emotionally attached to the foetus at this gestational age.

Choices between cell-free DNA testing and invasive testing

A total of 35% of pregnant women are willing to accept a risk of miscarriage provided they can have a test that can provide comprehensive genetic information. When compared to the question inviting participants to directly choose between cfDNA testing and invasive testing (Figure 2), 27% of women were inconsistent as to whether they prefer no miscarriage risk or comprehensive genetic information. This inconsistency may be explained by the way the two different questions were presented. Another explanation may be that the women who gave different answers changed their minds while answering the questionnaire or were uncertain about what to choose based on the complexity of prenatal tests.

In line with a previous study conducted in the UK [11], our study showed that women who have experienced invasive testing prefer comprehensive genetic information and place less emphasis on the risk of miscarriage than other women. The prior experience of invasive testing may reduce discomfort and fear of miscarriage as these respondents have experienced a successful invasive procedure before. Furthermore, the prior experience of being at high risk may make these women feel more concerned about foetal abnormalities and hence they may have a stronger preference for comprehensive genetic information. Women without experience with invasive diagnosis or high risk may intuitively go for the low-risk opportunity without the understanding that comes from personal experience. This difference may reflect more on the level on information that the women have than on different values. Likewise, educational cultures and different professional roles between foetal medicine experts and sonographers (HPs1) vs. midwives (HPs2) may explain why preferences for comprehensive genetic information differ significantly between the two groups [20]. HPs1 are more likely to experience a heavier-risk group than HPs2, and they are therefore more exposed to pregnancies with chromosomal aberrations. Accordingly, HPs2s may not have the same level of understanding of the implications of having comprehensive information and may therefore be more reluctant to discuss comprehensive information with the women. This highlights the importance of having educational materials and training accompany the introduction of cfDNA testing to further health professionals' confidence in discussing the test and its implications.

CONCLUSIONS

Our data demonstrate that no miscarriage risk has a crucial impact on the choice behaviour of both pregnant women and partners, which may lead them to choose a test simply because it is safe. Comprehensive genetic information is emphasised in a subgroup of women who have experienced invasive diagnosis and in the group of health professionals who discuss options for prenatal diagnosis on a daily basis. Therefore, careful pre-test counselling by experts performing prenatal screening is of paramount importance.

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