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UK NHS pilot study on cell-free DNA testing in screening for fetal trisomies: factors affecting uptake

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KEYWORDS: cell-free DNA; chorionic villus sampling; decision making; first trimester; first-trimester screening; prenatal diagnosis

ABSTRACT

Objective *This study reports on the clinical implementation of cell-free DNA (cfDNA) testing, contingent on the results of the combined test, in screening for fetal trisomies 21, 18 and 13 in two UK National Health Service hospitals. Women with a combined-test risk of ≥ 1:100 (high risk) were offered the options of chorionic villus sampling (CVS), cfDNA testing or no further testing and those with a risk of 1:101 to 1:2500 (intermediate risk) were offered cfDNA or no further testing. The objective of the study was to examine the factors affecting patient decisions concerning their options.*

Methods *Combined screening was performed in 6651 singleton pregnancies in which the risk for trisomies was high in 260 (3.9%), intermediate in 2017 (30.3%) and low in 4374 (65.8%). Logistic regression analysis was used to determine which factors among maternal characteristics, fetal nuchal translucency thickness (NT) and risk for trisomies were significant predictors of opting for CVS in the high-risk group and opting for cfDNA testing in the intermediate-risk group.*

Results *In the high-risk group, 104 (40.0%) women opted for CVS; predictors for CVS were increasing fetal NT and increasing risk for trisomies, while the predictor against CVS was being of Afro-Caribbean racial origin (*r = *0.366). In the intermediate-risk group, 1850 (91.7%) women opted for cfDNA testing; predictors for cfDNA testing were increasing maternal age, increasing risk for trisomies and university education, while predictors against cfDNA testing were being of Afro-Caribbean racial origin, smoking and being parous* (r = *0.105).*

Conclusions *This study has identified factors that can influence the decision of women undergoing combined screening in favor of or against CVS and in favor of or against cfDNA testing.* *Copyright © 2014 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

The established method of screening for trisomy 21 in all National Health Service (NHS) hospitals in England is the first-trimester combined test and the method of diagnosis is chorionic villus sampling (CVS), which is offered to women if their estimated risk is 1:100 or higher. The detection rate (DR) of trisomy 21 by this method of screening is about 90%, at a false-positive rate (FPR) of 5%[1]. A beneficial consequence of using the combined test for trisomy-21 screening is the detection of about 70% of cases of trisomies 18 and 13, but when specific algorithms for trisomies 18 and 13, in addition to that for trisomy 21, are also used, about 90% of fetuses with trisomy 21 and 95% with trisomies 18 and 13 can be detected for the same overall FPR of 5%[2]. Recent evidence suggests that the performance of screening for trisomies 21, 18 and 13 may be improved by the analysis of cell-free DNA (cfDNA) in maternal blood; a meta-analysis of clinical validation or implementation studies of cfDNA testing reported respective DRs of 99.0%, 96.8% and 92.1% at an overall FPR of 0.4%[3]. Consequently, there will be widespread uptake of cfDNA testing in routine clinical practice and we have demonstrated that this is feasible during the first trimester of pregnancy[4–6].

In screening for the major trisomies in the general population, cfDNA testing can either be used as a first-line method of screening or it can be contingent on the results of the combined test at 11–13 weeks' gestation[3]. Contingent screening could lead to a very high DR and very low invasive-testing rate at a considerably lower cost than would be possible using cfDNA testing as a first-line method of screening[7–9]. This strategy would also retain the advantages of first-trimester testing by ultrasound examination and biochemistry, including accurate pregnancy dating, early detection of many major fetal defects and prediction, with the potential for prevention, of a wide range of pregnancy complications[10].

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We report on the clinical implementation of cfDNA testing, contingent on the results of the combined test, in screening for fetal trisomies in two NHS hospitals in England. In this ongoing study, women with an estimated risk from the combined test of ≥ 1:100 are offered the options of invasive testing, cfDNA testing or no further testing and those with a risk of 1:101 to 1:2500 are offered cfDNA testing or no further testing. The objective of this study was to examine the factors affecting patient decisions concerning their options.

METHODS

The data for this study were derived from clinical implementation of cfDNA testing in screening for trisomies 21, 18 and 13 in women with singleton pregnancies attending King's College Hospital, London, UK, and Medway Maritime Hospital, Kent, UK, between October 2013 and August 2014. The study was approved by the NHS Research Ethics Committee. During the visit at 11–13 weeks' gestation, an ultrasound scan was carried out, first, to determine if the pregnancy was singleton with a live fetus and to confirm gestational age from the measurement of fetal crown–rump length; second, to diagnose any major fetal abnormalities; and third, to measure fetal nuchal translucency thickness (NT) as part of combined screening for aneuploidies[1,2].

Counseling before and after the combined test

All women received a leaflet before their hospital visit that provided information on trisomies 21, 18 and 13, the combined test, cfDNA testing and invasive testing. Before the combined test, they received verbal information concerning the content and performance of the test and provided verbal consent to screening for trisomies.

The estimated risk from the combined test was calculated and this was explained to the patients. Women with a risk > 1:2500 received further written information and counseling concerning their options. For women with a risk ≥ 1:100 (high risk), we offered the options of CVS, cfDNA testing of maternal blood for trisomies 21, 18 and 13 or no further tests. For women with a risk of 1:101 to 1:2500 (intermediate risk), we offered the options cfDNA testing or no further tests. For women with a risk of < 1:2500 (low risk), we provided reassurance that fetal trisomies were unlikely and they did not require further testing.

The information given to the high-risk group was that the only way they can be certain whether the fetus is affected by one of the trisomies and other rare chromosomal abnormalities is to have an invasive test, but the disadvantage of such a test is its 1% risk of causing miscarriage. The information given to both the high-risk and intermediate-risk groups was that the cfDNA test is not invasive and gives more accurate prediction of trisomies than does the combined test, but is less accurate than CVS. The cfDNA test detects 99% of fetuses with trisomy 21, 97% of fetuses with trisomy 18 and 92% of fetuses with trisomy 13, but it does not provide information on other rare chromosomal abnormalities. The women were also informed that the results from the cfDNA test would be available in about 2 weeks, but in about 5% of cases the test does not give a result.

Women opting for cfDNA testing provided written informed consent. Maternal blood was obtained by venepuncture (20 mL, in cfDNA BCT™ tubes (Streck, Omaha, NE, USA)), and sent via courier to the USA for cfDNA testing (Harmony™ Prenatal Test, Ariosa Diagnostics, Inc., San Jose, CA, USA)[11–13].

Maternal characteristics

Patients were asked to provide information on maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian or mixed), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs or *in-vitro* fertilization), cigarette smoking during pregnancy (yes/no), parity (parous or nulliparous if no previous pregnancy at or after 24 weeks' gestation), a previous pregnancy with aneuploidy (yes/no) and educational level (none or primary school/secondary school/college qualification/GCE A-levels (the standard high-level exam in schools in England and Wales)/university).

Statistical analysis

Descriptive data are presented as median and interquartile range for continuous variables and as *n* (%) for categorical variables. Comparisons between outcome groups were performed using the Mann–Whitney *U*-test for continuous variables and the χ^2-test or Fisher's exact test for categorical variables.

In the high-risk group, logistic regression analysis was used to determine which of the factors among maternal characteristics, fetal NT and estimated combined risk for trisomy 21 or trisomies 18/13 were significant predictors of opting for CVS. In the intermediate-risk group, logistic regression analysis was also used to determine which of these factors were significant predictors of opting for cfDNA testing.

The statistical software package SPSS 22.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis.

RESULTS

Patient characteristics and results of the combined test

During the study period, 6782 women with a singleton pregnancy and a live fetus were offered first-trimester combined screening for trisomies; 6651 (98.1%) accepted and 131 (1.9%) declined screening. Following combined screening, 260 (3.9%), 2017 (30.3%) and 4374 (65.8%) were classified as being at high risk, intermediate risk and low risk, respectively.

The maternal characteristics and results of combined screening for each risk group are summarized in Table 1. Compared to the low-risk group, the high-risk group

had a significantly higher median maternal age, fetal NT and estimated risk for trisomies, there was a higher prevalence of women of East-Asian racial origin and a higher prevalence of parous women. Compared to the low-risk group, the intermediate-risk group had a significantly higher median maternal age, fetal NT and estimated risk for trisomies, there was a higher prevalence of women of Caucasian racial origin, a higher prevalence of parous women, a higher rate of *in-vitro* fertilization and a greater number of women who had received a university education, while there was a lower prevalence of women of Afro-Caribbean and mixed racial origins and a lower prevalence of women who received secondary education and college qualifications.

Patient decisions in the high-risk group

In the high-risk group, 104 (40.0%) women opted for CVS, 149 (57.3%) opted for cfDNA testing and seven (2.7%) did not want any further investigations. In the latter group, the reason given by the women for their decision against further invasive or non-invasive tests was that they did not want to know if their fetus had a chromosomal abnormality because they would not contemplate having a termination of an affected pregnancy.

In the 104 cases choosing invasive testing, the fetal karyotype was abnormal in 31, including 16 cases of trisomy 21, 11 of trisomy 18, two of trisomy 13, one of 45,XO and one of 47,XXX. In 15 of the 16 cases of trisomy 21, all cases of trisomies 18 and 13 and the one case with 45,XO, the parents chose to undergo termination of pregnancy (TOP); in one case of trisomy 21 and the case of 47,XXX the pregnancies continued.

In the 149 patients from the high-risk group who opted for cfDNA testing, results were provided for 145, and in four (2.7%) there was no result owing to low fetal fraction or assay failure. In the 145 cases with cfDNA results, there was a low risk for each trisomy in 139 cases and a high risk in six, including four for trisomy 21 and two for trisomy 18. In three of the four patients with a positive cfDNA result for trisomy 21 and the two with a positive result for trisomy 18 the patients chose to have invasive testing, which confirmed the abnormal result in two of the three cases of trisomy 21 and the two cases of trisomy 18; in one of the two cases of trisomy 21 and in both with trisomy 18 the parents elected TOP, whereas in one of the two cases of trisomy 21 the decision was to continue with the pregnancy. The one pregnancy with a positive cfDNA result for trisomy 21 in which the parents decided against invasive testing resulted in the live birth of a baby with trisomy 21.

Table 1 Maternal and fetal characteristics of the study population of women with singleton pregnancy offered first-trimester combined test for screening for trisomies 21, 18 and 13 at King's College Hospital, London, UK, and Medway Maritime Hospital, Kent, UK, between October 2013 and August 2014, according to risk for trisomy

Characteristic	*High-risk* (n = *260*)	*Intermediate-risk* (n = *2017*)	*Low-risk* (n = *4374*)
Maternal age (years)	36.4 (32.9–39.8)*	34.9 (31.0–38.4)*	30.2 (26.1–33.3)
Racial origin			
Caucasian	169 (65.0)	1401 (69.5)*	2862 (65.4)
Afro-Caribbean	58 (22.3)	402 (19.9)*	1021 (23.3)
South-Asian	12 (4.6)	90 (4.5)	202 (4.6)
East-Asian	14 (5.4)*	60 (3.0)	94 (2.1)
Mixed	7 (2.7)	64 (3.2)*	195 (4.5)
Smoker	15 (5.8)	131 (6.5)	345 (7.9)
Parity			
Nulliparous	106 (40.8)*	778 (38.6)*	2247 (51.4)
Parous	154 (59.2)*	1239 (61.4)*	2127 (48.6)
Method of conception			
Spontaneous	249 (95.8)	1937 (96.0)*	4260 (97.4)
Ovulation drugs	1 (0.4)	17 (0.8)	22 (0.5)
In-vitro fertilization	10 (3.8)	63 (3.1)*	92 (2.1)
Educational level			
None/primary school	4 (1.5)	53 (2.6)	127 (2.9)
Secondary school	59 (22.7)	408 (20.2)*	1042 (23.8)
College qualifications	50 (19.2)	364 (18.0)*	939 (21.5)
GCE A-levels	7 (2.7)	95 (4.7)	199 (4.5)
University	140 (53.8)	1097 (54.4)*	2067 (47.3)
Previous pregnancy with aneuploidy	3 (1.2)	32 (1.6)*	9 (0.2)
Fetal nuchal translucency (mm)	2.1 (1.7–2.8)*	1.8 (1.6–2.1)*	1.7 (1.5–1.9)
Estimated risk for trisomy 21 or 18/13 (1 in *n*)	35 (64–12)*	976 (1628–444)*	8234 (14 119–4692)
Patient choice for further testing			
Cell-free DNA test	149 (57.3)	1850 (91.7)	—
Chorionic villus sampling	104 (40.0)	—	—
None	7 (2.7)	167 (8.3)	4374 (100)

Data are given as *n* (%) or median (interquartile range). Comparisons between groups were performed using Mann–Whitney *U*-test for continuous variables and the χ^2 or Fisher's exact test for categorical variables, with *post-hoc* Bonferroni corrections. $^*P < 0.025$.

Table 2 Regression analysis for the prediction of opting for or against chorionic villus sampling in pregnant women with singleton pregnancy at high risk for trisomy, offered first-trimester combined screening for trisomies

	Univariable analysis		*Multivariable analysis*	
Independent variable	*Odds ratio (95% CI)*	P	*Odds ratio (95% CI)*	P
Maternal age (years)	1.039 (0.990–1.091)	0.118	—	—
Racial origin				
Caucasian	1		1	
Afro-Caribbean	0.290 (0.144–0.586)	0.001*	0.182 (0.071–0.465)	< 0.0001*
South Asian	1.112 (0.345–3.589)	0.858	—	—
East Asian	0.303 (0.082–1.127)	0.075	—	—
Mixed	0.834 (0.181–3.842)	0.816	—	—
Smoker	2.368 (0.817–6.867)	0.112	—	—
Parity				
Nulliparous	1		—	—
Parous	0.495 (0.298–0.823)	0.007*	—	—
Method of conception				
Spontaneous	1		—	—
Ovulation drugs	0.000 (0.000–0.000)	> 0.999	—	—
In-vitro fertilization	1.515 (0.428–5.370)	0.520	—	—
Educational level				
None/primary school	1		—	—
Secondary school	0.000 (0.000–0.000)	0.999	—	—
College qualifications	0.000 (0.000–0.000)	0.999	—	—
GCE A-levels	0.000 (0.000–0.000)	0.999	—	—
University	0.000 (0.000–0.000)	0.999	—	—
Previous pregnancy with aneuploidy	0.000 (0.000–0.000)	0.999	—	—
Fetal nuchal translucency (mm)	2.277 (1.659–3.124)	< 0.0001*	1.788 (1.230–2.600)	0.002*
Estimated risk for trisomy 21 or 18/13 (1 in *n*)	1.073 (1.047–1.100)	< 0.0001*	1.056 (1.022–1.091)	0.001*

Data are given as median (interquartile range). Comparisons between groups were performed using Mann–Whitney *U*-test for continuous variables and χ^2 or Fisher's exact test for categorical variables, with *post-hoc* Bonferroni corrections. *$P < 0.025$.

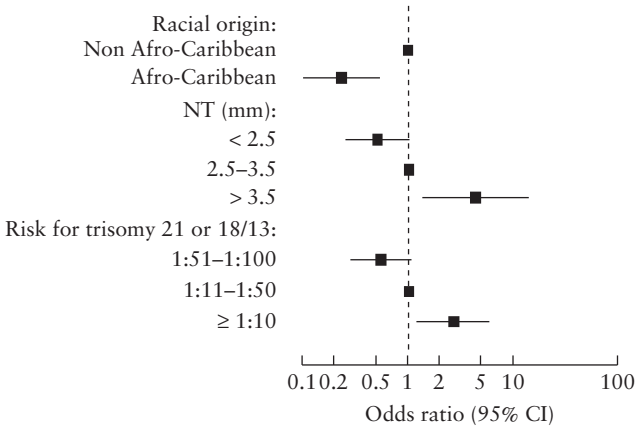

Figure 1 Forest plot of significant independent predictors of opting for or against chorionic villus sampling (CVS) in a group of pregnant women at high risk for trisomy ($n = 260$). Odds ratio < 1 opted against CVS; odds ratio > 1 opted for CVS. NT, nuchal translucency.

The rate of TOP in trisomy-21 pregnancies was 33% (1 of 3) in the high-risk group choosing cfDNA testing, compared with 94% (15 of 16) in those choosing CVS ($P = 0.05$).

Univariable regression analysis demonstrated that opting for CVS was significantly associated with increasing fetal NT and increasing estimated risk for trisomies, while opting against CVS was significantly associated with being of Afro-Caribbean racial origin and being parous (Table 2). Multivariable regression analysis demonstrated that significant independent prediction of opting for CVS was provided by increasing fetal NT and increasing estimated risk for trisomies, while prediction of opting against CVS was provided by being of Afro-Caribbean racial origin ($r = 0.366$; Table 2, Figure 1).

In the two participating NHS hospitals the method of screening for trisomies 21, 18 and 13 before the start of our study was the combined test. During the 2-year period before the onset of the study, the estimated risk for trisomies by the combined test was ≥ 1:100 in 723 cases, and 393 (54.4%) of these women opted for invasive testing while 330 (45.6%) chose to have no further investigations. Therefore, the introduction of cfDNA testing was associated with a 26.5% reduction in the rate of invasive testing from 54.4% to 40.0% and a 94.1% reduction in the rate of no further investigations from 45.6% to 2.7%.

Patient decision in the intermediate-risk group

In the intermediate-risk group, 1850 (91.7%) women opted for cfDNA testing and 167 (8.3%) did not want any further investigations. In the latter group, the reason given by the women for their decision against further tests was that they were happy with the risk from the combined test and did not want to endure the anxiety of waiting for the results of further tests ($n = 102$), they would not contemplate having a termination of an affected pregnancy ($n = 45$), they considered the cfDNA test to be experimental and did not want to participate in research

Table 3 Regression analysis for the prediction of opting for or against cell-free DNA testing in pregnant women with singleton pregnancy at intermediate risk for trisomy, offered first-trimester combined screening for trisomies

	Univariable analysis		*Multivariable analysis*	
Independent variable	*Odds ratio (95% CI)*	P	*Odds ratio (95% CI)*	P
Maternal age (years)	1.074 (1.046–1.104)	< 0.0001*	1.059 (1.028–1.091)	< 0.0001*
Racial origin				
Caucasian	1		1	
Afro-Caribbean	0.640 (0.444–0.922)	0.017*	0.627 (0.430–0.914)	0.015*
South Asian	0.744 (0.364–1.523)	0.419	—	—
East Asian	0.000 (0.000–0.000)	0.997	—	—
Mixed	0.976 (0.383–2.483)	0.959	—	—
Smoker	0.216 (0.141–0.332)	< 0.0001*	0.328 (0.206–0.524)	< 0.0001*
Parity				
Nulliparous	1		1	
Parous	0.509 (0.354–0.730)	< 0.0001*	0.517 (0.351–0.763)	0.001*
Method of conception				
Spontaneous	1		—	—
Ovulation drugs	0.000 (0.000–0.000)	0.998	—	—
In-vitro fertilization	1.850 (0.574–5.964)	0.303	—	—
Educational level				
None/primary school	1		—	—
Secondary school	1.831 (0.834–4.019)	0.132	—	—
College qualifications	1.568 (0.715–3.441)	0.262	—	—
GCE A-levels	0.721 (0.303–1.713)	0.458	—	—
University	3.951 (1.834–8.511)	< 0.0001*	1.644 (1.126–2.401)	0.010*
Previous pregnancy with aneuploidy	0.871 (0.262–2.889)	0.821	—	—
Fetal nuchal translucency (mm)	1.019 (0.691–1.504)	0.924	—	—
Estimated risk for trisomy 21 or 18/13 (%)	3.407 (1.268–9.152)	0.015*	4.037 (1.471–11.081)	0.007*

Data are given as median (interquartile range). Comparisons between groups were performed using Mann–Whitney *U*-test for continuous variables and χ^2 or Fisher's exact test for categorical variables, with *post-hoc* Bonferroni corrections. *$P < 0.025$.

($n = 17$) or they did not want their blood to be sent for testing in the USA ($n = 3$).

Univariable regression analysis demonstrated that opting for cfDNA testing was significantly associated with increasing maternal age, increasing risk for trisomies and university education, while opting against cfDNA testing was significantly associated with being of Afro-Caribbean racial origin, cigarette smoking and being parous (Table 3). All of these factors provided significant independent prediction in a multivariable regression analysis ($r = 0.105$; Table 3, Figure 2). However, their actual contribution was small: the uptake of cfDNA testing was 89% in women of Afro-Caribbean racial origin compared with 92% in Caucasian women, 95% in university graduates compared with 88% in those without a university education, 90% in parous compared with 95% in nulliparous women and 74% in smokers compared with 93% in non-smokers.

DISCUSSION

Main findings of the study

This study has demonstrated the feasibility of introducing cfDNA testing, contingent on the results of the first-trimester combined test for trisomies 21, 18 and 13, in routine clinical practice within NHS hospitals in the UK. About 98% of women attending for a routine ultrasound examination at 11–13 weeks' gestation accepted the offer of screening for fetal trisomies and on the basis of the results from the combined test the risk was ≥ 1:100 in about 4% of cases, 1:101 to 1:2500 in 30% and < 1:2500 in 66%. These percentages are as expected for a population with a median maternal age of 32 years[2,7,8].

In the high-risk group, 40% of women opted for CVS, 57% for cfDNA testing and 3% did not want any further investigations. The majority of women chose cfDNA testing despite our counseling that the results were not as accurate or extensive as those provided by an invasive test. This choice between invasive and non-invasive testing was influenced by objective evidence derived from the patient-specific risk obtained from the combined test and the appearance of the fetus as reflected in the measurement of NT. These results demonstrate that the pregnant women understood the meaning of the numbers and their decisions were based on such numbers rather than an arbitrary classification of high *vs* low risk. However, the choice between CVS and cfDNA testing was also influenced by parental attitudes in favor of or against termination of a potentially affected pregnancy; termination was chosen by 15 of the 16 women who had a fetus with trisomy 21 in the CVS group, compared to one in three of those choosing cfDNA testing. An additional finding is that women of Afro-Caribbean racial origin were more averse to invasive testing than were Caucasian women, which presumably reflects cultural differences between the two groups.

In the intermediate-risk group, 92% of women opted for cfDNA testing and 8% did not want any further investigations. The main reason given by the women

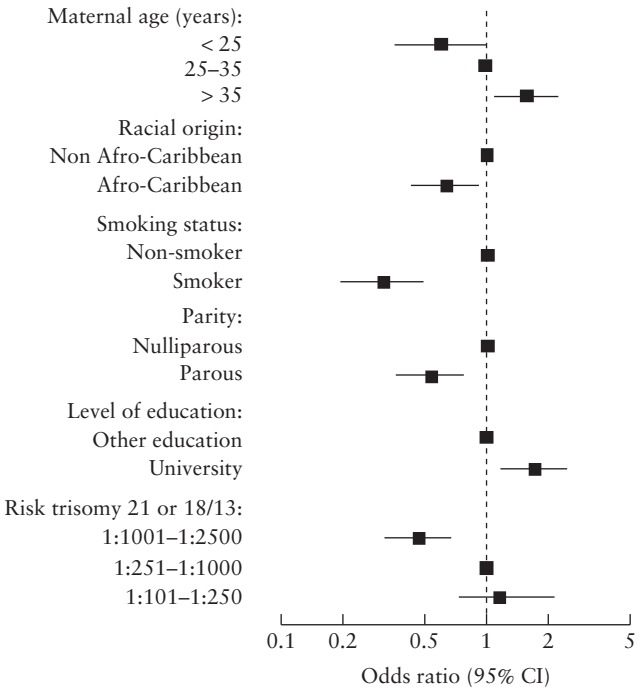

Figure 2 Forest plot of significant independent predictors of opting for or against cell-free DNA (cfDNA) testing in a group of pregnant women at intermediate risk for trisomy ($n = 2017$). Odds ratio < 1 opted against cfDNA testing; odds ratio > 1 opted for cfDNA testing.

in this group for avoiding further testing was that they were happy with the risk from the combined test and did not want to endure the anxiety generated by the 2-week wait for further results. The second most common reason for declining cfDNA testing was that the women did not want more accurate information on risks because they would not contemplate having a termination of an affected pregnancy. Multivariable regression analysis demonstrated that factors affecting their decision in favor of cfDNA testing were university education, increasing maternal age and increasing risk for trisomies, whereas predictors against testing were being of Afro-Caribbean racial origin, smoking and being parous.

Limitations of the study

The main limitation of our study was that we did not undertake a formal assessment of psychosocial variables and religious factors that may affect decisions concerning uptake of screening and invasive testing. We were surprised by the very high self-reported proportion of women who were university graduates in the socioeconomically deprived areas served by the two participating hospitals.

The results on the uptake of various options depending on risk categories defined by the combined test highlight some general principles concerning the factors that influence patient decisions. However, the exact rates of uptake of a specific option are unlikely to be generalizable to all populations from different racial and socioeconomic backgrounds in different countries and healthcare systems.

Comparison with findings from previous studies

Previous large studies on women identified as being at increased risk for trisomy 21, by the first-trimester combined test or second-trimester serum biochemistry, reported that the uptake of invasive testing by these women varied from 46% to 78%[14–19]. The studies also highlighted the fact that the rate of invasive testing increases with an increasing estimated risk for trisomies. A previous study of 30 564 singleton pregnancies undergoing first-trimester combined screening reported that the rate of invasive testing increased exponentially with the estimated risk for trisomies, from less than 1% for those with a risk of < 1:10 000 to about 20% for a risk of 1:300 to 1:500 and to more than 90% for a risk of > 1:50[15]. These results demonstrate that pregnant women are able to use sophisticated screening information to make scientifically and ethically rational decisions in favor of or against invasive testing[15].

In our study, the women in the high-risk group were asked to decide in favor of or against invasive testing but they also had the option of cfDNA testing. This can, at least in part, explain the lower rate of invasive testing in our population compared to the rates reported in the literature[14–19] and to the rate of invasive testing in the 2-year period before the introduction of cfDNA testing. We found that the introduction of cfDNA testing was associated with a modest decrease of 26% in the rate of invasive testing and, perhaps more importantly, with a 94% decrease in those who would have previously opted for no further investigations. A previous study of 398 pregnant women with a positive result from the first-trimester combined test or second-trimester serum biochemistry reported that 40% chose cfDNA testing, 39% had invasive testing and 21% declined further testing; in the year prior to the introduction of cfDNA testing, 47% had invasive testing and 53% had no further investigations[20].

In the intermediate-risk group the proportion of women deciding in favor of cfDNA testing was very high and although there were significant associations for such a decision with racial origin, age, education, smoking status and parity, the actual contribution of these factors was small. Previous studies have also reported that women of Afro-Caribbean racial origin are less likely to accept prenatal diagnosis for chromosomal abnormalities than are Caucasian women, which has been attributed to socioeconomic factors and cultural differences in attitudes toward pregnancy, termination and/or raising a disabled child[16,21].

Previous studies have explored potential factors that could influence patient acceptability of cfDNA testing if it was to be introduced into routine clinical care and have reported that 70–90% of women would welcome the new test[22–24]. Our study incorporated cfDNA testing into routine clinical practice and has shown a high acceptability of the test from prospective screening in many thousands of patients.

Conclusions

In England, all NHS maternity units offer routine screening for trisomy 21 by the first-trimester combined test, which detects about 90% of cases at an FPR of 5%[1]. We have previously proposed that extending this policy by offering cfDNA testing to those with a risk of > 1:2500 after first-trimester combined testing would substantially improve the DR to about 97% and reduce the FPR to less than 0.5%, without the major increase in cost that would arise from first-line screening by cfDNA testing of all patients[7,8].

This study has demonstrated that contingent screening can be incorporated easily into routine antenatal care within NHS hospitals. The majority of high-risk patients chose cfDNA testing, and the uptake of the test within this group was partly at the expense of invasive testing, but mainly as a new option in women who would have previously chosen to have no further investigations. In the intermediate-risk group, in which the women were not given the option of invasive testing, more than 90% chose to have the cfDNA test, which would provide them with further and more accurate information on their risk for the major trisomies.

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