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Cell-Free DNA Testing: What Is the Reason Why High-Risk Women Choose It?

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Cell-free DNA · Invasive diagnosis · First-trimester screening

Abstract
Objective: The aim of the study wasto describe the past medical history, sociodemographic, and pregnancy characteristics of women at high risk for aneuploidy and to determine which factors are related to her choice of cell-free DNA (cfDNA) testing instead of invasive diagnostic testing. ***Methods:*** We conducted a prospective descriptive study including pregnant women from the Western Barcelona public health area at high risk for fetal aneuploidy, defined as a trisomy 21 or 18 risk between 1/10 and 1/250 at the combined first-trimester or at the second-trimester biochemical screening. During 1 year (December 2018 to November 2019), these women were asked to fill in a confidential questionnaire about her past medical history, demographic and pregnancy characteristics, and her opinion about termination of the pregnancy after a counseling consultation with a maternal-fetal medicine specialist in which advantages and disadvantages of both testing methods, cfDNA or diagnostic testing, were discussed. Logistic regression analysis was used to determine which factors were related with cfDNA uptake. ***Results:*** During the study period, 82 pregnant women filled the questionnaire. The median maternal age was 39.6 years (interquartile range [IQR] 37.3–40.9 years), and 73 (89%) of them were 35 years or older. Forty-three (52%) women opted for cfDNA testing, while 39 (48%) chose invasive diagnosis. In a logistic regression analysis, the use of assisted reproductive techniques (OR 13.03; 95% CI: 1.47–115.56; $p = 0.021$) and Latin American origin (OR 6.66; 95% CI 1.73–25.66; $p = 0.006$) were shown to be related to a higher cfDNA uptake. In contrast, nonreligious women (OR 0.21; 95% CI: 0.06–0.72; $p = 0.013$) and a favorable opinion about termination of pregnancy (OR 0.23; 95% CI: 0.06–0.92; $p = 0.037$) were related with a lower uptake. ***Conclusion:*** Half of the pregnant women at high risk for fetal aneuploidy opted for cfDNA testing. The main reason to choose cfDNA was avoiding the risk of pregnancy loss. Women using assisted reproductive techniques and those of Latin American origin preferred cfDNA testing, while nonreligious women and those with a favorable opinion on termination pregnancy preferred invasive testing.

Introduction

The first-trimester combined screening has been the gold-standard for aneuploidy screening during the last 2 decades in Europe. According to our experience, it

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achieves a 90% detection rate for trisomy 21 for a 4% false-positive rate [1]. However, cell-free DNA (cfDNA) has been increasingly used as a new advanced aneuploidy screening method since its introduction in clinical practice in 2011 due to its higher accuracy [2–4]. According to a recent meta-analysis, cfDNA testing achieves detection rates as high as 99% for trisomy 21, 96% for trisomy 18, and 91% for trisomy 13, for about 0.1% false-positive rate for each screened trisomy [5].

Due to its high cost, cfDNA testing has not replaced the first-trimester combined test as a primary screening method yet, except for 2 European countries, the Netherlands [6] and Belgium [7]. Hence, the most widely accepted strategy for cfDNA as an aneuploidy screening method is as a secondary screening after a high risk is obtained at the combined test, either establishing excluding cutoffs for invasive testing and cfDNA as in France (1/2 to 1/50 for invasive testing, and 1/251 to 1/1,000 for cfDNA testing) or letting women choose between these 2 methods, like in Denmark and Finland [8, 9]. Women may choose cfDNA because maternal blood draw causes less maternal discomfort as compared to chorionic villi sampling or amniocentesis and avoids the excess risk of fetal loss.

In November 2018, the Catalan Health Service implemented the use of cfDNA testing as an option for high-risk pregnancies (first- or second-trimester risk between 1/10 and 1/250, or a previous pregnancy with a free trisomy 21, 18 or 13) together with invasive diagnostic technique. This study aims to describe the sociodemographic, pregnancy characteristics and past medical history of women at a high risk for aneuploidy in the Western Barcelona public health area and to determine which factors can be related to her choice of cfDNA testing.

Methods

This was a prospective, unicentric, non-randomized, non-blinded, descriptive study, including women at high risk for fetal aneuploidy from the Western Barcelona public health area. The first-trimester combined test is offered to all pregnant women booking before 14 weeks, except when an invasive test is performed due to a parental chromosomal rearrangement or there is a high risk of submicroscopic anomalies or monogenic disorders. Since November 2018, pregnant women in Catalonia were stratified into 3 risk categories: very high risk (between 1/2 and 1/9), high risk (between 1/10 and 1/250), and low risk (less than 1/250).

From December 2018 to November 2019, women considered to be at high risk (between 1/10 and 1/250) for trisomy 21 or 18–13 at the first-trimester combined screening or at the second-trimester maternal serum screening were invited to participate in the study. Women were excluded from the study in case of (a) fetal ultrasound anomalies, (b) increased nuchal translucency above the 99th percentile, (c) familial or past history of aneuploidies, and (d) insufficient knowledge of Spanish or Catalan to fill a questionnaire. According to the Catalan protocol, a microarray should be offered when a fetal anomaly or an increased nuchal translucency is observed at the 11–13-week scan [1]. Women with a previous aneuploid pregnancy were not entitled to opt for cfDNA until June 2019, in the middle of the study period, and for this reason these pregnancies were excluded.

Immediately after the 11–13-week scan, 3 estimated risks (trisomy 21, trisomies 18–13, and preeclampsia) were delivered to women by a midwife. When the aneuploidy risk was high, women were referred to a specialized clinic in which a maternal-fetal medicine specialist discussed the advantages and disadvantages of the available options: (a) cfDNA testing, (b) chorionic villi sampling or amniocentesis, and (c) no further tests. Women were told that cfDNA had the advantage of being safer because it avoids an excess risk of fetal loss and the disadvantage of targeting only 3 trisomies (13, 18, and 21) with a limited accuracy, and that any positive result should be confirmed by an invasive diagnostic testing. On contrary, women were told that chorionic villi sampling or amniocentesis had the disadvantage of carrying a 0.2% risk of fetal loss [10, 11] and the advantage of studying all the chromosomes with a higher accuracy. In the first 4 months of the study (December 18 to March 19), the genetic test performed was a conventional karyotype, while in the last 8 months (April–November 2019), it was replaced by chromosomal microarray analysis [12]. The schedule and turnaround time for both procedures were also detailed to pregnant women. Blood draw for cfDNA testing was available on Monday or Tuesday, and results reported 1 week later. Alternatively, chorionic villi sampling was performed on Wednesdays and Fridays, and the rapid test results (QF-PCR) were delivered after 2 working days, while those of the long-term karyotype or chromosomal microarray analysis were available in 2 or 1 week, respectively. In the second trimester, amniocentesis was offered instead of chorionic villi sampling.

After counseling, women were asked to fill in a confidential questionnaire about sociodemographic and pregnancy characteristics (maternal age, origin, educational level, religion, parity, intended pregnancy, and use of assisted reproductive techniques), past medical history (previous miscarriages), her opinion about termination of the pregnancy, and the reason of her choice. Written informed consent was signed by all the participants.

Pregnancy follow-up was obtained reviewing the medical records. This study was approved by the Hospital Clinic Barcelona's IRB (Reg. HCB/2019/0198). Microsoft Office Access 2007 and Stata statistical software v.15 were used for statistical analyses. Continuous variables were checked with the Shapiro-Wilk test and described by median and interquartile range if they did not follow a normal distribution. Categorical variables were described as number of observations and frequency. Univariate logistic regression analysis was used to explore which factors may affect the uptake of cfDNA testing. A p value of <0.05 was considered significant.

Results

During the study period (December 2018 to November 2019), 83 pregnant women with a risk between 1/10 and 1/250 with no fetal ultrasound anomalies or other

Table 1. Baseline demographics of pregnant women at high risk for fetal aneuploidy included in the study

Maternal age, years	39.6 (37.3–40.9)
Origin	
White European	56 (69)
Latin American	18 (22)
Non-white European, non-Latin American	8 (9.8)
Educational level	
Elementary	6 (7.3)
High school	10 (12)
Technical school	12 (15)
University	54 (66)
Religion	
Catholic	29 (36)
Muslim	2 (2.5)
Not religious	19 (24)
Others	30 (38)
Multiparous	56 (69)
Past history of miscarriages	32 (39)
Intended pregnancy	67 (85)
Use of assisted reproduction techniques	16 (20)
Favorable opinion about termination of pregnancy	67 (82)
Risk over 1 in 100 for T21/T18	23 (28)

Continuous variables are shown as median (interquartile range) and categoric variables as number (*n*) and frequency (%)

risk factors accepted to participate in the study, 78 after the first-trimester combined test, and 5 after second-trimester biochemical screening. There were no women with a sufficient knowledge of Catalan/Spanish languages that declined her participation in the study, although 1 woman preferred not to undergo any further testing. Baseline characteristics of the 82 remaining women are highlighted in Table 1. The median maternal age was 39.6 years (IQR 37.3–40.9 years), and most of them (n = 73; 89%) were 35 years or older.

Forty-three (52%) women opted for cfDNA testing, while 39 (48%) chose an invasive diagnosis, including 37 chorionic villi sampling and 2 amniocenteses. In logistic regression analysis, the use of assisted reproductive techniques (OR 13.03; 95% CI: 1.47–115.56; p = 0.021) and Latin American origin (OR 6.66; 95% CI: 1.73–25.66; p = 0.006) were shown to be a favorable factor for cfDNA uptake, while a significantly lower uptake was observed when women had no religious beliefs (OR 0.21; 95% CI: 0.06–0.72; p = 0.013) and a favorable opinion about termination of pregnancy (OR 0.23; 95% CI: 0.06–0.92; p = 0.037). Although nonsignificant, a trend to a higher cfDNA uptake was observed in women with a past history of miscarriage (OR 2.31; 95% CI: 0.92–5.83), while an estimated risk higher than 1/100 showed a trend to a lower uptake (OR 0.41; 95% CI: 0.08–2.03). Detailed logistic regression analysis is shown in Table 2. No differences were found in cfDNA uptake rate between the first 4 months of the study when the alternative genetic test offered was a conventional karyotype, and the last 8 months of the study when karyotype was replaced by chromosomal microarray analysis (46 vs. 54%, p value 0.482). The main reason (69.7%; 30/43) raised by women in favor of the cfDNA choice was pregnancy safety and avoidance of the fetal loss risk associated to invasive procedures, whereas a higher accuracy was claimed by most (69.2%; 27/39) of the women who opted for invasive testing.

A single woman changed up her mind and underwent a different type of testing to that chosen at the time of filling the questionnaire. She finally opted for invasive testing rather than her initial preference, cfDNA, because it is diagnostic. No miscarriages occurred in the cfDNA group, nor in the invasive testing group. Among women who chose cfDNA testing, there was one no-call, with a subsequent chorionic villi sampling revealing a normal female karyotype, and 1 case of high risk for trisomy 21 (2.3%) that was confirmed by subsequent invasive testing. Among the woman who preferred invasive testing, 1 trisomy 21, and 2 mosaic aneuploidies were revealed by the long-term culture of chorionic villi (mos 47,XX,+21[20]/46,XX[20] and mos 45,X[7]/46,XX[33]), both confirmed in amniotic fluid. An additional mos 47,XY,+18[2]/46,XY[14] was found to be confined to the trophoblast. The 3 women carrying trisomy 21 fetuses opted for termination of pregnancy, and the one with the monosomy X mosaicism decided to continue the pregnancy. At pregnancy follow-up, 63 delivered neonates were apparently chromosomally normal with a mean neonatal weight of 3,208 g. Adverse neonatal outcome defined as an Apgar score below 7 points or admission to neonatal intensive care unit occurred only in 2 cases.

Discussion

Among pregnant women of the Western Barcelona public health area of the city of Barcelona at high risk for aneuploidy, defined as an estimated T21 or T18-13 risk between 1/10 and 1/250, half (52%) of them chose cfDNA testing when both cfDNA and invasive testing were offered. The most relevant factors found to be related with cfDNA uptake were linked to the type of conception (by assisted reproduction techniques), to the woman's religious and ideological profile (having religious beliefs and

Table 2. Determinants for cfDNA uptake

	DNA uptake, % (*n*)	Odds ratio (95% CI)	*p* value
Maternal age	–	0.94 (0.72–1.21)	0.613
Origin			
White European	43 (24)	Reference	–
Latin American	83 (15)	6.66 (1.73–25.66)	0.006*
Non-white European, non-Latin American	33 (6)	1 (0.20–4.89)	0.999
Educational level			
Elementary	60 (3)	Reference	–
High school	50 (5)	0.73 (0.005–104.16)	0.91
Technique school	50 (6)	0.093 (0.001–7.99)	0.296
University	52 (28)	0.32 (0.05–18.81)	0.585
Religion			
Catholic	62 (20)	Reference	–
Muslim	0 (0)	–	–
Not religious	32 (6)	0.21 (0.06–0.72)	0.013*
Others	50 (15)	0.45 (0.16–1.30)	0.141
Multiparous	51 (28)	2.14 (0.34–13.76)	0.420
Past history of miscarriages	65 (20)	2.31 (0.92–5.83)	0.075
Intended pregnancy	53 (35)	1.28 (0.15–11.2)	0.822
Use of assisted reproduction techniques	75 (12)	13.03 (1.47–115.56)	0.021*
Favorable opinion about termination of pregnancy	46 (31)	0.23 (0.06–0.92)	0.037*
Risk over 1/100 for T21/T18	35 (8)	0.41 (0.08–2.03)	0.274
Total	52 (43)		

cfDNA, cell-free DNA.

being favorable to termination) and to specific origin (Latin American origin). Furthermore, a trend to an increased cfDNA uptake was observed in women with a previous miscarriage and having an estimated risk below 1/100.

A similar Danish prospective study reported that when pregnant women with a first-trimester high risk (>1/300) for trisomy 21 were entitled to choose between diagnostic or cfDNA testing, 75% of them chose an invasive test with microarray, 24% chose cfDNA testing, and 0.4% chose no further testing [11]. A high level of decisional conflict, experienced by 13% of women, was found to be associated with 3 factors: choosing cfDNA testing, receiving genetic counseling the same day, and with low satisfaction with the genetic counseling. Similar results were obtained in a retrospective study performed in Hong Kong Chinese women with a high-risk (≥1:250) result at first-trimester or second-trimester screening [12]. Sixty-seven percent of women elected to undergo a diagnostic test, 29% cfDNA testing, and 4.4% declined further testing. Nulliparous women, either with a spontaneous or assisted reproduction pregnancy, and women with a lower adjusted risk were more likely to choose cfDNA testing.

In another Nordic country, Finland, a retrospective study showed opposite results because 78% of pregnant women at high risk for trisomy 21 initially chose cfDNA testing, 19% chose chorionic villi sampling, and 3.3% chose amniocentesis differences on women's choice were observed among these 3 groups concerning gestational age (more advanced gestation higher amniocentesis uptake), and the counseling day (higher cfDNA uptake on the days that maternal blood could be drawn) [13]. A plausible explanation for discrepant preferences between the 2 Nordic countries is the differences in the genetic spectrum studied by invasive tests, targeted (QF-PCR) in Finland, and genomewide (chromosomal microarray analysis) in Denmark. In our study, cfDNA was restricted to 3 trisomies, while chromosomal microarray analysis or a karyotype was performed in invasive testing. It appears that the main advantage of invasive testing is a wider spectrum of anomalies to be studied, and when the spectrum is the same for both methods, cfDNA would be largely preferred by pregnant women. Unexpectantly, in our study, cfDNA uptake did not change when we offered microarray analysis instead of conventional karyotyping at invasive testing,

meaning that our population did not differentiate including or excluding submicroscopic anomalies when you offer to extend the study from 3 to all chromosomes.

In France, 2,436 consecutive women at high risk of trisomy 21 (≥1/250) were asked to answer a questionnaire before being randomized in 57 prenatal diagnosis centers: 21% expressed preference toward invasive testing with conventional karyotyping, whereas 76% favored cfDNA testing with almost certain but limited information. Factors likely associated with attitudes driven by aversion to fetal loss risk were mostly maternal age (OR 1.03) and religious beliefs (OR 1.62), whereas increased fetal nuchal translucency measurement was associated with attitudes driven by aversion to diagnostic ambiguity (OR 1.67) [14]. Aversion to fetal loss risk can now be reconsidered according to a recent meta-analysis in which the procedure-related risk of miscarriage following chorionic villus sampling and amniocentesis appears to be almost negligible, particularly when control and intervention groups have similar background-risk for aneuploidies [9].

Balanced choices for cfDNA versus invasive testing, as in our study, were observed by the Nicolaides group in the UK in a higher risk spectrum group 1/100 or greater, instead of 1/10–1/250 used in ours. In that study, 57% of women opted for cfDNA testing, 40% opted for chorionic villi sampling, and 2.7% did not want any further investigation. Predictor for cfDNA testing was being of Afro-Caribbean racial origin, while predictors for chorionic villi sampling were increasing fetal nuchal translucency and increasing risk for trisomies [15].

The link observed in our study between cfDNA uptake and being less likely to terminate or would have doubts, compared with those women who preferred invasive testing has been previously demonstrated in several studies [16, 17]. It appears that in countries with low screening uptake, women not considering termination are accepting cfDNA testing for "information only." We wonder whether the turnaround time differences between tests may have an influence in the studies, because we can speculate that women may opt for the fastest option, particularly if termination of pregnancy is an option for them.

As far as we know, this is the first study conducted in the public healthcare system in a Southern European country. Interestingly enough, in an international study where women from the general pregnant population from 9 countries were asked what they would directly choose between having cfDNA or invasive testing or no test, the only countries in which more women chose invasive testing than cfDNA were those in the south of Europe, Italy (52%), and Portugal (59%), countries that in the mid 90' had a high (about 40%) amniocentesis rate [18]. Regarding Spain, which did not participate in this study, we are aware of a single reported study conducted in a private clinic showing that 24% of pregnant women had cfDNA testing and 8.2% had an invasive test. The uptake of cfDNA increased with the risk for trisomies, maternal age, and being nulliparous. The uptake of invasive test increased also with the risk for trisomies and nuchal translucency thickness [19].

Nevertheless, our study has some inescapable drawbacks. The main limitation is that the vast majority of the Pakistani and Chinese pregnant women were excluded from the study because they do not understand Spanish or Catalan, and this could lead to a selection bias. On the other hand, the main strength of our study is that this is a prospective study in which pregnant women with a high risk for aneuploidies were offered either cfDNA or invasive testing free of charge in the setting of the public health system. Therefore, the choice between these options was not be influenced by monetary issues. In addition, women in the study made real pregnancy choices, which could vary from hypothetical questionnaire opinions or beliefs.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study was approved by the Hospital Clinic Barcelona's IRB (Reg. HCB/2019/0198). Written informed consent was signed by all the participants. We have attached an English version of the questionnaire as online suppl. material (for all online suppl. material, see www.karger.com/doi/10.1159/000509796).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Leticia Benitez: manuscript writing, data recording and processing, text revision, and questionnaire writing and translating. Montse Pauta: manuscript writing and revision. Isabel Matas: data recording. Irene Madrigal: cytogenetic and cfDNA studies. Antoni Borrell: pregnant women enrollment, obtaining informed consent, manuscript writing, and revision.

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