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Rare chromosomal abnormalities: Can they be identified using conventional first trimester combined screening methods?

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ABSTRACT

Objective: To evaluate the performance of first trimester combined screening for the detection of rare chromosomal abnormalities, other than Trisomies 21, 18 or 13 or 45 ×.

Study design: A database containing 36,254 pregnancies was analyzed. These patients were recruited at 15 US centers and included singleton pregnancies from 10 3/7–13 6/7 weeks. All patients had a nuchal translucency (NT) scan and those without a cystic hygroma (N = 36,120) underwent a combined first trimester screening test ('FTS' - NT, PAPP-A and fbHCG). A risk cut-off of 1:300, which was used for defining high risk for Trisomy 21, was also used to evaluate the detection rate for rare chromosomal abnormalities using the combined FTS test.

Results: 36,120 patients underwent combined FTS. Of these, 123 were found to have one of the following chromosomal abnormalities: Trisomy 21, Trisomy 18, Trisomy 13 or Turner syndrome. This study focuses on 40 additional patients who were found to have 'other' rare chromosomal abnormalities such as triploidy, structural chromosomal abnormalities, sex chromosome abnormalities or unusual chromosomal abnormalities (e.g. 47XX + 16), giving an incidence of 1.1 in 1000 for these rare chromosomal abnormalities. Of these 40 pregnancies, only 2 (5%) had an NT measurement of ≥3 mm. The detection rate for combined FTS, using a risk cut-off of ≥1:300, was 35 % (14 of 40 cases). Therefore, 65 % of cases of rarer fetal chromosomal abnormalities had a 'normal' combined FTS risk (<1:300) and 95 % had a 'normal' NT (<3 mm).

Conclusion: Traditional FTS methods are unable to identify the vast majority of rare chromosomal abnormalities. Our data do not support the potential detection of rare fetal chromosomal abnormalities as a reason to favour nuchal translucency-based first trimester screening over NIPT.

Introduction

Combined first trimester screening (FTS), which is the measurement of nuchal translucency from ultrasound examination combined with maternal age and serum makers (pregnancy associated plasma protein A (PAPP-A) and free B-hCG) has been widely available and validated since the early 1990s to assess the risk of a pregnancy with Down syndrome (Trisomy 21), Edwards syndrome (Trisomy 18) and Patau syndrome (Trisomy 13). More recently, non-invasive prenatal testing (NIPT) is being used more frequently to assess this risk. Little is known, however, about the relative performance of conventional FTS versus NIPT when it comes to screening for rare fetal chromosomal abnormalities in a general unselected obstetric patient population. These rare chromosomal abnormalities affect approximately one in 1000 pregnancies (0.1 %), and include triploidy, structural chromosomal abnormalities, sex chromosomal abnormalities and other rarer autosomal aneuploidies. It has been claimed that a reason to favor FTS over NIPT for general population screening is the potential ability of FTS to detect other rarer chromosomal abnormalities, other than Trisomies 21, 18 and 13. The aim of this study was to evaluate the performance of first trimester combined screening in the detection of these rare chromosomal abnormalities as well as describing the outcomes of these pregnancies.

Materials and methods

A database (The FASTER Trial) containing 36,254 pregnancies was analyzed. All of these patients had been recruited at 15 US centers from October 1999 to December 2002. Written informed consent had been obtained from all participants in the study.

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Inclusion criteria for the FASTER Trial were maternal age of greater than 16 years, a singleton pregnancy with a gestational age ranging from 10 weeks and 3 days to 13 weeks and 6 days. Patients with a septated cystic hygroma found on ultrasound examination were excluded.

All patients had a nuchal translucency (NT) ultrasound assessment and maternal serum testing for PAPP-A and fbHCG (N = 36,120) to provide a combined risk assessment for Trisomy 21. Ultrasonography was performed by specially trained sonographers using a standard validated protocol. Serum sample results were converted into multiples of the median which were adjusted for maternal weight, gestational age, diabetic status and race. The average of three NT measurements was used. For the purposes of this secondary analysis to evaluate the performance of FTS for screening for rare chromosomal abnormalities, an NT value of $\geq$3 mm, or a Trisomy 21 risk of greater than 1:300, were considered abnormal.

Chromosomal outcome information was obtained by invasive prenatal testing such as chorionic villus sampling (CVS) or amniocentesis, or alternatively by umbilical cord blood or fetal tissue in the case of termination of pregnancy/spontaneous pregnancy loss. All liveborn infants had detailed pediatric physical examination performed and all obstetric and pediatric medical records were reviewed by trained research personnel to maximize accuracy of outcome ascertainment.

Results

In the FASTER Trial, a total of 36,120 patients underwent combined first trimester screening. Of these, 123 were found to have one of the following "common" chromosomal abnormalities: Trisomy 21, Trisomy 18, Trisomy 13 or Turner syndrome.

In addition, 40 patients were found to have 'other' rare chromosomal abnormalities such as triploidy, structural chromosomal abnormalities, sex chromosome abnormalities (other than Turner syndrome) or unusual chromosomal abnormalities (e.g. 47XX + 16), giving an incidence of 1.1 in 1000 for these rare chromosomal abnormalities. Of these 40 pregnancies with other rare chromosomal abnormalities, 2 (5 %) had an NT measurement of $\geq$3 mm. The detection rate of combined FTS, using a risk cut-off of $\geq$1:300, was 35 % (14 of 40 cases) for rare chromosomal abnormalities. The remaining 26 (65 %) cases of rare fetal chromosomal abnormalities had a 'normal' or unremarkable combined FTS risk (<1:300). Additionally, 38 of these 40 (95 %) pregnancies had a 'normal' or unremarkable NT (<3 mm).

Pregnancy outcomes were also analysed for these rare chromosomal abnormalities. Of the 40 pregnancies with these rare chromosomal abnormalities, 9 (23 %) experienced a fetal loss before 24 weeks' gestation, 6 (15 %) underwent termination of pregnancy, 10 (25 %) were born with normal phenotypical features/no neonatal abnormalities noted, 9 (23 %) were liveborn with abnormal phenotypical features (of which 2 (5 %) were neonatal deaths), and 6 (15 %) were liveborn but had no additional pediatric outcome information recorded (Table 1).

Discussion

The incidence of rare fetal chromosomal abnormality is very low in a general, unselected obstetric population (approximately 1.1 in 1000). Combined first trimester screening has been the mainstay for the detection of common chromosomal abnormalities since the early 1990s. The accuracy of these methods for detecting common chromosomal abnormalities has been well established [1,2]. The detection rate for the common chromosomal abnormalities using combined FTS is 77 % for Down Syndrome [3] and 78 % overall for Trisomy 1318 and Turner Syndrome with a false positive rate of approximately 5% [4]. Our study has shown that traditional first trimester screening methods are unable to identify the majority of these rare chromosomal abnormalities. First trimester NT measurement on its own has been shown to identify 79 % of Trisomy 21 pregnancies, however, our latest study demonstrates that it is a very poor stand-alone screening test for rare chromosomal abnormalities with a detection rate of only 5%. The first trimester combined screening test, using a combination of NT measurement and the serum markers PAPP-A and fbHCG, is better, but also has poor performance for detecting these rare chromosomal abnormalities, with only 35 % being detected.

It is also important to note that the overall pregnancy outcomes of these rare chromosomal abnormalities are poor, with 70 % of known outcomes resulting in either fetal loss, termination, neonatal death or neonatal abnormality *(*Table 1*)*. This further underscores the point that potential performance in screening for rare chromosomal abnormalities is not a reason to justify preference for NT-based screening over NIPT.

It has been suggested that potential detection of rare chromosomal abnormalities justifies the continued use of traditional NT-based first trimester screening [5].

Given the superior sensitivity, as well as negative and positive predictive values, of NIPT for common chromosomal abnormalities, our data suggest that a paradigm shift to NIPT as primary screening methodology should result in overall higher detection rates for aneuploidy with a significant reduction in false positive results. These predicted detection rates utilizing NIPT are shown in Table 2. The Society for Maternal-Fetal Medicine (SMFM) and the American College of Obstetricians and Gynecologists [6] recommend that all women should be offered the option of either prenatal screening or diagnostic testing for fetal genetic disorders. Our data would suggest that relying upon traditional first trimester NT-based combined screening to detect rare chromosomal abnormalities would not be appropriate. The strengths of our study are that we analyzed a large unselected obstetric population encompassing several geographical locations, maximizing the applicability of our study to the general population. We also maximized outcomes ascertainment because genetic material was available for chromosomal analysis, thereby allowing us to correlate findings from first trimester screening with the clinical outcome. Pediatric follow-up was also utilized ascertain phenotypic impact of the chromosomal abnormality.

Limitations of our study are that some children with sex chromosomal abnormalities will be initially phenotypically

Table 1
Pregnancy outcomes for 'rare' chromosomal abnormalities.

	Triploidy N = 5	Sex chromosome N = 5	Other rare N = 30	Total 'rare' N = 40
Fetal loss before 24 weeks (miscarriage)	4	0	5	9 (23 %)
Termination of pregnancy	0	0	6	6 (15 %)
Live birth normal phenotype	0	3	7	10 (25 %)
Live birth abnormal phenotype	1	1	7	9 (23 %)
Live birth unknown pediatric Outcome	0	1	5	6 (15 %)
Neonatal death	0	0	2	2 (5%)

Table 2
: Detection rates for fetal chromosomal abnormalities using nuchal translucency (NT), combined FTS and NIPT.

	Trisomy 21 N = 92	Trisomy 18 N = 15	Trisomy 13 N=9	45,X N = 7	**Total "common" N = 123**	Triploidy N = 5	Sex Chromosome N = 5	Other Rare N = 30	**Total "Rare" N = 40**	**Total Abnormal N = 163**
NT $\geq$ 3 mm only	16	4	1	0	**21/123** (17 %)	0	0	2	**2/40 (5%)**	**23/163** (14 %)
Combined FTS $\geq$ 1:300	75	10	4	3	**92/123** (75 %)	2	1	11	**14/40** (35 %)	**105/163** (64 %)
Not Detected by NT/FTS	17	5	5	4	**31/123** (25 %)	3	4	19	**26/40** (65 %)	**57/163** (35 %)
Total Detected NT/FTS	75	11	4	3	**92/123** (74 %)	2	1	11	**14/40** (35 %)	**106/163** (65 %)
SNP NIPT *Predicted Performance	91	14	8	4	**117/123** (94 %)	3	2	0	**5/40** (13 %)	**122/163** (75 %)
Non-SNP NIPT **Predicted Performance	91	14	8	4	**117/123** (95 %)	0	0	0	**0/40 (0%)**	**117/163** (71 %)

* Based on a predicted performance of a SNP-based NIPT test, assuming T21 sensitivity of 99 %, T18 of 96 %, T13 of 90 %, Turner syndrome 90 %, triploidy 60 %, and sex chromosome abnormalities other than 45,X 40 %.
** Based on a predicted performance of a non-SNP-based NIPT test assuming T21 sensitivity of 99 %, T18 of 96 %, T13 of 90 % and Turner syndrome 90 %.

normal and may not manifest issues requiring medical investigation until later in life [7]. Therefore there may be an underestimation of the phenotypic impact of some of the rare chromosomal abnormalities. Overall, our study has shown that FTS is a poor screening test for rare chromosomal abnormalities and therefore it is not appropriate to claim this as a potential benefit of FTS compared with NIPT for increasing the overall detection rate of chromosomal abnormalities.

Statement of ethics

Written informed consent was obtained from all participating patients and the study had been given ethical approval.

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Author contributions

DK., FM. And MD contributed to the design and implementation of the research, and to the writing of the manuscript.

DK analaysed the results.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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