Original Article

First trimester screening in pregnancies with intermediate risk for fetal chromosomal abnormalities

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ABSTRACT

The first or second trimester are used to determine whether a pregnant woman's baby has an increased risk of having chromosomal abnormality. The aim of this study was to ensure necessary reassessment of pregnant women at intermediate risk to adjust their risk to high or low risk. 137 singleton pregnant women at 11-13(+6) weeks' gestational and intermediate-risk (risk of between 1:100 and 1:1000) detected in the first trimester screening using nuchal translucency (NT), β-hcG and PAPP-A protocol. Then, they were subdivided into a high-intermediate-risk group (risk score between 1:101 and 1:250) and a low-intermediate group (between 1:251 and 1:1000). All measurements performed by experienced gynecologist. Amniocentesis was offered to all women of our study. All cases were followed for chromosomally abnormal outcome until delivery. Of 137 cases at intermediate risk, 97 (70.8%) were under 35-year-old. The mean score of age was 32.12 ± 5.5. Only 21 (15%) accepted to undergo amniocentesis. Of 21 (15%) cases, 14 (66%) had low-intermediate risk. Ultimately, one case of Klinefelter syndrome and one case of Turner were detected among all patients who underwent amniocentesis. Both cases were in low-intermediate risk group. In addition, we followed-up those who did not undergo amniocentesis until delivery; they had not any chromosomal abnormality. Regardless of age, women at intermediate risk need further examination to adjust their risk to high or low risk for chromosomal abnormalities.

Keywords: First trimester screening, Nuchal translucency, Free-human chorionic gonadotropin, Pregnancy-associated plasma protein-A, Chromosomal abnormality

Introduction

Genetic disorders are one of the prevalent diseases initiated in the prenatal period. The incidence of structural defects varies between 2-3% in infants. The prevalence of pregnancies at an intermediate risk for chromosomal abnormalities (risk of 1:101 to 1:1000) is 16%. The first or second trimester are used to determine whether a pregnant woman's baby has an increased risk of having chromosomal abnormality (1). There is robust evidence that effective screening for main chromosomal abnormalities can be provided in the first trimester of gestation (2). First trimester screening is performed between 11 and 14 weeks of pregnancy to predict any probable chromosomal abnormalities. Serum markers including β-hCG (beta-human chorionic gonadotropin) and PAPP-A (pregnancy-associated plasma protein-A), along with ultrasonography (nuchal translucency (NT) thickness, ductus venosus Doppler flow) findings are used for the first trimester screening (3, 4). For enhancing the effectiveness of first-trimester screening, a risk-orientated two-stage approach is used. In this, the patients are subdivided into a high-risk group, requiring invasive intervention, a low-risk group, in which an abnormality is unlikely, and an intermediate-risk group (risk of 1 in 101 to 1 in 1000), in which further assessment is performed by first-trimester ultrasound examinations (fetal nuchal translucency thickness, presence/ absence of the nasal bone or presence/absence of tricuspid regurgitation or normal/ abnormal Doppler velocity waveform in the ductus venosus), and invasive intervention is performed if their adjusted risk becomes 1:100 or more (2, 5-7).

In trisomy 21 pregnancies, the maternal serum concentration of free β--hCG is higher than in chromosomally normal pregnancies, while PAPP-A is lower (about 2 MoM and about

0.5 MoM, respectively). Although, in trisomy 21, the divergence from normal in free β--hCG is higher and in PAPP-A is lower with advancing gestation, and these temporal changes with gestation should be taken into account in the calculation of risk. There is no significant association between fetal NT and maternal serum free β--hCG or PAPP-A in either trisomy 21 or chromosomally normal fetuses, and hence the ultrasound exams and biochemical markers can be combined to provide more effective screening than either method individually (8, 9, 2).

In addition to trisomy 21, other chromosomal abnormalities can be detected by the first trimester screening. In a study conducted by Nicolaides *et al.*, reported that the sensitivity of screening approximately is 90% for trisomies ***13*** and ***18*** (with a false-positive rate of 1%) (2). Therefore, the screening test may fail to detect some of fetal structural abnormalities. In addition, there is high relationship between the increased NT thickness and heart abnormalities (10). For these reasons, the American College of Obstetricians and Gynecologists (11) has recommended that in the presence of normal fetal karyotype and the NT >=3.5 mm, evaluation using ultrasonography or echocardiography or both should be performed (3, 11).

Combined method (nuchal translucency with serum markers) in the first trimester has high detection rate and low false positive rate of abnormal karyotype at 11-13(+6) weeks of pregnancy (12, 13).

The aim of this study was to ensure necessary reassessment of pregnant women at intermediate risk to adjust their risk to high or low risk.

Materials and Methods

Study design and population

A prospective study included 137 singleton pregnant women who are at intermediate risk for chromosomal abnormalities from April 2011 to September 2013. Screening was performed based on the wishes of women. All examinations performed by experienced gynecologist. Amniocentesis was offered to all women of our study. All subjects were followed-up until delivery to observe the presence of any chromosomal abnormality.

Assessment of risk for chromosomal abnormalities

The risk scores were estimated based on results of NT, β-HCG, and PAPP-A tests which performed in order to first trimester screening between 11 and 13+6 weeks of gestation. We applied the FMF UK program to our samples for calculating the risk of chromosomally abnormal outcome comprises the following parameters: maternal age, crown-rump length (CRL), nuchal translucency (NT), as well as the maternal serum markers PAPP-A and free beta-hCG. MOM values were used for sonographic fetal nuchal translucency and biochemical markers PAPP-A and free beta-hCG. Then, subjects of the study were subdivided into a high-intermediate risk group (risk of 1:101 to 1:250) and a low-intermediate risk group (risk of 1:251 to 1:1000).

Measurement of Fetal NT

All participants were examined by one skilled gynecologist sonographer. The minimum fetal crump-rump length was 45mm and the maximum was 84 mm. The lower limit was chosen to prevent missing of major fetal abnormalities, and the upper limit was used to provide women with affected fetus the option of an earlier and safer form of termination. Fetal NT was measured with the maximum usable magnification and transabdominal sonography by Accuvix V20 Prestige ultrasound imaging system (Samsung Medison Co., Ltd., Korea). Only the fetal head and thorax were included in the image. The maximum thickness of the subcutaneous translucency between the skin and the soft tissue overlying the cervical spine was measured. During the scan at least three measurements were taken and the maximum value was used for risk assessment.

Measurement of PAPP-A and free beta-hCG

Blood samples were collected. Specimen containers were labeled with patient's name. Cool packs (4 to 8°C) with overnight shipment were used for specimens' transportation to laboratory. Samples will be unacceptable if gestational age was out of range, insufficient quantity. Free beta-hCG and PAPP-A were determined from serum (B·R·A·H·M·S Kryptor Immunoassay, Germany).

Inclusion criteria

Women were included if they have singleton pregnancies and at intermediate risk for chromosomal abnormalities (risk of 1:100 to 1:1000).

Exclusion criteria

Women were excluded if they have twins or multiple pregnancies.

Ethical consideration

Participants' informed consent was gained; voluntary participation and confidentiality were guaranteed. The study was approved by the Ethics Committee of the department of Obstetrics and Gynecology (Ahvaz Jundishapur University of Medical Sciences).

All participants fully completed the study (we had not any missing data).

Sample size calculation

Sample size estimation was determined based on information from previous study (14) to achieve prevalence of chromosomal abnormalities in women at intermediate-risk. They found that 10.1% had an intermediate risk. Accordingly, we considered P = 0.101 for sample size estimation. A sample size of 140 subjects was calculated using following formula to have power of 90%.

The criterion for significance (alpha) was set at 0.05, 2-tailed, so that an effect in either direction will be interpreted.

$$n = (Z^2_{1-\frac{\alpha}{2}} * pq)/\mathrm{d}^2 \quad (1)$$

Statistical analysis

The analysis was carried out with SPSS version 17 software program (IBM Co., USA). Continuous variables were described with mean ± standard deviation, and qualitative variables were expressed as percentage value. Significance level (P-Value) of 0.05 was deemed to indicate the statistically significant difference for all tests.

Results and Discussion

137 singleton pregnant women were detected at intermediate risk for chromosomal defects by first trimester screening (NT and β-hCG and PAPP-A tests). **Table 1** shows mean score of maternal age for different group of these subjects. The mean score of maternal age had not statistically significant difference between low- and high-intermediate risk groups (P value = 0.2). 97 (70.8%) cases were less than 35 years; and 40 (29.2%) cases over 35 years. Of 137, 22 (16.1%) cases were at high intermediate risk and 115 (84.9%) cases were at a low intermediate risk Amniocentesis was offered to all women of our study from those 21 (15%) underwent elective amniocentesis. From these 21 cases, 7 (33%) were in high intermediate risk group, and 14 (66%) cases were in low intermediate risk group.

1) After tracking the cytological results, two cases (1.4%) of those who underwent amniocentesis had chromosomal abnormalities. Ultimately, one case of Klinefelter syndrome and one case of Turner were detected among all patients who underwent amniocentesis**.** Both cases were in low-intermediate risk group (risk of 1:251 to 1:1000). In addition, we followed-up those who did not undergo amniocentesis until delivery; they had not any chromosomal abnormality. **Table 2** summarizes characteristics information of these two patients who were at low intermediate risk.

Table 1. Average age women with moderate risk for chromosomal abnormalities

Parameters	Value
Age of patients (Mean ± SD)	32.12 ± 5.5
Age <= 35 years (Mean ± SD)	29.38 ± 3.8
Age >35 years (Mean ± SD)	38.78 ± 2.11
Age of low-intermediate risk (Mean ± SD)	32.35 ± 5.3
Age of high-intermediate risk (Mean ± SD)	30.74 ± 6.1
NT of all patients (min-median-max)	1.2-1.9- 4.4
Normal pregnancy outcome (n)	135
Abnormal pregnancy outcomes	2

Table 2. Details of chromosomal abnormalities in two patients with moderate risk

Parameters	The patient with Klinefelter syndrome	The patient with Turner
Age (years)	27	25
NT(mm)	1.6	1.8
β-hCG(MoM)	0.129	2.094
PAPP-A(MoM)	0.297	0.624
Estimated-risk	1:736	1:482
Karyotype	47XXY	45 X

The first or second trimester are used to determine whether a pregnant woman's baby has an increased risk of having chromosomal abnormality. In contrast to high-risk population, women at an intermediate-risk for chromosomal abnormalities do not undergo diagnostic procedures at the first trimester for decision making about miscarriage. In Iran, women at intermediate risk do not receive further examinations for second trimester screening using maternal serum biomarkers for decision making about miscarriage. It will definitely impact the moral issue if parents decide to abort the older fetus due to genetic disorders, as it is less stressful for the parents, the fetus and the community in general if they decide in the first trimester. The main finding of this study was that two cases of chromosomal abnormalities (Turner, 47X, and Klinefelter syndrome, 47XXY) were detected among women at intermediate-risk in the first trimester screening using combined method (biomedical markers and nuchal translucency thickness). This proves early intervention for diagnosing the chromosomal abnormalities as well as further sonographic examination in these subgroup pregnant women in the first trimester.

In our study, the prevalence of chromosomal abnormality in the women at intermediate risk was 2 in 137. Other 135 cases had eventually a normal outcome of pregnancy. The relevance of this observation is that it raises the question whether the first trimester diagnostic intervention is truly necessary for detecting chromosomal anomalies.

Patients in the intermediate risk group estimated by combined screening (NT, PAPP-A, and β-hCG) necessarily need reassessment by more detailed sonographic examination of the fetus at 11-13(+6) weeks of gestation (2). In agreement with previous research this study also shows necessary further sonographic examination to adjust risk of intermediate to high- or low-risk.

In terms of time, it is affordable to detect any chromosomal abnormalities in women at an intermediate risk using amniocentesis. It is due to decision about miscarriage which can be determined until 14th week of gestation; thus any decision can be made on time for the termination of pregnancy. The small number of cases at intermediate-risk for chromosomal abnormalities in our study does not allow us to draw safe conclusion. However, such screening strategy is effective in clinical practice for the Iranian ethnic population.

Conclusion

Women at intermediate risk need further examination to adjust their risk to high or low risk for chromosomal abnormalities.

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Conflict of interest: The authors of this study declare that they do not have any conflict of interest.

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Ethics statement: This study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ref No: FIRC-9203).

References

1. Bonacquisto L. Antenatal screening - the first and second trimester. Aust Fam Physician. 2011;40(10):785-7.
2. Nicolaides KH. First-trimester screening for chromosomal abnormalities. Semin Perinatol. 2005;29(4):190-4. doi: 10.1053/j.semperi.2005.06.001
3. Huang T, Hoffman B, Meschino W, Kingdom J, Okun N. Prediction of adverse pregnancy outcomes by combinations of first and second trimester biochemistry markers used in the routine prenatal screening of Down syndrome. Prenat Diagn. 2010;30(5):471-7. doi: 10.1002/pd.2505
4. Florjański J, Fuchs T, Zimmer M, Homola W, Pomorski M, Blok D. The role of ductus venosus Doppler flow in the diagnosis of chromosomal abnormalities during the first trimester of pregnancy. Adv Clin Exp Med. 2013;22(3):395-401.
5. Kagan KO, Staboulidou I, Cruz J, Wright D, Nicolaides KH. Two-stage first-trimester screening for trisomy 21 by ultrasound assessment and biochemical testing. Ultrasound Obstet Gynecol. 2010;36(5):542-7. doi: 10.1002/uog.7663
6. Maiz N, Valencia C, Kagan KO, Wright D, Nicolaides KH. Ductus venosus Doppler in screening for trisomies 21, 18 and 13 and Turner syndrome at 11-13 weeks of gestation. Ultrasound Obstet Gynecol. 2009;33(5):512-7. doi: 10.1002/uog.6330
7. Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. Lancet. 1998;352(9125):343-6. doi: 10.1016/s0140-6736(97)11280-6
8. Haddow JE, Palomaki GE, Knight GJ, Williams J, Miller WA, Johnson A. Screening of maternal serum for fetal Down's syndrome in the first trimester. N Engl J Med. 1998;338(14):955-61. doi: 10.1056/NEJM199804023381404
9. Malone FD, Canick JA, Ball RH, Nyberg DA, Comstock CH, Bukowski R,et al. First- and Second-Trimester Evaluation of Risk (FASTER) Research Consortium. First-trimester or second-trimester screening, or both, for Down's syndrome. N Engl J Med. 2005;353(19):2001-11. doi: 10.1056/NEJMoa043693
10. Simpson LL, Malone FD, Bianchi DW, Ball RH, Nyberg DA, Comstock CH, et al. Nuchal translucency and the risk of congenital heart disease. Obstet Gynecol. 2007;109(2 Pt 1):376-83. doi: 10.1097/01.AOG.0000250473.99575.72
11. American College of Obstetricians and Gynecologists (ACOG). Screening for fetal chromosomal abnormalities: ACOG practice bulletin, Number 77. Washington (DC); 2011. 11 p. Retrieved from: www.guideline.gov/content.aspx?id=10921
12. Chen X, Chang Y, Cui HY, Ren CC, Yu BY. [Study on several ultrasound markers combined maternal serum biochemical markers to screen fetal chromosomal aneuploidy at 11 to 13(+)6 weeks of gestation]. Zhonghua Fu Chan Ke Za Zhi. 2013;48(11):815-8.
13. Yang Y, Zhang Y. [Ultrasound soft markers and fetal cardiac structural assessment at 11-14 weeks]. Zhonghua Fu Chan Ke Za Zhi. 2014;49(3):188-92.
14. Muñoz-Cortes M, Arigita M, Falguera G, Seres A, Guix D, Baldrich E, Acera A, Torrent A, Rodriguez-Veret A, Lopez-Quesada E, Garcia-Moreno R, Gonce A, Borobio V, Borrell A. Contingent screening for Down syndrome completed in the first trimester: a multicenter study. Ultrasound Obstet Gynecol. 2012;39(4):396-400. doi: 10.1002/uog.9075