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Determining the role of mother race in neonatal outcome of trisomies 21, 18 and 13 using cell free DNA analysis

Najmie Saadati[1], Razieh Mohammad Jaafari[2*], Mojgan Barati[2], Maria Cheraghi[3], Gholamreza Shariati[4] and Maedeh Sohani[5]

[1]Associated professor of Obstetrics and Gynaecology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran and Fellowship perinatology ward , Maternal-fetal medicine research center, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Associated professor of Obstetrics and Gynaecology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Maternal-fetal Medicine Research Center , Ahvaz, Iran
[3]Associated professor of Social Determinant of Health, Research Center, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[4]Assistant professor of Medical Genetic , School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran and director of Narges Pathobiology and Genetic lab
[5]Resident of Obstetrics and Gynaecology, School of Medicine, Fertility Infertility and Perinatology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
**Corresponding email:Rmj417072@gmail.com*

ABSTRACT

To determine the role of mother race in neonatal outcome of trisomies 21, 18 and 13 using cell free DNA (cf-DNA) analysis. All women administered for a sonographic imaging at their 10-22 weeks' gestation which were qualified for cf-DNA testing were suggested for increasing aneuploidy risk, between March 1, 2015 to March 30 , 2016. The cf-DNA analysis was conducted after women received genetic counseling in a specialty laboratory. The results were validated by amniocentesis. A total of 1992 women were screened using cf-DNA analysis. The participants were 1631 Non Arabs (Fars, Kurd, and Lor) and 361 Arabs. The fetus risk for trisomy 21 in the Arab women of Arab race was two as much as Non Arab race, but trisomies 18 and 13 in women of Non Arab race were more than Arab race. The role of mother race (such as Arab and Non Arab) in neonatal outcome is very important.

Key words: Mother race, neonatal outcome . cell free DNA analysis

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INTRODUCTION

Cousin marriage is permissible in south-west Asia but it is banned in China and Taiwan, the majority of the United States, North Korea, and South Korea [1,2]. One of the most important elements in manifestation of genetic defects is cousin marriage in Iran. In a study conducted on the rate of cousin marriage among the Iranian populations (Fars, Kurd, Lor, Baluch, Zaboli, Azaris, Turkaman, and Arab) reported the rate of 38.6% [3].

The Holly Qur'an and the Holly Bible don't forbidden the marriage between first cousin [4,5].

The Journal of Genetic Counseling issued a report in 2002, which approximated the risk of birth defects in a neonate born of first cousins between 1.1–2% higher than non-cousin couples with the risk of 3% [6].

Invasive testing by amniocentesis or chorionic villus sampling (CVS) in pregnancies is administered for diagnosis of fetal aneuploidy that are identified by screening to be at high risk for such aneuploidies [7]. However, non-invasive prenatal testing in many developed countries is the most excessive accepted policy of screening is based on a combination of maternal age, maternal serum free beta-human chorionic gonadotropin (β-hCG), fetal nuchal translucency thickness, and pregnancy-associated plasma protein-A (PAPP-A),that could recognize approximately 90% of fetuses with trisomies 21, 18 or 13 at a false-positive rate of 5% [8]. In 2008, cell-free DNA (cf-DNA) in

maternal plasma for trisomy 21, with very low false-positive rate was described [9,10]. The studies have demonstrated that the test could diminish the incidence of unnecessary invasive procedures and iatrogenic fetal loss. Non-invasive prenatal testing has been advanced to prepared opportune and safe discovery of trisomy 21 in fetus and other common aneuploidies using shotgun sequencing, targeted sequencing, and single nucleotide polymorphism based sequencing of cf-DNA [11-17]. With firm reasons of non-invasive prenatal testing accomplish in small-scale populations of outstanding high-risk women, various professional societies suggested quickly that non-invasive prenatal testing could be considered as a second-tier screening test for women at increased risk for aneuploidy [18-20]. The studies have suggested that non-invasive prenatal testing in the general populations and in the high-risk populations can be accomplished comparably [21-23].

The aim of this study was to report the results of clinical implementation of cf-DNA analysis for trisomies13, 18 and21during 10–22 weeks' gestation in the general populations, and assessment the role of mother race in neonatal outcome with cf- DNA analysis for 13,18 and 21 trisomy.

MATERIALS AND METHODS

This study was a postgraduate thesis which was retrospective study included all women who had an ultrasound (US) examination during 10 to 22 weeks' gestation and they were qualified for cf- DNA namely prior trisomic fetus, positive first or second trimester trisomy screen , 35 years age and older , US findings suggestive of increased aneuploidy risk, between March 1, 2015 to March 30, 2016.

The cf-DNA testing was performed after women received genetic counseling in the unique laboratory. Exclusion criteria were women younger than 35 years old, low risk screening tests in first trimester, twin pregnancy, and disorders of sex chromosome .The results were validated by amniocentesis, chorionic villus sampling (CVS) or follow-up of clinical outcomes.

After receiving genetic counseling for women who had above mentioned inclusion criteria and referred to a unique laboratory.

Data Analysis:
An Excel database was used for data collection and the data were analyzed with statistical package of SPS (version 15). Sensitivity, specificity, and predictive values for trisomies 13, 18, and 21 all of the performed tests for were estimated.

RESULTS

A total of 2000 women were screened using cf-DNA analysis and all of them confirmed by amniocentesis, but 8 cases were excluded from our study because the fetus of them had disorders of sex chromosome (XXX, XO, XXY).Therefore we had to study in the 1992 singleton pregnancies. Participant women in this study were 1631 Non Arab race (Fars, Kurd and Lor) and 361 were Arab race. From 1992 screened women, fetus of 6 women had trisomy 21, where four of them were Non-Arab race and two of them were Arab race. Therefore, trisomy 21 in women of Arab race was 0.55%, whereas in Non Arab was 0.24%. Trisomies 18 and 13 were not observed in Arab race women. Fetus of 4 women had trisomy 18 only 3 cases confirmed by amniocentesis and all of them were Non Arab race. Fetus of 3 women had trisomy 13 using cf-DNA analysis and confirmed by amniocentesis and all of them were Non Arab race. Sensitivity of cf-DNA for trisomies 13, 18, and 21 were 100%. Specificity of cf-DNA for trisomies 13 and 21 were 100%, but it was 94.44% in trisomy 18. One out of six cases (16 %) of trisomy 21 showed negative results in the first trimester screening test but in second trimester had positive cf-DNA analysis.

CONCLUSION

The American College of Obstetrics and Gynaecology and the Society for Maternal–Fetal Medicine persuade all laboratories to report results for each aneuploidy tested and the results of Cf-DNA in all laboratories were as follows[24 – 27].(Table 1):

Table 1. Cf-DNA Test Accomplishment Characteristics Results by American College of Obstetrics and Gynaecology

	Sensitivity (%)	Specificity (%)
Trisomy 21	99.3	99.8
Trisomy 18	97.4	99.8
Trisomy 13	91.6	99.9

Several studies have indicated that cf-DNA analysis of maternal blood can detect about 99% of cases of trisomy 21, 97% of trisomy 18 and 92% of trisomy 13, with respective false-positive rates (FPR) of approximately 0.1%, 0.2% and 0.2%. Most of these studies were retrospective, using stored samples from pregnancies with known outcome, as well as prospective, using samples from high-risk pregnancies undergoing invasive testing [24].In the meanwhile, some studies were reporting on the clinical accomplishment of cf-DNA analysis in routine screening for trisomies in the general populations, but most of these studies do not supply data on complete pregnancy outcome and they cannot be used for assessment of the screening accomplish. However, three studies reported outcome data on nearly all cases examined as follows:

1- Nicolaides et al assessed 2049 singleton pregnancies during 11–13 weeks' gestation. They identified eight cases of trisomy 21 and two trisomy18, with a false-positive rate of 0.1% [7].
2- Song et al assessed total of 1916 singleton during 11–21weeks pregnancies by cf-DNA analysis prospectively [28].They could not supply a result in 3.8% of cases and there was loss to follow-up in 5.8% of cases. Therefore, of the 1741 pregnancies with cf-DNA analysis results and outcome data, they identified eight cases of trisomy 21, two cases of trisomy 18 and one trisomy 13, whereas there was only one false-positive result for trisomy 18.
3-Bianchi et al studied 2042 singleton pregnancies at their 8–39 weeks' gestation by cf-DNA analysis prospectively [3].They could not supply a result in 3.5% of cases because the fetuses of women were miscarriage or not karyotyped. Therefore they had to study in the 1952 singleton pregnancies and they identified five cases of trisomy 21 and the two with trisomy 18, with 0.5%false-positive result.

Role of maternal race in previous studies were as follows:
1-Gockley et al studied 167 complete mole patients and concluded that Hispanic patients with complete molar pregnancy had a significantly lower risk of developing gestational trophoblastic neoplasia than white patients [29].
2- Seto and colleagues investigated 438 infants (276 black and 162 white) and concluded that, Black infants with vitamin D deficiency had 2.4 greater adjusted odds (95**%**CI: 1.0, 5.8) of SGA. Vitamin D deficiency was not significantly associated with SGA in white infants [30].
In this study Characteristics results of Cf-DNA were as follows (Figure 1):

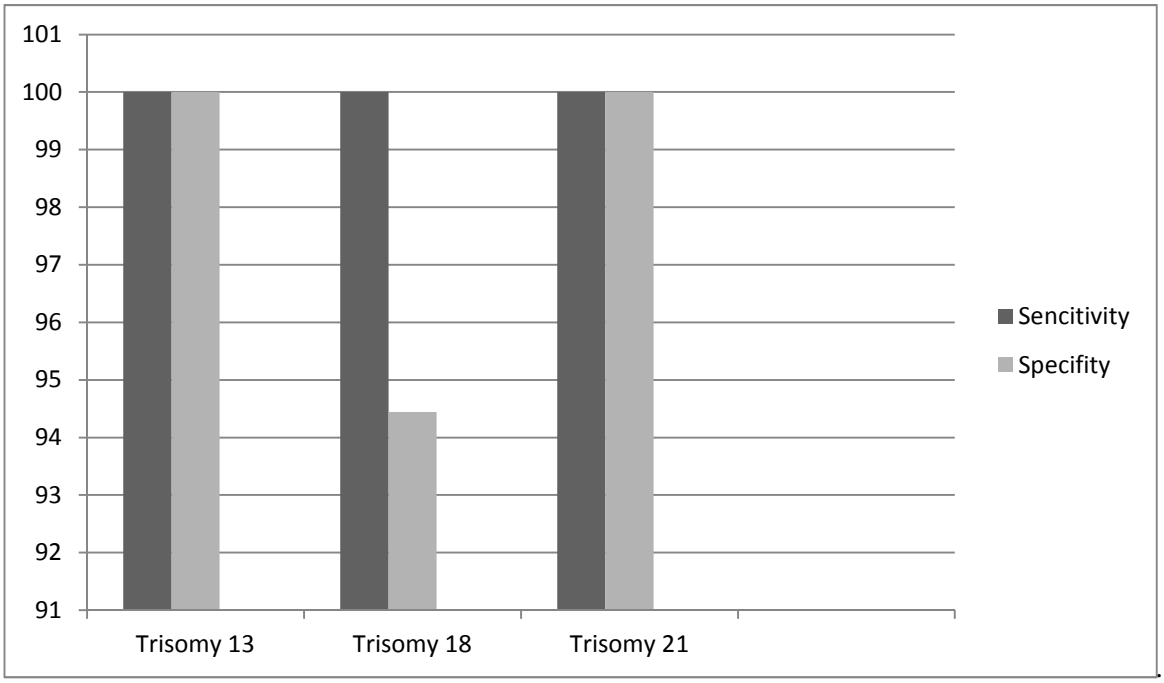

Figure 1: Sensitivity and Specificity of cf-DNA analysis of this study for trisomies 13, 18, and 21

In this study, we conducted cf-DNA analysis during 10–22 weeks' gestation for 2000 singleton pregnancies and of them 8 cases were excluded from the study because their fetus had disorders of sex chromosome (XXX, XO, XXY). Therefore, the results of the cf-DNA testing for the 1992 singleton pregnancies with cf-DNA analysis results and outcome data, the test correctly identified six cases of trisomy 21, three with trisomy 18 and four with trisomy 13 but there was only one false-positive result for trisomy 18.This study have shown that fetus risk for trisomy 21 in women of the Arab race was twice the Non Arab race women, but trisomies 18 and 13 in women of the Non Arab race were more than Arab race. The incidence of both trisomies 18 and 13 in the Non Arab race women were 0.18%, whereas the trisomies 18 and 13 were not observed in the Arab race women (Figure 2).

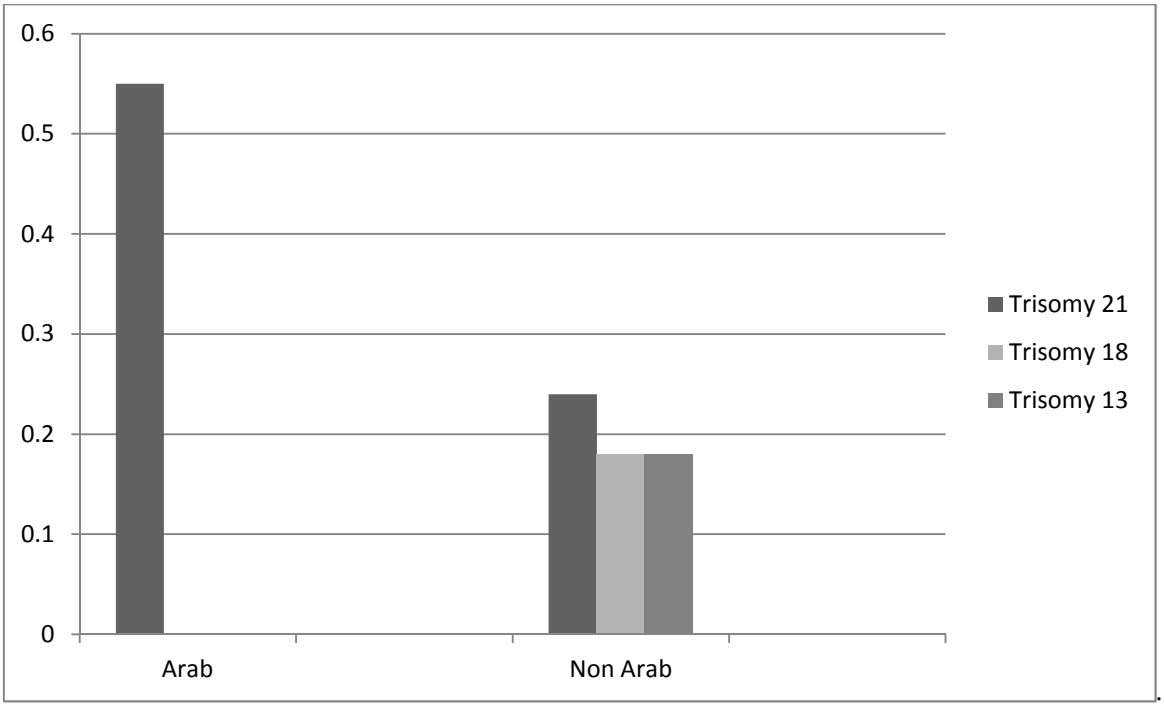

Figure 2: Accomplishment characteristics of risk for mother race with cf-DNA analysis for trisomies 21, 18, and 13

Our findings showed that cousin marriage was the most important factor of genetic disorders. Therefore suitable accomplishments should be done for diminution the incidence of genetic disorders with upgrade information of young persons (boys and girls) before wedding about the risks of cousin marriage and also accomplish genetic consulting and implementation of non invasive prenatal screening in first trimester. Consequently the fetus risk for trisomy 21 in women of Arab race are two as much as Non Arab race women and family marriage in Arab race are obviously more than Non Arab race, thus the role of mother race in neonatal outcome is very important and Obstetrics and Gynaecology specialists should strictly perform screening tests and cf-DNA analysis for women of some races such as Arab race women. In addition, our findings showed that in one out of six women cases (16%) the trisomy 21 had negative results in the first trimester screening test but in second trimester had positive cf-DNA analysis. Thus, if non-invasive prenatal testing or cf-DNA analysis in maternal plasma for trisomy was negative in the first trimesters, in high risk mothers it should be done in second trimesters again.

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Authors' Contributions
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Glossary of abbreviation: ultrasound (US), cell free DNA (cf-DNA), chorionic villus sampling (CVS)

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