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PREFRONTAL SPACE RATIO: COMPARISON BETWEEN NORMAL FETUSES AND FETUSES WITH TRISOMY 21 AT THE SECOND TRIMESTER OF GESTATION

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ABSTRACT

Screening prefrontal space ratio (PFSR) has a high effectiveness in screening at the second trimester of gestation for trisomy 21 and is considered a sonographic marker in screening and diagnosing chromosomal defects that can provide the possibility of correct diagnosis of chromosomal defects. Screening for fetal chromosome defects is considered a necessary prenatal measure of prenatal care. Trisomies are the most common chromosomal defects and the most common of them in human is trisomy 21 that has been named as Down syndrome. Though the main cause of this syndrome is not known but its mechanism is the lack of separation of chromosomes which results in the birth of an individual with 47 chromosomes. Those with this syndrome have various disorders in different organ in their body and though life expectancy has increased for them in recent years, this increase is still in 40-60 years. Thus, knowing medical problem of these individuals and dealing properly with them seems necessary. The aim of this study is determining a normal range for PFSR in normal fetuses and fetuses with trisomy 21 at second trimester of gestation. Ultrasonography was done with trans-abdominal method using Zimens-acousan device and the measurements were done in median profile view state. For achieving the objective of the study women with gestational age of 16 to 24 weeks visiting Shariati, Imam Khomeini and Women's university hospitals during 2011-2013 which are Tehran's university hospitals were taken into the study and sampling was done in non-random way. In addition, no significant relationship exists between fetus's age (weeks of gestation) and PFSR in normal fetuses and fetuses with Down syndrome. Thus, it seems that PFSR is a special and very sensitive marker in diagnosing trisomy 21 in screening at the second three months of gestation.

KEY WORDS: fetuses, prefrontal space ratio, trisomy, Tehran's university hospitals, trisomy 21.

INTRODUCTION

Screening for fetal chromosome defects is considered a necessary prenatal measure of prenatal care (Sheldon and Simpson, 1991, Phillips *et al*., 1992). Trisomies are the most common chromosomal defects and the most common of them in human is trisomy 21 that has been named as Down syndrome (Kaplan *et al*., 2003). Though the main cause of this syndrome is not known but its mechanism is the lack of separation of chromosomes which results in the birth of an individual with 47 chromosomes (Behrman *et al*., 2004; Crandall *et al*., 1980). Those with this syndrome have various disorders in different organ in their body and though life expectancy has increased for them in recent years, this increase is still in 40-60 years. Thus, knowing medical problem of these individuals and dealing properly with them seems necessary (Behrman *et al*., 2004).

In 1866 Langdon Down reported a case of trisomy 21 which had a surface skin which was more than body surface and it had small nose and flat face (Langdon, 1866). In recent studies PFSR has been mentioned as a marker in screening for trisomy 21. In a study by Briitayazdi et al PFS ratio has been reported to be significantly lower in fetuses with Down syndrome (0.2) compared to normal fetuses (0.97) (Digott *et al*., 1994; Wald *et al*., 1996; Watt *et al*, 1996). These findings have also been mentioned in a study by Sonek J et al. For measuring PFS ratio a line is drawn between the leading edge of the mandible and the maxilla and extended in front of the forehead then PFSR is calculated as follow:

PFS ratio = d2 /d1

D1 is considered as the distance between the leading edge of the skull and the leading edge of the skin and D2 is the distance between the skin and the point where the MM line is intercepted. These distances have been clearly shown in Figure 1.

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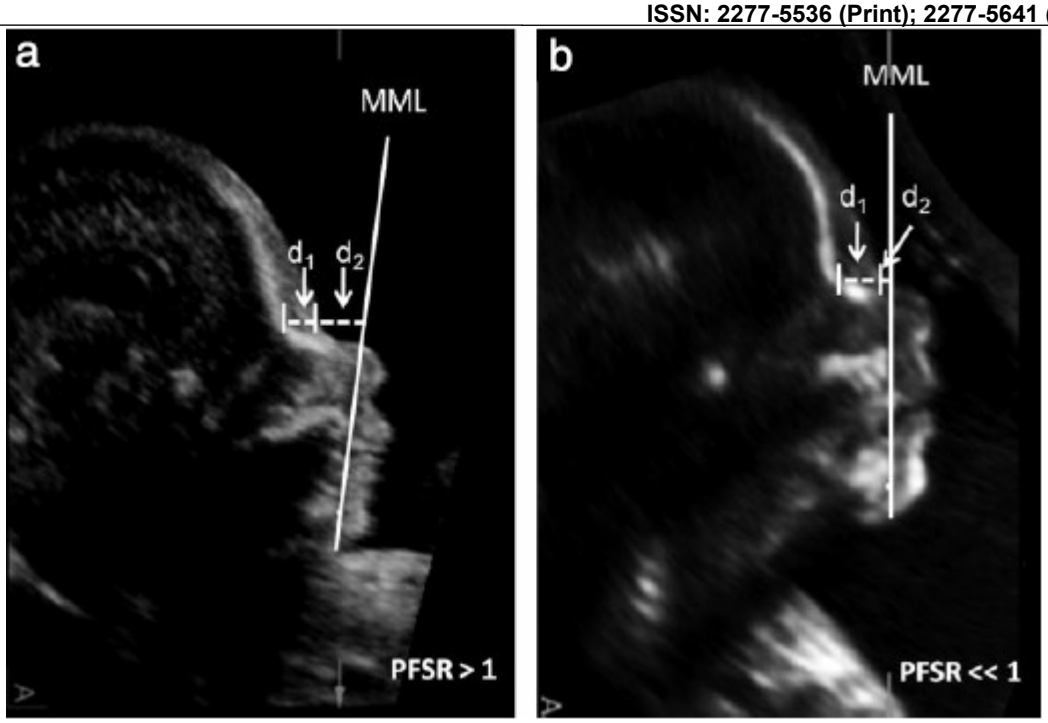

Figure 1. Measuring prefrontal space ratio| (a) a normal fetus (PFSR>1) and (b) a fetus with trisomy 21 (PFSR<<1). MML indicates line between the leading edge of the mandible and the maxilla. D1 is considered as the distance between the leading edge of the skull and the leading edge of the skin and D2 is the distance between the skin and the point where the MM line is intercepted (which is significantly smaller in (b) compared to (a)). PFSR is determined through d2/d1.

MATERIALS AND METHODS

This study is done in analytical-cross-sectional way on women with gestational age of 16 to 24 weeks visiting the three hospitals of Shariati, Imam Khomeini and Women's university hospital in Tehran during 2011-2013. The sampling is done in non-random way. 15 fetuses with Down syndrome and 200 normal fetuses at the second three months of gestation are investigated. After doing necessary coordination and explaining the objectives and stages of the study to patients and gaining patients' consent, their information is collected and completed in the checklist of the study. Then ultrasonography in trans-abdominal manner is requested for them. For preventing measurement error all instances of ultrasonography are conducted by a skilled specialist. It should be noted that ultrasonography was repeated 3 times for each case and the best obtained sample was chosen for conducting the study. For determining the indented values in mid-sagittal profile view Zimens-acousan ultrasonography device was used with 2D method and measurements were done in median profile view state.

After collecting data related to d1 and d2 and calculating PFSR values, we will analyze the value in normal fetuses and fetuses with Down syndrome (Wald *et al*., 1996). First we calculate PFSR in the samples and then we will present the results with the aid of descriptive statistics tools in the form of statistical tables. Then with the aid of statistical tests in inferential statistics, the study hypotheses are investigated and finally through generalizing the result of the samples to the main population we will give reach conclusion (Kromberg *et al*., 1980). The hypotheses that are investigated in this paper are the equality of PFSR in normal fetuses and fetuses with Down syndrome and also hypotheses related to PFSR values are by fetus's gender and age.

STATISTICAL ANALYSIS

Based on the reported data for normal fetuses and fetuses with trisomy 21, d1 and d2 values were descriptive analyzed and the results are reported in Tables 1 and 2. Based on these results d1 mean is higher in fetuses with Down syndrome than in normal fetuses while for d2 values, the mean is higher in normal fetuses

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Table 1 descriptive analysis of d1 data.

	Syndrome/normal	number	mean	median	MoM mean	Standard deviation	minimum	maximum
d1	Down syndrome	15	6.42	6.3	1.019	0.99	4.60	7.9
	normal	200	4.07	4.05	1.006	0.65	2	5.8

Table 2 descriptive analysis of d2 data.

	Syndrome/normal	number	mean	median	MoM mean	Standard deviation	minimum	maximum
d2	Down syndrome	15	1.85	1.7	1.09	0.73	0.9	3.4
	normal	200	4.38	4.4	1	0.85	1	8

In Table 3 the results of descriptive analysis of PFSR values that are obtained by dividing d2 values by d1 values, are presented. The ratio of the measured distance in the two investigated groups indicate lower values for fetuses with Down syndrome compared to normal fetuses. Thus, the PFSR mean in fetuses with Down syndrome is lower.

Table 3 descriptive analysis of PFSR data.

	Syndrome/normal	number	mean	median	MoM mean	Standard deviation	minimum	maximum
PFSR	Down syndrome	15	0.28	0.27	1.06	0.096	0.17	0.48
	normal	200	1.11	1.03	1.08	0.33	0.25	2.9

For testing the hypothesis of the normalness of PFSR distribution Kolmogorov-Smirnov test was used. The null hypothesis of this test is that the distribution is normal. This test was done using SPSS software. Based on the results of this test and as the sig or p-value is lower than 0.05 and equal to prenatal genetic diagnosis in 3000 amniocenteses which rejects the hypothesis of the normalness of PFSR distribution (Golbus *et al*., 1979, *Sepe et al*., 1982; Devore, 2010). Thus, for investigating PFSR characteristics in the two groups, non-parametric tests should be used (Lustig *et al.*, 1988). For this purpose, for investigating PFSR values between the two groups of normal fetuses and fetuses with Down syndrome, non-parametric Mann-Whitney is used (Cuckle *et al.*, 1984). In this test the null hypothesis is that there is no significant difference in PFSR ratio between the two groups. Sig in this test is equal to zero therefore as this value is smaller than 0.05 error level the null hypothesis is rejected. In other words, there is a significant difference in PFSR values between the two groups.

Also for conducting a comparison of MOM PFSR values first the normalness of the samples is investigated using Kolmogorov-Smirnov. Based on the results of this test and as the sig or p-value is lower than 0.05 and equal to 0, it rejects the hypothesis of the normalness of MOM PFSR distribution. Thus, for investigating MOM PFSR characteristics in the two groups, non-parametric tests should be used. Based on the results of Mann-Whitney as sig is higher than 0.05 and equal to 0.541, there is no significant difference between the two groups in terms of MOM PFSR values. Then the hypotheses of the impact of age and gender on prefrontal space ratio are investigated.

The results of this testing the hypothesis of the impact of fetus's gender on PFSR indicate that there is no significant difference between male and female fetuses in terms of PFSR values. Therefore, the fetus's gender does not impact PFSR values. This hypothesis was investigated using Mann-Whitney test and as in this test sig is equal to 0.274 which is higher than 0.05 error level therefore there is no reason for rejection of the null hypothesis which means that there is

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no significant difference in the PFSR values in male and female fetuses. Also for testing the hypothesis of existence of relationship between PFSR and fetus's age Spearman's correlation test was used. In this test the null hypothesis is the lack of significant relationship between the two factors. In other words, the null hypothesis is: there is no significant relationship between PFSR and fetus's age. Based on the results of the test as p-value is equal to 0.037 and is lower than 0.05 the null hypothesis is rejected which means that there is a significant relationship between PFSR and age in the two groups. The level of significance being lower than 5 indicates the significance of the correlation. But as without correlation p=0143, this relationship is very weak.

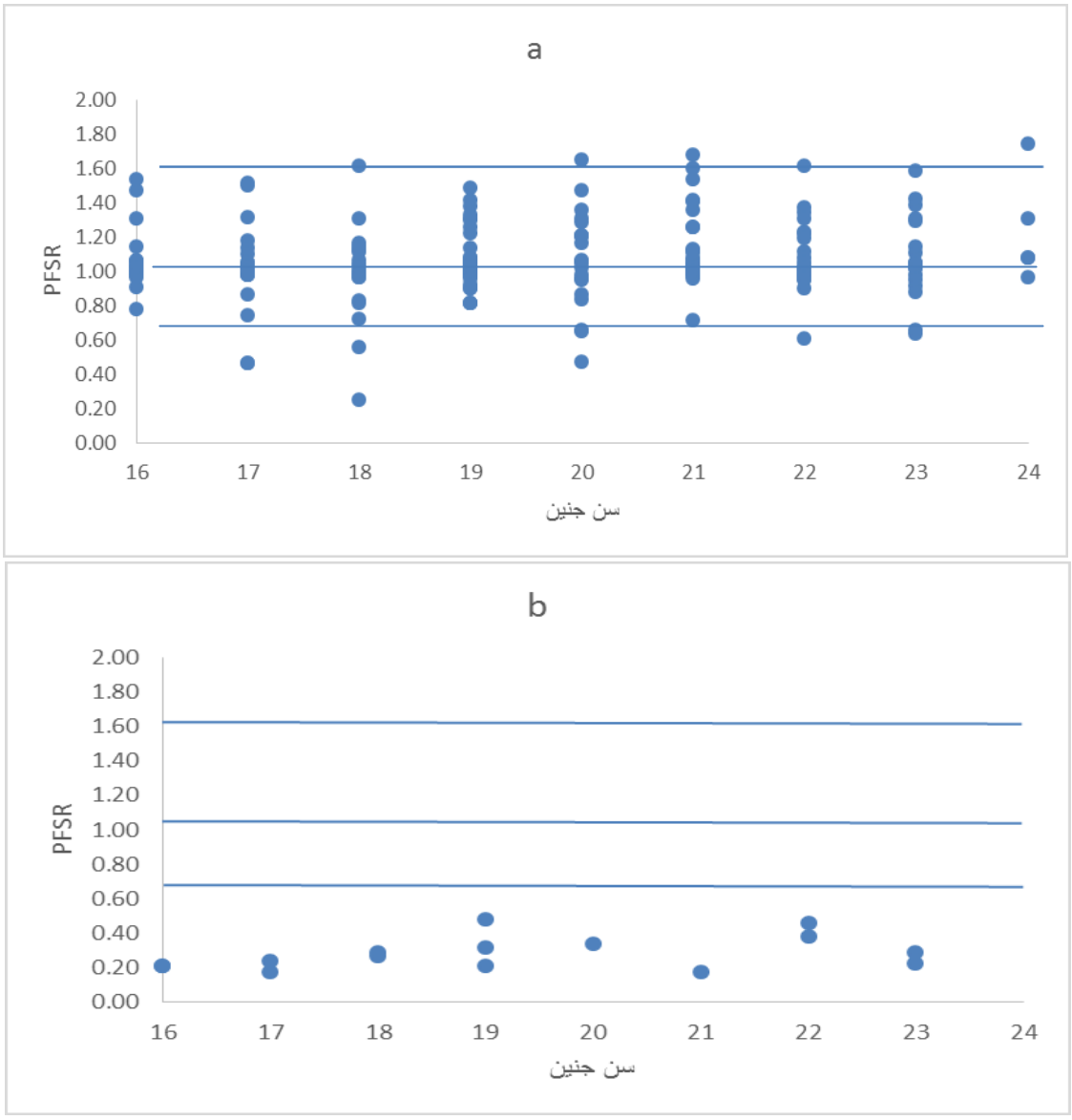

Figure 2. PFSR in 200 normal fetuses (a). PFSR in 15 fetuses with Down syndrome (b) which have been drawn on reference points (mean, 5th and 95th percentile) for normal fetuses by gestation age (weeks).

Discussion

The data collected using 2D ultrasonography indicates that during the second three months of gestation the prefrontal space ratio value in fetuses with trisomy 21 is significantly lower than that of normal fetuses. This value in normal fetuses is in [0.25, 2, 9] range while this range is [0.17, 0.48) for fetuses with Down syndrome.

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PFSR values in normal fetuses and fetuses with Down syndrome are shown by weeks of gestation in Figure 2. These values have been drawn on reference areas (mean, 5th and 95th percentiles) that have been determined based on data related to normal fetuses.

95th percentile of PFSR in normal fetuses is equal to 1.60 while no PFSR value related to fetuses with trisomy 21 are in this range. This can itself indicate the significant decrease of prefrontal space ration in fetuses with Down syndrome. The results of this study propose that measuring PFSR in the second trimester of gestation can be effective in screening for trisomy 21 and it is important to pay attention to this marker for correct and in time diagnosis of this chromosomal defect (Nicolaides *et al*., 2004, Merkatz *et al*., 1984).

CONCLUSION

Based on the results of the analyses and statistical test, the mean of PFSR in normal fetuses is equal to 1.11 and in fetuses with Down syndrome it is equal to 0.28 which indicates significant decrease of prefrontal space ratio in fetuses with trisomy 21. The results of Mann-Whitney test also confirms that there is a significant difference between the two groups in terms of PFSR values (sig=0). While the difference between normal fetuses and fetuses with trisomy 21 in terms of MOM PFSR value is not significant (sig=0.541). Also the results of investigating the impact of fetus's gender on PFSR values indicate that there is no significant difference between male and female fetuses in terms of values (Nicolaides *et al*., 2005). Therefore fetus's gender is not effective on PFSR value (sig=0.247). Another finding of the study indicate that the relationship between fetus's age and PFSR value is significant but as the correlation coefficient is low this relationship is very weak.

Therefore due to the significant difference between normal fetuses and fetuses with trisomy 21 (Sonek *et al*, 2012) in terms of PFSR values, this factor can be used as an applicable marker in screening at the second trimester of gestation for correct and in time diagnosis of Down syndrome (Wald *et al*., 1996).

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