1-1-2023

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Original Article

Anxiety and Uterine Artery Doppler Flow in A Population of Pregnant Women of High Risk Down Syndrome Fetus: A Prospective Cohort Study

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Abstract

Background: Fetal exposure to maternal anxiety is associated with low birth weight and maternal stress may be led to constriction of uterine arteries. This study compared the relation of anxiety and uterine artery doppler flow indices in pregnant women with the high and low-risk of Down syndrome.

Materials and Methods: This prospective cohort study was conducted among pregnant women in the second trimester that were classified as having a high or low risk according to their prenatal aneuploidy screening outcome. The high risk group underwent amniocentesis. Anxiety was initially assessed using the Spielberger State-Anxiety Inventory (STAI) and uterine artery blood flow indices were evaluated 2 times for the both groups. For the high-risk group first: immediately before amniocentesis and second: after two weeks follow up, when receiving the karyotype results and for the low-risk group in the first admission and two weeks later.

Results: Totally, 375 pregnant women participated in our study that sorted into 2 risk populations based on the aneuploidy screening test, low-risk=176 and high-risk women=199. The high-risk group for Down syndrome amniocentesis showed abnormal results in the 23 cases (23/199). The mean state (P=0.003) and trait (P=0.033) of the Anxiety Inventory scores were significantly different between the groups. Baseline uterine artery indices were no significant difference between the groups. Baseline Uterine artery indices in the high-risk group was significantly different with follow-up (in both positive-amniocentesis and negative amniocentesis sub-groups) indices. Also, there was a weak and significant correlation in the uterine resistance index and STAI scores (P=0.008, r=0.137) during the follow-up period.

Conclusion: All pregnant women experienced high level anxiety, especially in the high-risk group that may reduce after confirmation of prenatal aneuploidy screening test and also affects the Doppler indices. For all pregnant women; Stress management and emotional support training is recommended before and during pregnancy.

Keywords: Amniocentesis, Anxiety, Down Syndrome, Pregnancy

Citation: **Shirazi M, Torkzaban M, Ghaemi M, Moshfeghi M, Shirazi M, Emadzadeh M, Ahmadi L, Khazaeipour Z, Mirzaeian S. Anxiety and uterine artery doppler flow in a population of pregnant women of high risk down syndrome fetus: a prospective cohort study. Int J Fertil Steril. 2023; 17(1): 52-56. doi: 10.22074/IJFS.2022.534209.1159.**

Introduction

Pregnancy is a stressful event in a woman's life (1). Stress during pregnancy may lead to some complications such as abortion, intrauterine growth restriction, and preterm labor (2-4). These side effects may be associated with increased plasma cortisol levels and decreased placental perfusion, which reduces fetal oxygenation and nutrients (5, 6). In fact, fetal developmental disorders are also associated with abnormalities in uterine artery blood flow and its indicators in the second trimester with an increase in the plasticity index (PI) or an increase in the resistance index (RI) (7, 8).

However, it can be hypothesized that anxiety in

Received: 17/July/2021, Revised: 26/January/2022, Accepted: 14/February/2022
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Royan Institute
International Journal of Fertility and Sterility
Vol 17, No 1, January-March 2023, Pages: 52-56

pregnancy may lead to adverse changes in the uterine artery blood flow and adverse pregnancy outcomes. One of the most stressful events in pregnancy is the abnormal results of the aneuploidy screening (9) and amniocentesis could alternate uterine artery resistance index (10). Due to the fact that stress is a transient condition, anxiety may have a significant and lasting effect on the uterine blood flow (11, 12). Although, some studies found significant associations between maternal anxieties and changes in feto-placental blood flow, findings remain inconsistent in the length of alteration in uterine blood flow indices (13, 14). This study aimed to investigate the relationship between maternal anxiety and uterine artery blood flow indices in the pregnant women with high-risk aneuploidy test results, candidates for amniocentesis. Here, we evaluated whether the changes in the anxiety level would change the uterine artery doppler indices in the women with normal karyotype results after amniocentesis.

Materials and Methods

Study subjects

This prospective cohort study was conducted with the pregnant women from October 2018 to April 2020 who were referred to the Perinatology clinic of Yas hospital affiliated to Tehran University of Medical Sciences (TUMS), Tehran, Iran. This study was approved by the TUMS Ethics board (IR.TUMS.IKHC.REC.1397.174). Pregnant women at 15-18 weeks with recent prenatal aneuploidy screening test results were invited to this study. Subjects were excluded with a history of major psychological disorders, or a recent history of exposure to stressful events such as death or untreatable disease in a family member or close relatives, divorce and bankruptcy. Also, those with a history of preeclampsia or comorbid conditions, including hypertension or diabetes in previous pregnancies, between pregnancies, or in this pregnancy, cigarette smoking, or alcohol consumption were excluded. All participants provided their written informed consent in this study.

Sample size

The sample size was considered according to a previous study (15) with the type I error of 0.05 and 80% power as 81 subjects in each group. By 30% response rate (16) on phone invitation and a 20% dropout, the final sample size for recruitment was calculated to be 166 subjects in each group.

Study procedure

Pregnant women, according to the results of the prenatal aneuploidy screening test; were divided into high-risk and low-risk groups.

Due to the fact that this study was performed in a low socioeconomic region and cell-free test was not covered by insurance companies, all high-risk participants chose the amniocentesis method after consultation. All Subjects filled the Persian version of the Spielberger's State-Trait Anxiety Inventory (STAI) test questionnaire and underwent the baseline uterine arteries Doppler ultrasound. For high-risk group it was performed immediately before the amniocentesis. The follow-up STAI test and Doppler valuation were done two weeks later. In the high-risk group, they had already received the karyotype results and were referred to their perinatologist for further discussion.

The high-risk participants were categorized into the two sub-groups based on the positive or negative karyotype results for Down syndrome. We excluded other trisomy from this study.

Instruments

Anxiety levels were assessed using the Persian version of STAI. State anxiety mirrors the transient situation related to adverse situations. This questionnaire was translated and validated to Persian (17). Otherwise, trait anxiety referred to the individual differences in the tendency to be anxious about the present (18).

Persian version of STAI had 40 queries and was scored on a four-point Likert scale according to the intensity of the women's feeling (18). Scores >40 and also, a 20< scores <15 were considered high anxiety and lack of anxiety, respectively. A cut-off value of 39-40 was suggested to detect clinically significant symptoms for the scale.

Doppler ultrasound assessment

Only a perinatologist performed Doppler ultrasound screening for all participants by using a same device (Affinity 70, PHILIPS, USA). The Uterine artery plasticity index (UA-PI) and resistance index (UA-RI) were evaluated bilaterally at the origin of the uterine arteries and was repeated after 2 weeks.

Statistics analysis

Statistical analysis was carried out with the SPSS (version 20, IBM, USA) and $P<0.05$ was considered statistically significant. Mean ± standard deviation (SD) was used for continuous variables and categorical variables were presented as absolute frequencies and percentages. The proportions were compared by ANOVA. The correlation between study variables was assessed using Pearson correlation.

Results

A total of 418 patients, 214 in the high-risk group and 204 in the low-risk group, were included in the study with initial inclusion criteria. All of these women participated in the baseline evaluation of the study. To participate freely in this study, some participants (n=43) left the study, low-risk group=28 and in the high-risk group=15. Finally, 176 members of the low-risk group and 199 ones of the high-risk group completed both the baseline and follow-up assessment. The amniocentesis of 23 cases of the high-

risk group resulted in a Down syndrome (23/199). The average of the participants age was 33.11 ± 5.96 years (mean ± SD). The demographic characteristics of our groups are presented in Table 1.

Table 1: Demographic characteristics of study subjects in amniocentesis and control groups

Variable	Case (n=199)	Control (n=176)	P value
Age (Y)	33.81 ± 5.92	32.32 ± 5.91	0.016*
BMI (kg/m^2)	27.52 ± 4.00	27.01 ± 4.24	0.238*
GA (weeks)	16.59 ± 0.8	16.77 ± 1.01	0.129**
Gravida	2.48 ± 1.14	2.28 ± 1.23	0.116*
History of C/S	85 (42.7%)	59 (33.5%)	0.068***

Numbers are reported as in quantitative and frequency (%) in qualitative variables. The mean state and trait anxiety inventory scores were significantly different between high-risk and low-risk groups at baseline (P=0.003 and P=0.033 respectively).BMI; Body mass index, GA; Gestational age, C/S; Cesarean section, *; Independent t test, **, Mann-Whitney test, and *; Chi-Square test.**

In the high-risk group, the state and trait anxiety scores indicated high levels of anxiety (Fig.1). Also, the baseline UA-PI and UA-RI (mean ± SD) were not significantly different between the two groups.

The UA indices in the high-risk group had a significant difference between baseline and follow-up in the both positive-amniocentesis and negative amniocentesis sub-groups. This difference in the low -risk group was observed just in the UA-RI index (Table 2).

In terms of trait anxiety scores, there was a significant difference between baseline and follow-up scores in the high risk group (both positive-amniocentesis (P=0.017) and negative-amniocentesis subgroups (P<0.001, Table 2, Fig.2). State anxiety scores were significantly different between baseline and follow-up assessments only in the negative-amniocentesis sub group (P<0.001, Fig.2).

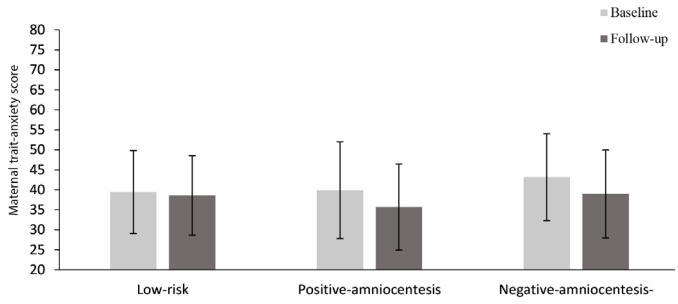

Fig.1: Changes in anxiety trait scores during the study duration as per study groups.

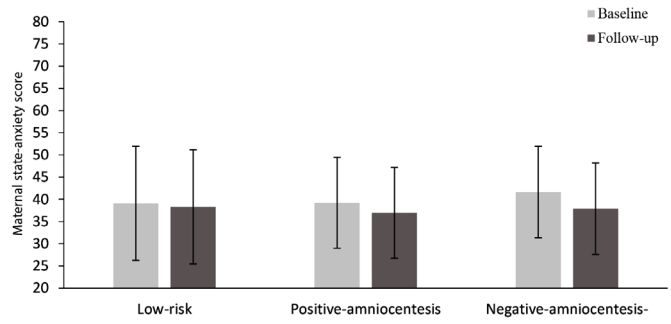

Fig.2: Changes in anxiety trait scores during the study duration in amniocentesis subgroups.

We found a significant and weak correlation between the UA-RI in the follow-up assessment in the both trait state anxiety score, otherwise, no significant correlation between baseline UA-RI and UA-PI levels with anxiety scores was observed. These results did not change after adjusting by maternal age (Table 3).

Table 2: Follow-up uterine artery blood flow indices and anxiety inventory scores among amniocentesis-positive, amniocentesis-negative, and control groups

Variable	Amniocentesis-positive (n=176)	Amniocentesis-negative (n=23)	Control (n=176)	P value*
Mean UA.PI	1.23 ± 0.55	1.17 ± 0.4	1.15 ± 0.43	0.70
Mean UA.RI	0.60 ± 0.16	0.62 ± 0.12	0.60 ± 0.12	0.50
Anxiety trait scores	38.34 ± 12.76	37.71 ± 10.25	38.31 ± 10.31	0.85
Anxiety state scores	36.91 ± 11.38	38.81 ± 10.96	38.63 ± 9.91	0.71

Data are presented as mean ± SD. UA.PI; Uterine artery pulsatility index, UA.RI; Uterine artery resistance index, and *; ANOVA test.

Table 3: Comparison of baseline and follow-up uterine artery blood flow indices among amniocentesis-positive, amniocentesis-negative, and control groups

Variables	Amniocentesis-positive (n=176)			Amniocentesis-negative (n=23)			Control (n=176)		
	Baseline	Follow-up	P (within group)*	Baseline	Follow-up	P (within group)*	Baseline	Follow-up	P (within group)*
Mean UA.PI	1.46 ± 0.59	1.25 ± 0.53	<0.001	1.49 ± 0.63	1.17 ± 0.41	0.004	1.65 ± 2.16	1.15 ± 0.43	0.409
Mean UA.RI	1.30 ± 0.37	0.60 ± 0.17	<0.001	1.31 ± 0.28	0.62 ± 0.12	<0.001	1.33 ± 0.28	0.61 ± 0.13	<0.001
Anxiety trait scores	39.91 ± 12.10	35.70 ± 10.75	0.017	43.18 ± 10.86	38.98 ± 11.01	<0.001	39.44 ± 10.36	38.60 ± 9.92	0.116
Anxiety state scores	39.22 ± 13.06	36.96 ± 12.86	0.192	41.65 ± 10.48	37.90 ± 10.23	<0.001	39.11 ± 9.51	38.31 ± 10.31	0.180

Data are presented as mean ± SD. UA.PI; Uterine artery pulsatility index, UA.RI; Uterine artery resistance index, and *; ANOVA test.

Discussion

The findings of the present study revealed that the pregnant women with high risk of fetal aneuploidy experienced more anxiety and this phenomenon may affect their uterine Doppler indices. The risk of Down syndrome increases significantly at age 35 and older. Therefore, it may happen at lower ages in some cases. Although, this difference was not clinically significant.

The mean scores of states and trait anxiety were higher in the high-risk group. This finding was consistent with previous studies showing that a positive result from a prenatal screening test may play a role in increased anxiety in the pregnant women (19, 20).

The normal ranges of the uterine Doppler scanning indices vary in the late first and early second trimester (21, 22), while decreasing parallel with pregnancy progression (22). On the other hand, a significant decrease in the blood flow of the uterine may happen due to stress and anxiety (8, 12, 23). In the current study, the baseline UA-PI level was not significantly different between high-risk and low-risk groups and was within the normal reported range. The baseline UA-PI level decreased after two weeks in the all high-risk participants but remained within normal reference ranges. It is not obvious that UA-PI level changes can be attributed to the significant decrease in the anxiety scores in the high-risk subgroups during the study period, since all of these changes could be due to the physiological pregnancy changes. It is still uncertain whether exposure to a stressful event has resulted in an increased baseline UAPI, albeit within the normal ranges. Unfortunately, this hypothesis could not be tested as there were no anxiety-free subjects in this study.

Mean UA-RI level was above the 95th percentile of the normal range among our participants at the baseline assessment and decreased to normal range at the follow-up assessment. While, Kent et al. (13) did not observe a significant difference in the UA-RI level in definite doubtful or absent cases of anxiety. In their study, the mean UA-RI level was within the normal ranges. Although, in the study of Teixeira et al. the association between maternal anxiety and UA-RI was not significant at 28 to 32 weeks of gestation (14). The abnormal baseline UA-RI levels in our study might be due to an increased level of anxiety among all participants, and the decrease can be due to the physiological pregnancy changes, but again it cannot be proved as there was no anxiety-free group in this study. The lack of significant differences in the UA-PI and UA-RI levels between our groups in baseline and follow-up assessments could be due to the high levels of baseline anxiety in the low-risk group. Overall, analyzed data reports that the higher baseline UA-PI and UA-RI levels may be related to higher baseline levels of anxiety in the amniocentesis candidates. In this study, we cannot verify if the reduced level of anxiety affects the significant reduction in mean uterine artery Doppler indices in the high-risk group, or it is just due to the physiologic adaptation after follow up.

The findings of this study revealed a significant reduction in trait anxiety scores over time in both sub-groups, while the follow-up state anxiety score was significantly lower only in the negative-amniocentesis subgroup. It might be due to the relief after observing a negative result or due to their coping skills.

The strength of the present study was all Doppler ultrasound screening were performed by the same perinatologist at both baseline and follow-up assessments. In this study, we have evaluated the anxiety level in a high number of participants in comparison with other studies. We also followed up with the groups after receiving the karyotype results to observe the actual changes in the anxiety level and its impact on the uterine artery flow, in the same population.

One of the limitations of the study is the lack of a control group without anxiety to evaluate the net effect of anxiety on uterine blood flow and short follow-up. We recommend a case-control study for future studies. The duration of follow-up was two weeks. We chose this duration to decrease the follow-up assessments losses because of our center location, a tertiary hospital with a substantial number of patients of other cities and provinces. Therefore, a longer cohort study to screen for uterine vascular characteristics and pregnancy outcomes among complex pregnancies with anxiety is suggested.

Conclusion

In conclusion, being identified as high-risk for Down syndrome by prenatal aneuploidy tests increases the level of state and trait anxiety and also affects Doppler ultrasound screening indices. High maternal anxiety may result in decreased UA-PI and UA-RI levels in the amniocentesis candidates. It seems stress management training and stronger emotional support are essential for all pregnant women, especially in cases of positive aneuploidy screening and the risk of Down syndrome fetus. We suggest the requirement of an anxiety level screening and stress-management training sessions before pregnancy.

Acknowledgments

There is no financial support and conflicts of interest in this study.

Authors' Contributions

Mahb.Sh.; Design of the work. M.T., M.E.; Drafting the manuscript and data gathering. M.Gh., M.M., Mahm. Sh.; Manuscript editing and interpretation of data. L.A.; Manuscript editing and data gathering. Z.Kh.; Interpretation of data. S.M: Design of the work and drafting the manuscript. All authors read and approved the final manuscript.

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