The effects of maternal anxiety prior to amniocentesis on uterine and fetal umbilical blood flow

Amniosentez öncesi maternal anksiyetenin uterin ve fetal umblikal kan akımı üzerine etkileri

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Abstract

Objective: To investigate the mothers' anxiety levels and determine its effect on fetomaternal circulation in pregnant women undergoing genetic amniocentesis.

Material and Methods: A prospective case-control study was conducted regarding the assessment of maternal anxiety levels by means of the Spielberger State-Trait Anxiety Inventory in 60 pregnant women having genetic amniocentesis and 60 control cases having their early second trimester ultrasonographic screening, 30 minutes before and immediately after the procedure. Additionally, maternal-fetal hemodynamic changes and Doppler ultrasonographic measurements of fetoplacental circulation were recorded in both groups.

Results: The maternal anxiety state scores were found to be significantly higher in the amniocentesis group ($p<0.001$). Maternal heart rate was significantly higher in the amniocentesis group ($p<0.05$), while the fetal heart rate was significantly lower ($p<0.05$) compared to the control group. Uterine artery Doppler measurements were comparable in the two groups but umbilical artery resistance index ($p<0.05$) and S/D ratio ($p<0.05$) were significantly higher in the amniocentesis group. Regression analysis revealed that the time which elapsed from offering amniocentesis until it was performed is the main predictor of fetal umbilical artery S/D ratio measured prior to amniocentesis in the amniocentesis group ($\beta=0.66$, $p<0.001$) and maternal anxiety state scores ($\beta=0.04$, $p=0.003$) are the main predictors of fetal umbilical artery S/D ratio measured prior to amniocentesis or ultrasonography in the two groups. The education of the patient in years decreased ($\beta=-0.13$, $p=0.04$), while the amniocentesis procedure ($\beta=1.44$, $p=0.02$) and the time which elapsed in days from offering amniocentesis or ultrasonography up to its performance ($\beta=0.41$, $p=0.04$) increased the S/D ratio measured after the procedures.

Conclusion: Our study provides the evidence that maternal anxiety and its duration has effects on the fetal blood flow. Early booking and patient support may help to overcome undesired consequences of an invasive prenatal procedure.

(J Turkish-German Gynecol Assoc 2009; 10: 162-7)

Key words: Maternal anxiety, genetic amniocentesis, Doppler ultrasonography

Received: 1 February, 2009 **Accepted:** 10 August, 2009

Özet

Amaç: Amniyosentez öncesi maternal anksiyete düzeylerinin araştırılması ve genetik amniosentez uygulanacak gebelerde fetomaternal dolaşım üzerine etkilerinin değerlendirilmesi.

Gereç ve Yöntemler: Genetik amniosentez uygulanan 60 gebe kadın ve erken ikinci trimester ultrasonografik incelemesi yapılan 60 kontrol vakasına, işlemden 30 dakika önce ve hemen sonrasında maternal anksiyete seviyesinin Spielberger Durumluk ve Sürekli Anksiyete Ölçeği ile değerlendirildiği prospektif bir vaka control çalışması uygulandı. Ek olarak, maternal-fetal hemodinamik değişiklikler ve fetoplasental dolaşımın Doppler ultrasonografik ölçümleri her iki grupta kayıt edildi.

Bulgular: Maternal durumluk anksiyete skoru amniosentez grubunda belirgin olarak daha yüksek saptandı ($p<0.001$). Maternal kalp hızı amniosentez grubunda belirgin olarak daha yüksek ($p<0.05$) ve kontrol grubu ile karşılaştırıldığında fetal kalp hızı belirgin olarak daha düşük ($p<0.05$) olarak saptandı. Uterin arter Doppler ölçümleri her iki grup arasında benzer iken, umblikal arter rezistans indeks ($p<0.05$) ve S/D oranı ($p<0.05$) amniosentez grubunda belirgin olarak yüksek ölçüldü. Regresyon analizinde amniosentez önerilmesinden uygulanmasına kadar geçen sürenin amniosentez öncesi ölçülen fetal umblikal arter S/D oranının öngörülmesinde amniosentez grubu için esas belirteç olduğu ($\beta=0.66$, $p<0.001$) ve maternal durumluk anksiyete skorlarının ($\beta=0.04$, $p=0.003$) amniosentez ya da ultrasonografi öncesi ölçülen fetal umblikal arter S/D oranının öngörülmesinde her iki grup için esas belirteçler olduğu sonucuna varılmıştır. Yıl olarak hasta eğitim süresi işlem sonrası ölçülen S/D oranlarını azaltırken ($\beta=-0.13$, $p=0.04$), amniosentez işlemi ($\beta=1.44$, $p=0.02$) ve amniosentez ya da ultrasonografi önerilmesinden uygulanmasına kadar geçen süre ($\beta=0.41$, $p=0.04$) bu oranı arttırmaktadır.

Sonuç: Çalışmamızda, maternal anksiyete ve süresinin fetal kan akımı üzerine etkileri olduğu sonucuna varılmıştır. Erken döneme randevu verilmesi ve hastalara yeterli destek sağlanması bu tipte invaziv prenatal bir işlemin istenmeyen sonuçlarının engellenmesine yardımcı olacaktır.

(J Turkish-German Gynecol Assoc 2009; 10: 162-7)

Anahtar kelimeler: Maternal anksiyete, Genetik amniosentez, Doppler ultrasonografi

Geliş Tarihi: 01 Şubat 2009 **Kabul Tarihi:** 10 Ağustos 2009

Introduction

The main concerns of the clinicians regarding invasive procedures such as amniocentesis are the diagnostic accuracy and a variety of fetal complications (1). Although the psychological impact of these procedures is of great importance, less extensive attention has been paid to psychological distress associated with invasive prenatal diagnostic procedures and

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various modulating parameters (2). Some authors reported a significantly higher maternal anxiety preceding genetic amniocentesis, while some others found an equal level of anxiety to that of women undergoing just a routine ultrasonographic scan (3, 4). In studies where a raised anxiety level was demonstrated to be clearly associated with amniocentesis, this anxiety was at its highest level just prior to the procedure (5). The results are difficult to compare due to differences regarding how and when anxiety is measured. It is important to quantify such concerns as amniocentesis has become a common procedure. Few studies addressed the possible negative influence of maternal anxiety due to invasive procedures on the fetoplacental circulation. Maternal stress in late pregnancy was reported to influence uteroplacental circulation and thus fetal cerebral circulation (6, 7). Abnormal uterine blood flow in anxious pregnant women is suggested to be related to adverse obstetric outcome, particularly fetal growth restriction and preeclampsia (7). It is not clear whether this relation exists earlier in pregnancy, when uterine artery resistance is usually measured and the opportunity to intervene in time to protect the fetus from any harmful effects of anxiety is greatest.

The present study was conducted to assess the maternal anxiety prior to and following genetic amniocentesis by using Spielberger's State-Trait Anxiety Inventory (STAI). Additionally, we aimed to demonstrate whether maternal distress evoked by this invasive intervention leads to altered Doppler ultrasonographic measurements of fetoplacental circulation, namely uterine arteries and fetal umbilical arteries. Consequently, emphasis has been placed on identifying potential predictors of Doppler ultrasonographic examination results.

Materials and Methods

This prospective case-control study was conducted on 60 pregnant women with singleton gestation undergoing genetic amniocentesis and 60 control cases having their routine 16-20-week ultrasonographic scan (USG). Subjects were recruited consecutively among pregnant women who were referred for either amniocentesis or routine USG between January 2004 and October 2006 at a University Hospital Department of Obstetrics and Gynecology. All subjects gave their written informed consent prior to inclusion and an approval from the local ethics committee was obtained.

Maternal anxiety levels of the subjects were measured by means of Spielberger's State-Trait Anxiety Inventory (STAI) 30 minutes before and immediately after the procedure (amniocentesis or USG). STAI is a widely used self-rating instrument for the assessment of the current (state) and inherent (trait) level of anxiety and has been extensively used in research and clinical practice (8). It is designed as a 40 item-scale; 20 items for evaluation of state anxiety and the other 20 for measurement of trait anxiety level. S-anxiety score demonstrates how anxious the patient feels in response to a defined situation while T-anxiety score points out how the individual generally feels. T-anxiety score seems to be the reflection of an inherent anxious personality that is not altered significantly secondary to a certain condition. Each item scores one to four. Total scores of STAI range between 20-80. STAI is also validated for Turkish speaking populations (9).

Hemodynamic variables and Doppler ultrasonographic measurements both preceding and following the procedure were determined. The same sonographer (EC) recorded the Doppler flow velocity waveforms using a Siemens versaplus ultrasonograhy machine with 3.5-7 MHz transabdominal probe. Colour Doppler imaging was used to identify bilateral uterine and umbilical arteries after placing the Doppler gate in an optimal manner over the defined vessels. The Doppler gate was located over the entire diameter of the uterine artery 1 cm distal to the crossover of external iliac artery and main uterine artery. Measurements with an angle of insonation $<60^{\circ}$ were accepted. Pulsatility index and resistance index of flow velocity waveforms were calculated from five consecutive uniform waveforms and a diastolic notch was looked for. Since the insonation angle could not be reliably determined due to the tortuous nature of the umbilical artery, the highest possible Doppler shifts were recorded. Maternal and fetal heart rates, Doppler ultasonography measurements of bilateral uterine arteries and umbilical arteries were determined in all study subjects before and just after the genetic amniocentesis. The same recordings were performed in control cases before and after the ultrasonographic scan.

Additionally, sociodemographic and clinical parameters such as age, education, employment, tobacco use, parity, obstetric history and gestational age were recorded. The couples were offered amniocentesis and this was performed whenever the couples decided to have it.

Pearson correlation analysis was performed to find out the relation between anxiety scores and hemodynamic variables measured prior to the amniocentesis or ultrasonography procedures such as heart beat and Doppler measurements. A regression model was built to determine possible predictors of fetal umbilical artery S/D ratio measured prior to the procedures (amniocentesis in the case group and ultrasonography in the control group). A model was built using backward linear logistic regression analysis where the group was included as a dichotomous variable (women in the amniocentesis group or control group), together with the presence or absence of tobacco use, education of the women in years, age of women in years, time elapsed in days from offering amniocentesis until performance, state anxiety and trait anxiety scores. The resulting β coefficient indicates the amount of change in the dependent variable which is the umbilical artery S/D ratio measured prior to the procedures. The β coefficient indicates the amount of change in the dependent variable for a one unit change in the independent variable, controlling for the variables in the model. The values of the β coefficient are in units of the independent variable. It is useful for assessing the practical magnitude of the effect of an independent variable, because variables can be statistically significant without having a substantially practical effect. In order to evaluate the effect of needle insertion during

the amniocentesis we also built a model using the same independent variables in addition to the localization of the placenta; anterior, posterior and lateral localizations.

The statistical analysis of the data was performed using the Statistical Package for Social Sciences for Windows (SPSS, Chicago, IL, USA). Results were reported as mean ± standard deviation or numbers and percentages. Differences between the groups were assessed using chi-square test or Fisher's exact test for categorical data whenever appropriate. Independent samples t test was used in order to detect the differences of continuous variables between the groups and paired samples t- test was used to assess within group changes of continuous variables measured prior to or after the procedures. Probability (p) <0.05 was considered statistically significant for all comparisons.

Results

Amniocentesis was performed for advanced maternal age in 14 (23.3%) women and for positive triple screen risk <1/ 250 in 46 (76.7%) women. In the amniocentesis group, the placenta was attached to the anterior uterine wall in 37 (61%) women, posterior wall in 17 (28.3%) and right lateral wall in 6 (10%). None of the fetuses had cardiac anomalies and two cases were diagnosed as trisomy 21.Demographic variables of the couples were similar in the two groups in terms of age, education, employment, tobacco use, parity, previous abortion, curettage and gestational age (Table 1).

The mean time which elapsed from offering until performing amniocentesis was 2.9±1.5 days (Range:0-7 days), and the time which elapsed from offering until performing detailed second trimester ultrasonography was 1.1±0.7 days (Range: 0-3 days, p<0.001). Patient state anxiety scores were significantly higher in the amniocentesis group (48.9±11.8) compared to the control group (33.5±6.5, p<0.001) ,while patients' trait anxiety was similar in the two groups (46.4±7.3, 45±5.1, p=0.2 respectively). In the amniocentesis group the state anxiety scores of patients with positive triple screen test and advanced maternal age as indications of amniocentesis were similar (p=0.2).

In the amniocentesis group the mean maternal pulse rate, fetal umbilical artery resistance index and systole/diastole were significantly higher than the control group, while the mean fetal heart rate was significantly lower (Table 2). After the procedures (amniocentesis for the study group, ultrasonography for the controls) the mean maternal pulse rate decreased significantly within the groups whereas the mean fetal heart rate increased only in the amniocentesis group (Table 2). There was a trend for increase in umbilical artery S/D due to amniocentesis with a borderline significance. The state and trait anxiety scores did not correlate with any of the maternal and fetal Doppler measurements and heart beat in the control group, while the state anxiety score correlated positively with the fetal umbilical artery S/D ratio, prior to (r=0.32, p=0.01) and after (r=0.35, p=0.007) amniocentesis and negatively correlated with the fetal heart beat after the amniocentesis (r=-0.26, p=0.04)

A regression model was built to determine possible predictors of fetal umbilical artery S/D ratio. The ages of the couples, anxiety scores of patients and husbands, gestational age, maternal serum alpha fetoprotein levels, nulliparity, the presence of prior abortions or curettages, the time elapsed since amniocentesis was offered up to performance, couples' education years and tobacco use were all included in the model. Regression analysis revealed that the time elapsing in days from offering amniocentesis or ultrasonography until performance (β=0.66, p<0.001) and every increase in maternal state anxiety scores (β=0.04, p=0.003) are the main predictors of fetal umbilical artery S/D ratio measured prior to the procedures (amniocentesis in the case group and ultrasonography in the control group). When independent variables that predict umbilical artery S/D ratio measured after the procedures were evaluated the education of the patient in years decreased (β=-0.13, p=0.04), while amniocentesis procedure (β=1.44, p=0.02) and the time elapsing in days from offering amniocentesis or ultrasonography until performance (β=0.41, p=0.04) increased the S/D ratio.

There was no case of absent end-diastolic flow. Two cases had umbilical artery PI>2SD in the control group and also in

Table 1. Selected couple variables according to the groups. Data are presented as mean ± standard deviation or numbers (percentages)

Variable	Amniocentesis Group (n=60)	Control Group (n=60)	P
Maternal age (year)	31.2±6.6	29.7±6.2	0.2*
Patient Education (year)	7.9±3.6	8.3±3.7	0.5*
Women unemployed	38 (63)	42 (70)	0.4**
Tobacco use	5 (8.3)	6 (10)	0.7**
Nulliparous	34 (56.7)	40 (66.7)	0.2**
Previous abortion ≥1	13 (21.7)	8 (13.3)	0.2**
Previous d&c≥ 1	7 (11.7)	8 (13.3)	0.7**
Gestational age (weeks)	18.7±1.6	18.9±1.4	0.6*

*Not significantly different (p>0.05), independent samples t-test
**Not significantly different, (p>0.05), chi-square test

Table 2. Maternal fetal hemodynamic changes and Doppler measurements before and after amniocentesis or before and after ultrasound examination in the control group. The data is given as means and 95% confidence intervals of the mean in parenthesis

Variable	Amniocentesis Group (n=60)		p	Control Group (n=60)		p
	Before	After		Before	After	
Maternal heart rate (beats/min)	95.8 (91.2-100)[a]	92.8 (89-96.2)[b]	0.02*	88.3 (86-90)	82.6 (80.6-84.5)	<0.001*
Fetal heart rate (beats/min)	147 (145.7-150.2)[a]	151 (148.8-154.4)	0.004*	152 (150.5-154.5)	152 (150-153.9)	0.5
Umblical artery PI	1.3 (1.19-1.44)	1.29 (1.22-1.35)[b]	0.6	1.2 (1.1-1.3)	1.17 (1.13-1.22)	0.2
Umblical artery RI	0.75 (0-73-0.78)[a]	0.77 (0.74-0.80)[b]	0.3	0.69 (0.68-0.70)	0.69 (0.68-0.71)	0.8
Umblical artery S/D	4.9 (4.2-5.6)[a]	5.7 (4.7-6.8)[b]	0.05	3.4 (3.2-3.6)	3.5 (3.3-3.7)	0.1
Right uterine artery PI	1.1 (0.98-1.21)	1.09 (0.99-1.19)	0.8	1 (0.96-1.13)	1.05 (0.96-1.13)	0.2
Right uterine artery RI	0.63 (0.59-0.66)	0.63 (0.60-0.66	0.7	0.60 (0.58-0.63)	0.60 (0.58-0.62)	0.5
Right uterine artery S/D	3.4 (2.6-4.1)	3.2 (2.7-3.78)	0.6	2.7 (2.5-2.9)	2.7 (2.55-2.90)	0.5
Left uterine artery PI	1.1 (1-1.2)	1.3 (1.12-1.47)	0.3	1.2 (1.09-1.45)	1.26 (1.09-1.44)	0.3
Left uterine artery RI	0.66 (0.60-0.72)	0.66 (0.63-0.68)	0.3	0.64 (0.61-0.67)	0.66 (0.63-0.69)	0.1
Left uterine artery S/D	3.2 (2.8-3.5)	3.2 (2.94-3.6)	0.8	3.2 (2.8-3.6)	3.5 (3.19-3.87)	0.1

PI: Pulsatility Index, RI: Resistance Index, S/D: Systole/diastole
*Significantly different (p<0.05), paired samples t-test
[a]Significantly different than the corresponding before measurement in the control group (p<0.05), independent samples t-test
[b]Significantly different than the corresponding after measurement in the control group (p<0.05), independent samples t-test

the amniocentesis group prior to and after ultrasonography and amniocentesis. IUGR developed in 8 (13.3%) cases in the amniocentesis group and 5 (8.3%) cases in the control group (p=0.3). Preeclampsia developed in 6 (10%) and 4 (6.7%) cases respectively (p=0.5). When umbilical artery S/D values were compared, no difference was found in cases diagnosed to have IUGR or not (p=0.3) and preeclampsia or not (p=0.09) later during pregnancy.

Discussion

Assessment of the psychological consequences of invasive prenatal diagnostic procedures is still a neglected area of research. We demonstrated that patient state anxiety scores were significantly raised due to amniocentesis in accordance with most of the previous studies (4, 5, 10-12). Although there are a number of studies reporting acute fetal hemodynamic changes secondary to anxiety associated with amniocentesis, such changes were not found to have a significant clinical relevance (3, 5, 13, 14). On the other hand, the newborns of the stressed or anxious women are reported to be small for gestational age and have a tendency to premature birth (15-17). Some experimental studies provided confirmation of those findings as they also indicated that birth weight was reduced and fetal behaviour was found to be influenced by maternal anxiety, possibly through a variety of hormonal mechanisms (18-20).

Teixeria and colleagues concluded that pregnant women with high state anxiety scores at STAI interviewed at their 28-32 weeks of gestation appeared to have significantly abnormal patterns of blood flow through uterine arteries with elevated resistance index values and faster maternal heart rates, although not significant (7). Impaired uterine artery blood flow is considered to be mostly due to a chronic phenomenon such as defective trophoblastic invasion in early pregnancy which is known to be predictive of preeclampsia and intrauterine fetal growth restriction. However short term changes such as transiently altered hormonal concentrations, invasive or noninvasive therapeutic interventions and exercise may probably lead to uterine artery blood flow changes (21-24). Likewise noradrenaline infusion is shown to diminish uterine blood flow in a number of studies, and in addition, reproductive tissues are found to be more sensitive to vasoconstrictive effects of noradrenaline than are other organs (21, 25). Based on these recent findings, elevated noradrenaline concentrations in women with high state anxiety levels suggest that the hypothalamus-hypophysis-adrenal axis may be responsible for abnormal uterine artery blood flow patterns (26).

It is uncertain whether altered uterine artery blood flow can be observed earlier in pregnancy. Kent and colleagues investigated the association between maternal anxiety using Hospital Anxiety Depression Scale (HADS) and uterine artery waveform patterns at 20 weeks of gestation and concluded that there was no significant association between maternal anxiety scores and uterine artery Doppler indices (13). Different population samples and the use of different questionnaires to assess anxiety levels and the time of gestation when the study was conducted

may explain why those studies achieved such different results.
In our study, uterine artery indices did not indicate significant changes when compared with the controls, and maternal anxiety was not found to be correlated with any of the uterine artery Doppler indices. On the other hand, mean maternal heart rate, fetal umbilical artery resistance index and umbilical artery systole/diastole were demonstrated to be significantly higher, while fetal heart rate was significantly lower in the amniocentesis group. Additionally, maternal anxiety scores were positively correlated with umbilical artery S/D before and after amniocentesis, while anxiety scores were significantly correlated inversely with fetal heart rate after the procedure. We used the same anxiety scale as Texieria et al, who found an association between anxiety and uterine artery Doppler measurements, but the gestational weeks of our study populations were earlier (7). We performed the study at similar gestational weeks with Kent and colleagues who found no association between anxiety and uterine artery Doppler, as we did (13).
Sjöström and colleagues demonstrated that women with higher trait anxiety scores had higher umbilical artery pulsatility index and lower middle cerebral artery (MCA) pulsatility index values at 37-40 weeks of gestation (6). Those measurements indicated increased resistance in the placental vascular bed and decreased vascular resistance in the fetal brain, leading to redistribution of fetal blood flow with increased cerebral blood flow, called the brain sparing effect. Again, humoral factors such as stress hormones, namely cortisol and noradrenaline, were suggested to be responsible for altered fetal hemodynamics in women who tend to have high trait anxiety scores (27).
In our study, umbilical artery RI and S/D measurements were significantly higher in the amniocentesis group in comparison with the controls and there was a trend for an increase in umbilical artery S/D due to amniocentesis, although not statistically significant. The state anxiety score correlated positively with the fetal umbilical artery S/D ratio before and after amniocentesis and the maternal state anxiety score was one of the main predictors of fetal umbilical artery S/D ratio in the amniocentesis group who displayed higher anxiety. All the se findings at the early second trimester stage were in accordance with most of the findings of Sjöström (6).
Our findings point to an increased anxiety response in the mother before an invasive procedure, which has prominent effects on fetal umbilical artery blood flow as the time to performance of amniocentesis since offered increases. Another interesting finding is that the normal fetal heart beat increase response after amniocentesis is reversed in mothers with high anxiety scores. These findings suggest that increased maternal anxiety may act through decreasing placental blood flow which causes an uncompensated response by the fetus in an acute stress setting caused by the amniocentesis procedure.
We conclude that high maternal anxiety may have profound effects on fetal umbilical artery blood flow as the time of onset increases. Counseling and immediate scheduling for amniocentesis may decrease the maternal stress response to an invasive procedure.

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