

THE RELATIONSHIP BETWEEN MATERNAL SERUM α -FETOPROTEIN AND UTERINE ARTERY DOPPLER FINDINGS AT 20-24 WEEKS' GESTATION FOR PREDICTION OF PREECLAMPSIA AND INTRAUTERINE GROWTH RETARDATION

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ABSTRACT

Objective: To estimate the relationship between maternal serum α -fetoprotein (MSAFP) levels and uterine artery Doppler findings at 20th week of pregnancy for prediction of preeclampsia and intrauterine growth retardation (IUGR).

Methods: Eighty pregnant women were followed as a study group prospectively. MSAFP levels at the 15-18th week of gestation and bilateral uterine artery Doppler findings at the 20th week of gestation were obtained.

Results: Bilateral early diastolic notch of the uterine artery was detected in 17 cases (21, 75%) at the 20th week of gestation. In 9 of them early diastolic notch was persistent at the 24th week while in 8 cases, it had disappeared. Uterine artery diastolic notch was found to be a significant predictive factor for preeclampsia, as well as for IUGR ($p < 0.001$, OR: 69.74; $p < 0.02$, OR: 10.11, respectively). MSAFP levels of 17 cases that showed early diastolic notch in uterine artery Doppler were significantly higher than in the notch negative cases ($p < 0.05$). The levels of MSAFP in 9 cases which demonstrated the persistence of diastolic notch, were significantly higher than the 8 cases where the notch had disappeared, at the 24th week of gestation ($p < 0.05$).

Conclusion: Our findings suggest that abnormal uterine artery Doppler findings at 20th week of gestation correlate with elevated MSAFP levels, and bilateral diastolic notch in uterine artery at 20 weeks' gestation together with elevated MSAFP, is associated with poor obstetric outcome.

Key Words: IUGR, Preeclampsia, MSAFP, Diastolic notch

INTRODUCTION

Maternal serum α -fetoprotein (MSAFP) evaluation was first used as a screening test for foetal neural tube defects and detection of trisomy 21 (1). Once the gestational age is accurately determined in the second trimester, unexplained elevation of MSAFP higher than 2.5 MoM (Multiples of Median) is associated with increased risk of preeclampsia, intrauterine growth retardation or pre-term labor when multiple pregnancies and foetal anomalies are excluded (2-4). On the other hand, there is a distinct relationship between the presence of early uterine artery diastolic notch and preeclampsia as well as adverse obstetric outcome (5,6).

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There are studies in the literature demonstrating that in cases with no foetal anomaly, at 18-22 weeks' gestation, there is a correlation between diastolic notch, abnormal uterine artery Doppler findings and high MSAFP level (2, 3, 7). Reports studying the relationship between Doppler findings and MSAFP level consider 2.5 MoM as a cut-off point.

However there is a wide range of normal MSAFP level (0.70-2.5 MoM), higher in foetal neural tube defects and lower in trisomy 21 (1). As a second trimester screening test, the correlation between normal MSAFP levels and abnormal uterine artery Doppler findings and their relation to gestational prognosis are not known yet.

Our study was designed to investigate the relationship between the MSAFP levels below 2.5 MoM and abnormal uterine artery Doppler findings with gestational prognosis. The relationship between uterine artery Doppler findings, early diastolic notch and MSAFP levels at the 18-20th gestational weeks, and their predictive value for preeclampsia and intrauterine growth retardation were investigated.

MATERIALS AND METHODS

This prospective, randomized study included 80 non-smoking pregnant women who were followed-up during the antenatal period and delivered by the perinatology unit of the Obstetrics and Gynaecology Department during the period 1998-2000. Cases with foetal anomaly, diabetes and multiple pregnancies were excluded from the study group. The patients were chosen among the 1400 women who attended perinatology clinics.

The patients in the antenatal follow-up protocol were screened with biochemical-screening tests (Down Screening Test) during 15-18th gestational weeks and maternal serum α -fetoprotein, unconjugated estriol and β -hCG levels were obtained.

The α -fetoprotein levels were determined by radioimmunoassay kits (Amerlex-M second trimester AFP RIA Kit) by "Ortho-Clinical Diagnostic Amersham, U.K.". In evaluating the results a computer program 'Prenatal Interpretive

Software' developed by Robert Maciel Associates was used. Therefore, the corrected levels of MoM for each gestational week, were obtained using the median levels for Turkish women and also taking into account factors like weight and smoking.

Between 18-20 gestational weeks, while ultrasonographic screening for anomalies was performed, double-sided uterine artery Doppler examination was also done. Pulsed color Doppler ultrasonography was performed transabdominally by an "HDL 3000" ultrasonography machine using a 3.5 MHz probe.

In the waveform; early diastolic notch, PI (Pulsatility Index), RI (Resistance Index) and S/D (Systolic / Diastolic ratio) measurements were taken. End systolic or early diastolic notch form was described as a notch as described in the literature (5). Patients who were bilaterally notch positive at 20th gestational week were examined again at 24th gestational week to see whether this persisted.

As preeclampsia criteria, arterial blood pressure higher than 140/90 mmHg after 24th gestational week and/or proteinuria higher than 300 mg/day was accepted (8). The intrauterine growth retardation, the foetal weight during follow-up and neonatal weight after birth had to be lower than 10% percentile (1).

On Doppler examination, the correlation between bilateral diastolic notch and preeclampsia and intrauterine growth retardation was searched. When an early diastolic notch was detected, increased risks for preeclampsia and intrauterine growth retardation were investigated using the Fisher's test.

On 20th week of gestation, the MSAFP levels belonging to cases which are notch (+) and notch (-) in uterine diastolic artery Doppler were compared. Subsequently, MSAFP levels of diastolic notch positive 9 patients and 8 notch negative patients at 24th gestational week were evaluated by Student's t test.

In our study group, MSAFP levels in cases with preeclampsia and intrauterine growth retardation were compared with those cases without these complications using Student's t test. The

relationship between normal accepted MSAFP levels and poor gestational outcome was searched for by this method. The statistical evaluations were carried out by 'Unistat for Windows 5.0' program.

RESULTS

Of 80 cases participating in our study, the majority was younger than 35 years and the mean age was 30.85 ± 6.11 (19-44). In this group, preeclampsia and IUGR were found in 12.5% and 11.25% respectively. Parity, risk factors for pregnancy characteristics are presented in table I. Pregnant women with chronic hypertension and autoimmune diseases did not have significantly different MSAFP levels compared to pregnant women without risk factors ($p > 0.05$).

Table I: Patient characteristics.

	(N=80)	%
Maternal age <35	59	73,75
Maternal age >35	21	26,25
Nulliparity	36	45
Multiparity (1-4)	44	55
Risk factor (-)	45	56,25
Risk factor (+)	35	43,75
Hypertension and PE*	15	18,75
Autoimmune dis.	8	10
Gestational DM**	6	7,5
Triple test (+)	6	7,5

* PE = Preeclampsia.
** DM = Diabetes Mellitus

Uterine artery Doppler waveform displayed double-sided early diastolic notch in 21.25% (17/80) of the cases. In 17 cases with diastolic notch during 18-20 gestational weeks, it persisted in 9 patients and disappeared in 8 patients. Cases with unilateral notching during 18-20 weeks or in the 24 weeks cut-off period were not included in the study.

In the overall study population, the median MSAFP level was determined as 1.07 ± 0.43 MoM (0.38-2.24) in the triple test at 15-18 gestational weeks. The presence of bilateral diastolic notch in uterine artery Doppler was a significant indicator of preeclampsia and intrauterine growth retardation ($p < 0.02$ and $p < 0.002$ respectively) (Table II).

Table II: The relationship between the, 'diastolic notch,' in the uterine artery at the 20th weeks of pregnancy and pregnancy outcome.

	Notch (+)	Notch (-)	P	OR
PE (N: 10)*	9	1	$p < 0.001$	69.74
IUGR (N:9)**	6	3	$p < 0.02$	10.11

* PE = Preeclampsia.
** IUGR = Intrauterine growth retardation

With respect to maternal α -fetoprotein and Doppler relationship in bilateral diastolic notch (+) cases, 17 notch positive cases were found to have a significant increase in MSAFP levels. The difference with normal α -fetoprotein levels in 63 cases that were notch (-) was statistically significant ($p < 0.05$) (Table III).

Table III: The relationship between "diastolic notch" in the uterine artery Doppler and the level of MSAFP

	Notch (+) N = 17	Notch (-) N = 63	P
MSAFP* (MoM)**	$1,33 \pm 0.61$	$0,97 \pm 0.32$	$< .05$

* MSAFP = Maternal Serum α -Fetoprotein
** MoM = Multiples of Median

Of 17 cases with bilateral diastolic notch (+), the levels of MSAFP in 9 persisting and 8 non-persisting patients at 24 weeks' were compared and the MSAFP levels were significantly higher in notch positive patients at both 20 and 24 gestational weeks ($p < 0.05$) (Table IV).

Table IV: MSAFP levels in the case of positive and persistent notch at both 20th and 24th weeks of pregnancy and in the case of lost notch during 24th week of pregnancy (total 17 cases)

	24. GH Notch (+) N = 9	24. GH Notch (-) N = 8	P
MSAFP* (MoM)**	$1,68 \pm 0,46$	$0,94 \pm 0.65$	$< .05$

* MSAFP = Maternal Serum α -Fetoprotein
** MoM = Multiples of Median

The MSAFP levels in patients with preeclampsia and intrauterine growth retardation were higher than pregnant women who did not show these complications. This increase was significant at $p < 0.01$ levels in women with preeclampsia and intrauterine growth retardation (Table V).

Table V: Increase in the level of MSAFP in the cases of PE and IUGR in comparison with normal pregnancy.

	N	MSAFP (MoM)
PE (+)**	10	1.65 ± 0.53*
PE (-)	70	0.97 ± 0.34
IUGR (+)***	9	1.86 ± 0.30*
IUGR (-)	71	0.95 ± 0.34

* P < .001
 ** PE = Preeclampsia
 *** IUGR = Intra Uterine Growth Retardation

DISCUSSION

Maternal serum α - fetoprotein levels (MSAFP) are determined as part of the antenatal follow-up protocol in "Down screening test" and for screening neural tube defects (1).

In the previous studies, high maternal serum α - fetoprotein levels of 2.5 MoM or higher, recorded in the second trimester, indicate increased risks of preeclampsia, intrauterine growth retardation, pre-term labor and placental abruption other than foetal anomalies and multiple pregnancies (7-10).

Although the incidence of preeclampsia is cited to be about 5 percent it can complicate up to 15% of pregnancies and the percentage of IUGR is estimated 10% when the infants whose weights are below the 10th percentile for their gestational age were accepted as growth restricted. In our study the incidence of pre-eclampsia and IUGR was 12.5% and 11.25% respectively. Our incidence rate was high because the population was consisting of women with high risk pregnancy.

In 36% of pregnancies with high MSAFP levels without a distinct reason, there is at least one etiologic cause for adverse pregnancy outcome. The most important factors of poor prognosis are preeclampsia, intrauterine growth retardation and pre-term labour. In case the MSAFP levels are 2.5 MoM or higher, the risks of the gestational complications increase 2-11 times (7).

During pregnancy, starting with implantation, there are physiological changes, which increase the blood flow in the intervillous space and decrease the blood pressure in the uterine

arteries. These changes consist of the trophoblastic vascular invasion of spiral arteries extending from the myometrium to the decidua in the first and second trimesters and their transformation to utero-placental arteries (5, 11). In preeclampsia and intrauterine growth retardation, these physiological changes, which should occur during placentation, are absent or are insufficient (6, 8). The absence or the inadequacy of these physiological changes is due to deciduas and/or trophoblastic functional disturbances. In Doppler studies, early diastolic notch and increase in resistance to blood flow is seen in the uterine artery Doppler waveform if the physiological changes are incomplete or absent (6, 12). In past studies, a significant correlation was found between preeclampsia and poor gestational prognosis with high RI, PI and S/D levels, which belong to Doppler waveforms and presence of early diastolic notch (5, 6).

In patients with high MSAFP levels of unknown cause, there is a marked increase in abnormal Doppler findings and presence of diastolic notch in the uterine artery Doppler during 18-22nd weeks of gestation (2,4,13). These Doppler studies are usually performed on pregnant women who have MSAFP levels of 2.5 MoM or higher.

In the second trimester biochemical-screening (Down screening) programme, the normal accepted values for MSAFP have a wide range as 0.70-2.5 MoM (1). There are no studies on whether there is a correlation between poor gestational prognoses and abnormal uterine artery Doppler findings with these values and between which MSAFP levels are present. For this reason, our study group consisted of pregnant women with normal MSAFP levels less than 2.5 MoM. The current literature points out that the diastolic notch in the uterine artery during the 18-24th gestational weeks is an important indication for determining preeclampsia and intra-uterine growth retardation (6, 14). In 21.25% of our patients, two-sided diastolic notch was observed.

The abnormal Doppler findings in our group were higher compared with the pregnant population without risk factors. This may be due to the various risk factors of our pregnant group (Table I). In this group, the diastolic notch in the uterine

artery Doppler during 18-20th gestational weeks indicates an increase in preeclampsia and intrauterine growth retardation, which correlates with current literature citing.

The sensitivity of the diastolic notch in indicating poor gestational prognosis is high for preeclampsia and intra-uterine growth retardation. Although, it is also significant for detection of pre-term labour, the odds ratio decreases (Table II). In patients with diastolic notch in their uterine artery Doppler, the MSAFP levels are higher than in those with normal findings (Table III).

On the other hand, the diastolic notch found in 17 of the cases during 20th gestational week disappeared in 8 cases at the 24th gestational week. Only one of the 8 patients whose diastolic notch disappeared in the 24th gestational week had preeclampsia. These findings point to the fact that the diastolic notch determined in the 20th gestational week is less sensitive than that determined during the 24th gestational week in showing poor prognosis. When the physiological changes are considered, this result is not surprising. The current literature also supports this finding (5,11,12). In normal pregnancies, trophoblastic invasion of utero-placental arteries is completed at 20-22nd gestational weeks (5,6). According to our results, 9 patients who were diastolic notch positive in uterine artery Doppler in 20th week of gestation, persisting until the 24th week, had considerably high levels of MSAFP (Table IV).

This shows that at 20th week of gestation, Doppler findings evaluated together with MSAFP levels are an indicator of poor prognosis and does not necessitate waiting for the 24th gestational week. Diastolic notch and poor gestational outcome may be due to the insufficient trophoblastic invasion of the utero-placental arterial endothelium and its damage, causing increase in transmission of foetal AFP to the maternal side. The results of our study support these conclusions. Mean MSAFP level of patients with abnormal Doppler results and adverse pregnancy outcome was 1.5 MoM or higher. On the other hand, in this group, patients with preeclampsia and intrauterine growth retardation had higher MSAFP values compared with uncomplicated cases (Table V).

Double-sided diastolic notch determined in the uterine artery Doppler at 20 weeks' gestation is a significant indicator of preeclampsia and intra-uterine growth retardation. In the presence of the notch, there is an increased risk of these disturbances.

In patients whose uterine artery Doppler showed diastolic notch or abnormal findings, the MSAFP levels were significantly high even if they were within normal ranges. In other cases where the diastolic notch was determined at 20 weeks' gestation and persisted until 24 weeks, the MSAFP levels increased significantly in comparison with those whose diastolic notch disappeared.

Also in patients with preeclampsia and intrauterine growth retardation, the MSAFP levels were higher in comparison with those who had good prognosis.

Our study shows that abnormal uterine artery Doppler findings and high levels of MSAFP at 20 weeks' gestation coexist in high-risk pregnancies.

Depending on these data, it is concluded that the abnormal uterine artery Doppler findings, when evaluated with MSAFP levels will be more sensitive in determining poor pregnancy outcome. This hypothesis should be supported by further studies carried out with more patients.

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