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— ***Book:*** Jones KL. Practical perinatology. New York: Springer; 1990. p. 112-9.

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Each table should be prepared on a separate page with table heading on top of the table. Table heading should be added to the main text file on a separate page when a table is submitted as a supplementary file.

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To Evaluate the Role of Lipid Profile in the Etiopathogenesis of Mild and Severe Preeclampsia

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Abstract

Objective: To evaluate the role of lipid profile in the etiopathogenesis of mild and severe preeclampsia.

Methods: Fifty-nine preeclamptic pregnant and 66 normotensive pregnants who applied to our clinic between January 2005 – December 2006 were included into the study. Preeclampsia patients were divided into two groups as mild preeclampsia (Group:1, n: 27) and severe preeclampsia (Group: 2, n: 32). Sixty-six normotensive pregnants composed the control group (Grup: 3). In cases, triglyceride, cholesterol, high-density lipoprotein, cholesterol, low-density lipoprotein and very low-density lipoprotein levels were measured. Correlation between lipid profile and markers of preeclampsia was investigated.

Results: Median triglyceride and VLDL levels of group 1 and 2 were higher than group 3, but only difference between group 2 and group 3 was statistically sigificant ($p<0.05$). Median cholesterol in group 2 was significantly higher than in group 1 and 3 ($p<0.05$). LDL and HDL levels were determined similar in all groups ($p>0.05$) ($p>0.05$). There was a significantly positive correlation between the amount of proteinuria and cholesterol, LDL, TG and VLDL levels (respectively, r: + 0.216 ($p<0.05$), + 0.194 ($p<0.05$), + 0.194 ($p<0.05$), + 0.208 ($p<0.05$). A significant negative correlation between proteinuria and HDL levels was determined (r:-0,202), $p<0.05$). There were significant positive correlations between systolic tension and cholesterol, TG, VLDL levels (respectively, r: +0.235 ($p<0.01$), + 0.311 ($p<0.01$), + 0.311 ($p<0.01$); and between diastolic tension and with LDL, TG, VLDL levels (respectively, r: +0.242 ($p<0.05$), + 0.280 ($p<0.05$), + 0.280 ($p<0.05$).

Conclusion: The changes in lipid profile was related with preeclampsia and especially severe preeclampsia.

Keywords: Preeclampsia, hypertension, pregnancy, lipid, dyslipidemia.

Hafif ve ağır preeklampsi olgularında maternal serum lipid profilinin değerlendirilmesi

Amaç: Lipid profilinin hafif ve ağır preeklampsi etiyopatogenezindeki rolünü araştırmak.

Yöntem: Ocak 2005 – Aralık 2006 tarihleri arasında, kliniğimize müracaat eden 59 preeklamptik gebe çalışmaya alındı. Preeklamptik olgular; hafif (Grup 1, n:27) ve ağır (Grup 2, n:32) olmak üzere 2 gruba ayrıldı. Kontrol grubu için de 66 sağlıklı gebe (Grup 3) alındı. Tüm olgularda trigliserid (TG), kolesterol, yüksek dansiteli lipoprotein (HDL), düşük dansiteli lipoprotein (LDL) ve çok düşük dansiteli lipoprotein (VLDL) düzeyleri ölçüldü. Lipid profili ile preeklampsi belirteçleri arasında korelasyonlar araştırıldı.

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Bulgular: Kolesterol düzeyi grup 2' de diğer iki gruptan anlamlı olarak yüksek idi ($p<0.05$). TG ve VLDL düzeyleri grup 1 ve 2' de grup 3' e göre yüksekti, fakat sadece grup 2 ile arasındaki fark anlamlıydı ($p<0.05$). LDL and HDL düzeyleri tüm gruplarda benzer bulundu ($p>0.05$; $p>0.05$). Proteinüri miktarı ile kolesterol, LDL, TG ve VLDL seviyesi arasında pozitif yönde bir korelasyon tespit edildi (sırasıyla, r: + 0.216 ($p<0.05$), +0.194 ($p<0.05$), +0.194 ($p<0.05$), + 0.208 ($p<0.05$). Proteinüri ile HDL arasında ise negatif yönde bir korelasyon tespit edildi (r: -0,202; $p<0.05$). Sistolik kan basıncı ile kolesterol, TG, VLDL arasında (sırasıyla, r: +0.235 ($p<0.01$), + 0.311($p<0.01$), +0.311 ($p<0.01$) ve diastolik kan basıncı ile LDL, TG ve VLDL arasında pozitif yönde korelasyonlar bulundu (sırasıyla, r: +0.242 ($p<0.01$), +0.280 ($p<0.01$), +0.280 ($p<0.01$).

Sonuç: Lipid profilindeki değişikler preeklampsi ve özellikle ağır preeklampsi ile ilişkili bulundu.

Anahtar Sözcükler: Preeklampsi, hipertansiyon, gebelik, lipid, dislipidemi.

Introduction

The relationship between essential hypertension and serum lipid profile was found in many trials.[1-3] Anormal lipid profile is strongly related with atherosclerotic cardiovascular diseases and causes endothelial dysfunction directly. The most important feature of pregnancy induced hypertension is hypertension via vasospasm in kidneys, uterus, placenta, and brain.[4] Primary source of prostacyclin and tromboxane are endothelial cells and thrombocytes, respectively. In normal pregnant woman endothelial prostacycline reaches 8-10 times more than a non pregnant woman. But in preeclamptic women this rising is only 1-2 times more. Besides in preeclamptic women thromboxane rises more than normal pregnant women.[5] Because prostocyclin is a vasodilator and thromboxane is vasoconstrictor, endothelial cell destruction causes rising in the thromboxane / prostacyclin rate which makes vasospasm.[6] Increasing lipid synthesis causes rising in the thromboxane / prostacyclin rate and takes a role in the pathogenesis of pregnancy induced hypertension.[7] That's why abnormal lipid profile may be an important marker for pregnancy toxemia. In this study, we aimed to evaluate the role of the alterations of lipid profile in the etiopathogenesis of mild and severe preeclampsia.

Methods

Fifty-nine preeclampsia patients, with no history of chronic HT, thyroid disease, renal disease, dislipidemi or diabetes mellitus (DM), and 66 healthy pregnant women who applied to Kahramanmaraş Sütçü Imam University Medical Faculty Obstetrics and Gynecology Clinic between January 2005 – December 2006 were included into the study. Research ethics approval from KSU Medical Faculty Ethics Committee was obtained before the initiation of the study.Preeclampsia patients were divided into two groups as mild preeclampsia (Group:1, n: 27) and severe preeclampsia (Group: 2, n: 32) according to the bulletin of American College of Obstetricians and Gynecologists (ACOG) named as 'Preeclampsia and Eclampsia Diagnose and Management'.[8] Sixty-six healthy pregnant women composed the control group (Grup: 3). From all cases after 12 hour fasting 8-10 ml blood samples were taken from antecubital vein.. The blood samples were centrifuged for 4 minutes at 4.000 rpm (Eppendorf santrifuge 5810) after waiting 30 minutes in room temperature to seperate the serum for study. In these serums, triglyceride (TG), cholesterol, HDL (High density lipoprotein), LDL (Low density lipoprotein) and VLDL (Very low density lipoprotein) levels were measured with kinetic method using ready kit at Dade Behring RXL (USA) machine. Results of 3 groups were evaluated. Correlations between

lipid profile and preeclampsia markers were investigated one by one . For statistical analysis SPSS 11.0 package program was used. Variables evaluated with One Way Anova test. Pearson correlation analysis was applied between laboratory parameters of preeclampsia.

Results

Demographic data as age, gravida, and parity was similar in all groups (p>0.05). Body mass index (BMI) was higher in group 2 than other groups. The difference from group 1 was not significant (p>0.05), but the difference from group 3 was significant (p<0.05). We thought that could be a relation between severe preeclampsia and obesity (Table 1). PT and PTT were similar in all groups (p>0.05) (Table 2). Cholesterol level in group 2 was significantly higher than other 2 groups (p<0.05)(Table 2). Triglyceride and VLDL levels in group 1 and 2

Table 1. Dissociation of demographic characteristics in groups (Median ± Standard erro)r.

	Mild preeclampsia (Group: 1) (n: 27)	Severe preeclampsia (Group: 2) (n:32)	Control (Group: 3) (n: 66)	P value
Age	29.7 ± 1.5	29.2 ± 1.2	28.8 ± 0.5	*, **, ***: p>0.05
BMI	23.3 ± 3.0	23.2 ± 3.2	23.3 ± 2.7	*, **, ***: p>0.05
Gravida	3.9 ± 0.6	3.8 ± 0.5	2.8 ± 0.2	*, ***: p>0.05 **: p<0.05
Parity	3.1 ± 0.5	3.3 ± 05	2.3 ± 0.2,	*, **, ***: p>0.05

*: Comparison between Group 1 and Group 2
**: Comparison between Group 2 and Group 3
***: Comparison between Group 1 and Group 3

Table 2. Dissociation of preeclampsia indicators and lipid profile among groups.

	Mild preeclampsia (Group: 1) (n: 27)	Severe preeclampsia (Group: 2) (n:32)	Control (Group: 3) (n: 66)	P value
Systolic TA(mmHg)	154.9 ± 2.5	182.6 ± 4.5	110.9 ± 1.5	
Diastolic TA(mmHg)	100.9 ± 1.5	108.8 ± 2.4	67.9 ± 1.1	
Amount of proteinuria at urine sample (mg/dL)	116.1 ± 15.9	211.7 ± 14.6	2.3 ± 10.2	
Platelet (K/uL)	265.5 ± 18.1	178.6 ± 16.4	240.1 ± 7.9	
AST(U/L)	32.4 ± 2.5	133.6 ± 22.8	20.5 ± 0.7	
ALT(U/L)	34.0 ± 2.1	96.1 ± 15.0	29.6 ± 0.9	
LDH(U/L)	243.1 ±12.6	526.8 ± 56.2	170.2 ± 5.3	
PT (second)	12.3 ± 0.2	12.6 ± 0.2	12.3 ± 0.2	*,**,***:(p > 0.05)
PTT (second)	28.2 ± 0.8	27.9 ± 0.7	29.5 ± 0.4	*,**,***:(p > 0.05)
Cholesterol (mg/dL)	234.9 ± 9.7	270.3 ± 15.1	240.8 ± 4.5	*,**:(p< 0.05); ***:(p> 0.05)
Triglyseride (mg/dL)	292.9 ± 23.0	306.1 ±22.8	266.8 ± 6.4	**:(p< 0.05); *,***:(p> 0.05)
VLDL (mg/dL)	58.9 ± 4.6	61.2 ± 4.6	53.4 ± 1.3	**:(p< 0.05); *,***:(p> 0.05)
LDL (mg/dL)	119.9 ± 6.4	137.4 ± 9.1	123.0 ± 3.7	*,**,***:(p> 0.05).
HDL (mg/dL)	59.4 ± 3.3	60.5 ± 3.5	68.8 ± 2.3	*,**,***:(p> 0.05).

*: Comparison between Group 1 and Group 2
**: Comparison between Group 2 and Group 3
***: Comparison between Group 1 and Group 3

were increased due to group 3. Only the difference between group 2 and 3 was significant (p<0.05). Group 2 LDL level was higher than other groups, but difference was not significant (p>0.05). HDL level was highest in group 3 but the differences were not significant (p>0.05) (Table 2). Gestational week at labour in group 1 and 2 was very low than group 3 (p<0.01) (Table 3). Cesarean section (C/S) ratio in group 1 and 2 (56%, 62%) was higher than group 3 (p<0.05) (Table 3). Birth weight, 1-minute and 5-minute Apgar scores in group 1 and 2 were very low than group 3 (p<0.01) (Table 3). Pearson correlation analysis was made between some parameters evaluated in our study (Table 4). Positive correlation was determined between amount of proteinuria and cholesterol, TG, VLDL, and LDL (respectively, r: + 0.216, + 0.194, + 0.194, + 0.208; p<0.05). On the other hand there was an inverse correlation between amount of proteinuria and HDL (r: - 0,202; p<0.05). Systolic tension correlated with cholesterol,TG, VLDL (respectively, r: +0.235, +0.311, +0.311; p<0.01) and diastolic tension correlated

Table 3. Dissociation of neonatal results among groups.

	Mild preeclampsia (Group: 1) (n: 27)	Severe preeclampsia (Group: 2) (n:32)	Control (Group: 3) (n: 66)	P value
Birth week	34.9 ± 0.9	35.4 ± 0.7	38.4 ± 0.3	*,**,***:(p< 0.001).
Vaginal delivery	12 (% 44)	12 (% 37.5)	48 (% 73)	
C/S	15 (% 56)	20 (% 62.5)	18 (% 27)	*,**:(p< 0.05); ***:(p> 0.05)
Birth Weight (g)	2403.7 ± 167.2	2381.6 ± 179.1	3399.3 ± 77.9	*,**: (p< 0.01); ***:(p> 0.05)
1-minute Apgar score	5.4 ± 0.6	5.6 ± 0.5	8.0 ± 0.1	*,**: (p< 0.01); ***:(p> 0.05)
5-minute Apgar score	6.9 ± 0.7	7.1 ± 0.6	9.5 ± 0.1	*,**: (p< 0.01); ***:(p> 0.05)

*: Comparison between Group 1 and Group 2
**: Comparison between Group 2 and Group 3
***: Comparison between Group 1 and Group 3

Table 4. Correlation values between lipid profile and other parameters (r values).

	Cholesterol	TG	VLDL	LDL	HDL
Proteinuria	+ 0.216*	+ 0.194*	+ 0.194*	+ 0.208*	- 0.202*
Sys. Tension	+ 0.235**	+ 0.311**	+ 0.311**	+ 0.091	- 0.044
Dia. Tension	+ 0.076	+ 0.280**	+ 0.280**	+ 0.242**	- 0.123
Fetal Weight	- 0.105	- 0.087	- 0.023	- 0.012	+ 0.034
1-minute. Apgar score	- 0.115	- 0.137	- 0.023	- 0.112	+ 0.134
5-minute Apgar score	- 0.127	+ 0.107	+ 0.025	- 0.123	+ 0.131
AST	+ 0.076	+ 0.128	+ 0.028	+ 0.124	- 0.124
ALT	+ 0.126	+ 0.125	+ 0.078	+ 0.129	- 0.144
LDH	+ 0.137	+ 0.108	+ 0.092	+ 0.122	- 0.196*
Platelet	- 0.124	+ 0.127	+ 0.035	- 0.126	+ 0.101
PT	- 0.228*	- 0.127	- 0.023	+ 0.124	+ 0.103
aPTT	- 0.344**	- 0.285**	- 0.285**	- 0.111	+ 0.103

* p < 0.05
** p < 0.01

with LDL, TG, VLDL (r respectively +0.242, +0.280, +0.280; p < 0.01). Hypertension and proteinuria, the most important two diagnostic criteria for preeclampsia, were found to be effected significantly in relation with lipid profile. No relation was found between 1 and 5 minute Apgar scores and lipid profile. At correlation analysis between AST, ALT, LDH and lipid profile, no other relation except negative correlation between LDH and HDL (r: -0.196; p< 0.05) was found. No relation was present between thrombocyte number and lipid profile. Between systolic, diastolic tension and birth weight, 1 and 5 minute Apgar scores negative relation was determined (respectively, r: -0.466, -0.458, -0.409; p< 0.01; respectively, r: -0.476, -0.466, -0.418; p< 0.01). At the correlation between coagulation parameters and lipid profile, there was an inverse correlation between PT and cholesterol levels (r:-0.228; p< 0.05), and no other relation was determined with other lipid parameters. But there was an inverse relation between PTT and cholesterol, TG, VLDL (respectively, r: -0.344, -0.285, -0.288; p< 0.01).

Discussion

At recent times there is a great interest about the role of lipid metabolism on the development of preeclampsia. The previous studies reported that plasma lipid levels were higher in preeclamptic pregnant women than healthy pregnant women.[9,10] It is thought that this lipid changes has a role at endothelial cell damage which is a characteristic symptom of preeclampsia. Oxidized LDL inhibits endotelial prostocycline syntesis and inactivates endothelial derived relaxing factor (EDRF) and also stimulates synthesis and release of endothelin hormone which has vascular smooth muscle contracting effect.[2,3] This changes cause thrombocyte activation that results in thromboxane releasing. In previous studies it has been shown that maternal obesity is an independent risk factor at preeclampsia development.[11] Again in a recent study Bodnar et al asserted BMI as a strong and independent risk factor for preeclampsia development.[12] In our study BMI was the highest in group 2 and the difference with group 3 was significant (p<0.05). Like the studied mentioned above, our result also supports that obesity is a risk factor for preeclampsia (especially severe preeclampsia). In two studies performed previously serum TG levels were found significantly high in early pregnancy in preeclamptic patients.[13,14] Both Ware-Jauregui et al and both Rossing et al reported high TG and low HDL levels in preeclamptic patients compared to control groups in their study.[15,16] Again other studies have also showed that TG rich lipoproteins increased significantly in preeclamptic patients[17,18] James T et al reported that maternal BMI, TG and fatty acids increase significantly in preeclamptic patients.[19] Parallel to this study, we determined increased TG, cholesterol, LDL and VLDL levels in severe preeclampsia cases . Ray et al, in a meta analysis including 19 case-control and 3 prospective cohort study comparing preeclamptic patients to normotensive pregnants, determined TG level high in 14 study, similar in 7 study.[20] Mikhail et al determined TG level high in mild preeclampsia group, but similar in severe preeclampsia group compared to control group and defended that no direct relation exists between TG level and severity of preeclampsia.[21] While Baksu et al found total cholesterol and LDL levels similar in preeclampsia and control groups; they found TG and VLDL levels high and HDL levels low in preeclampsia group.[22] In our study cholesterol level was similar in group 1 and 3, but was high-

er in goup 2 from both groups($p< 0.05$). TG and VLDL levels were the lowest in group 3 and highest in group 2. The difference of group 2 from group 3 was significant ($p<0.05$), the difference from group 1 was not significant. While group 1 level was higher than group 3, the difference was not significant. Although LDL level was the highest in group 2, differences from other groups were not significant HDL level was the highest in group 3, the differences were not significant ($p> 0.05$). As in many studies,[23, 24] 1 and 5th minute Apgar scores were obviously low in preeclamptic patients in our study. Fall et al have shown that fetal growth is in relation with blood pressure, serum lipid, plasma glucose and insulin levels, which are the risk factors for cardiovascular diseases[25] Sattar et al reported that LDL level was decreased in blood samples of mothers who has IUGR fetuses and this can be the reason of IUGR.[26] In our study, birth weight was determined very low in mild and severe preeclampsia group due to control group($p<0.01$). But in correlation analysis we couldn't show any significant relationship between lipid profile and fetal weight. It was claimed that abnormal lipid profile can be in relation with impaired liver function.[27] But we couldn't determined any significant relation between liver function tests (AST, ALT and LDH) and lipid profile. It is thought that increased lipid synthesis is effective at pathogenesis of pregnancy induced hypertension with increasing Thromboxane A2: Prostoglandine I2 (TXA2/PGI2) ratio.[7] Because hypertriglyceridemia causes hypercoagulability in this way.[28] In our study there was a negative correlation between cholesterol level and PT ($p< 0.05$). No relation was determined between other lipid levels and PT. But there was a negative relation between cholesterol, TG, VLDL and PTT ($p< 0.01$).

Conclusion

The changes in lipid profile was related with preeclampsia and especially severe preeclampsia. In correlation analysis hypertension and proteinuria which are the most important two diagnostic criteria for preeclampsia, were found in relation with lipid profile. Previously, in studies performed at early pregnancy period, preeclampsia risk was higher in patients with dyslipidemia.[13,14] When our results interpreted with literature, it must be thought that dyslipidemia could be important cofactor in preeclampsia etiopathogenesis that couldn't been explained up to present.

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Misoprostol Efficacy in Second and Third Trimester Pregnancy Terminations

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Abstract

Objective: Retrospective analysis and evaluating reliability and efficiency of misoprostol in 87 cases having pregnancy termination by using vaginal misoprostol between 12 and 35 weeks' gestation.

Methods: The present study was conducted at Celal Bayar University, Gynecology and Obstetrics Clinic, Perinatology unit between January 2006 and November 2008. A total of 87 cases at more than 12 weeks gestation, including 8 cases having uterine scars due to previous cesarean section and 79 cases having no previous uterine surgery, underwent pregnancy termination and were retrospectively analyzed. In all the cases, the induction agent administered was vaginal misoprostol. In cases having previous cesarean delivery, following the initial dose of 200 µg between 12-24 weeks' gestation and 100 µg at more than 24 weeks', misoprostol was administered 200 µg every 4 hours for a period of 24 hours until contractions started. In cases having no uterine scar, following the initial dose of 400 µg between 12-24 weeks' and 200 µg after 24 weeks', misoprostol was added 400 µg and 200 µg every 4 hours for a period of 24 hours, respectively. If needed, the same dose scheme was repeated after a 12 hours resting period and, in case of failure, an additional method was used.

Results: 53 cases (60.9%) were nulliparous and 34 cases (39.1%) were multiparous. 49 out of 87 (56%) cases were between 12 and 20 weeks' gestation, while 38 (44%) cases were at more than 20 weeks'gestation. The median induction-to-termination interval which was 28.5 h (1-137 h) for all the cases was 30.8 h in nulliparous cases and 24.8 h in multiparous cases, and no statistically significant difference was detected (p=0.32). In 16 cases duration of pregnancy termination was over 48 h. In 10 cases (11.5%) pregnancy termination was achieved by using an additional method. Compared to the cases having no uterine scar, additional methods were used significantly more in cases having previous cesarean delivery (25% versus 10%; p=0.000). 2 cases developed complications (23%): fever and hemorrhage in one case and hemorrhage in one case. 1 case underwent cesarean section due to hemorrhage. No uterine rupture was observed in the cases.

Conclusion: Using vaginal misoprostol is a fairly safe, efficient and non-invasive method in second and third trimester pregnancy termination. However, studies with wider series are needed to assess reliability of using misoprostol in cases with uterine scarring.

Keywords: Misoprostol, Termination of pregnancy, Induction, Second and third trimester.

İkinci ve üçüncü trimestr gebelik sonlandırmalarında misoprostol etkinliği

Amaç: 12-35.gebelik haftaları arasında vajinal misoprostol kullanılarak sonlandırma yapılan 87 olgunun retrospektif analizi ve 2. ve 3.trimestr gebelik sonlandırmalarında misoprostol kullanımının güvenilirlik ve etkinliğinin değerlendirilmesi

Yöntem: Bu çalışmaya Ocak 2006 ve Kasım 2008 tarihleri arasında Celal Bayar Üniversitesi Kadın Hastalıkları ve Doğum Kliniği Perinatoloji polikliniğine başvuran ve 12 haftanın üzerinde gebeliği sonlandırılan toplam 87 olgu dahil edildi. Sezaryan nedeniyle uterusta skarı olan 8 olgu ve geçirilmiş uterus cerrahisi olmayan 79 olgunun retrospektif analizi yapıldı. Tüm olgulara indüksiyon ajanı olarak vajinal misoprostol uygulandı. Sezaryan geçirmiş olgularda kontraksiyonlar başlayana kadar 12-24. haftalar arasında 200 µg, 24. haftadan sonra 100 µg misoprostol başlangıç dozunu takiben her 4 saatte bir 200 µg eklenerek 24 saat bitimine kadar devam edildi. Uterusta skarı olmayan olgularda ise 12-24. haftalar arasında 400 µgr başlangıç dozu sonrası her 4 saatte bir 400 µg, 24. hafta-

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dan sonra 200 µg başlangıç dozunu takiben her 4 saatte bir 200 µg uygulandı. 24 saat bitiminde kontraksiyonların başlamaması durumunda 12 saatlik dinlenme periyodunu takiben aynı doz şeması tekrarlandı, gerekirse başka bir yöntem de eklendi.

Bulgular: 53 vaka (%60.9) nullipar, 34 vaka (%39.1) multipardı. 49 (%56) olgu 12-20. gebelik haftaları arasında, 38 (%44) olgu 20. gebelik haftasının üstündeydi. İndüksiyon başlangıcı ile gebeliğin sonlanması arasında geçen ortalama süre tüm vakalar için 28.5 saat (1-137 saat), nulliparlarda 30.8 saat, multiparlarda ise 24.8 saat idi, istatistiksel anlamlı farklılık saptanmadı (p=0.32). 16 vakada (%18) gebeliğin sonlanma süresi 48 saatin üstündeydi. 10 vakada (%11.5) sonlandırmanın tamamlanması için ek bir yöntem kullanımı gerekti. Sezaryan geçirmiş olgularda ek yöntem kullanımı uterusta skarı olmayan olgulara göre anlamlı yüksekti (sırasıyla % 25, % 10; p=0.000). 1 olguda ateş ve kanama, 1 olguda ise kanama olmak üzere 2 olguda komplikasyon gelişti (%2.3), her 2 olguda nullipardı. Kanama nedeniyle 1 olguya sezaryan seksiyo yapıldı. Uterus rüptürü hiçbir vakada görülmedi.

Sonuç: Vaginal misoprostol kullanımı ikinci ve üçüncü trimester gebelik terminasyonu için oldukça etkili, güvenli ve non-invaziv bir yöntemdir. Ancak uterusta skarı olan olgular için güvenilirliği açısından daha geniş serili çalışmalar gereklidir.

Anahtar Sözcükler: Misoprostol, Gebelik terminasyonu, İndüksiyon, İkinci ve üçüncü trimestr.

Introduction

In recent years, prostaglandins and its analogs have been widely used for medical abortion in obstetrics practice. Today, increasing antenatal diagnosis of fetal malformations with prenatal ultrasonography and serum screening tests[1] and labor induction in 15% of all pregnancies[2] increase use of prostaglandin for this purpose. Also, increasing number of cesarean deliveries[3] and pregnancy termination due to medical indications increase use of prostaglandin analogs in patients with a history of previous cesarean. Pregnancy termination by using prostaglandins and its analogs provide a safe alternative to surgical termination.[4] Misoprostol is a synthetic prostaglandin E1 analog used in prophylaxis and treatment of gastroduodenal ulcers, and its usage in pregnancy is contraindicated due to its uterotonic effect.[5] Basic aims in the second and third-trimester pregnancy terminations are achieving a safe, effective, inexpensive and fast termination with minimum adverse effects. Owing to these, using misoprostol for induction is very common although it is not licensed in many countries.[6] Misoprostol is a cheap drug that does not require special transfer and storage conditions as other prostaglandin analogs used previously. It can be administered orally and causes less gastrointestinal adverse effects. Recently, it has been used to induce labor in live term fetuses too.[7] However, more uterine tacyhsystole[8] and uterine rupture when administered vaginally in the second trimester pregnancy terminations in women having a history of cesarean section[9] prevent elimination of concerns about this drug. Although there are increasing number of publications demonstrating that misoprostol is safe in the second trimester pregnancy termination in cases having uterine lower segment transverse incision,[10] real incidence of uterine rupture is not known. In this retrospective study, our aim was to evaluate the safety and efficacy of using intravaginal misoprostol in inducing of the second and third trimester pregnancy terminations.

Methods

In the present study, retrospective analysis were performed on 87 cases whose pregnancies were terminated by vaginal misoprostol at more than 12 weeks gestation due to maternal or fetal indications at Celal Bayar University Gynecology and Obstetrics Clinic Perinatology Unit between January 2006 and November

2008. Parity, gestation week, obstetric history, presence of uterine scar, requirement of additional method, indications, induction-to-termination interval and delivery complications were recorded for all the cases. After getting the approval of Celal Bayar University, Medical Faculty, Perinatology Committee for termination of pregnancies, all the patients were informed on the issue that misoprostol is not licensed for pregnancy terminations and asked to sign an informed consent form that includes detailed information on complications.

Vaginal misoprostol protocol to be used for termination was determined according to the gestational week and presence of uterine scar. 1x200 μg misoprostol was placed in the posterior vaginal fornix in pregnancies having uterine scar due to previous cesarean section while 2x200 μg misoprostol was used in cases having no uterine scar at less than 24 weeks gestation. During the first 24 hours following the initial dose, vaginal misoprostol administration at initial dose was repeated every 4 hours until uterine contractions started. Before misoprostol administration at more than 24 weeks gestation in pregnancies with live fetuses, fetocide was performed by intracardiac lethal dose potassium chloride administration under ultrasonographic guidance. Then, 1x100 μg and 1x200 μg vaginal misoprostol was started in cases having uterine scar and cases without uterine scar, respectively. When contractions did not start, 1x200 μg misoprostol was administered every 4 hours. If contractions did not start at the end of the first 24 hours, dose scheme appropriate to the characteristics of the cases in both groups were repeated the same way after a 12 hours rest period. When pregnancy termination was not completed after 48 hours following the initial misoprostol administration, an additional method was used. Additional methods included using oxytocin, foley catheter in cervical channel and traction or termination of pregnancy by cesarean section. Epidural analgesia was used for pain management when requested by the cases.

Following vaginal misoprostol administration, vital signs and adverse effects observed in the cases were recorded every 4 hours. In cases having fever was equal to or more than 38.5 C, 1 gr paracetamol and, if needed, cold compress were used. When required, 10 mg metoclopramide or 50 mg cyclizine were administered as antiemetic agents every 8 hours. While induction-to-termination interval was defined as the time that elapsed from the initial misoprostol administration until fetal expulsion, the need to use an additional method for termination was defined as failure of misoprostol. 1 hour was allowed for placenta removal after fetal expulsion. Patient was examined carefully by ultrasonography to see whether complete removal of fetus and placenta was achieved. When incomplete termination was suspected or findings of rest placenta were present, surgical evacuation of the uterus was planned, and all the cases were followed for bleeding control at delivery service for 2 hours. All women were called for controls 1 month after termination.

All the data obtained from the cases were evaluated using SPSS (15.0 for Windows) program. In statistical evaluations Mann-Whitney U test was used for continuous variables and chi-square test was used for categorical vari-

Table 1. Characteristics of the study group.

	Nulliparous (n=53)	Multiparous (n=34)	Total (n=87)
Mean maternal age (±SD)	25.33 (±4.62)	31.16 (±5.1)	27.6 (±5.5)
Gestational age at termination (±SD)	18.77 (±5.34)	20.81 (±6.83)	19.74 (+5.65)
Pregnancy ?24 weeks' gestation (%)	14 (26.4)	18 (53)	32/87 (37)

Table 2. Indications for termination.

Indication	n	(%)
Trisomy 21	3	(3.5)
Chromosal abnormalities other than trisomy 21	2	(2.3)
IUMF	10	(11.5)
Anhydramnios	9	(10.3)
Maternal disease	3	(3.5)
Other congenital abnormalities	53	(60.8)
Hydrops fetalis	4	(4.6)
Teratogen	1	(1.2)
Twin-to-twin transfusion syndrome	2	(2.3)

ables. P<0.05 was considered as statistically significant.

Results

In this study, results obtained from 87 women having termination between 12 and 35 weeks' gestation in a 3 years period were analyzed. Table 1 shows the characteristics of the women who underwent vaginal misoprostol induced termination at the second and third trimesters and Table 2 shows termination indications.

53 cases (60.9%) were nulliparous and 34 cases (39.1%) were multiparous. While no significant difference was observed between nulliparous and multiparous cases with respect to induction-to-termination interval (p=0.32), required total misoprostol dose was significantly higher in nulliparous women (p=0.019). Treatment results are given in Table 3. In 49% of the cases, termination was achieved in the first 24 hours. While the ratio of nulliparous women terminating within 24 hours after misoprostol administration was 52%, the ratio of multiparous women terminating within 24 hours was 44%. Pregnancy was terminated within 36 hours in 63% of the cases while termination was achieved within 48 hours in 70% of the cases. All the terminations were completed in 4 days. Only in one case, termination was not achieved despite using an additional method to misoprostol induction, and cesarean section was used for delivery. In the said case having in utero mort fetus at 17 weeks' gestation, termination was tried to be achieved vaginally using other also additional methods due to bleeding, but upon failure, cesarean decision was taken after 55 hours.

In 90.8% of the cases (n=79), there was no uterine surgery history while 9.2% had previous

Table 3. Treatment results of women having termination by misoprostol during the second and third trimester.

	Mean dose of misoprostol (μg)	Mean induction-to-abortion time (hours)
Nulliparous (n=53)	1200 (±802.6)	30.8 (±21.6)
Multiparous (n=34)	800 (±702.2)	24.8 (±28.35)
Total (n=87)	1035 (±783.44)	28.5 (±24.32)
P	0.019	0.32

Table 4. Complication rates and abort intervals in pregnant women having an abortion between 12 and 24 and > 24 weeks' gestation.

	12-24 weeks' gestation (n=55)	>24 weeks' gestation (n=32)
Mean induction-to-abortion interval (hours) (±SD)	27.7 (±24.6)	31.3 (±24.6)
Misoprostol failure (%)	1 (%1.8)	0
Fewer (%)	1 (%1.8)	0
Hemorrhage (%)	1 (%1.8)	0
Using additional method (%)	8 (%14.5)	2 (%6.3)

cesarean section. 3 cases out of those having previous cesarean section were at more than 24 weeks' gestation. Additional methods were required in 11.5% (n=10) of all the cases. 7 of the cases requiring additional methods were nulliparous, 3 were multiparous and there were two previous cesarean section cases among them. Both of these 2 cases having previous cesarean section and in whom additional methods were used for pregnancy termination were at more than 24 weeks' gestation; and foley catheter was inserted in cervical channel in 1 of them being at 28 weeks' gestation. The other case was at 34 weeks' gestation and her pregnancy was terminated using oxytocin additionally. Additional method was used when termination was not achieved when 48 hours elapsed after vaginal misoprostol administration and beginning of induction. Only in one case, additional method was used before 24 hours due to bleeding and oxytocin was added for termination in this case. Surgical evacuation of uterus due to placental retantion was needed in none of the cases.

Mean induction-to-termination interval was 31.3 hours in cases at more than 24 weeks' gestation while the said interval was 27.7 hours in those at less than 24 weeks' gestation; and there was no significant difference (p=0.62). In 2 cases at more than 24 weeks' gestation, termination was achieved by using an additional method; however no complications developed in these cases. Among all patients, complications after induction by misoprotol were observed in 2 cases. One case had hemorrhage while the other had both fever and hemorrhage. Both of these cases were at less than 24 weeks' gestation and nulliparous. Pregnancy was terminated by cesarean section in one of these cases while oxytocin was used for termination in the other case. Table 4 shows a comparison of cases at more than 24 weeks' and less than 24 weeks' gestation with regard to induction-to-termination intervals and complication rates.

Discussion

Misoprostol has been widely used in induction of pregnancy terminations during the second and third trimesters.[6] However, there exist a great range of variation in its administration route, frequency and dose. Misoprostol providing a noninvasive regimen for termination of pregnancy offers many advantages such as oral, rectal, sublingual or vaginal administration, low cost, stability at room temperature; and different doses of misoprostol have been shown to be effective.[11] However, effective minimum dose, either orally or vaginally, for labor induction or pregnancy termination with minimum adverse effects both for fetus and mother in case of presence of a live fetus should be evaluated in further studies.[7,12] There exist no standard regimen scheme neither for induction of labor in the third trimester nor for pregnancy termination in the second and third trimesters.

Pregnancies were terminated by vaginal misoprostol induction in 88.5% of our cases; however, in 11.5% of the cases an additional method was required along with misoprostol. Chawdhary et. al.[13] compared mifepristone oral followed by vaginal misoprostol (RU 486) with misoprostol alone for pregnancy terminations during first trimester and found that mifepristone oral followed by vaginal misoprostol provides a better success rate with fewer complications. They reported a success rate of 94% with combined mifepristone and vaginal misoprostol and 86% with only vaginal misoprostol. However, they stated that misoprostol alone was not as successful as combined regimen due to some limitations of their study. In a retrospective analysis of 252 cases, Mazouni et al.[14] showed a 99.2% success by combined vaginal misoprostol and mifepristone administration in pregnancy terminations at more than 15 weeks' gestation. In a study where they used a combination of misoprostol and mifepristone, Tang et al.[15] showed that sublingual administration was more effective than oral administration. In another study where they used only misoprostol,[16] they reported a success rate of 95% in vaginal administration and 91% success rate in sublingual administration after 48 hours. Similarly, in a retrospective study, Goh et al.[17] achieved termination of pregnancy at between 12 and 24 weeks' gestation by vaginal misoprostol with later addition of mifepristone, if required, and reported that termination was completed 97.9% and 99.5% after 24 and 36 hours from the beginning of termination respectively. Mifepriston is an antagonist of progesterone receptor and it has been shown that using mifepristone before analogue in second trimester pregnancy terminations with prostaglandin analogue decreases the time that elapses from the initial administration of prostaglandin until fetus expulsion.[18] This antigestagen sensitizes the pregnant uterus to exogenous prostaglandin. However, misoprostol is more commonly used in developing countries as it is cheap and requires no special storage conditions compared to mifespristone which is an expensive and requires special storage conditions. Bhattacharjee et al.[19] compared sublingual and vaginal administration of misoprostol in second trimester pregnancy terminations and found that both of the methods were equally effective. The failure rate was 9.42% after 48 hours in vaginal administration, which is a consistent with the results (9.5%) of Wong et al.[20] but higher than the rate (5%) reported by Tang et al.[16] While misoprostol was initially administered orally, today vaginal administration is preferred. Pharmokinetic studies showing that systemic bioavaliability of vaginally

administered misoprostol is three times higher than that of misoprostol administered orally supports its vaginal administration.[21] Behrashi et al.[22] compared oral and vaginal misoprostol administration in second trimester pregnancy terminations and found that vaginal administration of misoprostol resulted in a higher success rate with no significant differences in induction to delivery time and complications rates between vaginal and oral administration. By vaginal administration of misoprostol, in our study, we obtained a success rate of 85% in pregnancies at less than 24 weeks and 93.7% in those at more than 24 weeks, which makes a total success rate of 88.5%. In our study, termination was achieved within 48 hours in 70% of the cases. Except one case, all the pregnancies were terminated in 96 hours. Our results are not as high as those of the clinic studies reporting very high success rates; however, when compared to that of Tang et al.,[16] we used lower doses of misoprostol and observed fewer complications. Tang et al.[16] found that incidence of fever increased significantly in vaginal administration and there existed no significant difference between sublingual and vaginal administration with respect to other complications. They reported that this could have resulted from the higher bioavaliability of repeated vaginal misoprostol. As a result, Tang et al. stated that vaginal misoprostol should the first choice but sublingual administration could be used as an alternative. In our study, we observed fever in 1 case and hemorrhage in 2 cases. Compared to multiparous women, the total misoprostol dose used for termination was significantly higher in nulliparous women and although there was no statistically significant difference with respect to mean induction-to-termination interval between nulliparous and multiparous women, it was longer in nulliparous women. These results are consistent with the results of the previous studies reporting a difference between responses of nulliparous and multiparous women to induction agents.[17,23] Goh et al.[17] stated that this could be resulted from the difference between cervical compliances of two groups. Goh et al. reported that, compared to nulliparous women, surgical evacuation of uterus was twice more in multiparous women and stated that the same result had been obtained in some previous studies too. Goh et al. completed termination surgically if bleeding was more than 500 ml during fetus or placenta removal. Bartley et al.[24] stated that more efficient establishment of pregnancy in multiparous women might cause this. 37% of our cases were at more than 24 weeks' gestation, and mean induction-to-termination interval was moderately longer in these cases. Mozouni et al.[14] showed in their analysis that when terminations were achieved by misoprostol and mifepristone, pregnancies at more than 24 weeks' gestation were associated with longer induction interval and higher morbidity. However, with respect to morbidity in pregnancies at more than 24 weeks' gestation, results of our study differ from that of Mazouni et al. 8 of the 10 cases requiring additional method for termination were at less than 24 weeks' gestation and similarly 2 cases having complications were at less than 24 weeks' gestation too. However, compared to our study, Mazouni et al.[14] studied significantly more cases in their analysis.

Today, clinicians do not use a standard protocole in using misoprostol for pregnancy terminations. There is no consensus with respect to the administartion way, dose and frequency

as there is a few number of well planned randomized controlled trials on this subject. It has been found that vaginal administration is more effective than oral administration, possibly because of accumulation at plasma levels and causes less gastrointestinal complications.[21,25] However, there is a variability in the absorption of vaginally administered misoprostol among different individuals. For this reason, sublingual administration is favored; there may be variability in the absorption among different individuals but it has been reported that it reaches high serum peak concentrations by rapid absorption.[26] Tang et al.[16] reported in their study that patients prefer sublingual administration.

In pregnancies at more than 12 weeks' gestation, pregnancy terminations are carried out by medical methods rather than surgical procedures. Morbidity is lower in termination achieved by medical methods,[4] and genetic analysis of fetus is possible. Adverse effects of prostaglandins are related mainly dose. However, various administration methods, dose schemes and intervals related to misoprostol make it hard to compare data. In our study, complications were observed in only 2 cases and both of these cases were nulliparous. Requirement of higher misoprostol dose in nulliparous women may lead to this result. Sanches-Ramos et al.[9,27] showed in a study and meta-analysis that use of misoprostol increases risk of tachysystole and hyperstimulation without causing negative perinatal outcomes. Dodd et al.[6] found that use of misoprostol causes adverse effects at a low rate in the second and third trimester pregnancies; however, they showed that data were not sufficient to evaluate rare but life threatening complications such as uterine rupture. It has been drawn attention to the fact that history of cesarean section is not a contraindication for using misoprostol but there exist an increased risk of uterine rupture regardless of the gestational week.[8] In a retrospective analysis of 91 cases, Aslan et al[28] showed that induction of delivery with misoprostol causes a two fold increased risk of uterine rupture in women with previous cesarean section and they stated that one should be careful with respect to maternal reliability.

In our study we obtained a success rate of 88.5% by misoprostol in second and third trimesters pregnancies and termination was achieved by using an additional method in 11.5% of the cases. Among those where an additional method was used, in only one case, we had to terminate pregnancy by cesarean section due to hemorrhage. Our complication rate (2.3%) was rather low. With respect to failure of misoprostol, although some of which report lower rates,[16] our results are in consistency with many studies in the literature.[19,20,22] Taking these data into consideration, we can say that misoprostol is highly effective and reliable in second and third trimester pregnancy terminations.

Although number of cases with a history of cesarean section is low in our study, no complications related to misoprostol were observed in these cases. Additional methods were used two times more in terminating pregnancies of cases having history of cesarean section but these additional methods did not increase the risk of complications.

Conclusion

For standard usage of misoprostol in the future, detecting optimal dose and optimal administration method should be the most important concern of the studies. Thus, evalua-

tion of rare complications such as uterine rupture would be more objective and satisfactory. Once optimal dose and intervals are detected, further studies involving larger samples and multiple centers are required.

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Comparison of Maternal Serum Adiponectin and Leptin Measurements in Screening and Diagnosis of Gestational Diabetes Mellitus

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Abstract

Objective: To compare and to evaluate the measurements of maternal serum adiponectin and leptin levels in screening and diagnosis of gestational diabetes mellitus (GDM).

Methods: Two hundred and twelve pregnant women who were between 24-28 gestational weeks followed in our clinic and investigated concomitantly in two different studies ("Role of Serum Leptin Levels and Oxidative Stress Test in Screening and Diagnosis of Gestational Diabetes Mellitus" and "Role of Serum Adiponectin Levels in Screening and Diagnosis of Gestational Diabetes Mellitus") were included in our study. Single step 75 g oral glucose tolerance test (OGTT) was performed in 96 cases whereas two steps 50/100 g OGTT was performed in 116 cases and leptin and adiponectin levels have been measured in all women. The cut-off value has been accepted as 10.3 µg/ml for adiponectin and 43 ng/ml for leptin. Sensitivity and specificity of leptin and adiponectin are compared statistically.

Results: GDM has been diagnosed in 31 (26.7%) of 116 cases who underwent two steps OGTT and 23 (24.0%) of 96 cases who underwent single step OGTT. GDM was detected in 54 (25.5%) in total. Adiponectin levels were significantly low in patients with GDM compared to women without GDM in both 75 g and 50/100 g OGTT groups (p:0.001 and p: 0.007 respectively). Leptin levels were significantly high in patients with GDM compared to women without GDM in 75 g OGTT group (p: 0.021), but there was no significant difference in cases and controls in 50/100 g OGTT group. (p: 0.08) In 75 g OGTT group sensitivity, specificity and positive predictive value (PPV) of adiponectin is 85%, 53% and 65.3% respectively whereas in 50/100 g OGTT group sensitivity, specificity and PPV of adiponectin was 82%, 40% and 57.7% respectively. In 75 g OGTT group sensitivity, specificity and PPV of leptin was 70%, 55% and 60.8% respectively.

Conclusion: If these cut-off values are taken, in 75 g OGTT group adiponectin is more sensitive than leptin, and adiponectin is as equally specific as leptin. In 50/100 g OGTT group adiponectin is significantly lower in patients with GDM compared to women without GDM and leptin levels are not significantly different in two subgroups.

Keywords: Gestational diabetes mellitus, adiponectin, leptin, oral glucose tolerance test.

Gestasyonel diabetes mellitus tanı ve taramasında maternal serum adiponektin ile leptin ölçümlerinin karşılaştırılması

Amaç: Gestasyonel diabetes mellitus (GDM) tanı ve taramasında maternal serum adiponektin ve leptin ölçümlerinin karşılaştırmalı olarak irdelenmesi.

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Yöntem: "Gestasyonel Diabetes Mellitus Tanı ve Taramasında Serum Leptin Seviyesi, Oksidatif Stres Testin Önemi" başlıklı uzmanlık tezi ile eş zamanlı olarak yürütülen "Gestasyonel Diabetes Mellitus Tanı ve Taramasında Serum Adiponektin Önemi" başlıklı uzmanlık tezinde incelenen ve kliniğimizde takipleri yapılan 24-28 gebelik haftaları arasındaki 212 gebenin 96'sına tek aşamalı 75 gr OGTT ve 116'sına iki aşamalı 50/100 gr OGTT gebelik diyabeti tarama testi uygulanarak, tüm gebelerde aynı anda leptin ve adiponektin değerleri ölçüldü. Eşik değer adiponektin için 10.3 µg/ml, leptin için 43 ng/ml olarak alındı. İstatistiksel değerlendirmeler sonucunda leptin ve adiponektinin GDM tanı ve taramasındaki duyarlılık ve özgüllükleri karşılaştırıldı.

Bulgular: Yüz on altı hastadan oluşan iki aşamalı test grubunun 31'inde (%26.7) GDM tespit edilirken, 96 gebeden oluşan tek aşamalı test grubunun 23'ünde (%24.0) GDM tespit edildi. Toplam 212 hastanın 54'ünde (%25.5) GDM olduğu görüldü. Adiponektin düzeylerini incelediğimizde 75 gr ve 50/100g OGTT ile GDM saptanan gebelerde anlamlı derecede düşük olduğu görüldü (sırasıyla p: 0.001 ve p: 0.007). Leptin düzeylerine baktığımızda 75 gr OGTT ile GDM saptanan gebelerde leptin düzeyi anlamlı derecede yüksek (p: 0.021) bulunurken, iki aşamalı test ile GDM saptanan gebeler ile normal gebeler arasındaki fark anlamlı değildi (p: 0.08). Tek aşamalı 75 gr OGTT uygulanan grupta adiponektinin GDM tanı ve taramasındaki duyarlılığı %85, özgüllüğü %55, pozitif prediktif değeri (PPV) 65.3%; iki aşamalı 50/100 gr OGTT uygulanan grupta adiponektinin duyarlılığı %82, özgüllüğü %40, PPV %57.7 olarak hesaplandı. Tek aşamalı 75 gr OGTT uygulanan grupta leptinin GDM tanı ve taramasındaki duyarlılığı %70, özgüllüğü %55, PPV %60.8 olarak hesaplandı.

Sonuç: Gestasyonel diyabetin tanı ve taramasında uygulanan 75 g OGTT uygulanan grupta belirtilen eşik değerler kabul edildiğinde adiponektin, leptine kıyasla daha duyarlı; leptin ise adiponektinle eşit özgüllükte bulunmuştur. Buna karşılık 50/100 g OGTT uygulanan grupta adiponektin anlamlı derecede düşük bulunmuş, leptin değerlerindeki yüksekliğin istatistiksel olarak anlamlı olmadığı gösterilmiştir.

Anahtar Sözcükler: Gestasyonel diabetes mellitus, adiponektin, leptin, oral glukoz tolerans testi.

Introduction

Adiponectin is secreted from the adipose tissue and is the most abundant adipokine in circulation and it plays a key role in metabolic syndrome.[1] The plasma level is 2-30 µg/ml. Adiponectin has anti-inflammatory, anti-atherosclerotic and anti-diabetogenic effects. The most well-known effect of adiponectin is regulation of insulin sensitivity. Leptin is a hormone which is coded on the ob/ob gene, in the long arm of the 7th chromosome (7q31) mainly secreted from adipose tissue. It's first detected as a mutagenic gene product in ob/ob mutant rats.[2,3] In addition to adipose tissue, it's also shown to be secreted from placenta, gastric epithelium, skeletal muscle, pituitary gland and mammary glands.[4] Various methods have been suggested to be performed in screening and diagnosis of gestational diabetes mellitus (GDM). In some countries 75 g oral glucose tolerance test (OGTT) is used whereas in some others 100 g following 50 g OGTT are used. The populations screened for GDM are also different in different regions of the world, in some countries routine screening in all pregnant women is performed and in some countries only high risk women are screened. Leptin levels are shown to decrease and adiponectin levels are shown to increase significantly in GDM. According to the aim of the test, the cut-off values can be changed and the sensitivity and specificity may be adjusted. Our objective is to discuss if adiponectin and leptin can replace OGTT in screening and diagnosis of GDM as well as to determine which one of these markers is more sensitive or specific.

Methods

Two hundred and twelve pregnant women between 24-28 gestational weeks who were investigated in two concomittant studies performed in University of Istanbul, Cerrahpasa Medical Faculty, Department of Obstetrics and Gynecology: "Role of Serum Leptin Levels In

Screening and Diagnosis of Gestational Diabetes Mellitus and Importance of Oxidative Stress Test" and "Role of Adiponectin In Screening and Diagnosis of Gestational Diabetes Mellitus" and were followed in our clinic have been included. Our study is designed as a comperative study. All 212 pregnant women included in the study "Role of Serum Leptin Levels in Screening and Diagnosis of Gestational Diabetes Mellitus and Importance of Oxidative Stress Test" and the same 212 pregnant women which are a part of the 274 women included in the study "Role of Adiponectin In Screening and Diagnosis of Gestational Diabetes Mellitus" were enrolled into the comperative study. Single and two steps OGTTs were performed and presence of GDM was investigated. Blood samples were collected from all women and adiponectin and leptin levels were measured and compared. Gestational ages of the women were calculated according to the last menstrual period and early pregnancy ultrasound measurements if in doubt. 10 cc of venous blood samples from all patients in the study group were collected in dry tubes before performing the diabetes screening tests between 24-28 GWs. Serum parts were separated and preserved in -80°C till target patient population is reached to be evaluated at once. Leptin and adiponectin levels were measured in biochemistry laboratory. GDM screening and diagnosis tests were performed between 24-28 GWs in all 212 patients. Single step 2 hours 75 g OGTT was performed in 125 patients. The test results were interpreted according to the ADA criteria (≥2 values above treshold, fasting glucose levels: 95 mg/dl, 1 hour: 180 mg/dl, 2 hours 155 mg/dl). Two steps 50 g OGTT was performed in 149 patients. The patients with 1 hour blood glucose levels of ≥140 mg/dl were accepted as screening test positive according to ADA and ACOG criteria. The diagnostic test was performed in screening test positive patients after a 3 days standard diet (at least 250 g of daily carbonhydrate). After a fasting period of 12-16 hours, the blood samples were collected at 8 am and the 1st, 2nd and 3rd hours. Carpenter and Coustan's criteria were considered in the interpretation of 100 g OGTT and ≥2 levels above treshold (fasting: 95 mg/dl, 1 hour 180 mg/dl, 2 hour 155 mg/dl, 3 hour 155 mg/dl) were accepted to have GDM. Serum leptin levels were measured by a kit which is based on ELISA (Human Leptin Elisa DSL-10-23100i, Texas, USA). Leptin levels are expressed in ng/ml. Serum adiponectin levels were measured by a kit which is based on ELISA (Human adiponectin assaypro catalog no: EA2500-1). Adiponectin levels are expressed in microgram/ml (μg/ml). Cut off values were taken as 10.3 μg/ml for adiponectin and 43 ng/ml for leptin. Sensitivity and specificity rates of leptin and adiponectin in screening and diagnosis of GDM were compared statistically. Statistical Package for Social Sciences (SPSS Release 11,5, SPSS inc., Chicago, IL, USA) was used during statistical calculations. Student's t test was used for parametric variables and chi-square test was used for comparing qualitative data. 0.05 was accepted as treshold for statistical significance. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and area under curve values were calculated ROC (Receiver operating characteristic) curves.

Results

GDM was detected in 54 (25.4%) of 212 pregnant women. Two steps OGTT was performed in 116 cases and single step OGTT was performed in 96 women. These two groups were similar in age, gravidity, parity, maternal

weight, body mass index and gestational weeks at the time of test. GDM was diagnosed in 31 (26.7%) of 116 pregnant women who underwent 50/100 g OGTT and 23 (24%) of 96 pregnant women who underwent 75 g OGTT. Mean leptin concentration was 49.36±14.5 ng/ml in women with GDM compared to 40.10±17.12 ng/ml in women without GDM in 75 g OGTT group. This difference is found to be significant. (p:0.021) However the difference between two groups was not significant in 50/100 g OGTT group (44.41±15.22 ng/ml vs 38.29±17.02 ng/ml, p: 0.08). Area under curve (AUC) values were calculated from the ROC curves drown which was based on the leptin levels of the OGTT results of 212 women. (Graphic 1 and 2) AUC values were 0,653 for 75 g OGTT and 0.613 for 50/100 g OGTT. The treshold for leptin was set as 43 ng/ml. In 75 g group sensitivity, specificity and PPV are found to be 70%, 55% and 60.8% respectively. In 50/100 g OGTT group sensitivity and specificity are found to be 48% and 63% respectively, but since there's no statistical difference between cases and controls, these sensitivity and specificity values have no clinical benefit. Adiponectin levels of GDM patients diagnosed by 75 g OGTT had a median of 11.7±6.4 µg/ml, and normal patients had a median of 17±6.5 µg/ml, this difference was statistically significant. (p:0.001) Adiponectin levels of GDM patients diagnosed by 50/100 g OGTT had a median of 12.8±5.3 µg/ml, and normal patients had a median of 16.2±6.7 µg/ml. (p: 0.007) AUC was detected to be 0.734 for 75 g OGTT [0.73, Confidence interval (CI) %95, 0.60-0.76] and

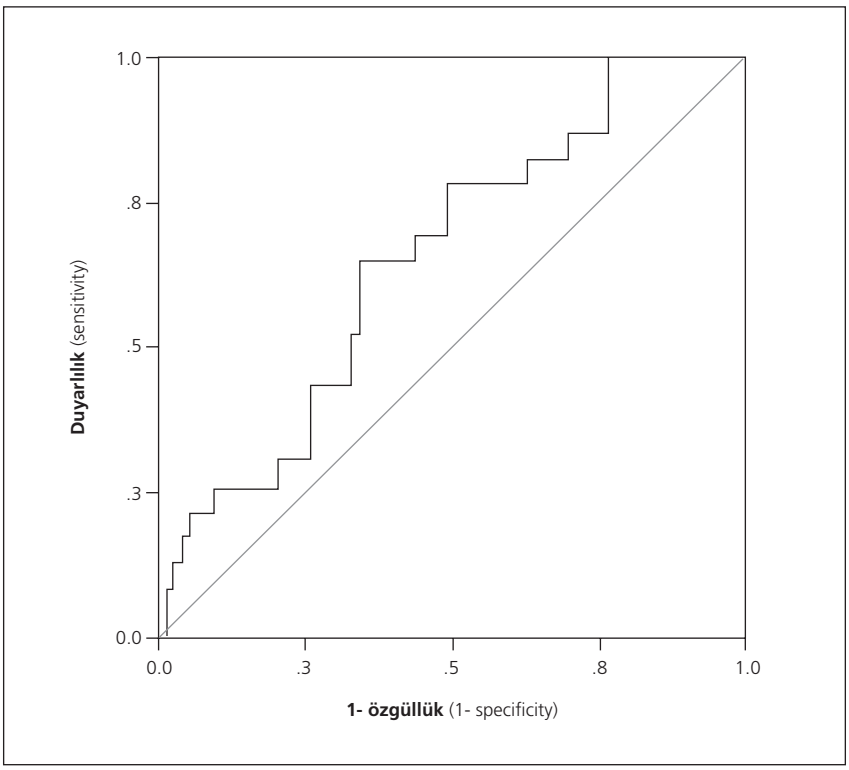

Figure 1. ROC curve for serum leptin levels in 75 g OGTT group.

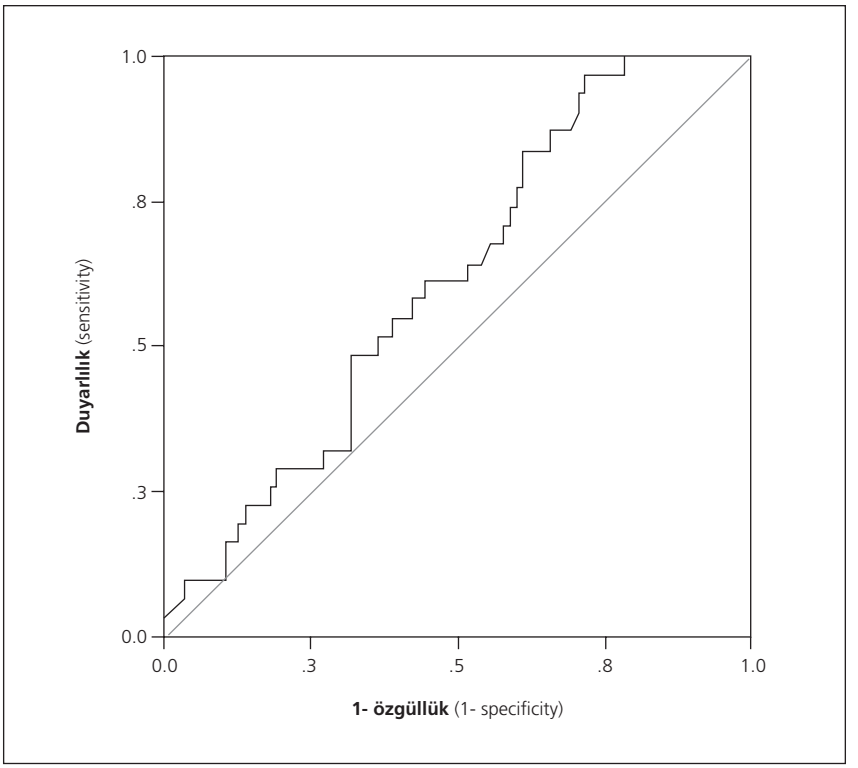

Figure 2. ROC curve for serum leptin levels in 50/100 g OGTT group.

0,617 for 50/100 g OGTT [0.61, Confidence interval (CI) %95, 0.49-0.73]. If we accept the treshold as 10.3 μg/ml, the sensitivity, specificity and PPV were 85%, 55% and 65.3% for 75 g OGTT and 82%, 40% and 57.7% for 50/100 g OGTT respectively (Figures 3 and 4) If cut-off value of adiponectin was taken as 5.3 μg/ml, sensitivity was 100% and specificity was 18% in 75 g OGTT group. If cut-off value was taken as 27 μg/ml, sensitivity was 11%, specificity is 100%. In our study, there are 4 and 8 patients whose adiponectin level was ≤5.3 μg/ml and ≥27 μg/ml respectively. If cut-off value of adiponectin was taken as 7 μg/ml, sensitivity was 100% and specificity was 23% in 50/100 g OGTT group. If cut-off value was taken as 20,5 μg/ml, sensitivity was 25%, specificity was 100%. In our study, there are 7 and 27 patients whose adiponectin level was ≤7 μg/ml and ≥20.5 μg/ml respectively. In conclusion if these cut-off values are taken, in 75 g OGTT group adiponectin is more sensitive than leptin, and adiponectin is as equally specific as leptin. In 50/100 g OGTT group adiponectin is significantly lower in patients with GDM compared to women without GDM and leptin levels are not significantly different in two subgroups.

Discussion

Gestational diabetes mellitus (GDM) is the most common complication seen during pregnancy. It threatens both mother and her fetus, hopefully pregnancy outcomes are much better if glycemic control is achieved. That's why today, GDM is a disorder which must not remain unnoticed. Different screening methods are used in different countries. In our clinic, we

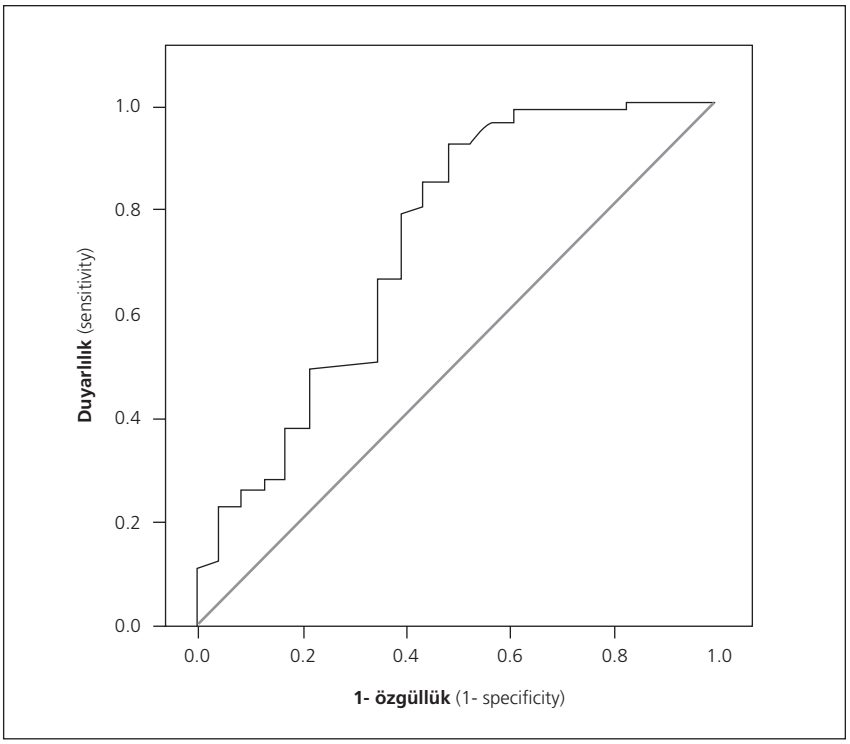

Figure 3. ROC curve for serum adiponectin levels in 75 g OGTT group.

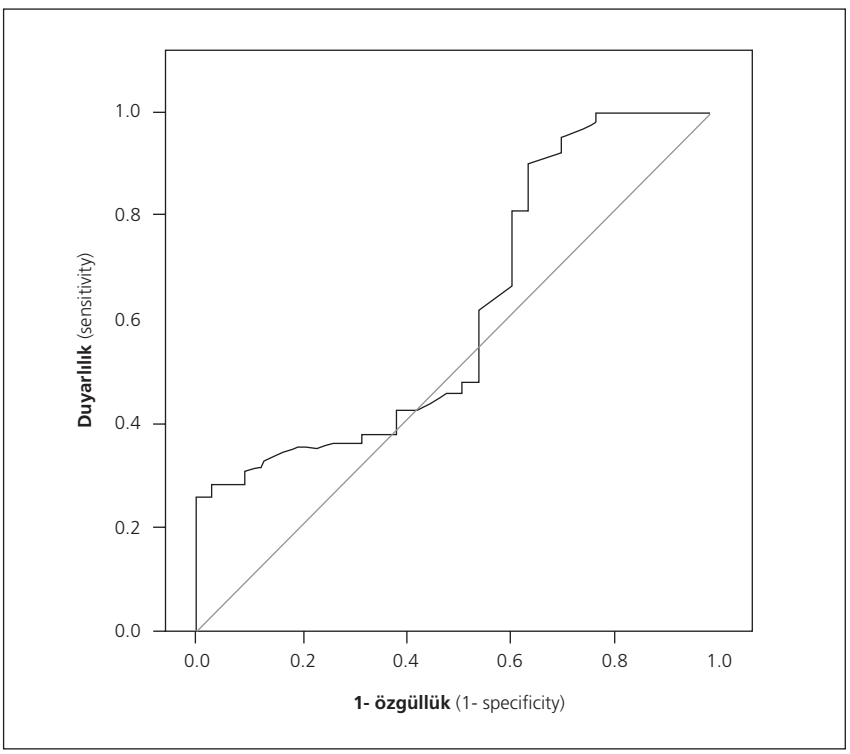

Figure 4. ROC curve for serum adiponectin levels in 50/100 g OGTT group.

Table 1. Sensitivity and specificity rates for 50, 75 ve 100 gr OGTTs.[8]

	Sensitivity (%)	Specificity (%)
50 g (cut off: 140 mg/dl)	58.3	67.8
50 g (cut off: 137 mg/dl)	66.7	63.2
75 g (cut off: 140 mg/dl)	41.7	90.8
75 g (cut off: 117 mg/dl)	66.7	64.4
100 gr	27.3	96.5

perform 50 g OGTT between 24-28 gestational weeks in all pregnant women. If 50 g OGTT is positive then 100 g OGTT is performed and diagnosis of GDM is established according to ACOG criteria. Management of GDM includes diet and exercise primarily to maintain glycemic control and insulin if necessary. There have been many studies till present to understand the pathophysiology of GDM, to diagnose GDM at an early stage and to improve maternal and fetal outcomes in women with fully established GDM. Some cytokines such as adiponectin and leptin have been investigated considering the relationship between GDM and other conditions associated with insulin resistance. Adiponectin (Acrp 30, AdipoQ, apM-1 veya GBP28) is a protein hormone which plays a role in a series of metabolic reactions including glucose regulation and fatty acid catabolism. Adiponectin is secreted into the blood manly from adipose tissue. The blood level of adiponectin is inversely proportional with the fat ratio. Maternal serum adiponectin levels are not correlated with maternal weight and BMI. Total liquid amount is increased during pregnancy and that's why body weight and BMI are not weak parameters to assess adiposity in early postpartum period. Maternal serum adiponectin concentrations do not correlate with serum glucose and insulin levels. However, the negative correlation between the maternal serum adiponectin levels and maternal fasting glucose/insulin ratio may indicate that adiponectin has a role in glucose regulation. It's possible that adiponectin levels change as a result of effective glucose management and this may make it a beneficial marker of insulin sensitivity. Altinova et al.[5] have shown that decreased adiponectin levels are associated with insulin resistance and GDM pathogenesis. In our study, we aimed to measure leptin and adiponectin levels in the same patients, and also to classify GDM patients acoording to the OGTT method preferred. Median leptin concentration was 49.36±14.5 ng/ml in women with GDM compared to 40.10±17.12 ng/ml in women without GDM. This difference is found to be significant. (p:0.021) However the difference between two groups was not significant in 75 g OGTT group (44.41±15.22 ng/ml vs 38.29±17.02 ng/ml, p:0,08). We do not know why the difference between leptin levels of case and control groups is not significant in the 50/100 g OGTT group, although in 75 g OGTT group leptin is significantly higher in case group compared with the controls. Kautzky-Willer et al.[6] investigated leptin levels in 25 healthy pregnant women, 55 women with GDM, 10 type I DM and 10 healthy nonpregnant women. Leptin levels are shown to be

increased in all pregnant women compared with nonpregnant women at the same age group.

Conclusion

In conclusion, if these cut-off values are taken, in 75 g OGTT group adiponectin is more sensitive than leptin, and adiponectin is as equally specific as leptin. In 50/100 g OGTT group adiponectin is significantly lower in patients with GDM compared to women without GDM and leptin levels are not significantly different in two subgroups. Considering that sensitivity and specificity rates of OGTT methods are not 100%, therefore the sensitivity and specificity rates of adiponectin interpreted according to the diagnosis of GDM which is established by OGTTs are not 100% precise.

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Does Ramadan Cause to Iron Deficiency in Pregnancy?

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Abstract

Objective: We designed this study to evaluate whether or not Ramadan fasting causes iron deficiency in pregnancy.

Methods: There was not a significant difference between the serum levels of CRP before and after Ramadan in Group1a-Group 1b and Group 2a-Group 2b.There was not a significant difference between Group 1a- Group 2a, Group 1b-Group 2b for serum CRP levels .There was a slight decrease in serum ferritin levels in all Groups, but this decrease was not statistically significant .The ferritin levels were similar in Group1a- 2a, and Group 1b-2b .The haemoglobin levels was increased in all groups, but this increase was not statistically significant. The haemoglobin levels were also similar in Group1a- 2a, and Group 1b-2b.

Results: This study was carried out in Obstetrics and Gynecology Department of Gaziantep University Hospital, between September 23th and October 23th in year 2006 (during Ramadan). Fourty-one consecutive healthy women with uncomplicated pregnancies of 20 weeks or more who were fasting during Ramadan were included in the study group (Group 1). The control group (Group 2) consisted of 31healthy pregnant women who were not fasting during the study period.Before and after Ramadan, we measured plasma C reactive protein levels (CRP), serum ferritin levels, and haemoglobin levels (Hb) in all patients.Any patients who had a sign of infections (elevated white blood cell, elevated CRP) excluded from the study to prevent the confusing ferritin elevations.The patients who had ferritin levels < 15 µg/L excluded from the study before Ramadan.

Conclusion: Ramadan does not cause a significant change in serum CRP, ferritin, and haemoglobin levels if enough iron supplemantation provides in pregnancy.

Keywords: Ramadan, prenancy, iron deficiency.

Gebe hastalarda ramazan demir eksikliğine neden olur mu?

Amaç: Bu çalışma Ramazan ayında oruç tutmanın gebe hastalarda demir eksikliğine yol açıp açmadığını araştırmak için yapıldı.

Yöntem: Bu çalışma Gaziantep Üniversitesi Tıp Fakültesi Hastanesi'nde, Kadın Hastalıkları ve Doğum Anabilim Dalı'nda 23 Eylül-23 Ekim 2006 tarihleri arasında (Ramazan ayı süresince) gerçekleştirildi.Ramazan ayında oruç tutan 41 tane sağlıklı, 20. ve daha büyük gebelik haftasındaki gebeler çalışmaya alındı (Grup 1)Grup 1a 28 (2.trimester), Grup 1 b (3.trimester) oruç tutan hastalardan oluştu.Kontrol grubuna oruç tutmayan sağlıklı, 20. ve daha büyük gebelik haftasındaki gebeler alındı (Grup2).Grup 2a (2.trimester), Grup 2b (3. trimester) oruç tutmayan hastalardan oluşturuldu.Tüm hastaların Ramazan öncesi ve sonrası plasma C reaktif protein (CRP), serum ferritin ve hemoglobin (hb) seviyeleri ölçüldü.Bir enfeksiyon belirtisi olan (lökositoz, yüksek CRP) hasta ferritin yüksekliğinde karışıklığa neden olmamak için çalışmadan çıkarıldı. Ramazan öncesi ferritin seviyesi < 15 µg/L tespit edilen hastalar çalışmaya alınmadı.

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Bulgular: Grup 1a-1b ve Grup 2a-2b'de Ramazan öncesi ve Ramazan sonrası CRP düzeylerinde önemli bir fark izlenmedi.Grup 1a ve Grup1b ve Grup 2a-2b rasında serum CRP değerleri farksız bulundu.Tüm gruplarda ferritin değerlerinde hafif bir artış saptandı ancak bu artış istatistiksel olarak anlamlı değildi.Grup 1a ve 2a (2.trimester) ve Grup 1b-2b (3.trimester) arasında ferritin seviyeleri benzerlik gösterdi.Hemoglobin değerleri tüm gruplarda artış gösterdi ancak bu fark istatistiksel olarak anlamlı değildi. Grup 1a ve 2a (2.trimester) ve Grup 1b-2b (3.trimester) arasında hemoglobin düzeyleri açısından fark izlenmedi.

Sonuç: Gebelerde yeterli demir desteği yapıldığında, Ramazan serum CRP, ferritin ve hemoglobin değerlerinde önemli bir değişikliğe neden olmamaktadır.

Anahtar Sözcükler: Ramazan, gebelik, demir eksikliği.

Introduction

Ramadan is the holiest month in the Islamic calendar and Muslims fast during this month.[1] Believers are commanded to abstain from food, drink and conjugal relationships from sunrise to sunset as a sing of restraint and introspection. The food and fluid intake are mainly nocturnal and usually, food frequency and quantity, sleep duration at night and daily physical activity are reduced. The food habits are not similar outside and during Ramadan in that the proportion of fat, protein and carbohydrate intake can differ during Ramadan.There is a tendency to consume foods and drinks that are richer in carbohydrates than those consumed during other months of the year.[2] The limitation in consumption of the meat and fresh fruit in daily diet causes to iron deficiency in low socioeconomic group.[3] In this study, we aimed to show whether Ramadan causes iron deficiency by measuring serum ferritin and haemoglobulin levels in pregnacy.

Methods

This study was carried out in Obstetrics and Gynecology Department of Gaziantep University Hospital, between September 23th and October 23th in year 2006 (during Ramadan). Fourty-one consecutive healthy women with uncomplicated pregnancies of 20 weeks or more who were fasting during Ramadan were included in the study group (Group 1a and 1b). Group 1a consisted of 28 fasting pregnant patients in second trimester, Group1b was also consisted of 13 fasting pregnant patients in third trimester. The control group (Group 2a and 2b) consisted of 31healthy pregnant women who were not fasting during the study period.Group 2a consisted of 19 non fasting pregnant patients in second trimester, Group 2b consisted of 12 non fasting pregnant patients in third trimester.Before and after Ramadan serum ferritin, haemoglobin, and CRP levels measured in all patients.Ferritin was measured by immunchemiluminescent method by using Immulite 2000 autoanalyser and kits from (Diagnostic Products Corporation, Los Angeles, ABD).Ferritin levels of <15 μg/L is consistent with iron depletion and ferritin levels of <12 μg/L are associated with iron depletion anemia.Any patients who had ferritin levels <15 μg/L was excluded from the study before Ramadan.

Hb values were measured in Sysmex XT 2000 I automated hematology analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Serum CRP levels were determined on a Behring BNA 100 nephelometrically (Dade, Behring Marburg, Germany).

Multivitamin (Materna, Wyeth), calcium 1 gr/day (Cal-D Vita, Roche) and iron (100 md/day) (Ferplex Fol, Abdi Ibrahim) supplementation were given to all subjects. All the subjects were advised to drink at least 2 liter water every night to prevent hypo-hydratation and urinary tract infections.

Results

Statistically Analysis: All comparisons in and between the groups was done by Simple Paired t-test. Sigma Stat 3.0 was used for statistical analysis. P value <0.05 was accepted as significant.

There was not a significant difference between the serum levels of CRP before and after Ramadan in Group1a-Group 1b and Group 2a-Group 2b (p=0.71, p=0.57).There was not a significant difference between Group 1a-Group 2a, Group 1b-Group 2b for serum CRP levels (p=0.62, p=0.71). There was a slight decrease in serum ferritin levels in all Groups, but this decrease was not statistically significant. The ferritin levels were similar in Group 1a- 2a, and Group 1b-2b (p=0.57, p=0.63). The haemoglobin levels was increased in all groups, but this increase was not statistically significant. The haemoglobin levels were also similar in Group 1a- 2a, and Group 1b-2b (p=0.71, p=0.67) (Table 1).

Discussion

During Ramadan, Muslims refrain from eating, drinking, smoking, and sexual relations from sunrise until sunset.The period in which the person fasts may vary depending on the geographical location of the country and the season of the year, and can be as long as 18 hours/day in the summer of temperate regions.[2] It has been established that a given nutrient ingested at an unusual time can induce different metabolic effects, and the Ramadan fasting provides an excellent opportunity to study the effects of the prolonged reduction of meal frequency on body metabolism.[4]

It has been showed that Ramadan fasting caused less weight gain and energy intake in second and third trimester in Turkish pregnant women. The percentage of protein (for first trimester) and corbohydrates (for all trimester) from total energy was higher in fasting group.[5] Another study has been showed that there is a tendency to consume foods and drinks that are richer in carbohydrates than those consumed during other months of the year.[2]

Nutritional anemias are considered to be one of the most common nutritional disorders of the world and are widespread in developing countries.[6] Less consumption of the meat and fresh fruits results in low dietary intake of iron espeacilly in low socio-economic pregnant women.[3]

In healthy subjects, the plasma ferritin concentration is a biomarker for mobilisable body iron reserves. In general, ferritin levels of <30 μg/L indicate a low iron status, small or no iron reserves as verified by the absence of bone marrow haemosiderin.Ferritin levels of <15 μg/L is consistent with iron depletion and ferritin levels of <12 μg/L are associated with iron deficincy anemia.[7,8] In women with inflammatory of infectious disorders, plasma ferritin can be falsely elevated out of proportion with body iron reserves. If such conditions are suspected, plasma CRP should be measured as well, in order to assess the degree of inflamation. We

also measured CRP levels to prevent any elevation in ferritin levels due to infections.[9] It has been suggested that women with plasma ferrin of >70 µg/L do not need iron supplements; those with ferritin of 30-70 µg/L should take 30-40 mg ferrous iron per day and those with ferritin of <30 µg/L should take 80-100 mg ferrous iron per day.[8] It has been reported that 65 mg ferrous iron / day from 20 weeks gestation was adequate to prevent iron deficiency anaemia in all women.[10] In our study, all patients' ferritin levels was slightly under 30 µg/L, and gestational age was ≥ 20 weeks therefore; we supplemented 80-100 mg ferrous iron per day.It is also prevent to increase ferritin levels during the Ramadan.

Conclusion

In conclusion, Ramadan fasting does not cause iron deficiency and does not change ferritin levels if enough iron supplementation provides in pregnancy.

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Sotalol Treatment in a Case with Fetal Atrial Flutter

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Abstract

Objective: Fetal tachycardia leads to nonimmune hydrops fetalis and increases fetal morbidity and mortality. Supraventricular tachycardia and atrial flutter are the most diagnosed by ultrasonography. We present a case with fetal atrial flutter in the second trimester, firstly digoxin then, digoxin plus sotalol therapy were given successfully.

Case: A thirty years old patient was sent to our clinic for having maternal diabetes mellitus at 24 weeks of gestation. Her gravidity was 3, parity was 2. A fetus in 24th weeks was seen on obstetric ultrasonography and fetal tachycardia was detected. Fetal atrial rate was 529 beats per minute (bpm) and ventricular rate was 312 bpm in fetal echocardiography and fetal atrial flutter was diagnosed. The first fifteen days digoxin, then digoxin plus sotalol treatment was given. After digoxin plus sotalol treatment fetal heart rate was decreased and returned to sinus rhythm. Pregnancy was continued until term without any complication and a girl baby was delivered by cesareansection

Conclusion: Fetal echocardiography is a safe tool for diagnosis and followingup for fetal tachycardia. Digoxin is a first choice drug for fetal tachycardia but we need second line drugs if tachycardia does not respond in therapeutic range. Sotalol does not have negative inotropic effect therefore, it is accepted a safe second line drug. If fetal tachycardia is resistant to these treatments, congenital heart disease or any organ abnormality should be considered

Keywords: Fetal atrial flutter, echocardiography, digoxin, sotalol

Fetal atrial flatterli bir olguda sotalol tedavisi

Amaç: Fetal taşiaritmi nonimmün hidrops fetalise neden olarak fetal morbidite ve mortaliteyi artırabilmektedir. Supraventriküler taşikardi ve atrial flatter ultrasonografi ile en sık tanı konulanlardır.İkinci trimesterde atrial flatter tespit edilen, önce digoksin, sonra digoksin ve sotalol ile başarılı bir şekilde tedavi ettiğimiz bir hastayı sunduk.

Olgu: Otuz yaşında gravidası 3, paritesi 2 olan hasta, 24. gebelik haftasında maternal diabet tanısı ile kliniğimize gönderilmişti.Obstetrik ultrasonografide 24 haftalık gebelikle uyumlu tek fetus tespit edildi ve taşikardisi olduğu görüldü.Fetal ekokardiografide atrial hız 529 atımdak ve ventriküler hız 312 atımdak tespit edildi ve fetal atrial flatter tanısını konuldu.İlk on beş gün tek başına digoksin, sonra yanıt alınamayınca digoksin ve sotalol ile tedavi edildi.Digoksin ve sotalol tedavisinden sonra fetal kalp atım hızının azaldığı ve sinus ritmine döndüğü görüldü.Gebelik terme kadar sağlıklı bir şekilde devam ettirildi ve sezeryanla 1.dakika Apgar skoru 9, 5. dakika Apgar skoru 10 olan bir adet 3500gram kız bebek doğurtuldu.

Sonuç: Fetal ekokardiografi fetal taşiaritmilerin tanısında ve takibinde güvenilir bir yöntemdir.Digoksin fetal aritmilerin tedavisinde ilk seçenek ajandır ancak terapötik düzeylerde iken yanıt alınamadığında ikinci seçenek ajanlara ihtiyaç duyulmaktadır.Sotalol negatif inotropik etkisi olmadığı için güvenle kullanılabilecek iyi bir ikinci seçenek antiaritmik ajandır.

Anahtar Sözcükler: Fetal atrial flatter, ekokardiografi, digoksin, sotalol.

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Introduction

Atrial flutter (AF) is a tachyarrhythmia involves generally a conduction system between atrias and originates from an extra source. It occurs in later pregnancy compared to supraventricular tachycardia.[1] Atrial rate ranges between 350 and 500 beats per minute (bpm). It usually associated with 2:1 atrioventricular block.[2] Fetal death was reported when ventricular rate is over 480 bpm. It has been shown that consequences of the cases with ventricular rate between 220 and 240 bpm are better when atrioventricular block is associated however; the risk of hemodynamic disturbance continues.[3] M mode and the analysis of Doppler wave forms are the most common diagnostic methods. Fetal echocardiography allows the diagnosis of an underlying congenital cardiac disease as well.[3,4] Transabdominal fetal echocardiogram (EKG) and magneto cardiogram (MKG) are two popular methods and they provide data for the electrophysiological side of the fetal heart.[5,6] In the treatment of fetal AF, it may be necessary to chose between emergency birth and pharmacological treatment. The method of treatment should be choose by considering the balance between the factors such as: gestational age and lung maturity, changes in the fetal circulation, existence of a new born unit appropriate for postnatal management and the preferences of the family. When a resistant tachycardia and an abnormality in the circulation exist, emergency procedures must be used to avoid congestive heart failure and fetal death.[7] Prenatal antiarrhythmic treatment can first be applied transplacental or to fetus directly. Maternal drug treatment should be reach to effective concentration in fetus to be efficient. Direct fetal application should be preferred in cases especially those associated with severe hydrops and placental edema and those resistant and fetus can not tolerate.[8] There is no prospective study showing the superiority of any antiarrhythmic treatment. Digoxin has been used safely as a first line treatment for the long time. Flecainide, sotalol and amiodarone are the widely used second line treatments.[9]

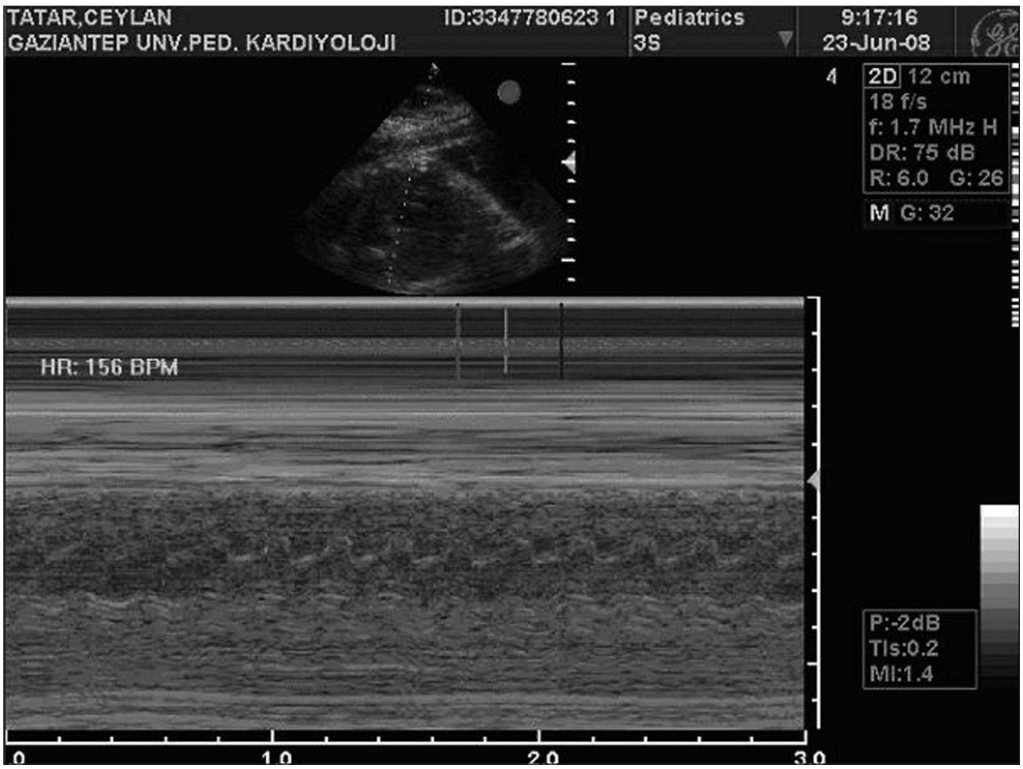
Case

Thirty-two years old woman with 24 weeks of pregnancy, gravidity 3, parity 2 was applied for routine following up to our hospital. She had gestational diabetes for 2 months and taking insulin treatment. Blood sugar regulation was good (HbA1C 6.3%).She had two cesarean section operations for cephalo-pelvic disproportion in the history. On the ultrasonography, a single fetus was seen with tachycardia. Fetal echocardiography (M-mode) was shown that atrial rate was 528 beats per minute, ventricular rate was 257 beats per minute and approximately 2:1 atrioventricular block was detected (Picture 1 and 2). Mitral and aortic valve in the left ventricle, inferior vena cava-descendant aorta, superior vena cava- ascendant aorta and, aorta-pulmonary artery, pulmonary artery-pulmonary vein were evaluated by Echocardiography for Doppler wave form. Doppler Echocardiography which is recorded the wave forms of mitral and tricuspid valves were showed a 2:1 block which belongs to atrial flutter. M-mode section was performed which includes both of atrium and ventricle. Atrial and ventricular rate were measured separately by time cursor in M Mode echocardiography. No structural abnormality was detected in the heart. Digoxin treatment, 0,25 mg oral three times a day was started and maternal plasma level was kept in recommended therapeutic dose (1.8 ng/mL). Fetal tachyarrhythmia continued for two weeks during digoxin treatment

and heart rate did not decreased. Sotalol treatment was added to digoxin treatment as secondary choice (twice a day, 80 mg). Because fetal heart rate did not decreased, sotalol dose was increased to 160 mg, twice a day. Three weeks after two drugs regimen was started, fetal heart rate turned back to normal. Heart rate was 132 beats/minutes with 1:1 sinus rhythm. Congestive heart failure was not detected in serial echocardiographies during treatment period. Thirteen weeks after the treatment was started, sub segment c-section was performed to the patient at 13th week and forth day of her pregnancy due to uterine contractions and repeated c-sections previously. A 3800 gram of baby girl was delivered. Electrocardiogram showed normal sinus rhythm after the delivery. Echocardiography showed normal anatomy.

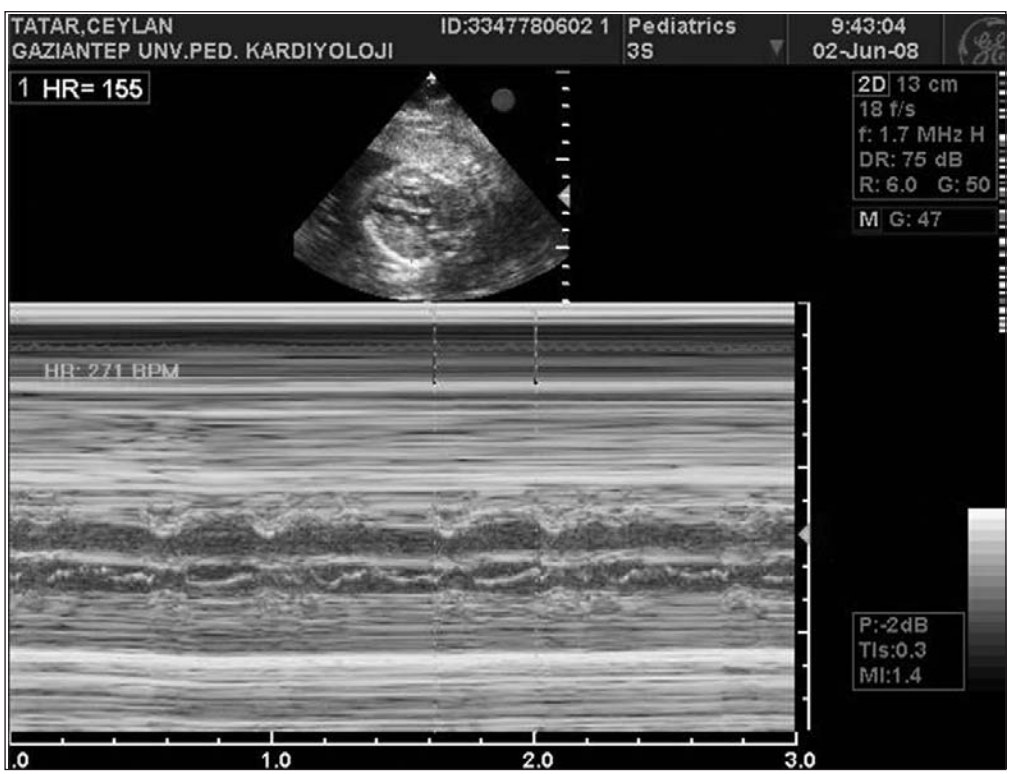
Discussion

Fetal AF is the most common form of fetal tachycardias following supraventricular tachycardia. It is described as a slow ventricular rhythm with regular atrial rate (300-600 beats/minutes) and frequent blocks. This condition might be associated with congestive heart failure, fetal hydrops, neurological morbidity and intrauterine death.[10] Therefore, it requires prenatal care. The aims of the prenatal care are to provide a sufficient ventricular speed, to prevent congestive heart failure and to avoid preterm delivery.[2] Two-dimensional ultrasonography is used in the diagnosis of specific arthymias, in the evaluation of cardiac anatomy, and in the detection of hydrops fetalis. Heart anatomy should be examined carefully, because arthymias could be associated with congenital heart diseases. A fluid collection accordant with hydrops is a finding shows that normal heart physiology is deterio-



Picture 1. Atrial Flutter in M-mode.

rated due to impact in ventricular filling and output. Fetal echocardiography with M-Mode imaging and Doppler wave form are the most common ultrasonographic methods in the evaluation of fetal arthymias.[3-5] M-Mode is performed most frequently at the level where the four chamber's imaging can be taken, and it helps to detect atrial/ventricular wall movement and/or semilunar and atrioventricular valve movement. This helps the detection of relative timing of cardiac findings and the features of arthymias. Examination of the Doppler wave forms of left ventricle inner and outer ways, the region of vena cava inferior- aorta, the region of superior vena cava- ascendant aorta, and the region of pulmonary artery – pulmonary vein helps to diagnosis. Examination of the Doppler wave form is dependant to fetal position however, the large size of the area to be investigated helps to avoid this problem.[3] Transabdominal fetal EKG and MKG are the methods enlightening the electrophysiology of the heart are becoming to be used more frequently. The success rate in the serial EKGs is reported to be 75-91%. The perception rate of efficient signals decreases between 27 and 36 weeks when fetal tachycardia and extrasystoles are associated.[5] Fetal MKG is to record the magnetic area created by fetal heart activity. Typically, P-QRS complex in EKG shows the wave form. The signal quality of MKG is better than that of EKG because the transition ability of magnetic signals is superior and this allows better results in the examination of cardiac time intervals. Atrioventricular time interval in the ultrasonography should be considered as PR interval in EKG. It is a useful method when fetal heart block was considered. The measurement of atrioventricular time interval during sinus rhythm in fetuses is the single method could be used in the diagnosis of first degree AV



Picture 2. During AF discordans between atrial and ventricular rate and AV block.

block. AV and ventriculoatrial intervals during tachycardia and their relation allow us to reach the data to understand the mechanism of tachycardia.[6]

Digoxin is one of the drugs used most commonly in the treatment of fetal tachyarrhythmia. The treatment is started with a dose of 0.25 mg twice a day then is increased to maximum 0.5 mg twice a day. Dose should be adjusted to keep maternal serum concentration in the therapeutic range of 0.8-2 ng/mL. In non-hydropic fetuses with tachyarrhythmia good prognosis can be provided with transplacental treatment.[11] In our case, initially digoxin was given with a dose of 0.25 mg twice a day then dose was increased maximum up to 0.5 mg twice a day by keeping the maternal serum concentration in the therapeutic range (1.8 ng/mL). Because fetal tachyarrhythmia did not respond to this treatment, sotalol treatment was started. Sotalol is a strong beta blocker agent with additional third class antiarrhythmic effect. It has intermediate or no negative inotropic effect. Sotalol should not be used in subjects who have the followings: QT interval longer than 450 milliseconds, bronchial asthma or chronic obstructive lung disease, or creatinine clearance less than 40 mL/minutes.[12] Quidijk et al. reported three intrauterine deaths following digoxin and sotalol treatment in 4 hydropic fetus with supraventricular tachycardia.[12] They suggested that proarrhythmic events in these fetuses might be started by sotalol. They stated that this should be considered when sotalol is used in hydropic fetuses.

In our case, a non-hydropic fetus who diagnosed as fetal AF by fetal echocardiography was successfully treated with digoxin and sotalol. Digoxin is the first choice in the treatment of fetal AF however; sotalol can be used safely as a second choice in non-hydropic cases who do not respond to digoxin.

Conclusion

In our case,atrial flutter was diagnosed by fetal echocardiography and perfomed for fetal tachycardia.First digoxin,then digoxin plus sotalol treatment were given successfully.

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