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Comparison of Ykl-40 In Patients With &Without Gestational Diabetes Mellitus In The First Trimester &At Weeks 24 – 28

İlk Trimester ve 24-28. Haftada Gestasyonel Diyabeti Olan ve Olmayan Hastalarda Ykl-40 Düzeyinin Karşılatırılması

Neslihan Erkal[1]

1 Antalya Training and Research Hospital, Department of Obstetrics and Gynaecology, https://orcid.org/0000-0003-3335-0894

Abstract

Objective: To elucidate whether the YKL-40 level in the first trimester is effective in predicting the development of diabetes in pregnant groups with and without gestational diabetes mellitus.
Methods: All first-trimester pregnant cases between the ages of 18 – 35 years who applied to the obstetrics and gynecology outpatient clinic of Antalya Training and Research Hospital with a single pregnancy, who did not have additional diseases and fetal anomalies, were included in the study (n=250). An oral glucose tolerance test of 75 gr (OGTT) was performed weekly to diagnose GDM in all pregnant women 24 – 28. During the administration of OGTT, fasting venous blood was taken to check the level of YKL-40.
Results: A total of 250 patients have been enrolled within the scope of this study. According to the results of OGTT, 18 individuals were diagnosed with GDM. Notably, while there was a difference in YKL-40 measurements in all patients, buts no difference in sub-group analysis. The differences between the first YKL-40, second YKL-40, and YKL-40 difference values of patients with and without GDM were evaluated. There was no statistically significant difference between the first, second, and YKL-40 difference values of patients with and without GDM ($p>0.05$).
Conclusion: Regarding the results of this research, YKL-40 might be valuable in detecting low-grade inflammation in pregnant women. However, there is a need for larger-scale prospective randomized studies from the early period to the end of pregnancy to better and more accurately evaluate the relationship between insulin resistance and inflammation.

Keywords: Gestational diabetes mellitus , HOMA-IR , YKL-40.

Özet

Amaç: Gestasyonel diabetes mellitusu(GDM) olan ve olmayan gebe gruplarında ilk trimesterdeki YKL-40 düzeyinin diyabet gelişimini öngörmede etkili olup olmadığını aydınlatmayı amaçladık.
Yöntem: Antalya Eğitim ve Araştırma Hastanesi kadın hastalıkları ve doğum polikliniğine tekil gebeliği bulunan, ek hastalığı ve fetal anomalisi olmayan 18 – 35 yaş arası tüm birinci trimester gebeleri çalışmaya alındı (n=250). GDM tanısı koymak için 24 – 28 haftalık gebelere 75 gr oral glukoz tolerans testi (OGTT) yapıldı. OGTT uygulaması sırasında, YKL-40 seviyesini kontrol etmek için açlık venöz kanı alındı.
Bulgular: Bu çalışma kapsamında toplam 250 hasta çalışmaya alındı. OGTT sonuçlarına göre 18 kişiye gestasyonel diabetes mellitus tanısı konuldu. Trigliserid değerleri farklıydı ($p<0.05$); her iki grup da ikinci trimesterde artmış seviyeler gösterdi. Özellikle, tüm hastalarda YKL-40 ölçümlerinde bir fark varken, alt grup analizinde fark bulunamadı. GDM'u olan ve olmayan hastaların birinci YKL-40, ikinci YKL-40 ve YKL-40 değerleri arasındaki istatistiksel olarak anlamlı fark saptanmadı ($p>0.05$). İkinci trimesterde trigliserit ve YKL-40 ölçümlerinde birinci trimestere göre artış gözlendi ($p<0.05$).
Sonuç: Bu araştırmanın sonuçları, YKL-40'ın düşük dereceli inflamasyonun saptanmasında değerli bir biyobelirteç olacağıdır. Bununla birlikte, insülin direnci ile inflamasyon arasındaki ilişkiyi daha iyi ve daha doğru bir şekilde değerlendirmek için erken dönemden gebeliğin sonuna kadar daha büyük ölçekli prospektif randomize çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Gestasyonel Diabetes Mellitus, HOMA-IR, YKL-40.

Corresponding Author: Neslihan Erkal, e-mail: drnboz@yahoo.com
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INTRODUCTION

Gestational diabetes mellitus (DM) is diabetes that begins and is first noticed during pregnancy. It is glucose intolerance independent of whether it continues after pregnancy and whether insulin is used in the treatment. Glucose intolerance is milder than Type I and Type II DM (1). Diabetes mellitus, the most common medical complication of pregnancy, is seen in approximately 2 – 3% of all pregnant women. An average of 90% of pregnancies complicated with diabetes are gestational diabetes. Type 2 diabetes accounts for 8% of pregestational diabetes and type 1 diabetes for 2% (2).

Gestational DM is important not only for pregnancy outcomes but also for the mother and child's future. Gestational DM is an important part of the increasing prevalence of diabetes, regardless of genetics and other known risk factors for diabetes (3). Although glucose intolerance will return to normal after delivery in most cases, at least half of these women will develop diabetes (especially type 2 DM) in the future (14). Diabetes can be permanent in 3 – 20% of patients with gestational DM. Considering the studies conducted in the last 30 years, quite different results (34–87.5%) are reported among the rates of diabetes development after GDM (5).

The infant of a mother with gestational DM is at risk of developing obesity at an early age, impaired glucose intolerance, and diabetes. The risk of developing diabetes/prediabetes in children with gestational DM is almost eight times higher (6). The dominant view is that intrauterine hyperglycemia is an increased risk factor for diabetes in children and a several-fold increased risk factor for early-onset diabetes/prediabetes is the dominant literature (7). Because of all these, the diagnosis of GDM should be made, and the mother and child should be followed up after pregnancy (8).

YKL-40 is a 40 kDa glycoprotein secreted by many cells, including neutrophils, macrophages, and vascular smooth muscle cells. It has been found that the level of YKL-40 in the circulation is increased in many diseases characterized by acute and chronic inflammation (8 – 10). Twelve studies according to a review, serum YKL-40 level was high in patients with Type 2 DM. In addition, YKL-40 was defined as a marker in evaluating metabolic and inflammatory parameters in type 2 DM (11).

Within the scope of this research, we aimed to elucidate whether the YKL-40 level in the first trimester is effective in predicting the development of diabetes in pregnant groups with and without gestational diabetes mellitus.

METHOD

All first trimester (6-12 weeks) pregnant cases between the ages of 18 – 35 years who applied to the obstetrics and gynecology outpatient clinic of Antalya Training and Research Hospital with a single pregnancy, who did not have additional diseases and fetal anomalies, were included in the study (n=250). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution with protocol number 2016-016 and informed consent has been obtained from all participants.

All patients were questioned regarding gestational diabetes (GDM) risks such as age, previous pregnancy, smoking, alcohol, hypertension, chronic disease, and family history of diabetes. Weight, height, and blood pressure measurements were conducted in the examination. During

the initial admission in the first trimester (6 – 12th gestational week), fasting venous blood samples were taken from all patients. An oral glucose tolerance test of 75 gr (OGTT) was performed weekly to diagnose GDM in all pregnant women 24 – 28. GDM was diagnosed when one or more abnormal plasma glucose values, fasting ≥92 mg/dL, 1 hour ≥180 mg/dL, 2 hours 153 mg/dL, using the criteria of The International Association of Diabetes and Pregnancy Study Groups. During the administration of OGTT, fasting venous blood was taken to check the level of YKL-40. Blood clotting was stored at room temperature for at least 30 minutes, followed by centrifugation to separate the serum (2500 rpm, 15 min, 4°C). Serum samples were divided and stored at -80°C until the levels of yCL-40 were analyzed.

YKL-40 serum levels were compared in 18 randomly selected pregnant among 18 patients who developed GDM and other normal pregnant women (Human YKL-40 ELISA Kit, MyBioSource USA). Glucose levels are available from a commercially available kit (Beckman AU5800; Beckman Coulter Diagnostics, USA). Insulin levels were processed with a chemiluminescent test (AccessDxI800; Beckman Coulter, Inc., Fullerton, CA, USA). Patients were followed up until birth. Infant birth weights, delivery mode, and birth weeks were recorded.

Homeostatic model evaluation of insulin resistance (HOMA-IR) was calculated as follows:

- Fasting glucose (mmol/L) × fasting insulin (IU/mL)/22.5

Statistical Analysis

The analyses were performed with SPSS 22.0 package program. Descriptive statistics are presented with frequency, percentage, mean, standard deviation (SD) and median (median), minimum (min), and maximum (max) values. Shapiro Wilks test was used for the normality test. In analyzing the difference between the measurement values of the groups with and without GDM, the Mann-Whitney U test was used when the data did not match the normal distribution, and the student's t-test was used when the data did not match. In analyzing the differences between the lab values in the trimester, the Wilcoxon Peer Test was used when the data did not match the normal distribution, and the paired T-Test was used when the data did not match. P values less than 0.05 were considered statistically significant.

RESULTS

A total of 250 patients have been enrolled within the scope of this study. According to the results of OGTT, 18 individuals were diagnosed with gestational diabetes mellitus.

The differences between the first and last insulin, glucose, HOMA, triglyceride, and YKL-40 values were evaluated. According to the inter-peer difference test, an increase was observed in triglyceride and YKL-40 measurements in the second trimester compared to the first trimester ($p<0.05$; Wilcoxon Signed-Rank Test). (Table 1).

The laboratory parameters of patients with and without gestational diabetes in the first and second trimesters have been investigated, and only triglyceride values were different ($p<0.05$; Wilcoxon Signed Rank Test). (Table 2). Both groups elaborated on increased levels in the second trimester. Notably, while there was a difference in YKL-40 measurements in all patients, there was no difference in sub-group analysis.

Table 1. Descriptive Statistics Of The Study Population

	Category	n Mean ± Sd	Percentage Median (Range)
Family History	Yes	11	30,6%
	No	25	69,4%
Smoking	No	32	88,9%
	Yes	4	11,1%
Treatment	Diet	15	83,3%
	Insulin	3	16,7%
Delivery Method	Cesarean	18	50,0%
	Normal	18	50,0%
Age		27,00 ± 4,38	26,00 (19-39)
Gestational week		9,78 ± 2,21	10,20 (4,6-13,2)
BMI		24,74 ± 4,41	23,62 (17,6-37,9)
Gravida		2,28 ± 1	2 (1-4)
Birth Age		39,13 ± 0,95	39,20 (36-40,5)
Weigth		3369,28 ± 364,46	3390 (2540-4150)

Table 2. Analysis of Differences Between Patients' First And Last Laboratory Parameters

	n	Mean	SD	Median	Min	Max	p-value
Initial insulin	35	8,71	9,53	5,66	2,49	55,39	0,134
Second insulin	35	10,09	7,89	7,64	2,29	31,76	
Inıtial glucose	36	82,00	7,53	81,50	63,00	99,00	0,099
Second glucose	36	77,17	13,80	78,00	40,00	109,00	
Initial HOMA	36	1,77	2,27	1,12	,00	13,54	0,167
Second HOMA	36	1,99	1,73	1,42	,39	6,90	
Initial triglycerides	36	114,31	47,55	104,50	60,00	245,00	**<0,001***
Second triglycerides	36	182,39	63,85	178,50	68,00	324,00	
Inıtial YKL-40	36	1344,69	649,24	1142,60	286,40	2904,60	**0,030***
Second YKL-40	36	1637,84	718,95	1545,15	435,90	3550,90	

* p<0,05; Wilcoxon Signed-Rank Test analyzed all comparisons

The differences between the first YKL-40, second YKL-40, and YKL-40 difference values of patients with and without GDM were evaluated. There was no statistically significant difference between the first, second, and YKL-40 difference values of patients with and without GDM (p>0.05; Mann-Whitney U Test). (Table 3).

Table 3. Analysis Of Differences Between Measurements In The First And Second Trimesters Of Patients With And Without Gestational Diabetes

	GDM (+)							GDM (-)						
	n	Mean	SD	Med	Min	Max	p-value	n	Mean	SD	Med	Min	Max	p-value
Initial insulin	17	7,33	3,52	6,10	3,65	18,39	0,076#	18	10,01	12,90	5,10	2,49	55,39	0,711#
Second insulin	17	10,47	6,07	8,28	3,19	27,53		18	9,74	9,46	5,29	2,29	31,76	
Initial glucose	18	82,22	8,05	83,5	63,0	97,0	0,419#	18	81,78	7,20	81,00	71,00	99,00	0,121+
Second glucose	18	78,78	12,45	79,5	40,0	99,0		18	75,56	15,23	76,50	40,00	109,00	
Initial HOMA	18	1,41	,85	1,22	,00	4,09	0,071#	18	2,13	3,10	1,05	,49	13,54	0,845#
Second HOMA	18	2,03	1,30	1,54	,43	5,37		18	1,95	2,11	,96	,39	6,90	
Initial triglycerides	18	107,83	46,82	87,0	68,0	228,0	**0,001*#**	18	120,78	48,74	110,0	60,0	245,0	**0,004*#**
Second triglycerides	18	194,33	69,65	187,5	77,0	300,0		18	170,44	56,91	163,5	68,0	324,0	
Initial YKL-40	18	1392,78	759,46	1082,55	286,4	2686,1	0,099+	18	1296,59	534,92	1154,75	785,6	2904,6	0,199#
Second YKL-40	18	1709,23	701,29	1550,85	716,3	3550,9		18	1566,44	749,4	1545,15	435,9	3181,7	

* p<0,05; # Wilcoxon Signed Rank Test; + Paired Samples t Test

From the descriptive statistics of patients with and without GDM, family history, smoking, mode of delivery, age, gestational age, BMI, gravida, birth week, and weight status were compared (Table 4). According to the different tests, the normal birth rate was higher in those without GDM (p=0.008). In addition, the age of GDM patients was higher (p<0.001), gestational age was lower (p=0.006), BMI value was higher (p=0.033), and delivery week was lower (p=0.021).

Table 4. Analysis Of The Differences Between The First YKL-40, Second YKL-40 And YKL-40 Difference Values of Patients With And Without GDM

	GDM	Mean	SD	Median	Min	Max	p-value
Inıtial YKL-40	Yes	1392,78	759,46	1082,55	286,40	2686,10	0,874
	No	1296,59	534,92	1154,75	785,60	2904,60	
Second YKL-40	Yes	1709,23	701,29	1550,85	716,30	3550,90	0,613
	No	1566,44	749,40	1545,15	435,90	3181,70	
Difference in YKL-40	Yes	316,44	769,58	480,00	-1361,40	1470,00	0,527
	No	269,85	876,94	112,65	-1447,90	1960,60	

Analyzed with Mann-Whitney U Test

DISCUSSION

In the first trimester, due to the continuous transfer of glucose from mother to fetus, maternal plasma glucose is approximately 15 mg/dL lower than that of a non-pregnant woman of the same weight. Therefore, hypoglycemia is frequently seen in the first trimester. A similar decrease is observed in amino acid levels. Postprandial glucose levels remain elevated for longer due to increased peripheral resistance to insulin (12).

The first trimester is the phase in which gluconeogenesis increases. It is the anabolic phase in which maternal protein, glycogen, and fat stores increase. Estrogen and progesterone increase

insulin production and secretion by causing pancreatic beta-cell hyperplasia (13). Hyperinsulinism in early pregnancy is an event that increases lipogenesis and inhibits lipolysis. Glucagon level is suppressed in normal pregnant women. The catabolic phase develops in the second half of pregnancy (14). HPL (human placental lactogen), a polypeptide hormone secreted from syncytiotrophoblasts, increases proportionately to placental mass. Human placental lactogen is a potent insulin antagonist. The HPL increase, which starts at the tenth week of pregnancy, reaches 300 times at the twentieth week. Human placental lactogen stimulates lipolysis, increasing free fatty acids and peripheral insulin resistance (15).

A 44% decrease in insulin sensitivity was found in normal pregnancy in the third trimester. Increased insulin production easily compensates for this increase in insulin resistance in non-diabetic pregnant women (16). In diabetic patients with limited or no insulin reserve, increased insulin resistance leads to hyperglycemia as pregnancy progresses. Gestational diabetes occurs in women who can secrete sufficient insulin under normal conditions but cannot tolerate the increased insulin resistance of pregnancy. In addition to increased HPL levels, the level of triglycerides, free fatty acids, HDL (high-density lipoprotein), VLDL (Very Low-Density Lipoprotein), lipoproteins, and free cortisol in the blood contribute to hyperglycemia (17).

The infant of a mother with gestational DM is at risk of developing obesity at an early age, impaired glucose intolerance, and diabetes mellitus. The risk of developing diabetes/prediabetes in children with gestational DM is almost eight times higher (18). The fact that intrauterine hyperglycemia is an increased risk factor for diabetes in children and a several-fold increased risk factor for early-onset diabetes/prediabetes is the dominant view in the literature. Because of all these, the diagnosis of GDM should be accurately investigated, and the mother and child should be followed up after pregnancy (16 – 18).

A review by Deng et al. stated that serum YKL-40 levels increased in conditions characterized by inflammation, such as asthma, inflammatory bowel diseases, rheumatoid arthritis, psoriasis, atherosclerosis, colorectal cancer, small cell lung cancer, and stomach cancer (19). Gybel-Brask et al. have elaborated on the effectiveness of serum YKL-40 levels in detecting inflammation. Their study confirmed that not only serum YKL-40 levels but also inflammation-related neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLO) increases were shown in pregnant women with GDM (20). Regarding the results of our research, it was found that YKL-40 measurements were elevated in the second trimester compared to the first trimester.

Aktulay et al. indicated that YKL-40 was associated with insulin resistance that develops due to macrophage infiltration into adipose tissue (21). This is especially important in pointing out the relationship between inflammation and insulin resistance in obese people. Pregnancy is a condition characterized by insulin resistance, and the pancreas increases insulin secretion to overcome this resistance, and a hyperinsulinemic environment occurs. Insulin resistance in pregnancy is observed due to the anti-insulin effect of many placental hormones, such as human placental lactogen (HPL), human placental growth hormone, estrogen, progesterone, cortisol, and prolactin. It is expected to correlate with BMI and insulin resistance parameters (22).

Rinnov et al. reported that serum YKL-40 level was higher in the postpartum period compared to the third trimester of pregnancy. They found that serum YKL-40 level was positively correlated with IL-6, an inflammatory cytokine, confirming the close relationship between inflammation and YKL-40 (23). In a study by Li et al., serum YKL-40 level was found to be higher in pregnant women with GDM compared to healthy pregnant women, and

they found this level to be positively correlated with HbA1c value, fasting insulin level, and HOMA-IR value. In our study, while there was an increase in YKL-40 measurements in all patients, no difference in sub-group analysis (24).

A recent study by Tuten et al. emphasized that serum YKL-40 levels increased in pregnant women with GDM, and was positively correlated with insulin resistance parameters. They have also elaborated that although the fasting glucose level was similar in pregnant women with GDM compared to healthy pregnant women, the HbA1c level, which showed long-term glycemic control, was significantly higher. In addition, maternal serum YKL-40 level was positively correlated with HbA1c, fasting insulin, BMI, and HOMA-IR in decreasing order (25).

Regarding the results of this research, YKL-40 might be valuable in detecting low-grade inflammation in pregnant women. However, there is a need for larger-scale prospective randomized studies from the early period to the end of pregnancy to better and more accurately evaluate the relationship between insulin resistance and inflammation.

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Competing interests: The authors declare that they have no competing interests.

Ethical Declaration

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution. Informed consent has been obtained from all participants.

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