ORIGINAL ARTICLE

EVALUATION OF MYONECTIN AND IRISIN LEVELS IN PREGNANT AND NON-PREGNANT WOMEN

Gebelerde ve Gebe Olmayan Kadınlarda Myonektin ve İrisin Düzeylerinin Değerlendirilmesi

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ABSTRACT

Objective: To compare serum myonectin and irisin levels between healthy pregnant and non-pregnant women, and to evaluate their relationship with metabolic parameters.
Material and Methods: We conducted a cross-sectional study including 40 pregnant women in their second trimester (between 14 and 28 weeks of gestation) (case group) and 45 healthy non-pregnant women (control group). Fasting blood samples were analyzed for myonectin, irisin, glucose, insulin, and lipid profile. Myonectin and irisin were measured by ELISA. Statistical analyses were performed using SPSS v28, with group comparisons by t-test/Mann-Whitney U, correlations by Spearman's rho, and diagnostic performance by receiver operating characteristic (ROC) curves.
Results: Pregnant women had significantly lower fasting glucose but higher total cholesterol, triglycerides, LDL-C, and HDL-C levels than controls (p<0.05 for all). Serum myonectin and irisin were significantly higher in the pregnant group (p=0.012 and p<0.001, respectively). Myonectin levels correlated negatively with fasting glucose (r=-0.225, p=0.038) and positively with triglycerides (r=0.381, p<0.001). Irisin showed positive correlations with total cholesterol (r=0.348, p=0.001) and triglycerides (r=0.421, p<0.001). In ROC analysis, the discriminatory AUC values for myonectin and irisin levels in pregnancy were found to be 0.689 and 0.806, respectively.
Conclusion: Healthy pregnancy is associated with elevated serum myonectin and irisin levels, which correlate with maternal lipid and glucose parameters. These myokines may play an adaptive role in gestational metabolic changes and could serve as metabolic biomarkers in pregnancy.

Keywords: *Miyonectin; Irisin; Myokines; Pregnancy*

ÖZET

Amaç: Sağlıklı gebeler ile gebe olmayan kadınlarda serum miyonektin ve irisin düzeylerinin farklı olup olmadığını araştırmak ve bu miyokinlerin metabolik parametrelerle ilişkisini değerlendirmektir.
Gereç ve Yöntemler: Kesitsel bir çalışma kapsamında ikinci trimesterde (gebeliğin 14. ve 28. haftaları arasında) olan 40 hamile kadın (vaka grubu) ve 45 sağlıklı hamile olmayan kadın incelendi. Açlık kan örneklerinde miyonektin, irisin, glukoz, insülin ve lipid profili analiz edildi. Miyonektin ve irisin düzeyleri ELISA yöntemiyle ölçüldü. İstatistiksel analizler SPSS v28 ile yapıldı; gruplar Student t testi veya Mann-Whitney U testi ile karşılaştırıldı, korelasyonlar Spearman analiziyle değerlendirildi ve tanısal performans ROC eğrisi ile incelendi.
Bulgular: Gebe grubunda açlık glukozu anlamlı derecede daha düşük, total kolesterol, trigliserid, LDL-K ve HDL-K düzeyleri kontrol grubuna göre daha yüksek bulundu (tümü için p<0,05). Gebelerde serum miyonektin ve irisin düzeyleri kontrol grubundan anlamlı olarak daha yüksekti (sırasıyla p=0,012 ve p<0,001). Miyonektin düzeyi açlık glukoz ile negatif (r=-0,225, p=0,038), trigliserid ile pozitif korelasyon gösterdi (r=0,381, p<0,001). İrisin düzeyi total kolesterol (r=0,348, p=0,001) ve trigliserid (r=0,421, p<0,001) ile pozitif koreleydi. ROC analizinde, miyonektin ve irisin düzeylerinin gebelikte ayırt edici AUC değerleri sırasıyla 0,689 ve 0,806 olarak bulundu.
Sonuç: Sağlıklı gebelikte serum miyonektin ve irisin düzeyleri, gebe olmayanlara kıyasla yüksektir ve bu miyokin düzeyleri maternal lipid ve glukoz parametreleriyle ilişkilidir. Bu durum, miyonektin ve irisinin gebelikteki metabolik adaptasyonda rol oynayabileceğini ve gebeliğin metabolik durumunu yansıtan biyobelirteçler olabileceğini düşündürmektedir.

Anahtar Kelimeler: *Miyonektin; İrisin; Myokinler; Gebelik*

INTRODUCTION

Myokines are cytokines and peptides secreted by skeletal muscle fibers that mediate communication between muscle and other tissues, influencing metabolic and inflammatory pathways (1). Myonectin, also known as CTRP15 (C1q/TNF-related protein 15), is a recently identified myokine predominantly expressed and released by skeletal muscle (2). Myonectin has been shown to play an important role in regulating systemic lipid and glucose homeostasis (3). Circulating myonectin levels are tightly regulated by nutritional and metabolic status: fasting suppresses myonectin, whereas refeeding causes a dramatic increase in its mRNA and serum levels (2). Likewise, myonectin levels are reduced in obesity and insulin-resistant states, while physical exercise can significantly elevate its expression and circulation (2). Functionally, myonectin acts in an insulin-mimetic manner on lipid metabolism - it promotes fatty acid uptake in adipocytes and hepatocytes by upregulating genes such as CD36 and fatty acid-binding proteins, leading to reduction of circulating free fatty acids (2). Through these effects, myonectin is considered to have “obesoprotective” and insulin-sensitizing properties, making it a potential therapeutic target (2,3).

Irisin is another hormone-like myokine, a 112-amino acid peptide cleaved from the transmembrane protein FNDC5, first identified in 2012 by Boström et al. (4). Irisin gained attention for its role in driving the browning of white adipose tissue and increasing energy expenditure (4). Subsequent studies revealed pleiotropic metabolic benefits of irisin: it enhances insulin secretion and pancreatic β-cell survival, improves insulin sensitivity, increases glucose uptake and storage in skeletal muscle, and reduces hepatic gluconeogenesis and lipogenesis (5). Overall, irisin administration has been shown to promote weight loss and decrease insulin resistance in experimental models (5). Beyond its metabolic effects, irisin may also exert anti-inflammatory influences - for example, it can attenuate proinflammatory cytokine production in adipose tissue while increasing anti-inflammatory adipokine levels (6). These multifaceted actions have made irisin a promising biomarker and potential therapeutic target for metabolic diseases (5).

Pregnancy induces significant changes in maternal metabolism. During mid to late gestation, women develop a state of physiological insulin resistance, believed to ensure adequate glucose supply to the growing fetus (7). Consequently, maternal fasting blood glucose tends to be lower, while postprandial glycemia and insulin levels rise as pregnancy progresses (7). Pregnancy is also characterized by hyperlipidemia - circulating triglycerides and cholesterol increase substantially in the second and third trimesters, providing essential nutrients for fetal development (7). The mother’s body adapts through hormonal and metabolic adjustments, but in some cases insulin resistance becomes excessive and leads to gestational diabetes mellitus (GDM), a condition associated with adverse outcomes (8). There is growing evidence that muscle-derived factors may be involved in these gestational metabolic adaptations. Notably, recent studies have implicated irisin in glucose homeostasis during pregnancy. Serum irisin levels have been reported to rise significantly in pregnant women compared to non-pregnant women and irisin concentrations are negatively correlated with indices of insulin resistance in pregnancy (e.g. homeostatic model assessment for insulin resistance (HOMA-IR) and 2-hour oral glucose tolerance test (OGTT) glucose) (5,9). This suggests that higher irisin in pregnancy could be a compensatory response to counterbalance insulin resistance (9). In support of this, Kuzmicki et al. observed that serum irisin increases markedly during pregnancy, but that this increase is blunted in women who develop GDM (9). Irisin has accordingly been proposed as a potential biomarker for predicting the development of GDM (5).

In contrast to irisin, myonectin’s role in human pregnancy has not been well characterized. To our knowledge, prior to our study there were no published data directly comparing myonectin levels between pregnant and non-pregnant women. Indirect evidence from a recent case-control study in pregnant women showed that myonectin levels were significantly lower in those with GDM compared to gestational age-matched healthy pregnancies (10). That finding suggests myonectin normally rises during healthy pregnancy (and failure to attain this rise may be associated with GDM). However, baseline myonectin levels in uncomplicated pregnancies versus non-

Bozok Tıp Derg 2026;16(1):56-64
Bozok Med J 2026;16(1):56-64

pregnant individuals remained undetermined. Given the metabolic functions of myonectin and irisin, we hypothesized that pregnancy would alter the circulating levels of both myokines. Specifically, we aimed to investigate whether serum myonectin and irisin concentrations differ between healthy pregnant women and non-pregnant women, and to evaluate the relationships of these myokines with metabolic parameters (glucose, insulin, lipid profile) in the pregnant state. Clarifying these differences could improve our understanding of gestational metabolic adaptations and the potential utility of myonectin and irisin as biomarkers of metabolic health in pregnancy.

MATERIAL AND METHOD

This research was designed as a cross-sectional case-control study. The study population comprised 40 pregnant women in their second trimester (between 14 and 28 weeks of gestation) (case group) and 45 healthy non-pregnant women (control group) who presented for gynecological examination or routine check-ups. Pregnant participants were recruited from routine antenatal clinic visits and had normal singleton pregnancies without any known obstetric complications or pre-existing chronic conditions. None of the pregnant subjects had GDM (gestational diabetes was ruled out by standard screening tests), hypertensive disorders, or other significant comorbidities. The control group consisted of age-matched and body mass index (BMI)-matched healthy women with no current pregnancy and no history of chronic metabolic diseases. All participants provided informed consent. The study protocol was approved by the Ordu University Scientific Research Ethics Committee, with the decision number 2024/103, and the research was conducted in accordance with the Declaration of Helsinki.

After an overnight fast (minimum 8-10 hours), venous blood samples were collected from each participant in the morning. For pregnant women, blood collection was performed during the second trimester at a routine prenatal visit (prior to any glucose tolerance test). Serum was separated and stored at -80°C until analysis. We measured serum myonectin and irisin levels using a quantitative enzyme-linked immunosorbent assay (ELISA) technique (high-sensitivity commercial ELISA kits specific for human myonectin and irisin were used, according to the manufacturers' protocols). Fasting glucose (mg/dL) and insulin (µIU/mL) levels were measured by standard automated methods. From glucose and insulin, insulin resistance was estimated by the homeostatic model assessment (HOMA-IR) formula. The lipid profile was assessed using enzymatic colorimetric assays: total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured in the hospital's biochemistry laboratory. In addition, basic clinical data (age, weight, height) were recorded to calculate BMI (kg/m²).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 28.0 (IBM Corp, Armonk, NY). Continuous variables were first tested for normality of distribution using the Shapiro-Wilk test. Accordingly, data are presented as mean ± standard deviation for approximately normally distributed variables, or as median and interquartile range (IQR) for non-normal variables. For comparisons between the pregnant and control groups, the independent-samples Student's t-test was used for variables with normal distribution, and the Mann-Whitney U test was used for variables with a non-normal distribution (as indicated in Table 1). Correlations between myokine levels (myonectin, irisin) and metabolic parameters (glucose, insulin, HOMA-IR, lipids) were assessed using Spearman's rank correlation coefficients, given some variables were non-normally distributed. To evaluate the discriminatory capacity of myonectin and irisin levels for pregnancy status, we constructed ROC curves and calculated the area under the curve (AUC) with 95% confidence intervals. Optimal cutoff values for distinguishing pregnant vs. non-pregnant were determined by the Youden index on the ROC curve. Statistical significance was set at a two-tailed p-value <0.05 for all analyses.

RESULTS

The demographic and biochemical characteristics of the participants are summarized in Table 1. The mean age of the pregnant women was 29.8±0.56 years and that of controls was 28.2±0.80 years, a difference that was not statistically significant (p=0.118). The BMI

Table 1. Comparison of clinical, hormonal and biochemical parameters in PCOS and control groups

	Control (n=45)	Pregnant (n=40)	p
Age (years)	28.24±0.8	29.83±0.56	0.118[a]
BMI (kg/m²)	24.84(4.1)	24.73(1.58)	0.954[b]
FSG (mg/dL)	85±1.11	78.88±0 .9	<0.001[a]
FSI (µIU/mL)	9.16±0.57	9.43±0.54	0.735[a]
HOMA-IR	1.85(1.1)	1.8(1.15)	0.891[b]
Total cholesterol (mg/dL)	166.03±4.86	199.3 6±4.24	<0.001[a]
Trigliserid (mg/dL)	85.11±4.66	143.17±8.65	<0.001[a]
LDL-C (mg/dL)	92.99 ±4.47	108.15±3.33	0.009[a]
HDL-C (mg/dL)	56.02 ±1.7	62.43±1.82	0.012[a]
Myonectin (ng/mL)	60.43±2.9	70.22±2.4	0.012[a]
Irisin (ng/mL)	442.73±26.73	638.67±27.31	<0.001[a]

Data are presented as mean ± SD/median(IQR). p<0.05 is significant. a: Student t test, b: Mann-Whitney U test, BMI: Body mass index, FSG: Fasting serum glucose, FSI: Fasting serum insülin, HOMA-IR: Homeostatic model assessment insulin resistance index, LDL-C: LDL cholesterol, HDL-C: HDL cholesterol, Polycystic ovary syndrome (PCOS), m²: Meter square

was also similar between the groups (pregnant 24.73 vs. control 24.84 kg/m², p=0.954) (Table 1). There was no statistically significant difference between pregnant and non-pregnant women in terms of mean age, BMI, fasting serum insulin (FSI) or HOMA-IR (all p>0.05). In contrast, fasting serum glucose (FSG) was lower in the pregnant group (p<0.05). Total cholesterol, triglycerides, LDL-C, HDL-C, serum myonectin and serum irisin concentrations were all higher in pregnant women than in controls (p<0.05 for each; Table 1, Figure 1). Figure 1 displays the distribution of myonectin and irisin across the two groups. Mean serum myonectin was significantly elevated in the pregnant group compared with the control group (p=0.012), and a more pronounced increase was observed for irisin, with markedly higher levels in pregnant women (p<0.001). Spearman's rho correlation analysis was used to explore the associations between myonectin/irisin and metabolic indices (Table 2). Myonectin showed a weak but statistically significant inverse relationship with FSG (r=-0.225, p=0.038), whereas the negative association between irisin and FSG did not reach significance (r=-0.204, p=0.062). Neither myokine was significantly related to FSI or HOMA-IR (all p>0.05). With respect to lipid parameters, irisin was moderately and positively correlated with total cholesterol (r=0.348, p=0.001), while the correlation between myonectin and total cholesterol did not achieve statistical significance

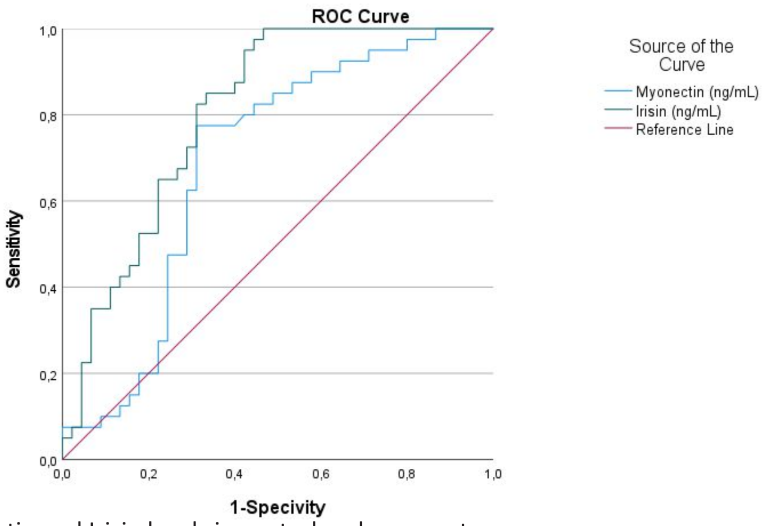

Figure 1. Myonectin and Irisin levels in control and pregnant groups

Bozok Tıp Derg 2026;16(1):56-64
Bozok Med J 2026;16(1):56-64

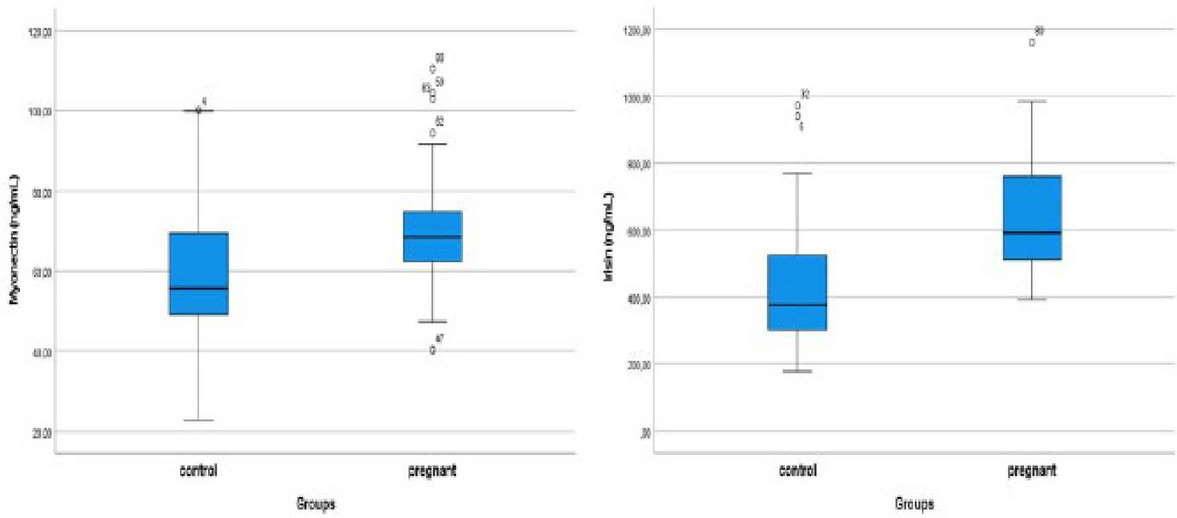

Figure 2. ROC Curve analysis of myonectin and irisin levels

Table 2. Correlation of serum irisin and myonectin level with metabolism parameters

	Myonectin	Irisin
FSG		
r	-0.225	-0.204
p	0.038	0.062
FSI		
R	0.74	0.155
p	0.501	0.156
HOMA-IR		
r	0.035	0.107
p	0.753	0.329
TC		
r	0.191	0.348
p	0.076	0.001
TG		
r	0.381	0.421
p	<0.001	<0.001
HDL-C		
r	0.160	0.101
p	0.144	0.360
LDL-C		
r	0.045	0.209
p	0.683	0.055

Spearman's Rho correlation test. FSG: Fasting serum glucose, FSI: Fasting serum insülin, HOMA-IR: Homeostatic model assessment insulin resistance index, TC: Total cholesterol, TG: Trigliserid, HDL-C: HDL cholesterol, LDL-C: LDL cholesterol (p=0.076). Both myonectin and irisin were positively and significantly correlated with triglycerides (myonectin: r=0.381, p<0.001; irisin: r=0.421, p<0.001). No significant correlations were detected between myonectin and HDL-C or LDL-C (p>0.05), whereas irisin showed a borderline positive correlation with LDL-C (r=0.209, p=0.055). Overall, these findings suggest that irisin has somewhat stronger associations with lipid parameters than myonectin.

To characterize the ability of myonectin and irisin to discriminate between pregnant and non-pregnant status, ROC curve analyses were carried out for both markers (Table 3). For myonectin, a threshold of 59.55 ng/mL provided 80.0% sensitivity and 57.8% specificity (AUC=0.689, 95% CI: 0.573-0.805; p=0.003). For irisin, the best cut-off was 389.54 ng/mL, at which sensitivity was 100% and specificity 53.3% (AUC=0.806, 95% CI: 0.713-0.898; p<0.001). Thus, compared with myonectin, irisin yielded a higher AUC and clearly higher sensitivity, indicating a better overall discriminative performance between the two study groups.

DISCUSSION

In this study, we found that pregnant women have significantly higher serum myonectin and irisin levels than non-pregnant women, supporting the concept that these muscle-derived hormones are involved in the physiological adaptations to pregnancy. Additionally, as expected in normal gestation, the pregnant group exhibited lower fasting glucose and a more elevated lipid profile (cholesterol, triglycerides) relative to controls. Our results also demonstrated distinct relationships between these myokines and metabolic parameters: myonectin was inversely related to fasting glucose and positively related to triglycerides, whereas irisin was positively related to total cholesterol and triglycerides. To our knowledge, this is one of the first reports characterizing the differences in myonectin levels between pregnant and non-pregnant individuals, alongside confirming previous observations regarding irisin in pregnancy.

The elevated myonectin levels in pregnancy observed in our study suggest that myonectin could play a role in maternal metabolic adaptation. One possible explanation for the increase is the change in nutritional and energy status during pregnancy. Myonectin release is known to be stimulated by feeding and suppressed by fasting (2,11). Pregnancy is a hyperphagic state with enhanced nutrient availability and postprandial lipemia, which might trigger greater myonectin secretion from skeletal muscle. In line with this, we found myonectin correlated positively with triglyceride levels; pregnant women with higher TG tended to have higher myonectin. This correlation is consistent with myonectin's proposed function as a lipid-sensing myokine that responds to elevated fatty acids by promoting their uptake into tissues (2). By increasing lipid clearance and storage in the liver and adipose tissue, myonectin may help prevent excessive accumulation of circulating free fatty acids during pregnancy, thereby protecting against lipotoxicity. The negative correlation between myonectin and fasting glucose in our data (though modest) raises the possibility that higher myonectin could be associated with better glycemic control. This fits with animal studies where myonectin administration reduced blood glucose and free fatty acid levels, mimicking some effects of insulin (2,12). It is conceivable that in pregnant women, those with a more robust myonectin response are able to maintain slightly lower fasting glucose. However, since we did not observe differences in HOMA-IR between groups, this relationship should be interpreted cautiously. Overall, our findings imply that myonectin is upregulated in normal pregnancy, potentially serving an adaptive role in handling the lipid surge of gestation and in modulating glucose availability.

The increase in irisin levels during pregnancy that we and others have documented may represent a compensatory mechanism to counteract pregnancy-induced insulin resistance. Irisin has been shown

Table 3. ROC Curve analysis of myonectin and irisin levels in pregnant group

	AUC (95% CI)	p	Cut-off (ng/mL)	Sensitivity (%)	Specificity (%)
Myonectin	0.689 (0.573-0.805)	0.003	59.55	80.0	57.8
Irisin	0.806 (0.713-0.898)	<0.001	389.54	100	53.3

Bozok Tıp Derg 2026;16(1):56-64
Bozok Med J 2026;16(1):56-64

to improve insulin sensitivity and glucose uptake in skeletal muscle and adipose tissue (5). In our study, pregnant women's irisin levels were ~44% higher than those of controls, and we noted a trend toward inverse correlation between irisin and fasting glucose (as well as a known inverse correlation with HOMA-IR reported in the literature (9)). These observations align with prior research suggesting that irisin helps mitigate insulin resistance in pregnancy (9,13,14). Kuzmicki et al. reported that maternal irisin concentrations rise significantly as pregnancy progresses, and importantly, women who develop GDM have lower irisin levels than those who remain normoglycemic (9). In the study by Kuzmicki et al., irisin levels were high during pregnancy and dropped after delivery, indicating that the pregnant state itself induces irisin production (15). They also found that irisin was negatively associated with 2-hour OGTT glucose and HOMA-IR in pregnant women with normal glucose tolerance, supporting irisin's link to improved metabolic profiles. Our results are in concordance: we studied only healthy pregnancies and found consistently elevated irisin, which presumably reflects a normal adaptive response (9). Moreover, the fact that irisin correlated positively with cholesterol and triglycerides in our cohort might seem paradoxical (as irisin is generally viewed as metabolically beneficial). This positive correlation could be explained by the notion that irisin secretion is stimulated in proportion to the magnitude of metabolic load. In other words, pregnant individuals with greater hyperlipidemia might stimulate more irisin release as an attempt by the body to increase energy expenditure and utilize excess substrates. Indeed, previous research has observed similar positive correlations between irisin and lipid levels (5). Irisin's action in promoting the browning of white adipose tissue and fatty acid oxidation could be particularly relevant in the context of gestational hypertriglyceridemia (5,16). By converting white fat to a more metabolically active brown-like state, irisin may facilitate the burning of extra calories and lipids, thereby preventing extreme maternal fat accumulation while ensuring energy supply to the fetus (5).

Our study provides additional evidence that both myonectin and irisin are dynamically regulated during pregnancy and closely tied to the metabolic milieu of gestation. The robust difference in irisin levels between pregnant and non-pregnant women (as reflected by an AUC >0.8 in ROC analysis) quantitatively underscores how profoundly pregnancy can alter certain biomarkers. Clinically, one would never use myonectin or irisin levels to diagnose pregnancy - that is not the intent. Rather, these biomarkers could have potential clinical relevance in identifying or monitoring metabolic complications of pregnancy. For instance, since healthy pregnancies showed higher myonectin and irisin while prior studies indicate GDM is associated with inadequate increases in these myokines (9,10), one could speculate that measuring myonectin/irisin in early pregnancy might help predict who is at risk for developing GDM. Irisin in particular has been proposed as a predictive marker for GDM onset (5,17-19). Our findings support this idea in that irisin was uniformly elevated in normal pregnancies; a pregnant woman with inappropriately low irisin (for example, below the ~389 ng/mL cutoff identified in our ROC analysis) might be a candidate for closer surveillance. Similarly, myonectin's role in pregnancy is less studied, but the lower myonectin observed in GDM cases by Onat et al. hints that it could also serve as an early warning biomarker or even a therapeutic target (e.g., interventions to raise myonectin might improve lipid handling). Of course, prospective studies are needed to evaluate the predictive accuracy of these myokines for GDM or other outcomes (10).

It is important to note that not all studies are in agreement regarding irisin dynamics in complicated pregnancies. While many report lower irisin in GDM, at least one study found no significant difference in serum irisin levels between women with GDM and those without GDM (20). These discrepancies could be due to differences in study design (case-control vs. longitudinal), timing of blood sampling, assay methodologies, or population characteristics such as BMI and ethnicity. Irisin levels can fluctuate with gestational age - one study noted that irisin concentrations increase by approximately 16% in mid-pregnancy and 21% in late pregnancy compared to early pregnancy (15). Therefore, the timing of measurement (first vs. third trimester) may yield different results, and inconsistent timing across studies could contribute to conflicting findings. Additionally, the regulatory mechanisms of irisin (and myonectin) in humans are complex; factors like exercise, diet, adiposity, and placental hormones might modulate their levels. Further research, including controlled longitudinal studies, will be valuable to clarify these issues. Our work adds to the literature by firmly establishing that normal pregnancy itself elevates myonectin and irisin, providing a reference point against which pathological states can be compared.

This study has several limitations. First, the sample size was relatively small, and all participants were recruited from a single center; thus, the findings should be interpreted with caution and need confirmation in larger, multi-center studies. Second, we examined myokine levels at only one time-point in mid-pregnancy and did not track longitudinal changes throughout gestation or postpartum. Third, our cohort consisted of healthy pregnancies without GDM or other complications - while this homogeneity was by design, it means we could not directly evaluate how myonectin and irisin differ in pregnancies with metabolic pathology. Future studies including GDM patients and serial measurements in each trimester would be valuable to extend our findings.

CONCLUSION

Pregnancy is associated with distinct changes in circulating myokines: we found that healthy pregnant women have higher serum myonectin and irisin levels compared to non-pregnant women. This indicates that skeletal muscle actively participates in the metabolic adaptations of pregnancy via myokine secretion. Elevated irisin and myonectin in pregnancy may facilitate increased lipid storage and energy expenditure, helping to maintain glucose homeostasis in the face of gestational insulin resistance. Our study suggests that myonectin and irisin could serve as novel biomarkers reflecting the metabolic state of pregnancy. Further research is warranted to elucidate the regulatory mechanisms of myonectin and irisin in pregnancy and to determine whether modulating these myokines could have therapeutic benefits for maternal and fetal health.

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Bozok Tıp Derg 2026;16(1):56-64
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