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ORIGINAL ARTICLE

Investigation of Serum Brain-derived Neurotrophic Factor, Leptin and Ghrelin Levels in Missed Abortion: A Prospective Study

Kaçırılan Düşüklerde Serum Beyin Kaynaklı Nörotrofik Faktör, Leptin ve Ghrelin Düzeylerinin Araştırılması: Prospektif Bir Çalışma

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ABSTRACT

Aim: This study aims to investigate the relationship between serum leptin, ghrelin, and brain-derived neurotrophic factor (BDNF) in missed abortion.
Methods: Thirty-four pregnant women diagnosed with missed abortion and thirty healthy pregnant women were included in this study. The participants were between the ages of 19 and 42, with women in the first and second trimesters selected for both the control and study groups. Missed abortion was defined as the absence of a fetal heartbeat in the first 20 weeks of pregnancy. The serum levels of leptin, ghrelin, and BDNF in these patients were compared with those of healthy pregnant women at the same gestational age in both groups.
Results: The median [IQR] serum level of ghrelin was significantly higher in women with missed abortion compared to the healthy controls (807.17 [IQR, 540.93-1385.61] vs. 267.14 [IQR, 211.63-360.65], U=961, p <.001, rrb=0.88 [95% CI: 0.80 to 0.93]). However, no significant differences were observed in serum level BDNF (270.28 [IQR, 196.91-639.57] vs. 265.31 [IQR, 171.46-422.85], U=394, p=.744, rrb=0.05 [95% CI: -0.25 to 0.35]) and leptin (0.40 [IQR, 0.27-0.62] vs. 0.53 [IQR, 0.29-0.65], U=362, p=.847, rrb=0.03 [95% CI: –0.27 to 0.33]) between healthy controls and patients with missed abortion.
Conclusions: Our study found that serum ghrelin levels were higher in patients with missed abortions compared to healthy pregnancies. Future studies should further investigate the potential role of ghrelin in the etiopathogenesis of missed abortion.

Keywords: BDNF, Ghrelin, Leptin, Missed abortion,

ÖZ

Amaç: Bu çalışmanın amacı, kaçırılan düşüklerde serum leptin, ghrelin ve beyin kaynaklı nörotrofik faktör (BDNF) arasındaki ilişkiyi araştırmaktır.
Gereç ve Yöntemler: Bu çalışmaya kaçırılan düşük tanısı almış otuz dört gebe kadın ve otuz sağlıklı gebe kadın dahil edildi. Katılımcılar 19 ila 42 yaşları arasındaydı ve hem kontrol hem de çalışma grupları için birinci ve ikinci trimesterdeki kadınlar seçildi. Kaçırılan düşük, gebeliğin ilk 20 haftasında fetal kalp atışının olmaması olarak tanımlandı. Bu hastalardaki serum leptin, ghrelin ve BDNF düzeyleri, her iki gruptaki aynı gebelik yaşındaki sağlıklı gebe kadınlarla karşılaştırıldı.
Bulgular: Düşük yapma riski olan kadınlarda ghrelin'in ortanca [IQR] serum düzeyi, sağlıklı kontrollere kıyasla anlamlı derecede yüksekti (807,17 [IQR, 540,93-1385,61] - 267,14 [IQR, 211,63-360,65], U=961, p<.001, rrb=0,88 [95% CI: 0,80-0,93]). Ancak, sağlıklı kontroller ile düşük yapmış hastalar arasında serum BDNF (270.28 [IQR, 196.91-639.57] vs. 265.31 [IQR, 171.46-422.85], U=394, p=.744, rrb=0.05 [95% CI: -0.25 ila 0.35]) ve leptin (0.40 [IQR, 0.27-0.62] vs. 0.53 [IQR, 0.29-0.65], U=362, p=.847, rrb=0.03 [95% CI: -0.27 ila 0.33]) seviyelerinde anlamlı bir fark gözlenmedi.
Sonuçlar: Çalışmamız, kaçırılan düşük olan hastalarda serum ghrelin düzeylerinin sağlıklı gebeliklere kıyasla daha yüksek olduğunu göstermektedir. Gelecekteki çalışmalar, kaçırılan düşük etiyopatogenezinde ghrelinin potansiyel rolünü daha fazla araştırmalıdır.

Anahtar Kelimeler: BDNF, Ghrelin, Leptin, Kaçırılan düşük,

Introduction

Missed abortion is defined as the unnoticed intrauterine death of the embryo or fetus without the expulsion of pregnancy products, accounting for 15% of clinically diagnosed pregnancies. Patients may exhibit mild or no clinical symptoms, such as vaginal bleeding or abdominal pain. The diagnosis of missed abortion is often confirmed via ultrasonography. Surgical evacuation is the standard treatment for missed abortion, with a success rate of up to 95%. However, the high costs associated with surgery and hospitalization present significant challenges (1, 2). Brain-derived neurotrophic factor (BDNF) is a neurotrophin that plays a crucial role in neuronal cell growth, survival, and synaptic plasticity. During pregnancy, BDNF is involved in follicular development, implantation, and embedding in reproductive tissues. Studies have shown that serum BDNF levels in pregnant women are 30-50% lower than those in non-pregnant women (3, 4).

Leptin, primarily produced by adipose tissue, is released into the bloodstream and reflects adipose tissue size. Its levels fluctuate according to nutritional status. Leptin is a pleiotropic hormone that regulates various functions,

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including vascular health, bone and cartilage growth, immune response, and the normal functioning of the reproductive system(5). Ghrelin, an orexigenic (appetite-stimulating) peptide mainly secreted by the stomach, regulates energy metabolism. Plasma ghrelin levels typically decrease after food intake, promoting satiety (6). Changes in serum ghrelin levels have been observed throughout pregnancy. Specifically, ghrelin levels peak in the middle of pregnancy and significantly decrease toward the end of the third trimester (7). Ghrelin is involved in intercellular communication and has been detected in the morula and later stages of embryo development. Additionally, it can be produced by the reproductive system and released into uterine fluid, where its concentration rises during fasting. Ghrelin negatively regulates cell viability and proliferation, suggesting that elevated ghrelin levels may inhibit embryo development through its receptor, GHS-R (8).

Leptin is also synthesized by the placenta, playing a critical role in energy homeostasis, fetal development, and immunological adaptation during pregnancy. It is believed that changes in leptin levels in missed abortion may indicate placental dysfunction or disruptions in maternal-fetal metabolic communication. Therefore, examining leptin levels may help understand the metabolic and inflammatory processes underlying missed abortion.

The role of ghrelin in maternal energy balance and placental growth is well-documented. It also plays a role in regulating the immune response during pregnancy, particularly through its anti-inflammatory effects. We included ghrelin in this study because we hypothesize that changes in its levels during pathological pregnancies like missed abortion may reflect maternal energy imbalance or inflammation.

BDNF contributes to placental and fetal development and is involved in maternal stress, inflammation, and fetal growth. Literature suggests that BDNF levels may differ between healthy pregnancies and those with complications. Therefore, we included BDNF in our study, as changes in its levels may indicate placental or neurological developmental disorders. Pregnancy involves complex neuroendocrine, immunological, and metabolic changes in the maternal body. Disruptions in these systems may lead to placental dysfunction and fetal loss, as seen in missed abortion. Our study hypothesizes that missed abortion may lead to alterations in biomarker levels, including leptin, ghrelin, and BDNF, which may present a distinct profile compared to healthy pregnancies. Measurement of these biomarkers could offer insights into the mechanisms underlying missed abortion and may serve as potential diagnostic or follow-up markers in clinical practice.

Materials and Methods

Study Design

This is a single-center, prospective study conducted at our clinic between December 2023 and January 2024. The study was approved by the Local Ethics Committee of Selcuk University Faculty of Medicine under decision number 2024/105.

Participants

The study included 34 pregnant women diagnosed with missed abortion and 30 healthy pregnant women. Participants were aged between 19 and 42 years, with women in the first and second trimesters selected for both the study and control groups. Notably, 80% of participants were in the first trimester. Women who did not have a fetal heartbeat before the 20th week of pregnancy were diagnosed with missed abortion. All patients who agreed to participate were informed about the study, and an informed consent form was obtained.

Inclusion Criteria

- Women with singleton pregnancies
- Aged 18-40 years
- In the first or second trimester of pregnancy

Exclusion Criteria

- History of hypertension, diabetes, hematological or rheumatological diseases
- Use of teratogenic drugs or radiation
- BMI ≥30
- Twin or multiple pregnancies
- Smokers or alcohol users
- Patients who refused to participate in the study

Biomarker Analysis

Serum concentrations of Brain-Derived Neurotrophic Factor (BDNF), leptin, and ghrelin were measured using commercially available ELISA kits (Bostonchem), specifically:

Human BDNF (SKU: BLS-5404Hu)

Leptin (SKU: BSL-1160Hu)

Ghrelin (SKU: BLS-1943Hu)

Sample Collection and Storage

Venous blood samples were collected and centrifuged to obtain serum. The serum was then stored at -80°C in 1.5 mL Eppendorf tubes until analysis.

ELISA Methodology

The analysis was conducted using the Sandwich enzyme immunoassay principle. The microtiter plate provided in each kit was pre-coated with an antibody specific to BDNF, leptin, or ghrelin. Standards or samples were added to the wells, followed by a biotin-conjugated antibody specific to the target biomarker. Avidin conjugated to Horseradish Peroxidase (HRP) was then added, and the plate was incubated. After adding the TMB substrate solution, wells containing the target biomarker underwent a color change, which was terminated by the addition of sulfuric acid. The color change was measured spectrophotometrically at a wavelength of 450 nm ± 10 nm. The concentration of BDNF, leptin, and ghrelin in the samples was determined by comparing the optical density (OD) of the samples to the standard curve.

Sensitivity of the ELISA Kits;

•Leptin: 0.058 ng/mL

•Ghrelin: 49.5 pg/mL

•BDNF: 12.7 pg/mL

Statistical analysis

All statistical analysis was performed using R Statistical Language (version 4.1.2; The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). To check the normality of the data, Shapiro-Wilk's normality test and Q-Q plots were used. Levene's test was used to assess the homogeneity of the variances. Variables presented as mean ± standard deviation (SD) or median with interquartiles [IQR, 25th percentile – 75th percentile], as appropriate. An independent samples t-test and Mann-Whitney U test were run to determine if there was a statistically significant difference in age and BDNF, leptin, and ghrelin values between healthy controls and patients with missed abortus. Hedges's g and rank biserial correlation (rrb) values with 95% confidence intervals (CIs) were given as effect size (ES) for age and BDNF, leptin, and ghrelin values, respectively. Besides, Spearman's rho correlation coefficients were calculated to examine the relationship between serum BDNF, leptin, and ghrelin levels age, and BMI in women with missed abortus. A two-tailed p-value of less than 5% was considered statistically significant.

Results

This study included 64 participants (34 women with missed abortions, and 30 healthy controls) with a mean age of 30.52±6.01, ranging from 19 to 43. The age, BDNF, leptin, and ghrelin distribution of the groups, and BMI values of the patients with missed abortion were given in Table 1.

Table 1. BMI characteristics of the patients, and age and TMAO values stratified by groups

		Healthy controls (n=30)	Missed Abortion (n=34)	p-value
Age (years)	Mean±SD	29.57±4.85	31.35 ± 6.84	.238[1]
BMI	Mean±SD		25.66 ± 3.91	
BDNF (pg/mL)				
	Mean±SD	458.35±472.91	504.48 ± 492.63	
	Median [IQR]	265.31 [171.46-422.85]	270.28 [196.91 – 639.57]	.746[2]
Leptin (ng/mL)				
	Mean±SD	0.50±0.26	0.58 ± 0.50	
	Median [IQR]	0.53 [0.29-0.65]	0.40 [0.27 – 0.62]	.847[2]
Ghrelin (pg/mL)				
	Mean±SD	295.18±143.16	1068.29 ± 682.64	
	Median [IQR]	267.14 [211.63-360.65]	807.17 [540.93 – 1385.61]	<.001[2]

[1]Independent samples t-test; 2Mann-Whitney U test, BDNF: Brain-derived neurotrophic factor, BMI: Body mass index, SD: Standard deviation, IQR: Interquartile range

The mean age of the groups was similar (29.57±4.85 vs. 31.35±6.84, Student's t=1.19, p=.238, Hedges's g=0.30 [95% CI: -0.19 to 0.78]). The median [IQR] serum level of ghrelin was significantly higher in women with missed abortions compared to the healthy controls (807.17 [IQR, 540.93-1385.61] vs. 267.14 [IQR, 211.63-360.65], U=961, p <.001, rrb=0.88 [95% CI: 0.80 to 0.93]) (Figure 1-A). However, no significant differences were observed in serum level BDNF (270.28 [IQR, 196.91-639.57] vs. 265.31 [IQR, 171.46-422.85], U=394, p=.744, rrb=0.05 [95% CI: -0.25 to 0.35]) and leptin (0.40 [IQR, 0.27-0.62] vs. 0.53 [IQR, 0.29-0.65], U=362, p=.847, rrb=0.03 [95% CI: -0.27 to 0.33]) between healthy controls and patients with missed abortion.

Discussion

In this study, we aimed to examine the relationship between missed abortion and serum BDNF, leptin, and

ghrelin levels.

In addition to its potential effects on perinatal mood, BDNF has been shown to play a role in placental pathology. Lower placental BDNF gene expression has been observed in women with preeclampsia, which is believed to be linked to impaired placental development (9). Moreover, low BDNF levels in pregnant women have been suggested to contribute to impaired fetal growth (10). However, in our study, no statistically significant difference was found between the serum BDNF levels of women with missed abortions and healthy pregnant women.

Ghrelin and leptin are peptide hormones that play important, but opposing, roles in regulating feeding behavior, energy homeostasis, and metabolism, primarily through their action in the hypothalamus. Ghrelin stimulates appetite, and promotes adiposity, weight gain, and energy conservation, while leptin inhibits appetite, decreases food intake, causes body weight loss, and increases energy expenditure, metabolic rate, and sympathetic activity (11).

Leptin levels physiologically increase during pregnancy, peaking in the second trimester. A study comparing leptin concentrations in serum, coelomic fluid, and amniotic fluid in healthy pregnant women and women with missed abortion found that while leptin levels in the coelomic fluid were higher in women with missed abortion, no significant difference was observed in serum leptin levels (12). Similarly, a study examining plasma leptin levels in hyperemesis gravidarum patients and healthy pregnant women found no significant difference between the two groups (11). In line with these findings, our study also found no significant difference in serum leptin levels between the two groups.

Leptin and BDNF are hormones subject to dynamic regulation in both maternal and fetal systems. Factors such as interindividual biological variation, maternal energy status, and placental function may influence the levels of these biomarkers, potentially masking group differences. Missed abortion cases may have a heterogeneous pathophysiology due to underlying causes such as genetic anomalies, immunological factors, or environmental influences. Consequently, leptin and BDNF may not serve as distinct biomarkers in these diverse pathologies. Additionally, the limited statistical power due to the sample size may have hindered the detection of small differences in leptin and BDNF levels. These results suggest that leptin and BDNF may not directly contribute to the pathophysiology of missed abortion or may act through more complex mechanisms. Further investigation into other biomarkers or mechanisms may be necessary and could contribute to advancing scientific understanding in this area.

Ghrelin in Pregnancy Complications

Pregnancy complications such as preeclampsia, intrauterine growth restriction, preterm birth, premature rupture of membranes, late spontaneous miscarriage, and placental abruption are often associated with defective deep placentation (13). Erol et al. found that serum ghrelin levels in women with mild and severe preeclampsia were significantly higher than in healthy controls (14). A study comparing plasma ghrelin levels in hyperemesis gravidarum patients and healthy pregnant women also reported higher levels of ghrelin in the former group (11). However, there is limited research on serum ghrelin levels in pregnancies with birth defects. Consistent with existing literature, our study found that serum ghrelin levels were higher in women with missed abortions compared to healthy pregnant women.

The increase in serum ghrelin levels in pregnancies with defects is thought to be related to its role in energy balance, appetite regulation, and metabolic processes. Ghrelin, a hunger peptide secreted by the stomach, promotes hunger signaling and regulates energy intake. During pregnancy, increased energy demands and metabolic changes can naturally affect ghrelin levels. Hormonal and metabolic irregularities are common in defective pregnancies, and elevated ghrelin levels may reflect a metabolic and energetic response aimed at fetal survival.

The immunomodulatory properties of ghrelin may also contribute to its increased levels in defective pregnancies. Ghrelin has been shown to reduce inflammation and modulate cellular immune responses. Inflammatory processes commonly observed in defective pregnancies may, therefore, contribute to the increase in ghrelin levels.

Furthermore, the relationship of ghrelin with placental function is crucial. If placental insufficiency is present, the body may increase ghrelin secretion as an adaptive mechanism to ensure adequate nutrient and energy supply for the fetus. This adaptive response may explain the observed rise in ghrelin levels in pregnancies with defects.

Conclusion

Ghrelin plays a primary role in regulating energy homeostasis and is more sensitive to conditions such as maternal stress, energy deficiency, or inflammation. In contrast, leptin and BDNF contribute indirectly to these processes, and their changes occur through more complex mechanisms. Ghrelin, as a hormone, responds rapidly to changes in stress, inflammation, and energy availability, while leptin and BDNF typically provide slower or longer-term responses. The time frame of the study or the progression rate of the pathophysiological processes might explain why changes in ghrelin levels were detectable, while no significant differences were observed in the levels of leptin or BDNF. Ghrelin levels may be regulated through mechanisms independent of leptin and BDNF. For instance, while orexigenic effects of ghrelin (stimulating hunger) are antagonistic to appetite-suppressing actions of leptin, the two hormones do not always change in parallel. This discrepancy in ghrelin levels could be attributed to the distinct biological regulatory pathways governing

this hormone compared to leptin and BDNF. Ghrelin responds more swiftly to alterations in maternal energy balance and acute stress, whereas leptin and BDNF likely exert more indirect, long-term effects on these processes. Therefore, these findings suggest that ghrelin may play a more specific role in the pathophysiology of missed abortion.

Limitations of the study

The small sample size is the primary limitation of our study. Expanding the sample size in future studies would allow for more robust and generalizable findings. Additionally, the lack of proportional distribution between trimesters is another limitation. Future research could benefit from a more balanced representation of participants from each trimester, or even an increase in the number of participants from each group, to enhance the statistical power and applicability of the results.

Conflict of interest

The authors declare no conflict of interest.

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