Alpha Psychiatry

ORIGINAL ARTICLE
Alpha Psychiatry 2021;22(5):230-236
DOI: 10.5152/alphapsychiatry.2021.21237

The Relationship Between Suicide Attempt and Gonadotropins, Gonadal Hormones, and Cortisol in Females

ABSTRACT

Objective: The aim of this study was to examine the relationship between suicidal behavior and gonadotropins, gonadal hormones, and cortisol in females.

Methods: The study included 3 groups of 23 females each, aged 18-45 years; one group comprising those who had attempted suicide, another group of females matched for age, menstrual phase, and body mass index, with depression but no suicidal tendencies, and a control group of 23 healthy females. For all participants, a sociodemographic information form was completed, and the Beck Depression Inventory, the Beck Anxiety Inventory, and the Beck Hopelessness Scale were used. Blood samples were taken at 8 AM (in the attempted-suicide group, within 24 hours of the attempt), and follicle-stimulating hormone, luteinizing hormone, estradiol, testosterone, progesterone, and cortisol levels were measured.

Results: No statistically significant differences were observed between the groups with respect to gonadotropin and gonadal hormone levels. There were statistically significant differences in the cortisol levels between the attempted suicide and control groups and between the depression and control groups ($P < .05$). The cortisol levels negatively correlated with all scale scores.

Conclusion: Studies on suicidal patients should pay more attention to the potential role of hypocortisolism. More studies with larger samples are needed to investigate the relationship between gonadotropins, gonadal hormones, and suicidal behavior.

Keywords: Suicide, gonadotropins, gonadal hormones, cortisol

Introduction

Suicide is the act of a person who decides to end their own life. According to the global data of the World Health Organization, a death by suicide occurred every 40 seconds on average in 2012. The number of attempted suicides is approximately 10 times as high.[1] Suicide has destructive outcomes for individuals, families, friends, and society. It also places a great burden on clinicians, who are faced with the great difficulty in estimating an individual's risk of suicidal behavior. The significant risk factors for suicide include psychiatric diseases, a history of suicide attempts, hopelessness, living alone, a family history of suicide, and stressful life events.[2] However, no demographic or clinical parameters are considered accurate predictors. Several endocrinological, neurochemical, and neuroimaging studies have examined suicide from a biological point of view.[2] The available data show that the gender paradox in suicide, that is, the fact that of the men and women who attempt suicide, more men than women actually take it to completion and commit suicide,[3] is related to aggressive, violent, and impulsive behaviors that play a role, together with androgens, in the pathogenesis of suicidal behavior. Several studies have reported that the gonadal hormones are associated with suicidal tendencies,[4,5] and that this effect is especially related to an increased prenatal androgen load and increased adult androgen activity.[6] Similarly, direct and indirect evidence show that high androgen levels and an impaired hypothalamic-pituitary-adrenal (HPA) axis

Mustafa Akan[1]
Nusret Ayaz[2]
Mehmet Çağatay Taşkapan[3]
Nilüfer Bulut[3]
Lale Gönenir Erbay[4]

[1]*Department of Psychiatry, Malatya Training and Research Hospital, Malatya, Turkey*
[2]*Department of Forensic Medicine, Niğde Training and Research Hospital, Niğde, Turkey*
[3]*Department of Biochemistry, İnönü University School of Medicine, Malatya, Turkey*
[4]*Department of Psychiatry, İnönü University School of Medicine, Malatya, Turkey*

Corresponding author:
Mustafa Akan ✉ drakanm@gmail.com

Received: March 2, 2021
Accepted: May 25, 2021
Available Online Date: August 18, 2021

Cite this article as: Akan M, Ayaz N, Taşkapan MÇ, Bulut N, Gönenir Erbay L. The relationship between suicide attempt and gonadotropins, gonadal hormones, and cortisol in females. *Alpha Psychiatry*. 2021;22(5):230-236.

can increase the risk of a suicide attempt in adults.[6] It has also been hypothesized that by increasing aggression, testosterone-mediated effects on some brain mechanisms lead to suicide, associated with the effects on mood and cognitive functions.[7] It has further been suggested that the impairment of the HPA axis could be related to emotional imbalance, impulsivity, and aggression, which can lead to suicide.[8] However, studies examining the relationship between the HPA axis and suicide have reported contradictory results. Suicide has variably been associated with both hyperactivity[9] and hypoactivity[10] of the HPA axis.

The fact that suicide attempts are more common in females than in males has been a focus of attention for researchers, and they have suggested that a suicide attempt may be associated with hormonal fluctuations in the menstrual cycle.[5,11] Baca-Garcia et al[12] reported that low levels of the gonadal hormones estrogen and progesterone have been associated with attempted suicide in females. In order to clarify the possible relationship between progesterone and suicide, progesterone derivatives (e.g., allopregnanolone) and progesterone have been reported to have anxiolytic effects, which suggests that females are less likely to manage their anxiety when progesterone levels are low during the follicular phase. Higher levels of anxiety may enhance interpersonal conflicts and lead to increased feelings of being a burden on others. Consistent with this opinion, lower levels of allopregnanolone and progesterone have been reported in patients with a variety of affective disorders with a high risk of suicide.[11] However, the results of the studies on this subject are varied. The study conducted by Mousavi et al[5] reports that when female hormones were examined in those females who had attempted suicide, 62.2% of them were in the luteal phase, and had higher progesterone levels.

The insufficient and conflicting clinical data do not allow the establishment of a biological basis for suicide. Methodological differences further prevent generalizations. Consequently, it remains impossible to predict suicide attempts. The identification of the risk factors and predictors of suicidal behavior may provide new insights into the physiopathology of suicide. Therefore, the aim of this study was to examine the relationship between suicidal behavior and the gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]), the gonadal hormones (testosterone, estrogen, and progesterone), and cortisol in females.

Methods

Study Sample

The study was conducted at a medical faculty hospital between March 2019 and December 2019. Approval for the study was granted by the Clinical Research Ethics Committee of İnönü University (Decision No. 2019/24; February 6, 2019).

MAIN POINTS

- *There were no statistically significant differences between the groups in terms of gonadotropin and gonadal hormone levels.*
- *There were statistically significant differences in the cortisol levels between the attempted-suicide and control groups, and between the depression and control groups.*
- *The cortisol levels negatively correlated with all scale scores.*

As gonadotropin and gonadal hormone values show differences according to sex,[13] the study included females only. Moreover, individuals aged 18-45 were included, as the hormones under examination change with age.[13] The study by Sher et al,[4] evaluating the association between testosterone levels and future suicide attempts in females with bipolar affective disorder was used for power analysis. Sher et al[4] reported that an increase of 0.1 ng/mL in testosterone levels increased the probability of a suicide attempt by 16.9 times. While planning this study, it was estimated that the intergroup difference in testosterone level would be 2.15, and the power analysis based on these data showed that at least 22 subjects were required in each group to obtain a difference of 2.15 units in mean testosterone hormone levels, with $\alpha = 0.05$ and power of $\beta = 0.2$. The study included 3 groups. In the study, 1 group comprised 23 females who were referred to the Emergency Department after attempted suicide. A second group comprised 23 selected females who referred to the Psychiatry Polyclinic and were diagnosed with major depressive disorder, but had no suicidal tendencies. It is known that there are changes in gonadal hormone and androgen levels in patients diagnosed with depression, compared to individuals without depression.[14] This group was formed to determine whether the parameters examined were related to the suicidal behavior itself or to depression, which is known to be frequently accompanied by suicidal behavior.[3] A third group consisted of 23 healthy controls with no history of referral to the psychiatry facility and no previous use of psychiatric drugs, selected from the hospital personnel. As the participants who attempted suicide were included for the suicide group in the study, the participants for the depression and the healthy control group were simultaneously included in this process. Participants with similar age, body mass index (BMI), and menstrual cycle period as the participants in the suicide group were included in the other 2 groups. The participants' menstrual cycle phases were determined by enquiring about their last menstruation and cycle durations. Those in the last 14 days of their cycle were considered to be in the luteal phase, those with bleeding were considered menstrual, and the others were considered to be in the follicular phase. Informed consent was obtained from all study participants.

Patients were excluded from the study if they had any neurological condition that could affect their cognitive capacity (such as dementia or head trauma), mental retardation, were using any drugs (such as oral contraceptives, exogenous steroids, or testosterone therapy), or had any disorders (such as Cushing's syndrome, polycystic ovary syndrome, or gonadal insufficiency) that could affect their hormone levels, had a history of irregular menstrual cycles (a cycle of 28 [SD = 7] days was considered regular), had a history of or were determined during interviews to have schizophrenia or other psychotic disorders, had a history of manic or hypomanic episodes, had an addiction to alcohol or any substance other than tobacco, or were pregnant or breastfeeding.

The Beck Depression Inventory (BDI), the Beck Anxiety Inventory (BAI), the Beck Hopelessness Scale (BHS), and a sociodemographic information form were completed by all participants. The patients were interviewed by a psychiatry specialist and resident using the Structured Clinical Interview for DSM (SCID) according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). The patients in the attempted-suicide group were interviewed after the necessary medical treatment was provided and hemodynamic stability was achieved.

Psychiatric Evaluation Scales

BDI: The BDI is a 21-item self-reported scale developed by Beck et al. in 1961.[15] Each item is scored from 0 to 3, giving a total score from 0 to 63, with higher scores indicating more severe depression. A reliability and validity study of the Turkish version was conducted by Hisli.[15] In that study Cronbach's alpha was found to be 0.80.

BAI: The BAI was developed by Beck et al. in 1988.[16] It is a 21-item self-reported 3-point Likert scale. Higher total scores indicate higher levels of anxiety. A reliability and validity study of the Turkish version was conducted by Ulusoy et al.[16] In that study Cronbach' s alpha was found to be 0.93.

BHS: The BHS is a 20-item self-reported scale developed by Beck et al. in 1974.[17] The total score ranges from 0 to 20, with higher scores indicating a higher level of hopelessness. A reliability and validity study of the Turkish version was conducted by Seber et al.[17] In that study Cronbach' s alpha was found to be 0.86.

Sociodemographic Data Form

The sociodemographic data were collected using a form prepared by the researchers. The data collected included the details on age, BMI, comorbid physical diseases, personal and family history of attempted suicide, menstrual cycle history, day of menstrual cycle on the day of the interview, and cycle regularity or irregularity.

Biochemical Methods

Venous blood samples from all participants were collected for FSH, LH, estradiol, progesterone, testosterone, and cortisol analyses. As the hormones under examination are affected by the circadian rhythm, and therefore blood samples were taken from all participants at 8 AM after an 8-hour fast and a half-hour rest. From patients in the attempted-suicide group, blood samples were collected at 8 AM within 24 hours of the attempt.

The samples were centrifuged at 4000 rpm for 4 minutes to obtain serum. The serum from each sample was then placed in 2 microcentrifuge tubes and stored at -80°C. The samples were warmed to room temperature prior to biochemical analysis. Testosterone was examined using a Siemens IMMULITE 2000 device (Siemens, Forchheim, Germany). The levels of FSH, LH, estradiol, progesterone, and cortisol were assessed using the chemiluminescence method on a Siemens ADVIA Centaur XP device (Siemens, Forchheim, Germany). The analysis was performed in the biochemistry research laboratory of the university.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 (IBM Corp.; Armonk, NY, USA). The categorical data were reported as numbers and percentages. Pearson's chi-square test, Fisher's exact test, and the Fisher-Freeman-Halton test were used to compare categorical variables. The conformity of quantitative data to normal distribution was assessed with the Shapiro-Wilk test. Quantitative data with normal distribution were expressed as mean (standard deviation [SD]), and those that did not show normal distribution were expressed as median (min-max). Analysis of variance was used in the analysis of quantitative data with normal distribution, and the Kruskal-Wallis analysis was used in the analysis of data that did not show normal distribution. Post hoc Tukey and Conover analyses were used to evaluate significant results between groups. Correlations between gonadotropin and gonadal hormone levels and the BDI, BAI, and BHS scores were investigated using Spearman's rank-order correlation. A value of $P < .05$ was accepted as statistically significant.

Results

Clinical Features of the Groups

The groups were similar to each other in terms of age, BMI, and menstrual cycle phase. Information on the age, BMI, and menstrual cycle phase of the participants in the 3 groups is shown in Table 1.

Clinical Features of the Attempted-Suicide Group

Based on the SCID with patients in the attempted-suicide group, depression was diagnosed in 11 (47.9%), acute stress response in 3 (13%), and personality disorder in 13 (56.5%) patients, 2 of whom were diagnosed with concomitant depression and 2 with acute stress disorder. Of the 13 personality disorder cases, borderline personality disorder was determined in 10 (43.5%), histrionic personality disorder in 2 (8.7%), and passive-aggressive personality disorder in one (4.3%).

Nineteen (82.6%) patients had attempted to commit suicide by taking drugs, 2 (8.7%) by taking a pesticide, 1 (4.35%) by cutting her abdomen with a knife, and 1 (4.35%) by trying to hang herself. Six (26%) patients had taken drugs that could affect gonadal hormone levels, such as antipsychotics. At the time of the study, all of them were receiving low-dose antipsychotic treatment due to sleep problems. The mean time from the suicide attempt to blood sampling was 14.5 (SD = 5.5) hours.

Scale Scores and Gonadotropin and Gonadal Hormone Levels

The BDI, BAI, and BHS scores differed significantly between the 3 groups (all $P < .001$). Conover analysis revealed a significant difference between the suicide and control groups and between the depression and control groups for all scale scores ($P < .001$ for all evaluations). The BDI, BAI, and BHS scores of the suicide and depression groups were higher than those of the control group. There was no significant difference between the suicide and depression groups in terms of BDI, BAI, and BHS scores. No statistically significant differences were found with respect to gonadotropin and gonadal hormone levels. The mean testosterone level in the suicide group (38.43 [SD = 15.13] ng/dL) was higher than those in the other 2 groups; however, the difference was not statistically significant. The difference in cortisol levels, on the other hand, was statistically significant ($P = .015$). The

Table 1. Age, BMI, and Menstrual Cycle Periods of the Groups

	Suicidal group, Mean (SD)	Depression group, Mean (SD)	Healthy control group, Mean (SD)	*P*
Age	25.60 (7.39)	27.17 (6.69)	25.52 (6.43)	.656
BMI	23.46 (3.76)	24.36 (5.52)	22.25 (3.59)	.269
Menstrual cycle period	n (%)	n (%)	n (%)	
Menstruation	1 (4.4)	1 (4.4)	1 (4.4)	1.000
Follicular phase	9 (39.1)	9 (39.1)	9 (39.1)	
Luteal phase	13 (56.5)	13 (56.5)	13 (56.5)	
Total	23 (100)	23 (100)	23 (100)	

BMI, body mass index; SD, standard deviation.

attempted-suicide group had lower levels than the other 2 groups. Post hoc analysis revealed a significant difference between the suicide and control groups ($P = .029$) and between the depression and control groups (the depression group had lower levels than the control group) ($P = .035$). There was no significant difference between suicide and depression groups in terms of cortisol levels. The scale scores and gonadotropin and gonadal hormone levels are displayed in Table 2.

Correlations Between the Scale Scores and Gonadotropin and Gonadal Hormone Levels

Cortisol levels negatively correlated with the BAI ($r = -0.455$, $P < .001$), BDI ($r = -0.448$, $P < .001$), and BHS scores ($r = -0.454$, $P < .001$). The correlations between the scale scores and gonadotropin and gonadal hormone levels are shown in Table 3.

Discussion

Recent epidemiological studies show that suicide and attempted suicide remain a significant public health problem.[18] Several models have been developed to explain the development of suicidal behaviors. The stress-diathesis model[19] and the process model[20] are the most commonly used. Several stress factors are associated with suicide. Stress hormones may have an effect on all 3 levels of the hypothalamic-pituitary-gonadal (HPG) axis by affecting the secretion of LH by the hypophysis, modulating the androgen levels, or changing the stimulating effect of gonadotropins on the gonads.[21] In light of these findings, this study aimed to examine the relationship between suicidal behavior and gonadotropins and gonadal hormones, which are part of the HPG axis related to stress, as well as cortisol, a component of the HPA axis.

The most significant finding of our study was a significant difference in cortisol levels between the groups. Cortisol levels differed significantly between the attempted-suicide and the control groups, and between the depression and control groups. Moreover, cortisol negatively correlated with the BDI, BAI, and BHS scores. Another finding was that there were no significant differences between the groups in terms of FSH, LH, testosterone, progesterone, and estradiol levels.

Studies on the relationship between HPA-axis cortisol and suicidal behavior have reported conflicting results.[8-10] It has been suggested that impairment of the HPA axis could be related to emotional imbalance, impulsivity, and aggression, which play a role in suicide.[9] Turecki et al[8] reported that the severity of impairment in the HPA axis is associated with the severity of the psychiatric pathology and the severity of attempted suicide.[8] Researchers observed a relationship between low HPA-axis cortisol levels and suicidal behavior, and suggested that long-term and severe psychiatric disorders deplete the HPA axis. They suggested that reduced HPA-axis activity could increase the risk of attempted suicide by impairing the ability of individuals with psychopathologies to respond appropriately to persistent stress factors.[10] These findings are consistent with the low cortisol levels that we observed in the attempted-suicide group. However, as our study included only females, our findings cannot be generalized.

It is difficult to establish a causal link between low HPA-axis activity and suicidal behavior in females based on our findings. The difference in HPA-axis function between the control group and the attempted suicide and depression groups raises the question of whether this is a long-term condition or a cross-sectional result. The acute stress that may accompany a suicide attempt can also lower cortisol levels.

Table 2. Comparison of Scale Scores and Gonadotropin, Gonadal Hormone, and Cortisol Levels Between Groups

	Suicidal group[1] Median (Min-Max)	Depression group[2] Median (Min-Max)	Healthy control group[3] Median (Min-Max)	*P*	Pairwise comparisons	
BDI score	28 (6-50)	22 (1-48)	3 (0-13)	< .001[a]	1; 2	$P = .132$
					1; 3	$P < .001$
					2; 3	$P < .001$
BAI score	21 (4-59)	25 (1-49)	6 (0-18)	< .001[a]	1; 2	$P = .992$
					1; 3	$P < .001$
					2; 3	$P < .001$
BHS score	10 (2-20)	10 (0-20)	2 (0-8)	< .001[a]	1; 2	$P = .763$
					1; 3	$P < .001$
					2; 3	$P < .001$
FSH	4.67 (1.21-10.39)	5.79 (2.39-13.56)	5.41 (2.07-14.27)	.274[a]	-	
LH	5.09 (0.14-22.98)	6.04 (3.06-52.66)	6.56 (2.01-26.71)	.298[a]	-	
Progesterone	1.42 (0.37-8.30)	1.27 (0.18-17.84)	3.21 (0.35-17.43)	.102[a]	-	
Estradiol	86.10 (3.94-177.4)	74.73 (23.55-263.31)	82.35 (6.00-309.67)	.334[a]	-	
	Mean (SD)	Mean (SD)	Mean (SD)			
Cortisol	15.30 (7.03)	15.45 (5.01)	19.69 (4.57)	.015[b]	1; 2	$P = .997$
					1; 3	$P = .029$
					2; 3	$P = .035$
Testosterone	38.43 (15.13)	33.69 (13.71)	33.32 (16.37)	.445[b]	-	

The ANOVA test was performed to compare cortisol and testosterone values between the 3 groups. Post hoc Tukey analysis was used to evaluate significant results between groups. The Kruskal–Wallis test was performed to compare BDI, BAI, and BHS scores and the FSH, LH, progesterone, and estradiol values between the 3 groups. Conover analysis was used to evaluate significant results between groups.

[a]*P* value for Kruskal–Wallis test; [b]*P* value for ANOVA test; $P < .05$.

1: suicidal group; 2: depression group; 3: healthy control group.

BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; BHS, Beck Hopelessness Scale; FSH, follicle stimulating hormone; LH, luteinizing hormone; SD: standard deviation.

Table 3. Examination of the Correlation Between Gonadotropin, Gonadal Hormone, and Cortisol Levels, and Scale Scores

Spearman's Rho	FSH	LH	EST	PRG	CRT	TES
BAI score						
r	0.160	−0.054	−0.045	−0.345	−0.455	0.058
P	.189	.658	.715	.004	<.001	.639
n	69	69	69	69	69	69
BDI score						
r	0.181	−0.024	−0.100	−0.437	−0.448	−0.103
P	.137	.844	.414	<.001	<.001	.398
n	69	69	69	69	69	69
BHS score						
r	0.319	−0.010	−0.108	−0.445	−0.454	−0.102
P	.008	.937	.377	<.001	<.001	.405
n	69	69	69	69	69	69

P < .05.
EST, estradiol; PRG, progesterone; CRT, cortisol; TES, testosterone; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; BHS, Beck Hopelessness Scale; FSH, follicle stimulating hormone; LH, luteinizing hormone.

Most previous psychiatric studies focused on HPA-axis hyperactivity.[8,9] Low HPA-axis activity, or hypocortisolism, is a relatively new phenomenon in stress research.[22] Low cortisol levels have been reported in patients with stress-related disorders, such as post-traumatic stress disorder, depression with atypical characteristics, fibromyalgia, and chronic fatigue syndrome.[22,23] As these disorders have some common symptoms, hypocortisolism has been suggested as the underlying physiological abnormality.[22] Hypocortisolism in the HPA axis could lead to an overactive immune system due to an increased inflammatory response.[22] Pro-inflammatory cytokines could play a role in the above-mentioned disorders, and also in psychiatric symptoms such as those observed in this study's attempted-suicide group. However, a hypoactive HPA axis may also be the result of a tendency of individuals with suicidal behavior to be exposed to severe and long-term stress.

Although we found no differences between the groups in terms of FSH, LH, testosterone, progesterone, and estradiol levels, other studies have reported such differences. A study on female patients with bipolar disorder estimated that an increase of 0.1 ng/mL in testosterone levels increased the probability of a suicide attempt by 16.9-fold.[4]

Another study, on females aged 15-49 years who had attempted suicide, reported high progesterone levels. The authors also found that progesterone levels were higher in those who had attempted suicide more than twice, the majority of whom were in the luteal phase.[5] In another study, low progesterone levels were associated with more intense feelings of depression, which were stronger during the follicular phase than during the luteal phase. As these relationships were not significant when depression was under control, the authors suggested that hormonal changes could be determinants of suicidal thoughts.[11] In our study, it is noteworthy that most patients in the attempted-suicide group were in the luteal phase. It is known that testosterone levels are higher in the luteal phase.[24] Several studies have reported changes in the serotonergic system during this phase.[25] Besides the serotonergic system, the observed high testosterone levels may have been due to the effects of premenstrual dysphoric syndrome on mood. However, this cannot be confirmed, as we did not screen for premenstrual dysphoric syndrome.

We included cases who attempted suicide in our study. Questions may arise about how the parameters investigated in our study will reflect the results for completed suicides? Some researchers have investigated hormonal parameters in post-mortem suicide cases.[26,27] Jokinen et al[26] reported that completed suicides had significantly lower baseline cortisol levels than survivors and that attempters had significantly lower baseline cortisol levels than non-attempters.[26] Another study, however, found no significant differences in testosterone levels between completed suicides and survivors.[27]

One of the reasons for the conflicting results reported in the literature regarding the relationship between suicide and gonadotropins and gonadal hormones could be the methodological differences between studies, such as the time of blood sampling, psychiatric evaluation, and group selection.[4,5,10] One of the main strengths of our study was that blood samples for hormonal analysis were taken within the first 24 hours of the suicidal attempt. Moreover, taking the circadian rhythm into consideration, all samples were taken at 8 AM.

Another strength of this study was that in consideration of the evaluation of the patients' menstrual phase, all included patients were aged 18-45 years and had regular menstrual cycles, while patients who had conditions or were taking psychotropic or hormonal drugs that could affect hormone levels were excluded from the study. The other strengths of our study were the inclusion of a depression group with no suicidal tendencies, to control for the effects of depression on the examined parameters; and the matching of the groups for age and BMI to ensure the robustness of our results, as it is known that these factors can affect hormone levels.[28]

This study, however, had certain limitations. First, the number of participants in each group was low. It should be noted, however, that in line with our findings, a study that included 1896 women found no association between androgens and suicidality.[29] Second, approximately a quarter of the patients in the attempted-suicide group had taken psychiatric drugs (such as antipsychotics) that can affect hormone levels, which may have influenced our results. Third, as previously stated, we did not screen for premenstrual dysphoric syndrome, which may be related to high testosterone levels. Fourth, like other studies,[4,5] we used radioimmunoassays for hormone analysis. Kushnir et al[30] reported that immunoassays are less reliable when measuring the low testosterone (<5.0 nmol/L) levels

that are present in females.[30] Fifth, due to methodological difficulties, we did not include a group of completed suicide cases. In our study, it was determined by a clinical interview structured according to the DSM-5 that the participants in the depression group and the healthy control group did not have suicidal ideation. A scale was not used in this regard. This is the sixth limitation of our study. The biological mechanisms of impulsive or planned suicide attempts may be different. Another limitation is that there was no evaluation of whether the participants who attempted suicide in a planned or impulsive manner. Moreover, the participants gave blood samples at different times of their menstrual cycle. This might have led to mistaken results. Finally, it should be noted that studies on the biological changes following an attempted suicide have inherent difficulties, as the results can be affected by many factors. Two of these are the stress accompanying an attempt and the stress of hospitalization when there is a serious medical condition. Moreover, after a violent attempt, there may be severe injuries requiring immediate treatment. One way to minimize the effect of such confounding factors is comparative analysis with groups of patients with similar medical conditions. For example, cases of violent attempts at suicide by jumping off a height could be compared with patients hospitalized after accidental falls. Such confounding factors were not controlled in this study, which can be considered another limitation.

It is difficult to establish a causal relationship between low HPA-axis activity and suicidal behavior in females. The duration of symptoms may be a factor related to this phenomenon, and further research is needed to clarify the underlying mechanisms. Studies on patients attempting suicide should pay more attention to the potential role of hypocortisolism. Moreover, when evaluating the risk for attempted suicide, factors contributing to long-term stress should be investigated. Further studies with larger samples are warranted to investigate the relationship between suicidal behavior and gonadotropins and gonadal hormones.

Ethics Committee Approval: *Ethics committee approval was received for this study from the Clinical Research Ethics Committee of İnönü University (Approval Date: February 6, 2019; Approval Number: 2019/24).*

Informed Consent: *Informed consent was obtained from the individuals who participated in this study.*

Peer Review: *Externally peer-reviewed.*

Author Contributions: *Concept - M.A., N.A., L.G.E.; Design - M.A., L.G.E.; Supervision - N.A., L.G.E.; Materials - M.A.; Data Collection and/or Processing - M.A.; Analysis and/or Interpretation - M.Ç.T., N.B., L.G.E.; Literature Review - M.A., N.A., M.Ç.T., N.B., L.G.E.; Writing - M.A., N.A., M.Ç.T., N.B., L.G.E.; Critical Review - L.G.E.*

Conflict of Interest: *The authors have no conflict of interest to declare.*

Financial Disclosure: *This study was supported by the Scientific Research Project Unit of İnönü University (Project No. TTU-2019-1921).*

References

1. World Health Organization. *Preventing Suicide: A Global Imperative*. Geneva: World Health Organization; 2019.
2. Costanza A, D'Orta I, Perroud N, et al. Neurobiology of suicide: do biomarkers exist? *Int J Legal Med*. 2014;128(1):73-82. [CrossRef]
3. Özsoy SD. Suicide. *Anadolu Psikiyatr Derg*. 2003;4:175-185.
4. Sher L, Grunebaum MF, Sullivan GM, et al. Association of testosterone levels and future suicide attempts in females with bipolar disorder. *J Affect Disord*. 2014;166:98-102. [CrossRef]
5. Mousavi SG, Bateni S, Maracy MR, Mardanian F, Mousavi SH. Recurrent suicide attempt and female hormones. *Adv Biomed Res*. 2014;3(1):201. [CrossRef]
6. Lenz B, Röther M, Bouna-Pyrrou P, et al. The androgen model of suicide completion. *Prog Neurobiol*. 2019;172:84-103. [CrossRef]
7. Sher L. Both high and low testosterone levels may play a role in suicidal behavior in adolescent, young, middle-age, and older men: a hypothesis. *Int J Adolesc Med Health*. 2016;30(2):18-20. [CrossRef]
8. Turecki G, Ernst C, Jollant F, Labonté B, Mechawar N. The neurodevelopmental origins of suicidal behavior. *Trends Neurosci*. 2012;35(1):14-23. [CrossRef]
9. Jokinen J, Nordström P. HPA axis hyperactivity and attempted suicide in young adult mood disorder inpatients. *J Affect Disord*. 2009;116(1-2):117-120. [CrossRef]
10. Melhem NM, Keilp JG, Porta G, et al. Blunted HPA axis activity in suicide attempters compared to those at high risk for suicidal behavior. *Neuropsychopharmacology*. 2016;41(6):1447-1456. [CrossRef]
11. Smith A, Miller S, Bodell L, et al. Cycles of risk: associations between menstrual cycle and suicidal ideation among women. *Pers Individ Dif*. 2015;74:35-40. [CrossRef]
12. Baca-Garcia E, Diaz-Sastre C, Ceverino A, et al. Suicide attempts among women during low estradiol/low progesterone states. *J Psychiatr Res*. 2010;44(4):209-214. [CrossRef]
13. Döhler KD, Wuttke W. Changes with age in levels of serum gonadotropins, prolactin, and gonadal steroids in prepubertal male and female rats. *Endocrinology*. 1975;97(4):898-907. [CrossRef]
14. Seidman SN, Walsh BT. Testosterone and depression in aging men. *Am J Geriatr Psychiatry*. 1999;7(1):18-33. [CrossRef]
15. Hisli N. Beck Depresyon Envanterinin üniversite öğrencileri için geçerliliği, güvenilirliliği [The validity and reliability of Beck Depression Inventory for university students]. *Psikol Derg*. 1989;7(23):3-13.
16. Ulusoy M, Sahin NH, Erkmen H. Turkish version of the Beck Anxiety Inventory: psychometric properties. *J Cogn Psychother Int Q*. 1998;12(2):163-172.
17. Seber G, Dilbaz N, Kaptanoğlu C, Tekin D. Umutsuzluk Ölçeği: geçerlilik ve güvenirliği [Hopelessness Scale: validity and reliability]. *Kriz Derg*. 1993;1(3):139-142.
18. Bachmann S. Epidemiology of suicide and the psychiatric perspective. *Int J Environ Res Public Health*. 2018;15(7):1425. [CrossRef]
19. Mann JJ, Waternaux C, Haas GL, Malone KM. Toward a clinical model of suicidal behavior in psychiatric patients. *Am J Psychiatry*. 1999;156(2):181-189. [CrossRef]
20. Cornelis VH. Understanding suicidal behaviour: the suicidal process approach to research, treatment and prevention. In Cornelis VH, ed. *Wiley Series in Clinical Psychology*; vol XIV. Chichester, UK: Wiley; 2001.
21. Rivier C, Rivest S. Effect of stress on the activity of the hypothalamic-pituitary-gonadal axis: peripheral and central Mechanisms. *Biol Reprod*. 1991;45(4):523-532. [CrossRef]
22. Heim C, Ehlert U, Hellhammer DH. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology*. 2000;25(1):1-35. [CrossRef]
23. Antonijevic IA. Depressive disorders - Is it time to endorse different pathophysiologies? *Psychoneuroendocrinology*. 2006;31(1):1-15. [CrossRef]
24. Fritz MA, Speroff L. Hirsutism. In: *Clinical Gynecologic Endocrinology and Infertility*. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2010:533-566.
25. Parry BL. The role of central serotonergic dysfunction in the aetiology of premenstrual dysphoric disorder: therapeutic implications. *CNS Drugs*. 2001;15(4):277-285. [CrossRef]

26. Jokinen J, Ouda J, Nordström P. Noradrenergic function and HPA axis dysregulation in suicidal behaviour. *Psychoneuroendocrinology*. 2010;35(10):1536-1542. [CrossRef]
27. Stefansson J, Chatzittofis A, Nordström P, et al. CSF and plasma testosterone in attempted suicide. *Psychoneuroendocrinology*. 2016;74:1-6. [CrossRef]
28. van Hooff MH, Voorhorst FJ, Kaptein MB, et al. Predictive value of menstrual cycle pattern, body mass index, hormone levels and polycystic ovaries at age 15 years for oligo-amenorrhoea at age 18 years. *Hum Reprod*. 2004;19(2):383-392. [CrossRef]
29. de Wit AE, De Boer MK, Bosker FJ, et al. Associations of plasma androgens with suicidality among men and women: a 9-year longitudinal cohort study. *J Affect Disord*. 2020;269:78-84. [CrossRef]
30. Kushnir MM, Rockwood AL, Bergquist J. Liquid chromatography-tandem mass spectrometry applications in endocrinology. *Mass Spectrom Rev*. 2010;29(3):480-502. [CrossRef]