Are plasma Brain-Derived Neurotrophic Factor or reproductive hormones related to depression in PCOS patients?: a prospective cohort study

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1. Introduction

Polycystic ovarian syndrome (PCOS) is a common reproductive endocrine disease in women of childbearing age and is characterized by chronic anovulation, hyperandrogenism, insulin resistance, and metabolic syndrome. The prevalence of PCOS according to the Rotterdam criteria is 11.9–19.9% worldwide [1, 2]. PCOS is associated with many comorbid conditions such as diabetes, cardiovascular disease, obesity, and endometrial cancer [3–5] as well as psychological and emotional difficulties such as depression, anxiety, and poor quality of life [6–9]. However, the etiology of PCOS and its association with depression remain uncertain.

Brain-derived neurotrophic factor (BDNF), which is a member of the neurotrophin family of growth factors and found in human ovaries and the human brain, plays physiological roles both in PCOS and depression. For example, accumulating evidence suggests that BDNF is an important molecule in the pathophysiology of mental disorders; in particular, the association between low BDNF levels and major depressive disorders is well known [10–12]. There have also been studies on the association between BDNF levels and ovarian functions. Russo et al. [13] reported that BDNF levels in the plasma and follicular fluid were higher in PCOS patients than in healthy menstruating women, and may result in increased granulosa cell proliferation and oocyte recruitment in polycystic ovaries. In other words, BDNF seems to be associated with both depression and PCOS, but its etiology is unclear.

The aim of this study was to investigate the association between the plasma BDNF levels and depression in PCOS patients, compared to in patients with secondary amenorrhea (SA) due to other causes. We also intended to analyze whether the severity of depression is related to the plasma BDNF level and/or hormonal and metabolic factors in patients with PCOS and in SA patients with other causes.
2. Materials and methods

2.1 Participants

For this prospective cohort study, we evaluated 71 patients aged 15 to 45 years who had symptoms of secondary amenorrhea by a reproductive endocrinologist between 1st March 2017 and 28th February 2018. All participants provided their written informed consent. The diagnosis of PCOS was made based on medical history, clinical signs, physical examination, laboratory tests, and sonographic evidence, using the Rotterdam criteria: (1) oligoovulation and/or anovulation, (2) symptoms of hyperandrogenism and/or biochemical signs (total T >70 ng/dL, Androstenedione >245 ng/dL, DHEA-S >248 g/dL), and (3) polycystic ovaries on ultrasound. Two or more of these criteria must be met for a diagnosis of PCOS. We excluded patients with hyperprolactinemia; acromegaly; and other causes of hyperandrogenism such as congenital adrenal hyperplasia, androgen releasing adrenal tumor, and Cushing’s syndrome. We also excluded patients with secondary amenorrhea due to diabetes, hypogonadotropic hypogonadism, diet restriction, hormone replacement therapy, and psychiatric medication-induced amenorrhea. In this study, participants were divided into two groups of the PCOS group and the non-PCOS group according to the causes of SA. The Institutional Review Board of Inje University Haeundae Paik Hospital approved the study protocol (No. 2017-01-018-002).

We calculated the body mass index (BMI) along with the height and body weight of each patient at their first visit and collected information including parity, menarche age, and current medications. Venous blood samples were collected after overnight fasting at amenorrhea status or at follicular phase. For this study, fasting glucose; insulin levels; and lipid profiles such as triglycerides (TGs), total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were measured. The serum follicle stimulating hormone, luteinizing hormone (LH), estradiol, anti-Müllarian hormone (AMH), prolactin, thyroid-stimulating hormone, free thyroxin 4, total testosterone, free testosterone, and dehydroepiandrosterone sulfate levels were also measured. In addition, the plasma BDNF concentrations were measured using enzyme-linked immunosorbent assay (ELISA) kits (Enzo Life Sciences, New York, NY, USA) according to the manufacturer’s protocol.

Psychiatric evaluation of participants was carried out by two psychiatrists using the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). None of the participants had taken psychoactive medications or hormonal preparations that may influence their mood symptoms for at least 6 months prior to the study. To assess depressive symptoms, all patients completed the Korean version of the Center for Epidemiological Studies-Depression Rating Scale (K-CES-D), which was developed by Radloff in 1977 [14, 15]. The CES-D is a 20-item patient-rated depression scale that assesses the occurrence of symptoms during the past week, with scores ranging from 0 to 3 for each item (0 = Rarely or None of the Time, 1 = Some or Little of the Time, 2 = Moderately or Much of the Time, 3 = Most or Almost All the Time). According to Park and Kim, a CES-D score of ≥16 indicates “probable depression”, whereas a CES-D score of ≥25 indicates “definite depression” [15, 16].

We also assessed the objective severity of depressive symptoms using the Korean version of the Hamilton Depression Rating Scale (K-HDRS), which was applied by a trained psychiatrist to increase the accuracy of the depression assessment [17, 18]. The K-HDRS is a clinician-rated measure of depression severity, consisting of a 17-item scale of depressive symptoms, with scores of 0–4 for the items of depressed mood, feelings of guilt, suicide, work and activities, retardation, agitation, psychotic anxiety, somatic anxiety, and hypochondriasis and scores of 0–2 for the items of early insomnia, middle insomnia, late insomnia, somatic-gastrointestinal, and somatic-general symptoms. The total score ranged from 0–52 points, with a higher score indicating more severe symptoms of depression.

2.2 Statistical analysis

The data are presented as mean ± standard deviation (SD). Differences in study participants’ characteristics between the PCOS group and the non-PCOS group were compared with independent t-test or Mann-Whitney’s U test as appropriate. To check if its distribution is normal, we used Shapiro-Wilk test. Partial correlation coefficients controlling for age and BMI were estimated to investigate the linear relationship between two continuous variables. For data visualization, scatter plots were also displayed. All statistical analyses were carried out using SPSS 24.0 (IBM Corp, Armonk, NY, USA) and the p value less than 0.05 was considered as statistically significant.

3. Results

A total of seventy-one women with SA were included for this study. Among them, forty-three participants were PCOS patients and 28 were non-PCOS patients (10 patients with premature ovarian insufficiency and 18 with chronic anovulation). The mean age of the participants was 26.08 ± 8.07 years and the mean BMI was 22.70 ± 4.64 kg/m². There was no significant difference in the CES-D and K-HDRS scores between the PCOS and in the non-PCOS groups. The PCOS group had hormonal profiles that were typical of hyperandrogenism. The clinical characteristics of both groups are presented in Table 1.

The mean plasma BDNF concentrations in the PCOS group was 9.56 ± 10.42 ng/mL and a range of plasma BDNF concentrations was 1.42–43.64 ng/mL. In the non-PCOS group, the mean plasma BDNF concentration was 8.89 ± 7.88 ng/mL with a range of 0.53–27.44 ng/mL. The mean plasma BDNF concentration did not significantly differ between the groups either.

In the PCOS group, the plasma BDNF concentrations seemed to have the tendency of a positive relationship with the total score of CES-D and of the K-HDRS (shown in
Fig. 1. Correlation of the plasma brain-derived neurotrophic factor level with the total Center for Epidemiological Studies-Depression Rating Scale (a) and Korean version of the Hamilton Depression Rating Scale scores (b) in the PCOS group and the non-PCOS group in SA patients. (a) Correlation of the plasma brain-derived neurotrophic factor level with the total Center for Epidemiological Studies-Depression Rating Scale (CES-D). (b) Correlation of the plasma brain-derived neurotrophic factor level with Korean version of the Hamilton Depression Rating Scale scores (K-HDRS).

However, there was no statistically significant correlation between the plasma BDNF concentrations and either total scores of the CES-D nor of the K-HDRS in the PCOS group \((r = 0.259, p = 0.106; r = 0.235, p = 0.144, \text{ respectively})\) after adjusting for age and BMI. On the other hand, the plasma BDNF concentrations were negatively associated with the CES-D and the K-HDRS scores in the non-PCOS group \((r = -0.641, p = 0.000; r = -0.570, p = 0.002, \text{ respectively})\) after controlling for age and BMI.
In the PCOS group, the total CES-D scores were negatively correlated with the AMH levels ($r = -0.461, p = 0.004$) and positively correlated with the levels of prolactin and free T4 ($r = 0.352, p = 0.026; r = 0.363, p = 0.027$, respectively). The total K-HDRS scores in the PCOS group were negatively correlated with the AMH, LH, and HDL cholesterol levels ($r = -0.521, p = 0.001; r = -0.318, p = 0.046; r = -0.412, p = 0.017$, respectively), but were positively correlated with the prolactin and free T4 levels ($r = 0.332, p = 0.036; r = 0.406, p = 0.013$, respectively). In the non-PCOS group, only the TG levels were positively correlated with the total K-HDRS scores ($r = 0.675, p = 0.023$). The results of the partial correlation analysis are presented in Table 2.

### 4. Discussion

In this study, plasma BDNF concentrations in patients with PCOS were not related to depression after adjusting for age and BMI. In SA patients due to other causes, there was a negative correlation between plasma BDNF concentrations and depression, which is similar to the negative relationship between plasma BDNF concentrations and depression in depressive patients. In other words, the relation between plasma BDNF concentration and depression was different in patients with PCOS and in other causes of SA patients. We also found a negative correlation between AMH levels and depression and a positive association with prolactin levels and free T4 levels to depression in PCOS patients among women with SA.

According to the previous literature, BDNF levels have been shown to be consistently decreased in patients with depression compared to healthy controls [20–22], and it was increased both after antidepressant treatment and electroconvulsive therapy in patients with depression [23, 24]. In addition, it has been reported that a lower serum BDNF level is related to higher depressive symptoms in both early and late pregnancy [25, 26]. However, in PCOS patients, BDNF...
Table 2. Partial correlation analysis between depression scores and biochemical variables in polycystic ovarian syndrome and non-polycystic ovarian syndrome patients.

| Variable          | PCOS group (n = 43) | Non-PCOS group (n = 28) |
|-------------------|---------------------|-------------------------|
|                   | CES-D              | K-HDRS                  | CES-D             | K-HDRS             |
| BDNF level (ng/mL)| 0.259 (0.106)      | 0.235 (0.144)            | -0.641 (0.000)    | -0.570 (0.002)     |
| AMH (ng/mL)       | -0.461 (0.004)     | -0.521 (0.001)           | -0.230 (0.279)    | -0.404 (0.050)     |
| LH (U/L)          | -0.279 (0.081)     | -0.318 (0.046)           | 0.312 (0.147)     | 0.079 (0.719)      |
| FSH (U/L)         | 0.029 (0.861)      | 0.016 (0.920)            | 0.040 (0.846)     | -0.216 (0.289)     |
| Estradiol (pg/mL) | -0.197 (0.235)     | -0.045 (0.789)           | 0.241 (0.237)     | 0.149 (0.466)      |
| DHEAS (µmol/L)    | 0.147 (0.373)      | 0.120 (0.467)            | -0.218 (0.319)    | -0.238 (0.274)     |
| Testosterone (ng/mL)| -0.177 (0.275)  | -0.266 (0.097)           | 0.178 (0.396)     | 0.198 (0.344)      |
| Free testosterone (pg/mL) | -0.163 (0.314) | -0.243 (0.130)           | -0.158 (0.450)    | -0.197 (0.345)     |
| Prolactin (ng/mL) | 0.352 (0.026)      | 0.332 (0.036)            | -0.135 (0.528)    | 0.030 (0.891)      |
| TSH (µmol/L)      | 0.131 (0.440)      | 0.103 (0.545)            | 0.053 (0.801)     | 0.177 (0.398)      |
| fT4 (ng/dL)       | 0.363 (0.027)      | 0.406 (0.013)            | -0.133 (0.525)    | -0.143 (0.495)     |
| Total Cholesterol (mg/dL) | -0.117 (0.479) | 0.002 (0.990)            | -0.035 (0.866)    | -0.151 (0.462)     |
| HDL (mg/dL)       | -0.236 (0.186)     | -0.412 (0.017)           | -0.276 (0.411)    | -0.517 (0.103)     |
| LDL (mg/dL)       | 0.129 (0.473)      | 0.251 (0.158)            | -0.092 (0.777)    | -0.132 (0.683)     |
| TG (mg/dL)        | 0.004 (0.982)      | 0.035 (0.845)            | 0.041 (0.905)     | 0.675 (0.023)      |
| Fasting Glucose (mg/dL) | -0.103 (0.531) | 0.209 (0.202)            | 0.032 (0.880)     | -0.135 (0.519)     |
| Somatomedin C (IGF-1) (ng/mL) | -0.037 (0.831) | -0.315 (0.061)           | -0.269 (0.280)    | -0.229 (0.361)     |

Values are partial correlation coefficient controlling for age and BMI (p value).

Abbreviations: PCOS, polycystic ovarian syndrome; BDNF, brain-derived neurotrophic factor; CES-D, Center for Epidemiological Studies-Depression Rating Scale; K-HDRS, Korean version of the Hamilton Depression Rating Scale; AMH, anti-Müllerian hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone; DHEAS, dehydroepiandrosterone sulfate; TSH, thyroid stimulating hormone; fT4, free thyroxin 4; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride.

Levels in plasma and follicular fluid were higher than those in normal menstruating women [13], and high levels of LH in the patients with PCOS may increase the secretion of BDNF from the granulosa cells [27].

In this study, there was no statistically significant difference in the plasma BDNF concentrations between PCOS patients and SA patients due to other causes, though the BDNF levels of PCOS patients were slightly higher than those of SA patients with other causes. Such abnormally increased BDNF is possible to be a result of the effect of increased ovarian innervation in PCOS patients by several studies of an animal model of PCOS, which in turn could affect to abnormal ovarian function due to AMH-induced hyperandrogenism [28]. Also, it is possible that increased BDNF in patients with PCOS, not like patients with other causes of SA and with depressive disorders, may stimulate folliculogenesis, which can affect abnormal ovarian function and mood state. However, there was no statistical difference due to the relatively small number of participants in this study. There is also a possibility of diurnal variation of plasma BDNF levels, though we collected the blood sample of participants in this study at the follicular phase or at amenorrhea status to control the possibility of variation in the plasma BDNF levels during the ovulatory cycle. Therefore, further study with larger sample size and well-controlled design of the ovulatory cycle and diurnal variation of the plasma BDNF concentrations is necessary to confirm our results.

In terms of the relationship between the plasma BDNF concentration and the severity of depression, there was a significant difference between the PCOS patient and SA patients with other causes. In other words, the negative correlation between the plasma BDNF levels and depression, which is seen in depressed patients in the previous studies or patients with other cause of SA in this study, was not found in PCOS patients. To the best of our knowledge, this study is the first to investigate the association between plasma BDNF levels and depression in PCOS patients.

According to the results of this study, we suggest that the pathophysiological mechanisms of depression in patients with PCOS will be different from those in patients with other causes of secondary amenorrhea. In other words, we suggest that abnormal reproductive hormone interaction such as anti-Müllerian hormone and prolactin might affect depressive symptoms in PCOS patients and such abnormal reproductive hormone levels without decreased BDNF secretion in neurons might independently influence the functioning of neurotransmitters and neural circuits in the brain.
Especially, Anti-Müllerian hormone (AMH) is produced primarily in the gonads and is produced by the granulosa cells of early developing follicles. In general, serum levels of AMH may represent the ovarian follicle pool, so AMH reflecting the decline of reproductive age could be a good marker for PCOS [29]. There have been growing interests in the effect of AMH on the hypothalamic-pituitary-gonadal axis and neuroendocrine development. According to recent studies, AMH can act centrally increasing the activity of GnRH, which have potent neurotrophic, neuroprotective, and neuroregenerative action in the animal study [30, 31]. Because of such positive function to the nervous system of AMH, it is possible that AMH have the protective function of depression in PCOS patients. The result of negative association between AMH levels and depressive symptoms in PCOS patients was similar to our previous study in which lower serum AMH levels were associated with higher depressive scores in patients with secondary amenorrhea [32]. However, the results of previous researches about the association between AMH levels and depression are still controversial. For example, there was a negative study results, which was conducted by Jurczak et al. [33], that the level of AMH and depressive symptoms was not related in the group of healthy late-reproductive-age women. Vermeulen et al. [34] also reported negative results of the association between AMH and change in symptom burden including depression, hot flush, and sexual dysfunctions after salpingo-oophorectomy. On the other hand, a recent study by Golenbock SW et al. [35], was reported that there were modest inverse associations between depression and low AMH among young and nulliparous women. Thus, further study is needed to confirm the possible role of AMH in depression among patients with PCOS.

Prolactin secretion is stimulated by estrogen, and changes in the serum prolactin level are highly correlated with the levels of estrogen during pregnancy and the lactating period [36]. Prolactin is also considered an adaptive hormone which plays in the modulation of the stress response through the hypothalamic pituitary adrenal axis [37, 38]. Given these associations, the possibility that prolactin levels have an important role in the pathophysiology of depression have suggested during the past decade. The positive correlation between depression and prolactin level in this study is consistent with the previous study which supported this possibility [39]. However, there were other studies that reported a negative relationship and even no difference in prolactin levels between in depressed patients and in non-depressed patients [40, 41]. But, these studies have limitations such as small sample sizes and the possible confounding factor of lactation state in participants. So, further research under well-controlled conditions is needed to clarify the relationship between depression and prolactin levels in PCOS patients.

This study has some limitations. The first limitation of this study is that generally healthy women without any infertility related symptoms should be included as controls for this study. However, it was difficult to recruit healthy women who volunteered to measure laboratory tests including various hormonal levels, metabolic parameters, and BDNF concentration, so we conducted this study in patients with SA who need such laboratory test as a workup for their diagnosis. Even had we controls as healthy ovulatory women, anovulation in the PCOS group itself may have been a bias, therefore recruiting a perfect control group was more difficult. Indeed, depression, which is negatively related to BDNF level, is common in patients with secondary amenorrhea and there was no difference in depression between PCOS patients and SA patients due to other causes in this study. In addition, in terms of the correlation between depression and BDNF level, it was assumed that patients with SA due to other causes were similar to general women without any infertility-related symptoms. In order to confirm the results of this study, a further study comparing the normal control group and PCOS patients should be needed. Second, although we found a link between depression and AMH and prolactin in PCOS, these results cannot be interpreted causal inferences. Third, due to the small study population with only one race, there is a possibility to the risk of selection bias or type II error and the generalizability of the results might be limited. Further studies using a larger population with age-matched healthy controls should be conducted. Despite of these limitations, this study is the first prospective observational study of the relationship between the plasma BDNF level and depression in Korean patients with PCOS, though there was no statistical correlation between them. And the association of AMH and prolactin level with depression in this study suggests the possibility that both hormones may be important biological factors in assessing mood state in PCOS patients.

5. Conclusions

In summary, depression is related to AMH and prolactin levels rather than plasma BDNF levels in patients with PCOS. This study provides further insight into the etiology of depression in women with PCOS that AMH and prolactin seem to play potentially crucial roles in the development and progression of depression in PCOS patients. We believe that our study makes a significant contribution to the literature because, to the best of our knowledge, this study is the first to investigate the association between plasma BDNF levels and depression in PCOS patients. And the association of AMH and prolactin level with depression in patients with PCOS is another important result, which suggests the possibility of a neuroprotective role of these hormones. If future studies would find that such a reproductive hormonal imbalance is a causal factor of depression in PCOS, hormone therapy without antidepressants could be incorporated into a treatment plan for reducing both PCOS symptoms and depression. Our findings could influence the treatment strategies available to these patients, and could therefore have a significant impact on their quality of life.
Author contributions
GMK and GHJ designed the research study. GMK, JAL, SWP, and GHJ performed the research. SWP and JGL provided help and advice on the ELISA experiments. GMK and GHJ analyzed the data and wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Informed consent was obtained from all subjects involved in the study. The Institutional Review Board of Inje University Haeundae Paik Hospital approved the study protocol (No. 2017-01-018-002).

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Conflict of interest
The authors declare no conflict of interest.

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