Cortisol Level Related to Depression in Women with Endometriosis

Adnan Abadi[1], Aria Indrabrata[2], Iskandar Zulqarnain[1], Theodorus[2], Abdullah Sahab[3], Kemas Yusuf Effendi[1], Heriyadi Manan[1], Fatimah Usman[1], Awan Nurtjahyo[1], Cindy Kesty[2*]

[1] Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sriwijaya/ Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia
[2] Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sriwijaya/ Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia
[3] Department of Pharmacology, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia
[4] Department of Psychiatry, Faculty of Medicine, Universitas Sriwijaya/ Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

A B S T R A C T

Background: Several main symptoms of endometriosis can lead to physical and psychological stress and also hormonal disturbances as the result of prolonged stress. Cortisol was associated with the onset of depression. This study aimed to determine the relationship between cortisol levels and depression in women with endometriosis at the Department of Obstetrics and Gynecology at Dr. Mohammad Hoesin General Hospital (RSMH) Palembang. **Methods:** A cross-sectional study was performed at the Reproductive Endocrinology and Infertility outpatient clinic and inpatient ward, Department of Obstetrics and Gynecology at Dr. Mohammad Hoesin General Hospital Palembang, from January to November 2020. There were 74 samples of endometriosis patients who met the inclusion criteria. The blood cortisol level was examined using the ELISA method. The determination of depression level was performed by filling out the Beck Depression Inventory questionnaire. Data were analyzed using SPSS version 22.0. **Results:** Seventy-four samples met the inclusion criteria. As many as 44 patients (59.5%) without depression, 20 patients (27%) with mild depression, 8 patients (10.8%) with moderate depression, and only 2 patients (2.7%) with severe depression. There were no differences in age, marital status, parity, menstrual cycle, and duration of treatment between endometriosis patients with and without depression (p > 0.05). There was a significant difference in cortisol levels between endometriosis patients with and without depression (p = 0.017). Endometriosis patients with cortisol levels ≤ 7.4 mg/dl were three times more at risk of depression than endometriosis patients with cortisol levels > 7.4 mg/dl. In addition, there was a significant relationship between cortisol level and depression status (OR = 3.023 (95% CI 1.153–7.942; p = 0.041). This study also found a significantly low negative correlation between cortisol levels and BDI scores (r = -0.249; p = 0.032). **Conclusion**: There was a significant relationship between serum cortisol levels and depression in women with endometriosis. Endometriosis patients with depression had significantly lower cortisol levels than endometriosis patients without depression.

1. Introduction

Endometriosis is a common benign gynecologic disorder defined as the presence of endometrial glandular tissue and stroma outside the normal location or outside the uterine cavity.[1] The prevalence of asymptomatic endometriosis was very small. It ranged from 2–22%.[2-4] Chronic pelvic pain, dysmenorrhea, dyspareunia, dysuria, and dyschezia occurred 40–80%, and infertility occurred 20–30%.[5,6] They were the main symptoms of endometriosis. Other symptoms, such as menstrual disorders, could also happen. This could lead to physical and psychological

stress, whereas the disorder could lead to chronic anxiety and depression and also lower women's quality of life.[1-3]

Dysfunction of the Hypothalamus-Pituitary-Adrenal (HPA) axis is found in patients with endometriosis, and it is related to an attenuated cortisol response, a condition known as burnout.[1] Cortisol was a steroid hormone originating from the adrenal cortex with the function of modulating intermediate metabolism and immune response through glucocorticoids, blood pressure, vascular volume, and electrolytes through mineralocorticoids, and secondary sex characteristics through androgen.[7]

A paradoxical hypocortisolism like adrenal fatigue may exacerbate painful symptoms by reducing the endogenous analgesia associated with stress (stress-induced analgesia). A blunted early morning cortisol response to the Corticotropin-Releasing Hormone (CRH) test was associated with greater menstrual and non-menstrual pain in endometriosis.[1]

Some studies reported that high cortisol levels and stressful events were associated with the onset of depression. However, other studies reported that increased cortisol levels depended on stress factors received by patients, but it did not mediate the occurrence of a depressive state.[5]

There was no study about how cortisol level was related to depression rates in women with endometriosis in Indonesia, especially in the population in Palembang. Besides that, typical and specific symptoms of endometriosis also distinguished it from other gynecological abnormalities. Due to the importance of maintaining a good quality of women's lives and preventing further morbidities, this study aimed to determine a basis of management in the field of psychiatry for looking at other causes of depression in endometriosis patients.

2. Methods

A cross-sectional study with consecutive sampling was conducted from January to October 2020 at the Reproductive Endocrinology and Infertility outpatient clinic and obstetrics and gynecology inpatient ward Dr. Mohammad Hoesin General Hospital Palembang.

This study included women between 15 and 45 years of age with endometriosis who agreed to participate in this study. Women who had other gynecological abnormalities, such as malignancy or benign tumors (uterine myoma), were excluded from this study. Moreover, pregnant women and patients with chronic diseases (such as diabetes mellitus, hypertension, heart disease, pulmonary disease, anemia, thyroid disease, obesity, malnutrition, neurologic disorder, extremities deformity, acne, recurrent pregnancy loss, recurrent intrauterine fetal demise, Cushing syndrome) who were more prone to have stress and depression, as well as increased cortisol, were not included in the study.

The samples were taken by history taking, physical examination (vital signs, head to toe), gynecological examination (external and internal examination, or as indicated), and ultrasonographic examination. The study subjects were then scheduled for laparoscopic surgery if indicated, and a laboratory examination of serum cortisol was performed. Serum samples of study subjects were taken 3 mL from 5.00 AM until 9.00 AM and inserted into a centrifuge tube without EDTA, and then sent to the Clinical Laboratory of Dr. Mohammad Hoesin General Hospital Palembang. The blood sample in the tube was placed on the tube rack. The sample was allowed to stand for 1-2 hours at room temperature until the blood clots. Then, blood sample centrifugation at a speed of 3000 rotations per minute (rpm) for 15 minutes was performed. Serum from the centrifugation results was taken using a micropipette. It was inserted into a microtube that had been coded according to the identity of the study subjects. Samples were sent to the laboratory using a cooler bag to be stored in a refrigerator at -20oC. Cortisol examination was performed using the ELISA method, collectively by using 8D15.02 Arch. Cortisol Calibrator Abbott®, 8D15.25 Arch. Cortisol 100T Abbott® and 5P76.10 Technopath Multichem 1A Plus Abbott®.

After that, all subjects were interviewed and filled out the Beck Depression Inventory (BID) questionnaire independently without intervention from the

researchers. Subjects were classified as non-depression if BID score 1–10, mild depression 11–20, moderate depression 21–30, severe depression 31–40, and extreme depression > 40. Then, the characteristics of the samples were determined. All data were recapitulated and tabulated in data tables and matched based on variables of age, marital status, obstetric status, chief complaint, menstrual cycle, and duration of treatment. The protocol of this study had been approved by the Ethical Committee of Medical Research at Dr. Mohammad Hoesin General Hospital Palembang (Ref No. 329/kepkrsmhfkunsri/2019.

The comparison of cortisol levels between patients with and without depression was analyzed using the Mann-Whitney test. The cortisol level cut-off points were analyzed using the ROC curve. Furthermore, the relationship between cortisol levels and depression in endometriosis patients was analyzed using a chi-square test. The correlation between cortisol levels and endometriosis patients with depression was used by Spearman Rho's test. Data were analyzed using SPSS version 22.0.

3. Results

A total of 74 samples were included in this study. The average age of endometriosis patients was 31.95 ± 7.47 years ranging from 16 to 45 years of age. Most of them aged more than 30 years (55.4%). The majority of patients were married (82.4%), nulliparous (56.8%), and had regular menstrual cycles (70.3%). In addition, most of them complained about dysmenorrhea (48.6%) and infertility (39.2%) and also had been treated for 1 to 5 years (56.8%) (Table 1).

Table 1. General characteristics of the patients

Characteristics	Frequency	Percentage
Age, mean ± standard deviation (yo)	31.95 ± 7.47	
Age Classification		
< 20 years old	4	5.4
20–30 years old	29	39.2
> 30 years old	41	55.4
Marital Status		
Married	61	82.4
Unmarried	7	9.5
Divorced	6	8.1
Parity		
Nulliparity	42	56.8
Primiparity	14	18.9
Multiparity	18	24.3
Chief complaint		
Dysmenorrhea	36	48.6
Infertility	29	39.2
Pelvic pain	9	12.2
Menstrual Cycle		
Regular	52	70.3
Irregular	22	29.7
Duration of treatment		
< 1 year	32	43.2
1 year	24	32.4
2 years	10	13.5
3 years	6	8.1
4 years	1	1.4
5 years	1	1.4

Furthermore, endometriosis patients had an average cortisol level of 7.42 ± 4.39 mg/dl with a range of 0.1 to 15.20 mg/dl. Only 2 patients (2.7%) had high cortisol levels. Besides that, a BDI score was 11.11 ± 9.42 mg/dl with a range of 0 to 43, with as many as 44 patients (59.5%) without depression, 20 patients (27%) with mild depression, 8 patients (10.8%) with moderate depression, and only 2 patients (2.7%) with severe depression (Table 2).

Table 2. Cortisol and Beck depression inventory (BDI) score level

Characteristics	Frequency	Percentage
Cortisol level, mean ± SD	7.42 ± 4.39	
Cortisol Level		
Normal	72	97.3
High	2	2.7
BDI score, SD ± Mean	11.11 ± 9.42	
Depressive Status		
Normal	44	59.5
Depression		
Mild	20	27.0
Moderate	8	10.8
Severe	2	2.7

The cortisol level for endometriosis patients who had depression was 5.97 ± 3.84 mg/dl, with a range of 0.1 to 12.80 mg/dl. Meanwhile, the cortisol level of endometriosis patients without depression was 8.41 ± 4.52 mg/dl, with a range of 0.1 to 15.20 mg/dl (Table 3). By using the ROC curve, the cut-off point of cortisol level, which had the best sensitivity and specificity, was 7.4 mg/dl. Of 35 endometriosis patients with cortisol ≤ 7.4 mg/dl, as many as 19 patients (54.3%) had depression. Meanwhile, among 39 endometriosis patients with cortisol levels > 7.4 mg/dl, as many as 11 patients (28.2%) had depression.

Table 3. The comparison of cortisol levels between patients with depression and without depression

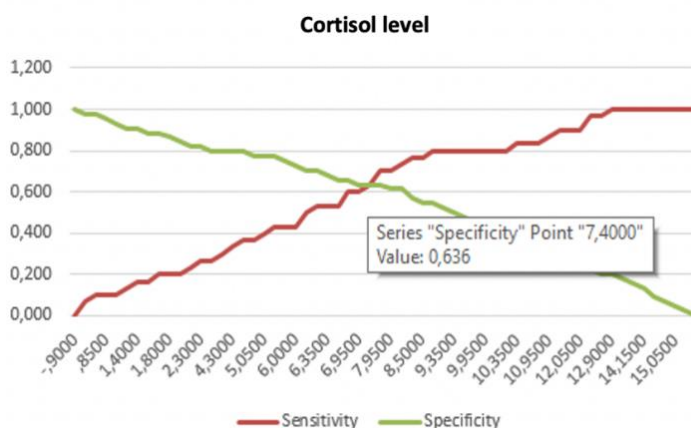| Cortisol level	Depression		p-value
	Yes	No	
Mean ± SD	5.97 ± 3.84	8.41 ± 4.52	0.017*
Median (Min-Max)	6.15 (0.1–12.8)	9.35 (0.1–15.2)	

* Mann-Whitney test, p = 0.05

Figure 1. The cut-off point of cortisol level based on depressive status

From statistical analysis, there was a significant relationship between cortisol level and depressive status (p = 0.041). Endometriosis patients with cortisol levels ≤ 7.4 mg/dl were three times more at risk of depression than endometriosis patients with cortisol levels > 7.4 mg/dl (Table 4).

Table 4. The relationship between cortisol levels and depression in women with endometriosis

| | Depression | | PR | p |
	Yes	No	(CI 95%)	value
Cortisol Level				
≤ 7.4 mg/dl	19 (54.3)	16 (45.7)	3.023 (1.153–7.942)	0.041
> 7.4 mg/dl	11 (28.2)	28 (71.8)		

Chi-square test, p = 0.05

In addition, there was a significantly low negative correlation between cortisol level and BDI score (r = -0.249; p = 0.032), which meant that the smaller the cortisol level was, the higher the endometriosis patient's BDI score was (Table 5).

Table 5. The correlation between cortisol level and depression in endometriosis patients

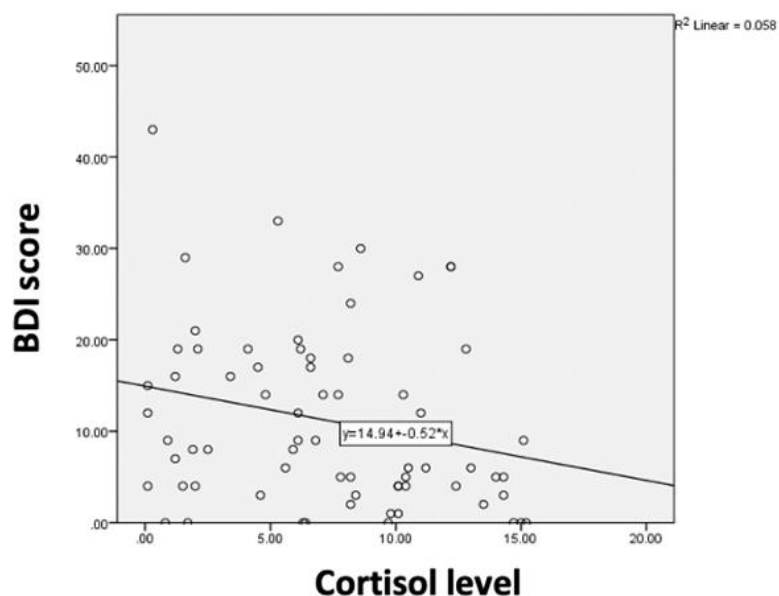|	Cortisol Level	BDI score	r	p value
Mean ± SD	7.42 ± 4.39	11.11 ± 9.42	-0.249	0.032
Median (Min-Max)	7.75 (0.1–15.2)	9 (0–43)		

Spearman Rho's test, p = 0.05

Figure 2. The correlation between cortisol level and BDI scores of patients with endometriosis

4. Discussion

Endometriosis is defined as the presence of endometrial tissue that grows outside of the uterine tissue. The prevalence of asymptomatic endometriosis ranges from 2% to 22%. The prevalence of endometriosis ranges from 20–50% in infertile women and 40–50% in women with pelvic pain.[8] The average age of women with endometriosis is between 25 and 35 years of age.[2] Endometriosis affects 10–15% of all reproductive-age women. Many women often experience a delay in the diagnosis of endometriosis which results in decreased quality of life. In patients aged 18–45 years, the mean delay in diagnosis of endometriosis is approximately 7 years.[9]

In this study, the age of endometriosis patients ranged from 16 to 45 years, with a mean of 31.95 years, and the majority were aged > 30 years (55.4%). This result is similar to the study conducted by Friedl et al. in 2015, which involved 123 samples (62 endometriosis patients and 61 control patients). It reported that the mean age of endometriosis patients was approximately 33.4 years, with an age range of 18 to 44 years.[10] Another study conducted by Rush et al. in 2019, involving 2,061 samples, reported a younger average age of endometriosis patients compared to this study, which was approximately 24 years of age with the highest age distribution in the range of 26 to 35 years (47.7%).[11] However, a study conducted by De Graaff et al. in 2013 reported the older mean age of endometriosis patients was approximately 36.1 years, with an age range of 14 to 67 years.[12]

In this study, the majority (82.4%) of endometriosis patients were married. This result is in line with a study conducted by Friedl et al. in 2015, which reported that the majority (61.3%) of endometriosis patients were married.[10] Likewise, De Graaff's study in 2019 reported that 56% of endometriosis patients were married.[12] In addition, in this study, the majority of endometriosis patients did not have children (56.8%). This is in line with a study conducted by Wu et al. in 2017, who reported that 51.9% of nulliparous endometriosis patients reported.[13] Likewise, the study conducted by Waller et al. reported that 95 of 147 (64.6%) endometriosis patients did not have children.[14]

Endometriosis is seen in infertile women with symptoms of dysmenorrhea, dyspareunia, or chronic pelvic pain. Approximately 40–80% of women with endometriosis will experience pain. Pain in endometriosis patients can be pain during menstruation (dysmenorrhea), pain during sexual intercourse (dyspareunia), pain during urinating (dysuria), pain during defecation (dyschezia), pelvic pain, and lower abdominal pain.[4,5] Another symptom felt by endometriosis patients is infertility. Infertility occurs in about 20–30% of women with endometriosis. In general, infertile women have a greater incidence of endometriosis than women using contraception. There is an increasing prevalence of severe-stage endometriosis in infertile women. Symptoms of infertility are closely related to the long onset of an endometriosis diagnosis in 7–8 years, starting from the appearance of the first symptoms to a definite diagnosis.[2-3]

In this study, there were 48.6% of patients complained about dysmenorrhea, 39.2% complained about infertility, and 12.2% the patients complained about pelvic pain. This was similar to Wu et al. in 2017, who reported as many as 44.4% of patients with the main complaint of dysmenorrhea, 3.7% complaining about infertility, and 27.8% complaining about pelvic pain. As many as 30–40% of women with endometriosis experienced infertility.[13]

Menstrual disturbances, apart from pain during menstruation (dysmenorrhea), are atypical symptoms of endometriosis. Menstrual disorders can be in the form of heavy bleeding (menorrhagia), irregular bleeding, blood clots, and irregular cycles.[6] In this study, it was found that 70.3% of endometriosis patients had regular menstrual cycles, as well as a study conducted by Waller et al. al. reported that 99 of 147 (62.6%) endometriosis patients had regular menstrual cycles (28–34 days).[14]

Statistical analysis in this study showed that there was no difference in age, marital status, parity, menstrual cycle, and length of treatment between

patients with and without depression. This shows that the effect of the hormone cortisol on depression in endometriosis patients in this study was not influenced by the five characteristics above.

Cortisol is a steroid hormone that originates from the adrenal cortex. This hormone functions to modulate intermediate metabolism and immune response through glucocorticoids, blood pressure, vascular volume, and electrolytes through mineralocorticoids, and secondary sex characteristics through androgens. Circadian rhythm. This rhythm is regulated by the suprachiasmatic nucleus (pacemaker) in the hypothalamus. Cortisol is the main glucocorticoid that has metabolic effects, adaptation to stress, anti-inflammatory, and immunosuppressive. Physical or emotional stress will increase cortisol secretion. Cortisol levels in a basal or non-stressed state are 8–2 5 mg/dl, with a mean of 9.2 mg/dl.[7]

Women with endometriosis usually experience chronic pelvic pain, dysmenorrhea, chronic fatigue syndrome, mood disorders (anxiety and depression), as well as infertility. The pain was caused by inflammatory process and fibrosis, especially mast cells that infiltrated the ectopic endometrium causing a hypersensitivity reaction. Thus, severe and typical pelvic pain happened. Women with endometriosis were reported to have high depression, anxiety, and stress due to perceived pain and infertility symptoms. It had negative effects on social, sexual, professional, and fertility life. This level of anxiety and depression increases as the symptoms of endometriosis or symptoms become chronic.[3,15-17]

Endometriosis patients had an average cortisol level of 7.42 ± 4.39 mg/dl, with a range of 0.1 to 15.2 mg/dl. Only 2 patients had high cortisol levels. There were significant differences in cortisol levels between endometriosis patients with and without depression. Endometriosis patients without depression had higher cortisol levels than endometriosis patients with depression. Furthermore, the results found that there was a significant relationship between cortisol level and depressive status. Endometriosis patients with cortisol levels of ≤ 7.4 mg/dl were three times more at

risk of depression than endometriosis patients with cortisol levels > 7.4 mg/dl. This was not relevant to the above theory stating that physical or emotional stress would increase cortisol secretion. This was likely because endometriosis patients had hypocortisolism due to overuse of the adrenal glands caused by long-term high stress.[18-19]

Cortisol regulation is regulated by the hypothalamic-pituitary-adrenal axis. The suprachiasmatic nucleus, modulated by physical or emotional stressors, secretes corticotropin-releasing hormone (CRH). This hormone will then stimulate adrenocorticotrophic hormones (ACTH) in the anterior pituitary. It will bind to receptors on the plasma membrane, causing an increase in the formation of free cholesterol. Free cholesterol is then converted to pregnenolone and then proceeds to the steps in steroidogenesis, which secrete cortisol in the adrenal cortex. When cortisol levels are excessive, the adrenal glands will give negative feedback to the anterior pituitary. Negative feedback will keep cortisol secretion constant. This negative feedback is influenced by two factors, namely circadian rhythm and stress.[7,20-22]

The limitations of this study are (1) that this study did not follow up on the treatment and condition of patients with depression and (2) that the socioeconomic status and family background as risk factors of depression were not determined. Another cohort study with a larger sample size can be conducted in the future.

5. Conclusion

There was a significant relationship between serum cortisol levels and depression in women with endometriosis. Endometriosis patients with depression had significantly lower cortisol levels than endometriosis patients without depression.

6. References

1. Vannuccini S, Clemenza S, Rossi M, Petraglia F. Hormonal treatments for endometriosis: The endocrine background. Rev Endocr Metab Disord. 2021; 1–23.

2. Hestiantoro A, Wiweko B, Harzif AK, Shadrina A, Silvia M. Konsensus tatalaksana nyeri endometriosis. Jakarta: HIFERI, POGI. 2017: 1–48.

3. Hoffman BL, Schorge JO, Bradshaw KD, Halvorson LM, Schaffer JI, Corton MM. Endometriosis. In: Hoffman BL, Schorge JO, Bradshaw KD, Halvorson LM, Schaffer JI, Corton MM. Williams Gynecology. 3rd Ed. New York: McGraw-Hill Education. 2017.

4. Gupta S, Harlev A, Agarwal A. Endometriosis. 1st Ed. Cham: Springer International Publishing. 2015.

5. Qin DD, Rizak J, Feng XL, Yang SC, Lu LB, et al. Prolonged secretion of cortisol as a possible mechanism underlying stress and depressive behavior. J Sci Rep. 2016; 6: 30187.

6. Agarwal SK, Chapron C, Giudice LC, Laufer MC, Leyland N, et al. Clinical diagnosis of endometriosis: A call to action. Am J Obstet Gynecol. 2019; 220(4): 354.e1–354.e12.

7. Adi S, Pranoto A. Gangguan korteks adrenal. Dalam: Adi S, Pranoto A. Buku Ajar Ilmu Penyakit Dalam. Edisi Keenam. Jakarta: Interna Publishing. 2014: 2484–87

8. Alan DeCherney, Kenneth Muse. Endometriosis. In: Alan DeCherney, Lauren Nathan, Murphy Goodwin, Neri Laufer, eds. (Lange) Current diagnosis & treatment obstetrics & gynecology. 10th Ed. California: The McGraw-Hill Companies. 2007.

9. Parasar P, Ozcan P, Terry KL. Endometriosis: Epidemiology, diagnosis and clinical management. Curr Obstet Gynecol Rep. 2017; 6(1): 34–41.

10. Friedl F, Riedl D, Fessler S, Wildt L, Walter M, et al. Impact of endometriosis on quality of life, anxiety, and depression: An Austrian perspective. Arch Gynecol Obstet. 2015; 292(6): 1393–9.

11. Rush G, Misajon RA, Hunter JA, Gardner J, O'Brien KS. The relationship between endometriosis-related pelvic pain and symptom frequency and subjective wellbeing. Health Qual Life Outcomes. 2019; 17(1): 123.

12. De Graaff AA, D'Hooghe TM, Dunselman GAJ, Dirksen CD, Hummelshoj L, et al. The significant effect of endometriosis on physical, mental and social wellbeing: Results from an international cross-sectional survey. Hum Reprod. 2013; 28(10): 2677–85.

13. Wu IB, Tendean HMM, Mewenkang ME. Description of the characteristics of patients with endometriosis in Prof. Dr. R.D. Kandou Manado General Hospital. E-Clinic. 2017; 5(2): 279–85.

14. Waller KG, Shaw RW. Risk factors for endometriosis: Menstrual and lifestyle characteristics. Med Principles Pract. 1998; 7(2): 127–33.

15. Cuevas M, Flores I, Thompson KJ, Ortolaza DLR, Reveron AT, Appleyard CB. Stress exacerbates endometriosis manifestations and inflammatory parameters in an animal model. Reprod Sci. 2012; 19(8): 851–62.

16. Iwabe T, Harada T. Inflammation and cytokines in endometriosis. In: Harada T. Endometriosis: Pathogenesis and treatment. Tokyo: Springer. 2014: 87–106.

17. Van Aken M, Oosterman J, Rijn TV, Ferdek M, Ruigt G, Kozicz T, et al. Hair cortisol and the relationship with chronic pain and quality of life in endometriosis patients. Psychoneuroendocrinology. 2018; 89: 216–22.

18. Johnson NP, Hummelshoj L, Adamson GD, Keckstein J, Taylor HS, et al. World Endometriosis Society consensus on the classification of endometriosis. Hum Reprod 2017; 32(2): 315–24.

19. American College of Obstetricians and Gynecologists. Dysmenorrhea and endometriosis in the adolescent. Obstet Gynecol. 2018; 132(6): e249–58.

20. Chan S, Debono M. Replication of cortisol circadian rhythm: New advances in hydrocortisone replacement therapy. Ther Adv

Endocrinol Metab, 2010; 1(3): 129–38.

21. Lee DY, Kim E, Choi MH. Technical and clinical aspects of cortisol as a biochemical marker of chronic stress. BMB Rep. 2015; 48(4): 209–16.

22. Sherwood L. The peripheral endocrine glands in human physiology from cells to systems. In: Sherwood L. Human physiology: From cells to systems. 7th Ed. Belmont, Calif: Brooks/Cole; 2010: 698–702.