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Original Article

Clinical efficacy of turtle shell decocted pills for endometriosis and their influence on cellular immunity

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Abstract: Objective: To explore the therapeutic efficacy of the levonorgestrel-releasing intrauterine system combined with turtle shell decocted pills for endometriosis and their effect on cellular immune function. Methods: Clinical data of 118 patients with endometriosis admitted to Taizhou First People's Hospital from January 2019 to January 2020 were retrospectively analyzed. The patients were assigned into a single-drug group (n=68) and a combined traditional Chinese medicine group (n=50) according to treatment methods. The single-drug group was treated with the levonorgestrel-releasing intrauterine system, and the combined traditional Chinese medicine group was treated with additional turtle shell decocted pills for three cycles for a total of 12 weeks. Enzyme-linked immunosorbent assay was adopted to measure the concentration of Th1 cytokines (tumor necrosis factor (TNF)-α and interferon (IFN)-γ) and Th2 cytokines (interleukin (IL)-6 and IL-10), and the protein level of programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1). The levels of serum luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol (E2) were compared between the two groups. The response rate of treatment, the control rate of blood pressure and the incidence of adverse reactions were recorded in both groups. Results: The response rate of treatment in the combined traditional Chinese medicine group was higher than that in the single-drug group ($P<0.05$). Compared to before treatment, the TNF-α and IFN-γ increased in both groups after treatment, and the expressions were higher in the combined traditional Chinese medicine group than in the single-drug group (all $P<0.05$). After treatment, the levels of IL-6, IL-10, PD-1, and PD-L1 decreased, and the decreases in the combined traditional Chinese medicine group were greater than those in the single-drug group (all $P<0.05$). Serum LH, FSH and E2 levels before and after the treatment in the two groups were not statistically different (all $P>0.05$). The incidence of treatment-related adverse reactions between the two groups of patients was also not statistically different ($P>0.05$). Conclusion: Turtle shell decocted pills can increase the clinical efficacy of levonorgestrel-releasing intrauterine system in the treatment of endometriosis, reduce levels of PD-1, and PD-L1 and improve cellular immune function. The pills do not affect the secretion of ovarian hormones or increase adverse reactions.

Keywords: Endometriosis, levonorgestrel-releasing intrauterine system, turtle shell decocted pills, cellular immunity, sex hormone

Introduction

Endometriosis (EMS), one of the common diseases in gynecology, is related to immune, genetic, and other factors [1-3]. EMS is commonly seen in women of childbearing age, with an incidence of nearly 1/4. The main pathogenesis of EMS is that endometrial tissue moves out the corpus uteri due to various reasons, causing discomforts such as menstrual pain, lower abdomen pain, menstrual cycle disorder, and even infertility. Those symptoms can bring different degrees of fertility pressure, and seriously affect patients' quality of life [4, 5]. It has been confirmed that EMS is a hormone-dependent disease [6]. Even though the growth of endometrium is benign, it has carcinoid manifestations such as implantation, invasion, and distant metastasis. With the increasing rate of cesarean section and induced abortion, the incidence of EMS is increasing annually, so improving the diagnosis and treatment has important clinical significance.

The main treatments for EMS in the past include surgical resection, uterine artery embolization,

hysterectomy, and progesterone antagonists [7, 8]. However, the above-mentioned treatments have disadvantages such as poor effect, high recurrence rate, or low acceptability from patients. Progesterone can correct the imbalance of sex hormones and obtain promising effects. Oral hormones are favored by patients and front-line doctors because of their better tolerance, but the treatment effect is affected by patient's compliance. In recent years, the intrauterine hormone release system has been widely used due to the advantage of sustained release of hormones. Among them, the levonorgestrel-releasing intrauterine system, also known as Mirena, is the most common. Previous studies have initially confirmed its effectiveness in the treatment of EMS [9, 10]. Traditional Chinese medicine can play a synergistic role in the treatment of EMS. Although a study confirmed the practical effect of turtle shell decocted pills in the treatment of adenomyosis, the study [11] was limited by the clinical endpoint, and the observation of corresponding objective immune function and serological indicators was missing. Therefore, research on the biological serum indices is of great significance to evaluate the clinical efficacy of turtle shell decocted pills for treating EMS. In this study, we explored the clinical effects of turtle shell decocted pills combined with a levonorgestrel-releasing intrauterine system in the treatment of EMS from a serum level, so as to provide novel research directions for treatment.

Materials and methods

General data

A total of 118 patients with EMS treated in the gynecological outpatient of Taizhou First People's Hospital from January 2019 to January 2020 were enrolled as the research subjects. The patients were assigned into a single-drug group and a combined traditional Chinese medicine group according to the treatment methods. The single-drug group was treated with levonorgestrel-releasing intrauterine system, and the combined traditional Chinese medicine group was given additional turtle shell decocted pills. This study was approved by the Ethics Committee of Taizhou First People's Hospital.

Inclusion criteria: 1) patients with an age ≥20 years old; 2) patients who met the related diagnostic criteria for EMS and the standard from French National Society of Gynecologists and Obstetricians [12]; 3) patients with enlarged uterus according to doppler ultrasound; 4) patients without previous treatment history; and 5) patients without a desire for pregnancy.

Exclusion criteria: 1) patients with a history of mental illness; 2) patients with fertility needs; 3) patients with a history of traditional Chinese medicines treatment; 4) patients who received hormone therapy; 5) patients complicated with other tumors including but not limited to gynecological oncology; 6) patients with abnormal blood coagulation function.

Treatment methods

To place the levonorgestrel-releasing intrauterine system, all patients underwent a comprehensive gynecological examination beforehand. The size and position of the uterus were checked with the combination of transvaginal Doppler ultrasound. The levonorgestrel-releasing intrauterine system was placed 5-7 days after the start of a menstrual period. Patients and their family members were told about related risks, follow-up matters, and precautions before the operation. A written consent form was also obtained before operation. After routine disinfection, the Mirena (52 mg levonorgestrel; Bayer Schering Pharma Oy, Guangzhou Branch of Bayer Healthcare Co., Ltd., China) was placed in the uterus, and various related indicators and the ovarian function were tested after the operation.

For patients in the combined traditional Chinese medicine group, turtle shell decocted pills (Sinopharm Zhonglian Pharmaceutical Co., Ltd., Nanjing, China) were orally administered, 3 g each time and twice a day except during the menstrual period. Patients were instructed to avoid smoking, drinking alcohol or having spicy food during the therapy. The treatment lasted for a total of 3 cycles.

Outcome measures

Primary outcome measures included immune-related indictors and clinical efficacy. Venous blood (3-5 mL) was drawn from the patients before and after treatment. The blood sample was centrifuged and stored for later analyses. The concentrations of Th1 cytokines, tumor

necrosis factor (TNF)-α (Art. No. SEKS-0003, from Ricky Biotech Co., Ltd, Shanghai, China) and interferon (IFN)-γ (Art. No. FT-B9136S, from Ricky Biotech Co., Ltd, Shanghai, China), and Th2 cytokines, interleukin (IL)-6 (Art. No. FT-B9580S, from Fantai Biotech Co., Ltd, Shanghai, China) and IL-10 (Art. No. FT-B9143S, from Fantai Biotech Co., Ltd, Shanghai, China), and the protein levels of programmed cell death 1 (PD-1, Art. No. Ab00377-1.32-BS, from Otwo Biotech, Shenzhen, China) and programmed cell death ligand 1 (PD-L1, Art. No. PL0402884, from Dakewe Biotech Co., Ltd, Beijing, China) were measured by double-antibody sandwich enzyme-linked immunosorbent assay. To assess the clinical efficacy, the pictorial blood loss assessment chart designed by Higham was used after three months of treatment to evaluate the menstrual volume of the patient [13]. According to the staining size of menstrual pads, the menstrual volume was divided into three levels. A stained area less than 1/3 was mild and scored as 1 point. A stained area of 1/3-3/5 was moderate and scored as 5 points. A full stained menstrual pad was severe and scored as 20 points. Meanwhile, Beta-ultrasound was used to assess the size of the uterus before and after treatment. The combination of menstrual volume and uterine size was used to evaluate the clinical efficacy. Markedly effective referred to normal menstrual volume, reduced uterine size and no dysmenorrhea. Effective referred to no change in uterine size but greatly reduced menstrual volume. Ineffective referred to aggravation in menstrual volume and dysmenorrhea. Response rate = (cases of markedly effective + case of effective)/total number of cases *100%.

Secondary outcome measures included sex hormone levels and incidence of adverse reactions. To measure the sex hormone levels, peripheral venous blood was collected from patients before and after treatment. Then, levels of luteinizing hormone (LH), follicle stimulating hormone (FSH) and estradiol (E2) were measured using an automatic chemiluminescence analyzer (ABBOTT ARCHITECT i2000SR, USA) and corresponding supporting reagents. In terms of the incidence of adverse reactions, menstrual disorders, facial acne, breast pain, and increase in body mass index (over 10% of the baseline) were recorded based on previous literature and the general conditions of the enrolled patients [14]. The incidence of adverse reactions = cases with adverse reactions/total number of cases *100%.

Statistical analyses

SPSS 23.0 statistical software was used. The measured variables were expressed as mean ± standard deviation ($\bar{x}$ ± sd). The intragroup comparison between pretreatment and posttreatment indicators was performed by paired t test. The intergroup comparison was performed by independent sample t test. The counted variables were compared by chi-square test. A difference of $P<0.05$ was significant.

Results

Intergroup comparison of baseline data

The two groups showed no statistically significant differences in disease course, age, body mass index, menstrual cycle, marriage history and childbearing history (all $P>0.05$). See **Table 1**.

Intergroup comparison of response rate

In the combined traditional Chinese medicine group, markedly effective was shown in 34 cases, effective in 12 cases, and ineffective in 4 cases, with a response rate of 92.00% (46/50). In the single-drug group, markedly effective was shown in 25 cases, effective in 22 cases, and ineffective in 21 cases, with a response rate of 69.12% (47/68). The response rate in the combined traditional Chinese medicine group was higher than that of the single-drug group ($\chi^2=7.717$, $P=0.005$). See **Table 2**.

Inter- and intra-group comparison of immune function related Th1/Th2 cytokines

No significant differences were shown in the concentrations of TNF-α and IFN-γ in intergroup comparisons before treatment (both $P>0.05$). The posttreatment TNF-α and IFN-γ in both groups were higher than those pretreatment, and the levels were higher in the combined traditional Chinese medicine group than those in the single-drug group, with significant differences (all $P<0.05$). See **Table 3**.

Inter- and intra-group comparison of levels of PD-1 and PD-L1

No significant differences were shown in the levels of PD-1 and PD-L1 in intergroup comparison before treatment (both $P>0.05$). The post-

Table 1. Comparison of general data between the two groups

Group	Single-drug group (n=68)	Combined traditional Chinese medicine group (n=50)	χ^2/t	P
Length of disease (years)	4.58±0.95	4.73±1.13	-0.782	0.436
Age (Y)	45.3±3.6	45.6±3.9	-0.505	0.614
BMI (kg/m^2)	22.63±2.83	22.07±2.91	1.050	0.296
Menstrual cycle (days)	28.27±3.29	29.08±3.27	1.325	0.188
Marriage history			0.005	0.945
Yes	49	42		
No	19	8		
Childbearing history			0.001	0.967
One	38	29		
Two or above	30	21		

Note: BMI: body mass index; χ^2: statistical value of chi-square test, comparison between the single-drug group and the combined traditional medicine group; t: statistical value of t test, comparison between the single-drug group and the combined traditional medicine group.

Table 2. Comparison of clinical efficacy between the two groups

Group	Combined traditional Chinese medicine group	Single-drug group
Clinical efficacy		
Markedly effective	34	25
Effective	12	22
Ineffective	4	21
Response rate	46/50 (92.00%)	47/68 (69.12%)
χ^2	7.717	
P	0.005	

Note: χ^2: statistical value of chi-square test, comparison between the single-drug group and the combined traditional medicine group; t: statistical value of t test, comparison between the single-drug group and the combined traditional medicine group.

treatment levels of PD-1 and PD-L1 were lower than those of pretreatment in both groups and were also lower in the combined traditional Chinese medicine group than in the single-drug group, with significant differences (all P<0.05). See **Figures 1** and **2**.

Intergroup comparison of postoperative ovarian function-related indicators

The differences in postoperative ovarian function-related indicators were not significant between the two groups (all P>0.05). See **Table 4**.

Intergroup comparison of the incidence of treatment-related adverse reactions

The incidences of adverse reactions between the two groups were not significantly different (all P>0.05). See **Table 5**.

Discussion

EMS is a common chronic and difficult-to-treat disease in gynecology. At present, the opinions about pathogenesis are not unified yet. The theories of menstrual blood reflux and EMS implantation are commonly seen, but these cannot explain the fact that some patients with menstrual blood reflux have no endometrium implantation [15]. Further research has shown that the baseline characteristics (such as genetics, endocrine hormone disorders and immune dysfunction) of patients also play an important role in the occurrence and development of EMS [16, 17]. Immune function cells, such as T cells for cellular immunity, are a type of multifunctional cells. Disorders in cell counts and cell function are the main cytologic abnormality of immune function. T helper type 1 (Th1) cells can secrete TNF-α and IFN-γ to enhance cellular immunity, while Th2 cells can secrete IL-6 and IL-10 to inhibit immunity [18]. In addition, targeted studies have confirmed that PD1 can inhibit T cell activation and proliferation through PD-L1, thereby inhibiting immune system-related function and causing T cell apoptosis, which has been initially confirmed in diseases of respiratory and digestive systems [19]. Therefore, Th1 and Th2 downstream factors and PD-1 related proteins can be used as main indicators to reflect the abnormal immune function of patients.

Table 3. Comparison of immune function before and after treatment between the 2 groups

Indicator	Time	Single-drug group (n=68)	Combined traditional Chinese medicine group (n=50)
Th1 cytokines			
TNF-α (ng/L)	Before treatment	16.01±3.51	15.88±3.44
	After treatment	35.82±9.32[a,b]	63.57±8.76[a]
IFN-γ (ng/L)	Before treatment	18.74±4.73	19.03±5.92
	After treatment	34.84±5.05[a,b]	56.39±7.46[a]
Th2 cytokines			
IL-6 (ng/L)	Before treatment	89.03±14.69	88.79±13.40
	After treatment	154.73±22.92[a,b]	65.70±4.82[a]
IL-10 (ng/L)	Before treatment	21.40±5.01	22.35±4.35
	After treatment	19.04±5.96[a,b]	15.56±3.21[a]

Note: a, P<0.05, compared with before treatment; b, P<0.05, compared with the combined traditional Chinese medicine group. TNF-α: tumor necrosis factor-α, IFN-γ: interferon-γ, IL-6: interleukin-6, IL-10: interleukin-10.

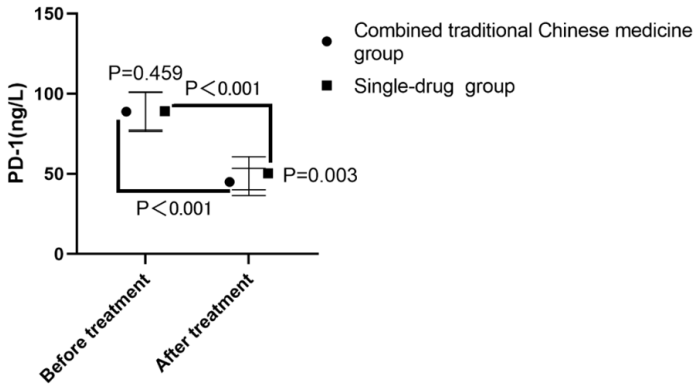

Figure 1. Comparison of PD-1 level before and after treatment between the two groups. Comparison between before and after treatment in the single-drug group or the combined traditional medicine group was conducted using paired t test. PD-1: programmed cell death 1.

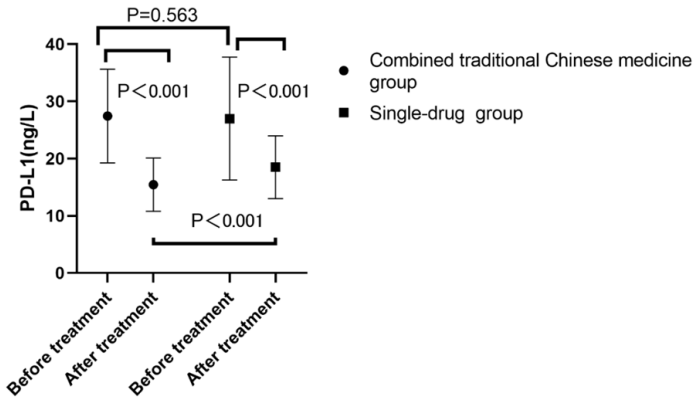

Figure 2. Comparison of PD-L1 protein between two groups before and after treatment. Comparison before and after treatment in the single-drug group or the combined traditional medicine group was conducted using paired t test. PD-L1: programmed cell death ligand 1.

This study showed that both groups obtained favorable clinical efficacy after using Mirena, which further confirmed that sustained release of progesterone can be used as a therapeutic target [20]. Possibly because of the increased secretion of estrogen and progesterone resistance in patients with EMS, effective estrogen suppression can alleviate clinical symptoms. Similar results have also been reported before [21]. Traditional Chinese medicine also plays an important role in the treatment of EMS. It dialectically believes that EMS is mainly "blood stasis and hard nodules", so the treatment focuses on removing blood stasis and dispelling nodules. Turtle shell decocted pills have a promising efficacy. Preliminary effects have been obtained in women with ovarian cysts and EMS, but the focus was only on clinical events. Therefore, this study further explored the clinical efficacy of turtle shell decocted pills combined with Mirena by measuring the immune function-related indicators [22, 23]. In the combined traditional Chinese medicine group, the clinical efficacy was higher than that of patients with Mirena alone, and the post-treatment TNF-α and IFN-γ were higher than those pretreatment. In addition, the levels of IL-6, IL-10, PD-1, and PD-L1 decreased in both

Table 4. Comparison of serum LH, FSH, and E2 levels before and after treatment between the two groups

Group	Single-drug group (n=68)	Combined traditional Chinese medicine group (n=50)	t	P
LH (U/L)				
Before treatment	8.82±1.32	8.77±1.53	0.190	0.850
After treatment	9.13±1.44	9.16±1.55	-0.108	0.914
FSH (U/L)				
Before treatment	9.76±1.48	10.14±1.69	-1.343	0.182
After treatment	9.98±1.38	9.81±1.52	0.633	0.528
E2 (pmol/L)				
Before treatment	104.38±13.46	102.85±12.84	0.622	0.535
After treatment	102.85±12.97	102.33±14.78	0.203	0.840

Note: LH: luteinizing hormone; FSH: follicle stimulating hormone; E2: estradiol; t: statistical value of t test, comparison between the single-drug group and the combined traditional medicine group.

Table 5. Comparison of the incidence of adverse reactions between the two groups

Group	Adverse reactions				Total
	Menstrual disorders	Facial acne	Breast pain	Increase in body mass index	
Single-drug group (n=68)	4	1	1	1	7/68 (10.29%)
Combined traditional Chinese medicine group (n=50)	2	1	2	1	6/50 (12.00%)
χ^2				0.000	
P				0.996	

Note: χ^2: statistical value of chi-square test, comparison between the single-drug group and the combined traditional medicine group.

groups after treatment, and the decreases were greater in the combined tradition Chinese medicine group than in the control group. This further confirmed that the traditional Chinese medicine, turtle shell decocted pills, can increase the clinical effect of Mirena.

At present, how to protect ovarian function is the main target in treating EMS [24, 25]. This study explored the effects of turtle shell decocted pills combined with Mirena on ovarian function. The results showed that there was no statistical difference in posttreatment serum levels of LH, FSH and E2 (ovarian indicators) between the two groups. Shan et al. have concluded that Hematinic and Blood Circulation-promoting Decoction for EMS do not increase ovarian damage, and Zhang et al. have verified the safety of turtle shell decocted pills in the treatment of liver diseases [23-26]. Therefore, we believe that turtle shell decocted pills did not pose a risk of ovarian damage to patients with EMS. Treatment-related adverse reactions also showed that there were no statistical differences in the incidence of adverse reactions such as menstrual disorders, facial acne, breast pain and increase in body mass index between the two groups, which confirmed the clinical safety of turtle shell decocted pills. Therefore, turtle shell decocted pills have promising application value and are recommended for clinical use, which is consistent with the research conclusions of previous scholars [27].

This was a single-center retrospective study, and the sample size was small. Thus, a multicenter prospective large-sample study is needed to confirm further the clinical applicability of turtle shell decocted pills. The correlation between progesterone and immune system indicators, T cells and PD-1/PD-L1, also needs to be further studied.

In summary, the turtle shell decocted pills combined with Mirena for patients with EMS can increase the clinical treatment efficacy, reduce the levels of PD-1 and PD-L1, improve the immune function, and show promising treatment effectiveness.

Disclosure of conflict of interest

None.

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References

[1] Gonzalez Salazar E, Mastroianni G, Vanetta C, Goransky J and Arbues G. Ileal endometriosis. An uncommon cause of bowel obstruction in women in fertile age. Medicina (B Aires) 2020; 80: 566-569.

[2] Zhang M, Li J, Duan S, Fang Z, Tian J, Yin H, Zhai Q, Wang X and Zhang L. Comprehensive characterization of endometrial competing endogenous RNA network in infertile women of childbearing age. Aging (Albany NY) 2020; 12: 4204-4221.

[3] Koninckx PR, Ussia A, Adamyan L, Wattiez A, Gomel V and Martin DC. Pathogenesis of endometriosis: the genetic/epigenetic theory. Fertil Steril 2019; 111: 327-340.

[4] Sachedina A and Todd N. Dysmenorrhea, endometriosis and chronic pelvic pain in adolescents. J Clin Res Pediatr Endocrinol 2020; 12 Suppl 1: 7-17.

[5] Sieberg CB, Lunde CE and Borsook D. Endometriosis and pain in the adolescent-striking early to limit suffering: a narrative review. Neurosci Biobehav Rev 2020; 108: 866-876.

[6] Jurkiewicz-Przondziono J, Lemm M, Kwiatkowska-Pamula A, Ziolko E and Wojtowicz MK. Influence of diet on the risk of developing endometriosis. Ginekol Pol 2017; 88: 96-102.

[7] Rolla E. Endometriosis: advances and controversies in classification, pathogenesis, diagnosis, and Treatment. F1000Res 2019; 8: F1000 Faculty Rev-529.

[8] Guo W, Hu S, Zeng D, Yan C, Zheng R, Gao J, Wan T, Zhuang W and Yang J. The prognostic role of ovarian endometriosis in symptomatic adenomyosis patients underwent uterine artery embolization. Ann Palliat Med 2021; 10: 2577-2583.

[9] Taneja A, Kaur S, Soni RK, Bhanupriya, Kaur J and Singla L. Evaluating the efficacy of levonorgestrel intrauterine system and danazol for relief of postoperative pain in endometriosis. J Clin Diagn Res 2017; 11: QC10-QC12.

[10] Motegi E, Hasegawa K, Kawai S, Kiuchi K, Kosaka N, Mochizuki Y and Fukasawa I. Levonorgestrel-releasing intrauterine system placement for severe uterine cervical stenosis after conization: two case reports. J Med Case Rep 2016; 10: 56.

[11] Carneiro MM, Farace BL, Ribeiro LSC, Silverio R, Moreira T, Filho A, Baroni A and Ferreira MCF. Using social media to educate women and healthcare providers on endometriosis: preliminary results. JBRA Assist Reprod 2020; 24: 9-12.

[12] Collinet P, Fritel X, Revel-Delhom C, Ballester M, Bolze P A, Borghese B, Bornsztein N, Boujenah J, Brillac T, Chabbert-Buffet N, Chauffour C, Clary N, Cohen J, Decanter C, Denouël A, Dubernard G, Fauconnier A, Fernandez H, Gauthier T, Golfier F, Huchon C, Legendre G, Loriau J, Mathieu-d'Argent E, Merlot B, Niro J, Panel P, Paparel P, Philip CA, Ploteau S, Poncelet C, Rabischong B, Roman H, Rubod C, Santulli P, Sauvan M, Thomassin-Naggara I, Torre A, Wattier JM, Yazbeck C, Bourdel N and Canis M. Management of endometriosis: CNGOF/HAS clinical practice guidelines - short version. J Gynecol Obstet Hum Reprod 2018; 47: 265-274.

[13] Higham JM, O'Brien PM and Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol 1990; 97: 734-739.

[14] Tamai H, Kinugasa M, Nishio M and Miyake M. Peritoneal inclusion cysts treated with a levonorgestrel-releasing intrauterine system: a case report. Case Rep Womens Health 2019; 22: e00113.

[15] Lagana AS, Garzon S, Gotte M, Vigano P, Franchi M, Ghezzi F and Martin DC. The pathogenesis of endometriosis: molecular and cell biology insights. Int J Mol Sci 2019; 20: 5615.

[16] Liang Y, Xie H, Wu J, Liu D and Yao S. Villainous role of estrogen in macrophage-nerve interaction in endometriosis. Reprod Biol Endocrinol 2018; 16: 122.

[17] Teasley HE, Jeong MP and Kim TH. A calcium-dependent phospholipase A2 (cPLA2) expression is regulated by MIG-6 during endometrial tumorigenesis. Biochem Biophys Res Commun 2019; 511: 129-134.

[18] Muhammad Yusoff F, Wong KK and Mohd Redzwan N. Th1, Th2, and Th17 cytokines in systemic lupus erythematosus. Autoimmunity 2020; 53: 8-20.

[19] Sun J, Zheng Y, Mamun M, Li X, Chen X and Gao Y. Research progress of PD-1/PD-L1 immunotherapy in gastrointestinal tumors. Biomed Pharmacother 2020; 129: 110504.

[20] Marquardt RM, Kim TH, Shin JH and Jeong JW. Progesterone and estrogen signaling in the endometrium: what goes wrong in endometriosis? Int J Mol Sci 2019; 20: 3822.

[21] Patel BG, Rudnicki M, Yu J, Shu Y and Taylor RN. Progesterone resistance in endometriosis: origins, consequences and interventions. Acta Obstet Gynecol Scand 2017; 96: 623-632.

[22] Zheng W, Wu J, Gu J, Weng H, Wang J, Wang T, Liang X and Cao L. Modular characteristics and mechanism of action of herbs for endometriosis treatment in Chinese medicine: a data

mining and network pharmacology-based identification. Front Pharmacol 2020; 11: 147.
[23] Shan J, Cheng W, Zhai DX, Zhang DY, Yao RP, Bai LL, Cai ZL, Liu YH and Yu CQ. Meta-analysis of Chinese traditional medicine bushen huoxue prescription for endometriosis treatment. Evid Based Complement Alternat Med 2017; 2017: 5416423.
[24] Abdul Karim AK, Abd Aziz NH, Md Zin RR, Mohd Mokhtar N and Shafiee MN. The effect of surgical intervention of endometriosis to CA-125 and pain. Malays J Med Sci 2020; 27: 7-14.
[25] Cacciottola L, Donnez J and Dolmans MM. Can endometriosis-related oxidative stress pave the way for new treatment targets? Int J Mol Sci 2021; 22: 7128.
[26] Zhang T, Yang Y, Wang B, Zheng X, Wang L, Feng X, Li G, Shi J and Cao N. Meta-analysis of influences of biejiajian pill combined with entecavir on serum liver fibrosis markers of compensatory period of hepatitis b cirrhosis: protocol of systematic review and meta-analysis. Medicine (Baltimore) 2019; 98: e18458.
[27] Dong S, Zhang J, Zhai F, Zhao X and Qin X. Comparative efficacy and safety of traditional chinese patent medicine for endometriosis: a Bayesian network meta-analysis protocol. Medicine (Baltimore) 2019; 98: e16473.