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ABOUT COVER

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The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Retrospective Study

Clinical observation of Kuntai capsule combined with Fenmotong in treatment of decline of ovarian reserve function

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statement: This manuscript was approved by the Medical Ethics Committee of Zhanjiang Central Hospital.

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Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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Abstract

BACKGROUND

Decreased ovarian reserve function is an ovarian hypofunction disease that occurs in women before 40 years of age, leading to a decline in fertility and perimenopausal symptoms, such as irregular menstruation, amenorrhea, infertility, decreased libido, and autonomic nervous dysfunction. Fenmatong (FMT) is a compound mixture of estradiol tablets and estradiol didroxyprogesterone tablets, which can improve ovarian reserve function by supplementation of exogenous estrogen. However, this treatment has also been shown to cause breast pain, gastrointestinal discomfort, irregular vaginal bleeding, and changes in sexual desire. In severe cases, FMT can promote the development of breast cancer, endometrial cancer, and venous embolic disease.

AIM

To observe the effects of Kuntai capsules and FMT on endocrine indexes and uterine artery blood circulation in patients with decreased ovarian reserve function.

METHODS

Patients (130) with decreased ovarian reserve function, who were treated in our hospital from May 2018 to May 2020, were divided into two groups: The FMT group, in which patients were treated with FMT, and the observation group, in which patients were treated with Kuntai capsules. Chinese medicine symptom scores, uterine artery blood flow parameters, ovarian ultrasound test indexes, pictorial blood loss assessment chart (PBAC) scores, and hormone levels were recorded, and total effective rates were calculated for both groups.

RESULTS

The total effective rate in the observation group was higher than that in the FMT group ($P < 0.05$). After treatment, primary symptoms, including low menstrual

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volume, delayed menstruation, red color and thick consistency of menses, dizziness, palpitation, weakness at the waist and knee, insomnia and excessive dreaming, irritability, and dryness and astringency of the pudendal canal in the observation group decreased, and scores for primary and secondary symptoms in the observation group were significantly lower than those in the FMT group ($P < 0.05$). The systolic peak flow rate (PSV), end-diastolic flow rate (EDV), ovarian diameter, sinus follicle count, and resistance index (RI) of the uterine arteries in the observation group and FMT group increased after treatment. Notably, the PSV, EDV, ovarian diameter, and antral follicle count in the observation group were higher than those in the FMT group, whereas the RI in the observation group was lower than that in the FMT group ($P < 0.05$). The PBAC scores in the observation and FMT groups increased after treatment, with that in the observation group becoming significantly higher than that in the FMT group ($P < 0.05$). After treatment, estradiol (E2) and anti-Müllerian hormone (AMH) levels increased, whereas follicle-stimulating hormone (FSH) levels decreased in the observation group and FMT group; E2 and AMH levels became significantly higher and FSH levels became significantly lower in the observation group than in the FMT group ($P < 0.05$).

CONCLUSION

Compared with FMT, Kuntai capsules promoted uterine artery blood circulation, improved menstruation, relieved symptoms, regulated endocrine function, and improved curative effects.

Key Words: Kuntai capsule; Fenmatong; Ovarian reserve function decline; Endocrine index; Blood circulation

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Core Tip: This paper verified that Kuntai capsule combined with Fenmatong in the treatment of decreased ovarian reserve function can promote uterine artery blood circulation, improve menstruation, alleviate symptoms, regulate endocrine and improve the curative effect.

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INTRODUCTION

According to the theory of traditional Chinese medicine (TCM), decreased ovarian reserve function belongs to the categories of "blood exhaustion", "early break of menopause," and "syndrome before and after menopause". The kidneys dominate reproduction, kidney qi filling and kidney essence deficiency lead to Tianguai failure, and blood stasis blocks collaterals. The syndrome of deficiency and excess is caused by a lack of liver qi. The principle of treatment is to nourish the liver and kidney, calm the mind, and eliminate stress. Kuntai capsules are a commonly used proprietary Chinese medicine in the clinical treatment of menopause and postmenopausal syndromes[1-3]. Although this treatment has been shown to alleviate symptoms[4], few studies have evaluated the mechanisms of action of this treatment[5-10].

In this study, we evaluated the effects of Kuntai capsules compared with FMT on endocrine indexes and uterine artery blood circulation in patients with decreased ovarian reserve function.

MATERIALS AND METHODS

General information

In total, 130 patients with decreased ovarian reserve function treated in our hospital from May 2018 to May 2020 (28–40 years old; mean \pm standard deviation: 33.88 ± 4.18 years) were divided into two groups according to the treatment plan after admission. There were no significant differences in general demographic characteristics between the two groups ($P > 0.05$; Table 1).

Diagnostic criteria

Decreased ovarian reserve function was defined according to the criteria defined by the Chinese Obstetrics and Gynecology committee[11–15], as follows: Less than 40 years of age; follicle-stimulating hormone (FSH) levels 15–25 IU and basic luteinizing hormone FSH greater than or equal to 2–3.6; menstruation disorders and rare menstruation occurring for more than 4 mo; and ultrasound showing fewer than five follicles in the ovary.

Syndrome differentiation for TCM was consistent with the standard of yin deficiency of the liver and kidney in the Diagnostic Efficacy Standard of TCM Diseases; the primary symptoms were reduced menstruation, delayed menstruation or amenorrhea, and discharge of a thick red substance, whereas secondary symptoms were dizziness and palpitations, sore waist and knees, insomnia and excessive dreaming, dryness of the vulva, irritability, and weak pulse.

Inclusion and exclusion criteria

The inclusion criteria were as follows: Diagnosed with decreased ovarian reserve function according to the above-listed criteria; TCM syndrome differentiation of liver and kidney yin deficiency syndrome; age greater than or equal to 18 years old and less than or equal to 40 years old; not taking other drugs; and complete clinical data available.

The exclusion criteria were as follows: History of endocrine drug use within the 3 mo prior to enrollment in the study; presence of pelvic infection, uterine fibroids, endometrial lesions, or other gynecological diseases; history of hyperandrogenemia, hyperthyroidism, hypothyroidism, or other endocrine diseases; presence of important organ diseases or hematopoietic, respiratory, and immune system diseases; and allergies to the study medications or components.

Methods

Patients in the FMT group were treated with a compound mixture of estradiol tablets and estradiol didroxyprogesterone tablets (trade name: Fenmatong; Dutch Abbott Biologicals B.V.; 2/10 mg; registration number H20150345), oral white tablets (containing estradiol 1 mg) once per day for 14 d before the menstrual cycle, and gray tablets (containing estradiol 1 or 10 mg) once a day during the last 14 d of the menstrual cycle; the course of treatment was 28 d, and three consecutive courses of treatment were administered. Patients in the observation group were treated with Kuntai capsules (Guiyang Xintian Pharmaceutical Co., Ltd.; 0.5 g; Chinese medicine no. Z20000083) at a dose of four tablets per treatment, three times per day; the course of treatment was 28 days, and three consecutive courses of treatment were administered.

Detection method

Uterine artery blood flow parameters, including the systolic peak flow rate (PSV), end-diastolic flow rate (EDV), resistance index (RI), ovarian diameter, and antral follicle count were measured by ultrasound before and after three courses of treatment. The patients were instructed to avoid urination until collection, and the above indexes were evaluated in urine samples using a Philips IE33 color Doppler ultrasound with a probe frequency of 3.5 MHz.

The levels of serum sex hormone estradiol (E2), anti-Müllerian hormone (AMH), and FSH were detected *via* radioimmunoassay before treatment and on days 2–3 of the menstrual cycle. In the morning, 3 mL venous blood was collected from patients after fasting overnight and centrifuged at 3000 rpm for 10 min. The above indexes were detected using Roche E601 chemiluminescence immunoassays and a kit from Nanjing Jiancheng Bioengineering Institute.

Table 1 Comparison of two groups of general data (*n* = 65)

Group	Age	Course of disease	Number of pregnancies	Pregnancy times (times)	BMI (kg/m ²)
Fenmatong group	34.02 ± 3.89	3.45 ± 0.61	2.05 ± 0.36	1.32 ± 0.28	23.17 ± 1.24
Observation group	33.74 ± 4.29	3.38 ± 0.57	1.98 ± 0.45	1.37 ± 0.26	23.06 ± 1.48
<i>t</i>	0.390	0.676	0.979	1.055	0.459
<i>P</i> value	0.697	0.500	0.329	0.293	0.647

BMI: Body mass index.

Analysis of curative effects

After the treatment course, the treatments were assessed as being highly effective, wherein symptoms such as menstrual disorder, rare menstruation, vaginal dryness, and decreased libido disappeared, E2 Levels returned to normal, and FSH levels decreased by at least 50%; effective, wherein the above symptoms improved, E2 Levels improved but did not reach normal, and FSH levels decreased by 20% to 50%; or ineffective, wherein the above criteria were not met.

Scoring standard

TCM symptom scores were evaluated before treatment and 4 wk after treatment based on the Therapeutic Effect Criteria for Disease and Syndrome Diagnosis of TCM, including primary and secondary symptoms. The severity of symptoms was classified as none, mild, moderate, or severe, with scores of 0 to 6 for primary symptoms and 0 to 3 for secondary symptoms.

Pictorial blood loss assessment chart (PBAC) scores for menstrual bleeding were evaluated before treatment and 4 wk after treatment, according to the common score of blood staining degree and lost blood clotting for a single sanitary napkin. The blood staining degree was calculated as follows: 1, blood staining area less than or equal to 1/3; 5, blood staining area between 1/3 and 3/5; and 20, blood staining of the entire sanitary napkin. Lost blood clot:

Statistical methods

The data were processed using SPSS19.0, and quantitative indexes were described as means and standard deviations. Student's *t*-tests and χ^2 tests were used to compare quantitative data.

RESULTS

Comparison of curative effects between the two groups

In the observation group, highly effective treatment was observed for 47 cases (72.31%), whereas effective treatment was observed for 14 cases (21.54%). The total effective rate was 93.85%, which was higher than that in the FMT group (32 cases of highly effective treatment, 21 cases of effective treatment; total effective rate of 81.54%); this difference was statistically significant ($P < 0.05$; Table 2).

Comparison of TCM symptom scores between the two groups

Before treatment, TCM syndrome scores did not differ significantly between the observation group and FMT group ($P > 0.05$). After treatment, scores for primary symptoms, such as low menstrual flow, delayed menstruation, thick red discharge, dizziness, heart palpitations, weakness of the waist and knees, insomnia, excessive dreaming, and irritability, and scores for secondary symptoms, such as genital dryness, were significantly lower in the observation group than in the FMT group ($P < 0.05$; Table 3).

Comparison of uterine artery blood flow parameters and ovarian ultrasound detection indicators in the two groups

Before treatment, there were no significant differences in uterine artery blood flow parameters and ovarian ultrasound detection indexes between the observation and FMT groups ($P > 0.05$). After treatment, the PSV and EDV of the uterine artery

Table 2 Comparison of curative effects between the two groups [$n = 65$, n (%)]

Group	Significant effect	Effective	Invalid	Total efficiency
Fenmatong group	32 (49.23)	21 (32.31)	12 (18.46)	53 (81.54)
Observation group	47 (72.31)	14 (21.54)	4 (6.15)	61 (93.85)
χ^2				4.561
P value				0.033

Table 3 Comparison of traditional Chinese medicine syndrome scores between the two groups (mean \pm SD, scores)

Group	n	Less menstruation		Delayed menstruation		The color is red and thick		Dizziness and palpitations	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Fenmatong group	65	4.63 \pm 1.14	2.03 \pm 0.75	4.37 \pm 1.23	1.89 \pm 0.64	4.12 \pm 1.05	1.95 \pm 0.54	2.36 \pm 0.54	1.32 \pm 0.39
Observation group	65	4.59 \pm 1.07	1.27 \pm 0.59	4.39 \pm 1.21	1.04 \pm 0.37	4.18 \pm 0.97	1.12 \pm 0.38	2.41 \pm 0.47	0.87 \pm 0.31
t		0.206	6.421	0.093	9.270	0.338	10.134	0.563	7.282
P value		0.837	0.000	0.426	0.000	0.736	0.000	0.574	0.000
Group	n	Sore waist and knees		Insomnia and dreaminess		Irritable		Pudendal dryness	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Fenmatong group	65	2.27 \pm 0.43	1.37 \pm 0.37	1.97 \pm 0.37	1.21 \pm 0.29	2.08 \pm 0.35	1.09 \pm 0.28	1.86 \pm 0.44	1.03 \pm 0.32
Observation group	65	2.31 \pm 0.37	0.87 \pm 0.49	2.03 \pm 0.41	0.74 \pm 0.23	2.11 \pm 0.37	0.79 \pm 0.25	1.81 \pm 0.46	0.58 \pm 0.27
t		0.568	6.565	0.876	10.238	0.475	6.444	0.633	8.665
P value		0.571	0.000	0.383	0.000	0.636	0.000	0.528	0.000

increased in the observation group, whereas the ovarian diameter and antral follicle count increased and the RI decreased in the FMT group. Additionally, in the observation group, the PSV (38.96 ± 3.11 cm/s), EDV (15.89 ± 1.57 cm/s), ovarian diameter (2.64 ± 0.14 cm), and antral follicle count (4.91 ± 0.43) were higher, whereas the RI (0.73 ± 0.10) was lower than those in the FMT group ($P < 0.05$; Table 4).

Comparison of PBAC scores between the two groups

The PBAC scores increased in both groups after treatment, and the PBAC score in the observation group was higher than that in the FMT group ($P < 0.05$; Table 5).

Comparison of hormone levels between the two groups

After treatment, E2 and AMH levels increased, whereas FSH levels decreased in both groups. In the observation group, E2 (57.96 ± 5.17 pg/mL) and AMH (0.29 ± 0.09 ng/mL) levels were higher than those in the FMT group, whereas FSH levels (10.14 ± 1.57 IU/L) were lower than those in the FMT group ($P < 0.05$). Additionally, the total effective rate in the observation group was higher than that in the FMT group ($P < 0.05$; Tables 6 and 7).

Safety analysis

None of the 130 patients had adverse reactions, such as abnormal echocardiograms, abnormal liver and kidney functions, or allergic reactions.

DISCUSSION

The mechanism of decline in ovarian reserve function is complex and related to heredity, immunity, environment, diet, psychological factors, repeated abortion,

Table 4 Comparison of uterine artery blood flow parameters between the two groups ($n = 65$, mean \pm SD)

Group	PSV (cm/s)		EDV (cm/s)		RI	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Fenmatong group	30.85 \pm 3.14	35.42 \pm 3.36	5.24 \pm 1.14	12.19 \pm 1.45	0.87 \pm 0.10	0.81 \pm 0.08
Observation group	30.41 \pm 3.52	38.96 \pm 3.11	5.30 \pm 1.07	15.89 \pm 1.57	0.86 \pm 0.13	0.73 \pm 0.10
<i>t</i>	0.752	6.234	0.309	13.958	0.492	5.036
<i>P</i> value	0.453	0.000	0.758	0.000	0.624	0.000

PSV: Systolic peak flow rate; EDV: End-diastolic flow rate.

Table 5 Comparison of ultrasonic detection indexes of ovaries between the two groups ($n = 65$, mean \pm SD)

Group	Ovarian diameter(cm)		Antral follicle count	
	Before treatment	After treatment	Before treatment	After treatment
Fenmatong group	2.56 \pm 0.12	2.60 \pm 0.10	3.08 \pm 0.57	4.64 \pm 0.51
Observation group	2.57 \pm 0.13	2.64 \pm 0.14	3.12 \pm 0.53	4.91 \pm 0.43
<i>t</i>	0.456	1.874	0.414	3.263
<i>P</i> value	0.649	0.063	0.679	0.001

Table 6 Comparison of pictorial blood loss assessment chart scores between the two groups ($n = 65$, mean \pm SD)

Group	PBAC score	
	Before treatment	After treatment
Fenmatong group	18.14 \pm 2.98	21.74 \pm 3.06
Observation group	17.95 \pm 3.15	23.45 \pm 2.77
<i>t</i>	0.353	3.340
<i>P</i> value	0.724	0.001

PBAC: Pictorial blood loss assessment chart.

Table 7 Comparison of hormone levels between the two groups ($n = 65$)

Group	FSH (IU/L)		E2 (pg/mL)		AMH (ng/mL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Fenmatong group	18.21 \pm 2.44	13.78 \pm 2.06	25.38 \pm 3.24	44.23 \pm 4.05	0.22 \pm 0.05	0.26 \pm 0.07
Observation group	18.14 \pm 2.26	10.14 \pm 1.57	24.89 \pm 4.77	57.96 \pm 5.17	0.21 \pm 0.08	0.29 \pm 0.09
<i>t</i>	0.170	11.330	0.685	16.855	0.855	2.121
<i>P</i> value	0.866	0.000	0.495	0.000	0.394	0.036

FSH: Follicle-stimulating hormone; E2: Estradiol; AMH: Anti-Mullerian hormone.

improper contraceptive methods, and chronic ovarian diseases, among other factors [16-18]. The incidence of decline in ovarian reserve function caused by increases in life and work pressures placed on modern women is increasing every year, with a tendency to occur at younger ages. Abrahams *et al* [19] believe that unexplained infertility in young women may be a risk signal for decreased ovarian reserve function and can be used as a quantitative rather than qualitative risk factor [19]. In a cohort study, Yücel *et al* [20] found that the decline in ovarian reserve function may be an

undiagnosed cause of unexplained infertility. In Western medicine, estrogen and progesterone replacement therapy is the first-line treatment for ovarian function decline, and FMT is a representative drug used for such treatment. Supplementation with exogenous estrogen and progesterone can inhibit the release of FSH and restore follicular development and ovulation through a negative feedback mechanism. The Leeangkoonasathian *et al*[21]' study suggested that estrogen and progesterone supplementation could improve the sleep quality of postmenopausal women.

In this study, we found that treatment with Kuntai capsules combined with FMT was associated with improved menstruation, reduced menstruation, delayed menstruation, thick red discharge, dizziness and palpitations, sore waist and knees, insomnia and excessive dreaming, irritability, pudendal dryness, and other symptoms. The mechanisms may be related to the effects of FMT on regulating the hypothalamus-pituitary-ovary axis through negative feedback by supplementation with estrogen and progesterone to promote follicular development and ovulation[21]. Water extracts of cooked *Rehmannia glutinosa* in Kuntai capsules can regulate the response of the human body to gonadotropin and modulate endometrial receptivity. Moreover, donkey-hide gelatin can promote the function of the hematopoietic system, regulate calcium balance, improve autonomic nervous function, and alleviate symptoms of the perimenopausal period. Berberine in *Coptis chinensis* and baicalin in *Scutellaria baicalensis* Georgi not only have antipathogenic effects but also have anti-inflammatory, antipyretic, sedative, and hypnotic effects. β -Sitosterol contained in *Radix Paeoniae Alba* has pharmacological effects, such as hypolipidemic, anti-inflammatory, and antitumor effects. *Poria cocos* can increase the level of sex hormone secretion and protect the secretory function of the ovary.

The decrease in blood supply to the uterus and ovary is an important cause of decreased ovarian reserve function. Some researcher studied the effects of ovarian blood supply on ovarian function in healthy hybrid adult female dogs. Ligation of ovarian vessels caused a continuous decrease in 17β -estradiol and progesterone in experimental animals as well as follicular necrosis and fibrosis of ovarian tissue. These findings suggest that ligation of ovarian vessels should be used as an alternative to ovariectomy. In the current study, we found that Kuntai capsules combined with FMT promoted uterine artery blood circulation, improved ovarian blood supply, prevented ovarian atrophy, and facilitated follicle formation, as demonstrated by detection of uterine artery PSV and EDV, RI, ovarian diameter, and antral follicle counts before and after treatment. This is because TCMs in Kuntai capsules that promote blood circulation and tonify blood, such as *Rehmannia glutinosa* and Ejiao, can dilate the uterine artery, reduce vascular resistance, increase local blood perfusion, and reduce ischemic injury to the uterus and ovary, which is beneficial to the recovery of ovarian function.

E2 is produced by granulosa cells of growing follicles and is a common index used to monitor follicular growth and ovarian reserve function. AMH is a glycoprotein secreted by primary follicles, preantral follicles, and antral follicular granulosa cells that can inhibit the activation of primordial follicles and slow the rate of ovarian reserve depletion. Because early follicular secretion of AMH is not regulated by FSH and the level of AMH is relatively stable throughout the menstrual cycle, AMH is used as a relatively objective index for evaluation of ovarian function. FSH is a sex hormone secreted by the pituitary under stimulation of hypothalamic gonadotropin-releasing hormone, which is regulated by negative feedback of E2 and inhibin B. Increases FSH levels can lead to early collection of follicles and shortening of the menstrual cycle. In this study, we found that Kuntai capsules combined with FMT regulated endocrine function in the treatment of decreased ovarian reserve function, as demonstrated by detection of the above hormone indexes. These findings provided important insights into the mechanisms through which Kuntai capsules and FMT improved ovarian reserve function.

CONCLUSION

In this study, we found that Kuntai capsules combined with FMT for the treatment of decreased ovarian reserve function promoted uterine artery blood circulation, improved menstruation, alleviated symptoms, regulated endocrine function, and improved curative effects. However, we only included patients with decreased ovarian reserve function, and not all patients had fertility problems. Therefore, we did not observe pregnancy and delivery rates for the patients after treatment. Therefore, in future clinical studies, patients with fertility problems can be screened to further explore whether Kuntai capsules combined with FMT could increase fertility rates in

the treatment of ovarian reserve function decline.

ARTICLE HIGHLIGHTS

Research background

Decreased ovarian reserve function, also known as premature ovarian failure, is characterized by a decrease in the level of estrogen in the body, resulting in a series of low-estrogen symptoms that adversely affect the physical and mental health of patients.

Research motivation

From the direction of traditional Chinese medicine (TCM) to find ways to treat the decline of ovarian reserve.

Research objectives

This study aimed to observe the clinical manifestations of Kuntai capsule combined with Femotong in treating decline of ovarian reserve function.

Research methods

Patients (130) with decreased ovarian reserve function, were divided into two groups: The FMT group, and the observation group, in which patients were treated with Kuntai capsules. The clinical indexes including TCM symptom score and uterine artery blood flow parameters were recorded, and the total effective rate of the two groups was counted.

Research results

The total effective rate in the observation group was higher than that in the FMT group ($P < 0.05$). Secondary symptoms decreased in both groups, and the scores of primary and secondary symptoms in the observation group were lower than those in the femoston group ($P < 0.05$). The observation group was more conducive to promoting uterine artery blood circulation, improving ovarian blood supply, preventing ovarian atrophy, and facilitating follicular formation.

Research conclusions

Effect of Kuntai capsule combined with femoston on ovarian reserve function decline is better than that of femoston alone.

Research perspectives

Therefore, we did not observe pregnancy and delivery rates for the patients after treatment. Therefore, in future clinical studies, patients with fertility problems can be screened to further explore whether Kuntai capsules combined with FMT could increase fertility rates in the treatment of ovarian reserve function decline.

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