

# Gongning granules plus low dose hormone in pubertal functional uterine hemorrhage: Analysis of hemodynamics and clinical efficacy

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**Abstract:** To evaluate the clinical effect of *Gongning* granules combined with low-dose hormone therapy in pubertal dysfunctional uterine bleeding (PDUB) and its effect on uterine hemodynamics. A total of 164 PDUB patients who were treated in the gynecological outpatient department of our hospital from December 2018 to June 2020 were randomized into study group and control group, with 82 cases each. The control group received estrogen progesterone, and the study group received *Gongning* granules plus. The clinical efficacy and uterine arterial hemodynamics were compared. The clinical efficacy of the study group was superior to the control group (91.46% vs. 76.83%,  $P < 0.05$ ). The study group yielded shorter bleeding control time and complete hemostasis time than the control group ( $P < 0.05$ ). The amount of menstrual bleeding and duration of menstruation in both groups decreased significantly with time and the study group was significantly lower than the control group (all  $P < 0.05$ ). The endometrial thickness in the study group was significantly thinner than the control group, and the maximum follicle diameter was significantly longer than that in the control group (all  $P < 0.05$ ). After treatment, the platelet count, hemoglobin level of peripheral blood, uterine arterial blood flow and mean flow velocity in the study group were significantly higher than those in the control group (all  $P < 0.05$ ). In addition, there was no significant difference in adverse drug reaction (ADR) between the two groups ( $P > 0.05$ ). In PDUB patients, *Gongning* granules plus low-dose hormone can significantly relieve bleeding symptoms, improve hemodynamic status and has good safety.

**Keywords:** Functional uterine bleeding, gongning granules, progesterone sequential therapy, hemodynamics.

## INTRODUCTION

Pubertal dysfunctional uterine bleeding (PDUB) is a condition of uterine bleeding caused by ovarian dysfunction, with a strong predominance in female gender from 13 to 18 years old. The principal presentations are irregular vaginal bleeding, abnormal menstrual flow, and long menstrual periods (Deligeoroglou *et al.*, 2013; Yaşa and Güngör Uğurlucan, 2020). PDUB is a kind of anovulatory dysfunctional uterine bleeding, which belongs to the category of abnormal uterine bleeding. The possible cause is that the immature ovarian function and ovulation mechanism in adolescence, plus the pressure of study, mental stress or intense exercise, nutritional disorders, etc. lead to ovarian dysfunction, abnormal secretion of sex hormones and irregular vaginal bleeding (O'Brien, 2018). A combination of progesterone and small doses of estrogen for PDUB, can not only overcome the shortcomings of single progesterone therapy, but also reduce the dosage of progesterone and prevent breakthrough bleeding. However, in spite of its numerous benefits, an array of adverse events such as obesity, premature bone healing and breakthrough bleeding may arise (Deligeoroglou and Creatas, 2015; Klein and Phillips, 2019). Traditional Chinese medicine (TCM) classifies “dysfunctional bleeding” into the category of “metrorrhagia”. TCM believes that it should be attributed

to deficient kidney *qi*, or imbalanced *yin* and *yang* and strained heart and liver due to study stress; or congenital insufficient kidney *qi* and lack of kidney essence (Jin and Ma, 2008). *Gongning* granules play a crucial role in promoting blood circulation, removing blood stasis, clearing away heat and pain, stopping bleeding and consolidating menstruation. The purpose of this study was to investigate the effect of *Gongning* granule combined with low-dose hormone therapy in PDUB and its effect on uterine hemodynamics.

## MATERIALS AND METHODS

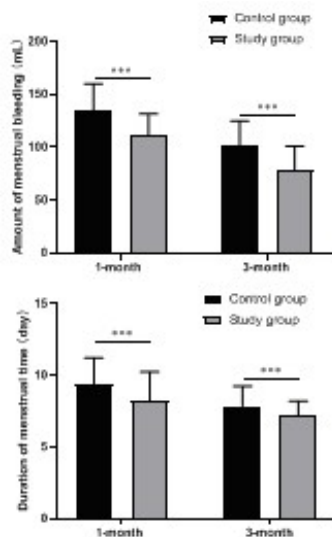
### Participants

A total of 164 PDUB patients treated in our hospital's gynecological clinic from December 2018 to June 2020 were divided into study group and control group by random number table, 82 cases each. Inclusion criteria: (1) Met the diagnostic criteria of PDUB (LaCour *et al.*, 2010); (2) Aged 12-18 years; (3) Unmarried, asexual life. Exclusion criteria: (1) Reproductive system diseases such as ovaries and uterus; (2) Blood system diseases such as anemia and coagulopathy caused by other reasons; (3) Severe liver and kidney dysfunction. Informed consents have been obtained from patients and guardians prior to the enrollment. There was no evident disparity in the baseline information between the two groups, as shown in table 1.

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### Treatment

All patients completed relevant examinations after admission, and regularly reviewed liver and kidney functions and blood routines. The control group was treated with estrogen 7yuand progesterone and the specific is as follows: Dydrogesterone tablets (specification: 10mg\*20 tablets; manufacturer: Abbott Biologicals BV; approval number: H20170221), oral, twice a day, 10mg/time; Desogestrel ethinyl estradiol tablets (specification: 0.15mg/30µg\*21 tablets; manufacturer: NVOrganon.; Approval number: H20171176), oral, 2 times a day, 0.30mg/time. The study group was given *Gongning* granules on the above basis (specification: 10 g/bag; manufacturer: Zhejiang Aisheng Pharmaceutical Co., Ltd.; Approval number: Z20010177), orally, one bag once, 3 times a day. Both groups of patients were treated for 3 months.



**Fig. 1:** Comparison of uterine bleeding between the two groups, \*\*\*means  $P < 0.001$

### Observation indicators

(1) Clinical efficacy. Cured was considered if there was no abnormal bleeding during the treatment and regular menstruation occurred and ovulation returned to normal ( $\geq 6$  times) after the treatment; markedly effective was deemed if there was no abnormal bleeding during the treatment, and regular menstruation occurred and ovulation returned to normal (3~6 times) after the treatment; effective was declared if there was a small amount of bleeding during the treatment and regular menstruation occurred and ovulation returned to normal (1~3 times); ineffective was considered if there was abnormal bleeding during treatment, and regular menstruation didn't occur and ovulation did not return to normal after treatment. The total effective rate = (cured + markedly effective + effective) / total number of cases  $\times 100\%$ . (2) The bleeding control time and complete hemostasis time were compared between the two groups. (3) The menstrual conditions of 1 month and 3 months

after treatment, including menstrual bleeding and menstrual duration were compared between the two groups. (4) B-ultrasound indicators during ovulation. On the 21st day of the 1st menstrual cycle after the treatment, B-ultrasound was used to monitor the maximum follicle diameter and endometrial thickness during ovulation. (5) Uterine hemodynamic indicators. The hemodynamic index test items include uterine artery blood flow and average flow velocity. Voluson 730 ProV color Doppler ultrasound diagnostic apparatus was used to determine the indicators. (6) Anemia. After treatment, an automatic blood cell analyzer was used to determine the patient's peripheral blood platelet count and hemoglobin content to assess the patient's anemia. (7) Adverse reactions. During treatment, adverse reactions such as headache, nausea, mood changes, abnormal leucorrhea and breast pain were evaluated and recorded to calculate the incidence of adverse reactions.

### Ethical approval

This study was reviewed by the hospital Ethics Committee vide approval No. 2017-220-12.

### STATISTICAL ANALYSIS

SPSS 23.0 software was applied to statistically analyze the data and Graph Pad Prism 9.0 software was used to plot graphics. Measurement data were expressed as (mean  $\pm$  standard deviation), independent sample t-test and paired t-test were used for comparison between groups and at different times within groups, respectively. The enumeration data were represented by [n(%)], and the chi-square test was used to examine the difference. A  $P$ -value of 0.05 or lower was declared as statistical significance.

### RESULTS

#### Comparison of clinical efficacy between the two groups

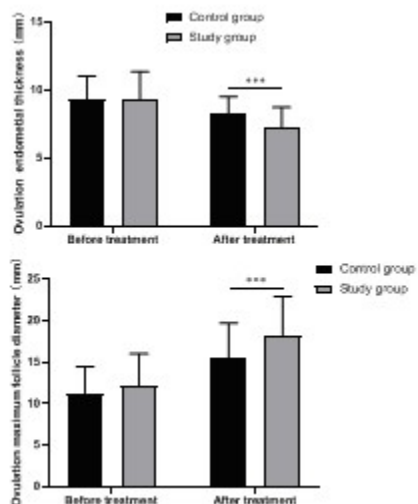
As shown in table 2, in the control group, 21 cases were cured, 28 cases were markedly effective, 14 cases were effective and 19 cases were ineffective and the total effective rate was 76.83% (63/82); while in the study group, these figs. were 30, 22, 23 and 7 respectively, and the total effective rate was 91.46% (75/82). Altogether, and the total clinical effective rate of the study group was significantly higher than that of the control group ( $P < 0.05$ ).

#### Comparison of bleeding control time and complete hemostasis time between the two groups

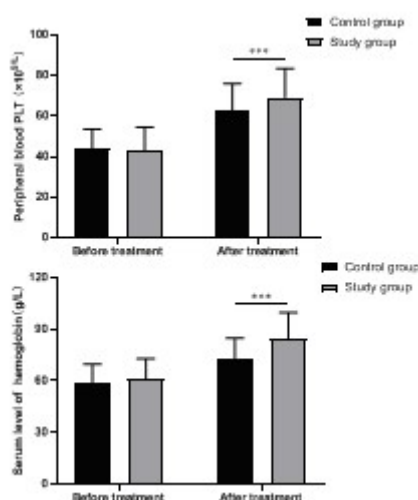
Table 3 shows that the bleeding control time and complete hemostasis time in the control group were  $25.77 \pm 3.45$ h and  $29.35 \pm 2.95$ h, respectively; while those in the study group were  $22.35 \pm 2.94$ h and  $26.42 \pm 2.84$ h, respectively. The bleeding control time and complete hemostasis time in the study group were significantly shorter than those in the control group ( $P < 0.05$ ).

### Comparison of menstrual conditions between the two groups of patients after treatment

Fig. 1 displays that 1 month and 3 months after treatment, the amount of menstrual bleeding and menstrual duration of the two groups of patients decreased significantly with time and the decrease in the study group was more remarkable than the control group ( $P < 0.05$ ).



**Fig. 2:** Comparison of B-ultrasound indicators during ovulation between the two groups, \*\*\*means  $P < 0.001$



**Fig. 3:** Comparison of anemia between the two groups of patients, \*\*\* means  $P < 0.001$

### Comparison of B-ultrasound indicators during ovulation between the two groups

On the 21<sup>st</sup> day of menstruation, B-ultrasound was used to monitor the maximum follicle diameter and endometrial thickness during ovulation. As shown in fig. 2, there was no significant difference in the maximum follicle diameter and endometrial thickness between the two groups of patients during ovulation before treatment ( $P > 0.05$ ); after treatment, the endometrial thickness of the two groups decreased drastically and the study group was evidently lower in comparison with the control group; the

maximum follicle diameters were substantially increased and the study group was considerably larger than the control group ( $P < 0.05$ ).

### Comparison of anemia between the two groups

Before treatment, there was no significant difference in the peripheral blood platelet count and hemoglobin level between the two groups of patients ( $P > 0.05$ ); after treatment, the above indicators of the two groups were markedly increased and the study group was apparently higher than the control group ( $P < 0.05$ , fig. 3).

### Comparison of hemodynamic indicators between the two groups

Prior to treatment, no significant difference was observed between the two groups of patients' uterine arterial blood flow and average flow velocity ( $P > 0.05$ ); after treatment, the above indicators were strikingly increased and the study group was distinctly higher than the control group ( $P < 0.05$ ), as presented in table 4.

### Comparison of the incidence of adverse reactions between the two groups of patients

The control group had 2 cases of headache, 1 case of nausea, 2 cases of mood changes, 3 cases of abnormal vaginal discharge, and 2 cases of breast pain. The total adverse reaction rate was 12.20% (10/82); the study group had 1 case of headache, 21 cases of nausea, 1 case of mood changes, 2 cases of leucorrhoea, and 1 case of breast pain. The overall adverse reaction rate was 8.54% (7/82). There was no statistically significant difference in adverse reactions between the two groups of patients ( $P = 0.442$ ), as listed in table 5.

## DISCUSSION

Functional uterine bleeding refers to bleeding from the uterine cavity that does not meet the normal parameters of the menstrual cycle, duration, and bleeding volume of normal menstruation. Adolescence is a vulnerable population with a high incidence of functional uterine bleeding. On the one hand, due to the undeveloped hypothalamus-pituitary ovarian axis (HPO) in adolescence, ovulation is not regular and dysfunctional uterine bleeding is prone to occur (Elmaoğulları and Aycan, 2018). In addition, adolescent girls are susceptible to high learning pressure, poor sleep quality and prone to endocrine disorders. Discouragingly, due to the lack of knowledge about the disease, it always evolves to moderate to severe anemia and even endometrial disease when seeking diagnosis and treatment, considerably impeding the normal life and study of patients (Deligeoroglou and Karountzos, 2017; Kazmi and Gupta, 2015; Puttemans et al., 2017). HPO will gradually develop when approaches adulthood, thereby conservative treatments such as hemostasis, adjustment of menstrual cycle, correction of anemia and maintenance of normal

**Table 1:** Comparison of baseline information of the two groups of patients

	Control group (n=82)	Study group (n=82)	t	P
Age (year)	14.17±3.82	13.29±3.48	1.542	0.125
Course of disease (d)	25.22±4.54	23.97±5.32	1.618	0.108
Age at menarche (year)	13.46±1.15	13.72±1.29	1.362	0.175
BMI (kg/m <sup>2</sup> )	22.46±3.21	21.94±3.62	0.973	0.332

**Table 2:** Comparison of clinical efficacy between the two groups of patients

	Cured	Markedly effective	Effective	Ineffective	Total effective rate
Control group (n=82)	21	28	14	19	63 (76.83)
Study group (n=82)	30	22	23	7	75 (91.46)
t	10.04				6.582
P	0.018				0.010

**Table 3:** Comparison of bleeding control time and complete hemostasis time between the two groups (x±s, h)

	Bleeding control time	Complete hemostasis time
Control group (n=82)	25.77±3.45	29.35±2.95
Study group (n=82)	22.35±2.94	26.42±2.84
t	6.832	6.479
P	<0.001	<0.001

**Table 4:** Comparison of hemodynamic indexes between the two groups

	Blood flow volume (mL/min)		Mean flow rate (cm/s)	
	Before treatment	After treatment	Before treatment	After treatment
Control group (n=82)	112.39±18.34	122.79±22.93	11.27±2.52	13.33±2.25
Study group (n=82)	110.93±20.28	136.57±24.12	10.83±3.17	15.26±3.02
t	0.484	3.749	0.984	4.641
P	0.629	<0.001	0.327	<0.001

**Table 5:** Comparison of the incidence of adverse reactions between the two groups

	Headache	Nausea	Mood fluctuation	abnormal leukorrhea	mastodynia	Total incidence
Control group (n=82)	2	1	2	3	2	10
Study group (n=82)	1	2	1	2	1	7
$\chi^2$						0.591
P						0.442

circulation are the mainstay for PDUB (Deligeorgiou *et al.*, 2006; Urbanska *et al.*, 2019). Sequential therapy of estrogen and progesterone is a common method for PDUB. Estrogen can allow the endometrium to proliferate, and repair the shed endometrial wound. It is suitable for acute bleeding, low hemoglobin and poor general conditions, yet it easily gives rise to gastrointestinal reactions, breakthrough bleeding and thrombosis (Matytsina *et al.*, 2006). Progesterone can transform the endometrium into the secretory period and the functional layer of the endometrium is completely peeled off after suspending the drug, which can improve the stability of the endometrium (Pennesi *et al.*, 2020). Sequential therapy of estrogen and progesterone combined with small doses of estrogen can overcome the shortcomings of

single progesterone therapy, reduce the dosage of progesterone and prevent breakthrough bleeding (Kulp *et al.*, 2008; Melkozerova *et al.*, 2016; Seravalli *et al.*, 2013). In this study, *Gongning* granules combined with low-dose hormone therapy has achieved good results. The results of this study showed that the clinical efficacy of the study group was significantly higher than that of the control group; the bleeding control time and complete hemostasis time of the study group were significantly shorter than those of the control group; the menstrual bleeding volume and menstrual duration of the two groups decreased significantly over time, with the study group being more evident; the endometrial thickness of the study group was significantly lower than that of the control group during ovulation and the maximum follicle diameter was

remarkably larger than that of the control group. Furthermore, after treatment, the study group's peripheral blood platelet count, hemoglobin level, uterine artery blood flow and average flow velocity were significantly higher than the control group. Noticeably, no striking disparity in adverse reactions between the two groups was witnessed. Functional uterine bleeding belongs to the category of uterine bleeding in TCM. Its pathogenesis lies in impaired impulse and *qi* deficiency, causing irregular menstruation. It is a challenging and critical illness, and mainly treated by replenishing *qi* and relieving pain, cooling blood and removing blood stasis, and contracting uterine to stop bleeding (Liu, 2007). *Gongning* granules is a pure natural Chinese medicine preparation, composed of madder, cattail pollen, pseudo-ginseng, scutellaria, white peony, codonopsis, licorice and etc. Among them, baicalin is a flavonoid compound isolated from the medicinal plant *Scutellaria baicalensis* Georgi, with the property of anti-inflammatory and antiviral activities and can reduce swelling and dispel lumps and remove cysts. Cattail pollen and pseudo-ginseng can dissipate blood stasis and relieve pain, promote blood circulation and stimulate menstruation; Codonopsis and licorice can invigorate spleen-stomach and replenish *qi* and dispel cold; white peony and madder can cool and promote blood circulation, invigorate *qi*, relieve pain and nourish blood. The whole prescription has the effects of promoting *qi* and blood circulation, removing blood stasis and warming menstruation, dispelling cold and relieving pain, and stopping bleeding and consolidating menstruation (Lee et al., 2015). Modern pharmacology states that *Gongning* granules mainly have the following functions in PDUB. First, it plays a two-way regulation role in uterine smooth muscle, which can increase the amplitude, frequency and tension of uterine contractions, but it also exerts a relaxing effect when uterine cramps. Second, it can improve microcirculation, reducing blood viscosity and expanding tiny blood vessels. Third, it can inhibit platelet aggregation and reduce blood viscosity, further significantly improve the uterine artery blood flow and average flow velocity. *Gongning* granules follow the three major principles of TCM for treating collapse, namely, plugging the flow, clearing the source, and involuting and adhere to the rule of treating symptoms if it is emergent, otherwise treating root, with an attempt to achieve hemostasis, consolidate the root, restore ovulation and establish a normal menstrual cycle.

## CONCLUSION

In conclusion, *Gongning* granules combined with low-dose hormone therapy in PDUB can significantly improve the clinical efficacy, promote the recovery of the menstrual cycle, and improve the hemodynamic status of the uterine artery. It is worthy of further promotion and popularization.

## REFERENCES

- Deligeoroglou E and Karountzos V (2017). Dysfunctional uterine bleeding as an early sign of polycystic ovary syndrome during adolescence: An update. *Minerva Ginecol*, **69**(1): 68-74.
- Deligeoroglou E, Karountzos V and Creatsas G (2013). Abnormal uterine bleeding and dysfunctional uterine bleeding in pediatric and adolescent gynecology. *Gynecol Endocrinol*, **29**(1): 74-78.
- Deligeoroglou E, Tsimaris P, Deliveliotou A, Christopoulos P and Creatsas G (2006). Menstrual disorders during adolescence. *Pediatr Endocrinol. Rev.*, **3**(Suppl 1): 150-159.
- Deligeoroglou EK and Creatsas GK (2015). Dysfunctional uterine bleeding as an early sign of polycystic ovary syndrome during adolescence. *Minerva Ginecol*, **67**(4): 375-381.
- Elmaoğulları S and Aycan Z (2018). Abnormal Uterine Bleeding in Adolescents. *J Clin Res Pediatr Endocrinol*, **10**(3): 191-197.
- Jin NN and Ma K (2008). [Study of traditional Chinese medicine syndrome factors of dysfunctional uterine bleeding based on cluster analysis and factor analysis. *Zhongguo Zhong Yao. Za. Zhi.*, **33**(5): 1622-1625.
- Kazmi Z and Gupta S (2015). Best practice in management of paediatric and adolescent hydrosalpinges: A systematic review. *Eur. J. Obstet Gynecol Reprod Biol.*, **19**: 40-51.
- Klein KO and Phillips SA (2019). Review of hormone replacement therapy in girls and adolescents with hypogonadism. *J. Pediatr Adolesc Gynecol.*, **32**(5): 460-468.
- Kulp JL, Mwangi CN and Loveless M (2008). Screening for coagulation disorders in adolescents with abnormal uterine bleeding. *J. Pediatr. Adolesc. Gynecol.*, **21**(1): 27-30.
- LaCour DE, Long DN and Perlman SE (2010). Dysfunctional uterine bleeding in adolescent females associated with endocrine causes and medical conditions. *J. Pediatr. Adolesc. Gynecol.*, **23**(2): 62-70.
- Lee W, Ku SK and Bae JS (2015). Antiplatelet, anticoagulant and profibrinolytic activities of baicalin. *Arch Pharm Res.*, **38**(5): 893-903.
- Liu X (2007). TCM treatment for severe climacteric dysfunctional uterine bleeding--a report of 43 cases. *J. Tradit. Chin. Med.*, **27**(1): 46-48.
- Matytsina LA, Zoloto EV, Sinenko LV and Greydanus DE (2006). Dysfunctional uterine bleeding in adolescents: concepts of pathophysiology and management. *Prim Care*, **33**(2): 503-515.
- Melkozerova OA, Bashmakova NV, Volkova EV, Tretyakova TB and Tsyvian PB (2016). The molecular and genetic aspects of adolescent girls anomalous uterine bleeding: The role of endothelial dysfunction syndrome. *Gynecol Endocrinol.*, **32**(2): 23-26.
- O'Brien SH (2018). Evaluation and management of heavy

- menstrual bleeding in adolescents: The role of the hematologist. *Hematology Am. Soc. Hematol. Educ. Program.*, pp.390-398.
- Pennesi CM, Quint EH, Rosen MW, Compton SD, Odukoya EJ and Weyand AC (2020). Outpatient management of heavy menstrual bleeding in adolescent and young women with inherited platelet function disorders. *J. Pediatr. Adolesc Gynecol.*, **33**(5): 489-493.
- Puttemans P, Benagiano G, Gargett C, Romero R, Guo SW and Brosens I (2017). Neonatal uterine bleeding as a biomarker for reproductive disorders during adolescence: A worldwide call for systematic registration by nurse midwife. *J. Matern Fetal Neonatal Med.*, **30** (12): 1434-1436.
- Seravalli V, Linari S, Peruzzi E, Dei M, Paladino E and Bruni V (2013). Prevalence of hemostatic disorders in adolescents with abnormal uterine bleeding. *J. Pediatr Adolesc Gynecol.*, **26**(5): 285-289.
- Urbanska E, Hirnle L, Olszanecka-Glinianowicz M, Skrzypulec-Plinta V, Skrzypulec-Frankel A and Drosdzol-Cop A (2019). Is polycystic ovarian syndrome and insulin resistance associated with abnormal uterine bleeding in adolescents? *Ginekol Pol.*, **90**(5): 262-269.
- Yasa C and Gungor Ugurlucan F (2020). Approach to abnormal uterine bleeding in adolescents. *J. Clin. Res. Pediatr Endocrinol.*, **12**(Suppl 1): 1-6.