

# A probe into effect of Shoutai pill on endometrial receptivity

LIJUN ZHAO<sup>1\*</sup>, YANG XU<sup>1\*</sup>, XIAOLING DUO<sup>1</sup>, XIAOYING TIAN<sup>2</sup> and PENG WANG<sup>3</sup>

<sup>1</sup>Department of Gynecology and Obstetrics, The Fifth People's Hospital of Jinan, Jinan, Shandong 250022;

<sup>2</sup>Medical School of Jinan University, Guangzhou, Guangdong 510632; <sup>3</sup>The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong 510120, P.R. China

Received October 19, 2017; Accepted December 15, 2017

DOI: 10.3892/etm.2018.5874

**Abstract.** The effect of Shoutai pill on endometrial receptivity was analyzed. A total of 160 patients with spontaneous abortion were enrolled in this study. They were treated in the Fifth People's Hospital of Jinan (Shandong, China) from February 2014 to June 2016. The following treatment regimen was performed for the patients: after menstruation, Shoutai pill was taken as continuous medication for more than 5 menstrual cycles, the pill was taken 20 days per month, medication was stopped during menstruation, and contraceptive measures were taken during this period. Statistics were recorded of endometrial thickness and morphology, hemodynamic parameters of uterine spiral artery, including pulsatility index (PI) and resistance index (RI), endometrial LIF levels before and after treatment, and follicular development and ovulation were strictly monitored, and statistics of pregnancy were recorded. The endometrial thickness, type A endometrium and endometrial spiral arterial PI and RI levels, endometrial LIF levels were significantly improved after treatment ( $P<0.05$ ); at the same time, pregnancy rate was 85%; during this treatment, patients had no significant side effects. In conclusion, improvement of endometrial acceptability with Shoutai pills can receive good effect, significantly promote embryo implantation and enhance pregnancy rate.

## Introduction

Unexplained spontaneous abortion, even repetitive abortion, seriously impacts physical and mental health of female population. Spontaneous abortion continued for three times or more is recurrent abortion. With the changes in people's living habits, as well as adjustment of dietary structure, currently, a gradually increased population faces spontaneous abortion.

According to the data survey, recurrent abortion accounts for ~5% of all pregnancy incidences. Among them, ~85% of recurrent abortion occurs in the early stages of pregnancy, that is, within 12 weeks of pregnancy, which means recurrent early abortion (1). So far, there is a lack of a unified theory in etiology and pathogenesis of spontaneous abortion, which has complex characteristics, and is subject to many factors, such as heredity, infection, immune, and endocrine factors.

In unexplained spontaneous abortions, immune factor occupies a high proportion, between ~40 and 60%, and anti-endometrial antibody (EmAb) (Fig. 1) plays an important role. It takes endometrium (Fig. 2) as a target antigen, and destroys structure of the endometrium via antigen-antibody reaction, thereby affecting embryo implantation (Fig. 3) and development, resulting in early spontaneous abortion (2).

In recent years, a wide range of traditional Chinese medicine has been used in treatment of natural abortion patients, with good effect and high safety and reliability. This study investigated the effect of Shoutai pill on endometrial receptivity.

## Materials and methods

**General information.** This study was conducted in 160 patients with spontaneous abortion (1-4 times), all of whom were treated in the Fifth People's Hospital of Jinan (Shandong, China) from February 2014 to June 2016. The existence of severe organic disease such as heart and kidney dysfunction, blood system diseases and mental disorder was ruled out. This study was approved by the Ethics Committee of the Fifth People's Hospital of Jinan. The studied patients and family members had the right to know the treatment, and signed the relevant informed consent. The 160 patients were aged 24 to 38 years, with an average age of  $28.7\pm 2.2$  years. Among them, there were 32, 58, 43 and 27 cases, respectively, with 1, 2, 3, 4 spontaneous abortions. The patients' immune antibodies as well as both of the couple's chromosomes, male semen quality examination results showed no abnormal problems. The general data of all the cases are comparable ( $P>0.05$ ).

**Method.** After the patient's menstruation was clean, she was instructed to take Shoutai pill comprising *Eucommia ulmoides*, *Cuscuta*, *Loranthus parasiticus*, radix pseudostellariae, *Atractylodes* and deer-horn glue, human placenta, *Salvia miltiorrhiza*, teasel root and ramie root (3). The dose was 6 g

**Correspondence to:** Dr Xiaoling Duo, Department of Gynecology and Obstetrics, The Fifth People's Hospital of Jinan, 24297 Jingshi Road, Jinan, Shandong 250022, P.R. China  
E-mail: xiaoling\_duo@163.com

\*Contributed equally

**Key words:** endometrial receptivity, Shoutai pill, spontaneous abortion, treatment effect

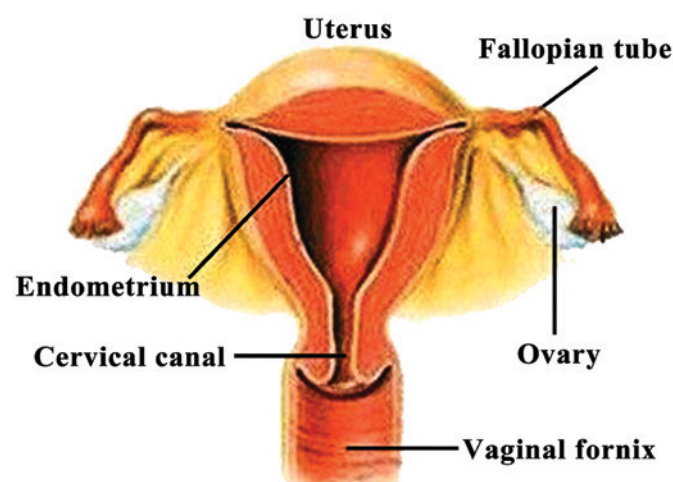


Figure 1. Anti-endometrial antibody.

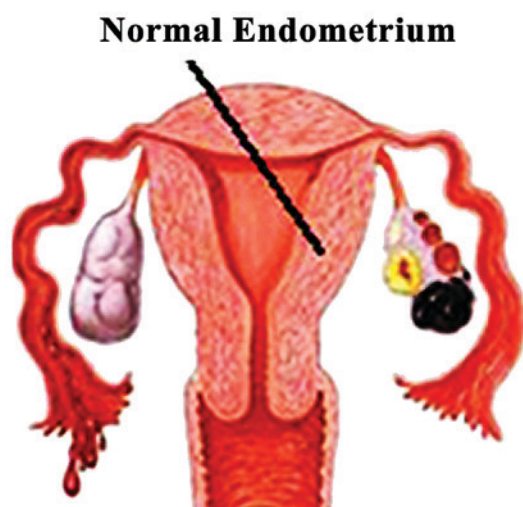


Figure 2. Endometrium.

per time and 3 times a day, continuous medication for 20 days. Medication was stopped in the menstruation, and continuous treatment was taken for more than 5 menstrual cycles. Based on the actual situation of the patient, if abortion exceeded 3 times, intermittent treatment time should be extended to 1 year, and contraceptive measures taken during the treatment (4). Then, the patient was tested for planning pregnancy based on the results. If B-ultrasound monitoring shows ideal round follicles, while endometrium is in good thickness and shape, the patient was instructed to have intercourse. On the 12th day after ovulation, blood HCG was checked as soon as possible. After the patient was pregnant, protection of the fetus with Chinese and Western medicine was carried out until 12th week based on the test indicators, and records on the success rate of pregnancy were kept (5).

**Observation indicators.** After treatment, vaginal ultrasound was used to monitor the follicles. If at least one follicle was of 18-20 mm or more, the urinary luteinizing hormone (LH) test strip was used for monitoring LH peak of ovulation day. Vaginal ultrasonography was taken to observe patient's endometrial thickness and morphology, with statistics of

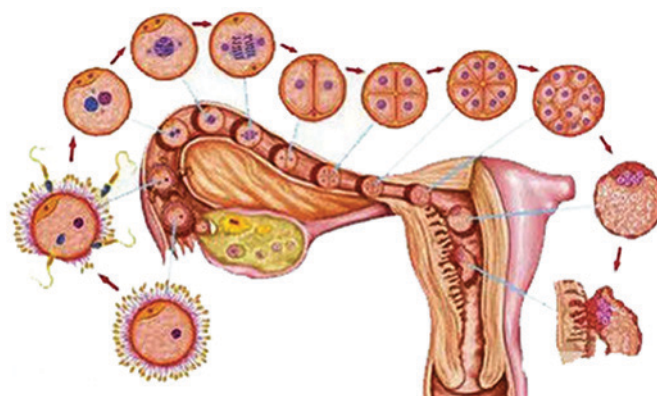


Figure 3. Embryo implantation.

hemodynamic parameters of uterine spiral artery made, including pulsatility index (PI) and resistance index (RI) (6). The endometrial morphological classification was based on Gonen-related criteria. Wherein, type A is typical three-line type, with strong echo line in the outer and center and low echo area or dark area between the outer layer and the uterine midline. Type B is moderate echo type, with intermittent and unclear uterine strong echo midline. Type C is homogeneous strong echo, without uterine midline echo. Within cervix, the uterine artery was observed by horizontal and longitudinal scanning of ostium uteri internum. The Doppler spectrum image analysis was automatically performed by color ultrasound, for pulsatility index and resistance index. Some endometrial tissues of the uterine cavity was taken by the endometrial sampler, and immunohistochemistry was used to determine endometrial LIF level (7).

**Statistical analysis.** The data were analyzed and processed by SPSS 21.0 statistical software (IBM Corp., Armonk, NY, USA). The enumeration data were expressed as (n, %) and tested by Chi-square. The measurement data are expressed in mean  $\pm$  SD based on t-test.  $P < 0.05$  was the difference considered statistically significant.

## Results

**Comparison of endometrial thickness, PI and RI before and after treatment.** As shown in Table I, endometrial thickness, PI and RI improvement after treatment are significantly superior to that before treatment ( $P < 0.05$ ).

**Changes in endometrial morphology before and after treatment.** As shown in Table II, the patient's endometrial morphological improvement shows significant advantages after treatment ( $P < 0.05$ ).

**Expression of endometrial LIF.** As shown in statistics of Table III, endometrial LIF expression levels are obviously improved after treatment ( $P < 0.05$ ) (Fig. 4).

**Patients' pregnancy, safety evaluation.** After treatment, 136 cases had successful pregnancy with pregnancy rate of 85%; during the treatment, 10 patients had abdominal pain, nausea, diarrhea and other adverse reactions, the symptoms

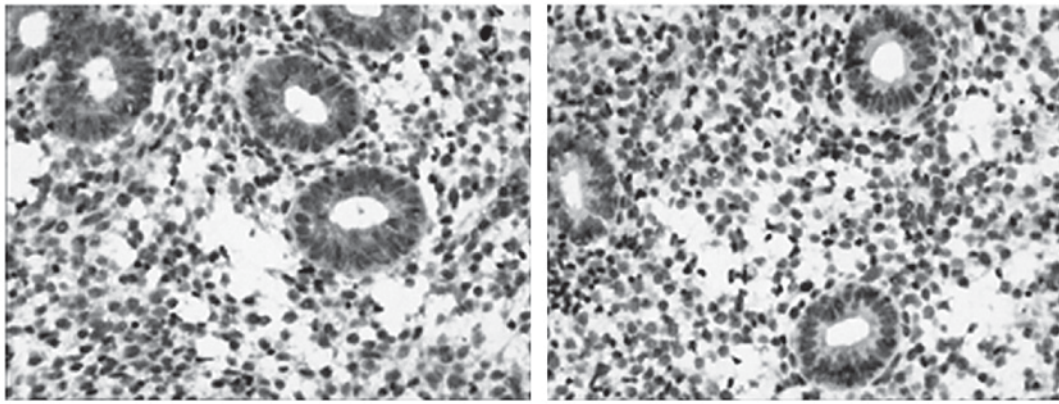


Figure 4. Expression of endometrial LIF.

Table I. Comparison of endometrial thickness, PI and RI before and after treatment (mean  $\pm$  SD).

| Time             | Case no. | Endometrial thickness (mm) | PI              | RI              |
|------------------|----------|----------------------------|-----------------|-----------------|
| Before treatment | 160      | 0.74 $\pm$ 0.19            | 2.15 $\pm$ 0.68 | 0.81 $\pm$ 0.04 |
| After treatment  | 160      | 0.97 $\pm$ 0.18            | 1.60 $\pm$ 0.40 | 0.60 $\pm$ 0.05 |
| P-value          |          | <0.05                      | <0.05           | <0.05           |

PI, pulsatility index; RI, resistance index.

Table II. Changes in endometrial morphology before and after treatment [n (%)].

| Time             | Case no. | Type A      | Type B     | Type C     |
|------------------|----------|-------------|------------|------------|
| Before treatment | 160      | 80 (50.00)  | 52 (32.50) | 28 (17.50) |
| After treatment  | 160      | 120 (75.00) | 28 (17.50) | 12 (7.50)  |
| P-value          |          | <0.05       | <0.05      | <0.05      |

Table III. Expression of endometrial LIF.

| Time             | Expression intensity in epithelial cells |       |       |       |
|------------------|--|-------|-------|-------|
|                  | -  | +     | ++    | +++   |
| Before treatment | 96                                       | 32    | 20    | 12    |
| After treatment  | 65                                       | 40    | 32    | 23    |
| P-value          | <0.05                                    | <0.05 | <0.05 | <0.05 |

were mild and subsided within 3 days. No serious side effect was seen in the remaining patients.

## Discussion

For blastocyst implantation, an important factor is the ability of endometrium to accept the embryo, that is, endometrial receptivity. If the endometrial tolerance is inappropriate, ~60% of embryo implantation will fail. The data show that endometrium thickness plays an important role in receptivity prediction. In >80% of successful pregnancies, endometrial thickness ranges from 9 to 12 mm, with ultrasound type of A (8). In addition, intimal pulsatility index and resistance index can well reflect endometrial blood flow perfusion, and can be used as an important indicator of endometrial receptivity in embryo implantation and pregnancy prediction. At the same time, LIF, as a secretory glycoprotein, has a wide range of biological functions. It has the largest secretion in 19-25 day of menstrual cycle, which overlaps with endometrial implantation, so it can also be used as an important indicator of endometrial tolerance (9).

From the Chinese medicine point of view, in case of kidney deficiency, uterus suffers from malnutrition, fetal origin cannot be maintained, embryo cannot be implanted and causes infertility, so reinforcing kidney to replenish essence, nourishing the blood and promoting blood circulation, regulating menstruation assisting pregnancy are essential to treatment (10,11). In this study, Shoutai pill for treatment of the patients includes *Cuscuta* as the main drug, supplemented by *Loranthus parasiticus*, deer-horn glue and teasel root. With *colla corii asini* to enrich the blood, plus deer-horn glue, Shoutai pill can give full effect of replenishing kidney and promoting generation of essence and blood. Human placenta can cultivate *Qi* and blood, and can be used as drug for infertility, in habitual abortion. Shoutai pill also comprises *Salvia miltiorrhiza* to significantly improve microcirculation; while such drugs as *Atractylodes*, *Caulis Spatholobi*, *Astragalus* can soothe the liver, regulate vital energy, regulate menstruation, tonify *Qi*, invigorate splenic *yang*, activate and harmonize *Qi*-blood.

In this study, the results showed that treatment by Shoutai pill could significantly increase endometrial thickness,



increase rate of endometrial type A, thicken endometrial spiral artery, make spiral artery spectrum show low resistance in blood flow, reduce PI and RI indexes. This indicates that Shoutai pill can improve endometrial blood flow state and endometrial receptivity, provide a good embryo implantation environment, and improve pregnancy success rate.

In conclusion, for improvement of endometrial receptivity, Shoutai pills can obtain good effect, significantly promote embryo implantation and improve pregnancy rate. At the same time, this treatment can significantly reduce the side effects. With good safety and reliability, it is more easily accepted by patients, enjoying great significance in promotion and practice.

### Acknowledgements

Not applicable.

### Funding

No funding was received.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Authors' contributions

LZ and XD contributed to the conception and design of the study. YX and XT collected the patients data. YX and PW analyzed and interpreted the data. XD drafted this manuscript. XT and PW revised it critically for important intellectual content. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Fifth People's Hospital of Jinan (Jinan, China). Signed written informed consents were obtained from the patients.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

### References

1. Gao J, Deng G, Hu Y, Huang Y, Lu L, Huang D, Li Y, Zhu L, Liu X, Jin X and Luo S: Quality of reporting on randomized controlled trials on recurrent spontaneous abortion in China. *Trials* 16: 172, 2015.
2. Perez N, Peterlin B, Volk M, Kapović M and Ostojić S: A critical update on endothelial nitric oxide synthase gene variations in women with idiopathic recurrent spontaneous abortion: Genetic association study, systematic review and meta-analyses. *Mol Hum Reprod* 21: 466-478, 2015.
3. Lu KA and Chen HN: Effect of modified Shoutai pill on anti-endometrial antibodies in patients with early recurrent spontaneous abortion. *Clin J Chin Med* 10: 10-11, 2014.
4. Nowak R, Szewczyk K, Gawlik-Dziki U, Rzymowska J and Komsta Ł: Antioxidative and cytotoxic potential of some *Chenopodium L.* species growing in Poland. *Saudi J Biol Sci* 23: 15-23, 2016.
5. Ali MA, Farah MA, Al-Hemaid FM, Abou-Tarboush FM, Al-Anazi KM, Wabaidur SM, Alothman ZA and Lee J: Assessment of biological activity and UPLC-MS based chromatographic profiling of ethanolic extract of *Ochradenus arabicus*. *Saudi J Biol Sci* 23: 229-236, 2016.
6. Plasencia W, Barber MA, Alvarez EE, Segura J, Valle L and Garcia-Hernandez JA: Comparative study of transabdominal and transvaginal uterine artery Doppler pulsatility indices at 11-13 + 6 weeks. *Hypertens Pregnancy* 30: 414-420, 2011.
7. Wang CY, Ding CF, Zhang W and Wan LY: Clinical study on the effect of Yulinzhu combined with Shoutai pill on pregnancy rate of hormone replacement cycle frozen-thawed embryo transplantation. *China Mod Doct* 14: 128-131, 2016.
8. Hashem A, Abd Allah EF, Alqarawi AA, Al Huqail AA, Egamberdieva D and Wirth S: Alleviation of cadmium stress in *Solanum lycopersicum L.* by arbuscular mycorrhizal fungi via induction of acquired systemic tolerance. *Saudi J Biol Sci* 23: 272-281, 2016.
9. Aldahlawi AM, Elshal MF, Damiaiti LA, Damanhori LH and Bahlas SM: Analysis of CD95 and CCR7 expression on circulating CD4(+) lymphocytes revealed disparate immunoregulatory potentials in systemic lupus erythematosus. *Saudi J Biol Sci* 23: 101-107, 2016.
10. Hyun TK, Kim HC, Ko YJ and Kim JS: Antioxidant,  $\alpha$ -glucosidase inhibitory and anti-inflammatory effects of aerial parts extract from Korean crowberry (*Empetrum nigrum* var. *japonicum*). *Saudi J Biol Sci* 23: 181-188, 2016.
11. Hu XS, Cheng DL, Li KJ, Wang LB, Yang X, Sun S, Wang YP, Li SH, Lei ZF and Zhang ZY: Glucose consumption and  $\alpha$ -glucosidase inhibitory activities of aqueous root extract of *Helicteres angustifolia*. *Eur Rev Med Pharmacol Sci* 20: 1423-1429, 2016.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.