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## Study on prevention effect of Zishen Yutai pill combined with progesterone for threatened abortion in rats

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## ABSTRACT

**Objective:** To observe preventive and therapeutic effects and the mechanism of actions on Zishen Yutai pill combined with progesterone on threatened abortion in rats.

**Methods:** After pregnancy, 50 SPF female SD rats were selected and divided into control group, model group, progesterone group, Zishen Yutai pill group, and progesterone plus Zishen Yutai pill group (combination group), with 10 rats in each group. The rats of control group and abortion model group were lavaged with 2 mL/kg normal saline on pregnancy day 1 for continuous 10 days. Rats in Zishen Yutai pill group were given 1.575 g/kg/d of Zishen Yutai pill for intragastric administration for continuous 10 days. Rats in progesterone group were given intramuscular injection treatment of 0.1 mL/d progesterin, continuous for 10 days. Rats in combination group were given injection therapy of aqueous solution of Zishen Yutai pill for continuous 10 days, and other treatments were the same as previous two groups. Abortion model were established then and live births, numbers of abortion and average rate of abortion were compared between the five groups. Peripheral blood was collected to detect the estradiol (E2) and progesterone (P), and obtain ratio of Th1/Th2 cytokines (IL-2, INF- $\gamma$ , IL-4, IL-10).

**Results:** Significant more live births of rats were found in the control group compared with other four groups ( $P < 0.05$ ). The numbers of live births of the rats in abortion model group were significantly less than that of progesterone group, Zishen Yutai pill group and joint group ( $P < 0.05$ ). The numbers of live births of rats in joint group were significant more than that of progesterone group and Zishen Yutai pill group. The serum E2 level of P of rats in the control group, progesterone group, Zishen Yutai pill group and joint group were significant higher than that of abortion model group ( $P < 0.05$ ). Serum levels of E2 and P of rats in the control group, progesterone group, Zishen Yutai pill group and joint group were not significant different ( $P > 0.05$ ) but these levels in the control group and Zishen Yutai pill group were significant lower than that of progesterone group and joint group ( $P < 0.05$ ). The maternal–fetal interface IL-4/IL-2, IL-10/IL-2 of model group were balanced deviating to Th1, while the IL-4/IL-2, IL-10/IL-2 of progesterone group, Zishen Yutai pill group and joint group were balanced deviating to Th2, and joint group' deviation was better than progesterone group and Zishen Yutai pill group ( $P < 0.05$ ).

**Conclusions:** Zishen Yutai pill combined with progesterone has a significant control effect for threatened abortion, which can obviously increase contents of maternal serums E2 and P, and regulate the Th1/Th2 balance with a remarkable effect.

## 1. Introduction

Threatened abortion is a common complication during pregnancy, which refers to a small amount of vaginal bleeding during the 28 weeks of pregnancy, paroxysmal abdominal pain symptoms of abortion, but cervix is not open and fetal membrane is intact without the passage of tissues [1–3]. The pathogenesis of threatened abortion is complex, which related to heredity, immune, general infection and endocrine disorder. It will develop into inevitable

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abortion or lead to slow development of embryonic, which may seriously affect pregnancy outcome or worse influences to the patients and their families if it is not treated in time [4]. Therefore, it is extremely significant to seek for a more effective prevention and control method to improve the threatened abortion pregnant outcome. Some scholars believe that threatened abortion is related closely to the unbalance of Th1/Th2 cytokines [5–8], for instance, to correct the imbalance of maternal Th1/Th2 cytokine can prevent threatened abortion. Other studies confirm that Th1/Th2 cytokines balance plays a vital role in the process of normal pregnancy, abortion, embryo damage, premature birth and pathologic pregnancy [9,10]. In order to observe the preventive and therapeutic effects and the mechanism of actions of Zishen Yutai pill combined with progesterone, SPF female SD rats were selected to establish threatened abortion model, and Zishen Yutai pill combined with progesterone was used for intervention treatment. The effect of the treatment on rate of abortion, E2, P and Th1/Th2 cytokines ratio was observed.

## 2. Materials and methods

### 2.1. Source of animal

Fifty healthy female SD rats (SPF, 12 weeks old, weighing 250–350 g) were selected and provided by Laboratory Animal Centre of Zhejiang Chinese Medical University (certification: SCXK20150013). Rats were fed with water and food *ad libitum* under 12 h/12 h light–dark cycle and packing was changed twice each week. The experiment was operated in experimental center of Zhejiang Chinese Medical University. All experimental procedures involving animals were strictly conducted in accordance to Regulations for the Administration of Affairs Concerning Experimental Animals and approved by ethics committee of the university.

### 2.2. Main reagents

Mifepristone was produced by Zhejiang Xianju Pharmaceutical Co., Ltd., (specification: 25 mg/tablet); Progesterone Injection was produced by Zhejiang Xianju Pharmaceutical Co., Ltd. (specification: 20 mg/mL); Zishen Yutai pill was produced by Guangzhou Baiyunshan Zhongyi Pharmaceutical Co. Ltd. (Approved: Z44020008, specification: 60 g/pill). Drugs dispensing: 25 mg mifepristone fine grinding was fully dissolved in 138 ml of distilled water, then the formulating concentration of 0.18 mg/mL was obtained for further use. Then progesterone injection was put into 2.75 mL of sterilization salad oil and formulating the concentration of 5.3 mg/mL for further use; the Zishen Yutai pill was changed into powder, then put into distilled water till it was fully dissolved and formulating concentration of 0.5 g/mL for further use; ELISA reagent boxes were all purchased from MultiSciences Company, and the operation was strictly conform to product specifications.

### 2.3. Experimental method

#### 2.3.1. Pregnancy method

Vaginal washing fluid was used for microscopic examination and observation to ensure the selected rats' estrous cycle, and the

estrus female and male rats were put in one cage according to the 2:1 ratio over night, and tested whether there was pessary *in vivo* of female rats on the next morning. If the pessary was discovered, the day could be identified as the first day of pregnancy after the test. If the pessary *in vivo* of female rats was not discovered, vaginal washing fluid could be taken for microscopic examination. The day can be identified as the first day of pregnancy if living sperms were discovered in the vaginal washing fluid; the rest rats without pregnancy were waiting for next estrous cycle.

#### 2.3.2. Establishment of abortion model and intervention methods

50 pregnant rats were randomly divided into 5 groups, which were control group, abortion model group, progesterone group, Zishen Yutai pill group and joint group respectively, with 10 rats each group. Abortion model was not established in the control group, while the rest pregnant rats in 4 groups were lavaged with 3.75 mg/kg of mifepristone on the 10th days of pregnancy and established abortion model. The rats in control group and abortion model group were lavaged with 2 mL/kg of body mass normal saline during pregnancy day for continuous 10 days. Progesterone group rats were given intramuscular injection treatment of 0.1 mL/d of progesterone for continuous 10 days. The joint group rats were given injection therapy of aqueous solution of Zishen Yutai pill for continuous 10 days, the therapy method was the same to the previous two groups.

### 2.4. Observation index

After pregnancy of 1, 5 and 9 days (T1, T2 and T3), body weight, fur color and diet condition of the rats were observed. Rats were executed by ether anesthesia after establishing the model, and the blood serum in peripheral was separated for inspection. The estradiol (E2); level and progesterone (P) level were tested by adopting ELISA method. The content ratio of Th1/Th2 cytokines (IL-2, INF- $\gamma$ , IL-4, IL-10) was tested, calculated and compared. Then rats in five groups were dissected, the numbers of live births and abortion were compared, and the average rate of abortion was calculated. Criterion: The embryo was intact, uterus was normal, the normal color was pink or reddish with no extravasated blood; partly abortion: the embryo was incomplete with extravasated blood in uterine cavity. Completely abortion: it was clearly visible of embryonic death, extravasated blood or embryo implantation site in uterus, with change of bamboo-structured in uterus, obvious decrease of body weight or vaginal bleeding before.

The formula of abortion rate: the abortion embryo numbers / (the abortion embryo numbers + normal embryo numbers) = rate of abortion.

### 2.5. Statistical analysis

The measurement data were expressed as mean  $\pm$  SD, and analyzed by One-way ANOVA and *t*-test. SPSS19.0 statistical analysis software was used for data processing. *P* < 0.05 was considered statistically difference.

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