

14. Genitourinary Tract Disorders (including Climacteric Disorders)**Reference**

Yasui T, Irahara M, Aono T. Studies on treatment with the combination clomiphene citrate and Toki-shakuyaku-san. *Nippon Funin Gakkai Zasshi (Japanese Journal of Fertility and Sterility)* 1995; 40: 83-91 (in Japanese).

1. Objectives

To compare the effects of clomiphene monotherapy with those of tokishakuyakusan (当帰芍薬散) plus clomiphene for infrequent menses, anovular menstrual cycle, and amenorrhea.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

The Department of Obstetrics and Gynecology of Tokushima University Hospital and related hospitals (13 institutions), Japan.

4. Participants

Ninety-three outpatients seen at the above institutions and diagnosed with infrequent menses, anovular menstrual cycle, or amenorrhea between January 1992 and March 1994.

5. Intervention

Arm 1: oral administration of clomiphene (50 mg) after meals for 5 days from day 5 of the menstrual cycle + TSUMURA Tokishakuyakusan (当帰芍薬散) Extract Granules 2.5 g t.i.d. before meals. If no ovulation occurred, clomiphene was increased by one tablet per day at each subsequent cycle (n=41).

Arm 2: oral administration of clomiphene (50 mg) after meals for 5 days from day 5 of the menstrual cycle. If no ovulation occurred, clomiphene was increased by one tablet per day at each subsequent cycle (n=52).

6. Main outcome measures

Ovulation and pregnancy as determined by confirmation of a period of high basal body temperature lasting 10 or more days, or increased progesterone level (≥ 10 ng/mL) in mid-luteal phase. Improvement in endocrine condition as indicated by blood levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone. Assessments were made after treatments for 3 or more cycles.

7. Main results

There were no significant between-group differences in the ovulation rates evaluated for each treatment arm at each cycle, as well as in the pregnancy rate for each arm. In patients who became pregnant, the number of cycles until pregnancy was significantly lower in the combination therapy group (1.86 cycles) than in the monotherapy group (3.82 cycles) ($P < 0.05$). There were also no significant between-group differences during any treatment cycle in pituitary hormone and estradiol levels, the number of growing ovarian follicles, cervical mucus volume, endometrial thickness in the mid-luteal phase, and the period of high basal body temperature. Both the progesterone level and progesterone/estradiol concentration ratio in the preovulatory period were higher in the clomiphene monotherapy group than in the combination therapy group ($P < 0.05$).

8. Conclusions

In patients with infrequent menses, anovular menstrual cycle, or amenorrhea, combination therapy, as compared with monotherapy, did not improve ovulation rate but did facilitate pregnancy, suggesting the normalizing effects of tokishakuyakusan on sex hormones in the ovary.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Not mentioned.

11. Abstractor's comments

The present study compared the efficacy of combination therapy with tokishakuyakusan with the efficacy of clomiphene (used as a positive control with proven effects on abnormal menstrual cycles). The conclusion is that tokishakuyakusan could shorten the time until pregnancy and is therefore clinically applicable. From the point of view of western medicine, more detailed classification of the primary disease would be useful for the determination of indications for tokishakuyakusan in women with abnormal menstrual cycles who want to become pregnant. To compare the physiological and endocrine data, the combination therapy group should be subgrouped on the basis of *sho* (証, pattern). Subgroup analysis of the data is expected.

12. Abstractor and date

Ushiroyama T, 28 August 2008, 1 June 2010, 31 December 2013.