Effects of traditional herbal-therapy on the infertile patients diagnosed by "zheng" who had not become pregnant following application of contra indicated step up therapy

Takashi KANO,a) Takahisa USHIROYAMA b) and Minoru UEKI b)

a)Medical Corporation Kano Clinic, 2-5-2, Nippombashi, Chuo-ku, Osaka City, Osaka 542-0073, Japan. b)Department of Obstetrics and Gynecology, Osaka Medical College, Osaka, Japan. (Received April 27, 2004. Accepted May 31, 2004.)

A total of 157 infertile patients diagnosed as having unexplained infertility who were treated unsuccessfully by Western so-called step up therapy, were treated with Kampo therapy following diagnosis by "zheng". Following Kampo therapy 40 pregnancies and 32 live births (live birth rate; 40.5%) were achieved after clomiphene, 22 pregnancies and 16 live births (32.5%) after clomiphene-AIH, and 11 pregnancies and 5 live births (20.7%) after IVF-ET. Kami-Shoyo-San was used in the majority of regimens (45.2%), followed by Toki-Syakuyaku-San (22.9%) and Keishi-Bukuryo-Gan (21.7%). The etiology of infertility in the majority of patients has been considered sporadic ovarian dysfunctions that are not indication for AIH and IVF-ET. Clomiphene suppresses cervical mucous secretion and endometrial proliferation, which may cause iatrogenic infertility. When cervical mucous volume is decreased and the Huhner-test result is poor, therapy is stepped up to clomiphene-AIH, but this therapy cannot overcome the suppressive effects of endometrial proliferation caused by clomiphene. Because of this, final step-up to IVF-ET should be made. Kami-Shoyo-San administered by "zheng" improved ovarian function associated with increased cervical mucous volume and endometrial proliferation. The first choice of therapy for ovarian dysfunctional infertilities that do not involve tubal disorder or male disorder should be Kampo therapy diagnosed by "zheng".

Key words step up therapy, Kampo preparation, clomiphene, AIH, IVF-ET.

Abbreviations AIH, artificial insemination of husband; ART, artificial reproductive technique; BBT, basal body temperature; CM, cervical mucus; DFMD, dominant follicle maximum diameter; EM, endometrium; IVF-ET, in vitro fertilization and embryo transfer.

Introduction

The primary approach to infertility involves measuring BBT and timing of coitus. If pregnancy is not achieved, so-called step up therapies are phased in clomiphene, clomiphene-AIH and IVF-ET. We have doubts about the effectiveness of these step up therapies that pay no heed to indications. Especially, it is questionable whether AIH and IVF-ET which are indicated for male infertility (poor Huhner-test) and tube infertility will surpass the pregnancy rate by natural (non ART) pregnancy. Since we are currently at the height of ART uses, AIH and IVF-ET are apt to be abused.

From the perspective of a Kampo specialist also providing ART treatments, we investigated the effectiveness of Kampo therapy diagnosed by "zheng" (Hakko-Ki-Ketsu-Sui-diagnosis) for patients who were diagnosed with unexplained infertility at other hospitals based on BBT, normal HSG and normospermia, but had failed to achieve pregnancy after so-called step up therapy with clomiphene (79 patients), artificial insemination (AIH) after clomiphene (49 patients) or in vitro fertilization (IVF-ET) after clomiphene-AIH (29 patients). These patients were treated with only Kampo preparations diagnosed by "zheng" (Hakko-Ki-Ketsu-Sui-diagnosis1)), and the incidences pregnancies, live births and abortions were investigated.

To investigate the effect of Kampo preparations on ovarian function, the effect of Kami-Shoyo-San on serum estradiol levels (19 patients), dominant follicle maximal diameters (18 patients), cervical mucous volume (26 patients), and thickness of the endometrium (16 patients) during the preovulatory period, serum progesterone levels (21 patients) on BBT +5–8 Days were investigated. The effects of Toki-Shakuyaku-San on serum prolactin levels classified as hyperprolactinemia (17 patients) and normoprolactinemia (7 patients) were also investigated.

When testing the significance of differences, Student's t-test was used for means and chi-square test for percent incidence.

Materials and Methods

The subjects were 157 patients with primary infertility for more than 2 years. They were diagnosed with unexplained infertility at other hospitals based on BBT, normal

Results

Ovarian function diagnosed by BBT. As shown in Table 1, ovarian functions during the past 6 cycles excluding clomiphene and IVF cycle were diagnosed by BBT

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*To whom correspondence should be addressed. e-mail: kanoclin@pearl.ocn.ne.jp
Patterns in 157 patients and demonstrated a normal biphase pattern in 44 patients (28.0%), sporadic luteal insufficiency in 87 patients (55.4%), sporadic anovulation in 26 patients (16.6%).

**Pregnant rate.** As shown in Table 2, the Kampo therapy achieved 40 pregnancies and 32 live births (live birth rate: 40.5%) after clomiphene, 22 pregnancies and 16 live births (32.5%) after clomiphene-AIH, 11 pregnancies and 5 live births (20.7%) after IVF-ET. The cross live birth rates of each step up therapy groups were statically analyzed. The live birth rate after clomiphene was significantly higher than that after IVF-ET (p<0.05). The duration of Kampo therapy ranged from 1 month at minimum to 2 years 8 months at maximum, with a mean duration of 8.5 months. A total of 71.7% of patients became pregnant within 6 months in live birth cases.

**Effects of Kampo preparations on ovarian and related function.** As shown in Table 3, Kamishoyo-San was used in the majority of regimens (45.2%), followed by Toki-Syaku-San (22.9%) and Keishi-Bukuryo-Gan (21.7%). Kami-Shoyo-San significantly improved not only, estradiol level (BBT 3 to 0 days), progesterone levels (BBT 5 to 8 days) and dominant follicle maximum diameters (DFMD; BBT -3 to 0 days) but also endometrial thickness and cervical mucus volume (Figure 1). Toki-Syaku-San significantly decreased prolactin levels in the group with an abnormally high pre-treatment level of 15 ng/ml or higher but did not influence the level in the normal group (Figure 2).

**Discussion**

Ovarian functions as well as the cervical mucous and endometrial function regulated by ovarian function changed depending on menstrual cycles. Therefore, the cause of infertility differs according to the menstrual cycle. However, unexplained infertility is simply diagnosed based on biphase BBT, normal HSG and normal sperm without considering cyclic ovarian functions which should be diagnosed by endocrinological and echographic examinations.

We have been concerned that so-called Western step up therapy including clomiphene, AIH and even IVF-ET has been indiscriminately used for unexplained infertilities who are diagnosed by the simple criterion described above.
In the present 157 patients, normal ovulatory cycles, which were diagnosed by BBT during past 6 cycles, were found in only 44 patients (28.0%). However, sporadic luteal insufficiency and sporadic anovulation were diagnosed with 87 patients (55.4%) and 26 patients (16.6%), respectively. Ovarian dysfunction could never be diagnosed by BBT. Therefore, the majority of unexplained infertilities diagnosed on the basis of BBT should be considered sporadic ovarian dysfunction. The first choice of therapy for ovarian dysfunctional infertilities in Western medicine is clomiphene.

In the present study, the most frequent previous therapy used for the women was clomiphene (51.4%, live birth rate; 40.5%). Why did they become pregnant relatively quickly after changing from unsuccessful clomiphene therapy to Kampo therapy using "zheng" diagnosis?

Clomiphene has anti-fertility effects such as suppression of cervical mucus secretion and endometrial proliferation through its anti-estrogen effects. This may cause iatrogenic infertility. When cervical mucus volume is decreased and Huhner-test result is poor in clomiphene therapy, the therapy is stepped up to clomiphene-AIH. The pregnancy rate of AIH essentially remains low, since this therapy cannot overcome the suppressive effects of endometrial proliferation caused by clomiphene. Therefore, clomiphene therapy may extend the duration of infertility therapy, finally making the step-up to IVF-ET necessary.

In this course of the therapy, AIH and IVF-ET which are not indicated for infertile patients with sporadic ovarian dysfunction are performed. Patients who receive such therapy will not achieve a better pregnancy rate than those who
become pregnant naturally (non ART).

The possible etiology of infertility, such as ovarian dysfunction and related factors, may vary from cycle to cycle. Therefore, unexplained infertility should be diagnosed only when all factors are normal for at least one cycle. From this perspective, many of the patients who became pregnant in this study had infertility associated with sporadic ovarian dysfunction.

Kami-Shoyo-San administered by "zheng" (Hakko-Ki-Ketsu-Sui-diagnosis) improved ovarian function associated with increased cervical mucous volume and endometrial proliferation. Toki-Shakuyaku-San and Keishi-Bukuryo-Gan also improved ovarian function similarly (data not shown). Kami therapy resulted in successful pregnancy by improving ovarian function without inhibiting cervical mucous secretion and endometrial proliferation.

Toki-Syakuyaku-San decreases abnormally high levels of prolactin, which are involved in homeostasis through glucose and electrolyte metabolism. Therefore, administration of such drugs is unnecessary when ovarian follicular function and luteal function are normal even if the prolactin level is more than 15 ng/ml, because it may jeopardize homeostasis.

The causes of ovarian stimulating effects of Toki-Shakuyaku-San, Kami-Shoyo-San and Keishi-Bukuryo-Gan have been considered due to their "ku-oketsu" and "risui" effects which improve the circulation of gonadotropine, estrogen and progesterone in the pelvic circulatory systems. Toki-Shakuyaku-San also has prolactin-decreasing effects.

The facts that the live birth rate of after IVF-ET was significantly lower than that of clomiphene and doubling of the abortion rate after IVF-ET compared with that after clomiphene, caused speculation that the etiology of infertility after IVF-ET was implantation insufficiency caused by immunological disorders related to recurrent abortions. When a patient does not become pregnant after more than one year, she should be examined for various factors related to recurrent abortion21 and appropriate therapy24 should be given.

In many cases, unexplained infertility diagnosed by BBT, normal HSG and normospermia simply, is in fact sporadic ovarian dysfunction. Therefore, Kami therapy diagnosed by "zheng" diagnosis, which lacks inhibitory effects on cervical mucous secretion and endometrial proliferation, is the first choice of therapy.

References


Japanese abstract

他院で卵管不妊症、男性不妊症を否定され、所謂ストップアップ療法（clomiphene、AIH、IVF-ET）を受けたものの妊娠が成立せず、当院を受診した157例に陰謀薬剤無効療法を行ったところ、73例で妊娠が成立、53例で受精を獲得し、受精獲得率も高かったのはclomiphene 投与後の32例（40.5%）であり、ついでclomiphene-AIH後16例（32.5%）、IVF-ET後5例（17.2%）と低率であった。最も受精率が高かった方剤は加味逍遥散（投与率：45.2%、受精獲得率：54.7%）、次いで当院加味散、桂枝茯苓丸であった。症例の多くは本来AIH、IVFの適応ではない散発性卵巣機能不全不妊症であり、clomipheneの卵管粘粘減少作用によってHuhner-Testがかから良好化したためAIHにstep-upしたものの妊娠しないため、最終的に全く適応ではないIVFを行なう事になった症例であった。したがって今回妊娠した症例はclomipheneによる医原性不妊症の可能性が高い。以上の結果より、適応がない症例に行わせたAIHとIVFは漢方療法を凌駕できない事が明らかとなった。漢方方剤は卵管粘粘減少、子宮内膜萎縮化を伴わず卵巣機能を改善する。卵管や精子所見に異常が認められない卵巣機能不全不妊症のファーストチョイスは陰謀漢方療法と結論された。