



Case Report

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Combined Effect of Acupuncture and Frozen Embryo Transfer in Recurrent Pregnancy Loss Patient: A Case Report



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Abstract

Despite recent technological advances of in vitro fertilization and embryo transfer (IVF-ET), the success rate of IVF-ET is only about 20% in Japan. Some reasons such as the quality of the ovum and others are listed but some remain unknown. This study aimed to assess the combined effect of acupuncture on the improvement of a poor uterus situation patient who has been experiencing long-term infertility due to unknown causes. We diagnosed her as a Spleen-Kidney Yang-deficiency type based on the analysis of clinical manifestations. After 4 months of acupuncture therapy according to the principle of warming Spleen, tonifying Kidney, invigorating Spleen, removing dampness and tranquilizing her mind, her subjective symptoms almost disappeared, her cycle tended to be normal and the state of the uterus following the changes of BBT was improved. These positive changes were advantageous for her first transplant in 2 years, connecting with the establishment of pregnancy, together with the health maintenance of parent and fetus during the pregnancy and finally the acquisition of the newborn baby thereafter. This case showed that acupuncture might be possible to assist embryo transfer and maintain the pregnancy, which would contribute to the rise in implantation rate, fertility index and the birthrate with ART as well.

Keywords: Acupuncture; Infertility; ART; FET; In vitro fertilization

Introduction

According to the Ministry of Health, Labour and Welfare of Japan, the average number of births per woman was 1.34 in 2020, which decreased 0.02 points from the previous year [1]. It is the 5th consecutive year that the birth rate was less than the previous year. The government considers the declining marriage rate to be one of the direct factors of determining the country's birth rate trend. As of 2019, 4.8 marriages per 1,000 inhabitants were newly registered in Japan.

In addition, not being able to be pregnant resulting in the low birth rate is a major problem. Infertility is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [2,3]. Assisted reproductive technology (ART) refers to treatments and procedures that aim to achieve pregnancy. *In vitro fertilization* and embryo transfer (IVF-ET), is now commonly employed as an infertility treatment throughout the world. In

recent years, the number of frozen-thawed embryo transfer (FET) cycles has increased dramatically due to the trend towards transferring fewer embryos after fresh in vitro fertilization (IVF) cycles and improved cryopreservation techniques [4]. Despite recent technological advances, the success rate of IVF-ET is only about 20% in Japan, and the treatment period is often lengthy [5]. Some reasons for a poor ovarian responder are late marriage and the following advanced age of child birth, which naturally influences the quality of the ovum. It is said that after 35 years old, the growth of a mature ovum will decay with age [6]. In addition, IVF-ET can be a serious financial burden for patients in Japan, because it is usually not covered by health insurance, though financial aid systems are currently being developed for these procedures for those with lower incomes.

On the other hand, as a main part of traditional Chinese medicine (TCM), acupuncture has been widely used as a treatment

for various conditions like infertility, especially in Asian countries such as Korea and China. It is safe with few side effects and has properties for normalizing total biological balances of the body. Now in Japan, ART skills are modern and quite popular for infertility patients. But according to the data by ICMART in 2016, Japan has the most executions numbers of IVF but the worst birthrate per egg collection once and show a level of a minimum among the 60 countries. Of course, there are many causes, the unidentified sterile patient who occupies 11% of sterile causes and approximately accompanying various subjective symptoms in varying degrees such as coldness, abdominal or lumber pain and headache etc. before and after menstruation, which influenced the

reproductive function greatly and work negatively to get pregnant by TCM could not be ignored. We performed a clinical study with Minoura Ladies Clinic under the approval (No. 447) of the clinical study Ethical Review Board of Suzuka University of Medical Science (SUMS), aimed to investigate the effect of acupuncture on the improvement of patients with a poor uterus situation and pregnancy rate in patients, who are experiencing long-term infertility due to either advanced age or unknown causes who do not become pregnant by ART. In this paper we report a case of recurrent pregnancy loss, mainly due to a thin endometrium. This patient got pregnant via transfer of FET after acupuncture and moxibustion treatment.

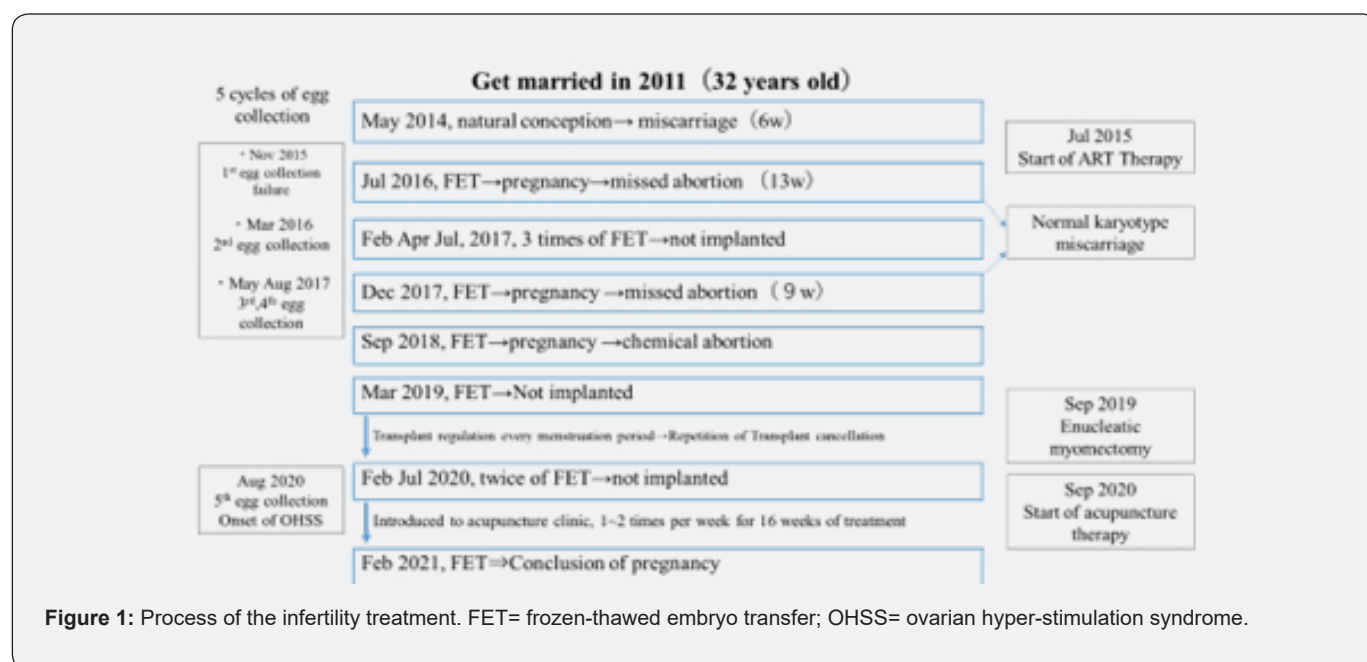


Figure 1: Process of the infertility treatment. FET= frozen-thawed embryo transfer; OHSS= ovarian hyper-stimulation syndrome.

Case Presentation

Ms. K. a 41-year-old woman housewife, who had been infertile for 6 years, came to our acupuncture center in Sep. 2020, accompanied by her husband. She got married in 2011 at 32 years of age. Her husband had trouble with a sexual intercourse disorder but could have sex after taking Viagra. In 2014, Ms. K. became pregnant and miscarried after 6 weeks. Worrying about her inability to become pregnant, she visited a local private infertility clinic (in Suzuka, Japan) for help. After having performed a routine examination about sterility, she was diagnosed with ovarian dysfunction. After failing three times using artificial fertilization, it was suggested that she step-up to IVF. She had been given 5 cycles of egg collection in 2015, 2016, 2017 and 2020, and at the last time an ovarian hyperstimulation syndrome (OHSS) was also developed just before visiting our acupuncture clinic. She had suffered 9 failed cycles of IVF, among them, delayed miscarriages occurred twice in 2016 and 2017, and a chemical miscarriage in 2018. After that, in order to improve the bad endometrium blood circulation due to a uterine myoma, she had enucleatic

myomectomy surgery. But unfortunately, following considered side-effects of the deteriorating views of the endometrium, even after repeating FET for several times, and being unable to become pregnant the wife was very disappointed and lost confidence in the continuation of treatment. So, she was introduced to our acupuncture center expecting a better combined result with her IVF treatment (Figure 1).

General Symptoms

The patient's 4 limbs felt cold and she tended to wear thick clothes constantly. Also she felt swelling on her face and lower limbs, and developed hives resulting mostly from cold air and heavy stress or other unidentified reasons. Also, when feeling anxious or hot, she always got sweaty and her underthings often got wet with sweat, and sweat ran down from her forehead in extreme cases; which also happened after walking or other movement. Maybe due to her character of turning inwards, she liked to stay at home and seldom went out or contracted with her family members or friends. Her worsened stress and nervousness,

restlessness, anxiety and despair due to infertility, which had existed for a long time and there was no way to diffuse, especially at the time of the present corona rage. Besides, her tongue proper showed pale and humid with a white and greasy moss on the surface and slightly teeth mark on the margin of tongue, along with some vein overselling on the back of the tongue. Her pulse was slippery and slow.

Acupuncture and Moxibustion Treatment

After a medical interview and counseling with the couple, she was strongly persuaded by her husband to receive our acupuncture and moxibustion treatment. Based on the information of four diagnostic methods, namely, inspection, auscultation and olfaction, inquiry, and pulse-taking and palpation, she was diagnosed with the type of Yang-deficiency of Spleen-Kidney and accompanied with phlegm-wetness. We gave her a treatment with the policy of Warming Yang and supplying the Kidney, Promoting Spleen and Clearing the wetness, the following acupoints were used for acupuncture with stainless steel disposable needles with tubes (Unico 0.20×48mm) such as Gongsun(SP-4), Sanyinjiao (SP-6), Yinlingquan(SP-9), Zusanli(ST-36), Taixi (KI-3), Zigong(Ex-CA1), Zhongji(CV-3), Guanyuan(CV-4), Qihai(CV-6), Baihui(GV-20), Shangxing(GV-23) Yintang(Ext), Taiyang(Ext),

Pishu(BL-20), Shenshu(BL-23), and Ciliao(BL-32) (Table 1). The depth of needle insertion varied with the thickness of the skin and subcutaneous fatty tissues at the site of acupuncture points; it was usually about 1-1.5 cm. After the de qi sensation in traditional Chinese acupuncture, we evenly twirled the needles using uniform reinforcing-reducing method for 1 minute and then retained the needles for 20 minutes in each positions of supine and prone. The same acupuncturist who had used acupuncture and in the clinic for over 15 years. Besides the needling, a warming acupuncture applied with a cut moxibustion (12 φ× 15 mm; Yamasho Ltd., Co.) on the top of the needles (Figure 2), was administered on the acupoints of SP-4, SP-6, SP-9, ST-36, CV-3, CV-4, CV-6, Ex-CA1, BL-23, BL-20. She was basically given acupuncture once or twice weekly, and had been received the treatment for 14 weeks until the IVF. However, this had to be stopped as a result of her following sudden strained back just before 10 days of the IVF. Nevertheless, when it was found out her pregnancy, low back pain was just reduced. In order to prevent another habitual miscarriage that she had experienced twice at 13th and 9th week of the fetus before, she hoped strongly for treatment again, so almost the same treatment described above were further added for three times to let her feel relieved and reassured more (Table 1), (Figure 2).

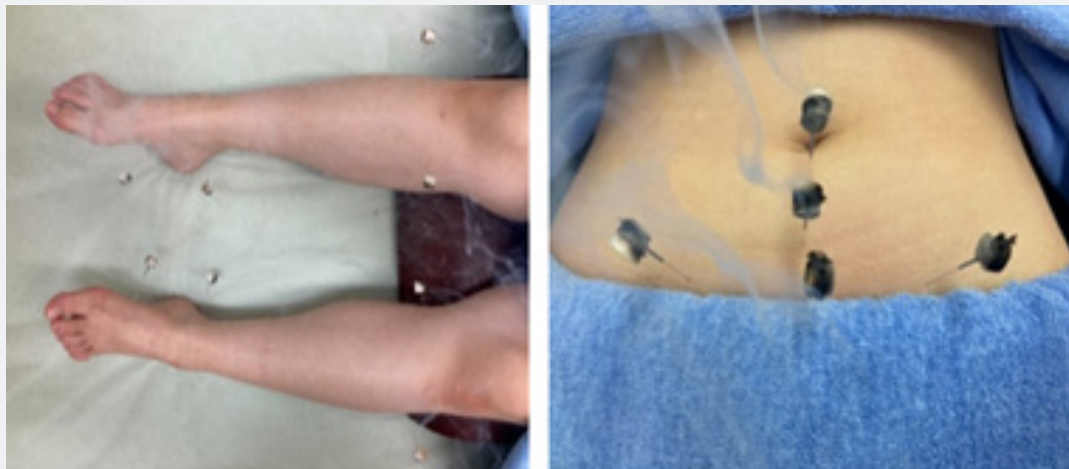


Figure 2: The scenery of warm acupuncture operation. Moxibustion with a warming needle was administered on the acupoints of abdomen and lower limbs.

Table 1: Point Prescription and the Indications.

Positions	Acupoints	Indications
Head	Baihui (Du-20), Shangxing (Du-23, Yintang (Ex-NH3), Taiyang (Ex-HN5)	Tranquilization
Abdomen	Zhongji (RN-3), Guanyuan (Rn-4), Qihai (RN-6), Zigong (Ex-CA1)	Regulating the Chong and Ren Channels
Back	Pishu (BL-20), Shenshu (BL-23), Ciliao (BL-32)	Promoting Spleen and Clearing the Wetness
Lower Extremities	Gongsun (Sp-4), Sanjinjiao (Sp-6), Yinlingquan (Sp-9), Zusanli ST-36), Taixi (KI-3)	Warming Yang and Supplying the Kidney

By the end of January 2021, a total of 23 times of acupuncture sessions occurred. The subjective symptoms such as the coldness on her limbs, edema in legs, fear and anxiety and easily occurred urticaria improved. When she subsequently visited her gynecologic consultant, the doctor was very pleased with her general condition including the remission of OHSS, together with the relevant hormonal levels of follicle stimulating hormone, luteinizing hormone and estradiol.

An informed consent from the patient prior to the initial treatment was written. We checked her individual body constitution and condition by using the Constitution in Chinese Medicine Questionnaire (CCMQ) consisting of 60 question items from the first medical examination once a month to conform her improving physical condition [7]. CCMQ-J is an investigative system based on a multivariate analysis of Japanese version, which comprise nine subscales representing nine body constitutions, labeled “gentleness”, “qi deficiency”, “yang deficiency”, “yin deficiency”, “phlegm wetness”, “wet heat”, “blood stasis”, “qi depression” and “special diathesis”, respectively. Gentleness represents health, while the other body constitutions represent a lack of health. Each question is answered using a Likert scale that ranges from 1 to 5, corresponding to “never”, “rarely”, “sometimes”, “often”, “always”, respectively [8]. According to the above-mentioned CCMQ-J with five phases, her top three differentiations were special diathesis with 57 points, yang deficiency with 46 points and phlegm wetness with 34 points, and at the end of treatment, the top three constitutions were still the same, but the scores were changed to 36, 39 and 34 respectively, only the phlegm-wetness constitution was unchanged.

Basal Body Temperature (BBT) and Menstrual Cycle

BBT is body’s temperature at complete rest, in general, the body’s resting temperature is stable from day to day. But in women, predictable changes in body temperature occur at specific points in the menstrual cycle. During the first half of the menstrual cycle, from menstruation until ovulation, the temperature is relatively low. Once ovulation occurs and progesterone levels rise, the body temperature increases by up to 0.5 degrees. The temperature remains relatively high until progesterone levels drop and menses occurs. This information also reflects the female hormone level changes which are closely related to general body tone (whole body condition) and influence the outcome of pregnancy to a great extent. Before Jan., her BBT was unstable and there was no difference in low and high temperature period, and the majority of the cycles seemed to be anovulatory. However, after about three months of acupuncture treatment in the cycle of Jan, it tended to become slightly steady and showed a biphasic curve and this tendency continued until February (Figure 4). There were many changes in her menstrual cycle as well, which are also shown in Figure 4. Her menstrual cycle had been almost infrequent since her first menstrual period at 11 years old, ranging from 30 to 60 days usually accompanied by menstrual pain before and on the first day of menses. After her visit to our acupuncture clinic, she had menstrual cycles of 50 days from August to October, 55 days from October to December with 3 days of bleeding, but on the last cycle before pregnancy, she had her menses for 4 days with a cycle of 32 days without any subjective symptoms like bellyache etc., which seemed to come back to her twenties for the first time in a while by her own words.

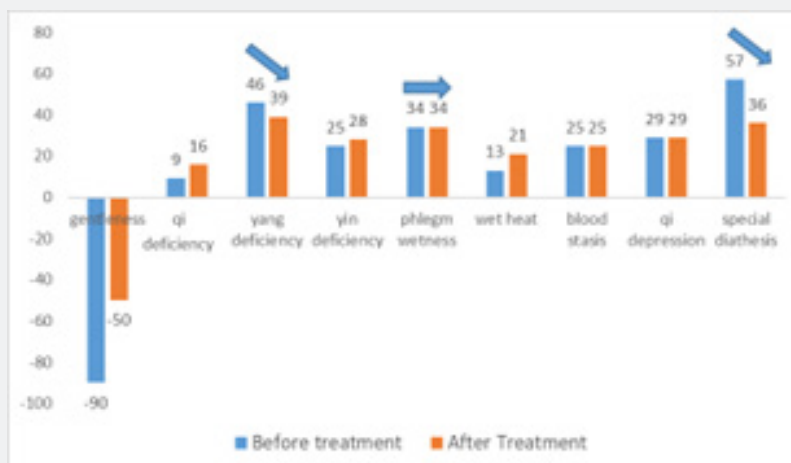


Figure 3: Body constitutions change over time with the treatment through CCMQ.

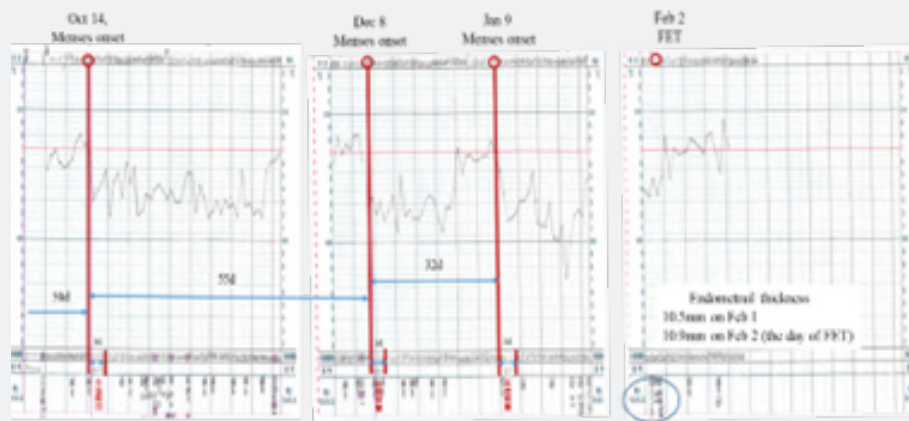


Figure 4: Basal body temperature (BBT) changes over time.

Condition of Endometrium, Pregnancy, and Childbirth

The patient had been troubled with her poor endometrium during a long medical history. In the past several years, especially after receiving uterine fibroids extirpation due to the complicated uterine myoma in September 2019, her endometrium was too deteriorated to be transplanted due to a substandard endometrial thickness. In March and July, 2020, when the endometrial thickness was occasionally over 8 mm, she had FET twice at Day5, but both of them failed to be implanted.

Nevertheless, after treating for about four months using

acupuncture, in the last menses of January, the endometrial thickness got to 10.5mm the day before FET (Figure5A) and 10.9 mm on the day along with a normal hormonal status, so she received a transplantation on 2nd February. On the 16th, positivity of the pregnancy was judged by urinalysis, and the heart rate was firstly confirmed on 9th, March by supersonic wave photograph (Figure 5B). Furthermore, the pregnancy continued smoothly without any onset such as pelvic position or pregnancy toxemias during the gestation period. And finally, on 7th October, she delivered a body of 3034g by Caesarean section at 37 weeks Figure 5B.

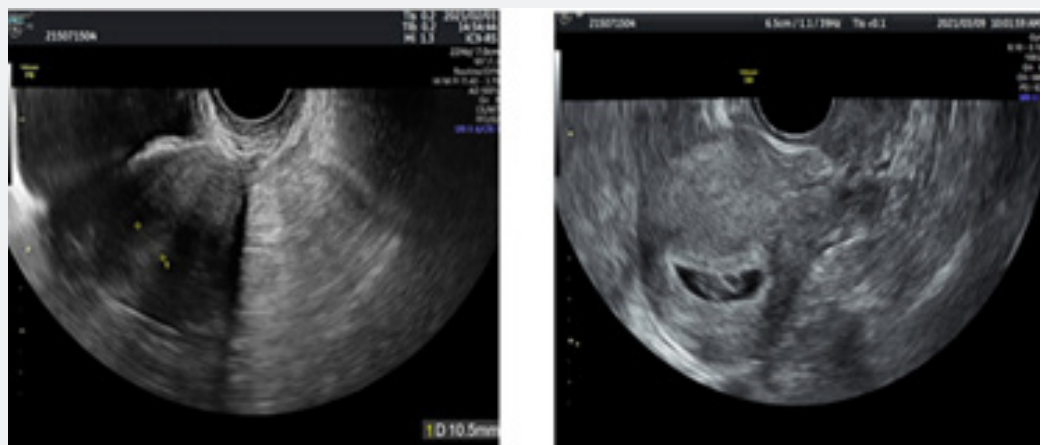


Figure 5A: Echo image of endometrium before FET, Figure 5B: Echo image of the fetus at 9 weeks.

Discussion

The outcome of ART in 2018 were nearly 57 thousand live births, one in 16 newborns in Japan. FET, which utilizes frozen

embryos that were produced in the previous cycle of in vitro fertilization was the most used and successful procedure of ART in the last decade. However, according to the report of study

group, the treatment result is passably considered good when a miscarriage occurred up to five times, but when the one with a history of 6 or more miscarriages, it would be intractable only by a normal cure, and some special cure seems to be necessary to be added [9].

On the other hand, the morbidity of uterine myoma is reported with 11.7-23.6% at reproductive age women [10]. It rises with age to increase to hormone dependence and is divided into submucous, interstitial and subserous according to the anatomical position. The handling is also different. In addition, submucous myoma reduces the fertility index in 30% degree in comparison with the normal uterus in the report of the meta-analysis, while the subserous myoma does not reduce a fertility index [10]. This patient had suffered submucosal fibroids, at first she was given priority to a preservation treatment at first due to her age and expected postoperative complications, but after repeated failing of FET and her thin endometrial, which seldom led to 8mm of the minimum thickness necessary for the pregnancy in the past several years, it was suggested she have a enucleatic myomectomy laparoscopically in September 2019, positively aiming to improve the state of the endometrium together with her infertility. However, even after the 2 surgeries of FET in the hormone adjustment cycle both failed, and the cause was not identified either. Therefore, she was going to give up because of the repeated great mental and physical pain along with the infertility treatment, as well as the financial strain. In addition, miscarriage, the use of ovulation inducers also increases the possibility of her poor endometrium were pointed out as well [11]. Being no effective cure but the routine treatment to thicken it, the doctor was also troubled by a better solution. □

Acupuncture has been used for centuries in China for the treatment of menstrual disorders, infertility and undefined symptoms without side effects and having properties for normalizing biological balances. We diagnosed her as Spleen-Kidney Yang-deficiency type basing with her overall analysis of clinical manifestations including the constitution questionnaire and her tongue and pulse. We used acupuncture on the points in accordance with the treating principle of warming Spleen, tonifying Kidney, invigorating Spleen, removing dampness and tranquilizing mind. In virtue of her coldness of limbs with edema, we added warming needles, especially on the points of BL-20, BL-23, SP-4, SP-6, SP-9 and St-36. With the treatment, her subjective symptoms almost disappeared, the improvements also contributed to the outcome of her constitution questionnaire changes, her cycle tended to be normal, the most satisfactory results were the great thickness of endometrial which was 10.9mm on the transplanting date, which was also the best state on morphology according to the doctor.

Torloni and others report that the acupuncture needle moxibustion treatment affects the bloodstream of the uterus [12]. The thinning of her inner membrane of the uterus, habitual abortion and non-implantation were thought to be resulted

from the deficiency both of Qi and blood by TCM. Since Qi is the commander of blood, Qi disorder including the causes of coldness and dampness causing the blood flow to be blocked and slow, which are connected to her symptoms such as period pain or a retarded confused menstruation. Whereas, her series of collateral subjective symptoms, the betterment of her constitution that can be proved by the score changes of the CCMQ-J, along with the thickness of endometrium, indirectly showed the improved bloodstream throughout.

Why and how does the applying of acupuncture is effective? According to her subjective symptoms and the total conditions, we used the points of Du-20, Du-23 and Ex-HN3 and Ex-HN5 to relieve her long-term anxiety and pressure, getting confidence so that one can become pregnant following her body constitution changes is the most important factor for her because the therapeutic effect is greatly related to her positive attitude on treatment and the trust in us. In addition, Chong channel is the sea of blood, while Ren channel is in charge of pregnancy, thus Chong and Ren Channels are closely related to menses [13], pregnancy and delivery, also involving with the function of Liver and Kidney. We used RN-3, RN-4 and RN-6, the points on the Ren channel to regulate the channels, and combine the points such like BL-20, BL-23, BL-32, SP-6, SP-4, SP-9 and KI-3 to promote the Spleen and Kidney actions helping to clear the coldness and dampness in her body. Especially, the warming needle plays a very important role of warming the Yang of Spleen and Kidney, which further assists to promote the above organs' functions. Moreover, BL-32 and Ex-CA1, as effective and experiential points for obstetric and gynecological disorders, were also used to enhance the generative function of the ovary and the uterus. These stimulations are thought to be connected to the disappearance of her subjective symptoms including the poor circulation that she suffered for many years, regulation of the basal body temperature, assistance to thicken the endometrium maybe because of a regulation and improvement of the hormone levels. Just these positive changes were advantageous for her first transplant in 2 years, connecting with the establishment of pregnancy, together with the health maintenance of parent and fetus during the pregnancy and finally the acquisition of the newborn baby thereafter. Since a patients' condition in trouble differs largely from person to person, we will only perform a case report at this time. Nevertheless, the study is still in progress, we would like to extract and study similar cases and report the intervention effects of TCM in the near future.

Conclusion

Acupuncture therapy according to the principle of TCM performed in this case study induced the improvement of the state of the uterus following the changes of BBT by fixing the mental and physical balance of the patient, which is thought to regulate the female hormone levels and finally work for the success of in-vitro fertilization. Consequently, it might be possible to assist embryo transfer and maintain the pregnancy, which would contribute to

the rise in implantation rate, fertility index and the birthrate with ART as well.

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