Measuring the Effectiveness of Chinese Herbal Medicine in Improving Female Fertility

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Keywords: Infertility, Chinese herbal medicine, ultrasound, hormone levels.

Abstract

Aim: To determine the relationship between female fertility indicators and the administration of Chinese herbal medicine (CHM). **Design:** A prospective cohort clinical study to measure accepted bio-medical factors that affect female fertility and to determine if CHM can improve these factors as well as pregnancy outcome. **Setting:** A private practice specialising in treating infertility with traditional Chinese medicine (TCM). The study took place between November 2003 and December 2004. **Patient(s):** Fifty women with the Western medical diagnosis of unexplained infertility. **Interventions:** One monitored menstrual cycle measuring pre-treatment fertility factors, followed by treatment with Chinese herbal medicine and subsequent measurement of the changes in the same fertility factors. **Results:** Significant differences were observed between the two time points for the majority of factors measured. Pregnancies in the sample group recorded 6 months after commencement of the last treatment were 28, with 11 live births and 7 miscarriages. **Conclusion:** The study outcome demonstrates that using Chinese herbal medicine results in higher success rates of pregnancy, with no patient side-effects and a reduction in the category of patients conventionally classified as having unexplained infertility.

Introduction

The research question this study seeks to answer is "Does administering Chinese herbal medicine (CHM) improve the physiological factors affecting human female fertility?" The hypothesis is that administering CHM improves the main physiological factors affecting human female fertility and therefore also the pregnancy rate. These factors are ovarian follicle number and size, uterine endometrium thickness, uterine artery haemodynamics, serum follicle stimulating hormone (FSH), serum progesterone levels and corpus luteum vascularity.

Research aims and objectives

i. Establish a sample group of 50 new patients registering for fertility treatment at a London natural health fertility clinic.
ii. Test and record a predetermined group of twelve measurements prior to treatment during one menstrual cycle.
iii. Administer CHM in capsule form for one menstrual cycle.
iv. Re-test the same parameters in the third cycle of treatment, continue to administer CHM for six months (or until pregnancy is achieved if this occurs in less than six months). Follow up six months after the beginning of the last patient's treatment
v. To determine the number of pregnancies achieved.
vi. Analyse results and discuss findings.
vii. Draw conclusions and make recommendations for further practice and study.

Methodology

The challenge for any investigative method when applied to traditional Chinese medicine (TCM) is that in everyday practice, the same disease in different patients will have a different treatment principle and herbal prescription. The information collected from the traditional Chinese examination and assessment determines a diagnosis based on pattern differentiation and hence a treatment principle and formula which is individualised for each patient. In our treatment of infertility there is, in addition, a weekly modification of each patient's formula. As there is thus no standardisation of formulae for patients it is not appropriate to discuss the formulae themselves in this study, but rather to simply study the effects of Chinese herbal medicine treatment on female fertility.

The method chosen was a prospective cohort primary study using a sample group of patients registered with the clinic for TCM infertility treatment.

Patients were selected for the study on the basis that they had no Western medical condition which might have affected their fertility. In other words they were described in Western medical terms as having unexplained infertility. They also entered the study on the condition that data obtained in the course of their treatment could be used in the study anonymously.

Sample size

The sample size needed to be sufficiently large to make the outcome statistically meaningful and yet allow data collection to be achieved within the time frame of one year. Data collection for each patient spanned three months (or longer in those patients with long menstrual cycles). A sample size of 50 was judged to be both statistically meaningful in pilot study terms and achievable within the 12 month duration of the study in a single location.

Collection of data

Data were collected over three menstrual cycles: the control cycle, the treatment cycle and finally the progress measurement cycle.

At the initial visit a diagnosis was made in TCM terms and the process of monitoring the cycle was explained to the patient. She was instructed to record her basal body temperature throughout her cycle, starting from day one. Although this procedure was not used as one of the fertility indicators in our study, it is used in modern Chinese fertility clinics as the changes in basal body temperature reflect hormonal changes during the cycle. The fluctuations are analysed in TCM terms, which allows for refinement of diagnosis and gives useful feedback during treatment.

Data collection took place between November 2003 and December 2004 and the total pregnancy outcome was measured on July 31st, 2004, six months after the commencement of the last patient's treatment.

Assessment of fertility indicators during monitored cycles

The range of tests used and their timing in the menstrual cycle are detailed below (table 1). A 28 day menstrual cycle was assumed; in the case of shorter or longer cycles the timetable was adjusted accordingly to suit the individual patient

Day 1: ultrasound scan to determine endometrial thickness and ovarian activity. Blood test to measure FSH levels.	At this stage ovarian activity should be low, as indicated by small (less than 3mm) primordial follicles on both ovaries and an endometrial thickness of between 2-3mm. FSH levels should be as low as possible – less than 10 and ideally between 4 and 8.
Day 11: ultrasound scan to track follicle numbers and size and identify if a dominant follicle is present.	These measurements establish whether the patient is producing primary follicles of sufficient number and adequate size, and whether a dominant follicle exists on one of her ovaries, indicating that ovulation is imminent.
Day 21: ultrasound scan to measure endometrial thickness, corpus luteum size, corpus luteum vascularity, uterine artery peak systolic velocity (PS) and pulsatility index (PI). Blood test to measure progesterone levels.	The endometrial thickness, at its maximum on day 21, should be sufficient to support a pregnancy should conception take place (at least 7mm is required, and ideally the thickness should be between 10mm and 15mm). Uterine artery dynamics should be PS= >30cm/sec and PI=<3.0. Ultrasound also measures if a corpus luteum (CL) exists, which would confirm that ovulation has taken place, and rates the CL vascularity from 1-3. The existence of the corpus luteum correlates with raised progesterone levels, ideally of over 50.

Table 1: **Tests used in the study**

Analysis of data

The main aim of the analysis was to compare the differences in the fertility indicators at two time points, i.e. before and after treatment. This is called a t-test. The choice of statistical test depends upon the distribution of the differences before and after treatment: if the differences are normally distributed, a paired t-test is used, but when this is not the case the Wilcoxen matched-pairs test is used instead.

The data measured twelve fertility indicators: pre-ovulatory endometrial thickness (day 1), serum FSH, the number of right and left ovary follicles, the total number of follicles, the size of the Graafian (dominant) follicle, post-ovulatory endometrial thickness, uterine artery PS (post-ovulatory), uterine artery PI (post-ovulatory), serum progesterone (post-ovulatory), corpus luteum size, corpus luteum vascularity.

The data were also analysed to determine if age had any effect upon treatment results.

For ease of analysis two groups were created according to age: ≤35 and >35 years. The differences between pre- and post- treatments were then compared between the two groups. Those differences that were found to be normally distributed were compared using a two-sample (or unpaired) t-test, whilst the differences that were not found to be normally distributed were compared using the Mann-Whitney test.

The results of all statistical analyses were determined by the size of the p-value resulting from each test, a p-value of less than 0.05 being usually regarded as evidence of a statistically significant result.

Results

Differences in fertility indicators before and after treatment

The differences in fertility indicators before and after treatment were statistically analysed and the results summarised below (tables 2 and 3). For those variables where the differences between pre- and post- treatment

Variable	Pre-treatment mean difference (SD)	Post-treatment mean difference (SD)	Mean difference (95% CI)	P-value
Endometrium pre-ovulatory (day 1)(mm)(*)	2.3 (1.9, 3.8)	2.2 (2.0, 2.9)	-0.1 (-0.5, 0.0)	**0.03**
FSH	10.7 (94)	9.1 (9.1)	-1.7 (-2.5, -0.9)	**<0.001**
R Ov follicles	5.2 (2.3)	5.9 (2.3)	0.7 (0.2, 1.2)	**0.01**
L Ov follicles	5.9 (2.7)	6.3 (2.2)	0.4 (-0.3, 1.1)	0.29
Total follicles	11.3 (4.7)	12.4 (3.9)	1.1 (0.0, 2.2)	0.05
Graafian follicle size in (mm)	11.7 (5.8)	14.4 (3.9)	2.8 (1.2, 4.3)	**<0.001**
Endometrium post-ovulatory (mm)	8.3 (2.8)	10.1 (4.0)	1.9 (0.8, 3.0)	**0.002**
UA PS (*)	27 (22, 32)	35 (30.5, 36)	6.0 (4.1, 7.9)	**<0.001**
UA PI (*)	4.8 (3.2, 7.6)	3.1 (2.3, 5.1)	-1.1 (-1.8, -0.7)	**<0.001**
Progesterone (*)	37 (20, 55)	52 (37, 64)	7.1 (4.6, 11.5)	**<0.001**
CL Size (mm)	9.4 (4.2)	11.5 (3.7)	2.1 (0.9, 3.4)	**<0.001**
CL vascularity (*)	1 (1, 2)	2 (2, 3)	1 (0, 1)	**<0.001**

Table 2: **(*) Median (IQ range) reported for each group, together with median difference (95% CI). Analysis using Wilcoxen matched-pairs test.**

values were found to be normally distributed, the mean value and standard deviation at each time point was recorded, in addition to the mean difference (and 95% confidence interval) between the two times. The p-values from the paired t-tests were also recorded. For those variables where the differences between pre- and post-treatment values were not found to be normally distributed, the median value (inter-quartile range) at each time point was recorded, in addition to the median difference (and 95% confidence interval) between the two times. The p-values from the Wilcoxen matched-pairs tests were also recorded.

The differences between time points were given as post-treatment minus pre–treatment. A positive difference implied that the values had increased as a result of treatment, whilst a negative value implied that the values had decreased as a result of treatment. In the measurements of follicle size, post-ovulatory endometrium, uterine artery peak systolic velocity (UA PS), progesterone and corpus luteum (CL) size and vascularity, increases in units represent increased fertility. In the case of FSH, pre-ovulatory endometrial thickness and uterine artery pulsatility index (UA PI), decreases in units indicate increased fertility.

The results indicated significant positive differences between the two time points for the majority of the indicators examined. For the pre-ovulatory measures, ovarian follicle number and Graafian (dominant) follicle size were found to be significantly higher after treatment. For example, Graafian follicle size was an average of 2.8 units higher than that observed before treatment. Conversely, the values for the endometrial thickness at day one of the cycle were significantly lower after treatment. There was a significant difference after treatment for all post-ovulatory measures. For example, there was a median increase of 6 units in the UA PS, and a mean increase of 2.1 units in the corpus luteum size. Conversely, there was a significant decrease in the UA PI, with a median decrease of 1.1 units between time points.

Comparison between age groups

In the second part of the data analysis, differences between pre- and post-treatment values were compared between the two age groups and summarised below (table 3). For those variables with a normal distribution of differences between pre- and post-treatment values, the mean value and standard deviation at each time point and the p-values from the t-tests were reported. For those variables with an abnormal distribution between pre- and post-treatment values, the median value (inter-quartile range) at each time point and the p-values from the Wilcoxen matched-pairs tests were reported. As in the first part of the study, the differences between time points were given as post-treatment value minus pre-treatment value.

The results of the comparison between age groups indicated that there was no statistically significant difference in response to treatment. There was very slight evidence that in the younger patients Graafian follicle size was larger and progesterone levels were higher, although these results were not quite statistically significant. As age was not found to influence the difference between pre- and post-treatment values, the effect of treatment can be assumed to be equal in both age groups from a statistical point of view. Thus it is not necessary to examine the effects of treatment separately for the two age groups for this data set.

Pregnancy outcome

Experience of treating infertility with Chinese Herbal Medicine (CHM) in both China and the West has shown that most pregnancies occur in the first six menstrual cycles after treatment is started. The pregnancy rate drops dramatically after six cycles, implying that CHM attains its maximum effect in the first six treatment cycles (around 5-7 months). This is our observation only since no studies have yet been published on this in the West as far as we know. With some patients, however, the effects are seen well before six months, with pregnancies occurring from as early as one menstrual cycle after treatment. In the study period of thirteen months the number of pregnancies achieved in the sample group of 50 patients on 31st July, 2005 was 28, giving a pregnancy rate of 56%. At this date 11 live births and 7 miscarriages had also been recorded.

Findings and discussion

Description of findings

The findings from this study were very encouraging, particularly in four respects. Firstly, there were statistically highly significant findings (p-values <0.001) in eight out of the fertility indicators measured, namely FSH levels, Graafian follicle size, post-ovulatory endometrial thickness, UA PS, UA PI, progesterone levels (post-ovulatory), corpus luteum size and corpus luteum vascularity. The remaining factors showed p-values of marginal or sub-marginal statistical significance.

Secondly, in our sample age did not seem to make much difference to the effectiveness of fertility treatment with CHM.

Thirdly, there were no reported side-effects with the herbal medicines. This is an important finding as assisted reproductive therapy (ART) involves strong synthetic hormone treatment to stimulate ovarian follicle production, and the side-effects can be quite unpleasant. Another benefit from herbal infertility treatment of the kind used in this study is that no breaks between treatment cycles are needed and treatment can continue from cycle to cycle for as long as is needed to achieve a pregnancy. IVF and ICSI require at least one cycle's break for recovery after a failed cycle before another treatment cycle can commence.

Finally, and most importantly, the pregnancy outcome was 56% overall. Considering all these aspects, CHM offers a viable alternative to ART, particularly if the patient is concerned about the side-effects of fertility drugs or wishes to take a natural approach to fertility treatment.

Variable	Age ≤35 Mean difference (SD)	Age >35 Mean difference (SD)	P-value
Endometrium pre-ovulatory (mm)(*)	-0.4 (-1.6, 1.5)	0.0 (-0.5, 0.4)	0.12
FSH	-1.7 (2.6)	-1.7 (2.9)	0.96
R Ov follicles	0.8 (1.8)	0.6 (1.9)	0.71
L Ov follicles	0.2 (2.1)	0.5 (2.8)	0.64
Total follicles	1.0 (3.2)	1.1 (4.2)	0.89
Graafian size in mm	4.4 (6.4)	1.6 (4.3)	0.07

Variable	Age ≤35 Mean difference (SD)	Age >35 Mean difference (SD)	P-value
Endometrium post-ovulatory (mm)	2.3 (4.3)	1.6 (3.7)	0.52
UA PS (*)	6.0 (2.5, 11.0)	6.5 (1.0, 8.8)	0.63
UA PI (*)	-0.9 (-2.9, -0.3)	-1.3 (-3.2, -0.5)	0.39
Progesterone (*)	11.2 (4.6, 23.4)	4.9 (1.6, 14.3)	0.07
CL Size	2.6 (4.9)	1.8 (3.6)	0.57
CL vascularity (*)	1 (0, 1)	1 (0, 1)	0.43

Table 3: (*) Median (IQ range) reported for each group. Analysis using Mann-Whitney test.

Discussion of research parameters

FSH

Follicle stimulating hormone (FSH) is the first hormone to be released at the beginning of each menstrual cycle. It is produced in the anterior pituitary gland and its role in the hormone 'symphony' that constitutes menstrual cycle physiology is to 'wake up' the ovaries and stimulate follicle development. The resulting ovarian activity initiates the growth of multiple follicles on both ovaries which then release oestradiol into the blood in increasing amounts, at levels proportional to the number and size of the developing follicles. The increasing amount of circulating oestradiol acts as a negative feedback on pituitary gland function, reducing FSH and thereby attenuating ovarian follicle growth and oestradiol levels. FSH is thus a well recognised measure of ovarian response to pituitary stimulation: the lower it is, the healthier the ovarian activity. In our study the significant reduction in FSH after treatment thus indicated improved ovarian function. There have been many studies of FSH levels and pregnancy outcomes in sample groups of women undergoing IVF treatments which show that women with lower FSH levels achieve higher pregnancy rates. At present there is no bio-medical treatment for reducing high FSH levels and unfortunately for these women IVF clinics select only those with low FSH levels in their screening process. In the situation where women register with high FSH, CHM has the potential to provide an effective method of treatment as a precursor to ART.

Endometrium changes

The status of the endometrium is particularly important for the implantation of an embryo: failed IVF and ICSI cycles are thought to be associated with factors affecting implantation. It has been well established by previous research on IVF cycles that an endometrial thickness of <7mm will not result in a sustained pregnancy (Steer, et al 1992) and (Glissant, et al, 1985, p.786). It is now accepted also that an endometrial thickness of between 10-15mm gives the best chance of a sustained pregnancy.

The two measures used in this study to determine if any improvements were made to the endometrium were its thickness at day 21 of the cycle and the uterine artery haemodynamics on the same day. The changes we observed showed that endometrial thickness had increased significantly. For patients with a marginal endometrial thickness, this change could be a significant factor in increasing their chances of a natural pregnancy. Although many ART clinics now recognise that endometrial thickness does influence success rates, and routinely evaluate endometrial thickness as part of their standard range of pre-treatment diagnostic tests, we believe there is still not sufficient focus given to the influence of endometrial quality on IVF outcomes. With increasing recognition of its importance to pregnancy rates, however, an opportunity exists for CHM to improve endometrial quality before IVF cycles are initiated.

Ovarian function and follicle development

The main function of the ovaries is to develop follicles containing eggs on both ovaries in each menstrual cycle, and to mature one of these follicles into a Graafian or dominant follicle which will go on to become the ovulatory follicle. The degree to which an ovary is able to achieve this is determined, firstly, by the ovarian reserve of eggs and the quality (age) of these eggs, and secondly, by the ovarian blood supply. Arterial blood to the ovary nourishes the developing follicles before ovulation, and venous blood transports the oestradiol secreted by the developing follicles back to the pituitary to reduce FSH production.

In our study the total number of follicles developed by both ovaries increased only marginally (p-value 0.05,), but we were surprised to find that the size of the Graafian (dominant) follicle increased from a mean of 11.7mm to a mean of 14.4mm, with a highly significant p-value of <0.001. Optimum Graafian follicle size should be between 18mm and 20mm.

IVF treatment aims to produce as many adequately sized follicles as possible for egg harvesting, using synthetic hormones to stimulate ovarian response. However there is an associated risk of over-stimulating the ovaries and causing hyper-stimulation syndrome (HSS), an undesirable and potentially fatal condition. If these side-effects can be avoided or reduced it would be a major improvement in patient care: CHM might be used alongside drug based ovarian stimulation so that the drugs and their side-effects could be reduced.

Uterine artery blood flow and velocity

As discussed above, the increase in follicle numbers and Graafian follicle size correlates directly with a rise in circulating oestradiol, the main function of which is to develop the endometrium to an adequate thickness in preparation for receiving a fertilised egg at around 5-7 days post-ovulation. Ovarian oestradiol is transported to the endometrium via the left and right uterine arteries: the amount of blood and its velocity in the uterine arteries is therefore a good indicator of the degree of oestradiol delivery to the endometrium. Increased blood flow and decreased velocity are both likely to increase the amount of oestradiol supplied to the uterus and therefore the thickness and quality of the endometrium. In this study, uterine artery blood flow increased from a mean peak systolic velocity (PS) of 27cm/sec to a mean of 35cm/s with a highly significant p-value of <0.001. The blood flow resistance in the uterine artery, or pulsatility index (PI), decreased from a mean of 4.8 to a mean of 3.1, again with a highly significant p-value of <0.001. Previous IVF studies have already established that a PS of less that 30cm/sec and/or a PI of more than 3.0 are unfavourable to sustained pregnancy, presumably because there is insufficient blood supply to transport ovarian oestradiol to the uterus. There is no doubt that improving the quality of blood flow is one area where ART could benefit from the administration of CHM. Since the herbal medicines employed to improve quality of blood flow do not affect the action of the stimulation hormones, their application could sit comfortably alongside bio-medical treatment for ovarian stimulation.

Progesterone

Once ovulation has taken place, the endometrium has been prepared for implantation by adequate levels of circulating oestradiol and hopefully an egg fertilised in the fallopian tube, the endometrium is now maintained by the effects of progesterone from the corpus luteum. Progesterone is at its highest level seven days after ovulation, or day 21 in a normal 28 day cycle, and is measured by blood test at this time. In this study progesterone levels increased from a mean of 37 nmol/L to a mean of 52 nmol/L, with a highly significant p-value of <0.001. The reference range for mid-luteal phase progesterone is between 5.3 and 86 nmol/L, with levels determined by ovarian blood supply and corpus luteum size. During IVF cycles it is now common to support the transferred embryos with synthetic progesterone, usually given in the form of a vaginal or rectal pessary (cyclogest). While there are little or no known side-effects from this treatment, synthetic progesterone may not be as effective in supporting pregnancy as endogenous progesterone from the corpus luteum. Using CHM to improve corpus luteum progesterone secretion would therefore seem to be preferable to supplementing with synthetic progesterone.

Corpus luteum development

As has already been explained, progesterone is produced by the corpus luteum and rises very rapidly immediately after ovulation to attain a maximum level around seven days after ovulation. It slowly decreases as the corpus luteum degenerates, and eventually becomes insufficient to sustain the spiral vessels which supply the endometrium, at which point menstrual bleeding and endometrial shedding begins.

Increased progesterone levels relate to increased corpus luteum size and increased vascularity. In this study the increases in corpus luteum size and vascularity were highly significant with p-values of <0.001. IVF does not currently take account of the corpus luteum size or vascularity, largely because it does not exist in a natural form during an IVF cycle: after egg harvesting normal corpus luteum structures are not present on the ovaries. It appears that CHM improves ovarian and corpus luteum blood flow, which in turn improves corpus luteum function in natural cycles. CHM may therefore play a role in natural cycle IVF after embryo transfer in improving production of endogenous progesterone from the corpus luteum. To date there has been no study published showing the role of corpus luteum blood supply in pregnancy outcome, either in natural cycles or IVF cycles, and more research is needed to understand this relationship

Age relationship

To determine if patient's age made any difference to treatment response in relation we compared results between one group aged less than 35 with the remainder of the sample aged over 35. There were 18 patients in the <35 group and 32 in the >35 group, which was in line with the age demographics of the clinic patient list in general. The p-values for the comparison on age with all parameters was >0.07 in all cases, showing no strong evidence in our sample of age-related differences in response to CHM.

Conclusion

The study was completed on schedule and met all the aims and goals initially set. It was a very rewarding endeavour and the outcome was very encouraging indeed. The study utilised well recognised and accepted qualitative statistical methods of evaluation, and the fertility indicators measured before and after treatment were accepted conventional medical measures of female fertility. As far as we know, there has not been any

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previous research carried out in the West into CHM and infertility with this degree of scientific analysis. This study should therefore be interesting to both the TCM and conventional medicine communities concerned with female infertility. The outcome clearly demonstrates improved fertility indicators, with no patient side-effects and a reduction of patients in the category traditionally labelled with unexplained infertility.

If adopting CHM as a complementary treatment alongside ART achieves higher success rates and reduced side-effects, maybe one of the fertility clinics would be interested in conducting a trial comparing the success rates of a conventional ART cycle with those using integrated CHM/western medicine treatment. If sufficient volunteers could be recruited for a placebo-based randomised control trial, further weight would be added to the initial findings of a study such as this.

Our next step would be to conduct a larger scale research project with a sample size of at least 1000 patients recruited from those considering IVF treatment, as a sample group of this size and demographic would be truly representative of the general population in terms of numbers and health. Again, a randomised control trial would add further weight to our findings, although, given the psychological pressure to fall pregnant as soon as possible that infertility patients are under, it might be difficult to get a sufficient percentage of women to accept the placebo treatment some would need to take with this approach. These are considerations that we might address in future work. ■

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