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Clinical Evaluation of Coded Herbal Medicine Fertinorm for the Treatment Female Infertility

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ABSTRACT

The aim and objective was to analyze the comparative efficacy between Fertinorm (herbal medicine) and Clomiphene citrate (allopathic medicine) for the treatment of female anovulatory infertility. A double blind, prospective, randomized two arm parallel groups clinical trial was conducted in WHO group II anovulatory female patients. The trial was executed on 200 subjects of ages between 20-37 years in four consecutive cycles. End results data analysis revealed no significant efficacy difference between two treatment arms as $p > 0.005$ and conception rate was same between these two groups however adverse effects were not seen in test group. In conclusion, on the basis of statistical analysis done by chi square test, Mann-Whitney *U* test and Kaplan-Meier method null hypothesis is accepted in female anovulatory infertility treatment ($p>0.05$) and strongly rejected with regard to safety as $p<0.05$. However, based on statistical analysis drawn by chi square test and Kendall's tau-b test, significantly greater side effects were noted in group B as $p = 0.001$ and $p = 0.028$ respectively.

Keywords: Female anovulatory infertility, herbal alternate treatment, Clomiphene citrate therapy

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INTRODUCTION

Infertility is a malaise of the reproductive system, which affects both men and women with almost equal frequency[1]. To reproduce is a global phenomenon that afflicts human population and considered to be a public health issue of significance. An estimation of a international survey executed by the World Health Organization (WHO) revealed that 60-80 million couples have unwanted infertility[2]. The ovulation is a complex process involving endocrine, autocrine and paracrine communication between the hypothalamus-pituitary-ovarian axes[3].

Despite the broad use of herbal medicine infertility treatment there is relative paucity of data available to demonstrate convincingly the safety and efficacy of these complementary and alternative therapies. Therefore, systematic analysis of alternative treatment for female infertility will be targeted and rigorous clinical investigation on herbal medicine as compared to allopathic medicine will be conducted. The NAPALERT plant literature data (Natural Product Alert Database, University of Illinois at Chicago) was also included for the coded herbal formulation Fertinorm. preparation as extract of *Withania somnifera* (L.) Dunal. root, *Asparagus racemosus* Wild. root, *Asparagus adscendens* Roxb. root, *Vitex agnus-castus* L. entire plant, *Myristica fragrans* Houtt nuts and *Cimicifuga racemosus* L. plant.

MATERIALS AND METHODS

A random technique was used for this anovulatory infertility research project was random[4]. A double blind, comparative clinical trial was conducted. After fulfilling the patient's criteria, subjects were randomly allocated to one of the two treatment group. In this study only those patients were selectively enrolled through clinical history and after being confirmed through lab reports that have female factor infertility. Then these were randomly allocated with the ratio of 1:1 for controlled treatment (n = 100) received Clomiphene citrate tablets twice daily for 5 days labeled as group A, and test treatment (n = 100) received Fertinorm twice daily for 5 days labeled as group B. The dosage of both treatments was 50 mg and was prescribed to 5-9 day of monthly cycle. Treatment lasted for 4 consecutive menstrual cycles. All general medical, biochemical and hematological measurements were performed according to routine procedures of the individual study centers. At each follow up visit, patients were judged for conception and the side effects during the treatment course of each group. Data collected about side effects included the skin irritation, gastrointestinal disturbance, menstrual irregularity and general weakness after administration of the treatment.

The cases suffering from infertility were selected on the following basis as: verbal consent, Female's patients between the ages of 20-37 years, infertility due to ovulation disorders (Anovulation) or, recurrent vaginal infection or cervicitis or, corpus luteal insufficiency or due to secondary amenorrhea, or female's patients trying unsuccessful in conception despite all normal repots, or patency or at least one normal fallopian tube, patients residing in Karachi, Pakistan, All socio-economic groups were inducted. In the same way those subjects excluded who were fall in exclusion criteria as infertility due to congenital abnormalities, or infertility due to bilateral tubal blockage, or infertility due to mayomas, or infertility due to pelvic tuberculosis, or infertility due to male factor oligospermia, azospermia etc, or infertility due to pituitary failure (Sheehan's syndrome) as well as patient residing outside Karachi due to follow up hurdles. This study was carried out during May 2010- April 2012 at the Gynecology ward of the Shifaul Mulk Memorial Hospital, Hamdard University campus, Karachi, Pakistan and The Ethical Committee consent has already been taken before the start of the study.

To compare different variables chi-square test was applied. The experimental design has been used into two (separate) groups of subjects. The cut point was set at 0.05. The acceptance or rejection of hypothesis was undertaken by statistical analysis by chi-square test. A two-sided *t* test for two independent samples was employed to compare the mean of ages.

The standardization and quality control of herbal drug is the most important factor to determine the efficacy and safety of the dosage form design. In order to determine the drug standardization of Fertinorm various physico-chemical techniques were utilized. The authenticity of Fertinorm was determined through infra red spectral identification. The infrared spectrums of Fertinorm powder was obtained which showed peaks at 1020, 1210, 1215, 1300, 1375, 1625, 1725 cm^{-1} in the fingerprint region. Other peaks obtained were at 2750, 2850, 2975, 3300 cm^{-1}. These peaks clearly exhibit the IR spectral assignment for the different chemical molecules such as the C-O stretch (1020 cm^{-1}), C=C stretch (1375 cm^{-1}), - CH stretch (2975, 2850, 2750 cm^{-1}), -OH stretch (3300 cm^{-1}) see Figure 1.

RESULTS AND DISCUSSION

A total of 200 women age 20-37 years, who have tried unsuccessfully to conceive, were randomized in five centers i.e. Shifa-ul-Mulk memorial Hospital, Civil hospital, Karachi, Al-Mumtaz hospital, Malir, Saudabad Hospital and Alkhidmat hospital. Both groups had comparable demographic characteristics (Figure 1). The overall mean age was 26.92 ± 5.18 years

in both groups. The mean age in group A was 27.11± 5.19 years and group B was 26.73 ± 5.19 years. The cause of anovulatory infertility was female in all cases.

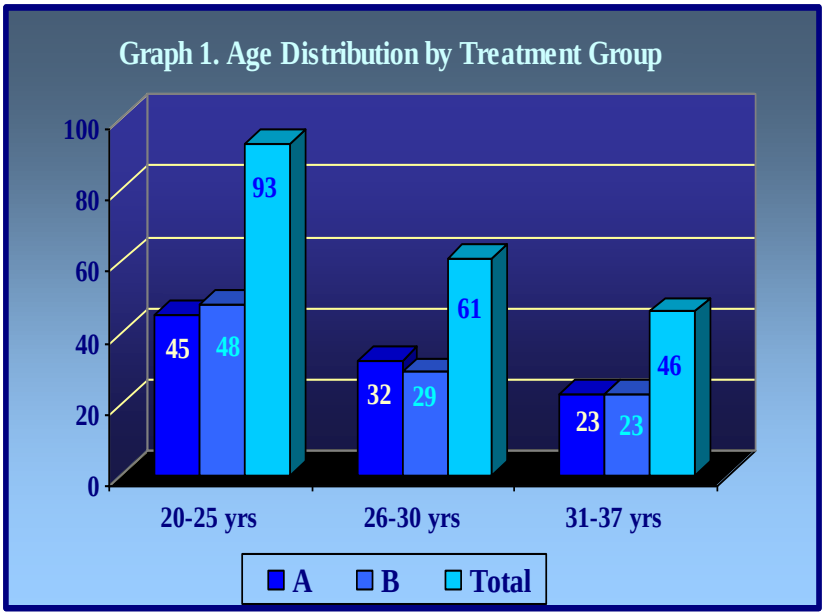

Figure 1: Age Distribution by Treatment Group

The data revealed that anovulation was the chief reason of infertility in most of the cases (90% vs. 85.5%). Overall patients of primary infertility (15.0%) and 170 subjects of secondary infertility (85.0%) were registered at the time of enrollment

At base line hormonal assessment were performed in order to ensure hormonal imbalance in trialed patients. The values of Follicular stimulating hormone (FSH), Luteinizing hormone (LH), testosterone and prolactin were listed in Table 1.

Table 1. Baseline Clinical, Hormonal and Metabolic Data by Treatment Group

Variables	Treatment Group		p value
	A	B	
Duration of Infertility	17.6 ± 4.6	14.2 ± 4.1	0.21
FSH (mIU/ml)	7.6 ± 1.9	8.1 ± 2.1	0.67
LH (mIU/ml)	17.8 ± 4.9	19.0 ± 5.1	0.23
TSH (µU/ml)	2.7 ± 0.5	2.6 ± 0.6	0.37

Numbers of ovulatory subjects after drug induction were tabulated in Table 2. The criteria for ovulation check were set either a urinary LH peak or ultrasonography. The measurement of follicle size was checked by ultrasonography and compared to the required size for ovulation which is 10 18 mm. At each follow up the number of subjects shown ovulation were greater in Group A as evident by $p < 0.005$. It was seen that 20 patients gained increased in their two follicle size after medication.

Table 3. Causes of Infertility in Whom Conception Occur per Treatment Group

Follow ups after treatment	Causes	Treatment Group		Total
		A	B	
1st	Anovulation	5	10	15
	Secondary amenorrhoea	3	2	5
	vaginal infection	0	0	0
	unexplained	1	2	3
2nd	Anovulation	5	6	11
	Secondary amenorrhoea	2	2	4
	vaginal infection	2	1	3
	unexplained	1	0	1
3rd	Anovulation	7	11	18
	Secondary amenorrhoea	2	3	5
	vaginal infection	1	1	2
	unexplained	0	1	1
4th	Anovulation	14	10	24
	Secondary amenorrhoea	5	2	7
	vaginal infection	4	2	6
	unexplained	2	2	4
Total Subjects		54	55	109

The 9 women conceived after first cycle treatment period (n = 3 with amenorrhea, n = 1with idiopathic infertility, n = 5 with luteal insufficiency/anovulation) in group A. Whereas 14 women (n = 2 with amenorrhea, n = 2 with idiopathic infertility, n = 10 with luteal insufficiency/anovulation) in group B. In women with amenorrhea or luteal insufficiency, pregnancy occurred in both the group with no significant difference as $p > 0.05$ as displayed in Table 3. In women with female factor infertility due to secondary amenorrhea and luteal insufficiency, both treatments can be recommended. No significant differences between the two groups were found ($p > 0.05$). Similarly after fourth cycle treatment period or fourth follow up 25 women conceived (n = 5 with amenorrhea, n = 2 with idiopathic infertility, n = 14 with luteal insufficiency/anovulation, n = 4 vaginal infection) in group A and 16 women (n = 2 with amenorrhea, n = 2 with idiopathic infertility, n = 10 with luteal insufficiency/anovulation, n = 2 vaginal infection) in group B as shown in Table 2.

Table 2. Ovulation and Pregnancy Rates per Treatment Group

Menstrual cycles	Ovulation rate			Pregnancy rate		
	Group A	Group B	p value	Group A	Group B	p value
1st	83	52	0.001	9	14	0.268
2nd	80	57	0.021	10	9	0.740
3rd	69	65	0.747	10	16	0.160
4th	68	42	0.030	25	16	0.314

Overall pregnancy rates were 54% and 55% in the group A verses group B respectively. No ectopic pregnancies were reported in each group. The number of ovulation and pregnancy were recorded in table 02. Statistical data revealed that no of ovulations varied in these treatment arms followed by the medication. In first, second and fourth follow ups while no statistical difference was seen in third follow up in both treatment groups. Whereas the pregnancy rate per ovulatory cycle there was no significant difference in any follow up when comparing the group A with group B ($p = 1.000$).

Maximum pregnancy rate was noticed in the fourth cycle. Although the original protocol advocates 4 cycles of treatment, 17% of enrolled patients received more than 4 cycle's treatment and 14% of registered pregnancies occurred during the 5th and 6th cycles. The patients who got abortion were also documented and seen no difference in two groups [6/100 (6%) vs. 13/100 (13%) groups A and B, respectively. It was also recorded that no ectopic pregnancy or multiple pregnancies seen in both treatment grouper medication. All abortion except one occurred before 10 weeks gestation.

Survival curves were analyzed by Kaplan-Meier method. These curves displayed the entire follow up sequence in cumulative way in both treatment arms. Curves quality was checked by log rank test. Life tables were also underway to check the age related first birth in patients. The Kaplan-Meier survival analysis exhibited similar results between two groups as seen in the case of chi square i.e. $p< 0.05$. This is clearly indicating that there is no difference in total conception and hence null hypothesis was accepted.

Rates of conception observed in both treatment groups were also estimated via Cox proportional hazards regression[5] Figure 2 to Figure 7. The 95% confidence interval was taken in this model. The hazard ratio applies to the rate of abortion recorded after treatment response. The ultimate result of Cox regression was the same as seen in previous tests results. No significant conception difference found between two treatment groups ($p = 0.004$). The relative risk of conception is 0.773 (95% confidence interval 1.26–3.702).

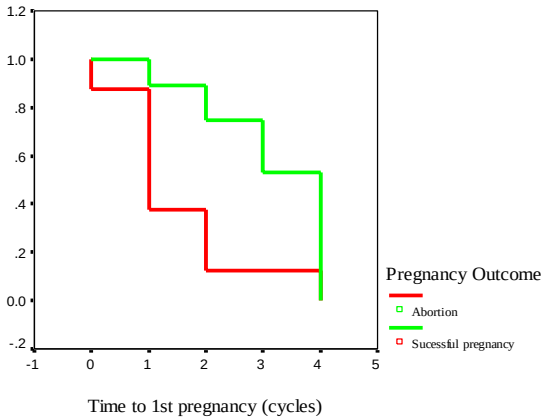

Figure 2: Survival Function in Test Group

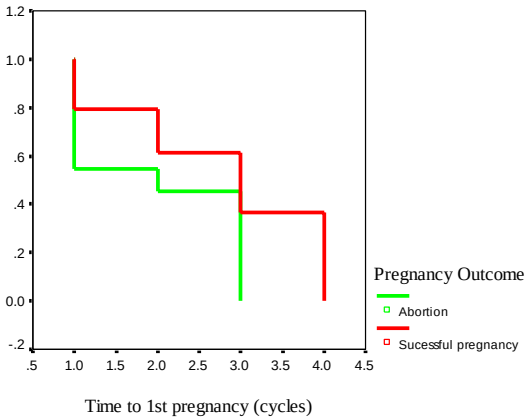

Figure 3: Survival Function in Control Group

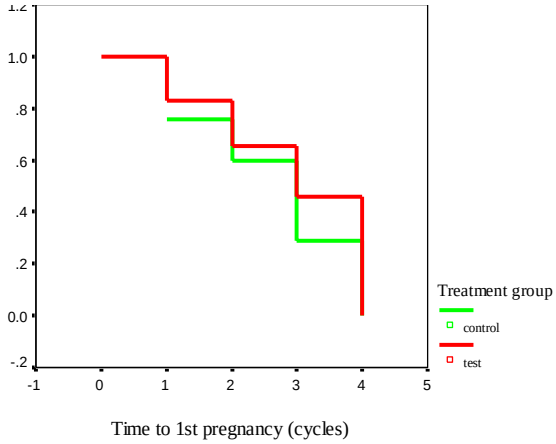

Figure 4: Survival Function at Mean of Covariates

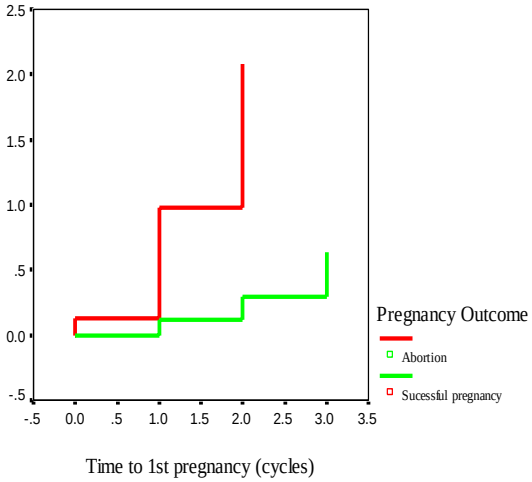

Figure 5: Hazard Function in Test Group

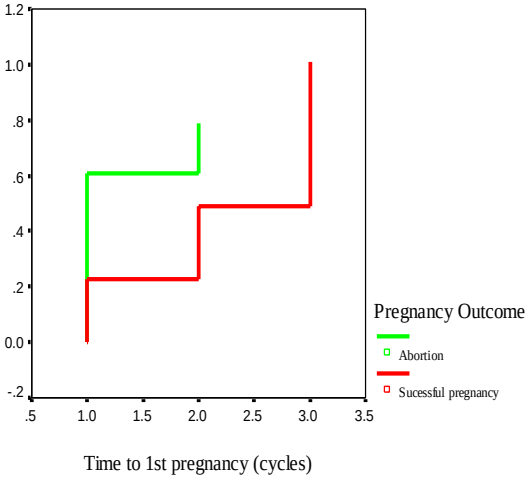

Figure 6: Hazard Function in Control Group

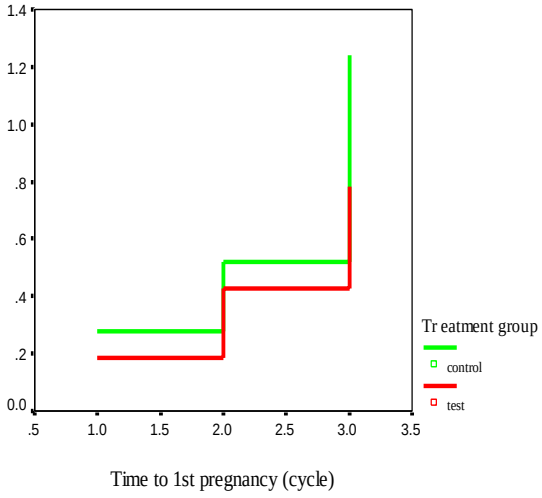

Figure 7: Hazard Function at Mean of Covariates

Conclusively on the basis of Kaplan-Meier method same results were obtained as previously proved with Pearson chi^2 test. Hence on the basis of these statistical significant results null

hypothesis was rejected, thus indicating that both treatment options have similar pregnancy outcomes and similar abortion rate results, and clearly specifying that control and test drugs have similar efficacy.

At the end of study it was noted that no serious side effects were recorded for Fertinorm and Clomiphene citrate, and also no ovarian hyper stimulation syndrome noted. Furthermore no patient's withdrawal seen due to side effects as enlisted in Table 4.

Table 4. Side Effects Observed in Both Treatment Groups

Observed Side-effects	Treatment Group		Total	p value
	A	B		
Abdominal Discomfort	1	6	7	0.001
Hot Flushes	1	14	15	
Visual Blurring	1	3	4	
Other Complaints	6	8	14	
No Complaints	91	69	160	

Infertility is the leading cause of social stress in developing countries especially South-East Region. In Pakistan its rate are higher may be due to concurrent reproductive tract infection. However, assisted reproductive techniques are also present and approached in affluent societies. Never the less the social stress on women's effect families, the infertility is not just the issue of children but also adjunct with mental and social comfort. So we are at the edge where we need safe, efficacious and cause effective medicine that would be effective and resolve the social burden[6].

We studied the literature of such effective therapies retrospectively and found many researches that had already been conducted. A comparative randomized controlled trial of Chinese medicine verses comphine citrate in 2002 to 2006. Total 1009 studies had been conducted in which research focused on the change in the basal body temperature, ovulation, endometrial change and conception through randomized trials. 1316 patients screened in fourteen randomized controlled trials who fulfill the inclusion criteria out of which four studies revealed increased in basal body temperature (risk relative 1.14), similarly six studies conducted to estimate the ovulation and found no significant difference as (risk relative 1.18), thickness of uterine endometrium increased in two trials (risk relative 1.78), while pregnancy rate increased up to 50 percent in thirteen studies. Hence, in a nut shell Chinese medicine might enhance the contraceptive therapy. No doubt these surveys were not fully fulfilling the randomized control trial criteria and in future there is a need of large scale control trials that would be according to the standard of good clinical practice[7].

A study on Letrozole has been described as an alternative to clomiphene citrate requiring

ovulation induction. In this study the maturation of follicle/ ovulation induction due to insulin resistance was studied by given Coptidis from Berberine. The 660 infertile women suffering from polycystic ovarian syndrome (PCOS) were followed up in China for conception. This was a multicentre randomized three armed study (a) berberine with letrozole, (b) letrozole and berberine with placebo and (c) letrozole placebo and berberine. The dosage of berberine was 1.5 g/day for thrice a day. Finally the results declared that the combine result of berberine and letrozole were significantly higher than other two groups [8].

A meta-analysis of study on infertile cases who were treated with Chinese herbal medicaments were retrieved in which 1659 patients were treated and benefited from this therapy as the odds ratio was 3.12, similarly the abortion rate was reduced as odds ratio was 0.2, ovulation ratio increased (odds ratio: 1.55) and cervical mucous score improved (odds ratio: 3.82). The confidence interval was 95% in all the cases and the clomiphene citrate was at the control arm. Chinese herbal medicine was found superior and safe for the cure of anovulatory infertility[9].

A comparative study between mushroom Maitake (*Grifola frondosa*) and clomiphene citrate was carried out on 80 PCOS patients. This mushroom is suppose to be insulin sensitizer and given to patients for 12-18 weeks. The end result analysis revealed that Maitake could be a drug of choice in those patients who failed on clomphine therapy as $p = 0.0006$[10]. A similar study on Kampo medicine *Unkei-to* were applied to patients who have anovulation due to hormonal imbalance. It was seen that ovulation achieved in 61.3 and 66.7% patients after 08 weeks of treatment. So it could be put up that the Kampo medicine is effective for ovulation due to gonadotropin upset [11].

Another comparative study between clomiphene citrate and *Wen-Jing-Tang* was conducted on 16 patients suffering from infertility. The dosage of was 150 mg per day for 05 days starting from day 05 of the cycle while *Wen-Jing-Tang* dosage was 5 gram a day for five days starting from day 02. The ovulation met in 43.8% patients[12]. Overall most of the researched revealed that clomiphene citrate was the drug of choice for anovulatory infertility and later and alternate therapeutic approach were mingled with the use of letrozole, and aromatase inhibitors. However satisfactory justification for the combined therapy is not present. Synergistic activity of clomiphene and letrozole were not yet investigated[13].

In our study the majority of patients selected in test and control group (90% vs. 85.5%), were treated for anovulation which play a definite role in infertility. Overall, the mean duration of infertility was 2.5 (range 0.7–9.0) year, and 30 subjects of primary infertility i.e. unprotected sexual inter course and female not pregnant after one year accounted of 15.0%, where as 170 subjects of secondary infertility i.e. female pregnant at least once, but not able to pregnant there

after determined as 85.0% were registered at the time of enrollment. Earlier studies on utilization of different herbal medicine to treat anovulatory infertility had been successful and comparable with conventional medicine. This study outlines an approach to the scientific and clinical support of traditional and conventional medicine to treat anovulatory infertility and the former can be justified as a new clad therapeutics. The null hypothesis has been approved for the safety measure depending on the p value calculated by the chi squire test as well as other statistical measure in female infertility. The different herbal medicinal constituents of Fertinorm together synergistically play a role to combat infertility. Further statistical parameters have conclusively proved the identical analysis of efficacy of Fertinorm with Clomiphene citrate.

The findings from this study concluded the following salient clinical assessments: There was statistically no significant difference when comparing the effectiveness of herbal treatment Fertinorm to Clomiphene citrate for the treatment of female anovulatory infertility. A significant difference was demonstrated, illustrating that Fertinorm significantly increased ovulation. This is clearly evident that Fertinorm possesses a therapeutic value for the treatment of female infertility and a suitable potential treatment modality for the treatment as part of gynecological practice.

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