



Does Prayer Influence the Success of *in Vitro* Fertilization–Embryo Transfer?

Report of a Masked, Randomized Trial

Kwang Y. Cha, M.D., Daniel P. Wirth, J.D., M.S., and Rogerio A. Lobo, M.D.

OBJECTIVE: To assess the potential effect of intercessory prayer (IP) on pregnancy rates in women being treated with *in vitro* fertilization–embryo transfer (IVF-ET).

STUDY DESIGN: Prospective, double-blind, randomized clinical trial in which patients and providers were not informed about the intervention. Statisticians and investigators were masked until all the data had been collected and clinical outcomes were known. The setting was an IVF-ET program at Cha Hospital, Seoul, Korea. IP was carried out by prayer groups in the United States, Canada and Australia. The investigators were at a tertiary medical center in the United States. The patients were 219 women aged 26–46 years who were consecutively treated with IVF-ET over a four-month period. Randomization was performed after stratification of variables in two groups: distant IP vs. no IP. The clinical pregnancy rates in the two groups were the main outcome measure.

RESULTS: After clinical pregnancies were known, the data were unmasked to assess the effects of IP after assessment of multiple comparisons in a log-linear model. The IP group had a higher pregnancy rate as compared to the no-IP rate (50% vs. 26%, $P=.0013$). The IP group showed a higher implantation rate (16.3% vs. 8%, $P=.0005$). Observed effects were independent of clinical or laboratory providers and clinical variables.

CONCLUSION: A statistically significant difference was observed for the effect of IP on the outcome of IVF-ET, though the data should be interpreted as preliminary. (J Reprod Med 2001;46:781–787)

Keywords: fertilization *in vitro*, embryo transfer, prayer, complementary medicine, alternative medicine.

**Our data suggest a benefit of IP
on IVF-ET.**

Introduction

In vitro fertilization–embryo transfer (IVF-ET) has emerged over the last 20 years as a viable option for the treatment of infertility. While the pregnancy rate was low in the first decade, in recent years the success rate has been increasing. The pregnancy rate for IVF-ET increased from 20.7% deliveries per retrieval in 1984¹ to 28% in 1997² (the last United States survey). Several factors have contributed to the increased success of IVF-ET.^{3–6} Among these are the greater experience of the clinical teams and the use of certain regimens, such as with a GnRH agonist.⁷ However, it is generally agreed that advances in the laboratory that result in good-quality embryos are perhaps the most significant reason why the success rate of IVF-ET has increased^{5,8} Variations between the practices of physicians also has been suggested as influencing success rates,⁹ as have biologic factors, such as cycle-to-cycle variability. These factors warrant further assessment by prospective, randomized trials.

Use of alternative or complementary medicine has been increasing in popularity.¹⁰ These

approaches include the use of healing touch and prayer, with several reports suggesting a potential therapeutic benefit in a variety of disorders.^{11,12} However, from an evidentiary medical perspective, these reports have not been substantiated.¹³ Specifically, intercessory prayer (IP) has been studied, and while preliminary experiments have been interpreted as suggesting a possible improvement in patients with heart disease and AIDS,^{14,15} a recent review of the literature does not indicate any conclusive benefit overall.¹⁶ However, a recent study¹⁷ suggested benefit for patients with heart disease, and another,¹⁸ the benefits of distal healing.

The data demonstrate a 50% statistically significant pregnancy rate in the IP treatment group....

There have been no studies, to our knowledge, on the application of IP to the treatment of infertility. Therefore, we carried out a prospective, randomized, double-blind study in which the efficacy of IP was assessed in patients undergoing treatment for IVF-ET who were unaware of the study. We chose the setting of IVF-ET in order to control for as many variables as possible and designed the study to be masked to patients, providers and investigators. In planning and conducting this trial in as rigorous a fashion as possible, we set out with the expectation that we would show no benefit of IP. None of the authors are employed by religious organizations, and we were not asked by any religious groups to conduct this trial, nor did we seek religious advice at any time.

Materials and Methods

Subjects

Two hundred nineteen women aged 26–46 (mean, 33.9±4.7) with weight 41–72 kg (mean, 54.7±5.2) were prospectively but blindly enrolled into this randomized trial. These women were consecutively treated between December 1998 and March 1999. They were candidates for IVF-ET; we did not consider patients destined for tubal transfer (zygote or gamete intrafallopian transfer). These patients were being seen at the Cha General Hospital, Seoul, Korea. Twenty of the 219 cases had incomplete data available due to fragmentary E-mail transmission and were eliminated from further consideration prior to randomization. Patients beginning the cycles were ultimately stratified based on: (1) age, (2) length of infertility, (3) type of infertility, and (4) number (if any) of prior attempts (all cases considered unless tubal transfer was scheduled). They were then randomized into two equal groups (described below) to test the potential effects of IP. Patients and their providers did not know that they were participating in this study. Randomization and data transmission for IP or no IP (described below) were the responsibility of an independent statistician in Korea and another in the U.S. who was not affiliated with the authors. Randomization codes were made available only when all pregnancy data were available at completion of the study.

Protocol (IVF-ET and IP)

All patients were treated with an identical protocol including the use of a GnRH agonist and gonadotropins (usually 3–75 IU ampules/d) until at least three follicles were mature. ET was carried out three days after retrieval.

The study examined the effect of a combination of directed and nondirected distant petitionary, or intercessory, prayer (IP) with patients undergoing IVF in a two-tier system. Petitionary or intercessory prayer is prayer participants' requesting God's intervention or assistance for the benefit of another individual.¹⁹ Directed IP is praying for a specific outcome for an individual or individuals—i.e., prayers for conception.²⁰ All prayer participants in this study were of various Christian denominations. There were two tiers of prayer groups. Tiers 1 and 2 each consisted of four blocks of prayer participants (A–D). Most intercessors were known by one of the authors (D.P.W.), and others were referred by known intercessors. Within each block (A–D), intercessors knew each other. Prayer participants in tier 1 prayed in a directed manner with a specific intent to increase the pregnancy rate

of the patients. Tier 2 prayer participants prayed in a directed manner for tier 1 prayer participants with the intent to increase their prayer efficacy.

IVF-ET patients were assigned to these prayer groups after randomization. For each treatment session, members of one prayer block in each tier randomly received a single sheet of paper with five IVF patients' pictures (a treatment unit) and were asked to pray for these patients. Prayer for a treatment unit commenced within five days of initial hormone injection and continued for three weeks. Tier 1A participants prayed in a directed manner with the intent to increase the rate of pregnancy for each group of five patients, and tier 2A participants prayed in a directed manner for tier 1A prayer participants with the intent to increase the efficacy of prayer intervention and in a nondirected manner for the patients with the intent that God's will or desire be fulfilled in the life of the patient. The groups of four blocks with two tiers each were distributed in three countries, and each group was composed of 3–13 participants. In addition to the above, a separate group of three individuals prayed in a general, nonspecific manner with the intent that God's will or desire be fulfilled for the prayer participants in tiers 1 and 2.

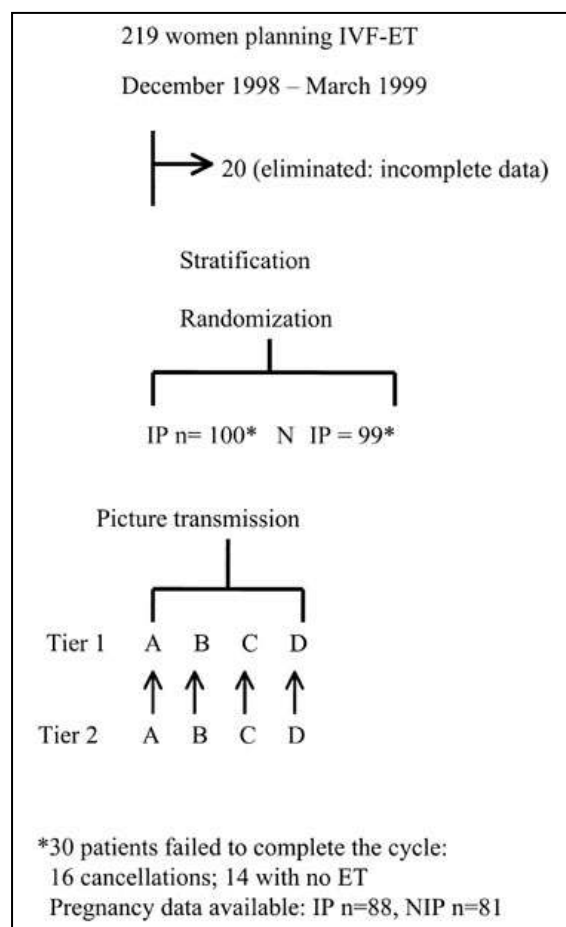


Figure 1 Flow chart of 219 women aged 26–46 planning IVF-ET randomized to IP vs. NIP. In groups of five, pictures of patients randomized to IP were sent to prayer groups in tiers 1 and 2.

Patient pictures and informational data, which are routinely obtained for all infertility patients, were collected at the Cha Medical Center during the trial dates by an independent statistician and transmitted to the United States via E-mail. E-mail was log-in and password protected, and the password was changed on a regular basis.

The pictures of treatment patients, for those patients randomized after stratification to IP, were pooled and divided into units of five pictures per unit. Five was an optimum number for this visual display. Each treatment unit of five pictures was digitally assembled onto one page and transmitted to the prayer participants via asynchronous facsimile transmission or express mail. Transmissions occurred electronically over secured systems and were sent only to prayer groups. No patient-identifying data (names, ages, etc.) were included. As stated above, prayer for a single treatment unit commenced within five days of initial hormone injection and continued for three weeks such that all patients randomized to IP had the intervention throughout the course of IVF-ET treatment.

Assignment

Patients were randomly divided after stratification of infertility status by computer allocation into treatment and control groups consisting of IP and no intercessory prayer (NIP), respectively. Figure 1 is the flow diagram of the randomized trial.

The experimental protocol for this study was approved by the internal review board of Cha General Hospital. Intercessory prayer was carried out in the United States, Canada and Australia without knowledge of the providers or patients.

Masking

No patient was informed about this study. After the independent Korean statistician retrieved the data and transmitted it to the U.S. a second independent statistician in the U.S., randomized subjects and transmitted pictures to the prayer groups in different countries for subjects randomized to IP. The prayer groups had only pictures and did not have any patient information. Once

pregnancy data were available for all the subjects over this trial period, these data were transmitted to the independent statistician in the U.S. to compile the results. The compiled results were then seen by the authors for the first time.

Participant Flow and Follow-up

After randomization, 16 patients had their cycles cancelled, and 14 cases did not result in ET. These 30 cases did not result in ET. Eighteen cases were eliminated from the NIP group and 12 from the IP group. The number of patients eliminated from each group was not statistically different. We therefore had 169 completed cases available for analysis (Figure 1).

Table 1 *Profile of Patients*

Profile	NIP	IP
No. of patients (ET cycle)	81 (81)	88 (88)
Mean (\pm SD) age (yr)	34.8 \pm 4.4	33.9 \pm 4.7
Duration of infertility (yr)	5.3 \pm 4.0	4.6 \pm 2.8
No. of oocytes retrieved	10.0 \pm 5.9	11.4 \pm 7.2
No. of oocytes fertilized	7.7 \pm 4.9	8.9 \pm 6.2
No. of oocytes transferred	4.3 \pm 1.4	4.3 \pm 1.2
No. of pregnancies/ET cycle (%)	21/81 (26)	44/88 (50)*

Values are mean \pm SD.

* $P = .0013$.

No cases were eliminated after we had pregnancy data available for the 169 patients who had undergone IVF-ET. The 169 cases that had been randomized were divided into 88 having IP and 81 with NIP. Their ages, duration of infertility and number of prior attempts at IVF-ET were similar (Table 1). Once pregnancy data were available, the study was completed. Patients were not

informed about the study or results.

Analysis

All data were subjected to multiple comparisons in a log-linear model. The end point in this study was a clinical pregnancy defined by an intrauterine fetal pole with a heartbeat on ultrasound. Possible confounders were taken into account in a stepwise fashion, where we used a model of logistic regression. Data were analyzed using ANOVA and the least squares method. The sole outcome of the study was the pregnancy rate. No sample size could be projected because there have been no previous such studies.

Results

During their treatment cycles, the groups (IP and NIP) had similar numbers of oocytes retrieved (11.4 \pm 7 vs. 10.0 \pm 5.9) (Figure 2), numbers of oocytes fertilized (8.9 \pm 6 vs. 7.7 \pm 4.9) and preembryos transferred (4.3 \pm 1.2 vs. 4.3 \pm 1.4). The IP group, however, had a significantly higher pregnancy rate as compared to the controls (44/88, 50% vs. 21/81, 26%; $P = .0013$) (Table 1, Figure 2). After seven weeks of pregnancy there were three spontaneous losses in the NIP group and three in the IP group. All other pregnancies delivered at term, and obstetric outcomes were similar in the two groups. Adjusting for the pregnancy loss data, the term pregnancy rates were 22.2% in the NIP group and 46.6% in the IP group ($P < .001$).

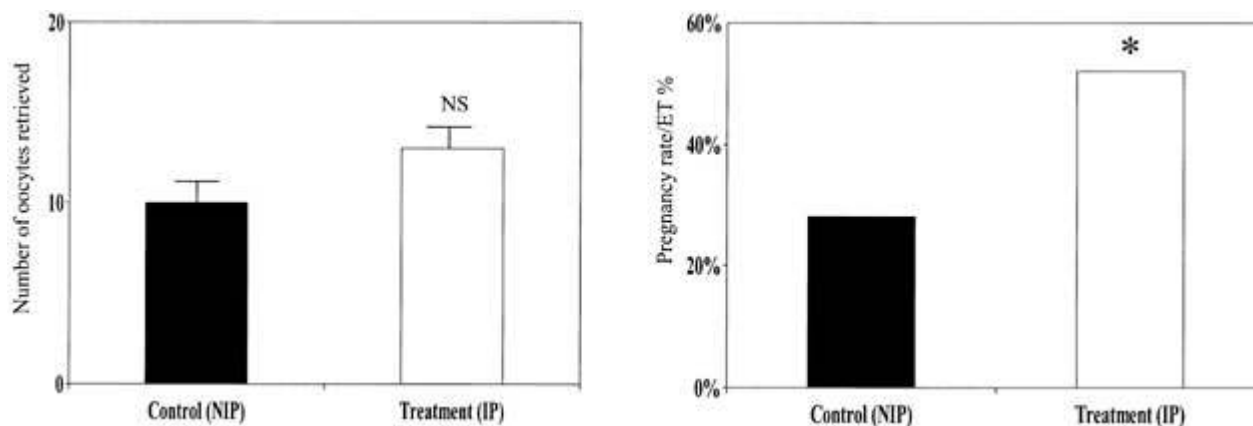


Figure 2 Number of oocytes retrieved and percentage pregnancy rate per ET in the control (NIP) and treatment (IP) groups. NS=no significance in the number of oocytes retrieved in the two groups. *Significantly higher pregnancy rate with IP ($P<.0013$).

The following variables were assessed using logistic regression: age, duration of infertility, type of infertility and number of prior attempts. None of these variables affected the pregnancy rate. The adjusted odds ratio for pregnancy (IP vs. non-IP) was 3.3 (95% CL, 1.6–6.6).

Details of the number of oocytes retrieved are in Table II. The fertilization rates were similar, but the cleavage rate was higher in the IP group after adjustment for variables (73% vs. 69%, $P<.0269$). The unadjusted cleavage rate was of borderline significance ($P<.07$). The implantation rate was significantly higher in the IP group (16.3% vs. 8%, $P=.0005$). The number of multiple pregnancies was also higher in the IP group (17% vs. 4.9%, $P=.0126$).

Table II Cycle and Pregnancy Outcome in Patients

Groups	No. of oocytes retrieved	No. of oocytes fertilized (%) ^a	No. of oocytes cleaved (%) ^a	No. of oocytes transferred (%) ^a	No. of preembryos implanted (%) ^b	Pregnancies/ET cycle (%)	Multiple pregnancies/ET cycle (%)
NIP	810	617 (76)	557 (69) ^c	352 (43) ^d	28 (8.0) ^e	21/81 (26) ^f	4/81 (4.9) ^g
IP	1,007	784 (78)	740 (73) ^c	380 (38) ^d	62 (16.3) ^e	44/88 (50) ^f	15/88 (17.0) ^g

^aPercentage of oocytes retrieved.

^bPercentage of oocytes transferred.

^c.0269, ^d.0134, ^e.0006, ^f.0001, ^g.0126.

The higher rate of pregnancies in the IP group was independent of the type of infertility. The rate in the tubal factor group was 26/51 (51%) for IP vs. 11/43 (26%) for NIP ($P=.0125$); in the nontubal-factor group the rate was 18/37 (49%) vs. 10/38 (26%) ($P=.0470$).

Patients in the two groups were analyzed according to various age groups: <30, 30–39 and >39. There was a consistent statistically higher pregnancy rate for IP in the 30–39-year group and in the >39-year group but not in the <30-year group. IP vs. NIP in the 30–39-year group was 51% (29/57) vs. 23% (14/62) ($P=.0013$), 42% (5/12) vs. 23% (3/13) in the >39-year group and 53% (10/19) vs. 67% (4/6) in the <30-year group. We could not identify a difference in pregnancy rates in women <30, in whom the pregnancy rates were extremely high.

Consistent with the higher implantation rate in the IP group, a greater number of preembryos reached the eight-cell stage in the IP group (66% vs. 45.5%, $P=.0001$). At the time of ET there were fewer preembryos at the five- to seven-cell stage in the IP group (14.5% vs. 28.6%, $P=.0001$) and more seven- to eight-cell embryos in the IP group (69.2% vs. 49.6%, $P=.0001$). Morphologic grading of embryos in the two groups did not differ significantly.

The overall pregnancy rate for IVF-ET during the study (December 1998–March 1999) was 38.5% when all pregnancies (both groups) were taken into account. This rate was similar to the historical

rate for the center's program; the rate during the preceding months, January–November 1998, was 32.8%. Data were analyzed for each of the seven clinician providers who carried out procedures during the treatment period. The total pregnancy rates for the six providers were similar and ranged from 36% to 50%. One provider had only 18 cases and an 11% pregnancy rate. For each of the other six providers, the pregnancy rates for the IP group vs. NIP were 46% vs. 38%, 60% vs. 33%, 57% vs. 22%, 53% vs. 25%, 36% vs. 36% and 67% vs. 22%. The clinical protocols were all identical. The number of embryos transferred and the cleavage stages of the embryos were similar in the cases carried out by the seven providers. There were no changes in the schedules of the team of three embryologists, who all participated equally in the cases during this time, and there were no changes in the laboratory protocols or techniques or new batches of reagents or media used.

Because of known male factor, 41 of the 169 patients had intracytoplasmic sperm injection (ICSI) performed at the time of their cycles. The pregnancy rate in the two groups were not significantly different, IP 11/24 (46%) vs. NIP 9/17 (53%). Nevertheless, in the couples not receiving ICSI, the IP group had a higher pregnancy rate (33/64, 52% vs. 12/64, 19%; $P=.0001$).

Discussion

Several factors are known to either positively or negatively affect the success of IVF-ET procedures. The majority of physicians trained in allopathic medicine, however, would not consider prayer intervention to be one of them.²¹ This was our view in designing this trial. The findings of this study suggest, however, that the inclusion of prayer intervention in the treatment protocol may provide a significant impact upon the success of IVF-ET in women over age 30. This is demonstrated by the IP treatment group, which exhibited statistically increased pregnancy rates for two categories of IVF patients who traditionally demonstrate decreased pregnancy rates, patients 30–39 years of age and those >39. Randomization took into account such variables such as type of infertility. The overall treatment success during the time of the study was in line with the current rates of the program.

The findings of this study are enhanced by the utilization of a methodologic design that eliminated belief, expectation and a placebo effect as confounding variables.²² The fact that patients and clinician providers were unaware of the existence of the study and the investigators were also kept blind to treatment and control groupings ensured isolation of the treatment intervention. Further design restrictions ensured that prayer participants were from a different country and had no information about the IVF patients, thereby eliminating any confounding effect or bias.

The data suggest that the higher pregnancy rates in the IP group occurred as a result of increased implantation in that the oocyte yield and fertilization rates were comparable, as were the numbers of preembryos transferred. IP began early in the ovarian stimulation cycle, and there were no effects of it on the characteristics of the cycle. Because this experiment required a uterine ET, most patients who were candidates for this study had evidence of tubal disease. Although our data suggest an effect of IP on implantation, we cannot speculate further about a mechanism for this observation. We are highly cognizant of multiple unknown variables, which might affect pregnancy rates.

The only two groups who did not show any benefit from IP by subanalysis were couples undergoing ICSI and women <30. At least two possibilities may exist to explain this discrepancy: the smaller number of subjects in these groups and the high pregnancy rates. A minority of patients, 25, were under 30. Similarly, only 41 couples underwent ICSI procedures. In both these groups, the pregnancy rates were extremely high (56% overall in the <30-year group, 49% with ICSI). A much greater number of subjects would have been needed to show an effect if there was one. Further, in randomization of the 25 women <30 years in whom the pregnancy rates were similar, there were more women ($n=19$) in the prayer group. Nevertheless, these pregnancy rates were extremely high and not statistically different. Age was not a confounding variable in these data.

The data demonstrate a 50% statistically significant pregnancy rate in the IP treatment group; it was well above the 26% pregnancy rate in the control group, which in turn was similar in the crude pregnancy rate for this IVF program during the time period. The 50% pregnancy rate is also statistically higher than the overall pregnancy rate in the program for the year before the trial period (32.8%). However, we view these data as preliminary. We are keenly aware of the multiple biologic

factors and unknown variables inherent in the treatment process of IVF-ET.^{23,24} Nevertheless, confidence in pursuing future work in this area is enhanced by the unique prospective, double-blind protocol utilized. Imperative to the integrity of this protocol was the design feature that ensured that patients and clinician providers were unaware of the details of the intervention.

Although this study was approved by the internal review board, in Korea, the fact that subjects were unaware of the intervention remains an area of controversy for future studies but was necessary in our view to eliminate any bias. Additional factors, which need to be explored in subsequent studies, include religiosity and psychological profiles of the participants, the type and duration of IP, and the mechanisms explaining the purported benefit.

Our data suggest a benefit of IP on IVF-ET. However, we reiterate that we view these data to be preliminary and that they may not be confirmed in future investigations.

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From the Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York Presbyterian Hospital, Columbia-Presbyterian Center, New York, New York; Cha Hospital, Seoul, South Korea; and Wirth & Wirth Esq., North Wales, Pennsylvania.

Dr. Cha is Associate Research Scientist.

Dr. Wirth is Attorney with the law firm of Wirth & Wirth Esq.

Dr. Lobo is Professor and Chairman, Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons.

Address reprint requests to: Rogerio A. Lobo, M.D., Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, 622 West 168th Street, New York, NY 10032.

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