Impact of a group mind/body intervention on pregnancy rates in IVF patients

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Objective: To determine if women who were randomized to a mind/body program before starting their first IVF cycle would have higher pregnancy rates than control subjects.
Design: Randomized, controlled, prospective study.
Setting: Private academically affiliated infertility center.
Patient(s): A total of 143 women aged ≤40 years who were about to begin their first IVF cycle.
Intervention(s): Subjects were randomized to a ten-session mind/body program (MB) or a control group and followed for two IVF cycles.
Main Outcome Measure(s): Clinical pregnancy rate.
Result(s): Only 9% of the MB participants had attended at least one-half of their sessions at cycle 1 start. Pregnancy rates for cycle 1 were 43% for all subjects; 76% of the MB subjects had attended at least one-half of their sessions at cycle 2 start. Pregnancy rates for cycle 2 were 52% for MB and 20% for control.
Conclusion(s): MB participation was associated with increased pregnancy rates for cycle 2, prior to which most subjects had attended at least half of their sessions. (Fertil Steril® 2011;95:2269–73. ©2011 by American Society for Reproductive Medicine.)

Key Words: IVF, mind/body, depression, pregnancy, stress management

The relationship between stress and infertility has remained a subject of controversy for many years. Women undergoing infertility treatments exhibit high anxiety and/or high depressive scores at the start of treatment as well as over the course of treatment (1–4). Stress may also have a negative impact on pregnancy rates in women undergoing in vitro fertilization (IVF) (5–8). A recent large study (9) did not reveal a relationship between distress and IVF outcome, so it is possible that there might be differences among patient populations or cultural influences on emotional expression. A meta-analysis which included 14 relevant studies on this topic (10) also did not find a relationship between distress and outcome. However, patient distress in these studies was assessed only once, up to 3 months before cycle start, so the relationship between distress while actually cycling and subsequent pregnancy rates remains unknown. However, distress is the most common reason given by women who voluntarily terminate treatment (11–13), and baseline depressive symptoms can predict treatment termination after only one cycle (14).

A recent study on the impact of stress on fecundity indicated that distress significantly reduced the probability of conception in women just starting to attempt pregnancy (15). The authors concluded that couples need to relax and minimize stress when attempting to conceive. The purpose of the present study was to determine if a mind/body (MB) group intervention was associated with an increase in pregnancy rates in a group of women who were about to undergo their first IVF cycle.

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MATERIALS AND METHODS

Patients and Study Design

This study was conducted at Boston IVF (BIVF), a large academic private practice in the Boston area, during the period of May 2007 to September 2009. The protocol was approved by the Western Institutional Review Board.

All BIVF patients who were scheduled to begin their first IVF cycle and who met the study criteria were eligible for the study. Eligibility criteria were: aged ≤40 years, day 3 FSH/E_2 levels of <12 mIU/mL and <80 pg/mL (respectively), no previous participation in an MB group, daily access to the internet, and fluent in English. Subjects were recruited by a dedicated research assistant through physician or nurse referral, chart review, or patient response to study flyers.

A total of 334 women were identified as being eligible to participate; 148 agreed to enroll. Patients who expressed interest in the study underwent a telephone screening interview with the research assistant and then came in for the intake appointment to sign the consent form. The subject then completed a demographic and contact form. Each subject met or spoke over the phone with one of two study psychologists who administered the Structured Clinical Interview for the Diagnostic and Statistical Manual II, personality disorders section (16). Subjects who scored above the cutoff for normal were deemed to be ineligible for the study and were referred to the BIVF social workers.

Subjects who qualified received a phone call from the research assistant as well as an e-mail with instructions on how to log on to the study website to complete the baseline questionnaires within 48 hours. A custom web-based data capture portal was used. Subjects were asked to log on to the portal to

complete all study questionnaires. Participants' health care teams remained blinded to patient assignment for the duration of the study. Randomization was achieved through the use of a computer-generated random numbers table, and each subject received a phone call or e-mail notifying them of their assignment.

Subjects randomized to the MB arm of the study were referred to the Mind/Body Program for Infertility at the Domar Center for Mind/Body Health located at BIVF. A new group began every 6–8 weeks, and MB subjects simply joined the next scheduled group. All MB programs are heterogeneous for patient diagnosis and stage of treatment.

Control subjects were told that they would receive a $50 spa gift certificate for every 3 months that they remained in the study, with a bonus $100 certificate if they remained in the study for a year. The control patients had the identical amount of contact with the research assistant as the intervention patients, and all other study expectations, other than MB group attendance, were equivalent. The research assistant did not have any extra contact with the MB patients after randomization took place; she simply referred each patient to the Domar Center mind/body group coordinator.

All subjects underwent their first and second IVF cycles at BIVF, where all medical and laboratory variables are collected electronically. Cycle progress was monitored by the research assistant, and β-hCG levels were recorded. A clinical pregnancy was determined to be confirmed by a fetal heartbeat at 7 weeks' gestation with appropriate crown rump length.

Data Analyses

Demographic and clinical characteristics of the women in the two arms were compared by using a Wilcoxon rank sum test for continuous measures and a chi-square test for categoric measures. Pregnancy rates were compared between the two arms by using Fisher exact test.

RESULTS

A total of 143 women met the eligibility criteria and were included in the study. The reasons given by the 186 who elected not to enroll were: not being able to commit to the MB program because of the commute; time conflict; time commitment; or they simply did not respond to the recruitment efforts. A total of 46 withdrew or were ineligible, resulting in 97 subjects who completed at least one IVF cycle. There were 46 MB and 51 control subjects. The reasons for withdrawal were: 1) no longer eligible owing to no subsequent IVF cycle (15 patients); 2) too great a time commitment (15 patients); 3) noncompliance with study requirements (7 patients); 4) dislike of study tasks (6 patients); and 5) other (3 patients). There were no significant differences between the study subjects who participated and those who withdrew for any of the medical or demographic variables collected at intake.

Because most of the subjects were anxious to move on to their first IVF cycle, it was not possible to delay infertility treatment until after they had completed the MB program. Therefore, most MB subjects were already cycling by the time their MB group began.

There were no differences at baseline in any demographic or medical characteristics between MB and control subjects except that more MB subjects worked full-time (Table 1). There were no differences between the two groups in any IVF parameters except that MB subjects had significantly lower rates of ICSI use during cycle 1 (Tables 2 and 3).

The clinical pregnancy rates for the two groups for cycles 1 and 2 are presented in Table 4. Pregnancy rates did not differ between the two groups for cycle 1; however, a difference was seen for cycle 2. A total of 54% of the MB subjects had not attended any sessions before beginning their first cycle, but the majority (76%) had attended at least one-half of their sessions before their second cycle. All MB patients continued through the 10-week program, regardless of their cycle outcome.

TABLE 1

Baseline patient characteristics, mean (SD) or %.

	Mind/body	Control	*P* value
Sample size	46	51	
Age, y	34 (3.7)	34 (3.8)	.90
Years trying to conceive	2.0 (1.2)	2.5 (2.2)	.49
Race			.28
White	89%	82%	
Asian	4%	6%	
African-American	0%	4%	
Hispanic	2%	4%	
Other	4%	4%	
Smoking: yes	4%	6%	1.0
Alcohol use: yes	74%	75%	1.0
Work status			.01
Full time	93%	78%	
Part time	0%	18%	
Not working	7%	4%	
Diagnosis			.44
Ovulation disorder	5	3	
Male factor	8	20	
Tubal	4	5	
Other	10	4	
Unexplained	19	19	
CD3 FSH, mIU/mL	7.1 (1.8)	7.3 (2.1)	.70
CD3 E_2, pg/mL	42.2 (11.3)	44.9 (13.9)	.73

Note: CD3 = cycle day 3.

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While there was an imbalance between the two study arms regarding male factor and ICSI, additional analyses were performed to correct for these imbalances. The analyses confirmed the higher pregnancy rates in the MB patients during cycle 2. When adjusting for ICSI through logistic regression, the *P* value comparing cycle 2 pregnancy rates between MB and control subjects actually decreased slightly to .038, and adjustment for male factor increased the *P* value slightly to .063.

TABLE 2

Cycle 1 patient characteristics, mean (SD).

	Mind/body	Control	*P* value
Sample size	46	51	
Peak E_2, pg/mL	2,174 (1,123)	1,943 (1,144)	.27
No. of follicles	13.4 (7.9)	11.9 (7.1)	.37
No. of mature follicles	11.0 (6.6)	9.3 (4.8)	.29
No. of oocytes inseminated	13.2 (7.8)	11.7 (6.5)	.39
No. ICSI	2.2 (4.8)	5.2 (6.4)	.01
No. fertilized	7.8 (5.5)	8.3 (5.1)	.38
No. of embryos transferred	1.8 (0.7)	1.8 (0.7)	.61
No. cryopreserved	1.5 (1.9)	0.9 (1.3)	.17
No. discarded	4.6 (4.3)	3.9 (3.4)	.66

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TABLE 3

Cycle 2 patient characteristics, mean (SD).

	Mind/body	Control	*P* value
Sample size	21	20	
Peak E_2, pg/mL	2,105 (1,320)	2,211 (1,118)	.59
No. of follicles	11.4 (7.7)	9.2 (4.7)	.54
No. of mature follicles	9.7 (6.6)	7.9 (3.8)	.69
No. of oocytes inseminated	11.2 (7.8)	9.2 (4.7)	.62
No. ICSI	1.5 (3.3)	3.5 (4.1)	.12
No. fertilized	7.0 (5.8)	5.9 (3.4)	.92
No. of embryos transferred	2.0 (1.0)	2.4 (0.8)	.11
No. cryopreserved	1.0 (2.2)	0.4 (0.8)	.88
No. discarded	3.9 (3.8)	3.1 (2.9)	.79

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DISCUSSION

Mind/body–based interventions have been shown to be an effective stress-management approach for the treatment of numerous physical and psychologic conditions. The Mind/Body Program for Infertility was first described in 1990 (17). It is a 10-week group stress management program whose focus is on cognitive behavior therapy, relaxation training, negative health behavior modification, and social support components. Infertility patients with varied diagnoses and at different stages of treatment who participated in the Mind/Body Program for Infertility experienced significantly higher pregnancy rates than control subjects (18). However, there is minimal research on the impact of a stress management program with IVF patients. In a recent meta-analysis on psychologic interventions with infertility patients (19), there was only one randomized study that investigated the impact of an MB-based intervention on IVF patients. First-time IVF patients were randomized to four sessions of "Eastern body-mind-spirit" group sessions (20). The intervention patients had lower anxiety scores and a nonsignificant trend to higher pregnancy rates. The efficacy of psychologic interventions in increasing pregnancy rates with assisted reproductive technology (ART) patients for all psychologic interventions was not supported by the meta-analysis (19), suggesting that identifying the most effective way to decrease distress and potentially increase pregnancy rates has not yet been accomplished for ART patients. It was noted that interventions with at least six sessions were more effective than shorter ones.

Another comprehensive review (21) concluded that group interventions that included education and skills training, such as relaxation training, were "significantly more effective in producing positive change across a range of outcomes than counseling interventions." It is quite possible that some interventions are more effective than others, and it is also possible that the efficacy of different interventions may be affected by the diagnosis of the patient, the form of treatment the patient is receiving, and the baseline psychologic status of the patient.

If one includes the recommendations of the two meta-analyses, theoretically the most effective psychologic intervention would be skills-based of six or more sessions.

The results from the present study support earlier research on the impact of MB-based interventions (17, 18) and add more evidence for the stress-pregnancy relationship in infertility patients. This is the first study to examine a comprehensive stress-reduction program with IVF patients. The results also answer one important question about the possibility of a placebo effect raised after the publication of the first paper reporting on the outcome of participants in the MB program (17). In earlier research, only cumulative pregnancy rates were reported, so it was unclear if the higher pregnancy rates observed in the MB patients were associated with the actual MB skills acquisition or if instead it was simply a placebo effect, because pregnancies in patients who were randomized to the group but had not yet attended any sessions were reported as MB pregnancies.

In the present study, there were no differences in pregnancy rates in cycle 1, in which all subjects knew their group assignment yet most MB patients had yet to acquire any skills. It has been observed in the MB program from patient self-reports that physical and psychologic symptom improvements are noted beginning approximately midway through the program and increase thereafter. There has never been an analysis of potential benefits per session; all earlier research has been on patients who have completed the whole program. Therefore, it is possible that patients who had attended less than one-half of their MB sessions before cycle start had not acquired enough skills to relieve their stress level. There was, however, a difference in cycle 2 when the majority of patients had attended more than one-half of the sessions.

The choice of a control group is an important one. Earlier research which randomized patients to either an MB group, a support group, or a routine care control group showed the MB intervention to have equal pregnancy rates to the support group (18), but the MB patients had healthier psychologic test scores than the support group patients (22). A no-treatment control group was chosen for the present study to more fully expand on the research on the impact of a stress-reduction modality on pregnancy rates in IVF. If a support-group modality had instead been chosen as the control group, the possible outcome of no differences in pregnancy rates between the two groups would have merely shown that the two psychologic interventions were equivalent, and limited knowledge would have been gained. The goal of the present study was to determine the

TABLE 4

Pregnancy rates by group and cycle.

	Mind/body	Control	*P* value
Cycle 1	43% (20/46) (54% 0 sessions, 37% 1–5 sessions, 9% 6–10 sessions)	43% (22/51)	1.0
Cycle 2	52% (11/21) (5% 0 sessions, 19% 1–5 sessions, 76% 6–10 sessions)	20% (4/20)	.05

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impact of a psychologic intervention, i.e., the MB program, on IVF patients. It was not to determine if an MB intervention was better or worse than any other kind of psychologic intervention. However, the control group in this study was not a placebo control group and therefore could and did not control for nonspecific benefits such as expectation for improvement and group support.

The negative effect of stress in reproductive health is generally accepted as occurring through increased hypothalamic-pituitary-adrenal axis activity . The distress-conception relationship is complicated. Numerous studies have shown that distress is associated with lower IVF success rates (5–8, 23, 24): The more distressed the patient is, the less likely she is to conceive, although not all research supports this (9, 10). In addition, infertile women are twice as likely as control women to have depressive symptoms (25), which would suggest that depression might be a detriment to IVF success.

Because the MB program has numerous components, including not only strategies known to lead to reductions in anxiety and depressive symptoms, but also ones that support healthier lifestyle habits, one can not definitively state that the observed increase in pregnancy rate in the MB group was directly due to stress reduction.

There are other limitations in this study. The first is the sample size. It was anticipated, based on the only prior comparable study (17), that 75 participants per arm were adequate to demonstrate differences in pregnancy rates between the two groups. Although fifteen of the participants did not undergo an IVF cycle, so were obviously ineligible for inclusion, it had not been expected that so many of the other participants, especially MB patients, would drop out of the study. The study was funded for 2 years, which was anticipated to be sufficient to recruit enough patients and then follow each one for a year. Due to the resulting budget and time constraints, it was not possible to expand the recruitment period.

The intent of the gift certificates was to provide patients with an incentive to remain in the study for the full year despite not being in the study group. The decision to offer the control subjects an incentive to remain in the study stemmed from a previous randomized trial on the MB program in which the control subjects were simply a no-treatment control group and the attrition rate was 60% owing to dissatisfaction with group assignment (17). Spa gift certificates were chosen because of the success with their use in comparable stress-reduction research by two of the coinvestigators (26). It was hoped that a $50 spa certificate was enough to keep the control subjects in the study but not enough to be an intervention itself.

Because the intervention was the same as in the previous study where there were no dropout issues noted in the MB patients (17), it is possible that IVF patients differ from a heterogeneous group of infertility patients; they may simply feel too overwhelmed by the daily demands of the medical regimen to also participate in a research study or to attend a weekly MB program during their first IVF cycle.

It is noted that the generalizability of these findings to the IVF general population as a whole is limited owing to the attrition issue. The women who chose to participate in the study, and subsequently chose to remain in the study, might well be different from many other IVF patients.

The fact that so many of the MB patients had not attended most of their MB sessions before undergoing their first IVF cycle was also unanticipated. It had been expected that obtaining insurance approval and the down-regulation process would allow for most participants to have attended at least one-half of their MB sessions before cycling. As it turned out, however, it was impossible to truly assess the impact of the MB program on their first cycle, although all subjects knew of their group assignment.

This study supports the theory that psychologic distress may be an important detriment to IVF outcome. It is premature to conclude that an MB intervention definitely causes increases in pregnancy rates. However, the fact that there were more pregnancies in the MB patients for their second cycle does suggest a possible link between distress and IVF outcome. The results of this study support the research regarding the positive impact of group skills-based interventions (20). However, further research on a larger patient population is still needed.

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