Impact of hypnosis during embryo transfer on the outcome of in vitro fertilization–embryo transfer: a case-control study

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Objective: To investigate whether hypnosis during ET contributes to successful IVF/ET outcome.
Design: Case-control clinical study.
Setting: Academic Fertility and IVF Unit, Soroka Medical Center, Beer-Sheva, Israel.
Patient(s): Infertile couples undergoing IVF.
Intervention(s): Ninety-eight IVF/ET cycles with hypnosis during the ET procedure were matched with 96 regular IVF/ET cycles.
Main Outcome Measures: Comparison of clinical pregnancy and implantation rates between the two groups.
Result(s): We obtained 52 clinical pregnancies out of 98 cycles (53.1%) with an implantation rate of 28% among hypnosis IVF/ET cycles, and 29 out of 96 (30.2%) clinical pregnancies and an implantation rate of 14.4% in the control cycles. Our overall IVF program pregnancy rate for the same period was 32.1%. Logistic regression analysis was performed emphasizing the positive contribution of hypnosis to the IVF/ET conception rates.
Conclusion(s): This study suggests that the use of hypnosis during ET may significantly improve the IVF/ET cycle outcome in terms of increased implantation and clinical pregnancy rates. Furthermore, it seems that the patients' attitude to the treatment was more favorable. (Fertil Steril® 2006;85:1404–8. ©2006 by American Society for Reproductive Medicine.)

Key Words: IVF/ET, hypnosis, implantation rate, pregnancy rate

The procedure ET during IVF is defined by many investigators (1–3) as a crucial event for determining IVF outcome. Patients perceive it as the culmination of the IVF treatment, and therefore stress is often present. Patient fears are related to a potentially negative treatment outcome as well as to any possible discomfort related to the procedure.

Successful outcome of IVF treatment requires the combined efforts of the clinician and the reproductive biologist. The work of embryologists to maintain the viability of embryos might be futile if the ET procedure causes stress to the patient with a variety of autonomous nervous system expressions, such as increased blood pressure, tachycardia and tachypnea, or an increase in uterine contraction frequency.

To the best of our knowledge, a linkage between IVF outcome and hypnosis was never described, however, hypnosis is one of the oldest psychological tools for pain and anxiety relief and is reported in relation to surgery before the development of chemoanesthesia (4). A retrospective study (5) showed that hypnosis provides better patient comfort, reduces intra- and postoperative pain and postoperative anxiety, results in less postoperative nausea and vomiting, and improves surgical conditions as compared with conventional stress-reducing strategies. Those results were confirmed by a prospective randomized study comparing hypnosis with other stress-reducing strategies for plastic surgery (6).

The aim of this study was to combine the benefits provided by hypnosis, such as anxiety and stress reduction, with the most awaited and therefore stressful event during IVF—the transfer of embryos into the woman's uterus—with the objective of improving pregnancy and implantation rates.

MATERIALS AND METHODS

Patients and Design

All IVF female patients without known psychiatric disorders and not using sedatives or tranquilizers were offered enrollment for hypnosis during the ET study. Those who consented underwent a prehypnosis interview by a physician certified to induce hypnosis, and if they were found to be suitable, they signed an informed consent.

The clinical and laboratory data from the hypnosis group's IVF/ET cycles were compared with data from a control group undergoing regular IVF/ET. Matching criteria included patient's age, peak preovulatory E_2 level, number of oocytes retrieved, and number and quality of embryos transferred. The control group cycles were obtained from IVF/ET

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cases immediately after the hypnosis cycles provided that the criteria matched. The study was performed at the IVF Unit of the Soroka University Medical Center in Beer-Sheva from June 2001 to August 2003 and was approved by the Institutional Review Board at the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

The study population included couples treated mainly for tubal, male factor, and unexplained infertility and women with evidence of a normal uterine cavity and absence of contraindications for pregnancy. We excluded cycles using donor oocytes or frozen-thawed embryos.

IVF Treatment Protocols

All women participating in the study were treated with GnRH agonist (GnRH-a). The standard treatment regimen was according to the "long protocol," and ovarian down-regulation was achieved by administration of controlled-release GnRH-a 3.75 mg (Decapeptyl C.R. 3.75 mg, Ferring Pharmaceutical, Kiel, Germany) at the midluteal phase of the preceding cycle. Serum E_2 levels <50 pg/mL on days 12–14 after GnRH-a injection were used to define ovarian quiescence.

In women having a reduced ovarian response to gonadotropin stimulation, the "short protocol" was administered using daily injections of GnRH-a 0.1 mg (Decapeptyl 0.1 mg, Ferring) commenced at the first day of the menstrual cycle, concomitantly with daily gonadotropin injections. Controlled ovarian hyperstimulation was performed using hMG (Menogon, Ferring) or recombinant FSH (Gonal-F 75, Laboratories Serono S.A., Aubonne, Switzerland) according to an individually adjusted technique monitored by serum E_2 and transvaginal ovarian ultrasound. HCG (Chorigon 5000U, Teva, Ramat-Gan, Israel) 10,000 U was injected IM when serum E_2 levels were at least 500 pg/mL and at least two follicles >15 mm in diameter were observed.

Transvaginal ultrasound-guided ovum retrieval was performed under general anesthesia 36–38 hours after hCG administration. According to semen quality on the day of oocyte retrieval, the oocytes were inseminated or subjected to intracytoplasmic sperm injection.

ETs for both study groups, hypnosis and regular, were carried out with the "clinical touch technique" using embryos with the highest number of blastomeres and having the highest embryo grading score. We applied a five-grade embryo scoring system according to the number of embryonic fragmentations, size, and shape of blastomeres. No ultrasound-guided ETs were done, and the same group of IVF/ET providers performed the ETs in the hypnosis and the control groups. Most of the ETs in both groups were performed using the T.D.T. catheter (Prodimed, Neuilly-en-Thelle, France).

Luteal phase was supported by five injections of hCG 1,250 U (Chorigon 2500 U, Teva, Ramat-Gan, Israel) every other day starting 48 hours after oocyte retrieval, or daily IM administration of 50 mg P (Gestone, Paines & Byrne Limited, West Byfleet, Surrey, UK) in patients at high risk for developing ovarian hyperstimulation syndrome (peak E_2 levels $>2{,}000$ pg/mL), or combined luteal support, adding four injections of hCG 1,250 U every other day in P-supported cycles in which the serum E_2 and P levels dropped sharply 7 days after ET.

In all patients, serum β-hCG was obtained 14–17 days after ET and pregnancies were confirmed by the presence of a pregnancy sac and cardiac activity on ultrasound.

Hypnosis

During the prehypnosis session, every patient was requested to choose a very pleasant life experience to relive during the ET. The hypnotic state during ET was induced by the same hypnosis therapist using eye fixation, relaxation, and permissive and indirect suggestions. It was suggested that the patient compare the procedure of ET with the reception of long-awaited and very welcome guests. Only when the patient was thought to be at an adequate trance level (± 10 minutes) was the ET procedure initiated.

After ET, and previous to dehypnotization, the patient was given posthypnotic suggestions to produce calm, relaxation, and optimism for the future.

Statistical Analysis

Univariate analysis was performed using χ^2, Fisher's exact test, Wilcoxon matched-pairs signed-ranks test, and one-way analysis of variance test when appropriate.

To evaluate the effect of hypnosis during ET on pregnancy occurrence adjusted to the different confounding factors, logistic regression analysis was performed for the dichotomic dependent variable—pregnancy—with the independent variables found significant in univariate analysis, such as hypnosis during ET.

Statistical analyses were performed using Statistical Programs for the Social Sciences (SPSS, version 11.0, Chicago) software programs. $P<.05$ was considered statistically significant.

RESULTS

A total of 89 couples underwent 98 IVF/ET treatment cycles with hypnosis during ET, while the regular ET group included 96 IVF/ET cycles from 96 couples.

A comparison of data between the study groups showed (Table 1) patients' age (mean $\pm$ SD) of 31.8 $\pm$ 4.2 and 32.1 $\pm$ 4.6 years; day 3 FSH levels of 5.9 $\pm$ 2.0 and 6.1 $\pm$ 2.1; male factor infertility in 44.9% and 44.3% of cases; tubal factor infertility in 14.3% and 16.5% of cases; unexplained infertility in 18.4% and 10.3% of cases; and other causes of infertility in 22.4% and 28.9% of cases for the hypnosis and

TABLE 1

Patient characteristics for hypnosis versus regular ET cases.

Characteristics	Hypnosis ET	Regular ET
No. of patients	89	96
Age (y)[a]	31.8 ± 4.2	32.1 ± 4.6
FSH level (day 3)[a]	5.9 ± 2.0	6.1 ± 2.1
Duration of infertility (years)[a]	4.7 ± 3.1	7.4 ± 4.3[b]
Primary infertility (%)	46.9	74.2[b]
Male factor infertility (%)	44.9	44.3
Pelvic and tubal factor (%)	14.3	16.5
Unexplained (%)	18.4	10.3
Other causes of infertility (%)	22.4	28.9

[a] Values are expressed as mean ± SD.
[b] $P<.001$ vs. the hypnosis cases.

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regular ET groups, respectively. A difference ($P<.05$) was observed for the duration of infertility, 4.7 ± 3.1 and 7.4 ± 4.3 years, and the percentage of primary infertility, 46.9% and 74.2%, for the hypnosis and regular ET groups, respectively.

Clinical and laboratory data displayed in Table 2 could not disclose statistically significant differences between the hypnosis and regular ET groups concerning the following parameters per cycle (mean ± SD): peak follicular phase E_2 levels in units of pg/mL (1,514 ± 659 and 1,541 ± 710), number of ovarian follicles >15 mm in diameter (6.18 ± 2.64 and 5.47 ± 3.08), number of oocytes collected (11.45 ± 5.86 and 12.11 ± 5.57), and number of fertilized two-pronuclear oocytes (6.69 ± 3.68 and 6.57 ± 3.97).

ETs were performed on day 2 or 3 after oocyte retrieval, using (mean ± SD) 2.66 ± 0.74 and 2.98 ± 0.92 embryos per cycle for the hypnosis and regular ET groups, respectively. The leading embryo contained (mean ± SD) 5.3 ± 2.21 and 5.59 ± 2.17 blastomeres and a score (out of 5) of 3.59 ± 1.11 and 3.46 ± 1.18 for the hypnosis and regular ET cases, respectively. It is important to emphasize that more ($P<.05$) easy transfers and more cycles using the long protocol have been recorded in the regular ET group compared with the hypnosis group (95.8% vs. 85.7% and 95.8% vs. 77.6%).

The differences regarding the type of luteal phase support after ET, that is, hCG, P, or combined, were not found to be statistically significant. In particular, among 98 hypnosis ET cycles, the distribution of luteal support was hCG in 29 (29.6%) cycles, P in 64 (65.3%) cycles, and combined support in 5 (5.1%) cycles. The luteal phase in 96 regular ET group patients was supported by hCG in 33 (34.4%) patients, P was administered in 59 (61.5%) women, and 4 (4.2%) patients had combined support.

A significantly higher pregnancy rate ($P<.05$) was observed in the hypnosis group compared with the regular ET cycles (Table 3). In the hypnosis group, 52 clinical pregnancies were conceived with a clinical pregnancy rate (PR) per patient of 58.4% (52/89) and per cycle of 53% (52/98), compared with 29 clinical pregnancies in the regular ET group and a clinical PR of 30.2% (29/96) per patient and per cycle.

TABLE 2

Cycle characteristics for hypnosis versus regular ET cases.

Characteristics	Hypnosis ET	Regular ET
No. of IVF/ET cycles	98	96
Long protocol (%)	77.6	95.8[a]
E_2 level on hCG day (pg/mL)	1,514 ± 659	1,541 ± 710
No. of follicles >15 mm	6.18 ± 2.64	5.47 ± 3.08
No. of oocytes collected	11.45 ± 5.86	12.11 ± 5.57
No. of fertilized (2-PN) oocytes	6.69 ± 3.68	6.57 ± 3.97
No. of ETs/cycle	2.66 ± 0.74	2.98 ± 0.92
No. of blastomeres leading embryo	5.30 ± 2.21	5.59 ± 2.17
Index of leading embryo	3.59 ± 1.11	3.46 ± 1.18
Index of ETs	3.34 ± 0.81	3.40 ± 0.80
Easy ET (%)	85.9	95.9[a]

Note: Values are expressed as mean ± SD.
[a] $P<.05$ vs. the hypnosis cycles.

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TABLE 3

IVF/ET cycle outcome for hypnosis versus regular ET cases.

Characteristics	Hypnosis ET	Regular ET
No. of clinical pregnancies	52	29
Clinical PR/patient (%)	58.4 (52/89)[a]	30.2 (29/96)
Clinical PR/cycle (%)	53.1 (52/98)[a]	30.2 (29/96)
Implantation rate (%)	28 (73/261)[b]	14.4 (39/271)
Multiple PR (%)	36.5	31

[a] $P<.05$ vs. the regular ET cycles.
[b] $P<.001$ vs. the regular ET cycles.

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Our overall IVF program clinical PRs per ET were 28.8%, 33.8%, and 33.8% for the years 2001, 2002, and 2003, respectively, with a mean of 32.1% clinical PR for this 3-year period.

Although a different and significantly ($P<.001$) higher implantation rate per cycle was observed among women after hypnosis during ET, 28% (73/261) versus 14.4% (39/271), the multiple PR remained similar in both groups—36.5% and 31% for the hypnosis and the regular ET groups, respectively.

All the parameters in the study were compared and analyzed according to their impact on conception. Parameters such as type of infertility and difficulty of transfer or type of treatment protocol were not significant in relation to pregnancy occurrence. Therefore, logistic regression analysis was performed on those factors that demonstrated a significant influence on pregnancy occurrence: presence of hypnosis during ET, duration of infertility, age of female patient, FSH levels, and number of follicles above 15 mm in diameter. As shown in Table 4, the calculated odds ratio (corrected for the other confounding factors) for the presence of hypnosis during ET was 7.59, with a 95% confidence interval of 1.82–29.9, which emphasizes the significance of hypnosis during ET as a determinant factor for the increased PR in the hypnosis group.

DISCUSSION

Many strategies aiming to improve ET, and thereby IVF/ET outcomes, are reported in the literature (7). The importance of the type of ET catheter has been mentioned in relation to PRs (8, 9); ultrasound-guided soft catheter ETs (10, 11) and ET performed away from uterine fundus (12) were associated with higher PRs when compared with IVF cycles using the traditional "clinical touch" ETs. Vaginal administration of P on the day of oocyte retrieval, despite high endogenous P levels (13) or preference for blastocysts instead of cleavage-stage embryos in patients with multiple previous IVF failures (14), was related to improved IVF/ET outcome.

The effect of uterine contractions on embryo implantation has already been described in animals (15, 16). In addition, increased uterine contractility at the time of ET is known to adversely affect embryo implantation and PRs in IVF as reported by Fanchin et al. (17). The investigators digitized 5-minute ultrasound scans to objectively quantify the frequency of myometrial contractile activity. They found that the pregnancy and implantation rates decreased as the frequency of uterine contractions increased, emphasizing the importance of uterine quiescence. Furthermore, the same investigators (13) observed a significant reduction in uterine contraction frequency at the time of ET when vaginal P was administered and uterine quiescence achieved.

Another study (18) found that 8.7% of reportedly routine transfers had embryos in the uterine cervix or on the speculum, probably because of the mechanical expulsion of some of the embryos from the uterine cavity.

Induction of hypnosis is intended to produce uterine relaxation and quiescence during ET, which probably leads to a reduction in embryo displacement from the uterine cavity. A prospective randomized study (6) compared conventional stress-reducing strategies (emotional support) and hypnosis as adjunct therapy to conscious sedation for surgery using local anesthesia. The investigators disclosed a significantly attenuated increase in the heart rate and the systolic arterial pressure, as well as a decrease in the respiratory rate and the diastolic arterial pressure for the hypnosis patients compared with controls.

Our study was able to demonstrate a 53.1% clinical PR for the hypnosis group, which is significantly higher when compared with 30.2% in the control group and 32.1% in our overall IVF program during the same 3-year period.

Data providing evidence that hypnosis may reduce immunological dysregulation associated with acute stressors was re-

TABLE 4

Regression analysis for the different factors found to have a significant impact on conception.

Factor	Odds ratio	95% Confidence interval
Hypnosis during ET	7.58	1.82–29.9
Age of female patient	0.92	0.85–.99
Duration of infertility	0.98	0.86–1.1
FSH level	0.84	0.72–0.9
No. follicles (>15 mm)	1.15	1.04–1.29

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ported. Wood et al. (19) have described a differential expression of cytokines by T-cell subsets and the hypothalamus-pituitary-adrenal axis related to induction of hypnosis. In addition, the absolute number and percentages of CD3(+) CD4(+) and CD3(+) CD8(+) T lymphocytes, CD3(−) CD56(+) natural killer cells, and natural killer cell cytotoxic activity were correlated with perceived stress (20). Some of those effects were buffered by hypnosis.

On the other hand, growth factors and cytokines were related to signaling between blastocyst and uterus, endometrial prostaglandin production, endometrial invasion, proliferation and differentiation, vascular permeability, and remodeling. Nevertheless, some immunologic factors were linked to immunosuppression and prevention of immune recognition and rejection of fetal semi-allograph (21). Therefore, an improvement in interaction between the blastocyst and the endometrium should be considered for the hypnosis patients.

The methodological challenge in constructing this case-control study was to produce optimal matching between the hypnosis and the control cases. All parameters in the study were analyzed to evaluate their influence on conception. Duration of infertility was not one of the matching criteria between the hypnosis and the control groups, and it was found to be significantly longer for the control group patients. This parameter, along with other factors (Table 4) that demonstrated a significant impact on pregnancy occurrence, underwent logistic regression analysis; hypnosis during ET (corrected for other confounding factors) was found to be the most significant determining factor for the higher pregnancy and implantation rates.

Collectively, and based on our data, we believe that the significant increase in the pregnancy and implantation rate in the hypnosis group patients is a result of this novel approach. We can hypothesize that hypnosis relieves the sensation of stress and thereby reduces the uterine activity and improves the interaction between the embryo and the uterus while increasing the chances of embryo implantation. Based on our results, prospective and randomized studies may be helpful in confirming our findings.

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