Reproductive Performance of Patients Undergoing Intracytoplasmic Sperm Injection with 100% Implantation Rate

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Purpose: To characterize the differences between two matched groups of patients treated by ICSI: those pregnant after all embryos transferred implanted (100% implantation rate) compared with nonpregnant patients.

Methods: Twenty-one patients in whom one transferred embryo achieved a singleton pregnancy (group A) and 21 pregnant patients to whom two or three embryos were transferred and achieved 11 twin and 10 triplet pregnancies (group B) compared with matched nonpregnant patients (group C and D, respectively).

Results: The singleton pregnant patients were significantly older than the twin and triplet pregnancy patients. Although a similar number of human menopausal gonadotropin ampules were used in the singleton compared with the twins and triplets a significantly lower number of oocytes and embryos were achieved at lower levels of estradiol on the human chorionic gonadotropin day in the former than in the latter respectively. No difference was found between the pregnant women and their nonpregnant controls in any of the mentioned parameters. Good embryo morphology was found in 86% of the embryos in group A compared with 62% in group C ($P = 0.08$) and 92% in group B compared with 66% in group D ($P < 0.002$).

Conclusions: The only parameter in which pregnant patients with 100% implantation rate differ from their nonpregnant controls was embryo quality.

KEY WORDS: Embryo quality; implantation; intracytoplasmic sperm injection; in vitro fertilization.

INTRODUCTION

Much effort has been made to improve controlled ovarian hyperstimulation protocols, oocyte recovery, fertil-

ization, and transfer techniques of embryos in in vitro fertilization-embryo transfer (IVF-ET). Nevertheless, implantation failure has remained the main limiting step that prevents a further increase in pregnancy rates.

Laboratory-assisted reproduction, while helping couples in the establishment of pregnancies, has been associated with an increase in multiple implantation, resulting from the transfer of more than one embryo following IVF (1).

Different parameters influence the success of intracytoplasmic sperm injection (ICSI) treatment such as maternal age (2–4), the type of stimulation (5, 6), endometrial receptivity (7), and the quality of the transferred embryos (8–10).

Our purpose was to characterize the parameters influencing successful implantation of pregnant ICSI patients demonstrating a 100% implantation rate, i.e., all transferred embryos that were successfully implanted, to provide an ongoing clinical pregnancy. We further compared the reproductive performance of the pregnant women undergoing one or multiple embryo transfer to nonpregnant patients in whom the same number of embryos were transferred but no pregnancy was established.

MATERIAL AND METHODS

Patients

Between 1/1996 and 10/1997, 1018 ICSI cycles were performed. In 926 (91%) of them, embryos were replaced. In 111 (12%) cycles one embryo was transferred, since only one was available for transfer. In 204 (22%) cycles two embryos were replaced and in 278 (30%) 3 embryos were transferred. Two hundred eighty-four clinical pregnancies were achieved (28%

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pregnancy per cycle). Forty-two patients had 100% implantation rate, meaning that all transferred embryos developed into visible sacs by vaginal ultrasonic scan. Twenty-one (19%) of the patients with a single embryo transfer conceived and composed the first study group A. In 11 (5%) of all cycles in which 2 embryos were transferred, a twin pregnancy was established. Ten of the patients (3.6%), who had a transfer of 3 embryos, had a triplet pregnancy. These two series of twin and triplet pregnancy composed the second study group B.

Every patient in the study group was compared with a nonpregnant patient who was transferred with the same number of embryos and had similar characteristics, such as indication for IVF, age, number of oocytes and embryos, and was in the IVF program at the same period of time. These nonpregnant patients created the control group for group A (group C) and the controls for group B (group D).

Among the patients in group A, there were 10 previous abortions, 2 ectopic pregnancies, and 6 deliveries compared with 16 previous abortions, 3 ectopic pregnancies, and 11 deliveries in their control group C. Four of the above pregnancies in group A were achieved by assisted reproductive technology (ART): two of them ended in deliveries and two were ectopic pregnancies. None of the patients in the control group C were pregnant by ART. The patients with the multiple embryo transfer, group B, had two abortions, one ectopic pregnancy, and eight prior deliveries, six in ART as opposed to two abortions, one ectopic pregnancy, and two deliveries, none of them in ART, in their control group D.

The indications for ICSI in group A and in group C were male factor in 17 patients, unexplained infertility in 2 patients, and in the remaining 2 patients tubal factor. The indications for ICSI in patients in group B and in group D were male factor in 19 cases and unexplained infertility in another 2 patients. ICSI is performed in our program when at least two out of three semen parameters are pathological, namely sperm concentration $< 5 \times 10^6$ cells/cc, sperm motility $< 10\%$, and normal sperm morphology $< 10\%$. In addition, ICSI is preferred in patients with absence or very low ($< 20\%$) fertilization rates in a previous IVF cycle.

The uterine cavity was delineated by hysterosalpingography in all cases except in two cases in group B in whom hysteroscopy already had been performed before being referred for ART. Hysteroscopy was done in some of the patients: in 10 and 11 patients in group A and B and in 8 and 13 in group C and D, respectively. In two cases in each group A, B, and D, hysteroscopic lysis of old intrauterine adhesions was performed prior

to the ICSI attempts, and subsequently the cavity was reported as normal.

Controlled ovarian hyperstimulation (COH) was similar in both groups: 3.75 mg Triptorelin (Decapeptyl, Ferring, Malmö, Sweden) was used 2 weeks prior to individualized administration of menotropins. Oocyte retrieval was performed by vaginal route guided by ultrasound under general anesthesia.

ICSI Procedure

ICSI was carried out according to the methodology described by Van Steirteghem et al. (11). Fertilization was confirmed after 16 to 18 hr if two distinct pronuclei were observed under the inverted microscope. Cleavage was assessed 24 hr later and the embryos were classified according to their morphological appearance: class I—symmetrical blastomeres with no anucleated fragments; II—asymmetrical blastomeres without or with $< 20\%$ of the volume filled with fragments; III—with 20 to 50% of the volume covered with fragments; and IV—extreme asymmetrical blastomeres and $> 50\%$ of the volume filled with anucleated fragments. Embryo classified I to III were considered for transfer and were introduced into the uterine cavity 48 to 72 hr after the ICSI procedure. Grade I, I–II, and II embryos were defined as “good-quality” embryos and grade II–III, III, III–IV, and IV as “low-quality” embryos.

Embryo transfer was performed with a Wallace catheter (Simcare, Lancing, England). Luteal supplementation consisted of either human chorionic gonadotropin (hCG) administration, 2500 IU every third day for four doses or progesterone in oil (Gestone, Paines & Byrne, Surrey, England) 50 mg/day intramuscularly in cases where estradiol (E_2) level on hCG administration day was > 2500 pg/ml.

Pregnancy rate was calculated considering only clinical pregnancies, determined by visualization of at least one gestational sac by transvaginal ultrasound 4 weeks after embryo transfer (12).

Statistical Analysis

Statistical analysis for fertilization and cleavage rates was performed on the percentage values of the variables within each cycle. The number of embryos replaced also was expressed as the mean of the values of the variables within each cycle. Global significance was tested by paired comparison by the Student *t* test. Probability values less than 5% were considered statistically significant. Chi-square analysis was used to

compare the proportion of embryo quality grades within each group.

RESULTS

The pregnant women with singleton pregnancy (group A) were significantly older than those having twins or triplets (group B): 35.9 ± 3.5 (mean $\pm$ SD) years; 26.5 ± 3.7 and 29.4 ± 2.3 years, respectively ($P < 0.01$). They had a trend of longer infertility period and a higher number of previous IVF attempts (Table I).

Ovarian responsiveness was similar in all groups regarding treatment duration and human menopausal gonadotropin (hMG) ampules used (11.8 ± 3.1 days and 40.4 ± 15.2 ampules in group A, 13.2 ± 3.7 days and 35.5 ± 15.4 ampules in the twins, and 12.7 ± 2.2 days and 42.0 ± 14 ampules in the triplets). The E_2 level was lower in group A on the day of hCG administration compared with the multiple pregnancies: 1094 ± 608 pg/ml, 3267 ± 1686 pg/ml, and 2784 ± 1354 pg/ml, respectively ($P < 0.01$).

In vitro fertilization outcome of the 42 conceptual ICSI cycles is depicted in Table I. The mean number of follicles, oocytes, fertilizations, and transferred embryos of group A patients was significantly lower compared with group B. In 18 patients from group A a single oocyte was aspirated, leading to a single embryo which was replaced. In the remaining three women, two and three oocytes were retrieved and fertilized; however, only one of them cleaved and was replaced.

Tables II and III show the comparison of the characteristics of the patients having 100% implantation rate with their matched nonpregnant controls. Similar to group A, in 18 cases of group C a single nonselected embryo was transferred. Therefore, group A and C represented a nonselected group considering ET in most of the cases, since in only three cases in group D, selection of embryos was not feasible: two cases with only three cleaving embryos and one case with two cleaving embryos. Groups B and D were considered as groups with selected embryos for transfer.

The E_2 level on hCG day in group C was lower than the one on the corresponding day in group A (767 ± 594 pg/ml compared with 1094 ± 608 pg/ml, respectively, $P = 0.08$). Likewise, the incidence of good morphological embryos in group C was much lower (62%) compared with the incidence in group A (86%) ($P = 0.08$; Fisher's exact test). In all cases in both groups the replacement of the embryos was uncomplicated. Table III shows two parameters in which a statistically significant difference was found between group B and their nonpregnant control (group D). Infertility duration was 4.4 ± 2.9 years in group B compared with 2.8 ± 1.7 years in group D ($P < 0.04$). The proportion of good morphological embryos that were replaced into the uterus was 92% compared with 66% ($P < 0.002$). There was no technical difficulty in embryo transfer in 20 of 21 patients in each group.

Human chorionic gonadotropin was administered for luteal support in 20 of 21 patients of group A and in 19 of 21 of its control. Progesterone in oil was the

Table I. Characteristics of the Pregnant Patients after the Replacement of One, Two, or Three Embryos in ICSI Cycles^a

	Singleton group A <i>n</i> = 21	Twins group B <i>n</i> = 11	Triplets group B <i>n</i> = 10
Women's age (years)	$35.9 \pm 4.0^{b,c}$	26.5 ± 3.7^b	29.4 ± 2.3^c
Duration of infertility (years)	6.8 ± 4.9	4.0 ± 3.4	4.7 ± 2.2
No. previous IVF cycles	2.9 ± 2.7	1.8 ± 2.5	1.7 ± 2.2
No. previous IVF pregnancies	4/21	2/11	4/10
Dose of hMG (ampules)	40.4 ± 15.2	35.5 ± 15.4	42.0 ± 14.0
Days of hMG treatment (days)	$11.8 \pm 3.0^{b,c}$	13.2 ± 3.7	12.7 ± 2.2
E_2 on hCG day (pg/ml)	1094 ± 608	3267 ± 1686^b	2784 ± 1354^c
No. of follicles	$6.9 \pm 9.5^{b,c}$	18.8 ± 11.1^b	18.6 ± 8.7^c
No. of oocytes retrieved	$3.1 \pm 2.2^{b,c}$	13.2 ± 7.4^b	15.0 ± 9.0^c
No. of transferred embryos	1	2	3
Embryo quality			
Good (%)	18/21 = 86%	20/22 = 91%	28/30 = 86%
hCG on day 14 per embryo (IU)	242 ± 132	165 ± 58	224 ± 109

^a Values are mean $\pm$ SD.

^b Student's *t* test comparing singleton with twin pregnancies, $P < 0.01$.

^c Student's *t* test comparing singleton with triplet pregnancies, $P < 0.01$.

Table II. The Comparison of Patients' Characteristics and ICSI Outcome in Conception and Nonconception Cycles with a Single-Embryo Transfer^a

	Pregnant group A <i>n</i> = 21	Nonpregnant group C <i>n</i> = 21	<i>P</i>
Women's age (years)	35.9 ± 3.5	36.3 ± 5.8	NS ^b
Duration of infertility (years)	6.8 ± 4.9	6.0 ± 3.3	NS ^b
No. previous IVF cycles	3.0 ± 2.7	4.4 ± 3.1	NS ^b
No. previous IVF pregnancy	4/21	0/21	
Dose of hMG (ampules)	40.4 ± 15.2	47.4 ± 19.3	NS ^b
Days of hMG treatment (days)	11.8 ± 3.1	12.2 ± 3.0	NS ^b
E ₂ on hCG days (pg/ml)	1094 ± 608	767 ± 594	0.08
No. of follicles	5.0 ± 9.5	3.5 ± 2.5	NS ^b
No. of oocyte retrieved	3.1 ± 2.2	2.4 ± 2.0	NS ^b
No. of transferred embryos	1	1	
Embryo quality			
Grade I	6/21(29%)	2/21(10%)	
Grade I–II	8/21(38%)	8/21(38%)	
Grade II	4/21(19%)	3/21(14%)	
Good (%)	18/21 = 86%	13/21 = 62%	0.08 ^c
E ₂ on midluteal phase (pg/ml)	600 ± 447	343 ± 319	NS ^b
hCG on day 14 per embryo (IU)	242 ± 132	<10	

^a Values are means ± SD.^b Student's *t* test.^c Fisher's exact test.

prominent luteal supplementing hormone in group B (15 of 21 cases and 16 of 21 in its control group).

Fifteen patients of group A had a vaginal delivery, in three a cesarean section was performed due to breech presentation, and three patients aborted in the first trimester. Their mean birth weight was 3228 ± 490 g

(range, 2400–4100 g) at 38.1 ± 1.6 weeks of gestation (range, 35–40 weeks). No fetal malformations were reported among group A.

Out of 11 twin deliveries 6 were delivered per vagina; the remaining 6 patients were delivered by cesarean section at 33.8 ± 3.9 weeks of gestation

Table III. The Comparison of Patients' Characteristics and ICSI Outcome in Conception and Nonconception Cycle with Two and Three Embryo Transfer^a

	Pregnant group B <i>n</i> = 21	Nonpregnant group D <i>n</i> = 21	<i>P</i>
Women's age (years)	27.9 ± 3.5	28.9 ± 3.8	NS ^b
Duration of infertility (years)	4.4 ± 2.9	2.8 ± 1.7	<0.04 ^b
No. previous IVF cycles	1.8 ± 2.5	1.5 ± 2.2	NS ^b
No. previous IVF pregnancy	6/21	0/21	
Dose of hMG (ampules)	38.8 ± 14.8	35.9 ± 9.8	NS ^b
Days of hMG treatment (days)	13.0 ± 3.1	11.9 ± 2.0	NS ^b
E ₂ on hCG days (pg/ml)	3037 ± 1556	3657 ± 2467	NS ^b
No. of follicles	18.7 ± 10	16.9 ± 9.4	NS ^b
No. of oocyte retrieved	14.0 ± 8.3	13.6 ± 7.5	NS ^b
No. of embryos	8.4 ± 5.9	7.6 ± 4.5	NS ^b
No. of transferred embryos	2.5 ± 0.5	2.5 ± 0.5	NS ^b
Embryo quality			
Grade I	27(51%)	17(32%)	
Grade I–II	14(26%)	9(17%)	
Grade II	8(15%)	9(17%)	
Good (%)	49/53 = 92%	35/53 = 66%	0.002 ^c
E ₂ on midluteal phase (pg/ml)	589 ± 551	364 ± 338	NS ^b
hCG on day 14 per embryo (IU)	192 ± 88	<10	

^a Values are means ± SD.^b Student's *t* test.^c Fisher's exact test.

(range, 24–38 weeks) with birth weights of 2074 ± 612 g (range, 700–3000 g).

Only six of the ten triplets reached delivery, all by cesarean sections, with maximal gestational age of 35 weeks, mean birth weight of 1605 ± 480 g. The remaining four sets of triplets included (i) an inevitable late abortion at 19 weeks of gestation; (ii) premature rupture of membrane followed by abrupt bleeding and placental abruption at 21 weeks of gestation; (iii) late missed abortion at 20 weeks of gestation due to *Listeria monocytogenes* infection; and (iv) immature delivery (24 weeks of gestation) with neonatal death of all three. The maximal week of gestation attributed to the triplets was 35 weeks. One of the newborns among the triplets died at the age of 96 hr due to respiratory distress syndrome.

DISCUSSION

It is well accepted that the number of transferred embryos affects the probability of achieving pregnancy. The correlation between the number of embryos transferred and the chances to conceive were already clear from the early days of ART. More implantations will occur when more good morphological embryos are transferred into the uterine cavity. Therefore, the dilemma of the proper number of embryos to replace is part of our daily practice.

Most IVF centers transfer no more than two to three embryos into the uterine cavity in order to prevent high numbers of multiple pregnancies. The relatively low pregnancy rate of 4–7% following the transfer of a single embryo recovered in natural unstimulated cycle bears witness to this fact (13).

The increasing number of twins, even after double transfer, has raised the questions as to whether it is time to accept the transfer of only a single embryo. Vilska et al. (14) performed 74 single ET, with the only one available embryo, leading to a pregnancy rate of 18.9% per transfer. Higher pregnancy rates (28.4%) were reached when an elective single ET was performed. Coetsier et al. (15) suggested an ET reduction from two to one in a selected subgroup of patients having first second and third IVF trials with more than five embryos of which the embryos to be transferred were of good morphology. By this strategy, the total number of multiple pregnancies was reduced by 24%.

In view of this trend it seemed very important to us to characterize the patients with good chances for successful ICSI treatments, namely, those cases in whom 100% implantation took place. We then wished to compare them with nonpregnant ICSI patients who

underwent the same procedure with the same number of transferred embryos. Since couples referred to ICSI normally have only male factor infertility and their spouses are assumed to have a normal endometrium, we chose this cohort of patients to investigate the issue of implantation.

We found that pregnant patients with multiple pregnancies, twins, and triplets, were younger, with shorter period of infertility, less previous ICSI attempts, better ovarian response expressed by significantly higher E_2 levels along the cycle, and more follicles, oocytes, fertilizations, and embryos than the pregnant patients with a single ET. Not surprisingly, despite the fact that almost a homogeneous nonselected (the singletons) and selected (the multiple pregnancies) subgroup of pregnant patients were compared, no difference was noticed in terms of embryo quality. However, when we matched conception cycles to nonconception cycles in both groups, we found that the ovarian response was similar and the incidence of intact uterine cavity was similar within each group. Nevertheless, embryo quality in general was better in the conception cycles as opposed to the nonconception ones. This also may be the reason that none of group C and D patients conceived after previous IVF trials compared with four and six previous pregnancies in the present pregnant groups. The number of previous abortions in group C was higher compared with the number of previous abortions in group A (16 abortions vs. 10 abortions), hinting at worse uterine receptivity. The total number of previous abortions in group B and D was lower compared with the number found in group A and C, probably due to better endometrium, uterine receptivity, and/or hormonal milieu.

Our results may shed light on the question raised by Staessen et al. (16, 17) whether the chances of conception in patients with good prognosis for successful IVF-ET treatment are affected by reducing the number of transferred embryos to two. Their criteria for good performance in IVF were in accordance with our findings: first attempt in IVF, patients' age of <37 years, and at least three available embryos of good quality for transfer.

The thickness and appearance of the preovulatory endometrium, as judged by ultrasonic examination, have been shown to be an important factor for prediction of the outcome of gonadotropin stimulated IVF cycles. However, Friedler et al. (18) in a review article stated that the correlation between endometrial thickness as a single parameter and pregnancy seemed to be of low predictive value for uterine receptivity. We do not routinely measure the endometrial thickness,

thus we never cancel any case because of thin endometrium.

Navot et al. (19) tried to find whether the decline in female fertility with advancing age is attributed to diminished oocyte quality or to uterine–endometrial inadequacy. Based on their data coming from oocytes donated by young patients to older women and from the comparison of young donors and older recipients from the same induced cohort, they suggested that the decline in fertility with age is mainly attributed to oocyte quality. The uterus can sustain pregnancies even in older women. Since embryo quality is closely correlated with oocyte quality and maternal age, these data are in accordance with our finding that the main parameter on which pregnant patients with 100% implantation differ from their nonpregnant controls, after ICSI attempts to establish pregnancy, was embryo quality. When one transfers only one embryo in an ICSI cycle, the chances for the establishment of a pregnancy are higher in a younger patient with good ovarian response, when an embryo is selected out of several, the patient is on her first ICSI trial, and after a short period of infertility. Among the pregnant women with 100% implantation rate, women with multiple pregnancies are younger in age and have better ovarian response than women with singletons. The only parameter in which patients with 100% implantation rate differ from nonpregnant ICSI patients was embryo quality.

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