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Varicocelectomy Does Not Impact Pregnancy Outcomes Following Intracytoplasmic Sperm Injection Procedures

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ABSTRACT: There are many studies in the literature suggesting an acquired, apparently progressive infertility due to varicocele. In fact, varicocelectomy has become the most commonly performed male infertility surgery. Assisted reproductive technologies such as intracytoplasmic sperm injection (ICSI) are also important for couples with male factor infertility associated with varicocele. Therefore, the aim of this study was to evaluate the effect of varicocelectomy on sperm quality and pregnancy rate with ICSI. Data were analyzed from 248 patients who had varicocele or underwent a previous varicocelectomy and were treated with ICSI between 2000 and 2008. Patients with varicocele were divided into two groups: men with clinical varicocele (group 1, n = 79) and men who underwent varicocelectomy before ICSI (group 2, n = 169). In all cases, female infertility was not detected. We evaluated and compared the two groups' semen characteristics as defined by the World Health Organization and Tygerberg's strict criteria: the female partner's age; the number of oocytes retrieved; and the fertilization, implantation, pregnancy, and miscarriage rates. We used the Wilcoxon signed rank test or the Mann-Whitney test for these analyses. No differences were detected in the age of the female partners between group 1 (33.0 ± 0.46 years) and group 2 (33.8 ± 0.38 years; $P = .1872$). Semen volume was higher in group 1 (3.3 ± 0.3 mL) than it was in group 2 (2.5 ± 0.14; $P = .0043$). No differences were detected between groups 1 and 2 with regard to sperm concentration (30.08 ± 4.01 million/mL and 24.1 ± 2.42 million/mL, respectively; $P = .138$), sperm motility (38.2% ± 2.69% and 38.7% ± 2.08%, respectively; $P = .881$), and morphology according to Tygerberg's strict criteria (2.6% ± 0.44% and 2.4% ± 0.37%, respectively; $P = .7202$). Also, no differences were detected in the number of oocytes retrieved between group 1 (14.8 ± 1.74) and group 2 (14.9 ± 1.04; $P = .9515$). The fertilization rate was higher in group 1 (73.2%) than it was in group 2 (64.9%; $P = .0377$); however, no differences were detected in the pregnancy rates (31.1% vs 30.9%; $P = .9806$), implantation rates (22.1% vs 17.3%; $P = .5882$), or miscarriage rates (21.7% vs 23.9%; $P = .8401$) between groups 1 and 2. Although a varicocelectomy should always be performed before assisted reproduction is pursued, this surgery does not increase pregnancy rates or decrease miscarriage rates following ICSI.

Key words: Varicocele, ICSI, spermatozoa, male infertility, assisted reproductive technology.

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Fertility problems occur in approximately 10% to 15% of reproductive-age couples, due to female factor or male factor infertility (Witt and Lipshultz, 1993; Schlesinger et al, 1994; Kamal et al, 2001). Male factor infertility is at least partially responsible for 50% of infertility cases. Varicocele is present in approximately 10% to 20% of the healthy male population, but in 30% to 40% of the infertile male population (Witt and Lipshultz, 1993; Schlesinger et al, 1994; Kamal et al, 2001). A number of theories have been proposed to explain the decreased semen quality detected in infertile men with varicocele. Semen quality uniformly declines in animals with induced varicoceles, even when only a left varicocele is present (Sofikitis and Miyagawa, 1994). The decrease in scrotal temperature following varicocele ligation supports the causative role of increased temperature in varicocele-related infertility (Sofikitis et al, 1992). Additionally, it has been hypothesized that varicoceles cause hypoxia, which may play a role in impairing spermatogenesis in the patient with varicocele. Furthermore, infertile men with varicocele have elevated levels of spermatozoal reactive oxygen species (Hendin et al, 1999; Pasqualotto et al, 2000, 2008; Loutradi et al, 2006).

The effects of varicocele vary, but they often result in an overall impairment of sperm production characterized by abnormal semen quality and a reduced fertilizing capacity of the male gamete (Sofikitis et al, 1996; Gat et al, 2003, 2004). Currently, surgical repair of varicocele is reported to be more cost-effective than intracytoplasmic sperm injection (ICSI; Garceau et al, 2002; Meng et al, 2005). However, even when varicocele is repaired and all beneficial improvements in semen quality appear to have been obtained, unassisted pregnancy rates vary from 19% to 35% (Marmar and Kim, 1994; Gat et al,

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2003, 2004; Pasqualotto et al, 2006), and these rates are significantly lower in patients who had germ cell aplasia before surgery (Pasqualotto et al, 2005).

Varicocele repair has induced or enhanced spermatogenesis in 40% to 60% of men with azoospermia and severe oligoasthenozoospermia (Matthews et al, 1998; Kim et al, 1999; Kadioglu et al, 2001; Pasqualotto et al, 2006; Inci et al, 2009). However, few pregnancies have been reported to result after varicocelectomy in men with varicocele and azoospermia. Therefore, ICSI is a valuable tool for couples in which the male partner has varicocele and azoospermia, because not all couples achieve pregnancy after varicocele repair alone.

The aim of this study was to evaluate the effect of varicocelectomy on sperm quality and pregnancy rate following ICSI.

Materials and Methods

Patients

This study was approved by the University of Caxias do Sul review board, and the patients involved gave informed consent. A retrospective study of 248 patients who had varicocele or had previously undergone a varicocelectomy, and who were treated with ICSI between 2000 and 2008, was performed. Only patients presenting varicocele grade III were included in the study.

For the purposes of this study, infertility was defined as the failure to establish a pregnancy after at least 1 year of unprotected intercourse. A basic infertility evaluation, including a detailed history and a complete physical examination, was conducted. Only patients who were diagnosed with varicocele grade III were submitted to receive assisted reproduction treatment or varicocelectomy. In addition, semen analyses were performed in all patients, and only those presenting poor semen parameters according to World Health Organization (WHO) 2010 guidelines were included. All couples participating in the study underwent ICSI cycles for the first time.

Patients who had varicocelectomy and recurrence of the varicocele were excluded from the study. Patients who were taking antioxidants, such as vitamins C and E, and those who had azoospermia or leukocytospermia were also excluded from the study.

Patients with varicocele were divided into two groups: men with clinical varicocele (group 1, n = 79) and men who had undergone varicocelectomy before ICSI (group 2, n = 169). All 248 patients underwent a subinguinal varicocelectomy with magnification, as previously described (Marmar and Kim, 1994).

Semen Analysis

Semen samples were obtained by masturbation after at least 48 hours of abstinence. Samples were collected into sterile containers and allowed to liquefy at 37°C for 30 minutes and then analyzed for sperm concentration, percent motility according to WHO criteria (Cooper et al, 2010), and morphology according to Tygerberg's strict criteria (Kruger et al, 1986). At least two centrifuged semen samples were carefully examined.

White Blood Cells

The presence of granulocytes in the semen specimens was assessed by a myeloperoxidase test (Kruger et al, 1986). A 20-μL volume of liquefied specimen was placed in a Corning 2.0-mL cryogenic vial (Corning Costar Corp, Cambridge, Massachusetts), to which 20 μL of phosphate-buffered saline (pH 7.0) and 40 μL of benzidine solution were added. The mixture was vortexed and allowed to sit for 5 minutes. A 5-μL portion of the specimen was placed on a Makler chamber (Sefi Medical, Haifa, Israel) and examined for cells that stained dark brown, which indicated that they were positive for neutrophils. Leukocytospermia was defined as the presence of at least 1×10^6 white blood cells per milliliter. In our study, we excluded patients who had more than 1.0×10^6 white blood cells per milliliter.

Ovarian Stimulation and Oocyte Retrieval

The patients' female partners completed an infertility workup consisting of at least one evaluation assessment and hysterosalpingography. Female partners' mean age ± SD was 30.6 ± 3.9 years.

The patients' female partners underwent a unique controlled ovarian stimulation protocol. Gonadotropin-releasing hormone agonist (leuprolide acetate) was administered for at least 14 days. Ovarian stimulation with recombinant follicle-stimulating hormone (Gonal F; Merck Serono Laboratories, Geneva, Switzerland) was initiated in a step-down protocol until a minimum of 2 follicles reached an average diameter of 18 mm. Oocyte retrieval was performed using transvaginal ultrasonography 36 hours after the administration of 10 000 IU of human chorionic gonadotropin. The oocytes were kept in human tube fluid medium supplemented with 7.5% synthetic serum substitute for approximately 3 to 5 hours before cumulus cell removal. The cumulus cells were removed from the oocytes by placing them in hyaluronidase at a concentration of 80 IU/mL for approximately 30 to 60 seconds. The oocytes were transferred to fresh medium, and the corona cells were removed gently with a pipette.

ICSI Procedure

ICSI was performed with oocytes in metaphase II (MII), following the technique described by Palermo et al (1992). The microinjection dish was prepared by pipetting seven 4-μL droplets of human tubular fluid medium and adding HEPES and 15% synthetic serum substitute to the center of the dish. The center droplet was removed and replaced with 4 μL of polyvinylpyrrolidone solution. Prepared sperm was added to the drop of polyvinylpyrrolidone solution and the oocytes, and then placed into the drops of medium. The droplets were overlaid with mineral oil. ICSI was performed microscopically on a heated stage. After the oocytes were injected, they were rinsed and placed in equilibrated growing medium (15% human tubular fluid–synthetic serum substitute). The micro-

Table. *Parameters evaluated in patients with varicocele (n = 79) and patients who underwent a previous varicocelectomy (n = 169)*

Variable	Group 1	Group 2	*P*
Female age, y	33.0 ± 0.46	33.8 ± 0.38	.1872
Male age, y	36.1 ± 0.55	37.8 ± 0.47	.0319
Time to pregnancy, y	2.7 ± 0.36	6.0 ± 0.49	<.0001
Semen volume, mL	3.3 ± 0.30	2.5 ± 0.14	.0043
Sperm concentration, million/mL	30.8 ± 4.01	24.1 ± 2.42	.1380
Sperm motility, %	28.2 ± 2.36	28.7 ± 1.70	.8736
Morphology, %	2.6 ± 0.44	2.4 ± 0.37	.7202
Left testicle volume, mL	19.4 ± 0.61	18.8 ± 0.66	.4929
Right testicle volume, mL	20.3 ± 0.60	19.9 ± 0.67	.6556
FSH, IU	2371.7 ± 100.69	2249.4 ± 63.68	.2943
Estradiol, pg/mL	1926.8 ± 364.73	2002.4 ± 201.33	.8490
Mean follicles	22.3 ± 2.54	22.4 ± 1.55	.9752
Mean MII oocytes	8.8 ± 1.34	10.4 ± 0.79	.2805
MII oocytes, %	61.2	66.4	.6217
Mean injected oocytes	10.3 ± 1.16	9.6 ± 0.60	.5532
Fertilization rate, %	73.2	64.9	.0377
Mean embryos transferred	2.8 ± 0.18	2.4 ± 0.13	.0785
Pregnancy rate, %	31.1	30.9	.9806
Implantation rate, %	22.1	17.3	.5882
Miscarriage rate, %	21.7	23.9	.8401
Cycles canceled, %	5.1	10.1	.2277

Abbreviations: FSH, follicle-stimulating hormone; MII, metaphase II.

manipulated oocytes were incubated in 50- to 100-μL drops in a culture dish overlaid with mineral oil. The oocytes were observed for fertilization for 16 to 18 hours after the injection procedure. Abnormally fertilized or unfertilized oocytes were removed from the dish. Twenty-four hours later, cleavage of fertilized oocytes was assessed. Embryo transfer was performed approximately 72 hours after injection.

Clinical Follow-Up of Pregnancy

Clinical pregnancy was determined by the visualization of at least one gestational sac by ultrasound at 7 weeks.

Statistical Analysis

We compared the age of the male patients with their female partners, the men's semen characteristics (according to WHO and Tygerberg's strict criteria), right and left testicular volume, the women's follicle-stimulating hormone and estradiol levels, the number of oocytes retrieved, the number of MII oocytes retrieved, the number of cycles canceled, fertilization, implantation, the number of embryos transferred, and pregnancy and miscarriage rates between the two groups. For this analysis, we used the Wilcoxon signed rank test or the Mann-Whitney test.

Results

No differences were detected in the age of the men in group 1 (36.1 ± 0.55 years) and group 2 (37.8 ± 0.47 years; $P = .1872$; Table), and no differences were detected in the age of the women in group 1 (33.0 ± 0.46 years) and group 2 (33.8 ± 0.38 years; $P = .1872$). The couples in group 2 had had tried longer to achieve a pregnancy (6.0 ± 0.49 years) than those in group 1 (2.7 ± 0.36 years; $P < .001$).

Semen volume was higher in group 1 (3.3 ± 0.3 mL) than in group 2 (2.5 ± 0.14 mL; $P = .0043$). However, no differences were detected between groups 1 and 2 in sperm concentration (30.08 ± 4.01 million/mL and 24.1 ± 2.42 million/mL; $P = .138$), sperm motility (38.2% ± 2.69% and 38.7% ± 2.08%; $P = .881$), and morphology according to Tygerberg's strict criteria (2.6% ± 0.44% and 2.4% ± 0.37%; $P = .7202$). The mean volume (in milliliters) of the left testicle did not differ between group 1 (19.4 ± 0.71) and group 2 (18.8 ± 0.66; $P = .4929$), nor did the mean volume of the right testicle (20.3 ± 0.60 and 19.9 ± 0.67 for groups 1 and 2, respectively; $P = .6565$).

The mean follicle-stimulating hormone levels of the female partners in both groups were not different (2371.7 ± 100.69 IU and 2249.4 ± 63.68 IU for groups 1 and 2, respectively; $P = .2943$), nor were mean estradiol levels (1926.8 ± 364.73 pg/mL and 2002.4 ± 201.33 pg/mL for groups 1 and 2, respectively; $P = .8490$).

There were no differences in the number of oocytes retrieved in group 1 (14.8 ± 1.74) and group 2 (14.9 ± 1.04; $P = .9515$), and there was no difference in the percentage of oocytes retrieved (65.4% for group 1 and 67.6% for group 2; $P = .6401$). No differences were detected in the mean of number of MII oocytes retrieved in group 1 (8.8 ± 1.34) and in group 2 (10.4 ± 0.79; $P = .2805$). There was no difference in the mean number of

oocytes injected per couple in group 1 (10.3 ± 1.16) and group 2 (9.6 ± 0.60; $P = .5532$).

The fertilization rate was higher in group 1 (73.2%) than in group 2 (64.9%; $P = .0377$). However, no differences were detected in the pregnancy rates (31.1% vs 30.9%; $P = .9806$), implantation rates (22.1% vs 17.3%; $P = .5882$), and miscarriage rates (21.7% vs 23.9%; $P = .8401$) in groups 1 and 2. No differences were detected in the mean number of embryos transferred in group 1 (2.8 ± 0.18) and group 2 (2.4 ± 0.13; $P = .0785$), or in the number of cycles cancelled per cycle (5.1% and 10.1%, respectively; $P = .2277$).

Discussion

Varicocelectomy has become the most commonly performed male infertility surgery. In fact, according to Zini et al (2008), men with poorer baseline characteristics are more likely to opt for varicocele repair. Furthermore, couples electing not to repair the varicocele are more likely to undergo ICSI procedures to improve their chances of conception.

The relationship between varicocele and azoospermia is controversial. The main question is whether azoospermia is caused by varicocele or by coexisting primary testicular failure. Therefore, there is no consensus on whether to correct varicocele in azoospermic men with maturation arrest or Sertoli cell–only syndrome. Furthermore, the question remains whether surgical repair of varicocele should be recommended for the above conditions to avoid the need to obtain sperm by testicular sperm extraction (TESE) for ICSI. Motile sperm from the ejaculate provide better fertilization, cleavage, and pregnancy rates with ICSI than those from TESE (Loutradi et al, 2006). It is generally accepted that sperm production recovers somewhat after varicocele repair, but remains suboptimal. In a recent study, Inci et al (2009) evaluated 96 men with complete nonobstructive azoospermia and a history of clinical unilateral or bilateral varicocele. Their results suggest that varicocele repair significantly increases the sperm retrieval rate in patients with clinical varicocele and nonobstructive azoospermia. The authors concluded that men with clinical varicocele and nonobstructive azoospermia who undergo varicocelectomy are not likely to retain sufficient sperm quality to achieve pregnancy either with intercourse, intrauterine insemination, or ICSI without the use of TESE.

The development of ICSI as the method of choice in cases of severe male factor infertility has encouraged scientists to modify their diagnostic and therapeutic approaches (Van Steirteghem et al, 1993; Penson et al, 2002). Thus, a frequent question regarding the therapeutic approach for infertile couples with varicocele is whether to treat this condition before using TESE/ICSI. Treating varicocele is more cost-effective than other infertility treatments, especially if future pregnancies are planned (Van Steirteghem et al, 1993; Penson et al, 2002). On the other hand, Lee et al (2009) demonstrated that when direct costs are considered, microsurgical TESE appears to be more cost-effective than varicocelectomy for treating varicocele-associated nonobstructive azoospermia (Haydardedeoglu et al, 2010). The cost-effectiveness of both treatments has improved with time. Most importantly, the authors concluded that cost-effectiveness analyses may be tailored to institution-specific data to allow more individualized results.

A retrospective study by Haydardedeoglu et al (2010) evaluated whether a history of varicocele repair in men with nonobstructive azoospermia improved ICSI outcomes. The authors found a significantly higher sperm retrieval rate in the varicocele repair group compared with the group of men who had not undergone varicocele repair. The clinical pregnancy and live birth rates were significantly higher in the varicocelectomy group. Therefore, varicocele repair might be considered in patients with nonobstructive azoospermia who are undergoing an ICSI cycle.

Smit et al (2010) in a very elegant study prospectively evaluated sperm chromatin structure changes in infertile patients before and after surgical varicocele repair and their impact on pregnancy rates. After varicocelectomy, sperm parameters significantly improved and sperm DNA fragmentation was significantly decreased. Low DNA fragmentation index values were associated with a higher pregnancy rate (both spontaneous and with assisted reproductive techniques). Therefore, the authors argued that varicocelectomy should be considered in infertile men with palpable varicocele, men with abnormal semen analysis, and female partners with no major infertility factors. However, the study included only 49 men, which was too small a sample to allow for conclusive results.

In our study of 248 patients who had varicocele or who had previously undergone a varicocelectomy, we found that although the fertilization rate was higher in the varicocele group, the pregnancy, implantation, and miscarriage rates did not differ between the groups. Further studies are needed to confirm our results.

Conclusions

We conclude that although past evidence indicates that varicocelectomy may be of benefit in some circumstances and should always be considered before recommending assisted reproductive techniques when appropriate, this surgical procedure was not shown to have an impact on pregnancy or miscarriage rates following ICSI in

couples where the male partner had an existing or previously repaired varicocele.

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