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# Microsurgical Varicocelectomy for Infertile Couples With Advanced Female Age: Natural History in the Era of ART

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**ABSTRACT:** Varicocele represents the most common cause of male infertility, and most reports indicate that varicocelectomy has a beneficial effect on male fertility and pregnancy outcome. Assisted reproductive technologies (ARTs) are an alternative to varicocelectomy for the management of couples with a varicocele. The age of the female partner is important in the decision-making process; however, the true influence of female age on pregnancy outcome following varicocelectomy or ART in these couples is unknown. We evaluated the outcomes of 2 cohorts of infertile men with a varicocele and a female partner 35 years of age or older; one group selected varicocelectomy and the other a nonsurgical approach. We reviewed a group of consecutive infertile men who underwent microsurgical varicocelectomy and whose partners are 35 years of age or older (n = 110). We also reviewed a consecutive group of men with varicoceles who elected not to have surgery and whose partners are 35 years of age or older (n = 94). The outcome measures included changes in semen parameters, pregnancy rates (assisted and unassisted), and use of ART. The surgical and nonsurgical groups had comparable semen parameters and female ages. Mean sperm concentration and motility increased significantly after varicocelectomy ($P < .05$). At a mean of 30 months follow-up, 35% of couples in the surgical group achieved a spontaneous pregnancy and an additional 6% achieved a pregnancy via ART (20% of this group attempted ART). In the nonsurgical group, 25% achieved a spontaneous pregnancy and an additional 16% achieved a pregnancy with ART (40% of this group attempted ART). This study on the natural history of infertile men with varicocele and advanced female age suggests that the surgical and nonsurgical approaches offer comparable pregnancy outcome (combined assisted and unassisted pregnancy rates are about 40%). Overall, these data suggest that varicocelectomy is an acceptable option for couples with advanced female age, but other female factors must be considered in the decision-making process.

Key words: Male infertility, varicocele, assisted reproduction.

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Varicocele represents the most common identifiable pathology in infertile men (Greenberg et al, 1978). A clinical varicocele is detected in about 35% of men who present for infertility evaluation, whereas it is found in about 15% of all adult males (Clarke, 1966; Greenberg et al, 1978). The mechanisms responsible for the detrimental effects of varicocele on male fertility have been well described (Donohue and Brown, 1969; Zorgniotti and MacLeod, 1973; Comhaire and Vermeulen, 1974). The effect of adult varicocelectomy on male fertility potential has been studied extensively, and a critical analysis of treatment outcome suggests that, in general, there is a significant improvement in semen quality and pregnancy outcome after surgery (Stewart, 1974; Cockett et al, 1979; Nilsson et al, 1979; Newton et al, 1980; Vermeulen and Vandeghe, 1984; Rageth et al, 1992; Breznik et al, 1993; Madgar et al, 1995; Nieschlag et al, 1998). However, this must be qualified by the fact that most of the outcome data are based on uncontrolled or poorly controlled (non-randomized) studies. As such, the beneficial effect of adult varicocelectomy on male fertility potential is probably real but remains unproved (Schlesinger et al, 1994; Kamischke and Nieschlag, 1999; Evers and Collins, 2003).

The recent advent of advanced forms of assisted reproductive technology (ART) has made it possible for many infertile couples to achieve a pregnancy. In most instances, ARTs have been used for the treatment of couples with idiopathic infertility, but ARTs can also be used as an alternative to varicocelectomy for the management of couples with clinical varicocele and suboptimal seminal parameters. The age of the female partner is believed to be important in the decision-making process; however, the true influence of female age on pregnancy outcome following varicocelectomy or ART in these couples has not been formally studied. The article of Nieschlag et al, indeed, observed that female age may be an important predictor of pregnancy outcome after varicocelectomy (Nieschlag et al, 1998). Moreover, the issue of advanced female age on fertility outcome has become commonplace as many more women are now electing to delay childbearing until they are in their 30s.

In order to investigate the influence of female age on pregnancy outcome following varicocelectomy, we com-

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pared the outcomes of 2 cohorts of infertile men, both groups with a varicocele and a female partner 35 years of age or older. One cohort chose to undergo microsurgical varicocelectomy and the second group chose not to undergo varicocelectomy (controls), but both groups were free to undergo ART. As such, the objective of our study was to examine the pregnancy outcome of these 2 cohorts (one cohort adopting a surgical and the other a nonsurgical approach) in the era of advanced ARTs.

## Methods

We performed a retrospective review of consecutive couples who presented for infertility evaluation at the Mount Sinai Hospital—Andrology clinic between July of 1996 and December 2002. We identified a group of men with varicoceles and whose female partners were 35 years of age or older (n = 202). All men presenting to our clinic with 1 year or more of infertility, a clinically palpable varicocele, and abnormal semen parameters (reduced sperm concentration, motility or morphology on 2 or more semen samples) were deemed to be candidates for varicocele repair. Couples in whom the wife had tubal obstruction or ovulatory failure were not included. From the original group, we identified a cohort who elected to have microsurgical varicocelectomy (n = 108). The remaining cohort elected not to have surgery (n = 94).

All varicoceles were evaluated and graded based on the Dubin grading system (grades I–III) and were based solely on clinical exam (subclinical varicoceles were not included in this study) (Dubin and Amelar, 1977). All microsurgical varicocelectomies were performed by the same surgeon (A.Z.) as previously described (Goldstein et al, 1992).

Couples were counseled about the available treatment options, their costs, and potential complications. These treatment options included varicocelectomy and ARTs (intrauterine insemination [IUI] and in vitro fertilization [IVF] with intracytoplasmic sperm injection [ICSI]) (Jarow et al, 2002).

Nearly all men had at least 2 semen analyses before and 2 semen analyses after surgery. However, in order to be consistent, we used the semen analysis performed 1 to 3 months before varicocelectomy (preoperative analysis) and the semen analysis done at 6 to 8 months after surgery (postoperative analysis) for data analysis in this study. Samples were obtained by masturbation after 3 to 5 days of sexual abstinence. After liquefaction of semen, standard semen parameters (volume, density, motility, morphology) were obtained according to World Health Organization guidelines (World Health Organization, 1992). The total motile sperm count was calculated as semen volume times sperm concentration times percent motility divided by 100.

Follow-up assessment was conducted by chart review and telephone calls. The gathered information included details regarding patient history and physical examination, semen parameters, and pregnancy outcome (spontaneous and/or assisted). The outcome measures included changes in semen parameters, pregnancy rates (assisted and unassisted), and use of ART.

Patient information for this study remained confidential and within the institution. In our institution, Institutional Review Board (IRB) approval is not necessary for retrospective studies. IRB approval was therefore not obtained.

Results are expressed as means plus or minus 1 standard error of mean (SEM). Parametric and nonparametric tests were used (as appropriate) to estimate differences between the prevaricocelectomy and postvaricocelectomy semen parameters and to estimate differences between the surgical and nonsurgical groups (SAS Institute, Cary, NC). The time to pregnancy was estimated using the Kaplan-Meier method. $P$ values less than .05 are considered statistically significant.

## Results

Of the 108 men who elected to have surgery, 72 underwent a left and 46 a bilateral microsurgical varicocelectomy. In this group, 73% of couples suffered from primary infertility and the remaining 27% had secondary infertility. Clinical, preoperative semen parameters and pregnancy outcome data of the 108 men who underwent varicocelectomy are presented in Table 1. After surgery, mean ($\pm$SE) total motile sperm count increased significantly compared with prevaricocelectomy (33.0 $\pm$ 5.4 vs 19.4 $\pm$ 3.0 million sperm/mL, respectively $P < .01$). The mean postoperative percentage morphology was not significantly higher than the preoperative value (38.2% vs 35.4%, respectively, $P > .05$). Of couples in whom the man underwent varicocelectomy, 66% (71/108) were contacted for pregnancy outcome data with a mean follow-up of 30.1 months (range: 10 to 53 months). Of these couples, 35% (25/71) achieved a spontaneous pregnancy and an additional 2% and 4% achieved a pregnancy following IUI and IVF/ICSI, respectively, for an overall pregnancy rate of 41%. In total, 20% (14/71) of these couples attempted some form of ART and 29% (4/14) achieved a pregnancy (15% [11/71] attempted a mean of 2.5 cycles of IUI [range: 1 to 5] and 11% [8/71] attempted a mean of 1.9 cycles of IVF/ICSI [range: 1 to 3]). The 37 patients that did not have pregnancy outcome data did not differ from the 71 men with available pregnancy data with respect to age (male and partner), initial sperm concentration, or initial sperm motility (data not shown).

Of the 94 men who elected not to undergo varicocelectomy, 65 had a left and 29 a bilateral varicocele (not significantly different from surgical group, $P > .05$). In the nonsurgical group, 64% of couples suffered from primary infertility and the remaining 36% had secondary infertility (not significantly different from surgical group, $P > .05$). Clinical, preoperative semen parameters and pregnancy outcome data of the 94 men who underwent varicocelectomy is presented in Table 1. Of couples who elected not to undergo surgery, 56 (60%) were contacted for pregnancy outcome data with a mean follow-up of 32.9 months (range: 9 to 55 months). Of these couples, 25% (14/56) achieved a spontaneous pregnancy and an

Table 1. *Clinical and preoperative semen parameters, pregnancy rate (unassisted and combined assisted and unassisted), and use of ARTs in couples who selected surgery (varicocelectomy) and those who opted for a nonsurgical approach*

| | Surgery* | No Surgery* | *P*† |
|---|---|---|---|
| n | 108 | 94 | |
| Follow-up, mo | 30.1 ± 1.2 | 32.9 ± 1.7 | NS‡ |
| Duraton of infertility, mo | 35.5 ± 2.9 | 36.6 ± 3.3 | NS |
| Male age, y | 39.0 ± 0.5 | 39.3 ± 0.5 | NS |
| Female age, y | 37.4 ± 0.3 | 38.5 ± 0.3 | .01§ |
| Serum follicle stimulating hormone, IU/mL | 5.3 ± 0.4 | 5.8 ± 0.5 | NS |
| Sperm concentration × $10^6$/mL | 21.1 ± 2.4 | 30.4 ± 3.4 | .03§ |
| Sperm motility, % | 25.0 ± 1.6 | 35.0 ± 2.2 | .0001§ |
| Spontaneous pregnancy rate, % | 35 | 25 | NS |
| Overall preganancy rate, % | 41 | 41 | NS |
| ART use, % | 20 | 45 | NS |

* Values are means plus or minus standard error of mean.
† Comparison between surgery and no surgery groups.
‡ NS, not significant ($P \geq .05$).
§ Mann-Whitney rank sum test.

additional 7% and 9% achieved a pregnancy following IUI and IVF/ICSI, respectively, for an overall pregnancy rate of 41%. In total, 45% (25/56) of these couples attempted some form of ART and 36% (9/25) achieved a pregnancy (36% [20/56] attempted a mean of 3.7 cycles of IUI [range: 1 to 8] and 27% [15/56] attempted a mean of 2.3 cycles of IVF/ICSI [range: 1 to 5]). The 38 patients that did not have pregnancy outcome data did not differ from the 56 men with available pregnancy data with respect to age (male and partner), initial sperm concentration, or initial sperm motility (data not shown).

Mean (±SE) female age was significantly lower in the surgical compared with the nonsurgical group (37.4 ± 0.3 [range: 35 to 49 years] vs 38.5 ± 0.3 [range: 35 to 48 years], $P < .05$, Table 1). However, mean sperm concentration and motility were significantly lower in the surgical compared with the nonsurgical group (21.1 ± 2.4 vs 30.4 ± 3.4 million sperm/mL and 25.0% ± 1.6% vs 35.0% ± 2.2% motility, respectively, $P < .05$, Table 1). Spontaneous (natural) pregnancy rates were higher in the surgical compared with the nonsurgical group, although the difference did not reach statistical significance (35% vs 25%, $P > .05$, Table 1). ART use was higher in the nonsurgical compared with the surgical group, although the difference did not reach statistical significance (45% vs 20%, $P > .05$, Table 1). The unassisted pregnancy outcome of the varicocelectomy group (n = 108) did not differ significantly from that of the 15 couples who underwent IVF/ICSI alone (35% vs 40%, respectively). Female age, sperm concentration, and sperm motility were not significantly different in those couples who achieved a pregnancy compared with those couples who did not achieve a pregnancy (data not shown). We observed within each subgroup (surgery vs no surgery) a trend toward lower pregnancy rates as maternal age increases, but this did not reach statistical significance (Table 2).

Table 2. *Spontaneous (SPON) and combined (COMB) assisted and unassisted pregnancy rate (PR) in couples who had surgery and those who opted for a nonsurgical approach, by female age group*

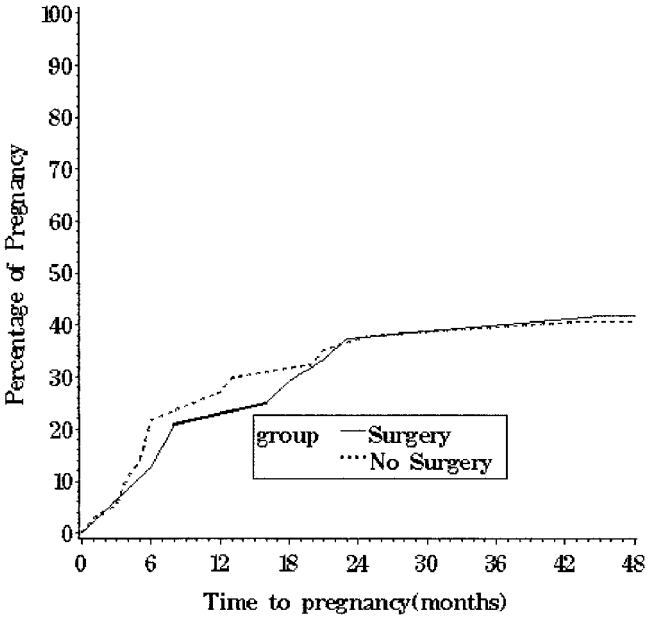
| | Surgery | | No Surgery | |
|---|---|---|---|---|
| | SPON PR, % (n) | COMB PR, % (n) | SPON PR, % (n) | COMB PR, % (n) |
| Female age group | | | | |
| 35–39 y | 39 (61) | 45 (61) | 30 (37) | 54 (37) |
| 40–42 y | 29 (7) | 29 (7) | 20 (10) | 30 (10) |
| >42 y | 0 (3) | 0 (3) | 22 (9) | 22 (9) |
| *P* value* | NS† | NS | NS | NS |

* Comparison among age groups (35–39, 40–42, >42); Kruskal-Wallis analysis of variance on ranks.
† NS, not significant ($P > .05$).

The mean (±SE) time to pregnancy (starting from the time that couples elected or not to undergo surgery to the time that a pregnancy was established) of the varicocelectomy group was not significantly greater than that of the no surgery group as a whole (16 ± 5 vs 11 ± 2 months, respectively, $P > .05$) (Figure). Similarly, the time to pregnancy for the varicocelectomy group was not significantly greater than that of the subset of couples in the no surgery group who underwent some form of ART (16 ± 5 vs 13 ± 2 months, respectively, $P > .05$).

## Discussion

This is the first study to specifically examine the effect of varicocelectomy on pregnancy outcome in couples with advanced female age (35 years of age or older) in the era of ART. We have reported that after varicocelectomy, mean postoperative sperm concentration and motility increased significantly compared with preoperatively and that 35% of couples achieved a natural pregnancy.




Kaplan-Meier estimates of time to pregnancy by treatment group.

An additional 6% of these couples achieved a pregnancy following IUI or IVF/ICSI (20% of the couples attempted some form of ART). Our results on sperm quality improvement and spontaneous pregnancy rates after varicocelectomy in this population are in keeping with previously published data on varicocelectomy in unselected couples with varicocele (Schlesinger et al, 1994). Indeed, an analysis of treatment outcome following varicocele repair indicates that spontaneous pregnancy rates are in the range of 30% to 60% (Schlesinger et al, 1994). However, most of the outcome data on varicocelectomy are based on uncontrolled or nonrandomized studies and, therefore, these results must be interpreted with caution (Schlesinger et al, 1994; Kamischke and Nieschlag, 1999).

There are no previously published data on the natural history of infertile couples with untreated varicocele and advanced female age (35 years of age or older) in the era of ART. In our series, 25% of couples who chose a nonsurgical approach achieved a natural pregnancy at a mean of 33 months follow-up. An additional 16% of these couples achieved a pregnancy following IUI or IVF/ICSI (45% of the couples attempted some form of ART). The spontaneous (natural) pregnancy outcome in this group is in keeping with the reported natural history of couples with unexplained infertility (Collins et al, 1995).

The female age in the surgical group was significantly lower than that in the nonsurgical group (albeit only by a mean of about 1 year), and this may have favored natural pregnancy outcome in the surgical group. On the other hand, both sperm concentration and motility were significantly higher (~30% higher) in the nonsurgical group, and this may have favored natural pregnancy outcome in the nonsurgical group. Taken together, the influence of these unequally distributed factors (female age and semen parameters) in the nonsurgical and surgical groups suggests that the 2 groups are comparable. Therefore, we can say that the surgical group had a higher natural pregnancy rate than the nonsurgical (control) group, although the difference (35% vs 25%, respectively) was not statistically significant. More importantly, the natural pregnancy rate in the varicocelectomy group was comparable to the assisted pregnancy rate in the subset of couples in the nonsurgical group who attempted ARTs (35% vs 36%, respectively) or to those who underwent IVF/ICSI alone (35% vs 40%, respectively). Varicocelectomy is reported to be a more cost-effective approach than IVF/ICSI in infertile couples with varicocele (Schlegel, 1997; Bonduelle et al, 1999). As such, given that varicocelectomy is at least equivalent to ARTs and, additionally, may be superior to a nonsurgical approach in terms of pregnancy outcome, we propose that varicocelectomy is a more cost-effective approach than ARTs (IUI and/or IVF/ICSI) in infertile couples with varicocele and advanced female age.

It has been suggested that female age may be an important predictor of pregnancy outcome, but this factor has not been formally studied in couples undergoing varicocele repair. In 1998, Nieschlag et al examined the pregnancy outcomes of couples with clinical varicoceles in a prospective, randomized study, comparing varicocelectomy to counseling (Nieschlag et al, 1998). They observed that although sperm concentration increased significantly only in the surgical group (not in the counseling group), pregnancy rates were not significantly greater in the surgical compared with the counseling group. However, they found that the only parameter associated with positive pregnancy outcome was female age at the time of admission to the study. They reported that the 34 couples who achieved a natural pregnancy had a significantly lower mean female partner age than the 91 couples who did not become pregnant (28.8 vs 31.2 years, respectively, $P < .05$). In the present study, female age, sperm concentration, and sperm motility were not significantly different in those couples who achieved a pregnancy compared with those couples who did not achieve a pregnancy.

This study on the natural history of infertile couples with varicocele and advanced female age suggests that the surgical and nonsurgical approaches offer comparable pregnancy outcome (combined assisted and unassisted pregnancy rates are about 40%). Although not significant, the varicocelectomy group had a higher spontaneous pregnancy rate and a lower rate of ART use than the nonsurgical group. Overall, these data suggest that varicocelectomy is an acceptable option for couples with advanced female age but other female factors, health, and

cost issues must be considered in the decision-making process.

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