The varicocele dilemma

Sherman J.Silber

Infertility Center of St Louis, St Luke's Hospital, 224 South Woods Mill Road, Suite 730, St Louis, MO 63017, USA

There is probably no subject that is more controversial in the area of male infertility than varicocele. The overwhelming majority of non-urologist infertility specialists in the world are extremely sceptical of the role of varicocele or varicocelectomy in the treatment of male infertility. Directors of most assisted reproductive technologies (ART) programmes view the enthusiasm with which urologists approach varicocelectomy as a potential impediment to the couple that is getting older and do not have much time left to become pregnant using ART. There are many credible, well-controlled studies which show no effect of varicocelectomy on fertility. There are also a few 'controlled' studies that favour varicocelectomy, but all can be criticised on the basis of patient selection bias. Thus the great weight of evidence from controlled studies is against varicocelectomy and the reports supporting varicocelectomy are extremely weak. Finally, the reports that semen parameters are improved by varicocelectomy is flawed by uncontrolled observations and the failure to take into account the variability of semen analysis in infertile men and its regression toward the mean. Many control studies have demonstrated that, because of this variability, men with an initially low sperm count tend later to have higher sperm counts in the absence of any treatment whatsoever.

Key words: ART/pregnancy rate/semen parameters/varicocelectomy

TABLE OF CONTENTS

Introduction

Varicocelectomy entails risk

Lack of effect of varicocele on pregnancy rate following vasovasostomy

Evidence-based practice of medicine

Varicocelectomy and sperm count

Controlled studies challenging the effectiveness of varicocelectomy Controlled studies supporting varicocelectomy

Does varicocele cause a progressive decline in fertility?

References

Introduction

There have been many years of debate over the causes and therapy of male infertility. Many treatments have been strongly advocated for male infertility over the past four decades, e.g. clomiphene citrate, testosterone, human menopausal gonadotrophin (HMG), human chorionic gonadotrophin (HCG), corticosteroids (for sperm antibodies), cold wet athletic supports, vitamins, and even more recently very aggressively marketed nutritional supplements such as 'Proxceed', without any documented evidence of effectiveness (Devroey *et al.*, 1998). It is becoming clear that many spermatogenic defects in the human are genetic in origin, and clearly impervious to improvement with any current therapy (Reijo *et al.*, 1995; Silber *et al.*, 1995, 1998; Page *et al.*, 1999). Furthermore, the development of intracytoplasmic

sperm injection (ICSI) as an effective therapy for all cases of male infertility which have failed to respond to conventional treatment has caused a major reassessment and critical analysis of the diagnostic and therapeutic approaches to male infertility (Van Steirteghem *et al.*, 1993). In that light, the varicocelectomy operation must be re-evaluated.

Varicocelectomy entails risk

In May 1998, an azoospermic patient of ours finally had twin boys after a fourth cycle of testicular sperm extraction (TESE) and ICSI. He had undergone bilateral varicocelectomy at a major university 2 years earlier, for a sperm count of 19×10^6 spermatozoa/ml, with a volume of 10 ml, and 60% sperm motility with normal morphology, and had suffered complete left testicular infarction and right testicular atrophy. His wife's pregnancy was no thanks to her husband's varicocelectomy. A different patient who had sperm counts that fluctuated between 2.8 and 94×10^6 spermatozoa/ml had a similar experience several years earlier, and also required TESE–ICSI. These occasional complications of varicocelectomy have been known for >20 years (Silber, 1979).

Of course, this is not the usual disastrous result with bilateral varicocelectomy. In fact, a microsurgical approach to varicocelectomy has been designed to avoid such complications (Silber, 1979; Goldstein *et al.*, 1992; Marmar and Kim, 1994; Girardi and Goldstein, 1997; Scherr and Goldstein, 1999). Nonetheless, the occasional serious risk of varicocelectomy cannot be disregarded.

If it were not for this risk, microsurgical approaches to varicocelectomy would never have been developed. The more common risk of post-operative hydrocele (5%) is obviously just a nuisance and not as serious as devascularization (Dubin and Amelar, 1975).

Semen analyses are often highly variable, and spontaneous pregnancies without treatment are so common that there is much scepticism about many treatments for male infertility (Baker *et al.*, 1981, 1984, 1985, 1993; Baker and Kovacs, 1985; Baker and Burger, 1986; Baker, 1986, 1993; Silber, 1989a; Devroey *et al.*, 1998; Devroey, 1999). Because no treatment of male infertility is without risk, if for no other reason than simply the delaying of more effective treatment until the wife is older, I would like to review in this paper the pitfalls of trying to evaluate either pregnancy results or sperm count results in patients undergoing varicocelectomy or, indeed, any other treatment for male infertility, without properly controlled studies.

Lack of effect of varicocele on pregnancy rate following vasovasostomy

In 1989, we reported a 10 year follow-up of men undergoing vasovasostomy (who had spermatozoa in the vas fluid without secondary epididymal blowouts), and their long-term results (Silber, 1989b). This experience was the origin of my scepticism regarding the value of varicocelectomy. Out of 282 patients undergoing vasovasostomy ten or more years earlier, who had good sperm in the vas fluid (meaning there was no secondary epididymal obstruction), 42 (14.8%) had a discernible (moderate or large) varicocele upon physical examination, and 240 (85.2%) had no such varicocele (Table I). These men had no other medical or surgical treatment other than vasovasostomy. The wives of 78.5% of those men with varicocele (not operated upon), became pregnant, and the wives of 81.2% of those without varicocele became pregnant. Thus, there was no statistically significant difference (78.5 versus 81.2%) in pregnancy rate in those with varicocele versus those without varicocele for older men undergoing vasovasostomy. There was also no difference in postoperative semen parameters. Our conclusion from this study was that in a group of men with prior fertility who have a varicocele (who were fertile except for their vasectomy, but many years later decide to have their vasectomy reversed) the presence of a varicocele did not have any discernible effect on their long-term fertility.

A decade later, essentially the same question was addressed (Mulhall *et al.*, 1997) when varicocelectomy was performed simultaneously with vasovasostomy in 10 vasectomy reversal patients who had varicocele but varicocelectomy was not carried

 Table I. Lack of effect of varicocoele (not operated on) on pregnancy rate
 following vasovasostomy (taken from Silber, 1989b). Values in parentheses

 are percentages
 1989b)
 Values in parentheses

	Total no. of Patients	No. of patients with varicocoele	No. of patients without varicocoele
Pregnant	228 (80.9)	33 (78.5)	195 (81.2)
Not pregnant	54 (19.1)	9 (21.14)	45 (18.5)
Totals	282 (100)	42 (14.8)	240 (85.2)

out in the other 37 vasectomy reversal patients who had a varicocele. There was no statistically significant difference between the two groups (although their major point was the safety of performing simultaneous varicocelectomy).

Evidence-based practice of medicine

In 1995, Nieschlag proposed a basic axiom that needs to be followed in male infertility treatment: 'Therapeutic interventions in male infertility should be based on properly controlled clinical trials' (Nieschlag et al., 1995). Several reports on spontaneous pregnancy rates with no treatment in couples with severe male factor justify Nieschlag's axiom. In 1993, Hargreave reported on patients with severe oligozoospermia, high serum FSH concentrations, and varicocele whose wives became pregnant after an initial infertility consultation without any treatment of the male (Hargreave and Elton, 1983; Hargreave, 1993). A total of 33% of men in this category had a varicocele, and did not have time to undergo varicocelectomy before their wife became pregnant. The point of his study was that, with alarmingly low sperm counts, women can become pregnant without any treatment of the male, verifying concepts that have been clear for many years (Smith et al., 1977; Zukerman et al., 1977; Steinberger and Rodriguez-Rigau, 1983; Silber, 1989a).

To understand the importance of a controlled study in evaluating the validity of varicocelectomy, one has only to look at the spontaneous conception rates in the wives of men with various low sperm counts. Hargreave and Elton's work was not just about varicocelectomy, but also was about the issue of 'what is male infertility' (Hargreave and Elton, 1983; Silber, 1989a). They found that even in men with sperm counts of $\leq 2 \times 10^6$ spermatozoa/ml, and with a duration of infertility of as long as 4 years, 20% of the wives eventually have a spontaneous conception without ever having any improvement in the sperm count. In men with sperm counts of 5×10^6 spermatozoa/ml with only 1 year of infertility, 36% of the wives became pregnant without any treatment (Table II). Thus, if one had performed a varicocelectomy on such men prior to their wife's conception, without a controlled study, we might have mistakenly concluded that the operation is what enabled the pregnancy, even though it was simply a spurious, unrelated event.

Baker and Burger in 1986, reported life-table pregnancy rates over 3 years in couples with varying categories of semen parameters compared to control groups (Baker and Burger, 1986). Although lower sperm counts resulted in lower pregnancy rates, a

Table II. Percentage chance of conception for the next year (wife with normal results after investigation) (Hargreave and Elton, 1983)

Motile density	Duration of infertility (months)			
$(\times 10^6 \text{ motile spermatozoa/ml})$	12	24	48	96
0	0	0	0	0
).5	16	12	9	6
l	25	19	14	9
2	34	26	19	13
5	36	28	21	14
10+	37	28	21	14

S.J.Silber

substantial percentage of couples achieved pregnancy spontaneously despite severe oligoasthenozoospermia (Figure 1).

In 1983, Schoysman reported an extensive 12 year experience following 1291 oligozoospermic men who underwent no improvement in semen parameters (Schoysman and Gerris, 1983). They found that for men with sperm counts of $1-5 \times 10^6$ spermatozoa/ml, 12% of wives became pregnant within 5 years and 27% of wives became pregnant within 12 years without any treatment (Table III). Even when the sperm count was <1 ×10⁶ spermatozoa/ml, 4% of wives conceived spontaneously within 5 years, and 9% within 12 years without any treatment. When sperm counts were $15-20 \times 10^6$ spermatozoa/ml, 69% of wives became pregnant within 5 years and 82% within 12 years, again with no treatment of the male. These studies demonstrate the difficulty of interpreting whether any treatment of the male with oligozoospermia, e.g. varicocelectomy, has any discernible effect on the pregnancy rate.

In 1975, Amelar and Dubin compiled a summary of all varicocelectomy studies prior to that time (Dubin and Amelar, 1975). None of the 11 papers on varicocelectomy published by 1975 was controlled. Most of them showed ~60–70% of patients had an improvement in sperm count, and most of the studies showed pregnancy rates from a low of 30% to a high of 55%. None of the studies controlled for the pregnancy rate in couples not undergoing varicocelectomy, and just assumed that these

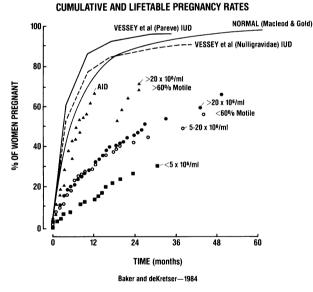


Figure 1. Cumulative and life-table pregnancy rates (Baker and Burger, 1986).

 Table III. Pregnancy rates in 1291 oligozoospermic men (Schoysman and Gerris, 1983)

Motile sperm count $(\times 10^{6}/\text{ml})$	Pregnancy (%) after 5 years	Pregnancy (%) after 12 years
0.1–1	3.9	8.7
1–5	11.9	26.6
5-10	22.1	34.3
10-15	45.0	58.5
15–20	68.6	82.0

couples would not have become pregnant without the surgery. Nieschlag concluded in 1998, as did Mordel in 1990, 'Studies since 1952 advocating varicocelectomy have been uncontrolled and not evidence-based' (Mordel *et al.*, 1990; Nieschlag *et al.*, 1998).

It is easy to become enthusiastic about any treatment of male infertility that is performed without adequate controls. In a series of men with either azoospermia or extremely severe oligozoospermia, the pregnancy rate in 56 severely oligozoospermic men following varicocelectomy was 23% (13 out of 56), and for 'azoospermic' men was 9% (two out of 22) (Steckel et al., 1993; Matthews et al., 1998). The problem with these studies again is that there is no control group, no longitudinal follow-up, and it pays no attention to the concept of 'regression toward the mean.' More recently a similar study (Kim et al., 1999) resulted in no spontaneous pregnancies even in the varicocelectomy group even though these authors maintained that sperm count 'improved' after surgery. Once again there is no control group of similar patients who did not receive surgery. We all have seen men who are initially azoospermic, who will eventually, in subsequent semen analyses, have spermatozoa in the ejaculate without any treatment (MacLeod and Gold, 1953; Baker and Kovacs, 1985). Without a control group to compare with, one should not be surprised to see a spontaneous pregnancy rate of 9-23% without any treatment of the male partner with severe sperm defects, particularly if the couple has had a short period of infertility, and/ or if the wife is young (Hargreave and Elton, 1983; Schoysman and Gerris, 1983; Silber, 1989a).

Varicocelectomy and sperm count

MacLeod and Gold, as far back as 1951 (MacLeod and Gold, 1951; MacLeod and Gold, 1953), first demonstrated that sperm concentration and motility tend to increase with time with repeated testing in oligozoospermic and asthenozoospermic men despite no treatment. This was a peculiar mathematical quirk related to the highly variable nature of the sperm count. That means that, without any treatment whatsoever, if you continue to get sperm counts and semen analyses longitudinally on men who initially have low sperm counts and poor motility, the low sperm count and the poor motility will routinely tend to increase with repeated tests and no treatment (MacLeod and Gold, 1951, 1953).

Baker et al. were the first to clearly and mathematically explain this phenomenon of 'regression toward the mean' (Baker et al., 1981; Baker and Kovacs, 1985; Baker, 1986). 'Regression toward the mean' has profound implications for all clinical trials. Whenever there is a highly variable measurement, if patients have a controlled period followed by a treatment period, there is likely to be a significant improvement even if the treatment is ineffective. Baker et al. observed the same phenomenon that McLeod and Gold had observed 30 years earlier, that sperm concentration and motility increased progressively in their study of day-to-day variability of semen analyses in infertile men. Sperm motility increased equally on both active drug and on placebo treatment in a double-blind controlled trial of erythromycin for asthenozoospermia (Baker et al., 1984). Clearly, erythromycin had no impact whatsoever on either sperm count or sperm motility. However, in this double blind control study, it was obvious that the sperm motility increased in an equal manner in patients that were on erythromycin and patients that were on placebo. 'In a similar fashion, sperm motility increased in men with varicoceles whether or not they had testicular vein ligations performed' (Baker *et al.*, 1985). No matter what the treatment, whether erythromycin, or watchful waiting, clomiphene citrate or varicocelectomy, an initially low sperm count (because of intrinsic variability) will gravitate higher because of 'regression toward the mean.'

Baker and Kovacs also concluded in 1985 that 'a group of subjects selected for low results will on average have higher results on re-measurement' (Baker and Kovacs, 1985). This phenomenon of 'regression toward the mean' signifies that whenever you have a phenomenon that is highly variable, and you have a select group of couples on the low end of that phenomenon, whether sperm count or sperm motility, because of the intrinsic variability, repeated tests will generally show an increase which has nothing to do with biology but is simply a mathematical event that has to occur. As Baker and Kovacs showed, therefore, a low sperm count will generally improve, with or without any treatment. Similarly, a very high sperm count will generally become worse with or without any treatment. Men with an average first sperm count of 28×10^6 had an average second sperm count of 56×10^6 . Men with an average first sperm count of 271×10^6 had a mean second sperm count of 145×10^6 . Among 216 semen donors whose initial motility averaged 42%, the second semen analysis showed a mean of 55% motility. Thus, whenever uncontrolled varicocelectomy studies mention an improvement in motility, or sperm count, this is what one often would expect to find with no treatment whatsoever when you are beginning with oligozoospermic couples (Baker and Kovacs, 1985; Baker, 1986).

Controlled studies challenging the effectiveness of varicocelectomy

Nieschlag's group performed a very meticulously controlled study to attempt to evaluate the effect of varicocelectomy (Nieschlag *et al.*, 1995, 1998). They studied 125 infertile couples with varicocele. Of those couples, 62 underwent varicocelectomy and

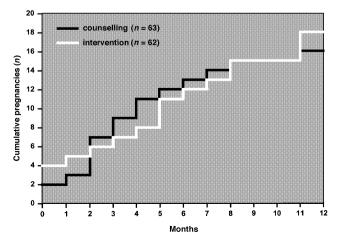


Figure 2. Cumulative pregnancy rates over 12 months in couples with male varicocele treated by intervention (ligation or embolization) or counselling alone (taken from Nieschlag *et al.*, 1998. Previously published in *Hum. Reprod.* 13, 2147-2150).

63 of them underwent counselling. It is important to point out that it was not just a 'treatment versus no treatment' group, but rather it was a 'surgical varicocelectomy treatment group' versus a 'psychological counselling group' (Figure 2) shows the survival curve results of the two different groups. There was no significant difference in pregnancy rate measured over time between those couples that underwent varicocelectomy and those couples that underwent psychological counselling. Furthermore, Nieschlag's group found no relationship of pregnancy to semen parameters, hormone concentrations, grade of varicocele, or the age of the male. The only relationship to pregnancy rate was the age of the wife and that was the only factor that could help predict the chances of pregnancy.

Nieschlag's controlled study attempted to put us on a more scientific footing in evaluating varicocelectomy, and also helped us realize how differences in the population characteristics of the wives of these infertile men would have potentially a major confounding effect. For example, one might, without proper control studies, be very enthusiastic about varicocelectomy in a practice involving younger couples, and less enthusiastic in a practice involving older ones. We discovered a similar confounding phenomenon in the treatment of obstructive azoospermia with

 Table IV. Obstructive azoospermia and intracytoplasmic sperm injection (ICSI): female age-related variation in pregnancy rate

Age of wife (years)	Number delivered pregnancy (% of cycles)
<30	44
30-36	34
37–39	13
≥40	4
Total	36

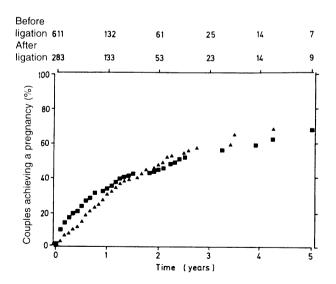


Figure 3. Life-table curves of pregnancy rates for before ligation (n) and after ligation (s) groups. Number of patients initially and those followed up to the end of each year is shown at top of figure. Symbols indicate those months in which the life table changed, i.e. pregnancies occurred. Although some patients were followed up for >5 years (those in before ligation group for maximum of 92 months, after ligation group for 108 months), the longest duration of follow up to pregnancy was 60 months. There was no significant difference between the two curves by log rank test (Baker *et al.*, 1985. Reprinted with permission from British Medical Journal).

S.J.Silber

sperm retrieval and ICSI. The only factor that significantly affected the variation in pregnancy rate in couples undergoing ICSI with retrieved spermatozoa was the age of the wife (Silber *et al.*, 1997) (Table IV). The delivery rate with ICSI using retrieved spermatozoa was 44% in women under aged <30 years; 34% with women aged 30–36; 13% with women ages 37–39; and only 4% with women aged >40 years the delivery rate per cycle. With women aged <37 years, who also had a good ovarian reserve, the delivery rate was 42%. Thus, it seems that in any kind of infertility treatment for male factor, regardless of sperm count, and whether for varicocele or obstructive azoospermia, the most important confounding factor, aside from duration of infertility, is the age and ovarian reserve of the wife.

In the controlled varicocele study performed earlier by Baker's group (Baker et al., 1985), 651 infertile couples with varicocele were studied for pregnancy rate per month with or without varicocelectomy. Biases due to any difference in prognostic factors were allowed for by using the Cox regression analysis. Of the couples, 324 had sperm counts of $<20 \times 10^6$ spermatozoa/ml and 327 had sperm counts of $>20 \times 10^6$ spermatozoa/ml. There was no significant difference in the sperm concentration or motility after varicocelectomy. There was no difference in pregnancy rate after varicocelectomy. Figure 3 demonstrates the pregnancy rate of these couples over a course of 5 years. Looking at the 'before ligation' and the 'after ligation' groups reveals that the two curves essentially overlap each other. There is no significant difference in log rank test between these curves. In fact, in the first few months of the study, the pregnancy rate appeared to be higher before varicocele ligation but eventually after 1 or 1/2 years, the curves had completely coalesced (Baker et al., 1985).

The studies of Nieschlag's group in 1995 and 1998, and the study by Baker et al. a decade earlier, seemed to dampen any overwhelming enthusiasm for varicocelectomy on the part of many infertility physicians, even though there is still registered throughout the urology world a strong defensive posture regarding this procedure. There were, however, other controlled studies, not quite as carefully designed as the aforementioned, that also revealed the shaky ground on which the pro-varicocelectomy forces stood. In 1986, Vermuelen from Belgium reported on 90 patients undergoing varicocelectomy and 25 patients not undergoing varicocelectomy. Both groups were comparable in terms of duration of infertility, age, sperm count, and motility. Cumulative pregnancy rates in these two groups were the same over a 12 month follow-up period. Interestingly, both groups showed 'slightly improved sperm characteristics' (Vermeulen et al., 1986).

In 1978, Rodriguez-Rigau *et al.* from Texas reported a large group of patients which was not prospective and not randomized, but was controlled, some of whom underwent varicocelectomy and others who did not (Rodriguez-Rigau *et al.*, 1978). Rodriguez-Rigau *et al.* noted a slightly increased percentage motility in patients undergoing varicocelectomy. However, there was no difference in pregnancy rate among those who had varicocelectomy versus those who did not. Furthermore, there was no relation of improvement in post-operative sperm count to pregnancy rate. Those patients who conceived after varicocelectomy had a mean sperm count of 28×10^6 spermatozoa/ml and those who did not conceive had a mean sperm count of 26×10^6

spermatozoa/ml. Of patients with sperm counts of >10 \times 10⁶ spermatozoa/ml, those who conceived had a mean sperm count of 40 \times 10⁶ spermatozoa/ml, and those who did not conceive had a mean sperm count of 48 \times 10⁶ spermatozoa/ml.

In 1979, Nilsson *et al.* questioned the efficacy of varicocelectomy with a boldly titled paper: 'Improvement of semen and pregnancy rate after ligation and division of the internal spermatic vein: Fact or fiction?' (Nilsson *et al.*, 1979). They randomized their patients to 51 having varicocelectomy and 45 serving as controls. All had similar varicocele characteristics and all the patients had suffered 2–8 years of infertility. Varicocelectomy produced no change in semen parameters. Most importantly, pregnancies were achieved in four out of 51 (8%) patients undergoing varicocelectomy, and in eight out of 45 (17%) having no surgery.

In 1992, Rageth *et al.* studied 89 patients with varicocele, poor semen, and duration of infertility of up to 7 years (Rageth *et al.*, 1992). Of the 56 patients undergoing varicocelectomy, the wives of 23 (41%) became pregnant eventually with treatment. Of the 33 who did not undergo varicocelectomy, the wives of 14 became pregnant (42%) with treatment. Thus, there was no difference at all in pregnancy rate between those who had surgery and those who did not. Rageth *et al.* observed an improvement in sperm count after surgery from 9 to 15×10^6 spermatozoa/ml, an improvement in morphology from 22 to 28%, and an improvement in motility of 36 to 38%.

In all fairness, we need to mention the peculiarities of some of these control studies in the following critical way. In the study of Baker *et al.* (1985), the sperm count did not improve with varicocelectomy, but sperm motility improved equally with or without varicocelectomy. Patients who had a varicocele did have a higher pregnancy rate than those who did not have a varicocele whether operated on or not. In Rodriguez-Rigau *et al.*'s group, the sperm count and motility improved after varicocelectomy, but pregnancy rate was not affected (Rodriguez-Rigau *et al.*, 1978). In Nieschlag *et al.*'s group, the sperm count increased in the varicocelectomy group, but not in the control group. Sperm motility did not change with or without varicocelectomy, Sperm morphology decreased simply over time in both groups, the varicocelectomy and the control.

Additional criticisms have been offered on the Nieschlag study. It does not appear to be well-controlled for varicocele size, and the follow-up was limited only to several years. In Vermeulen's study (1986), some patients in the non-operated group got pregnant before surgery could be performed. In Nilsson's group (1979), the pregnancy rates were rather low in both groups, though they may not be a valid criticism since they were treating couples with a long duration of infertility in an older age group. Despite these possible criticisms, for the most part the control studies showing no effect of varicocelectomy have been viewed by most andrologists to be reliable.

Controlled studies supporting varicocelectomy

There have been three reported 'control' studies that suggest a beneficial effect of varicocelectomy. Marmar and Kim (1994), reviewed retrospectively a series of 466 varicocelectomies and only 19 controls. Of the 466 couples that underwent varicocelectomy, 186 became pregnant (pregnancy rate

35.6%). The pregnancy rate in the small number of 19 'controls' that did not undergo varicocelectomy was 15.8%. The large difference in the size of the varicocelectomy group and the control group certainly suggests an unwitting selection bias. This kind of a skewed population would make it very likely that the 'controls' were simply people whose semen was so poor that there was no desire to undergo surgery, or possibly there may have been a problem with the wife that made surgery also very problematic. At any rate, being a retrospective study with such unbalanced varicocelectomy control groups, indicates a probable selection bias.

Another 'control' study often referred to is that of Girardi and Goldstein in which 1500 infertile males underwent varicocelectomy, and only 47 controls underwent varicocelectomy (Girardi and Goldstein, 1997). This is clearly the same problem of balance between patients undergoing varicocelectomy and patients serving as 'controls' that occurred in the study of Marmar and Kim. They reported a 43% pregnancy rate in couples in whom the husband had a varicocelectomy and a 17% pregnancy rate in those whose husbands did not have a varicocelectomy. They also noted an improvement in sperm count from 40 to 47 $\times 10^6$ spermatozoa/ml. This is not a very dramatic increase in mean sperm count and is most likely simply related to 'regression toward the mean.' This study also suffers from a great likelihood of selection bias in that only 3% of the men in the study were 'controls' for the other 97% who had surgery.

The World Health Organization (WHO) study was an attempt to settle the varicocele issue employing thousands of couples in a multi-centre trial design (WHO, 1992). This study was never published in its original form because of problems with protocol deviations (Nieschlag et al., 1995, 1998). It is very difficult with multi-centre studies involving a highly controversial subject to be certain that all programmes that want to serve their patients in the way they think is best, can stick to a rigid protocol. However, such a rigid protocol would be necessary in order to give the study credibility (WHO, 1992). One group that pulled out of the WHO study did publish the results of 45 couples out of their 210 who were split off from the original group of 9034 infertile couples originally entering the study, 1326 of whom had a clinical varicocele. This group maintained that varicocelectomy did have a beneficial effect. However, such a splitting off from the original study group of five times as many patients as originally started, even in their local programme and representing only 3% of the original WHO couples, has a great risk of unwitting selection bias (WHO, 1992; Madjar et al., 1995).

Does varicocele cause a progressive decline in fertility?

For years, urologists talked about an excess number of 'tapered' forms of spermatozoa, i.e. the 'stress pattern,' as a distinctive feature of patients with varicocele. It was called a 'stress pattern' to reflect what was thought to be a 'stress' on testicular function created by the varicocele. However, Baker *et al.* in 1985 questioned whether there is a 'specific abnormality of sperm morphology with varicoceles?' In fact, they found no significant difference in the morphological patterns with or without varicocele. Contrary to popular myth, there was 'no characteristic morphologic stress pattern in infertile men with large left varicoceles' (Baker *et al.*, 1981, 1985; Baker, 198). This raised

the question of whether or not varicocele really created 'stress' that results eventually in deterioration of testicular function.

As far back as 1968, Uehling studied the fertility of 440 married men in the military coming in for routine physical examination, with and without varicoceles. Of this group, 138 had no children (31.4%) and 302 did have children (68.6%). To break it down further, of the 75 men with a varicocele, 69% had children and of the 227 men without a varicocele, 68% had children. Thus, there was no difference in fatherhood of those young married military recruits who had varicocele versus those who did not have varicocele. The presence or absence of a varicocele in these young men had no influence on whether or not their wives were able to get pregnant (Uehling, 1968). At least in young men, varicocele seemed to have no negative impact on fertility.

So what is the prevalence of varicocele in a group of otherwise healthy young men? Thomason et al. in a similar study of military recruits, in 1979, concluded, 'It is apparent that the prevalence of varicoceles in young men occurs with significant frequency and does not interfere with the fertility in all individuals' (Thomason and Farris, 1979). It was found that 30.7% of all recruits had a left varicocele (14% were small, and 16.7% were moderate or large). and 29.4% of recruits who had fathered children also had a varicocele (15% were moderate or large). This is similar to the frequency of large or moderate left varicocele in older vasectomy reversal patients (Silber, 1989b). They concluded, 'the prevalence of a left-sided varicocele occurs with such frequency among a group of healthy men that one would question the association of a varicocele and poor semen quality.' Although I have observed no difference in fertility after vasovasostomy in older men with or without varicocele, there are, nonetheless, many other reports which suggest a deterioration caused by varicocele as one gets older.

It has been commonly thought that secondary infertility, (i.e. the couple gets pregnant without treatment for their first child, and then cannot get pregnant years later when they want another one) was due to increased age and declining fertility of the female (Nieschlag et al., 1995, 1998; Silber et al., 1997). Gorelick and Goldstein, however, have suggested that a varicocele is found in 35% of men with primary infertility, and in 81% of men with secondary infertility, implying that secondary infertility is caused by declining semen parameters related to the long-term deleterious effect of an uncorrected varicocele (Gorelick and Goldstein, 1993). Out of 1001 men with 'primary' infertility, 352 (35%) had a varicocele on routine physical examination, but when couples came for 'secondary' infertility,' 79 out of 98 (81%) had a varicocele present. This is an impressive incidence of finding a varicocele in infertile couples. Witt and Lipshultz (1993) have made a similar claim that 50% of couples with primary infertility have a varicocele and 69% of couples with secondary infertility have a varicocele (Witt and Lipshultz, 1993).

The authors suggested this meant that over time the presence of a varicocele causes a diminution in sperm quality and indeed is the major cause of secondary infertility. This would suggest a need for varicocelectomy in virtually all young men with a varicocele in order to prevent subsequent decline of testicular function. That's a lot of varicocelectomies. Of course, there were some problems with these reports. Firstly, there was no demonstrated decline in sperm count caused by the varicocele,

S.J.Silber

but rather simply an increased incidence of varicocele found in the older couples. Secondly, the mean FSH concentration in their patients with primary infertility was 7.9 IU/ml, and in their patients with secondary infertility the mean FSH was 17.6 IU/ml. These findings are confusing in that one would not expect an FSH to be so elevated in men with mean sperm counts of 30×10^6 spermatozoa/ml. Thirdly, the group of men defined as having primary male infertility had normal mean sperm counts.

Nonetheless, if other centres were able to confirm that 81% of older couples with secondary infertility have a varicocele, and only 20% of younger couples with primary infertility have a varicocele, the conclusion would be enormous in terms of recommending varicocelectomy for 15–35% of the entire world.

On the contrary however, other authors have demonstrated no difference in the incidence of varicocele in men with primary or secondary infertility (Jarow *et al.*, 1996). They found the primary determinant of secondary infertility was the age of the wife. We have also found no such increase in the incidence of varicocele either in secondary infertility or in other men with infertility. So this fascinating speculation that in 81% of couples with secondary infertility, the cause is varicocele, may not turn out to be valid.

Infertility centres see many older couples who did not try to have their baby when they were in their 20s. These couples might very well have been couples with 'secondary' infertility if it were not for the fact that they did not marry until they were 35 and did not already have children. One would expect in this group of older couples also to see a higher incidence of varicocele if the presence of varicocele over the period of time causes a decline in fertility and/or sperm count. However, we do not see a higher incidence of varicocele in older couples than in younger couples coming in for primary infertility. Furthermore, we have found no difference in pregnancy rate or semen parameters with long-term follow-up of older vasovasostomy patients who did or did not have a varicocele (Silber, 1989b).

However, there are studies which suggest that varicocelectomy may be of benefit in some selected cases. In 1991, Wensing's group in Holland studied testis volumes, semen quality and morphological patterns of spermatozoa in adolescents with and without varicocele, trying to nail down the issue of whether early varicocelectomy could be recommended as a preventative in adolescents with left testicular atrophy (Haans et al., 1991; Laven et al., 1992). They showed a small increase in the adolescent's left testicular volume after varicocelectomy. They found that 'varicocele-related' unilateral or bilateral growth failure is not clearly associated with a decrease in sperm counts or semen quality, but could be prevented by adolescent varicocelectomy in those young men presenting with a left varicocele and a smaller left testicle. It was not clear, however, whether this 'growth failure' continued during adulthood and could lead to future disturbances in infertility. Differences in semen parameters were not at all convincing. Furthermore, despite their enthusiasm for studying the early impact of varicocele on testicular atrophy, they could find no evidence to suggest further deterioration of testicular size in adulthood.

I do not wish to conclude on a 100% negative note regarding the varicocele issue, because we must always have an open mind in science. It appears fairly conclusive that varicocelectomy does not do much, if anything, to help the average infertile couple. That should not be controversial. The speculation that the occasional varicocele in adolescents with reduced left testicular size may have a long-term effect on sperm count, if not on fertility, requires a carefully controlled longitudinal study. In science, our minds must always remain open, and not be driven by what we merely wish were true.

References

- Baker, G. (1992) The use of the semen analysis in predicting fertility outcome. [Editorial comment.] Aust. N.Z. J. Obstet. Gynecol., **32**, 154–155.
- Baker, H.W.G. (1986) Requirements for controlled therapeutic trials in male infertility. *Clin. Reprod. Fertil.*, 4, 13–25.
- Baker, H.W.G. (1993) Management of immunological infertility. In Berger, H.G. and Oshima, H. (eds), An Approach to Clinical Andrology. Serona Symposia Reviews, no. 29, pp. 105–110.
- Baker, H.W.G. and Burger, H.G. (1986) Male infertility in reproductive medicine. In Steinberger, E., Frajese, G., Steinberger, A. (eds.) *Reproductive Medicine*. Raven Press, New York, USA, pp. 187–197.
- Baker, H.W.G. and Kovacs, G.T. (1985) Spontaneous improvement in semen quality: regression towards the mean. *Int. J. Androl.*, **8**, 421–426.
- Baker, H.W.G., Burger, H.G., de Kretser, D.M. *et al.* (1981) Factors affecting the variability of semen analysis results in infertile men. *Int. J. Androl.*, 4, 609–622.
- Baker, H.W.G., Straffon, W.G.E., McGowan, M.P. et al. (1984) A controlled trial of the use of erythromycin for men with asthenospermia. Int. J. Androl., 7, 383–388.
- Baker, H.W.G., Burger, H.G., de Kretser, D.M. *et al.* (1985) Testicular vein ligation and fertility in men with varicoceles. *Br. Med. J.*, **291**, 1678– 1680.
- Baker, H.W.G., Liu, D.Y., Bourne, H. and Lopata, A. (1993) Diagnosis of sperm defects in selecting patients for assisted fertilization. *Hum. Reprod.*, 8, 1779–1780.
- Devroey, P., Vandervorst, M., Nagy, P. and Van Steirteghem, A. (1998) Do we treat the male or his gamete? *Hum. Reprod.*, **13** (Suppl 1), 178–185.
- Devroey, P. (1999) The relevance of semen analysis. Presented at Thirty-Second Annual Postgraduate Program of the American Society for Reproductive Medicine in Toronto, Canada, September 1999. pp. 15–32.
- Dubin, L. and Amelar, R.D. (1975) Varicocelectomy as therapy in male infertility. J. Urol., 113, 640.
- Girardi, S.K. and Goldstein, M. (1997) Varicocele. Curr. Ther. Endocrinol. Metab., 6, 355–358.
- Goldstein, M., Gilbert, B.R., Dicker, A.P. *et al.* (1992) Microsurgical inguinal varicocoelectomy with delivery on the testis: an artery and lymphatic sparing technique. *J. Urol.*, **148**, 1808–1811.
- Gorelick, J.I. and Goldstein, M. (1993) Loss of fertility in men with varicocele. *Fertil. Steril.*, 59, 613–616.
- Haans, L.C.F., Laven, J.S.E., Mali, W.P.Th. M. *et al.* (1991) Testis volumes, semen quality, and hormonal patterns in adolescents with and without varicocele. *Fertil. Steril.*, 56, 731–736.
- Hargreave, T.B. and Elton, R.A. (1983) Is conventional sperm analysis of any use? Br. J. Urol., 55, 774–779.
- Hargreave, T.B. (1993) Varicocele a clinical enigma. Br. J. Urol., 72, 401–408.
- Jarow, J.P., Coburn, M. and Sigman, M. (1996) Incidence of varicocoeles in men with primary and secondary infertility. Urology, 47, 73–76.
- Kim, E.D., Leibman, B., Grinblat, D. and Lipshultz, L. (1999) Varicocele repair improves semen parameters in azoospermeric men. J. Urol., 162 737–740.
- Laven, J.S.E., Haans, L.C.F., Mali, W.P.T.M. *et al.* (1992) Effects of varicocele treatment in adolescents: a randomized study. *Fertil. Steril.*, 58, 756–762.
- MacLeod, J. and Gold, R.Z. (1951) The male factor in fertility and infertility. II. Spermatozoon counts in 1000 men of known fertility and in 1000 cases of infertile marriage. J. Urol., 66, 436–449.
- MacLeod, J. and Gold, R.Z. (1953) The male factor in fertility and infertility. VI. Semen quality and other factors in relation to ease of conception. *Fertil. Steril.*, 4, 10–33.
- Madjar, I., Weissenberg, R., Lunenfeld, B. *et al.* (1995) Controlled trial of high spermatic vein ligation for varicocele in infertile men. *Fertil. Steril.*, 63, 120–124.
- Marmar, J.L. and Kim, Y. (1994) Subinguinal microsurgical varicocelectomy:

A technical critique and statistical analysis of semen and pregnancy data. *J. Urol.*, **152**, 1127–1132.

- Matthews, G.J., Matthews, E.D. and Goldstein, M. (1998) Induction of spermatogenesis and achievement of pregnancy after microsurgical varicocelectomy in men with azoospermia and severe oligoasthenospermia. *Fertil. Steril.*, **70**, 71–75.
- Mordel, N., Mor-Yosef, S., Margalioth, E.J. et al. (1990) Spermatic vein ligation as treatment for male infertility. J. Reprod. Med., 35, 123–127.
- Mulhall, J.P., Stokes, S., Andrawis, R. and Buch, J.P. (1997) Simultaneous microsurgical vasal reconstruction and varicocele ligation: Safety profile and outcomes. *Urology*, **50**, 438–442.
- Nieschlag, E., Hertle, L., Fischedick, A. and Behre, H.M. (1995) Treatment of varicocele: counselling as effective as occlusion of the vena spermatica. *Hum. Reprod.*, **10**, 347–353.
- Nieschlag, E., Hertle, L., Fischedick, A. *et al.* (1998) Update on treatment of varicocele: counselling as effective as occlusion of the vena spermatica, *Hum. Reprod.*, **13**, 2147–2150.
- Nilsson, S., Edvinsson, A. and Nilsson, B. (1979) Improvement of semen and pregnancy rate after ligation and division of the internal spermatic vein: Fact or fiction? Br. J. Urol., 51, 591–596.
- Page DC, Silber S, Brown LG. (1999) Men with infertility caused by AZFc deletion can produce sons by intracytoplasmic sperm injection, but are likely to transmit the deletion and infertility. *Hum. Reprod.*, 14, 1722– 1726.
- Rageth, J.C., Unger, C., DaRugna, D. et al. (1992) Long-term results of varicocelectomy. Urol. Int., 48, 327–331.
- Reijo, R., Lee, T., Salo, P. *et al.* (1995) Diverse spermatogenic defects in humans caused by Y chromosome deletions encompassing a novel RNAbinding protein gene. *Nature Genet.*, **10**, 383–393.
- Rodriguez-Rigau, L.J., Smith, K.D. and Steinberger, E. (1978) Relationship of varicoccle to sperm output and fertility of male partners in infertile couples. J. Urol., 120, 691–694.
- Scherr, D. and Goldstein, M. (1999) Comparison of bilateral versus unilateral varicocelectomy in men with palpable bilateral varicoceles. J. Urol., 162, 85–88.
- Schoysman, R.G. and Gerris, J. (1983) Twelve-year follow-up study of pregnancy rates in 1291 couples with idiopathically impathically impaired male fertility. *Acta Eur. Fertil.*, 14, 51–56.
- Silber, S.J. (1979) Microsurgical aspects of varicocele. Fertil. Steril., 31, 230– 232.
- Silber, S.J. (1989a) The relationship of abnormal semen parameters to male fertility. [Opinion.] Hum. Reprod., 4, 947–953.

- Silber, S.J. (1989b) Pregnancy after vasovasostomy for vasectomy reversal: a study of factors affecting long-term return of fertility n 282 patients followed for 10 years. *Hum. Reprod.*, 4, 318–322.
- Silber, S.J., Nagy, Z., Liu, J. *et al.* (1995) The use of epididymal and testicular spermatozoa for intracytoplasmic sperm injection: the genetic implications for male infertility. *Hum. Reprod.*, 10, 2031–2043.
- Silber, S.J., Nagy, Z., Devroey, P. et al. (1997) The effect of female age and ovarian reserve on pregnancy rate in male infertility: treatment of azoospermia with sperm retrieval and intracytoplasmic sperm injection. *Hum. Reprod.*, **12**, 2693–2700.
- Silber, S.J., Alagappan, R., Brown, L.G. and Page, D.C. (1998) Y chromosome deletions in azoospermic and severely oligozoospermic men undergoing intracytoplasmic sperm injection after testicular sperm extraction. *Hum. Reprod.*, **13**, 3332–3337.
- Smith, K.D., Rodriguez-Rigau, L.J. and Steinberger, E. (1977) Relation between indices of semen analysis and pregnancy rate in infertile couples. *Fertil. Steril.*, 28, 1314–1319.
- Steckel, J., Dicker, A.P. and Goldstein, M. (1993) Relationship between varicocele size and response to varicocelectomy. J. Urol., 149, 769–771.
- Steinberger, E. and Rodriguez-Rigau, L.J. (1983) The infertile couple. [Review.] J. Androl., 4, 111–118.
- Thomason, M. and Farris, B.L. (1979) The prevalence of varicocele in a group of healthy young men. *Milit. Med.*, **144**, 181–186.
- Uehling, D.T. (1968) Fertility in men with varicocele. Int. J. Fertil., 13, 58-60.
- Van Steirteghem, A.C., Nagy, Z., Joris, H. et al. (1993) High fertilization and implantation rates after intracytoplasmic sperm injection. Hum. Reprod., 8, 1061–1066.
- Vermeulen, A., Vandeweghe, M. and Deslypere, J.P. (1986) Prognosis of subfertility in men with corrected or uncorrected varicocele. J. Androl., 7, 147–155.
- Witt, M. and Lipshultz, L. (1993) Varicocele: A progressive or static lesion? Urol., 42, 541–543.
- World Health Organization (1992) The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. *Fertil. Steril.*, 57, 1289–1293.
- Zukerman, Z., Rodriguez-Rigau, L.J., Smith, K.D. and Steinberger, E. (1977) Frequency distribution of sperm counts in fertile and infertile males. *Fertil. Steril.*, 28, 1310–1313.
- Received on February 3, 2000; accepted on November 8, 2000