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Varicocele treatment in the light of evidence-based andrology

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Treatment of varicoceles became the most common treatment for male infertility merely on an empirical basis. However, in the age of evidence-based medicine it is surprising that only a few, and mainly recent, randomized controlled clinical trials with relevant outcome parameters have been published to allow adequate judgement of treatment effectiveness. Moreover, difficulties in study design could also be detected in most of these high-quality studies. Despite these difficulties and in contrast to the majority of uncontrolled studies on varicocelectomy, meta-analysis of these randomized controlled clinical studies involving 385 patients showed no significant treatment benefit and questions the common practice of varicocelectomy. Even the high-quality studies show conflicting results and therefore the topic of varicocele treatment will remain controversial and further randomized clinical trials should readdress this issue. For the time being, intervention by surgical or angiographic occlusion of the spermatic vein cannot be recommended.

Key words: controlled clinical trials/counselling/evidence-based infertility/male infertility/varicocele

CONTENTS

Empirical varicocelectomy

Varicoceles are the most frequent physical finding in infertile men (World Health Organization, 1992; Behre *et al*., 1997) and are believed to cause testicular and epididymal damage via hypoxia and stasis, increased testicular pressure, elevated spermatic vein catecholamines and/or increased testicular temperature (Fujisawa *et al*., 1989; Comhaire, 1991; Sweeney *et al*., 1995; Wright *et al*., 1997). Although J.Delpech (1772–1832), one of the first surgeons to perform a simultaneous bilateral varicocelectomy, was killed by the patient one year later because of the unsuccessful surgical intervention (Nöske and Weidner, 1999), beginning in the 1950s, varicocelectomy via ligation became the most common operation for male infertility (McClure and Hricak, 1986). In the 1980s embolization and sclerosing of the spermatic vein were introduced and, merely on an empirical basis, ligation, embolization or sclerosing of the spermatic vein became accepted as the treatment of choice (Takihara *et al*., 1991). Recent publications of clinical trials (yet again uncontrolled) even suggest significant improvements in sperm output following varicocele ligation in azoospermic men which then facilitated intracytoplasmic sperm injection to achieve pregnancy (Lindstedt *et al*., 1998; Matthews *et al*., 1998; Kim *et al*., 1999). However, despite the common practice of varicocelectomy for decades, evidence of treatment efficacy was based mainly on non-randomized uncontrolled trials (Marsman and Schats, 1994).

The concept of evidence-based andrology

The concept of evidence-based medicine de-emphasizes intuition, unsystematic clinical experience and pathophysiological rationale as sufficient grounds for clinical decision-making. Evidence-based medicine stresses the examination of evidence from clinical research using epidemiological and biostatistical methods (Evidence-Based Medicine Working Group, 1992). In the concept of evidence-based medicine, clinical decisions should be based on the best available evidence arising from outcome research-oriented randomized controlled clinical trials in the literature.

Andrology was especially late in applying the paradigm of evidence-based medicine in clinical practice, notwithstanding the exponential increase in the number of published randomized controlled clinical trials concerning infertility treatment over the last decade (O'Donovan *et al*., 1993; Vandekerckhove *et al*., 1993; Kamischke and Nieschlag, 1998). In addition to the

development of evidence-based andrology, the focus of reproductive medicine changed from single-partner oriented therapy to couple-oriented therapy. As a consequence, pregnancy as the relevant outcome parameter became more important compared with improvement of semen parameters or inhibition of venous reflux. As result of these changes in reproductive medicine there is now consensus that 'treatment effectiveness can be judged fairly only in randomized controlled clinical trials, because conception without therapy can occur in most infertile couples over time' (ESHRE Capri Workshop, 1996).

Varicocele treatment in the age of evidence-based andrology

Applying the principles of evidence-based andrology to the treatment of varicocele, it is surprising that only a few, and mainly recent, randomized controlled clinical trials with relevant outcome parameters (induction of pregnancy, improvement in sperm parameters) have been published (Nilsson *et al*., 1979; Laven *et al*., 1992; Yavetz *et al*., 1992; Breznik *et al*., 1993; Nieschlag *et al*., 1993, 1995; Madgar *et al*., 1995; Yamamoto *et al*., 1996; Hargreave, 1997; Nieschlag *et al*., 1998). In the following discussion, the effectiveness of varicocelectomy will be considered solely on the basis of these randomized controlled clinical trials.

Three trials investigated only whether surgical or embolization procedures are superior in achieving fertility (Sayfan *et al*., 1992; Yavetz *et al*., 1992; Nieschlag *et al*., 1993). Sayfan *et al*. (1992) first showed that, concerning pregnancy rates, embolization ($n = 36$ patients) was equally effective as high ligation of the internal spermatic vein ($n = 55$ patients) or transinguinal simultaneous ligation of the internal and external spermatic veins ($n = 28$ patients). However, Yavetz *et al*. (1992) found a significant benefit of high ligation versus embolization and transinguinal ligation concerning pregnancy rates. In addition, sperm concentration and sperm motility was significantly increased through embolization and high ligation, while transinguinal ligation has no significant effect on sperm parameters. This increase in sperm parameters was also found by Sayfan *et al*. (1992), who saw an increase in sperm counts following surgical treatment. We confirmed the increase in sperm counts in the ligation group, although in our study, as in the study by Yavetz *et al*. (1992), an increase in sperm count was also seen in the embolization group (Nieschlag, *et al*., 1993). In addition, in both treatment groups (ligation $n = 38$; embolization $n = 33$) during the 12 month follow-up period we found a significant increase in sperm motility whereas sperm morphology remained unaffected. Confirming Sayfan *et al*. (1992), we also found no differences in pregnancy rates within 1 year after intervention between the ligation group and the embolization group. These initial findings of our first varicocele study were confirmed in the intervention groups of our later study (Nieschlag *et al*., 1995, 1998), now altogether comprising a total of 133 patients treated with embolization or ligation in randomized clinical trials in our centre.

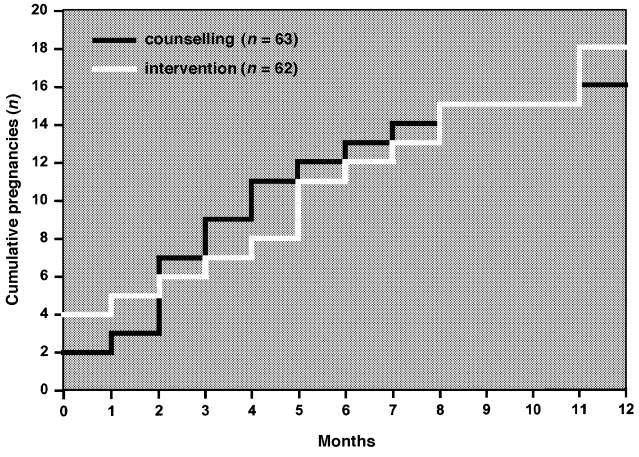

Figure 1. Cumulative pregnancy rates over 12 months in couples with male varicocele treated by intervention (ligation or embolization) or counselling alone (taken from Nieschlag *et al*., 1998. Previously published in *Hum. Reprod.* **13,** 2147-2150).

However, in the course of this comparative study we recognized that all techniques used for treatment of varicocele have been introduced without proof of their effectiveness in achieving fertility. Only one randomized controlled study was conducted at the time of our first varicocele study comparing treatment versus no treatment in 96 patients with varicoceles (Nilsson *et al*., 1979). However, this study showed a cumulative pregnancy rate of only 12% (8% in the treatment group; 18% in the control group) despite an observation period of 5 years and despite the fact that 74% of men had a sperm concentration of $>20\times10^6$/ml even before therapy. Therefore the low pregnancy rate casts doubt on the integrity and appropriate treatment of female reproductive functions. No changes in any conventional semen parameter were seen in this study. In a study involving 79 men with varicoceles (Breznik *et al*., 1993), female factors might also have been overlooked, as normozoospermia was diagnosed in 30% of patients involved in the trial. In addition to the data on pregnancy rates (34% in the treatment group; 54% in the control group), the authors reported a non-significant increase in sperm concentration and sperm motility in the treatment group. A significant increase in sperm concentration and testicular volume was also seen previously by another group investigating the influence of varicocelectomy on semen parameters and testicular volume in young probands (age range 17–20 years) screened for military service in a randomized trial ($n = 53$) (Laven *et al*., 1992). The effects of ligation of varicocele on pregnancy rates and semen parameters in 85 patients with subclinical varicoceles were investigated in the study by Yamamoto (Yamamoto *et al*., 1996). The low pregnancy rates in this study (7% in the treatment group; 10% in the control group) might be explained by the fact that only subclinical varicoceles were investigated. Thus despite a significantly higher sperm concentration and total motile sperm count in the treatment group, it appears likely that subclinical varicocele contributes only marginally to the couple's infertility.

In agreement with the above-mentioned studies, our initial study (Nieschlag *et al*., 1995) and its extension (Nieschlag *et al*., 1998) showed no benefit of varicocelectomy or embolization (pregnancy rate 29%) versus no treatment (pregnancy rate 25%) in 125 couples (Figure 1). In addition, in this largest single-centre study, in both groups sperm concentrations tended to increase during the observation period but were

significantly elevated only in the varicocelectomy group which also showed a significant increase in left testicular volume, thus confirming prevoius findings (Laven *et al*., 1992). Difficulties seen in the above-mentioned studies were carefully ruled out in our study and only patients with clinically palpable (with or without Valsalva manoeuvre) varicoceles (varicocele grades were equally distributed between the groups), subnormal semen parameters, no other known cause of infertility (including hypogonadotrophic hypogonadism) and female partners free of any reasons for infertility were included in the study. Reduced presurgical testicular volume or elevated FSH concentrations were not selection criteria. Patients were randomly allocated to the treatment or counselling groups. Patients of the treatment group were further randomized to undergo either surgical ligation or angiographic embolization. After randomization, patients were reinvestigated and counselled every 3 months up to the end of the follow-up period of 1 year.

In contrast to our study and all other randomized studies mentioned above, two trials which were originally planned as one World Health Organization (WHO) multicentre trial (Madgar *et al*., 1995; Hargreave, 1997) suggested significant benefits for male fertility after surgical varicocele repair (pregnancy rate 35 and 60%) compared with unoperated controls (pregnancy rate 17 and 10%). However, both studies revealed considerable difficulties. In the multicentre WHO study, the major problem appears to arise from the multicentre design with differing interpretations of the study protocol and serious protocol violations. It was especially evident that, of the 238 men initially included in the WHO study, only 89 were adequately randomized and completed the 1 year follow-up period. Because of these difficulties in the design, the study has met major criticism and has not been published in a peer-reviewed journal. However, the question of incorrect allocation to the treatment group was not evident in the study by Magdar *et al*. (1995) which had 45 patients enrolled, but low statistical power.

At first sight the difference in the major outcome parameter, pregnancy, is surprising between the Hargreave (1997) and Magdar *et al*. (1995) studies compared to our own study (Nieschlag *et al*., 1998) which had similar inclusion and exclusion criteria. From a careful look at the results it is evident that pregnancy rates in the treatment groups of both large-scale studies were not very different [Hargreave *et al*. (1997): 35%; Nieschlag *et al*. (1998): 29%]. In contrast to these larger studies, the smaller single-centre study by Magdar *et al*. (1995) has a clearly higher pregnancy rate in the treatment group (60%), which might be attributed to random fluctuations due to low number of patients. Major differences also exist between the pregnancy rates of the control groups (10 versus 25%) in the Magdar *et al*. (1995) study and (25%) in the Nieschlag *et al*. (1998) studies, whereas the pregnancy rate of the control group of the Hargreave (1997) study was intermediate between these studies (17%). It appears possible that the different conclusions drawn from the Hargreave (1997) and Magdar *et al*. (1995) studies were mainly due to different handling of the control patients.

The major difference appears to be the counselling we performed not only in the treatment group but also in the control group. Both patient groups in our study were seen at 3 monthly intervals and at each visit a semen and hormone analysis was performed; previous results, problems of sexual life, coitus frequency, optimal conception time and personal problems of the patient were intensively discussed. In addition, the gynaecologist of the female partner was informed about the results and was asked to optimize female reproductive functions whenever necessary. We therefore believe that the difference in pregnancy outcome between our study and the Hargreave (1997) and Magdar *et al*. (1995) studies is mainly due to non-specific counselling (placebo) effects associated with the medical intervention. Consistent with this, psychological counselling of the female partner alone has recently been shown to improve pregnancy rates in women, apparently irrespective of the underlying cause of female infertility (Domar *et al*., 2000). Therefore our study suggests that regular counselling of the infertile couples and optimization of female reproductive functions are as effective as interventionist treatment of the varicoceles in achieving pregnancy.

Another possible reason for the differences between our study (Nieschlag *et al*., 1998) and the Hargreave (1997) and Magdar *et al*. (1995) studies might be the diagnosis of varicocele and the influence of female age. Our study was the only randomized prospective study using an objective method of assessment of varicocele (sonographic measurement of venous diameter before and during Valsalva manoeuvre plus Doppler sonography), which might have influenced the selection of the patients, thus leading to different results. In our earlier study (Nieschlag *et al*., 1995), patients achieving pregnancy had a greater presurgical testicular volume and lower presurgical FSH concentrations than those whose partners did not become pregnant. Moreover, in the extension of this earlier study (Nieschlag *et al*., 1998), we tried to analyse all physical (including the grades of the varicocele) and laboratory findings (including sperm concentration) in our patients with respect to their prognostic value for the occurrence of pregnancy. The only significant factor regardless of treatment modality, was the wife's age at admission to the study. The wives of patients achieving a pregnancy were significantly younger (28.8 $\pm$ 0.6 years) than the wives failing to do so (31.2 $\pm$ 0.3 years).

This established prognostic influence of female age on pregnancy rates (Collins *et al*., 1995; Snick *et al*., 1997) might therefore also explain the higher pregnancy rate of the intervention group in the Hargreave (1997) study, as female partners in that study were clearly younger (mean 27.3 years) than female partners of our patients.

Despite the above-mentioned difficulties in most studies, we subjected all randomized trials available to meta-analysis (Figure 2). However, for reasons of statistical heterogeneity [χ^2-test and graphical approach (Egger *et al*., 1997)] the studies of Magdar *et al*. (1995) and Hargreave (1997) had to be excluded before meta-analysis [combined odds ratio (OR)] of the remaining four randomized clinical trials (only the update was included in Nieschlag *et al*., 1998) on the effect of varicocele treatment on pregnancy rate. The statistically correct metaanalysis involving 385 patients revealed no significant difference in the cumulative pregnancy rate [OR 0.69; 95% confidence interval (CI) 0.42–1.13]. If the studies by Hargreave (1997) and Magdar *et al*. (1995) were also included in the analysis (Figure 2), still no significant benefit of varicocelectomy on pregnancy rates was evident (OR 1.2; 95% CI 0.79–1.83). Our results are also in agreement with a

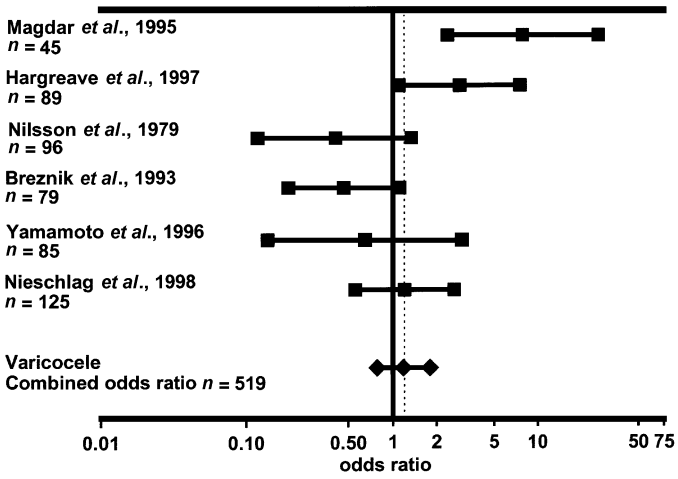

Figure 2. Individual and combined odds ratios of pregnancy rates based on analysis of randomized, controlled clinical trials on varicocele treatment. Results are presented as odds ratio with 95% confidence interval. The dashed line represents the combined odds ratio of all included studies (squares) A dashed line crossing the individual study indicates homogeneity.

previous meta-analysis in which the study from Hargreave was not included (Evers, 1998), showing no benefit of intervention (OR 0.85; 95% CI 0.49–1.46).

Conclusions

In contrast to the majority of uncontrolled studies on varicocelectomy, randomized controlled clinical studies question the common practice of varicocelectomy. However, even the high-quality studies show conflicting results and therefore the topic of varicocele treatment will remain controversial. Further randomized clinical trials should readdress this issue, preferably in patients with third-grade varicocele where the presumed treatment effect should be highest. However, regarding pregnancy rates, the following facts can be unequivocally drawn from the randomized trials. (i) The biggest single-centre study shows no benefit of varicocelectomy compared to counselling only. (ii) The majority of high-quality studies on varicocelectomy showed no benefit. (iii) After meta-analysis the OR of all randomized patients included in the studies showed no significant treatment benefit. (iv) From the two studies which suggest a significant benefit on pregnancy rates, the non-peer-reviewed multicentre study suffers from a high loss of patients during follow-up, and from inadequate allocation to the treatment groups in 30% of patients; moreover, data presentation does not allow recalculation of the data for the randomized patients only.

In our opinion, for the time being there are no convincing reasons indicating that interventive treatment is superior to counselling combined with optimization of female reproductive functions in terms of pregnancy. Therefore intervention by surgical or angiographic occlusion of the spermatic vein cannot be recommended to date. This conclusion is in agreement with the recommendations arising from the 35th Royal College of Obstetricians and Gynaecologists Study Group which concluded that: 'There is insufficient evidence to recommend occlusion of the left internal spermatic vein in subfertile or oligozoospermic men with a varicocele' and that 'Occlusion of the left internal spermatic vein in young men with a varicocele should be performed only in the context of an appropriately designed, large prospective study' (RCOG Study Group, 1998).

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