Clinical and Animal Studies of the Varicocele: Current Concepts and Treatment

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Introduction

Idiopathic varicocele was first described in ancient times, and various modes of treatment have been attempted. In 1952, after performing varicocelectomy in a patient with azospermia, Tulloch² reported a rise in the sperm count to $27 \times 10^9$/ml, and a patient's wife became pregnant 1 year after the operation. Since then, this condition has come to be suspected as an important cause of male infertility.

The pathophysiology of this common condition remains to be fully investigated, and no theory fully explains either its cause or the physiological alterations by which varicocele induces infertility. When a varicocele is present and a chief complaint is male infertility, the pregnancy rate (PR) after surgery has been reported to be higher than with other types of therapy³⁴³. Thus, author generally performs high ligation as the treatment of choice for varicocele. This article reviews the author's investigations into the pathophysiology of varicocele, together with the surgical treatment.

Incidence

The incidence of varicocele in healthy males has been reported to be approximately 8 to 23%, with the left side affected in 70 to 100% of cases, the right in 0 to 9% of cases, and both sides in 0 to 23% of cases³⁴³. Varicocele is generally considered to be an important factor in approximately 21 to 41% of infertile males visiting andrology clinics, and from 20 to 25% of these patients eventually undergo varicocelectomy³⁴³.

Disorders of spermatogenesis resulted from varicocele

Opinions vary widely as to whether varicocele uniformly affects spermatogenesis. In fact, seminal abnormalities are not observed in the majority of males with varicocele. It has been stated that abnormal spermatogenesis occurs in about one of every five patients with varicocele³⁴³ and that no semen abnormalities were detected in 14% of infertile outpatients with this condition³⁴³. The other side of this argument is that a fall in relative sperm motility compared with the sperm count has been observed in men with varicocele and normal sperm count. The PR in the spouses of men within a given range of sperm counts who has undergone varicocelectomy was significantly higher than in a corresponding idiopathic infertility group. A slight deterioration of semen analysis or even early endocrinologic testicular failure has been reported in a varicocele group before surgery, compared with a normal control group. Therefore, investigators should be based on the working hypothesis that abnormal spermatogenesis could occur in patients with varicoceles.
During varicocelectomy of left-sided varicoceles in patients with a chief complaint of infertility, bilateral testicular biopsies were performed, and the deoxyribonucleic acid (DNA) content of the testicular tissue was analyzed by flow cytometry (FCM). At the same time, the germinal cell maturity was assessed using Johnsen’s score⁹. The testicular size was measured using Yamaguchi Orchiometer (Medox Enterprise Inc., Tokyo, Japan)⁸,⁹.

Varicoceles were classified into grade I (small) to grade III (large). The left testis was found to be smaller than the right testis for all grades of varicocele, and the left testis in patients with grade II and III varicoceles was smaller than those in the normal control group⁹. By contrast, the right testis in patients with varicocele was significantly smaller than those in the normal control group only for grade III varicoceles and a difference in size was seen between grade I and III⁹. Johnsen’s mean score is often used as an index of germinal cell maturity⁹. No significant difference in score was noted between the right and left testicles in patients with grade I or II varicocele, whereas significantly lower values were observed in left testicles with grade III varicoceles. Compared with the normal control group, significantly lower values were found only in the left testicles with grade II and in both testicles with grade III varicoceles⁹.

The percentage of haploid cells (%1C), which indicates the spermatid ratio, was significantly lower in the left testicles of patients with all grades of varicoceles compared with the control group. The right testicles of patients with grade I and III varicoceles showed slightly lower %1C values than the normal controls. To summarize, disorders of spermatogenesis, though observed in both testicles, tended to be more severe on the affected side, and with larger varicoceles⁸,⁹.

In most studies of varicoceles, the subjects have been infertile. The clinical impression is that most men with this condition is not necessarily infertile. Therefore, establishing whether or not a strict cause-and-effect relationship exists between varicocele and male infertility requires further investigation using animal model of this condition. To study the effect of unilateral varicocele on the bilateral testicles in an animal model, the changes of spermatogenesis in rat with surgically induced varicoceles were investigated⁹. The same methodology above described were also applied in this study. We found that in rats with varicoceles, the testicular weight, the %1C, and the mean seminiferous tubular diameter decreased in both testicles in contrast to rats undergoing sham operation, with the decrease being greater on the left testicles. These results suggest that unilateral varicocele impairs spermatogenesis in both testicles, with impairment being greater ipsilaterally. Our results based on FCM DNA analysis in human and animal studies confirm a detrimental effects of a unilateral varicocele on spermatogenesis in both testicles.

**Mechanisms leading to impairment of spermatogenesis by varicocele**

Various possibilities have been hypothesized to explain the impairment of spermatogenesis associated with varicocele, however none has been proven. Through our investigations, the two most possible hypothesis seem to be the testicular temperature elevation hypothesis and the toxic substance reflux hypothesis.

The temperature hypothesis maintains that a left varicocele raises the temperature of both testicles and elevated testicular temperature is known to have an adverse effect on spermatogenesis."³ We have measured the deep testicular regional temperatures in patients with varicocele, infertile patients without varicocele and postvaricocelectomy patients."³,⁴,⁵ No difference was observed in deep testicular regional temperatures in the supine position, however, higher temperatures were revealed in both the right and left testicles in the varicocele group in the standing position. The temperature was highest and the temperature elevation from the supine to the standing position was greatest on the left testis of patients with large varicocele.

A number of researchers have examined the hypothesis that a high concentration of metabolic byproducts from the kidney or
adrenal glands might have an adverse effect on testicular functions. Attention has been paid
to the hypothesis that prostaglandin (PG) E₂ and F₂α formed in the kidneys
reflux into the testicles and disorder the testi-
cular functions⁴⁰. Our finding that
phospholipase A₂ levels in semen decreased signifi-
cantly after varicocelectomy appears to be
consistent with this theory⁴⁰. We have can-
nulated the internal spermatic vein during
high ligature for varicocele and collected
blood samples with the cannula tip directed
toward the kidney. Peripheral vein blood
was simultaneously collected and PGE₂ and
PGF₂α were measured. Higher levels of
PGE₂ and PGF₂α were disclosed in the inter-
nal spermatic vein blood than in the periph-
eral vein blood. At the same time, a signifi-
cant correlation between PGE₂ and PGF₂α
concentrations in the internal spermatic vein
blood was observed, further supporting the
PG backflow hypothesis. Abnormalities of
blood flow because of vasoconstriction in-
duced by PG and inhibition of the action of
luteinizing hormone (LH) by PGF₂α acting
on LH receptors in the testicles may be one
mechanism adversely affecting sper-
matogenesis in varicocele¹⁶. Moreover, in
vitro animal experiment performed by the
authors¹⁷ has also demonstrated a close rela-
tion between epididymal contractility
and PG. Therefore, the possibility exists that
sperm transportation and maturation in the
epididymis is affected by PG backflow in
varicocele.

**Long-term effect of the surgical treatment**

The long-term effect of the surgical treat-
ment of varicocele vary widely, and this has
made it confused to define the clinical signifi-
cance of this disorder. The ratio of improve-
ment and PR of patient’s partners after the
surgical treatment has been reported to range
from 53 to 92% and 20 to 55%, respective-
ly²,³. These figures can not be accepted
unconditionally in view of the spontaneous
variations that can occur in semen analysis,
as well as differences in the procedures of
measurement and assessment of preoperative
severity. Surgical treatment (high ligation
and embolization) was performed in 335
patients with varicocele and infertility in a
multicenter study in Japan involving the fol-
lowing institutions: Kawasaki Medical Un-
derway, Tokyo Medical and Dental Univer-
sity, Yokohama City University, Chiba Uni-
derway, Toho University, and Yamaguchi
University¹⁸ in 1985. Significant improve-
ment was observed in semen analysis, partic-
ularly in sperm concentration and sperm
motility. The PR of the partners was 23.5%
in the treated group and 18.0% in the
untreated group. The cumulative PR tended
to rise in the treated group 18 to 24 months
after the surgical treatment. The PR was
significantly higher in the treated group
members with sperm concentrations of 10×
10⁶/ml to 40×10⁶/ml and a sperm motility
less than 20%.

To improve the results of treatment, the
more precise and noninvasive methods for
the diagnosis of varicocele should be estab-
lished. Recently, author has reported a
usefulness of color Doppler ultrasonogra-
phy¹⁹, deep testicular regional temperature
measurement¹¹–¹³ and scrotal radioisotope
(RI) angiography²⁰ to divide the varicoceles
into subgroups to decide the indication for
operation and to diagnose subclinical var-
icocele.

Recent clinical data of the authors’ large
series of varicocelectomy have demonstrated
a significantly improved PRs from 429
patients with varicocele over 16 years²¹.
The PR of left varicocelectomy group result-
ed in 71.1% and PR of bilateral var-
icocelectomy group was 53.2%²¹.

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Reference


