Glutathione S-transferase T1: a potential marker for the selection of varicocelectomy in infertile male patients with varicocele

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Dear Editor,

Varicocele is a common cause of male infertility, and the prevalence of varicocele among men attending infertility clinics ranges from 30% to 40%. The effects of varicocele are diverse, but often result in semen abnormalities, decreased testicular volume and decline in Leydig cell function.

Although varicocele can cause serious complications, its surgical treatment is quite simple. Previous studies have shown that varicocelectomy is an effective treatment for varicocele and can result in an improvement in semen parameters as well as the natural pregnancy rates of infertile couples.¹ These findings suggest that varicocelectomy improves sperm variables and fertility rates. Therefore, varicocelectomy is widely used for the treatment of infertile men with varicocele. To improve the therapeutic effect of varicocelectomy, it is performed in patients with subclinical varicocele.² Varicocelectomy is also performed in adolescents to prevent the development of male infertility due to varicocele, and this procedure may be more effective in adolescents than in adults.³ However, there is a significant risk of excessive usage of varicocelectomy.

Contemporary research suggests that varicocelectomy may have limited therapeutic efficiency. Some studies have shown that men undergoing varicocelectomy exhibit only a slight improvement in postoperative semen parameters, and the procedure might not result in an increase in pregnancy rate.⁴ These study results suggest that while varicocelectomy is an effective therapy for varicocele, it might not be suitable for all patients. Moreover, the risk of excessive usage of varicocelectomy is a concern. Therefore, clinicians face the tough problem of identifying suitable candidates for varicocelectomy and preventing its excessive usage.

To preselect patients who would benefit the most, it is important to define factors predictive of a positive response to varicocelectomy in infertile men. Several studies have suggested that oxidative stress mainly caused by reactive oxygen species (ROS) is involved in the pathogenesis of varicocele.⁵,⁶ Glutathione S-transferases (GSTs) – an important superfamily of phase 2 drug-metabolizing enzymes generated in response to oxidative stress – play an important role in cell protection by performing functions like catalyzing the conjugation of a large variety of endogenous and exogenous compounds including ROS, carcinogenic compounds, and their metabolites. A previous study clearly demonstrated an abundance of GSTs in the male reproductive tract and showed that GSTs play important roles in the protection of sperm against oxidative stress.⁷ Genes encoding human cytosolic GSTs exhibit genetic polymorphism, and homozygous deletions in these genes result in null genotypes. Many genetic polymorphisms lead to altered activities of GSTs, which may be partially responsible for an individual’s susceptibility to oxidative damage. GSTT1, a member of the GST gene family, is polymorphic in the human population. Our previous study has shown a possible relationship between the GSTT1 null genotype and the susceptibility to male infertility in patients with varicocele, and we found that the GSTT1 positive genotype improved the antioxidant capacity, reduced the levels of ROS in seminal plasma, and prevented injury caused by ROS to the sperm DNA in infertile patients with varicocele.⁸ A Japanese group has reported that after varicocelectomy, the GSTT1 positive genotype is associated with an improvement in the seminal findings of infertile patients with varicocele.⁹ In recent clinical practice, we have also found that patients with the GSTT1 positive genotype have better responses to varicocelectomy than do patients with the GSTT1 null genotype (data not shown). Based on the findings of these studies, we propose that a GSTT1 positive genotype is a potential marker for the selection of varicocelectomy in infertile male patients with varicocele.

Accordingly, we propose that only infertile male patients with the GSTT1 positive genotype should be selected to undergo varicocelectomy; patients with the GSTT1 null genotype need not undergo varicocelectomy because of their negative responses to this surgery. If this proposal is approved, we must reevaluate the necessity of treatment of varicocele in adolescents with the GSTT1 positive genotype because these adolescents might not develop male infertility in the future. We think that varicocelectomy should be performed in the population with the GSTT1 positive genotype, especially the adolescent population, only when changes in sperm function or structure are detected. This will lower the risk of excessive usage and improve the therapeutic effect of varicocelectomy. Apart from the GSTT1 polymorphisms, there are some gene polymorphisms in other phase 2 drug-metabolizing enzymes that have shown potential as markers for the selection of infertile male patients with varicocele to

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undergo varicocelectomy. However, more prospective cohort studies and large-scale randomized trials are needed to further evaluate all these potential markers.

In addition, the causes of male infertility are complex, only a small fraction of cases of male infertility is related to varicocele. Reduced male fertility can be caused by congenital and acquired urogenital abnormalities, infections of the male accessory glands, endocrine disturbances, genetic abnormalities, and immunological factors. Therefore, to lower the risk of excessive usage of varicocelectomy, we still need to evaluate the infertile male patients carefully to rule out other possible reasons for infertility before performing varicocelectomy.

AUTHOR CONTRIBUTIONS
JHS conceived and created the framework for the letter, collected the data, and drafted the manuscript. KFT conceived and created the framework for the letter, collected the data, and drafted the manuscript. QFW conceived and created the framework for the letter, evaluated the data, drafted the manuscript, and edited the manuscript. JPX conceived and created the framework for the letter, evaluated the data, and edited the manuscript. All authors have read and approved the final manuscript.

COMPETING INTERESTS
All authors declare no competing interests.

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