

SUMMARY OF PROPOSED RESEARCH
(Do not exceed the space provided)

Describe clearly and concisely, in language readily understandable to a biomedical scientist who may not be a specialist in the research project's field, the broad objectives, specific aims, general procedures, and the potential significance of the research.

Project Summary

Varicocele is one of the most common conditions associated with male infertility. It occurs in 10 -20% of the general population, but in 30 - 40% of men presenting to infertility clinics.^{1,2} Men with varicocele exhibit impaired semen characteristics, in terms of both the total number of sperm, as well as the quality of those sperm. Approximately 50 - 75% of men who undergo varicocele treatment (surgical ligation or varicocele embolization) will demonstrate improvement in semen quality, and 30 - 40% will initiate a pregnancy.²⁻⁴ Still, the mechanisms by which varicoceles reduce fertility, and varicocele treatment improves sperm quality have not been elucidated.

Reactive oxygen species (ROS) include hydrogen peroxide and highly unstable oxygen free radicals (the hydroxyl radical and superoxide anion). Normal spermatozoa produce ROS in low amounts, and ROS are important physiologically to sperm hyperactivation, capacitation, and the acrosome reaction.⁵ Elevated ROS levels, however, have been implicated as a mediator of sperm dysfunction.⁶⁻⁸ Indeed, spermatozoa and seminal plasma are equipped with antioxidants to scavenge ROS, thus maintaining ROS levels in the physiologic range.⁹⁻¹¹ Several studies have demonstrated an association between oxidative stress (imbalance between ROS production and ROS scavenging) and infertility.⁶⁻¹² In addition, various cytokines present in seminal plasma have been implicated in normal and abnormal spermatozoal function.¹³ Elevated interleukin-6 (IL-6) concentrations have been found in patients with varicoceles.¹⁴ It is not known if varicocele treatment affects seminal IL-6 concentrations.

Recently, our lab has demonstrated increased reactive oxygen species production from the spermatozoa of men with varicoceles when compared to normal donors. In addition, seminal plasma total antioxidant capacity (TAC) was shown to be deficient among varicocele patients compared to normal donors.¹⁵ Despite this association between oxidative stress and the presence of varicocele, it is not known how varicocele treatment affects oxidative stress in the semen of these patients. It is also unknown if reducing seminal oxidative stress in these patients will result in improved semen parameters and/or fertility.

The purpose of this study, then, is to clarify the role of oxidative stress and IL-6 production in reducing fertility in men with varicoceles. Reactive oxygen species levels, TAC, IL-6 concentration and semen analysis for overall sperm quality and morphology will be measured in semen samples obtained both before and after varicocele treatment. In addition, sperm membrane lipid peroxidation (LPO), an indicator of ROS-induced damage, will be measured in the semen samples before and after varicocele treatment. Correlations between these parameters and fertility status will be assessed, and the results compared to a group of normal controls.

This research is potentially significant in that it may elucidate the etiology of sperm dysfunction in men with varicoceles. This may then guide future studies and/or medical therapy, such as antioxidant supplementation, for these patients. Effective medical therapy would obviate the need for invasive varicocele treatments and may reduce the need for assisted reproductive techniques, donor insemination, or adoption in this patient population. This would reduce overall healthcare costs in treating these patients. Finally, by correlating changes in oxidative stress and IL-6 production before and after varicocele treatment to fertility status, a novel assay for sperm dysfunction may be developed, permitting early identification and treatment of clinically significant varicoceles.

Please provide five Key Words that best describe your project:

- (1) Infertility (2) Varicocele treatment (3) Reactive oxygen species
(4) Antioxidants (5) Sperm function