



## Review Article

# Improvement in Sperm Capacitation Measured by Cap-Score™ Demonstrated after Varicocele Repair

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### Abstract

Approximately 30% of infertile men have a significant varicocele, which may affect testicular function. Semen analysis remains an essential part of initial male fertility evaluation. However, its predictive ability is limited and therefore its use to assess fertility before and after varicocelectomy can be problematic. Cap-Score™ is a validated test using Monosialotetrahexosylganglioside (GM1) localization patterns to measure sperm capacitation and has been shown to prospectively predict male fertility. In this case report, Cap-Score™ and semen analysis were used to evaluate improvement in fertility after varicocelectomy. A 37-year-old Asian male presented with secondary infertility. Evaluation included scrotal ultrasound, serum testosterone, the Cap-Score™ male fertility assay and standard semen analysis before and after surgery. Following varicocele correction, there was improvement in Cap-Score™ from abnormal to normal, as well as in semen parameters of motility and Kruger morphology. Addition of Cap-Score™ to semen analysis may offer urologists a complementary tool to better evaluate the effectiveness of treatment of causes of male infertility, including varicocele.

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### Introduction

Semen analysis remains a fundamental part of the male infertility evaluation. The test is an assessment of gross physical and observable microscopic characteristics of semen including a measurement of semen volume, pH, viscosity as well as measurements applicable to sperm such as the sperm density, percent motility, quality of motility and morphology. Despite the pervasiveness of its use, there is recognition of limitations of semen analysis with respect to accuracy, reliability and its ability to predict male fertility. This is likely due in part to the fact that standard semen analysis does not measure sperm function. Recently, Androvia Life Sciences introduced the Cap-Score™ male fertility assay, a sperm function test that measures sperm capacitation and the ability to undergo acrosome exocytosis, both of which are necessary events for a sperm to fertilize an egg.

Varicoceles are the most common surgically correctible cause of male infertility [1]. A large number of reports show improvement in semen parameters after correction of varicocele [2-4]. Using Cap-Score™ as an adjunct to the semen analysis may serve to provide a more reliable method of evaluating infertility caused by varicoceles and a better measurement of change in fertility after repair. In this case report, we evaluated a patient with bilateral varicoceles, abnormal preoperative semen analysis and Cap-Score™ with subsequent improvement in semen analysis and correction of Cap-Score™ from “abnormal” to “normal” post-varicocelectomy. This is the first such case report in the literature where the Cap-Score™ has been used in a clinical setting for assessing improvement after intervention.

### Case Presentation

A 37 year old Asian male presented for evaluation of secondary infertility after 12 months of trying to conceive. The patient denied any interval changes in medical history since his prior live birth. He denies any significant past medical or surgical history. On physical exam, genital exam was significant for Grade 3 left varicocele. Pre-operative laboratory values demonstrate a total serum testosterone of 326 (normal 264-916) ng/dl, serum FSH 4.4 (normal 1.5-12.4) IU/mL and serum estradiol 28 (normal <39) pg/mL. Scrotal sonography shows 11 and 10 cc for left and right testicular volumes, a large left varicocele of 0.32 cm and moderate right varicocele of 0.23 cm. Post-operative serum and semen specimens were collected approximately four months after varicocelectomy.

With respect to performing the Cap-Score™ male fertility assay, a kit is provided by Androvia Life Sciences (Mountainside, NJ) that includes all necessary media, reagents and consumables. Following standard semen collection, the sperm are washed through a density gradient to remove seminal plasma. The sperm concentration is determined and modified human tubal fluid (Irvine Scientific, Santa Ana, CA) is added to each of two tubes. One tube is void and one contains 2-hydroxypropyl-β-cyclodextrin, which serves to capacitate the sperm [5]. After 3hr incubation, a fixative is added to the cells, which are then shipped overnight to Androvia's laboratory, where the assay is performed. Androvia assesses over 150 sperm having different patterns of GM1 localization using fluorescence microscopy and

the percentage of sperm having patterns consistent with capacitation is defined as the Cap-Score™ [6].

Pre- and post-operative results shown below, demonstrate overall improvement in semen analysis parameters (Table 1), serum testosterone (Table 2) and correction of Cap-Score™ from “abnormal” to “normal” (Table 3).

	Volume	Sperm Density	Percent Motile	Kruger Morphology
*WHO 5 <sup>th</sup> percentile [7]	≥1.5 mL	≥15 M/mL	≥40%	≥4%
Pre-Operative	2.4 mL	49 M/mL	33%	3%
Post-Operative	2.0 mL	51 M/mL	65%	6%

**Table 1:** Semen analysis parameters, pre- and post varicocelectomy.  
\*World Health Organization (WHO) [7].

	Testosterone
Pre-Operative	326 ng/dl (normal range 264-916 ng/dl)
Post-Operative	426 ng/dl

**Table 2:** Total testosterone values pre- and post-varicocelectomy.

	Cap-Score™
Pre-Operative	19.1% (normal range >27.6%, mean 35.3; SD = 7.7%)
Post-Operative	35%

**Table 3:** Cap-Score™ values pre- and post-varicocelectomy.

## Discussion

Cap-Score™ provides urologists with another diagnostic assay to assist in the evaluation and treatment of male infertility. Selvaraj et al., demonstrated that during sperm capacitation, a series of molecular mechanisms result in focal enrichment of GM1 on the plasma membrane of mature sperm [8]. They were also able to demonstrate that sperm with this specific GM1 localization pattern on the plasma membrane could undergo the acrosome reaction and induce fertilization. While there have been other assays developed to determine sperm capacitation, they are technically demanding and have not been incorporated into clinical practice [9]. Unlike the previous assays, the Cap-Score™ is technically feasible with a quantitative result and has been shown prospectively to predict male fertility [6,10]. In addition, the assay results are reproducible, whereas semen analysis results can have significant variability. Moody et al., was able to present the accuracy, repeatability and precision of Cap-Score™ [5].

As suggested by the results in this case study, Cap-Score™ could also be used to determine the effects of interventions designed to improve male fertility, such as surgical repair of varicocele. The functional changes that result from varicocele, which impede a man’s fertility, are poorly defined and remain somewhat contentious [11-13]. Nonetheless, increased Reactive Oxygen Species (ROS) and decreased antioxidant capacity have been observed in spermatozoa and semen samples obtained from individuals with varicocele [14].

While ROS play an important role in capacitation and maintenance of fertilizing ability, an over production may lead to the oxidation and dysfunction of lipids and proteins necessary for proper sperm function [15-17]. In fact, multiple studies have shown that patients presenting with varicocele produce sperm with modified membrane permeability, decreased protein tyrosine phosphorylation a hindered ability to undergo acrosome exocytosis and reduced zona pellucida and oolemma binding [18-21]. Interestingly, the surgical correction of varicocele can reduce the levels of ROS and increase antioxidants within seminal plasma, potentially improving the ability of sperm to respond to capacitation stimuli [22].

In this report, we found that although sperm density did not change appreciably from pre- to post-operative assessments, serum testosterone, the Cap-Score™, and sperm motility and morphology improved. Traditional semen analysis parameters do not always correlate with male fertility, suggesting that improvements in Cap-Score™ might more reliably reflect possible improvements in male fertility observed in response to varicocelectomy [23,24].

## Conclusion

This is the first documentation in the literature about the clinical application of using Cap-Score™ to assess the effect of varicocelectomy on male fertility. Cap-Score™ may offer urologists a complementary tool for the evaluation of male infertility when used in conjunction with a semen analysis in the setting of varicocele or other male fertility related disorders.

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