

MALE INFERTILITY *and* SPERM DNA FRAGMENTATION

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UNTIL SEVERAL YEARS AGO, THE BELIEF AMONG MOST REPRODUCTIVE SPECIALISTS (INCLUDING MYSELF) WAS THAT IF A MAN HAD LIVE SPERM, THEN THEY WERE SUITABLE FOR USE WITH IVF-ICSI (IN VITRO FERTILIZATION THROUGH INTRACYTOPLASMIC SPERM INJECTION). If the female partner didn't get pregnant or a miscarriage ensued, then it was probably due to an egg quality issue. Several studies had implied that the conventional sperm parameters of count, motility and morphology, as measured on a routine semen analysis, had no bearing on success when ICSI was used. Many couples pursued egg donation after failed IVF attempts because the husband's semen parameters were relatively normal and yet conception had not occurred. Some of these couples were unable to conceive even with the donor eggs, leaving the doctors and the couples frustrated and perplexed. Thinking it was both an egg quality and implantation issue, some couples went on to use egg donors and surrogates, again without success.

About four years ago, the relatively new concept that sperm quality was dependent on the amount of damage to the sperm DNA (DNA fragmentation) was introduced to clinical practice. Simply put, DNA is arranged in a double helix or ladder configuration with side rails and rungs. If the rungs are broken, then the ladder is unsteady and will not function properly. Several recent studies have shown that sperm DNA fragmentation is a completely independent variable with little or nothing to do with the parameters that we measure on the routine semen analysis. In addition, studies have shown that men with otherwise normal semen analyses can have a high degree of DNA damage, and that men with what is typically called poor sperm quality can have little DNA damage.

Importantly, what has also been demonstrated is that the degree of DNA fragmentation correlates highly with the inability of the sperm to initiate a birth, regardless of the technology used to fertilize the egg. Sperm with high DNA fragmentation may fertilize an egg and embryo development may stop before implantation. The sperm may initiate a pregnancy but with a significantly higher likelihood of miscarriage. By testing for sperm DNA fragmentation, many cases of "unexplained"

infertility can now be explained. Couples who have been unable to conceive have been diagnosed with high sperm DNA fragmentation and treated.

TESTING FOR SPERM DNA FRAGMENTATION

The most widely used, and statistically robust test for sperm DNA fragmentation is the Sperm Chromatin Structure Assay (SCSA) in which the semen samples are frozen and shipped in a liquid nitrogen container to the SCSA reference laboratory. The sperm are thawed and a stress is applied (low pH). The sperm are then labeled with an orange dye that attaches to the ends of broken DNA within the sperm cell. No dye will attach to the sperm if the DNA is intact. A flow cytometer is then used to analyze 10,000 sperm from the sample. The sperm are passed in single file across a beam of light that hits the dye inside the sperm cell and reflects light at a specific wavelength, causing the sperm to appear either orange (damaged) or green (normal). Computer software counts the normal and damaged sperm and creates a graph showing the percent of damaged sperm and an index known as the DNA fragmentation Index (DFI).

The data from thousands of SCSA tests has been analyzed. Correlating this data with clinical outcomes provides statistical references. A normal sample has less than 15 percent of sperm with DNA damage. A sample with poor fertility potential has greater than 30 percent of sperm with DNA damage. A DFI of between 16 percent and 29 percent represents good to fair fertility potential, with that potential becoming poorer as the DFI approaches 27 percent. These numbers are thresholds, meaning that the outcome for most couples was failure to have a birth when the DFI was above 30 percent and that most couples achieved success when the DFI was under 15 percent. Bear in mind that this test does not have a predictive value of 100 percent, as healthy babies have been born, albeit at much lower rates, to men with high levels of damaged sperm.

WHY DON'T THE UNDAMAGED SPERM WORK?

DNA fragmentation can be thought of as a marker for other types of damage to the sperm—akin to seeing the tip of the iceberg. Apparently, in semen samples with greater than 30 percent DNA fragmentation, abnormalities that the SCSA does

not measure are present in the non-fragmented sperm. That is why samples used with a DFI above this level have lower chances of resulting in a birth.

WHAT CAUSES SPERM DNA FRAGMENTATION?

The causes of high DNA fragmentation include chemical or toxin exposure, heat exposure, varicocele (enlargement of the veins within the scrotum), infection, age, smoking, testicular cancer, radiation, increased levels of the free radicals in the semen, and other causes.

CAN DNA FRAGMENTATION BE REDUCED AND THE SPERM QUALITY IMPROVED?

Sperm DNA fragmentation can change with time and can be improved in many cases. Infections can be eradicated, varicoceles can be repaired and free radicals in the semen can be reduced with antioxidants, to name a few common scenarios that have high treatment success rates. The goal of a male factor evaluation is to seek out the causes of poor sperm quality and attempt to correct them so conception can occur naturally, or to improve the sperm quality and maximize the chances of success for IVF.

When a patient's DFI cannot be improved, there is evidence to suggest that removing the sperm directly from the testicle via biopsy and using it with ICSI may lead to better outcomes than using ejaculated sperm of a poor quality. Other options include counseling patients regarding the use of donor sperm either by insemination or fertilizing a portion of the eggs harvested for ICSI with donor sperm and a portion with the patient's sperm.

THE CLINICAL UTILITY OF THE SCSA

The clinical utility of the SCSA is readily apparent. All men with an abnormal semen analysis as well as men with normal semen analyses who have failed IVF for unexplained reasons are candidates for this test. Couples considering egg donors or surrogates may also benefit from screening. These new concepts have significant impacts on how we practice and what we recommend to our patients.

Dr. Philip Werthman, Director of the Center Of Male Reproductive Medicine, specializes in microsurgery, vasectomy & vasectomy reversal, and the treatment of male factor infertility. Dr. Werthman's offices are located in Century City, Los Angeles and in Thousand Oaks, Ventura County.

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