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Perspectives and Editorials

Editorial Commentary

Subnormal Hypo-Osmotic Swelling Test Scores as an Important Cause of Cryptic Infertility

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Tartagni M, Schonauer MM, Cicinelli E, Selman H, de Ziegler D, Petruzzelli, F, D'Addario V. Usefulness of the hypo-osmotic swelling test in predicting pregnancy rate and outcome in couples undergoing intrauterine insemination. *J Androl*.2002 ;23:498–502. [Abstract/Free Full Text]

Previous studies have demonstrated extremely low pregnancy rates following intercourse, intrauterine insemination (IUI), or in vitro fertilization (IVF)—embryo transfer (ET) when the male partner has a hypo-osmotic swelling test (HOST) score <50%, even if all other semen parameters are normal. It is interesting that low pregnancy rates seem to be related to a toxic effect of supernumerary sperm binding to the zona pellucida so that fertilization is not impaired, but the defect lies with embryo implantation. Unfortunately, most studies have been performed by one fertility center, and confirmation by another fertility center has been needed. The study by Tartagni et al independently confirms that women partners of men with subnormal HOST scores, but otherwise normal semen parameters, have very low pregnancy rates. A unique group never before reported was evaluated; those undergoing superovulation and IUI.

The authors state that standard semen parameters have not been successful in predicting men with subfertility. However, when HOST scores are <50%, it has been demonstrated as highly effective in predicting men who are subfertile. Even with conventional IVF, a subnormal HOST score was found to be far more predictive of a poor pregnancy rate when compared to either motile density or normal morphology using strict criteria (Kiefer et al, 1996).

Although HOST is inexpensive, simple to perform, and is stable over time once subnormality has been determined (Shanis et al, 1992), in contrast to other semen parameters, which seem to fluctuate, the test is rarely performed by most clinicians. Whereas the first in vivo study (in 1989) demonstrated

no pregnancies despite normal semen parameters, the in vivo study by Tartagni et al is the first designed to corroborate or refute the 1989 study by Check et al quoted by the authors. Tartagni et al not only corroborated the previous study, but they did it in a different manner, demonstrating that superovulation and IUI do not overcome subnormal HOST scores.

Finding low pregnancy rates following IUI is not surprising, because even conventional IVF fails to overcome the HOST abnormality.

It is interesting that several IVF studies published in 1989 and 1990, including one by Barratt et al (1989), found that subnormal HOST scores did not produce low fertilization rates. At that time, and even now, the traditional concept is that the role of the sperm is to fertilize the egg, and that once fertilization has been achieved, the sperm poses no threat to the future implantation of the embryo. It is interesting to note that none of these studies of the effect of subnormal HOST scores on fertilization rates mentioned pregnancy rates at all. I suspect they were left out because the rates were embarrassingly low and would serve to confuse the authors' conclusions that subnormal HOST scores do not adversely affect fertilization rates.

Tartagni et al referred in their manuscript to our matched control study, published in *Human Reproduction*, in 1995, in which we agreed that low HOST scores did not lead to lower fertilization rates with IVF-ET, but resulted in extremely poor implantation rates. These conclusions were corroborated by another study using shared oocytes (ie, an infertile woman needing IVF-ET shares equally the retrieved oocytes with a recipient in need of donated oocytes). We evaluated the outcome of 22 donor-recipient pairs in which one male partner had normal semen parameters and a normal HOST score, and the other had normal semen parameters but a HOST score of <50%. The fertilization rates, the number of embryos transferred, and embryo morphology were the same. However, in this study, in which conventional fertilization techniques were used rather than intracytoplasmic sperm injection (ICSI), the clinical pregnancy rate was 50% for those women whose partners scored ≥50% in their HOST score, but it was zero for those with subnormal HOST scores (Katsoff et al, 2000).

The demonstration of normal fertilization rates but poor implantation rates suggested that the male partner can contribute to a given couple's infertility by producing sperm that are associated with a toxic factor that permits normal fertilization but somehow inhibits implantation. This phenomenon may be related not to the one sperm fertilizing the oocyte, but to the supernumerary sperm that attach to the zona pellucida. If this provocative hypothesis is true, then it should follow that bypassing exposure of sperm to the zona pellucida by performing ICSI should improve pregnancy rates. Indeed, the authors referred to our study published in 2001 in the *Journal of Andrology* in which we demonstrated a 49% pregnancy rate with IVF-ET and ICSI within a series of infertile couples in which male partners had subnormal HOST scores.

How frustrating it is for couples having unexplained infertility, or those with a seemingly obvious problem of tubal factor infertility to repeatedly fail to achieve a pregnancy despite transfers of what appear to be perfectly normal embryos because HOST was not performed even though it is simple, reliable, and inexpensive. At least when failed fertilization is unexplained, only one IVF cycle is wasted before proceeding to ICSI. However, with the low HOST score scenario, the couple may have invested in many expensive, invasive IVF cycles without achieving their goal of pregnancy. I certainly hope that the manuscript of Tartagni et al will now increase the credence of the conclusions about the subnormal HOST that up to this time came from only one research center. Corroboration from another center was greatly needed.

This study by Tartagni et al should generate interest among andrologists to better define this toxic

factor and to find alternate, less expensive methods than IVF with ICSI to overcome this abnormality. Some preliminary data suggest that the factor may be proteinaceous in nature. In one study of just 12 patients, 67% had improved HOST scores following treatment of sperm with the protein digestive enzyme chymotrypsin, resulting in good pregnancy rates following IUI in the eight couples in which improvement of the score to >50% was demonstrated (Katsoff et al, 1997). This concept of sperm toxicity leads to a provocative recommendation for infertile couples undergoing IUI after attempts to neutralize this toxic factor with chymotrypsin: to avoid unprotected intercourse before insemination. Furthermore, andrologists may be encouraged to look for toxic factors inhibiting embryo implantation not manifested by subnormal HOST scores.

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Response to Commentary

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Tartagni M, Schonauer MM, Cicinelli E, Selman H, de Ziegler D, Petruzzelli F, D'Addario V. Usefulness of the hypo-osmotic swelling test in predicting pregnancy rate and outcome in couples undergoing intrauterine insemination. *J Androl*.2002 ;23:498–502.

We thank Dr Check for his positive comments. We know that Dr Check has performed a great deal of work in this field, and we are pleased that he shares our conviction that sperm quality plays a relevant role in spontaneous and assisted reproduction. We also agree with Dr Check's suggestion that better investigations and definitions are needed of the toxic factors that could affect fertilization and pregnancy rates with the aim of finding alternate, less expensive methods than in vitro fertilization with intracytoplasmic sperm injection to overcome this abnormality. This in turn could offer a new occasion for andrologists to play a more relevant role in the management of infertile couples. We also thank Dr Check for reporting new and interesting experimental data on

detrimental factors coated to abnormal spermatozoa through the hypo-osmotic swelling test and for the provocative hypothesis that supernumerary sperm could be responsible for the low pregnancy rate observed with abnormal hypo-osmotic swelling tests. Even though a few groups are still involved in this field, we are persuaded that a better understanding of spermatozoa abnormalities is crucial for improving the results of low technology and high technology procedures.

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