

## Perspectives and Editorials

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### Editorial Commentary

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

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.

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  $\geq 50\%$  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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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 abnormal-

ity. 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 un-

derstanding of spermatozoa abnormalities is crucial for improving the results of low technology and high technology procedures.

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### Editorial Commentary

Oliva A, Giami A, Multigner L. Environmental agents and erectile dysfunction: a study in a consulting population. *J Androl.* 2002;23:546–550.

The extremely provocative study by Oliva et al comes at a time when increasing emphasis is being given to the public health significance of erectile dysfunction. A host of epidemiologic studies have emerged confirming various risk factors associated with erectile dysfunction. Thus, this article is particularly timely.

The investigators have constructed an interesting hypothesis, that occupational exposure to chemical and physical environmental agents constitutes a risk factor for erectile dysfunction, and they tested this hypothesis with an elegant study. The genesis of their study borrows from concepts that were developed in the field of male reproductive function with concerns that certain pesticides, solvents, and related chemical agents may affect fertility, but erectile ability as well. The impetus to carry out this study also derives from early citations of men presenting to clinics with erectile dysfunction reporting occupational exposure to environmental chemicals. This study also takes on an evaluation of the mythical contention that heat may also be an environmental risk factor for erectile dysfunction. In exploring occupational and environmental risk factors, these investigators have gone beyond the often cited medical correlates that have appeared recently, such as cardiovascular disease, diabetes mellitus, and neurological illnesses. Thus, their study carries a certain novelty. The focus is on exposure risks for erectile dysfunction, similar to increased interest in smoking and alcohol consumption as possible risk factors for erectile dysfunction.

The investigators should be applauded for producing a solid clinical and epidemiologic study. The study used a small population of men who presented with erectile dysfunction to an andrology clinic in Argentina, who then underwent a comprehensive evaluation for their erectile

disorder, and whose clinical, demographic, and occupational historical information was subjected to rigorous epidemiologic analysis. A highlight of the investigation was the application of nocturnal penile tumescence testing and rigidity using RigiScan as an objective assessment of erectile ability. Thus, the subjective complaint of the disorder was not relied on in order to ascertain the significance of the problem. It is noteworthy that 29 of the 199 individuals in the study (15%) were considered normal by this determination as a result. The approach carries certain potential limitations. Whereas it may assess nocturnal erection as a surrogate for sexual-related erectile ability, the concern exists that the presence of nocturnal erections does not always equate with those needed for sexual function. False positives may occur in the event of psychological or interpersonal variables, vascular steal syndrome, and sensory neuropathies, among others.

Some discussion is warranted with regard to the epidemiologic component of the study. In general, the epidemiologic analysis is rigorous, with an analysis that draws out some important relationships despite the relatively small size of the population studied. There is an assessment of relative risk, based on a calculation of odds ratios according to the different types of exposure in correlation with the degree of abnormality found with nocturnal penile tumescence testing. There are, however, several limitations from the epidemiologic perspective that should be acknowledged. Because the study involved a consulting population, there is the concern of inherent selection bias. The study was not population-based, but it was more like a case series because the evaluation did not represent the entire population, and represented only those who presented with complaints of erectile dysfunction. Data retrieval was retrospective in nature. It relied

on patient interviews and recollection of the characteristics of exposure, such as whether there was exposure, how much was sustained, and when this occurred. Only a prospective evaluation with other validated techniques to define the type and amount of exposure with longitudinal assessment would allow utmost confidence in establishing the occupational and environmental risk. It is noteworthy to mention that a randomized controlled trial in which exposure could be completely regulated offers the optimal assessment, but it is obvious that such an investigation would hardly be feasible.

A unique feature of the investigation is the high amount of exposure to environmental agents sustained by the population at hand. The investigators indicate that about 40% of the men in the study were exposed to either chemical or physical environmental agents. This prevalence, as acknowledged by the investigators, relates to the given region of the study in which industrial and agricultural work predominates. In some respects, this feature offers an opportunity to assess the extent to which environmental agents are responsible for erectile dysfunction in this unique population. On the other hand, there is a concern that confounding variables may be introduced by such a homogeneous background. Is it the environmental exposure that constitutes the risk or some other characteristic of this highly exposed population? A study based on a population with this high level of exposure also runs the risk that a definitive estimate from these data of erectile dysfunction probability from chemical agent exposure may be skewed. Data in the article indicate that patients with organic erectile dysfunction had a higher prevalence of exposure to pesticides or solvents than patients in the nonorganic erectile dysfunction group, which therefore supports these concerns.

The estimation of risk factors for erectile dysfunction might reasonably comply with the causality criteria promoted by the First Surgeon General's Advisory Committee on Smoking and Health in 1964, which evaluated the significance of the association between cigarette smoking and a condition in the host (US Department of Health, Education, and Welfare, 1964). Several criteria to be considered with respect to an association include consistency, specificity, strength, temporality, and coherence. Consistency is met by repeated studies that examine different clinical settings, subjects, eligibility criteria, and exposure opportunities. Specificity implies a dose-response effect with an assessment that establishes independence of a potential risk variable. Strength pertains to relative risk es-

timation. Temporality implies that the effect occurs with the onset of the exposure and, conceivably, the effect is diminished with cessation of the exposure. Coherence means that a biological mechanism has been explored and found to be tenable. In light of these issues, this study provides a useful initiation to an analysis of occupational and environmental risk factors for erectile dysfunction, which will need to be fortified by additional studies that support all of the necessary criteria before causality can be affirmed.

Overall, this article is solid for bringing attention to occupational and environmental risk factors that may lead to erectile dysfunction. It expands concepts of potential risk factors for the disorder. Certainly, more investigation is needed. A true population-based, longitudinal assessment would be most valuable. Further assessment of the mechanism of the effect would be most interesting with further scientific exploration. There may be antiandrogenic properties of certain environmental agents, or perhaps these serve as neurotoxins. As further information is gathered, recommendations may nonetheless be issued, based on the awareness of a possible link between environmental agents and erectile dysfunction. Similar concerns have arisen with regard to the smoking risk for erectile dysfunction that has prompted the Sexual Medicine Society of North America to issue a policy statement recently that smoking is a risk factor for erectile dysfunction. With prevailing wisdom, the discontinuation or avoidance of smoking may preserve a man's erectile ability. Similar beliefs could apply to an argument to limit occupational and environmental agent exposure. This issuance is all the more compelling, given recent epidemiologic results showing that a high lifetime exposure to cigarette smoking may not reverse the effect of erectile dysfunction (Derby et al, 2000).

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