as the authors suggested. Preliminary data from our laboratory indicate that administration of diclofenac significantly reduces DNA fragmentation in males with high DNA fragmentation values (Alvarez et al., unpublished data). Diclofenac, in addition to being an anti-inflammatory agent, is also a known scavenger of the hydroxyl radical (Aruoma and Halliwell, 1988) and readily crosses the blood–testis barrier.

References


Submitted on December 31, 2004; accepted on January 25, 2005

J. G. Alvarez

Centro de Infertilidad Masculina ANDROGEN, La Coruña, Spain and Harvard Medical School, Boston, Massachusetts, USA

E-mail: jalvarez@androgen.es
doi:10.1093/humrep/deh814

Reply: ‘Efficient treatment of infertility due to sperm DNA damage by ICSI with testicular spermatozoa’

Sir,

We have read with interest the letter by Alvarez concerning our recent paper about the use of ICSI with testicular sperm in the treatment of infertility due to sperm DNA damage (Greco et al., 2005a). This letter contains stimulating ideas for future research into the mechanism, diagnosis and treatment of this pathological condition.

Sperm nuclear DNA fragmentation is known to reduce implantation and pregnancy rates after ICSI, but the resulting embryo handicap remains latent during the first 3 days after ICSI (Tesarik, 2005). Our observation that testicular sperm show a lower incidence of DNA fragmentation and a higher developmental potential than ejaculated sperm in men with elevated sperm nuclear DNA damage supports the hypothesis that the DNA damage mainly occurs after sperm release from the seminiferous tubules. Alvarez cites several other studies supporting this hypothesis and puts forward the idea that incomplete disulphide cross-linking of the protamines of sperm chromatin, a process which is normally completed during sperm passage through the epididymis, is responsible for this phenomenon. This is a plausible explanation, but it has to be underscored that other possible pathophysiological mechanisms may also come into play. These mechanisms are essentially related to functional disorders of Sertoli cells. In a previous work, in which the relationship between caspase activity and germ cell DNA fragmentation was analysed, we showed that those DNA-fragmented germ cells which remain firmly associated with Sertoli cells also display caspase activity, and their plasma membrane externalizes phosphatidyl serine (Tesarik et al., 2004). The Sertoli-associated germ cells thus appear to undergo a classical apoptotic pathway. The externalized phosphatidyl serine is known to be a surface marker of apoptotic cells to be recognized as targets for phagocytosis. In fact, fragmented DNA was detected in the cytoplasm of Sertoli cells clearly outside their own nuclei, indicating that germ cells with fragmented DNA are recognized and actively removed by Sertoli cells (Tesarik et al., 2004). In contrast, DNA-fragmented germ cells that are detached from Sertoli cells do not display caspase activity and do not externalize phosphatidyl serine (Tesarik et al., 2004). It is thus tempting to speculate that the premature detachment of germ cells makes them particularly susceptible to oxidative DNA damage which may begin during their passage through the seminiferous tubules. Because most of the Sertoli-associated germ cells undergoing the classical apoptotic pathway are probably not released from the testis, the DNA damage detected in ejaculated sperm can be supposed to result mostly from non-apoptotic oxidative DNA damage occurring in prematurely released late spermatids.

The recourse to testicular biopsy to recover sperm for ICSI makes it possible to shorten the Sertoli cell-protected time-period during which maturing spermatids and sperm are particularly vulnerable to DNA-damaging agents. However, the need for testicular biopsy makes this therapeutic approach more invasive and expensive than ICSI with ejaculated sperm. A search for more conservative treatment alternatives, aimed at the limitation of the extent of DNA damage in ejaculated sperm, is thus warranted. Alvarez has suggested an approach based on the use of diclofenac, a prostaglandin synthesis inhibitor and hydroxyl radical scavenger. Interestingly, earlier work has demonstrated a significant activation of dog spermatogenesis by subcutaneous application of diclofenac for 42 days (Moskovitz et al., 1987). We look forward to seeing the publication of the new data on the application of this...
drug in males with high sperm DNA fragmentation values announced by Alvarez.

In our clinics we have recently tested another conservative approach to the problem of sperm DNA fragmentation, based on combined oral treatment with two antioxidants, vitamins C and E. In a prospective randomized study we found that the oral treatment with these two antioxidants for 2 months significantly alleviates DNA damage to ejaculated sperm (Greco et al., 2005b). The effect of this treatment on clinical outcomes of ICSI performed with ejaculated sperm from men whose initially elevated DNA fragmentation values return to normal values after treatment is currently under study.

References

Submitted on January 24, 2005; accepted on January 25, 2005
Ermanno Greco1,3, Filomena Scarselli1, Marcello Iacobelli1, Laura Rienzi1, Filippo Ubaldi1, Susanna Ferrero1, Giorgio Franco1, Nazareno Anniballo1, Carmen Mendoza2 and Jan Tesarik2
1Centre for Reproductive Medicine, European Hospital, Via Portuense 700, 00149 Rome, Italy and 2MAR&Gen, Molecular Assisted Reproduction and Genetics, Gracia 36, 18002 Granada, Spain
3To whom correspondence should be addressed.
E-mail: cmendoza@ugr.es
doi:10.1093/humrep/deh815

Request for information on unreported cases of severe ovarian hyperstimulation syndrome (OHSS)

Sir,

On various occasions, at conferences, I have been invited to speak about the epidemiology of OHSS. Occasionally after these talks, some of our colleagues have told me about severe complications with sometimes fatal outcomes, which have never been mentioned in the scientific literature. This suggests an underreporting of OHSS. Currently I am writing a paper about the mortality related to OHSS. Some cases with a fatal outcome were reported during the 1950s. Although more recent anecdotal cases have been discussed in workshops, no publication has ever described their circumstances in detail. We believe that some information is particularly pertinent: (i) when and where the death occurred (how long after stimulation, in a reference centre, time lapse between diagnosis and treatment,base of treatment, admission in an intensive care unit?); (ii) what was the cause of death, which may have been different in earlier days (renal failure) as compared to today (thromboembolic disorders)?

We feel certain that additional data regarding these circumstances could help us to define safer treatments for our patients. Obviously, our goal is not to criticize, after the fact, the therapeutic decisions made by our colleagues. We will ensure anonymity to those who wish it. They can reply to E-mail: http://users.skynet.be/sky98426/survey.html. On the other hand, those who would like to be mentioned will be acknowledged for their help and can contact me directly on E-mail: annick_delvigne@stpierre-brussels.be.

Submitted on September 22, 2004; accepted on January 12, 2005
Annick Delvigne
IVF Clinic, St Pierre Hospital, Free University Brussels, Hospital Universitaire Saint-Pierre, Rue Haute 322, B-1000 Bruxelles, Belgium
E-mail: annick.delvigne@ycom.be
doi:10.1093/humrep/deh816

The effects of the human immunodeficiency virus on semen parameters and intrauterine insemination outcome

Sir,

We have read with great interest the paper about the effects of the human immunodeficiency virus (HIV) on semen parameters by Nicopoullos et al. (2004).

The authors performed a case–control study, comparing semen parameters of 106 asymptomatic HIV-1 infected men with semen parameters of 234 HIV negative men requiring IVF, because of a partner with tubal infertility. In addition, the study compared 133 pre-wash semen parameters on the day of intrauterine insemination (IUI) of HIV positive men with 222 pre-wash semen parameters on the day of IUI of non-infected men. Finally, the authors attempted to analyse which factors predict IUI outcome in HIV-infected men. Based on their analysis, the authors conclude that semen parameters are impaired in the presence of HIV infection and that both viral load and antiretroviral therapy predict IUI outcome in HIV infected men. However, there are several problems with the study that make us question whether these conclusions are justified.

First, the conclusions are based on a comparison between a group of HIV positive men with an unmatched group of HIV negative men. It is thus unclear if differences other than the presence of an HIV infection exist in these cases and controls that could explain the observed differences in semen quality. Furthermore, the variability of semen parameters between individuals limits the conclusions of a case–control study design (Guzick et al., 2001). The ideal situation to