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## Smoking and sperm viability—a never-ending story

*To the Editor:*

I would like to comment on the article by Dr. Saleh and colleagues, which adds new information to the growing body of evidence about the negative effects of smoking on reproductive health (1). In 1998, two consecutive papers were published by our group dealing with the effects of smoking on human sperm viability via the seminal plasma factor and at the ultrastructural level of the sperm tail axoneme (2, 3). In one of the studies (2), spermatozoa from nonsmokers were exposed to seminal plasma from smokers (> 30 cigarettes/d for at least 3 years), and spermatozoa from smokers to seminal plasma from nonsmokers. Our findings indicated that exposure of nonsmoker spermatozoa to seminal plasma from smokers significantly reduced sperm motility and membrane functional integrity. The negative effects on sperm viability increased during short- and long-term incubation in smokers seminal plasma. On the other hand, incubation of smokers' spermatozoa with seminal plasma from nonsmokers improved viability. Thus, the negative effect of smokers' seminal plasma seems to be reversible to some extent, as seen when reconstituting spermatozoa with nonsmoker seminal plasma or by washing with culture media.

Irreversible damage to spermatozoa from smokers was confirmed in a second study, in which the architectural elements of the sperm tail axoneme from smokers was assessed at the ultrastructural level (3). Various types of damage were observed, including absence of one or more fiber doublets, central fibers, and coarse outer fibers. In light of the data presented by Saleh and colleagues, it is possible that a link between the high incidence of reactive oxygen species in seminal plasma from smokers may have been a contributing factor to the results obtained in the studies mentioned above. It is interesting to note that penetration of reactive oxygen species into the sperm tail region may occur, causing damage to the axonemal structure, in a similar manner to the mechanism of penetration into the sperm head resulting in DNA damage as previously reported (1).

With regard to the observation of a high incidence of leukocytes in smokers, the authors should review the paper by Klaiber et al. (4), in which the authors point out that smoking seems to increase circulating levels of catecholamines, with high concentrations reported in the spermatic vein of men with varicoceles via retrograde flow from the renal vein (4). High concentrations of catecholamines and their accumulation in tissues was suggested as a cause of damage to the seminiferous epithelium in smokers with varicoceles. Evidence of a high concentration of leukocytes was not reported in this study. However, the authors suggested that the combination of smoking and varicoceles could

result in more damage to the seminiferous tubules than either a varicocele or smoking alone. One can also infer that smoking could increase the likelihood of developing varicoceles.

This earlier evidence by Klaiber et al. could explain the hormonal trigger by cigarette smoke components, through catecholamines or glucocorticoids of adrenal origin, as the mechanism that stimulates increased leukocyte infiltration into the semen of infertile smokers.

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*December 10, 2002*

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*Reply of the Authors:*

We appreciate the interest of Dr. Correa-Pérez in our article (1) and their supporting data on smoking and semen quality (2). The presence of heavy metals and trace elements along with circulating levels of catecholamines in smokers may augment oxidative stress and DNA damage. In ejaculated spermatozoa, DNA repair capacity declines drastically. Transmission of altered spermatozoa DNA from smoking has been demonstrated in preimplantation embryos in association with increased risk of childhood cancer (3). However, the relationship of smoking with semen parameters is difficult because of the subjective nature of the smoking history. Additional randomized studies are needed to elucidate the impact of cigarette smoking on male infertility.

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## Suggestions on the use of LH

*To the Editor:*

Dr. Filicori's editorial on the role of LH in infertility treatment (1) was thoughtful and provocative. He, pointed out that during the normal menstrual cycle, LH progressively increases during the few days before the LH surge, during the critical final stages of oocyte maturation. However, not only do the levels of immunoreactive LH increase, but the concomitant increase in estrogen causes the pituitary to secrete LH that is more bioactive (2). This marked increase in bioactive LH is likely related to the optimal health of the oocyte, and it is becoming increasingly clear that improved IVF outcome can be aided by providing LH activity with certain GnRH agonist and antagonist regimens.

We reported data (3) indicating that leuprolide, at full dose, is associated with levels of bioactive LH/hCG before hCG injection that are significantly lower than early follicular phase levels in spite of injection of three vials of hMG which contains an average of 10 U of hCG per vial in addition to the 75 U per vial of LH. The frequent use of pretreatment with the oral contraceptive pill causes LH levels to be even lower.

The innovative use of low-dose hCG during gonadotropin treatment may restore physiologic aspects to treatment regimens, but perhaps some caution is warranted to ensure that levels are not excessive in magnitude or duration. We have compared levels of bioactive LH during leuprolide with levels in controls receiving only hMG. Despite giving hCG at about a mean diameter of 14 mm in the controls 2 days earlier than with agonist, we observed more than a two-fold increase in bioactive LH compared with day 3 levels. It is possible that prolonged levels of high bioactive LH played some part in the lower pregnancy outcome before introduction of agonists and in the observation of lower implantation rates with less than optimal doses of GnRH antagonist (4). Low-dose hCG is a logical method to provide LH-like activity. We have shown that in normal women with a 14-mm follicle given a GnRH antagonist, 50 U of hCG restored the levels of bioactive-LH/hCG to normal (5). Dr. Filicori subsequently showed that this dose was sufficient to induce the development of oocytes with excellent implantation potential in a woman with hypogonadotropic hypogonadism; we

have had similar success using this dose in that clinical setting. Since 50 U was not excessive at 14 mm, before the preovulatory increase in bioactive LH, it is possible that brief use of 200 IU, as suggested, may induce regression of small follicles without an adverse impact on mature follicles.

The prospect that such a simple and inexpensive approach could be used to reduce the risk of ovarian hyperstimulation syndrome and multiple pregnancies in hyperresponding patients is exciting, and Dr. Filicori should be congratulated on his innovative look at controlled ovarian hyperstimulation.

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*February 8, 2003*

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*Reply of the Author:*

I wish to thank Dr. Meldrum for the kind comments contained in his letter related to my editorial published in the February issue of *Fertility and Sterility* (1). I feel that no further specific response is needed to his letter.

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## Does it all come down to postnatal aging of the primary oocyte?

*To the Editor:*

I read with interest the article by Chuang et al. (1). We have reached similar conclusions that when evaluating out-