

# Do Environmental Agents Affect Semen Quality?

Shanna H. Swan

In the early 1990s, Skakkebaek and colleagues<sup>1</sup> noted the decline in semen quality in Danish men and reviewed the literature for evidence of a global trend. Although there had been earlier reports of declining semen quality<sup>2-4</sup> it was not until Skakkebaek's paper that this issue received wide public attention. This paper concluded that "there has been a genuine decline in semen quality over the past 50 years." Sharpe and Skakkebaek<sup>5</sup> linked this decline to trends in testicular cancer and other male reproductive parameters, suggesting that all shared a common etiology, hypothesized to be prenatal exposure to environmental agents, particularly xenoestrogens.

After this publication, researchers reviewed historical records from sperm banks and infertility clinics and published numerous reports on trends in semen quality. The results of this intensive effort were conflicting and inconclusive, suggesting the need for a new approach to this problem. If xenobiotics had produced global trends, as suggested by Sharpe and Skakkebaek,<sup>5</sup> these exposures (unless uniformly distributed), should also produce geographic variation. Moreover, geographic differences, unlike historical trends, can be examined using well-controlled, cross-sectional studies—and, in fact, two recent studies provide convincing evidence of such variation in semen quality.<sup>6,7</sup> However, neither study addresses the causes of these geographic differences in semen quality.

Researchers are now searching for environmental agents that may have contributed to the reported geographic (and temporal) variability in male reproductive function; agents that are reproductive toxins in the laboratory and prevalent in the environment are natural candidates. The papers by Storgaard *et al.*<sup>8</sup> and Duty *et al.*<sup>9</sup> in this issue of *EPIDEMIOLOGY* are among the first to examine such exposures in humans.

Storgaard and colleagues<sup>8</sup> study maternal smoking in relation to semen quality, sex hormones and sperm deoxyribonucleic acid (DNA) integrity in the offspring.

Duty *et al.*<sup>9</sup> ask whether adult exposure to phthalates can alter semen quality. Because the exposures examined by these authors are prevalent, the reported associations could, if causal, explain a substantial fraction of the reported decline in semen quality.

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Although there has been considerable work on adult smoking and semen quality (most indicating a negative association), data on the effects of maternal smoking are few and inconclusive.<sup>10,11</sup> Storgaard *et al.*<sup>8</sup> report lower sperm density, inhibin-B and elevated follicular stimulating hormone associated with high (>10 cigarettes per day) *in utero* exposure. Interestingly, this study suggests a U-shaped dose response, with modestly increased sperm density in men prenatally exposed to lower levels of tobacco compared with nonsmokers. The authors are appropriately cautious in interpreting these results because exposure is based on maternal recall, information on potential confounders is limited, and the study population includes only 267 of 2000 invited participants.

Duty and colleagues<sup>9</sup> examine men's recent exposure to phthalates in relation to sperm concentration, motility and morphology using urinary metabolites as biomarkers. They find that higher levels of two of these metabolites (methylbutyl phthalate and methylbenzyl phthalate) are associated with reduced sperm concentration and (for methylbutyl phthalate) sperm motility—findings supported by the toxicologic literature. It is interesting that the "higher levels" in these men were not particularly high (less than half the levels found in a representative U.S. population<sup>12</sup>), suggesting that

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these chemicals may adversely affect male reproductive function even at the low ambient levels measured in this study.

These two studies have different strengths. Exposure assessment in the study by Storgaard *et al.*<sup>8</sup> is not optimal; it is based on recall of a distant exposure by the man's mother, and smoking is dichotomized (at 10 cigarettes/day). On the other hand, assessment of outcomes in this study is very detailed, including semen parameters, serum levels of sex hormones and sperm chromatin structure assay for sperm chromatin damage. The availability of parameters of both hormonal activity and semen quality allows the authors to consider several interesting alternative mechanisms of action. The exposure assessment by Duty *et al.*,<sup>9</sup> based on urinary biomarkers, is very sophisticated. However, their data on semen quality is more limited, with outcomes only presented dichotomously.

Taken together these two studies provide good (though not conclusive) evidence that environmental agents, even at low levels, can alter semen quality. Several other plausible agents are currently being investigated for their ability to alter male reproduction (organochlorine pesticides, bisphenol-A, triazines, etc.) and the number is likely to increase. Because these exposures are fairly ubiquitous, it is probable that subjects in both these studies have been exposed to low levels of multiple agents. The next challenge, teasing out the separate and combined effects of this "chemical soup," must be met before concluding that any specific exposure has altered semen quality, let alone caused a worldwide decline in semen quality.

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### About the Author

SHANNA H. SWAN is Research Professor in Family and Community Medicine at the University of Missouri-Columbia. She became intrigued by the question of declining sperm count while serving on the NAS Committee on Hormonally Active Agents in the Environment. She recently published results of a multicenter study showing poor semen quality in agricultural mid-Missouri compared with urban centers. She is now studying semen quality in relation to biomarkers of exposure to agricultural chemicals.

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