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COMMENTARY

Our environment and our gametes: what human ARTs can add to the discourse

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As the Gulf of Mexico oil spill continues to generate toxic metabolites, via the marine organisms whose ecosystem has been permanently tainted, there is little doubt that the true consequences of this latest environmental disaster will not be felt for many years to come. Species will be eliminated and the plant and animal survivors will bear the genetic scars of yet another case of humanity altering our planet. As Rachel Carson predicted in *Silent Spring*, over 50 years ago, the real victims of environmental change will be our gametes and embryos, rather than the somatic containers (bodies) that protect and counsel the basic processes of reproduction.

In the July issue of JARG, Perin and colleagues reported the somewhat disturbing finding that in Brazil, urban air pollution has reared its ugly head in the outcome measures of ARTs. The troubling patterns of infertility around the world resulting from environmental pollution are facts that can no longer be questioned. Instead, global efforts to identify and ameliorate the impact of environmental change on the fecundity of *Homo sapiens* have reached the top of the priority list for those countries that have acknowledged the enormity of the problem. Can human ARTs provide insights into the nature and extent of damage to our reproductive performance? In fields such as endocrine disruption, it is tacitly assumed that alterations in reproductive behavior and outcome are best evaluated from the animals that live in contaminated environments—so-called sentinel organisms. Of course laboratory studies on rodent models account for much of the research in this area as well, but the question of translational relevance to human biology remains a valid one. It is in the spirit of this dilemma that JARG draws attention to the legacy of Rachel Carson in two articles demonstrating the impact of Cadmium (Cd) toxicity on spermatogenesis.

The first paper, by Dr. Al-Azemi and colleagues, extends a rich history of research on the environment and reproduction in males, wherein the effects of Cd on decreased fertility have been attributed to an enhancement of apoptotic germ-cell loss in the testis. Using the rat as a model system, testicular damage due to Cd exposures was confirmed and the co-administration of Lithium (Li) (a commonly used antidepressant in humans) was shown to abrogate testicular damage. Most interesting was the finding that the same pathways used to eliminate selectively sperm-bearing DNA damage (due to aging, radiation, or chemotherapeutics), the so-called p53 trigger for apoptosis, are up-regulated in response to Cd exposure, but down-regulated upon co-treatment with Li. Besides providing insights into the mechanisms by which environmental toxins impair spermatogenesis in infertile men (note that the rat dosing was comparable to levels of exposure to which humans are subjected), this work opens the door for adjuvant treatments that may ameliorate the toxic effects of pollutants or cancer therapies.

Our second highlighted article comes from a group of investigators in New York State which, together, demonstrate the importance of converging public health and ART interests for the sake of advancing the human condition. Once again, the culprit is Cd. And once again, the issue is male factor. Combining sophisticated analyses of urinary or blood-borne Cd concentrations—thought to be reflective of normal dietary exposures—a link is discovered between

Capsule How our changing environment is impacting on the quality of gametes is discussed in the context of what outcome measures in human ARTs should be adding to debates on international trends in human fecundity.

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male blood levels and fertilization failure during IVF. Bloom et al., explain that while their data are preliminary in nature, amassing databases for environmental contaminants in populations that will be undergoing infertility treatments offers a telling glimpse into the impact of the environment on our gametes—a welcome byproduct of the treatments for infertility offered around the world. This is the kind of interaction that could go a long way in sorting out cause and effect when it comes to our environment and our gametes. The major finding of this study was in fact that, while Cd levels in males due to recent exposures were associated with decreased fertilization, this was not true for females bearing Cd levels in the same range. This clearly aims the sights of Cd toxicity on the impact of what are estimated to be levels maintained from days to weeks, well within the time frame for spermatogenesis in men. Distinctions in toxin sensitivity between male and female gametes are expected, given the gender-specific chronology of gametogenesis—and the precarious protracted existence of oocytes has typically raised suspicions having to do with the prolonged periods of exposure to which oocytes are subjected. But as shown here, relying on a stem-cell based mechanism for gamete production, as the testis does, by no means obviates the risks of environmental exposure, as both spermatogonia and later spermatogenic stages are likely targets of environmental contaminants.

While many of the causes of human infertility have a tractable origin, we remain ignorant of the cases attributed to "unknown." Making an educated guess as to the role of the environment in these cases simply will not do. Rather, human ARTs present an opportunity, through the coordinated efforts of testing agencies, epidemiologists, clinicians, and basic scientists, to bring our own reproductive health status to a tangible state of knowledge. Once in hand, such an effort will provide a powerful case for the management of health care, the mechanisms behind environmental toxicity, and the formation of a policy that will guide our understanding of the future of reproductive medicine.