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Study suggests father's environmental exposure affects sperm epigenetics

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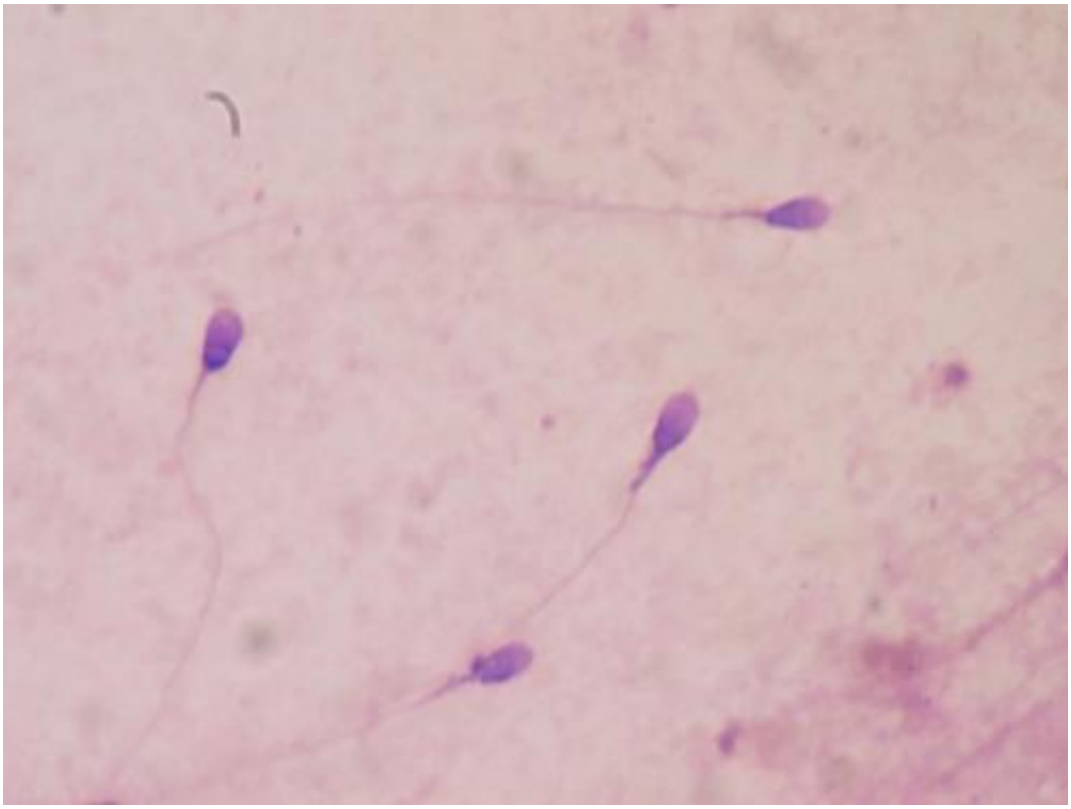

Human sperm stained for semen quality testing in the clinical laboratory. Credit: Bobjgalindo/Wikipedia

Early results from a larger, ongoing study led by environmental health scientist Richard Pilsner at the University of Massachusetts Amherst suggest that phthalate levels in expectant fathers have an effect on couples' reproductive success via epigenetic modifications of sperm

DNA.

Details appear in the current issue of *Human Reproduction*, a monthly journal of the European Society of Human Reproduction and Embryology published by Oxford Journals.

Phthalates are compounds found in plastics and personal care products such as shaving cream, and are estimated to be detectable in nearly 100 percent of the U.S. population. Exposure is known to disrupt some hormones and is associated in human studies with changes in such male reproductive measures as semen quality and androgen levels, Pilsner says.

The authors believe theirs is among the first human studies to investigate the influence of phthalate exposure on sperm epigenetics, embryo development and whether DNA methylation in sperm cells may be a path by which a father's environmental exposure influences these endpoints. DNA methylation, one mechanism of epigenetics, is a chemical tag on DNA that does not change the gene sequence but is involved in controlling gene expression.

Pilsner explains, "There has always been this heavy concern in the past with expectant moms not smoking and not drinking, for example, to protect the fetus. In this study, we see that dad's environmental health contributes to reproductive success. For sperm to mature is a 72-day process, almost three months, and our study shows that this preconception time-period may represent an important developmental window by which environmental exposures may influence sperm epigenetics, and in turn, early life development. So in the same way mom needs to be careful, dad also needs to."

Their new findings are from the first 48 couples in a study they hope will eventually reach 250. Pilsner's research team includes Ph.D. student and

first author Haotian "Howie" Wu, Dr. Cynthia Sites, director of the in vitro fertilization (IVF) clinic at Baystate Medical Center in nearby Springfield, and others at Wayne State University in Detroit. The work was supported by the National Institutes of Health.

The researchers recruited couples at the IVF clinic and took a single urine sample from the men on the same day they donated sperm. They measured 17 metabolites from 8 different phthalate parent compounds in that sample, then performed DNA methylation analyses on sperm cells to examine statistical associations.

Wu, who performed many of the analyses, explains that after receiving sperm cells from the IVF clinic, DNA was extracted and analyzed on a genomics system that examines approximately 485,000 sites for DNA methylation.

They identified 6,479 regions of interest in assessing a possible correlation between phthalate metabolite exposure and DNA methylation. Wu says, "Rather than looking for methylation changes at individual sites on the DNA, we looked at DNA regions or clusters on genes that might be more biologically meaningful than individual sites. It's not just numbers we were interested in. We wanted to pay attention not only to the statistical relationships, but also the biology."

Of the 6,479 regions examined, 131 were associated with at least one of the phthalate metabolites, he reports. Further, the researchers say that most of the phthalates that were associated with sperm DNA methylation were known or suspected to be anti-androgenic compounds, which means they can influence hormones.

He says, "The next step, after identifying associated regions, is to try to determine the possible biological meaning. We examined the biological pathways, or common links between genes, that might be affected in

these 131 regions that were identified." They found many of the 131 regions were related to genes involved in growth and development and cellular function and maintenance.

The authors were also interested to see if these phthalate-associated changes in sperm DNA methylation could affect early-life development. They found that some sperm DNA methylation regions were also associated with poor blastocyst stage of embryo quality as defined by the IVF clinic's standards related to embryo quality before transfer into the uterus of the female partner to establish a pregnancy, Pilsner says.

The researchers stress that these early results represent a small sample, and note that it is unclear from this study if these methylated changes are inherited and persist during prenatal and postnatal development. Wu adds, "We are finding interesting things and raising interesting questions, and we will certainly want to explore further.

Pilsner has recently received a multi-million dollar grant to replicate and validate the findings with a dose-dependent experiment in mice. He adds, "It doesn't surprise me that sperm carry some sort of environmental legacy to the next generation. What the sperm cell encounters during its development can influence these chemical tags or DNA methylated, and it may well have an effect on the developing embryo and offspring."

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