



## EDITORIALS

# Sperm counts, testicular cancers, and the environment

Disturbing trends in men's reproductive health demand urgent attention

Niels E Skakkebaek *professor of paediatric endocrinology and andrology*

Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Denmark

A recent meta-analysis by Levine and colleagues<sup>1</sup> showing significant declines in sperm counts among men in the Western world caught considerable media attention.<sup>2</sup> The Levine study followed a similar report in *The BMJ* 25 years ago.<sup>3</sup> Should we be concerned? Is male reproductive health really at risk?

Meta-analyses have some inherent limitations. However, an important and often overlooked point about data on the quality of semen is that trend data should be interpreted with a holistic view of male reproductive health problems, including parallel trends in testicular germ cell cancer (TGCC). Incidence of this cancer has risen substantially over the past few decades, particularly in young men.<sup>4</sup> Increases seem to be occurring even in countries that have had low incidence. TGCC is linked to risk of poor semen quality: reports suggest that countries with a high incidence of this cancer have generally lower semen quality and vice versa.<sup>5</sup>

Another good reason to pay special attention to the trends in testicular cancer is that registry data are considered to reflect true disease incidence. There are no large screening programmes that might skew incidence rates, as there are with cancers such as prostate. Importantly, strong clinical evidence exists that testicular cancer and spermatogenic disorders are biologically interrelated.<sup>6</sup> This relation seems to have a fetal origin—congenital cryptorchidism is a risk factor for both TGCC and poor semen quality.<sup>6,7</sup> One hypothesis is that these male reproductive disorders may be linked through a testicular dysgenesis syndrome,<sup>8,9</sup> also affecting the function of testosterone producing Leydig cells. The serum testosterone concentrations among healthy men in the US, Denmark, and Finland have shown noteworthy falls over recent decades.<sup>10,11</sup>

## Environmental influences

What could be causing such disturbing trends? The short answer is that we do not know. However, data suggesting that the incidence of testicular cancer has more than doubled in recent decades<sup>4</sup> leaves little doubt that we should look into environmental causes—including lifestyle effects. Alterations in our genome cannot explain the observations as changes have occurred over just a couple of generations.

Environmental exposures can come through food, water, skin, and work and home environments. Both wildlife research and

experimental studies suggest that modern lifestyles are associated with increased exposure to various endocrine disrupting chemicals such as pesticides that together may be harmful to wildlife and humans even though exposure to individual chemicals is low.<sup>12,13</sup> However, little has been done to explore their potential effects on semen quality and testicular cancer. In particular, studies of maternal exposures in pregnancy and the subsequent reproductive function of their sons are needed.

Should we be worried about our future ability to reproduce ourselves, as some media coverage has claimed?<sup>14</sup> This inconvenient question makes sense when we look at what is going on in fertility clinics all over the world—more and more children are now born after in vitro fertilisation, intracytoplasmic sperm injection, and insemination with partner or donor sperm.<sup>15</sup> However, despite increased use of assisted reproduction, fertility rates in many countries remain well below the replacement rate of an average of 2.1 children per woman. In many European countries, including Germany, Japan, and Singapore, fertility rates range between 1.0 and 1.5, and fertility has become important in political and economic debates.

In order to help future generations we must act now to prioritise new basic and clinical research programmes in reproductive medicine. Simple research questions urgently need answers. What is the role of exposure to endocrine disrupting chemicals in reproductive trends? What is the role of lifestyle factors, including recreational drugs? What is the role of dysgenesis of fetal testis caused by maternal exposures? Why is the incidence of testicular cancer increasing among young men of reproductive age?

Medical researchers cannot do it alone. We need health and research authorities that can see the urgent need for research in reproductive medicine, not just more infertility treatments, which are a short term solution for individuals not for the fertility of future generations. It's even possible that the use of intracytoplasmic sperm injection to overcome poor semen quality may be producing new generations with poor reproductive health.<sup>16</sup>

We have already waited too long. As *New York Times* columnist Nicholas Kristof recently wrote: "Our human future will only be as healthy as our sperm."<sup>17</sup>

Competing interests: I have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: Not commissioned; externally peer reviewed.

- 1 Levine H, Jørgensen N, Martino-Andrade A, et al. Temporal trends in sperm count: a systematic review and meta-regression analysis. *Hum Reprod Update* 2017 Jul 25. [Epub ahead of print.] doi:10.1093/humupd/dmx022
- 2 Walsh B. Male fertility crisis in US has experts baffled. *Newsweek* 2017 Sep 22. <http://www.newsweek.com/2017/09/22/male-infertility-crisis-experts-663074.html>
- 3 Carlsen E, Giwercman A, Keiding N, Skakkebaek NE. Evidence for decreasing quality of semen during past 50 years. *BMJ* 1992;359:609-13. doi:10.1136/bmj.305.6854.609 pmid:1393072.
- 4 Znaor A, Lortet-Tieulent J, Jemal A, Bray F. International variations and trends in testicular cancer incidence and mortality. *Eur Urol* 2014;359:1095-106. doi:10.1016/j.eururo.2013.11.004 pmid:24268506.
- 5 Serrano T, Chevrier C, Multigner L, Cordier S, Jégou B. International geographic correlation study of the prevalence of disorders of male reproductive health. *Hum Reprod* 2013;359:1974-86. doi:10.1093/humrep/det111 pmid:23670171.
- 6 Berthelsen JG. Andrological aspects of testicular cancer. *Int J Androl* 1984;359:451-83. doi:10.1111/j.1365-2605.1984.tb00804.x pmid:6526512.
- 7 Rajpert-De Meyts E, McGlynn KA, Okamoto K, Jewett MA, Bokemeyer C. Testicular germ cell tumours. *Lancet* 2016;359:1762-74. doi:10.1016/S0140-6736(15)00991-5 pmid:26651223.
- 8 Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum Reprod* 2001;359:972-8. doi:10.1093/humrep/16.5.972 pmid:11331648.
- 9 van den Driesche S, Kilcoyne KR, Wagner I, et al. Experimentally induced testicular dysgenesis syndrome originates in the masculinization programming window. *JCI Insight* 2017;359:e91204. doi:10.1172/jci.insight.91204 pmid:28352662.
- 10 Travison TG, Araujo AB, O'Donnell AB, Kupelian V, McKinlay JB. A population-level decline in serum testosterone levels in American men. *J Clin Endocrinol Metab* 2007;359:196-202. doi:10.1210/jc.2006-1375 pmid:17062768.
- 11 Perheentupa A, Mäkinen J, Laatikainen T, et al. A cohort effect on serum testosterone levels in Finnish men. *Eur J Endocrinol* 2013;359:227-33. doi:10.1530/EJE-12-0288 pmid:23161753.
- 12 WHO. *UNEP. State of the science of endocrine disrupting chemicals 2012: an assessment of the state of the science of endocrine disruptors prepared by a group of experts for the United Nations Environment Programme and World Health Organization*. WHO, 2013.
- 13 Hass U, Scholze M, Christiansen S, et al. Combined exposure to anti-androgens exacerbates disruption of sexual differentiation in the rat. *Environ Health Perspect* 2007;359(Suppl 1):122-8. doi:10.1289/ehp.9360 pmid:18174960.
- 14 Ghosh P. Sperm count drop "could make humans extinct." *BBC News* 2017 Jul 25. <http://www.bbc.com/news/health-40719743>
- 15 Calhaz-Jorge C, de Geyter C, Kupka MS, et al. European IVF-Monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 2012: results generated from European registers by ESHRE. *Hum Reprod* 2016;359:1638-52. doi:10.1093/humrep/dew151 pmid:27496943.
- 16 Belva F, Roelants M, De Schepper J, Van Steirteghem A, Tournaye H, Bonduelle M. Reproductive hormones of ICSI-conceived young adult men: the first results. *Hum Reprod* 2017;359:439-46. doi:10.1093/humrep/dew324 pmid:28007789.
- 17 Kristof N. Are your sperm in trouble? *New York Times* 2017 Mar 11. <https://www.nytimes.com/2017/03/11/opinion/sunday/are-your-sperm-in-trouble.html>

Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to <http://group.bmj.com/group/rights-licensing/permissions>