Chapter 42
Can spermatozoa be targets for drugs? If so, what are the consequences of such drug exposures?

Drugs that affect sperm structure or function; male-mediated developmental toxicity

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There are more than 100,000 chemicals in our environment. Men are exposed to chemicals in air, water, and food, in daily life, in occupational settings, and as drugs. Some of these chemicals do target spermatozoa (Chapter 41). Drugs and chemicals may have adverse effects on male germ cell numbers, decreasing production by blocking mitosis and/or meiosis or increasing cell death by inducing apoptosis, an active process by which cells commit suicide. Alternatively, chemicals may affect germ cell quality, without an accompanying effect on sperm counts. Chemicals may disturb the male germ cell genome, by mutating the DNA sequence itself, or altering the epigenome (Chapters 13-15). Finally, chemicals may be present in seminal fluid and thus have direct effects on fertilization and/or embryonic development. Effects on germ cell quality that are not repaired during spermatogenesis may decrease fertilizing ability or lead to post-fertilization adverse effects on progeny outcome. Such effects may include pregnancy loss or spontaneous abortion and birth defects, or effects manifested only later in life, such as childhood cancer, behavioral effects or learning deficits and metabolic syndrome. Paternally-mediated adverse effects on progeny may be transmitted to subsequent generations.

Male germ cells are engineered to fertilize an oocyte and to provide the paternal genome to the conceptus; chemicals that target male germ cells may decrease their fertilizing ability or induce post-fertilization adverse effects on progeny outcome. Adverse progeny outcomes include early or late pregnancy loss, preterm delivery or delivery of a small-for-gestational age infant, malformations, behavioral abnormalities, childhood cancer or later life onset effects, such as diabetes, breast cancer or Alzheimer disease. Animal studies

provide convincing evidence that paternal exposures to specific environmental or therapeutic agents do result in a higher incidence of adverse progeny outcomes. Treatment of male rats with cyclophosphamide, an anticancer and immunosuppressant drug, results in increased pre- and post-implantation loss as well as abnormal progeny. This drug induces sperm chromatin damage as well as epigenetic and telomere modifications, resulting in altered zygotic gene activation and a dysregulation of gene expression in the early embryo. A wide range of environmental chemicals (e.g., lead, dibromochloropropane, phthalates, bisphenols, polybrominated diphenylethers), drugs (e.g., cyclophosphamide), and lifestyle exposures (smoking, obesity) produce abnormal progeny outcomes after paternal exposure. One can deduce the stage specificity of the susceptibility of germ cells during spermatogenesis to damage based on the timing between toxicant exposure and the effect on offspring, (Chapter 9).

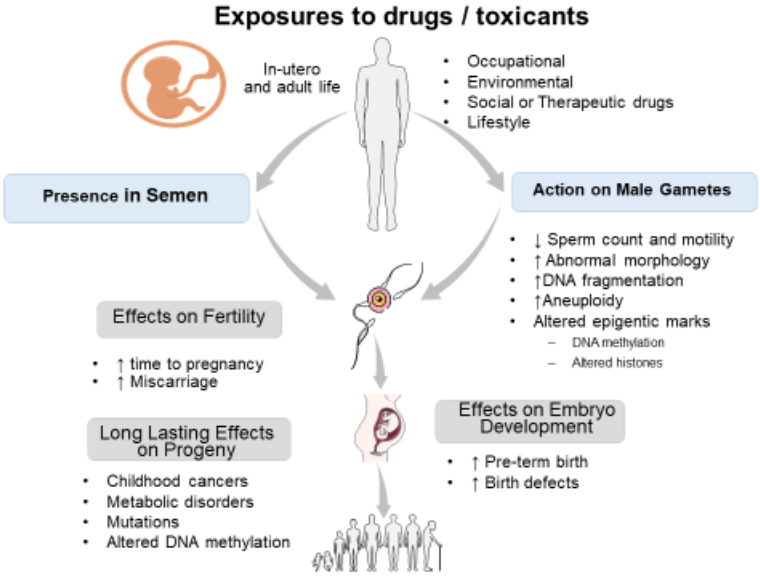

Figure 1. Paternal exposures may have an adverse impact on fertility and progeny outcome.

A number of epidemiological studies have reported that certain paternal occupations, e.g. as a welder, painter, auto mechanic, greenhouse worker or fireman, involving exposure to metals, combustion products, solvents, or pesticides, are associated with altered sperm quality and an increase in time to pregnancy, spontaneous abortions, birth defects, or childhood cancer. Therapeutic drug exposures may also be of concern with respect to progeny outcome. There is a high incidence of transient or permanent infertility after men are treated with anticancer drugs (Chapter 47). Lifestyle exposures, such as smoking, alcohol consumption and obesity, have been linked to decreased fertility and an increased incidence of some childhood cancers in progeny. The extent to which the sperm produced during recovery from chemotherapy are "normal" depends on the drug(s), doses and duration of treatment; this area of research deserves further investigation.

It is very difficult to associate a paternal exposure with a specific birth defect or childhood cancer. This is because there are relatively few studies and these are usually small, exposure assessment methods are frequently imprecise, and the outcomes are rare; thus, the lower limits of the confidence intervals surrounding the risk estimates are often less than half a unit away from the null value. Nevertheless, one should not automatically dismiss cause-and-effect relationships based on the study size. Interestingly, a clear association between drug exposure among fathers who preconceptionally took metformin for diabetes and birth defects in their male offspring, particularly genital birth defects was established in a recent large cohort study. However, other drugs, such as anxiolytics, were not found to have such effects on offspring.

It is of concern that the germ cell line of progeny may also be affected by paternal exposures, thus increasing the risk for subsequent generations (Chapter 16). Generally, the basic premise has been that the chemicals that are capable of affecting subsequent generations do so by inducing mutations in the germ cell genome. Studies with human populations and mice have provided evidence that paternal irradiation exposures result in elevated mutation rates in progeny. However, in recent years it has become evident that the male germ cell transmits more than its genome, as specified by DNA sequences, to the conceptus. In animal studies, there is a large gap between the generally low rate of genetic "damage" induced by many chemicals after the exposure of male germ cells and the associated adverse progeny outcomes. This gap has led to the

hypothesis that a key mechanism by which chemical perturbation of sperm may lead to heritable alterations in progeny is epigenetic, i.e. the alteration of DNA function without affecting the DNA sequence, (Chapter 13-15). Deregulation of the programming of the paternal genome may be responsible for altered expression of genes and impaired post-implantation development.

Future research is needed to elucidate the implications to public health of the finding in animal experiments that chemical exposures may have transgenerational effects. Nevertheless, there is already suggestive evidence from human studies indicating that this is possible. There are reports of altered sex ratios in children born after exposures to chemicals such as dioxins; one explanation for these observations could be an effect on the survival of Y bearing sperm. Defects in the DNA methylation of paternally imprinted genes may contribute to imprinting errors and diseases in children conceived with assisted reproductive techniques (ART) (Chapter 38).

It is apparent from both animal and epidemiological studies that there are paternal exposures to chemicals that result in abnormal progeny outcome. Men exposed to certain drugs, chemicals, and lifestyles should be made aware that there is concern with respect to an increased risk of adverse progeny outcome. Paternal counseling after exposures that are known to affect male germ cells should be highly encouraged. The development of a battery of new diagnostic tests to detect the effects of deleterious exposures on sperm chromatin and function should be a high priority.

Suggested reading

Anderson D, Brinkworth MH, editors. Male-mediated Developmental Toxicity. Issues in Toxicology. Cambridge (UK): RSC Publishing; 2007.

Beal MA, Yauk CL, Marchetti F. From sperm to offspring: Assessing the heritable genetic consequences of paternal smoking and potential public health impacts. Mutat Res Rev Mutat Res. 2017;773:26-50.

Buck Louis GM, Barr DB, Kannan K, Chen Z, Kim S, Sundaram R. Paternal exposures to environmental chemicals and time-to-pregnancy: overview of results from the LIFE study. Andrology. 2016;4(4):639-47.

Downey AM, Robaire B, Hales BF. Paternally Mediated Developmental Toxicity. In: McQueen CA, editor. Comprehensive Toxicology. 3rd ed. Oxford (UK): Elsevier Ltd; 2018. Vol. 5, pp. 100–117.

Gabrielsen JS, Tanrikut C. Chronic exposures and male fertility: the impacts of environment, diet, and drug use on spermatogenesis. Andrology. 2016;4(4):648-61.

Hales BF, Robaire B. The Male Germ Cell as a Target for Toxicants. In: McQueen CA, editor. Comprehensive Toxicology. 3rd ed. Oxford (UK): Elsevier Ltd; 2018. Vol 4, pp. 82-95.

O'Flaherty C, Hales BF, Chan P, Robaire B. Impact of chemotherapeutics and advanced testicular cancer or Hodgkin lymphoma on sperm deoxyribonucleic acid integrity. Fertil Steril. 2010;94(4):1374-9.

Robaire B, Delbes G, Head JA, Marlatt VL, Martyniuk CJ, Reynaud S, Trudeau VL, Mennigen JA. A cross-species comparative approach to assessing multi- and transgenerational effects of endocrine disrupting chemicals. Environ Res. 2022;204(Pt B):112063.

Sharma R, Biedenharn KR, Fedor JM, Agarwal A. Lifestyle factors and reproductive health: taking control of your fertility. Reprod Biol Endocrinol. 2013;11:66.

Shiau CY, Wang JD, Chen PC. Decreased fecundity among male lead workers. Occup Environ Med. 2004;61(11):915-23.

Wensink MJ, Lu Y, Tian L, Shaw GM, Rizzi S, Jensen TK, Mathiesen ER, Skakkebaek NE, Lindahl-Jacobsen R, Eisenberg ML. Preconception Antidiabetic Drugs in Men and Birth Defects in Offspring : A Nationwide Cohort Study. Ann Intern Med. 2022;175(5):665-73.