Brief Report

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Male infertility and environmental factors

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Abstract

Semen quality in men is decreasing. Numerous chemicals act as endocrine-disrupting agents and their detrimental effect on fertility and spermatogenesis has been shown in rodent studies. Consequences in humans are challenging to study and effects of fetal exposure on fertility are apparent only 2 decades later. Appropriate animal models are needed to study the reproductive effects of the thousands of chemicals that humans come in contact with. The burden of proof of chemical safety must shift from the individual and health care provider to the manufacturers similar to the licensing of medical drugs.

Key Words: Infertility, Fertility, Semen, Sperm, Endocrine-disrupting chemical, Antiandrogen, Testicular dysgenesis syndrome

There is clear evidence of decreasing semen quality during the past decades[1]. Whereas this finding appears to be rather consistent, the cause for this alarming change remains to be proven. Genetic factors, lifestyle, environmental exposures all affect semen quality and male fertility. The rate of the observed change in semen quality suggests that genetic factors alone are unlikely the explanation. Individual factors that have a significant negative effect on male fertility have been identified. Perhaps surprisingly, maternal smoking during pregnancy has been shown to be more detrimental to male offspring fertility than the individual's own smoking. This along with numerous other findings suggests that particularly antiandrogenic chemicals during the sensitive fetal masculinization window may result not only in reduced sperm count but also cryptorchidism and hypospadias. The entity of testicular dysgenesis syndrome (TDS) suggested by Skakkebaek and Sharpe comprises in addition to the undescended testis, hypospadias, decreased sperm count also increased incidence of testicular germ cell cancer. TDS is thought to originate via disturbed androgen action during sensitive fetal development[2].

Endocrine-disrupting chemicals (EDC) and their mechanism of action

Environmental EDC are exogenous chemical agents or mixtures of compounds that interfere with aspects of hormonal action(s) that ensure maintenance of homeostasis and regulation of normal growth and development. Classically the EDCs bind to the androgen or estrogen receptor triggering an agonist or antagonist action. These in turn lead to increased or decreased gene expression of sex-specific genes. In addition, EDCs act on steroidogenic enzymes and the metabolism of hormones, for example, inhibit the activity of 5-α reductase, which is the most important enzyme in the production of dihydrotestosterone and hence the regulation of the masculinization of the external genitalia and the prostate. Furthermore, P450 enzymes in the liver that metabolize steroid hormones may be affected. In animal models EDCs affect hormone receptor levels. In addtion to the effect on hormone action, animal experiments suggest that EDCs may also result in epigenetic changes and miRNA levels.

The long list of chemicals includes agents found in pesticides, metals, additives, and contaminants in food and personal care products (Table 1). EDCs can be transferred from the mother to the developing child through the placenta as well as breast milk. Epidemiological associations in human populations raised the suspicion that man-made chemicals could cause adverse effects on the fetus and male fertility.

Proving the direct causality of fetal EDC exposure and abnormal testicular function in humans is challenging. However, the causal relationship between EDC and disturbed masculinization has been shown in numerous rodent experiments. The effect of EDC exposure during early fetal development results in TDS-like features. A combination of EDCs results in a more severe phenotype.

Major challenges in estimating the real danger of EDC to male fertility in reality exist. The delay of at least 2 decades between the fetal exposure and the measurable effect on semen quality make the estimation and rate of change of this phenomenon difficult. Validated early markers of androgen action, for example, anogenital distance (AGD) are needed. As there are thousands of new chemical brought into use each year, understanding the clinical importance of each one presents a further challenge.

Masculinization programming window (MPW)

The timing of the EDC exposure appears to be of clear importance in men, even if a strict MPW cannot be identified as is the case in rodent studies. Whereas the exposure to EDCs prior to puberty can lead to adult disease and dysfunction, the fetal developmental period is of paramount importance and animal studies suggest that

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Table 1

Major environmental disrupting chemicals, sources and effects observed on male reproductive health including human and animal studies on adult and developmental exposure.

		Reported Male Reproductive Health Effects	
EDC	**Sources**	**During Adulhood**	**During Development**
Chlorinated hydrocarbons			
Dioxins/furans	By-products of the manufacture and burning of products that contain chlorine	Transgenerational epigenetic reproductive disorders	Reproductive tract malformations Reduced fertility
Polychlorinated biphenols (PCBs)	Industrial insulators and lubricants, accumulate in the food chain	Reduced fertility, impaired sperm DNA integrity	Reduced fertility
Disinfection by-products	Chemical disinfectants (often chlorine) react with natural organic matter, hundreds of compounds	Sperm and embryo toxicity	Fetal growth retardation
Ethylene oxide	Chemical sterilizer used in medical practices and devices	Decreased semen quality	
Glycol ethers	Paints, enamels, varnishes, thinners, wood stains, printing inks, electronics industry, leather, cosmetics	Decreased semen quality/fertility	
Nonylphenol	Surfactants, pesticides, paints, plasticizers	Reduced semen quality	Decreased semen quality, decreased
Octylphenol	Exposure primarily from drinking water		Testicular size, hormonal changes, altered puberty onset
Perfluoronated compounds (PFOS, PFOA)	Water-repellant treatment of fabrics and carpets, nonstick-coating for cooking pans, insecticides, food wraps, floor polish	Inconsistent findings on semen quality	Hormonal changes reduced semen quality PFO
Metals			
Cadmium	Batteries, pigments, metal coatings, plastics	Damaging to spermatogenesis, damaging to Sertoli cells	Damaging to Sertoli cells and testicular development
Lead	Batteries, ammunition, metal products, lead-based paint in older homes common source of exposure	Reduced spermatogenesis, abnormal spermatozoa, hormonal changes, fetal loss	Altered puberty onset
Manganese	Pesticides, fertilizers, gasoline additive, dietary supplements, production of batteries		
Mercury	Thermometers, dentals fillings, batteries, industries emission contaminates air and water—accumulates in the food chain	Damaging to spermatogenesis	
Pesticides	Insecticides, fungicides, herbicides and rodenticides in industrial, agricultural, and residential setting, exposure through food, drinking water, inhalation, and skin	Decreased semen quality, sperm chromosome abnomalities	Altered sex ratio, malformation of reproductive tracts, altered puberty onset
Phthalates	Plasticizers to soften plastic, cosmetics, toys, pharmaceutical, medical devices, lubricants	Decreased semen quality	Decreased semen quality malformation of the reproductive tracts
Polybrominated diphenyl ethers (PBDEs)	Flame retardants in furniture, matresses, textiles, computers and electronics	Decreased semen quality	
Solvents (organic): benzene, toluene, xylene, styrene, etc.	Plastics, resins, rubbers, synthetic fibers, lubricants, dyes, detergents, drugs, pesticides, glues, paints, thinners, food containers,cleaning products, exposure mainly through respiration	Decreased semen quality, hormonal changes	
Tobacco smoke	Active as well as passive smoking, hundreds of components	Decreased semen quality	Decreased semen quality

EDC indicates endocrine-disrupting chemical.

Modified and updated from Mortimer et al[3]. Adapted from Woodruff et al[4]. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

gestational weeks 8–14 in humans may be crucial for appropriate fetal testicular development and adult function.

AGD appears to give a reliable lifelong read out of androgen exposure within the ever important MPW and is a relatively sensitive marker of antiandrogen exposure. Androgenic environment during the early fetal life exerts a fundamental influence on AGD and sperm counts in both humans and in rodents. AGD is routinely used in animal toxicology for antiandrogen exposure.

AGD has been shown to be associated with sperm concentration, total count, motility, total motile count, and morphology. Furthermore, an AGD below the median is associated with a significantly increased risk for low sperm count[5].

The cost of EDC exposure

The effect of EDC on male reproductive disorders comes at a high cost. In Denmark 8% of children are born following assisted reproductive technologies and 4% after intracytoplasmic sperm injection. Effects of phthalates on male fertility alone are estimated to result in 618,000 additional ART procedures with an annual cost of approximately 4.7 billion euros. Significant additional costs from polybrominated diphenyl ether causing 4615 cases of cryptorchidism (130 million euros) and PBDEs exposure resulting in 6830 cases of testicular cancer (annual cost 848 million euros)[6].

Challenges of studying the effect of EDCS on reproduction

It is obvious that experimental studies in humans are not possible. The potential consequences of developmental exposure of EDCs are difficult to study. Therefore finding suitable animal models is of importance. Consequences of dramatic accidents involving chemicals may be studied carefully in addition to cross-sectional epidemiological studies. Fertility effects following any exposure will become apparent after a delay of about 2 decades. Experiments may evaluate 1–3 chemicals—in reality a mixture of hundreds of chemicals is at effect. Even if relevant doses are applied in animal studies significant cross species differences may exist.

Conclusions

The majority of human studies suggests an association between exposure to EDC and disruption of the male reproductive system causing decreased fertility and infertility. The "no adverse effect levels" concept is challenged by the findings of exposure by a combination of chemicals. The undisputed relationship between EDC and male infertility remains to be established in humans, of particular urgency is which chemicals cause decrease in semen quality and perhaps TDS.

It has become clear that preventing exposure to EDCs should be a priority for all health professionals with the goal of ensuring global equity and health for all. The burden of proof of chemical safety must shift from the individual and health care provider to the manufacturers similar to the licensing of medical drugs. Policies must be put in place to protect all vulnerable populations present and future.

Conflict of interest statement

The author declares that there is no financial conflict of interest with regard to the content of this report.

References

[1] Levine H, Jorgensen N, Martino-Andrade A, *et al*. Temporal trends in sperm count: a systematic review and meta-regression analysis. Hum Repro Update 2017;23:646–59.
[2] Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Hum Repro 2001;16:972–8.
[3] Mortimer D, Barratt CLR, Björndahl L, *et al*. What should it take to describe a substance or product as "sperm-safe". Hum Repro Update 2013;19(suppl 1):i1–48.
[4] Woodruff TJ, Carlson A, Schwartz JM, *et al*. Proceedings of the summit on environmental challenges to reproductive health and fertility: executive summary. Fertil Steril 2008;89:281–300.
[5] Thankamony A, Pasterski V, Ong KK, *et al*. Anogenital distance as a marker of androgen exposure in humans. Andrology 2016;4:616–25.
[6] Hauser R, Skakkebaek NE, Hass U, *et al*. Male reproductive disorders, diseases, and costs of exposure to endocrine-disrupting chemicals in the European Union. J Clin Endocrinol Metabol 2015;100:1267–77.