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Environmental influences on male reproduction

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Summary

Considerable concern has been raised in recent publications that oestrogen-like compounds in either food or the environment cause adverse effects on reproductive health. There is clear evidence that reproductive disruption in wildlife may be caused by environmental pollutants and more specifically by endocrine-disrupting compounds. The increase in the incidence of disorders of the male reproductive tract (e.g. testicular cancer, cryptorchidism, hypospadias) and the possible decline of sperm quality led to the hypothesis in 1993 that the reported increases stem from fetal or neonatal exposure of the developing male to oestrogens. Cryptorchidism, hypospadias, testicular cancer and poor semen quality have also been proposed to be symptoms of one underlying cause, the testicular dysgenesis syndrome, which may develop during fetal life under the influence of environmental factors. However, there is only circumstantial evidence in humans that exposure to endocrine disrupters, especially diethylstilbestrol, during pregnancy causes problems of reproductive health. Oestrogen-like effects have been reported for a variety of naturally occurring oestrogens (so-called phytoestrogens) and for numerous synthetic compounds. The critical issue is whether there are sufficiently high levels of endocrine disrupters in the ambient environment to exert adverse health effects on the general population.

Introduction

Reproductive functions in most species are under the control of the endocrine system. Colborn [1] described in detail the possible threat from environmental pseudo-oestrogens on reproductive function in wildlife, e.g. the small penises of alligators in Lake Apopka, Florida, decreasing sperm quality in panthers, the decreasing number of bald eagles, behavioural changes in seagulls (e.g. supranormal clutch size and female-female pairing) and pseudo-hermaphroditism in fish. Chemicals in the environment that mimic or block endogenous hormones might disturb the fine balance of the endocrine system [2]. The potential implications for human health and for numerous other species are obvious. Endocrine disruption is thus of growing public health and environmental concern. From the perspective of human pathology, the environmental endocrine hypothesis might be the most significant environmental health hypothesis. Much of the emphasis of research has been on changes in male reproductive health.

The incidence of testicular cancer has increased in almost all countries which have reliable cancer registers. There is circumstantial evidence for a decline in sperm counts, and there are indications that the incidence of cryptorchidism and hypospadias is increasing.

There is controversy about whether oestrogens in the environment would cause significant male reproductive disorders. Exposure to endocrine-disrupting compounds is almost entirely through the diet, particularly milk and other dairy products, fish and meat, and fruit and vegetables. Furthermore, there is industrial exposure to, e.g. dioxins in workers producing phenoxy herbicides and chlorophenols, in subjects exposed in the industrial accident in Seveso and in subjects exposed during herbicide application [3].

Hypothesis

The increasing incidence of reproductive abnormalities in the male may be related to increased oestrogen exposure *in utero* [4], disrupting the development of the testis and the rest of the male reproductive tract (Fig. 1). Regression of the Müllerian ducts, and the development and descent of the testes into the scrotum occur during fetal life. Increased exposure to oestrogens may suppress FSH secretion by the fetal pituitary gland, which subsequently reduces the multiplication of Sertoli cells and the secretion of Müllerian inhibiting substance (MIS), which causes regression of the Müllerian ducts. Persistence of these ducts is usually associated with impaired testicular descent (cryptorchidism). MIS may also be responsible for suppressing the multiplication of germ cells during fetal life. Masculinization of the male reproductive tract, via effects on the Wolffian ducts and external genitalia, and the second phase of testicular descent is achieved by testosterone production in the Leydig cells. Exposure to oestrogen could also compromise testosterone production, leading to hypospadias. Thus abnormal

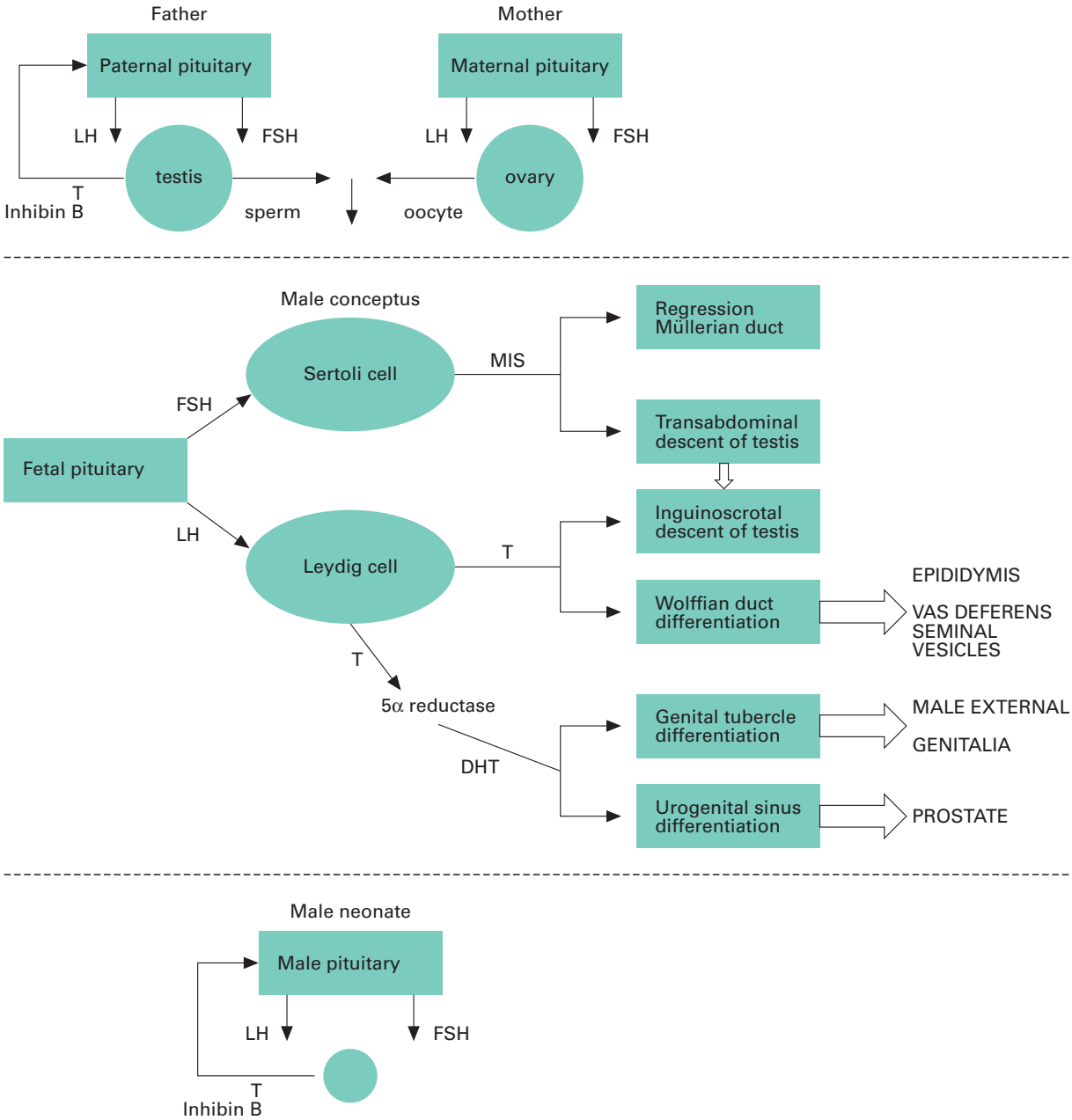

Fig. 1. A schematic representation of male reproductive function and development. T = testosterone.

development of the Sertoli and germ cells may lead to abnormal sperm production and/or infertility. The latter findings may also be caused by cryptorchidism itself.

Recently, it was proposed that poor semen quality, cryptorchidism, hypospadias and testicular cancer are symptoms of one underlying entity, the testicular dysgenesis syndrome (TDS) [5]. TDS may be caused by genetic or environmental factors, or both. Even though clinically the symptoms appear postnatally, the cause might be irreversible testicular dysgenesis during early fetal development. TDS may arise through disturbed Sertoli cell function, causing impaired germ cell differentiation and eventually reduced semen quality, carcinoma *in situ* and testicular cancer. TDS is also accompanied by decreased Leydig cell function, causing androgen insufficiency, and leading to hypospadias and cryptorchidism. Skakkebæk *et al.* [4] proposed that the presence of symptoms may vary with the severity of the syndrome.

Despite this hypothesis it is apparent that, as depicted in Fig. 1, adults of both sexes are also affected by

endocrine disrupters [6]. Much of the knowledge of the action of endocrine disrupters in adult humans is derived from the use of various steroids as pharmacological agents.

Endocrine disrupters

In recent years there has been increasing concern about the potential of substances in the environment to disrupt endocrine systems in humans and wildlife. The primary emphasis to date has been on substances which might mimic oestrogen activity and can interfere with the normal functioning of the endocrine system.

The list of chemicals that are known to affect reproduction in humans via endocrine mechanisms include pesticides (DDT and its metabolites), polychlorinated biphenyls, dioxins, naturally occurring plant oestrogens (phytoestrogens), and mycotoxins. Several other chemicals (e.g. alkylphenols, phthalates and bisphenol A) have been shown to interfere with some endocrine-mediated processes, but evidence for effects on reproductive functions *in vivo* is lacking. Current methods for assessing human and wildlife health effects are generally targeted at detecting effects rather than mechanisms, and may not adequately evaluate effects on the endocrine system.

Hypospadias

There is some evidence for an increase in hypospadias rates during the last few decades [6,7]. Several explanations have been proposed, including increased exposure to endocrine disrupters during fetal life [4]. As published hypospadias rates are exclusively derived from birth-defect registries, artefacts in case ascertainment in these registers may account for the reported changes over time. The existing registries rely on the completeness of detection and reporting by doctors. Differences in case ascertainment may introduce variations in reported hypospadias rates, but the extent of confounding by these differences is unknown. Moreover, assumptions are made about the number of reference subjects, who are not all examined for the anomaly. Hospital registry data have been shown to be unreliable [5].

Dolk [8] recently discussed the possibility that the rise in hypospadias is caused by an increasing tendency to report minor hypospadias. This hypothesis is difficult to prove, as very few studies report the total distribution of cases by severity. As an example, the often cited increase in hypospadias rates in the USA is hampered by the lack of information on severity in most cases (63%) [6]. As shown in Fig. 1, the development of male external genitalia depends on normal androgen action. Defects in the production of DHT or androgen insensitivity result in hypospadias.

Cryptorchidism

There are also indications that cryptorchidism may have increased in incidence in several countries [9] but in general cryptorchidism is registered more unreliably than is hypospadias. The reported values are 4–42 per 10 000 births. In England, the incidence of cryptorchidism increased by >60% between the 1950s and 1980s. Also, this anomaly is regarded as being associated with exposure to endocrine disrupters *in utero*.

Transinguinal descent of the testes also depends on androgens [10] but disrupted androgen action can only explain a very small proportion of cases with cryptorchidism. In mice it has been shown that the formation of the gubernaculum, which is necessary for testicular descent, depends on insulin-like factor 3 (Insl 3) and its deletion causes cryptorchidism [11].

In male mice, fetal exposure to 17α-ethinyl oestradiol (17-EE) results in an increased incidence of cryptorchidism [12], azoospermia, atrophy of seminiferous tubules, and altered Sertoli and Leydig cell differentiation [13]. In all these studies the mothers were exposed to high concentrations of 17-EE. Recently, the administration of very low doses prenatally to mice resulted in an increased prostate weight by 5 months of age and reduced daily sperm production during adolescence [14]. However, other studies were unable to repeat the finding of an increased prostate weight. Neonatal exposure to DES in male rats caused major developmental abnormalities of the testis, epididymis, vas deferens, seminal vesicles and prostate, when evaluated at the time of normal onset of puberty [15].

Testicular cancer

The most convincing evidence for a general decline in male reproductive health in humans is the increase in testicular cancer noted in the recent past in several Western countries [16–19]. Both cryptorchidism and hypospadias are associated with an increased risk of testicular cancer, based on the observation that men with cryptorchidism and/or hypospadias are over-represented among patients with testicular cancer.

The hypothesis that endocrine disruption can cause cancer in humans is based on the association between DES exposure of pregnant women and clear cell adenocarcinoma of the vagina and cervix in their female offspring. Some of the male offspring of women who took DES show pseudohermaphroditism [20] and genital malformations, including epididymal cysts, small

testes, microphallus and reduced semen quality [21–23]. Follow-up surveys of DES-exposed male offspring have shown no impairment in fertility or sexual function [24,25], or evidence of an increased risk of testicular cancer [24]. Dysgenic testes have a very high risk of developing testicular cancer in adulthood; these cancers seem to arise from premalignant gonocytes or carcinoma *in situ* cells.

Declining sperm quality

The possible decline in human semen quality has become a major issue of concern within the last decade. The decline in sperm count and/or sperm concentration, decrease of sperm motility and an increase in morphologically abnormal cells have been described as major factors for defining the impairment of semen quality. There is good evidence for positive associations between semen characteristics and the likelihood of achieving a pregnancy. However, the possible decline in semen quality has not yet resulted in reports of any reduction in male fertility. Moreover, as shown in Fig. 2, the outcome of the different studies is not unequivocally a decrease in sperm [26–40]. This makes it even more difficult to find a cause/effect relationship between decreasing sperm quality and the hypothesized exposure of pregnant women and their male offspring to hormone disrupters, and especially environmental oestrogens. The most commonly used variables in the various reports are sperm concentration (equivalent to sperm density, millions/mL), and total sperm count per ejaculate (millions/ejaculate).

The assessment of sperm morphology has changed over the years; currently $>70\%$ of the spermatozoa have to be abnormal for the indication 'teratozoospermia' (abnormal morphology), but even this value has been considered to be too low. Some laboratories consider samples with 86% abnormal spermatozoa to be 'normal'. The cause for the rapid lowering of the threshold value of 'normal-abnormal' is not the deterioration of sperm quality, but the method of evaluating sperm morphology. Moreover, even the WHO manual for examining human semen and semen–cervical mucus interaction gives no unequivocal description of normal morphology.

The variability in a man's semen characteristics may be considerable, possibly through several factors, e.g. the period of abstinence, recent and present disease, use of certain medication, drug and alcohol abuse, and the circumstances under which the sample is produced [41]. In addition to the well-known fluctuations of semen quality, the methods of assessment also have many limitations and inherent errors. These inadequacies are augmented by the different methods still being used to count sperm cells. Although the WHO has made recommendations to standardize the procedures for analysing human sperm, these have not been generally applied. In an external quality-control programme, the semen analysis showed wide between-laboratory variation in both the sperm concentration and morphology assessments.

The comparability of publications reporting declining sperm quality is limited because they comprise different populations (infertile men, sperm donors with or without known fertility, and men cryopreserving sperm before vasectomy) in different countries. None of these populations can be regarded as representative of the normal population.

Also, there are many complicating factors, most of which are not addressed in studies on sperm quality (Table 1), but that can have an effect on sperm quality. Some of these factors may even be considered as 'environmental'.

Various illnesses may affect semen characteristics; fever can even lead to azoospermia. A moderate increase in the scrotal temperature may have deleterious effects on spermatogenesis, leading to severe decreases in sperm concentration. The increase in scrotal temperature caused by wearing tight underwear, taking hot baths or a sauna has been associated with a decrease in sperm concentration [42]. The presence of a varicocele may lead to an impairment of scrotal temperature regulation. Whilst cooling of the scrotum is normally best when a man is walking or standing, in men with a varicocele the scrotal temperature is increased in these conditions.

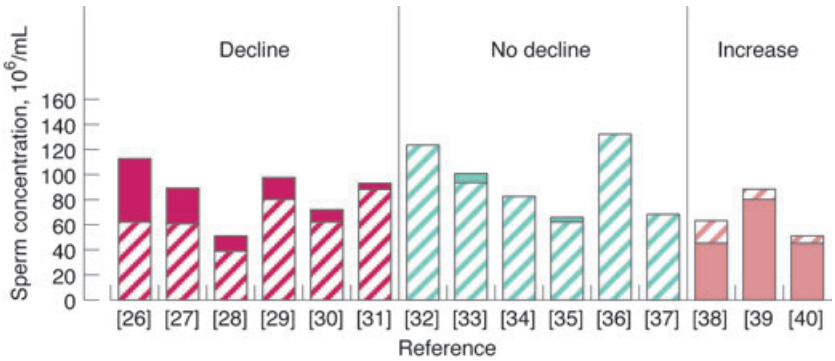

Fig. 2. Studies on sperm concentration published since 1992. The hatched areas show sperm concentration after decline, no decline and increase, respectively.

Table 1 A summary of factors that may affect sperm quality

Factor/Details
Methodology of sperm analysis
Lack of standardization of sperm collection
Lack of standardization of laboratory procedures
Complicating factors
Season of sampling
Lifestyle
Profession
Diseases
Medication
Stress
Age
Trends
Higher prevalence of varicoceles associated with increased body height
Changes in lifestyle
Environmental changes
Changes in occupational activities
Fluctuations over the year
Seasonal changes
Influence of geography
Ethnicity
Fertility status
Influence of study population
Changes in composition of the population visiting fertility (related) clinics
Region of habitation

Some therapeutic drugs, e.g. sulphasalazine and cytostatic drugs, are known to have direct side-effects causing infertility. Smoking, alcohol abuse, drug abuse (anabolics), and both physical (especially endurance training) and psychological stress have a negative effect on spermatogenesis. Acute stress resulting from an earthquake reduced sperm concentration and motility in one study.

Geographical differences in sperm quality

The sperm count may vary among different geographical locations. Variations in sperm counts have been described between different states in the USA (with values from New York being the highest [43]) and in Europe [44,45]. A meta-analysis of 61 studies [26] created considerable debate. The question that remains unanswered is whether data on sperm quality may be analysed and compared, in view of the numerous complicating factors that contribute to sperm quality. There is doubt whether the decline in sperm quality can be explained by environmental factors. Indeed, environmental exposure to endocrine disrupters has increased over the last decades, but it is impossible to conclude that a decline in sperm concentration, if any, can be attributed to environmental factors.

Policy

In 1996 the USA Environmental Protection Agency identified endocrine disruption as an environmental health problem. In 1999 the European Commission began the implementation of the Community strategy for endocrine disrupters. During 2000, a candidate list of 553 man-made substances and nine synthetic/natural hormones were identified. The Commission and Member States continue to participate in the Endocrine Disrupter Testing and Assessment Task Force, which was set up in 1998 with the goal of developing agreed test methods for endocrine disrupters.

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Abbreviations: **MIS**, Müllerian inhibiting substance; **TDS**, testicular dysgenesis syndrome; **Insl 3**, insulin-like factor 3; **17-EE**, 17α-ethinyl oestradiol.