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Male Reproductive Health

Its impacts in relation to general wellbeing and low European fertility rates

Contents

Foreword

Research in the area of male reproductive health has in the past focused mainly on birth control and family planning in non-developing countries, contraception, and sexually transmitted diseases such as HIV. Only little attention has been paid to male reproductive health disorders that lead to impaired fertility resulting in lower birth rates especially in industrialised countries. There is therefore an urgent need for better understanding the status of male reproductive health, especially in Europe and in industrialised countries where lifestyle and environmental factors may have a negative impact.

This Science Policy Briefing is the first to highlight this important issue which could have a dramatic impact on future birth rates and demographic changes in industrialised countries. It summarises the various exogenous and endogenous factors which can have an impact on male reproductive health and provides policy advice to national and European funding institutions.

The report was developed by a group of leading European experts. The issue was first raised by Professor Niels E. Skakkebæk during a mini symposium organised at the European Medical Research Councils (EMRC) plenary meeting in Strasbourg in April 2009. A first strategic meeting was held in Copenhagen on 20 May 2009 and the report was then written and finalised by the high level expert group present at this meeting.

This paper aims to increase awareness about the major consequences that reduced male reproductive health can have. It also provides advice on where and how to strengthen research in this area. Male reproductive health has been a low priority for funding agencies in European countries over the last 25 years. This has led to a lack of continuity in funding and a large translational gap between basic scientists and clinicians working with European patients.

The main policy recommendations are as follows:

- Increase awareness of male reproductive health issues
- Strengthen interdisciplinary, translational research in the area of male reproductive health issues
- Implement long-term, epidemiological studies aimed at better understanding the causes and effects of male reproductive disorders
- Target research efforts at preventing/minimising the occurrence of disorders rather than developing drug treatments.

Recommended funding instruments are transdisciplinary research networks which should be implemented at the European and international level to strengthen this highly important research area for the benefit of society.

We would like to thank the members of the high level expert group for their excellent work.

Professor Marja Makarow, ESF Chief Executive
Professor Liselotte Højgaard, EMRC Chair

Introduction

In most European countries fertility rates have declined drastically to below replacement level – the level at which the rate of new births can replace a population (1,2). This decline is primarily due to changes in social and economic conditions, such as wider use of contraception and more women seeking careers and postponing childbirth (1). However, declining fertility rates may also partly result from a decreased ability to conceive. In Europe there is a growing demand for use of assisted reproduction techniques (ART; 3,4), and a growing body of evidence points towards adverse trends in male reproductive health, including reduced semen quality, increased incidence of testicular cancer and increased or an already high incidence of congenital reproductive malformations (cryptorchidism and hypospadias; 5). It is to be expected that poor semen quality in young men, when combined with the high prevalence of increased age at attempting for pregnancy in women (when fertility is already declining), will lead to increased fertility problems in couples and its attendant socio-economic impacts.

Other than cancers, reproductive problems in men are generally not life-threatening, but in the last five years there has been a growing recognition that male reproductive function and risk of cardiometabolic disorders, including abdominal obesity, type 2 diabetes and hypertension are interlinked, as late-onset hypogonadism (low/subnormal testosterone levels) in men is an important determinant and/or consequence of these disorders (6,7). Moreover, the (normal) age-related decline in testosterone levels in men (8) clearly predisposes to such disorders with broad effects on wellbeing and mortality (7,9). Estimates of the incidence of hypogonadism vary from ~10% (10) to nearer 40% in men >45 years (11). The European-wide increase in the proportion of the male population that are of older age

thus carries with it the prospect of an increasing proportion of men with hypogonadism, and thus a progressive increase in prevalence of cardiometabolic disorders in the male population, irrespective of any change in diet and exercise. However, perhaps more worrying is the evidence that these problems may also be emerging in much younger men. Thus, large studies in both Europe and the US document a trend for declining testosterone levels in men (of any age) according to more recent year of birth (12,13), and have shown a clear negative correlation between visceral fat levels and lower testosterone levels (14). At present, it is not clear to what extent it is abdominal obesity that is causing lower testosterone levels and to what extent it is the other way around. The most likely scenario, especially in relation to aging, is that it is a 'vicious circle'. Thus, more research is needed to better understand these mechanisms.

Based on the issues described above, there are cogent reasons for concern about the remarkably poor state of male reproductive health across Europe. Not only does this have implications for population maintenance and replacement, but it also augurs for more pervasive and more life-threatening changes in men's cardiometabolic health, a change that may not just be restricted to the aging population. These changes pose huge financial and healthcare issues for European governments. There is therefore an urgent need for implementation of a common research strategy to better understand the status of male reproductive health in Europe and the causes of its problems and its inter-relations with wider health issues. This is the focus of this report.

Issues and challenges

Declining semen quality

Semen quality has been declining throughout the past half century in industrialised countries (15,16). Studies indicate a significant ~50% decrease in semen quality in men without fertility problems (dropping sperm counts from 113×10^6/ml to 66×10^6/ml; 15). There has been a lot of discussion about these results and different attempts to reanalyse the data within the scientific community (16-18; Figs. 1 and 2). Nevertheless, the question of temporal changes in semen quality still remains controversial, and there are reports of unchanged or even increasing semen quality in some regions (17). However, recent prospective investigations have, in accordance with the reported adverse trend, found a remarkably poor semen quality among young men from general populations in Northern Europe (18,19). Approximately 20% of young men in various European countries had a sperm concentration below the lower WHO reference level ($<20\text{x}10^6$ sperm/ml) and 40% of the men had a sperm concentration below the level that has been associated with prolongation of the waiting time to pregnancy ($40\text{x}10^6$/ml; 20). These trends in semen quality may also have wider implications for health in general, as men with poor semen quality seem to have increased mortality rates and shorter life expectancy (21).

Worldwide studies of fertile men using standardised protocols have shown significant regional differences in semen quality (22-24). Finnish (Turku) men have a 35% higher sperm concentration than do Danish men, while Scottish and French men have sperm counts in between these extremes (22). Similar regional differences in semen quality were found between fertile men from different US cities (23). Japanese fertile men had a sperm concentration at the same low level as Danish men (24) and men from Singapore had even lower concentrations (25). The reasons for these significant geographical differences in semen quality are largely unknown and should be further examined. Similar regional differences in other disorders of the male reproductive system have been observed, including testicular germ cell cancer (TGC) and congenital malformations of the male reproductive tract (5).

One reason for discrepancies in the results of semen quality studies could be insufficient quality management systems in different geographic areas which may affect the validity of the results. To assure comparability of

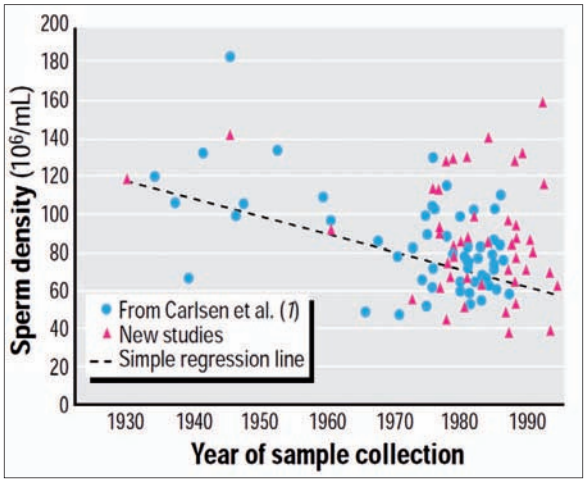

Figure 1. Mean sperm density in 101 studies published between 1934 and 1996 and simple regression line (from ref. 16).

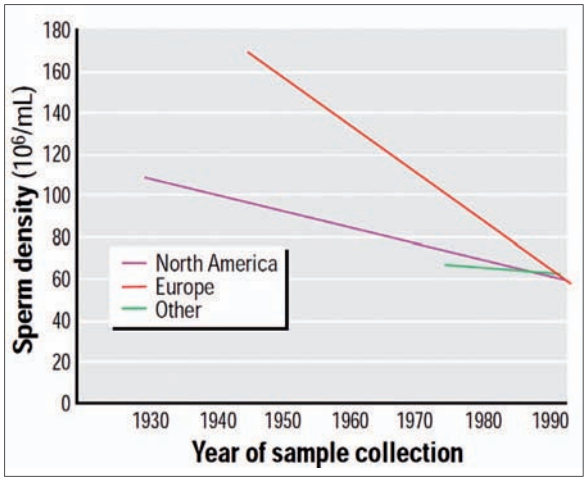

Figure 2. Interactive regression model for mean sperm density by year and geographic region after controlling for proven fertility (from ref. 16).

all endpoints of semen analysis, the WHO Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction provides a basis for global standards. To verify high standards, quality management systems for semen analysis have been implemented by various Andrology Societies in several European countries (e.g. QuaDeGA, Germany; UK NEQAS Andrology; EQA programme, ESHRE). These quality control systems have been running successfully for years and provide a good basis and training for all participants to harmonise and maintain a high standard of analysis. It will be important for the field to maintain quality control programmes and to extend these schemes throughout Europe.

Testicular germ cell cancer (TGC)

TGC is the commonest cancer in young men in many countries. It is well documented to be associated with impaired semen quality (26) and lower fertility rates, even prior to development of the cancer (27). The incidence of TGC has been increasing over the past 40 to 50 years in the majority of industrialised countries (28-30; Fig. 3) coincident with the declining trend in semen quality. The aetiology of TGC is unknown, but there is abundant evidence that cancer *in situ* of the testis, which is a precursor for TGC, is generated during fetal development and TGC therefore has a prenatal origin (31,32). The regional differences in TGC incidence in Europe follow the same pattern as observed for semen quality, as semen quality in high-risk TGC areas is lower than in low-risk TGC areas (33). As an example, studies in Denmark and Finland indicate that the age-standardised incidence rates of TGC in 1995 were 15.4 per 10^5 and 3.1 per 10^5, respectively, following the pattern of lower semen quality among Danish men compared to Finnish men. These studies have to be expanded at European level to better understand these results.

Congenital malformations (see also TDS section below)

Cryptorchidism (undescended testis) and hypospadias (incomplete fusion of the urethral folds that form the penis) are among the most common congenital malformations in human males. These two congenital abnormalities share common risk factors (34,35) and are both associated with reduced fertility (36,37). Cryptorchidism is also associated with poor semen quality (36) and a considerably increased risk of TGC (38). The incidence of these malformations appears to have been increasing in the Western world over recent decades, with an apparent levelling off in hypospadias incidence in most European countries during the 1980s (39). At present there is only a limited number of studies available. Recent prospective, cohort studies in Denmark and in the UK indicate that the incidence of cryptorchidism at birth may be far higher than had been supposed (40,41) although a much lower incidence was found in Finland. A similar difference in the incidence of hypospadias was also found between Denmark and Finland (42). Thus, the geographic difference in incidence of both cryptorchidism and hypospadias parallels the pattern for TGC and semen quality in these countries. Much more research is needed to better understand these health problems and their relationships.

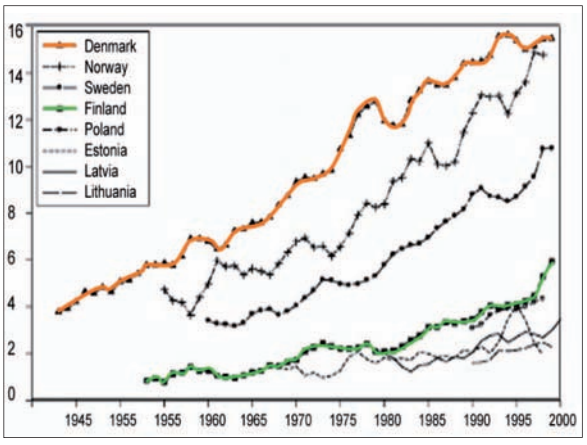

Figure 3. Trends in incidence of testicular cancer in Northern Europe. Age-standardised (world standard population) incidence of testicular cancer by year of diagnosis, country and histological type (from ref. 30).

Fertility and fecundity

The crucial question is whether semen quality among young men in Europe is now so low that it has reached a threshold at which fertility rates may be affected. In a recent study of pregnancy rates among native Danish women born between 1960 and 1980 (43), a 'total natural conception rate' (TNCR) was calculated, which included both the total number of births and induced abortions, and excluded births after the use of ART. Among the younger cohorts, who had not finished their reproductive career, projections were used to estimate their future fertility. Younger Danish cohorts of women had progressively lower TNCR, while the use of ART substantially increased, partly compensating for the decline in TNCR. The results suggest a cohort-related decline in fecundity (ability to conceive). Due to the partly prognostic nature of the study the results are, however, hedged with a degree of uncertainty, and new studies including the most recent registry data will be informative to examine the precision of the projections. On the other hand, the findings are consistent with a growing demand for ART in Denmark. It has been estimated that more than 7% of all children born in 2007 in Denmark were conceived by use of ART, which includes *in vitro* fertilisation, intracytoplasmic sperm injection (ICSI), and intrauterine insemination (44). Poor semen quality may be part of the reason for the increasing use of ART, which is confirmed by the increasing use of ICSI. Dependency on ART would dramatically influence society, since only limited resources are available for state-supported healthcare and those who do not qualify to receive free ART have to pay for the possibility to have children. The high costs of ART will certainly put people in an unequal position for their chances to conceive. Thus more research at international level is needed to provide information from other countries and to implement a common strategy to improve the situation.

Declining serum testosterone levels in American Men

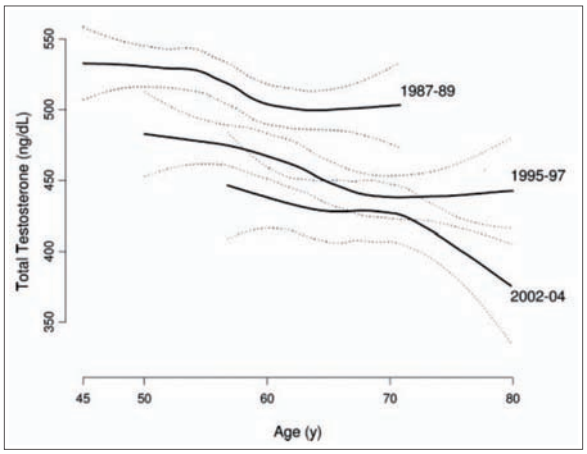

Figure 4. A substantial age-independent decline in testosterone that did not appear to be attributable to observed changes in explanatory factors, including health and lifestyle characteristics such as smoking and obesity. The estimated population level declines were greater in magnitude than the cross sectional declines in testosterone typically associated with age (from ref. 12).

Testosterone levels

Testosterone is the major driver of male reproductive development and function and suppression of its levels within the adult testis shuts down spermatogenesis (the process by which mature sperm cells are formed) and induces infertility. Testosterone levels within the testis are around 200-fold higher than in peripheral blood. However, lower intratesticular testosterone levels can sustain spermatogenesis. Studies of men with idiopathic infertility and low sperm counts often show evidence for abnormal function of Leydig cells (cells that produce testosterone) when compared with normospermic fertile men, such that their blood testosterone levels are either low or show evidence of 'compensated failure' – a situation in which increased luteinising hormone drive to the Leydig cells is required to maintain testosterone levels within the normal range (45,46). It is suspected, but unproven, that such compensation will predispose to more overt Leydig cell failure during aging (46), with its attendant health consequences, as outlined above.

The fact that across Europe the prevalence of oligozoospermia (low sperm numbers) in young men (18-25 years) is of the order of 20% (see above) could suggest that the prevalence of Leydig cell dysfunction in this population may also be high or may occur with high frequency as the men begin to age, thus predisposing them to cardiometabolic disease. Abdominal obesity is clearly associated with reduced testosterone levels (6,14) and it is also established that obesity (BMI >25) is associated with an approximate 20% reduction in sperm counts (47), although it is not clear if it is the obesity that causes the low sperm counts or whether there is an underlying common cause for both conditions. As mentioned earlier, studies in both Denmark and the US indicate a birth cohort-related decline in testosterone levels in men (12,13; Fig. 4), echoing the similar decline in sperm counts.

Testicular dysgenesis syndrome (TDS)

In Europe there has been a synchronised upward trend in incidence of TGC and congenital reproductive tract malformations at the same time as a downward trend in semen quality and testosterone levels (although there are only data for the latter in Denmark). In addition, most of these disorders share common risk factors and are risk factors for each other. It has been proposed (5) that these conditions may represent a syndrome of disorders, a testicular dysgenesis syndrome (TDS; Fig. 5) caused by a common underlying entity, which results in a disturbance of the development of the testes during fetal life. Resulting from TDS one or more of the following symptoms may occur: cryptorchidism, hypospadias, decreased spermatogenesis and TGC. The aetiology of TDS is unclear, but the apparent rapid increase in male reproductive health problems during a few generations suggests that changes in lifestyle and/or in environmental factors are more likely causes than genetic factors (see sections above).

Endocrine disrupting chemicals (EDC)

EDC are exogenous substances that alter one or more functions of the endocrine system and consequently cause adverse health effects in an intact organism, or its progeny, or (sub)populations (WHO, International Programme on Chemical Safety, IPCS).

Scientific focus has in particular been directed towards EDC as possible contributing factors to the rise in incidence of TDS disorders (49). EDC have the potential capability of interfering with the sexual organs in early fetal life. The process of a fetus developing into a male

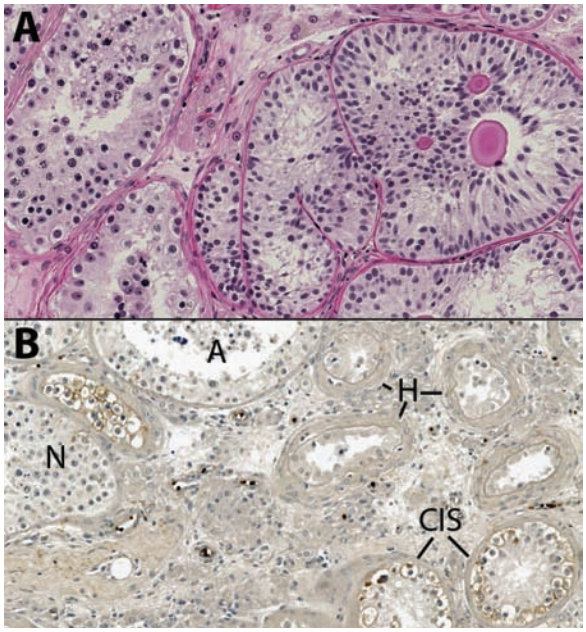

Figure 5. Testicular specimens from patients with TDS. A) Infertile man. Note abnormal spermatogenesis (left) and tubules containing only undifferentiated Sertoli cells and intratubular microliths (right). B. Mixed pattern with normal (N) and abnormal (A) spermatogenesis, hyalinised tubules (H) and tubules with carcinoma *in situ* (CIS).

involves a complex cascade of events. This is initiated by sex-determining genes, which activate the process of testis formation, which is a hormone-independent process. In contrast, subsequent steps in masculinisation, which include formation of the external genitalia and descent of the testes into the scrotum, are hormone-dependent (48). Three hormones are involved, anti-Müllerian hormone, testosterone and insulin-like factor 3, but of these testosterone (an androgen) has the widest ranging effects. Androgens are responsible for masculinisation of the external genitalia and final testis descent into the scrotum, events which are programmed or induced during the first trimester of pregnancy, so the timing of testosterone secretion is critical for normal development of the reproductive organs. Impairment of action of androgens in a male fetus leads to undermasculinisation, while exposure of a female fetus to androgens will cause masculinisation (49). EDC with anti-androgenic and estrogenic (e.g. diethylstilboestrol) and possibly other properties may therefore potentially disturb the development of reproductive organs during fetal life.

Animal experiments have shown that certain EDC can cause adverse effects in the male reproductive system that resemble the disorders described in human TDS, except for TGC (50). Wildlife exposed to environmental contaminants also exhibit abnormal reproductive development (51). The list of chemicals that have been identified as having endocrine disrupting properties in animal studies is growing and includes numerous substances found in household and consumer products; e.g. phthalates in many domestic, commercial and personal care products, and dioxin in fish and milk products (see examples in Table 1).

The mechanisms via which synthetic chemicals affect hormone action during masculinisation are only known for a few compounds. Some substances have been identified as being anti-androgenic because they bind to, but do not activate, the androgen receptor (AR), e.g. p,p'-DDE, which is a metabolite of the pesticide DDT, and the fungicide vinclozolin (52). In contrast, certain phthalate esters (e.g. diethylhexyl phthalate and di-n-butylphthalate) interfere with androgen biosynthesis in the fetal testis, resulting in anti-androgenic effects (49). Other chemicals exhibit estrogenic activity, and the adverse effects of estrogens in male animals are to an extent similar to those of anti-androgens (49). An example of an estrogenic chemical is bisphenol A, which in the 1930s was identified as a weak synthetic estrogen (53). Bisphenol A exerts estrogenic effects through binding to estrogen receptors (54,55) but it may also exert effects that are not estrogen-mediated. Some chemicals can act through multiple mechanisms, for example the fungicide prochloraz, which acts both by blocking the AR and by inhibiting fetal androgen production (56).

The effects of EDC are usually studied in animals at (maternal-fetal) exposure levels higher than those to which humans are typically exposed. However, in several studies exposure to mixtures of between three and seven chemicals with anti-androgenic properties, at doses at which each chemical alone was without significant effect, caused major impairment of masculinisation and occurrence of hypospadias (57,58). As humans are exposed to a complex cocktail of environmental chemicals (59), it is assumed that similar additive effects will also occur. This being the case, it introduces enormous complexity to identifying the causal contribution to TDS disorders of individual chemicals. The administrative regulation of such chemicals presents similar complexity (60).

Some human studies have found associations between exposure to EDC and malformations of the male urogenital tract. Higher concentrations of persistent pesticides (61) and flame retardants (62) in human breast milk as well as maternal occupational pesticide exposure early in pregnancy have also been found to be related to increased risk of cryptorchidism among the offspring (63).

Few studies have examined the effects of prenatal exposure to EDC on future semen quality and risk of testicular cancer, probably due to the challenging lag time between exposures and the occurrence of these disorders, which do not manifest until after puberty (64).

The epidemiological evidence of current exposure to EDC on semen quality is also still sparse (65), but a number of studies have found associations between PCBs and reduced semen quality.

In relation to the marked Danish-Finnish difference in incidence of male reproductive disorders described above, it is of note that Danish mothers have higher concentrations of several persistent chemicals in breast milk compared to Finnish mothers (66,67). In addition to

Table 1. Examples of endocrine disrupters and human exposure sources

Endocrine disrupters	Human exposure sources
Polychlorinated biphenyls (PCBs)	Transformers, cutting oils, plastic, paint, food
Phthalates (e.g. diethylphthalate, dibutyl phthalate)	Paint, plastics, food wrapping, cosmetics, food, dust
Brominated flame retardants	Building materials, electronic equipment, food
Parabens (e.g. butylparaben, propylparaben)	Preservatives in food and cosmetics
Bisphenol-A (e.g. polycarbonate)	Baby and water bottles, electronic equipment, food
UV-filters (e.g. 3-(4-methylbenzylidene)-camphor, hydroxylated benzophenones)	Sunscreens, coloured industrial products
Dioxin (e.g. 2,3,7,8-tetrachlorodibenzo-p-dioxin)	By-product from combustion processes, food
Polyfluorinated chemicals (e.g. PFOA, PFDoA)	Paints, impregnation of clothes and footwear, waxes for floors and cars, air
Pesticides (e.g. vinclozolin, dieldrin, hexachlorobenzene, DDT/DDE)	Food

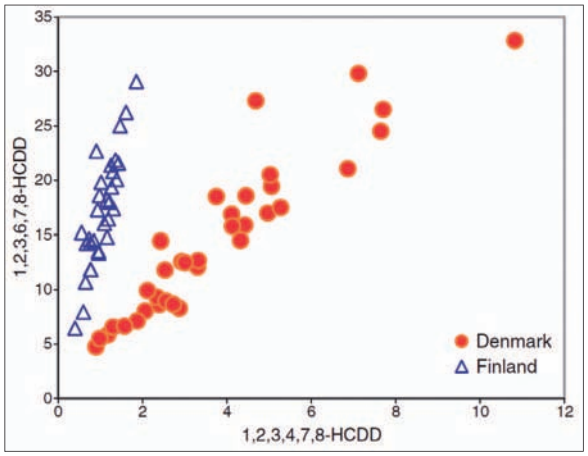

Figure 6. A 2-dimensional scatter plot showing the concentration of the two chemicals, 1,2,3,4,7,8-HCDD (x-axis) and 1,2,3,6,7,8-HCDD (y-axis), in each breast milk sample (pg/g lipids). The Danish (red) and Finnish (blue) samples are completely separated into two distinct groups. In each country, the two chemicals are clearly linearly correlated. However, the slopes are different in the two groups (from ref. 67).

quantitative differences in the exposure levels, the Danish and Finnish children have qualitatively distinct exposure patterns, typical chemical signatures that exemplify differences in their environmental impacts (Fig. 6) indicating a higher exposure for Danish infants, and presumably also indicating higher exposure during fetal life.

Although there is probably enough evidence overall to support the conclusion that exposure to EDC, probably during fetal life, may have contributed to the increase in male reproductive health problems, this evidence does not provide grounds for concluding that this is the sole causal factor (64). On the other hand, the complexity of current human exposure to environmental chemicals and the likelihood for additive effects of similarly acting chemicals, as seen in animal studies, means that identifying the importance of the role played by EDC in human male reproductive disorders is quite difficult. Despite this difficulty, there is a strong incentive to improve our understanding in this area, as it is certainly feasible to take steps to minimise exposure to identified causal agents, and this can only have positive effects in terms of improving reproductive health.

Epidemiological studies at an international level are urgently needed to provide a definitive association, or its lack, between exposure to individual environmental chemicals and any of the male reproductive disorders in humans (64). As described above the impact on male reproductive health can be very high.

Lifestyle factors

Lifestyle factors may also contribute to the observed adverse trends in male reproductive health. During the past 50 years huge changes in Western lifestyle have occurred; for example obesity is reaching epidemic proportions worldwide (68,69) and the prevalence of smokers has increased and then more recently declined in many Western countries (70). Several studies among men from the general population or infertile men (71-74) have shown that male obesity is associated with reduced semen quality. Smoking has also been found to impair semen quality. A meta-analysis published in 1994 based on 20 studies (75) found that smokers had a significant reduction in sperm concentration and a recent Danish study among men from the general population found a dose–response relationship between smoking and sperm motility and total sperm count (76). Interestingly, maternal smoking during pregnancy has a quite pronounced negative impact on semen quality among the offspring indicating that prenatal exposures are also important (77-80). Maternal smoking in pregnancy has also been shown in some (but not all) studies to increase the risk of hypospadias (81) and cryptorchidism (82,83) in male offspring. On the other hand, a meta-analysis has shown that maternal smoking during pregnancy is not associated with increased risk of TGC in sons (84). Nevertheless, the considerable increase in smoking prevalence among young women in most European countries in recent years can only exacerbate the incidence of male reproductive problems as some of these women will continue to smoke during pregnancy.

Genetic factors

There is growing evidence that genetic and epigenetic factors play a pivotal role for male reproductive health (85,86,87). The presence of a supernumerary X chromosome leads to Klinefelter syndrome (47, XXY), which is the most frequent chromosomal aneuploidy with an incidence of 1:400 male births and is characterised by hypergonadotropic hypogonadism and infertility. Recent studies clearly show that methylation and genetic polymorphisms are impacting the highly variable phenotype of Klinefelter patients. Moreover, further development of microsurgical techniques has led to the recovery of spermatozoa from these patients, which in principle allows them to father children. However, in more than 50% of the patients no sperm can be recovered, indicating that the same chromosomal background could have significantly different effects on spermatogenesis.

Familial aggregation of TDS disorders indicates that genetic factors may be involved in the aetiology. For example, the risk of developing TGC is markedly increased among brothers and sons of patients with TGC (88), and likewise cryptorchidism as well as hypospadias aggregate among male twin pairs and first-, second- and third-degree relatives (89). Besides rare point mutations (e.g. SRY mutation) and abnormal chromosome constitutions (e.g. 45X/46, XY), which are associated with increased risk of TGC, little is known about the role that specific genes play in the aetiology of TDS disorders. Mutations in the AR gene or in the gene encoding the 5-α-reductase type II enzyme, are associated with cryptorchidism and/or hypospadias, but these mutations are also extremely rare. Furthermore, there is, to date, virtually no evidence for the existence of specific genotypes predisposing to adverse effects of environmental or lifestyle factors (90). Racial differences in TDS, however, indicate a genetic component. US white men exhibit a markedly higher incidence of TGC than both Afro-American and other non-white US men (91). Geographical differences in TDS disorders, e.g.

between Danish and Finnish men as described above, could also reflect genetic differences in susceptibility to induction of these disorders by EDC and/or lifestyle factors or a combination of both. In this regard, several Scandinavian studies have shown that the incidence of TGC among Finnish first generation immigrants to Sweden is comparable to the country of origin, whereas among second generation immigrants it resembles that of the host country. This strongly suggests that environmental factors are an essential component in many TGC cases (92,93). Further research at international level is needed to get more knowledge about these severe reproductive health problems. As with many diseases it seems likely that the risk of developing male reproductive disorders/TDS will involve interplay between genes and the environment.

During recent years numerous candidate genes for male infertility have been screened for mutations. However, it turns out that mutations in autosomal genes are rare and do not play a substantial role in male infertility, while in 2% of oligo- or azoospermic men, microdeletions in the male-specific region of the Y chromosome can be detected (94,95). Our knowledge about X-chromosomal genes and their role in spermatogenesis is scant and should be improved.

A new concept has recently been proposed predicting that single nucleotide polymorphisms (SNPs) either alone or in combination with other SNPs are associated with modulation of spermatogenesis. In the worst scenario these polymorphisms may cause male infertility. Finally, epimutations leading to aberrant methylation of imprinted genes are considered a clear-cut phenomenon in men with impaired spermatogenesis. Several studies have convincingly shown that sperm morphology and sperm counts are significantly associated with the degree of normal methylation patterns of imprinted genes (96). Genetic alterations of the male germline are specifically relevant for patients undergoing ART. It will be of great importance to ensure that the sperm used for ICSI or IVF procedures is as well selected in terms of DNA integrity as under natural conception. It is biologically plausible, and preliminary data indicate, that children conceived by ART procedures show an increased risk of developing DNA methylation-specific diseases such as Beckwith-Wiedemann- or Angelman syndrome (97). Whether these genetic changes are associated with the disturbed genetic background of infertile couples or with the IVF procedures remains uncertain at present and has to be clarified.

Thus the research field of epigenetic changes has great importance for male reproductive health and needs to be more deeply explored as it brings qualitative aspects of male germ cells into the centre of attention which are highly relevant for the health of offspring conceived through ART procedures.

Conclusions

During recent years we have witnessed significant adverse trends in reproductive health problems in ***young*** men, with large geographical variations. In many European countries at least 20% of young men exhibit semen quality below the lower WHO reference level and this will most likely affect their fertility. The increasing use of ART also indicates that infertility is a growing problem. These widespread male reproductive health problems may contribute to decreasing birth rates, and the attendant socio-economic consequences. A significant proportion of men with TGC, poor semen quality, cryptorchidism and hypospadias may have a TDS of prenatal origin. The recently observed rapid increase in male reproductive disorders indicates that they are caused by environmental factors or changes in our lifestyle rather than genetic factors; this means that such disorders are intrinsically preventable, provided that the cause(s) can be identified. Of concern is also the mounting evidence that these male reproductive disorders may be associated with, and may contribute causally to, the explosive increase in cardiovascular and metabolic diseases in men, possibly via effects on testosterone levels. The recent recognition of the dynamic interplay between testosterone levels and abdominal obesity and its sequelae in men, in combination with the evidence for a secular decline in testosterone levels in men, suggests that the parallel increases in male reproductive and cardiometabolic health disorders may to some extent be interrelated. Our present understanding of the origin, and especially of the causes, of human male reproductive disorders is unfortunately very poor. Increased understanding would not only improve our ability to prevent or treat male reproductive disorders, but would also have a much wider impact on aspects of men's health that look set to dominate the European scene for the coming decades. From a socio-economic perspective, the impact of deteriorating male reproductive health in Europe thus looks pervasive.

Thus action is needed to improve national and international collaborative research in the field of male reproductive health to resolve the many remaining questions.

Recommendations for a common research strategy in male reproductive health

There is an urgent need to strengthen and to interlink research in male reproductive health at the national, European and international levels. This should take into account other factors which could interact with reproductive health at various levels, such as, for example, the growing obesity-related health issues across Europe or the influence of EDC. As mentioned above there remain many open questions both at the molecular and at the population/patient level so that it is generally important to strengthen translational research to better understand the consequences of certain disorders and their underlying mechanisms.

The **main recommendations** are therefore the following:

- **Increase awareness of male reproductive health issues**
  Currently, reproductive health of young men is not considered an important issue (other than sexually transmitted infections), despite growing evidence that it has a major influence on the frequency of male infertility and subsequent need for ART. In addition poor male reproductive health may be intrinsically linked to general health and life expectancy. It is therefore important to increase awareness of the major consequences that can arise from reduced male reproductive health.
- **Strengthen interdisciplinary, translational research**
  Male reproductive health might be influenced by different factors. As an example there is growing evidence that modern lifestyle not only causes obesity, it may also adversely affect both sperm counts and blood testosterone levels in men. However, the mechanisms involved and the long-term health implications are largely unknown. The susceptibility to develop infertility and reproductive dysfunction/diseases can start during testicular development as a result of exposure of pregnant women to environmental chemicals. Indeed there is the possibility, shown in animal models, that subferfility may be transmitted through several generations. In light of the current low birth rates and high need for ART, interdisciplinary, translational research is needed to better understand the different interacting factors which can have adverse effects on male reproductive health.
- **Implement long-term, epidemiological studies**
  To truly understand the etiology of poor male reproductive health, it will be critical to mechanistically understand the genetic and environmental contributions and their interactions in male reproductive health. Since environment, as opposed to genetics, can be changed, there is the possibility to intervene to prevent infertility and other reproductive diseases as well as co-morbidity factors by reducing environmental exposures. Therefore it is necessary to conduct long-term epidemiological studies to better understand the interacting mechanisms in male reproductive disorders.
- **Target research efforts**
  Better understanding of the mechanisms involved in these processes will provide paths forward for improving male reproductive health and will also likely have an impact on wider aspects of general health because of the emerging interconnections between these. It is envisaged that the results of such a research effort will be to identify the means of preventing/minimising occurrence of the disorders rather than the lengthy and costly development of drug treatments.

Proposed funding instruments

- **Strengthen national funding**
  Transdisciplinary, translational national research networks in human male reproductive health and fertility/infertility should be established as a focus area by national research councils and should be part of and contribute to the European network described below.
  National funds needed will vary with size of country, probably between 1 and 5 million euros per country per year.
- **Establish a European transdisciplinary, translational 'Research Network of Excellence' in male reproductive health**
  The role of such a network would be to evaluate the causes and consequences of the current low European fertility rates. The network should include expertise in andrology, endocrinology, management of infertility (IVF, ICSI), EDC, environmental health sciences, experimental systems, demography, sociology, epidemiology and bioinformatics/statistics. This network should use this multidisciplinary expertise to **establish robust methods** for accurately determining the extent of involuntary infertility across Europe, especially male-mediated infertility, and the **importance of societal factors** including **exposures to environmental chemicals** (individually and in mixtures), and **genetic background**. It should **utilise available methods, birth and adult cohorts**, to tease apart the relative importance of developmental versus adult causes of low sperm counts/infertility; this should take into account and make use of established geographical differences in sperm counts/related male reproductive disorders within Europe. The network should maintain quality control schemes to establish high and consistent standards of analytical methodology and patient care and include a **scientific advisory board** to assess progress and integration. Suggested funding level: 5 million euros per year for 10 years.
- **Establish links between the proposed European research network and similar networks in the US, Asia and other parts of the world**
  Such transnational cooperation would enable coordination of research, intervention and prevention efforts across the globe. The links should result in the formation of an effective international taskforce to tackle the alarmingly low fertility rates and other male reproductive diseases/dysfunctions in industrialised countries across the world, including all European countries, Japan, South Korea, Singapore as well as the US and developing countries. It is expected that the international groups will depend on their own core funding. However, running the taskforce activities (workshops, exchange of young scientists, common publications) are estimated to cost 1 million euros per year (European share: 25%).

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Abbreviations

ART: assisted reproduction techniques
EDC: endocrine disrupting chemicals
ICSI: intracytoplasmic sperm injection
IVF: *in vitro* fertilisation
TDS: testicular dysgenesis syndrome
TGC: testicular germ cell cancer
TNCR: total natural conception rate

Definitions

Testicular Germ Cell Cancer
- Commonest cancer in young men
- Associated with impaired semen quality and lower fertility rates
- Aetiology unknown

Congenital Malformations
- Cryptorchidism: undescended testis
- Hypospadias: incomplete fusion of the urethral folds

Total Natural Conception Rate
- Includes total number of births and induced abortions
- Excludes births after the use of ART

Endocrine disrupting chemicals (EDC)
Definition by WHO, International Programme on Chemical Safety (IPCS):
Exogenous substances that alter function(s) of the endocrine system and consequently cause adverse health effects in an intact organism, or its progeny, or (sub)populations

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