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Review Article

RECENT TRENDS IN MALE REPRODUCTIVE HEALTH PROBLEMS

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ABSTRACT

This review critically evaluates the current trends of male reproductive health problems in relation to semen quality. Increasing trend in male reproductive disorders observed in recent years, are principally found to associate with lifestyle and environmental factors. Lifestyle-allied diseases could be controlled with modification in diet, living and working environment etc. This review outlines the changing trends in male reproductive health and highlights the alterations in semen quality, in scientific manner. Though scientific and public concern regarding the changes on male reproductive health has grown in past few decades but the demonstration of a geographical differences in sperm concentration, still appears to be controversial. The amplitude of the difference observed cannot only be explained by methodological or confounding factors, and must to some extent be attributed to ethnic, genetic or environmental factors. However, there are numerous reports indicating the chronologically declining sperm count and standard semen parameters in various population indicating the increasing trend of male reproductive health disorders.

Keywords: cryptorchidism, infertility, sperm count, semen quality, testicular cancer

INTRODUCTION

Reproductive health is the basic human right which refers a state of complete physical, social and mental well-being and not merely the absence of disease and infirmity in all matters relating to the reproductive system and to its functions and processes.[1] But during the past two decades, a number of reports have appeared which have raised serious concerns about the development of reproductive problems in animals and man. There are numerous reports of alligators with abnormal male genital development[2] and of reproductive changes in fish and birds.[3] Simultaneously, there have been controversial reports of alterations in human semen quality (*i.e.* changes in semen volume, sperm concentration, sperm motility and sperm morphology)[4], along with reports of an emerging incidence of congenital malformations of the male reproductive tract, such as cryptorchidism and hypospadias[5], and of an increasing trend of testicular cancer[6]. However, there is controversy over whether or not these reported changes in male reproductive health are genuine[7], and if so, what the causes and implications are, in particular the implications for clinicians caring for couples with infertility.

Testicular cancer

Even though a lot of the changes observed in male reproductive health are controversial, there seems little disagreement that testicular cancer is increasing in rate of recurrence (Fig 1A), with unexplained increase in the age-standardized incidence observed in Europe (Fig 1B)[8] and the USA[9]. In the west of Scotland, the number of testicular germ cell tumours registered has more than doubled over 1990 than it was in 1960[10], while a study from Norway reported that the age-related frequency of testicular cancer increased from 2.7 per 1 lakh individuals in 1955 to 8.5 per 1 lakh individuals in 1992.[6] A similar study reported 61% increase in testicular cancer in southern Norway from 1986-87 to 1991-92.[6] In the USA, the overall age-related incidence of testicular and germ cell cancer has increased 3.5-fold during the past 60 years (Fig 2).[9] There is considerable geographical variation in both the occurrence of testicular cancer and in the observed rate of its growth[11]. This geographical variation may be linked with that observed in semen quality - testicular cancer is four times more common in Denmark, where studies have shown low sperm concentrations in men[12], than in Finland where sperm concentration is higher[13]. Bergstrom and colleagues[8] evaluated data from Denmark, Norway, Sweden, the former German Democratic Republic, Finland and Poland, including data on over 30,000 cases of testicular cancer from 1945 to 1989 in men aged 20-84. They reported considerable regional variation in both the incidence of testicular cancer and in the observed rate of increase, ranging from a 2.3% increase per annum in Sweden to 5.2% per annum in the former East Germany. Similarly, Zheng *et al.*[9] concluded that the increase in testicular cancer observed in men born after 1910 in USA was enlightened mainly by a strong birth cohort effect. However, from some other studies it is now clear that men with a history of cryptorchidism, inguinal hernia, hypospadias and hydrocele have a significantly increased risk of testicular cancer.[14] It has been suggested that paternal occupation before conception may alter the testicular cancer risk of offspring[15], as may the parental use of pesticides or fertilizers[16] or childhood residence in areas with a high nitrate concentration in ground water[17]. While fathers of testicular cancer patients have been found to have a slight increase in their own risk of the disease, a much more significant risk attaches to the brothers of men with testicular cancer.[18] These latter observations support the possible involvement of a genetic component in the aetiology of testicular cancer. In a case control study in the UK, Davies *et al.[*19] found that, while cryptorchidism was a major risk factor for testicular cancer, each extra quarter pint of milk consumed amplified the risk by 1.39-fold.

Congenital reproductive tract defects in male

The incidence of congenital malformation of the male genital tract is also changing its pattern, with increase in the prevalence of cryptorchidism and hypospadias[20]. Cryptorchidism has increased by as much as 65-77% over recent decades in the UK[5], while USA data have shown that rates of cryptorchidism have not changed[21], although a large study from the USA reported that rates of hypospadias have doubled between the 1970s and 1980s[22]. In one Kallen *et al.[*23] who conducted a multicentre study of 8,122 boys from seven malformation surveillance systems around the world, resolved that a true geographical variation exists in the prevalence of hypospadias at birth. Berkowitz *et al.[*24] who were considering at the risk factors for cryptorchidism, suggested that maternal obesity, low birth weight, the presence of other congenital

malformations, ethnic group and a family history may be relevant. Others have

suggested strong associations between cryptorchidism and low social class[25].

Altering semen quality

Classical reports

The proposition that semen quality is changing is not new. In 1974, Nelson and Bunge[26] reported data on 386 men presenting for vasectomy in the USA. The mean sperm concentration of this group was 48×10^6/ml, only 7% of them were reported to have sperm concentrations above 100×10^6/ml which is far below than the concentrations reported in the earlier studies of 120×10^6/ml[27], 145×10^6/ml[28] and 100.7×10^6/ml[29] respectively. In 1951, MacLeod and Gold[30] had published their landmark study of semen quality in 1,000 male partners in infertile relationships, together with a similar number of men of proven fertility and reported an average sperm concentration of 107×10^6/ml, with 5% of them having sperm concentrations under 20×10^6/ml, and 44% having above 100×10^6/ml. Nelson and Bunge[26] speculated that their data 'would tend to incriminate an environmental factor to which the entire population has been exposed'[26]. Later, several reports of semen quality in fertile men found intermediate values for average sperm concentration of 70×10^6 - 81×10^6/ml[31]. Then MacLeod and Wang[32] who investigated infertile marriages reported that there was no evidence of a general drop in semen quality. Leto and Frensilli[33] reported a decline in semen quality amongst potential semen donors. In 1980, James[34] reported the first review of published data on semen quality in men of proven fertility and in unselected normal men. Bostofte *et al.[*35] compared 1,077 Danish men presenting for evaluation of infertility in 1952 with 1,000 similar men presenting 20 years later in 1972. They observed a significant drop in sperm concentration, a decrease in sperm motility and an increase in the proportion of abnormal spermatozoa. Similar findings were reported in a Swedish study in 1960-61.[36] These early publications failed to raise major public health concerns, perhaps because the data came from selected groups of men, unrepresentative of the general population, including men attending infertility clinics[36] or semen donors[33,37].

Jensen *et al.[*12] in 1992 reawakened concern over the possibility of secular trends in semen quality, publishing a meta-analysis of data on semen quality published since 1930 in normal men. Data were obtained on 14,947 men, published in 61 papers during 1938-1990. Using linear regression, they observed a decline in average semen volume from 3.40 ml in 1940 to 2.75 ml in 1990. A similar analysis for sperm concentration suggested an apparent decline from 113×10^6/ml in 1940 to 66×10^6/ml in 1990. There was no change in the average age of the men studied, and no apparent influence of age on the observed secular trend in semen quality. Predictably, the central message of this meta-analysis, that sperm counts had declined by about 50% over the past 50 years, attracted enormous attention and generated much controversy[38,39]. Bromwich and colleagues[38] later speculated that much of the apparent change in semen quality could be accounted for by a change in the 'accepted' definition of the lower limits of 'normal' semen from around 60×10^6/ml in the 1920s[40] to 20×10^6/ml, which is the figure commonly accepted today [41]. However, it has been pointed out that at least some of the earlier papers did include men with semen quality in this range[42]. Keiding and Skakkebaek [43] then pointed out, all of the statistical models agree on one qualitative message - a decline in semen quality over time. However, it is surely legitimate that all the available data, as presented, even if imperfect, help to define questions and priorities for future study.

Recent reports

Most of the reports that appeared closely after the meta-analysis of Jensen *et al.*[12] provided alternative interpretations of the data. Unfortunately, the available data still fail to reach a definite conclusion as to whether or not there is any secular trend in semen quality. Auger *et al.[*44] published data on semen quality in fertile Parisian men by examining 1,750 fertile men with consistent methods of subject recruitment and laboratory technique, during a 20 year period. They observed a fall in all of the classical measures of semen quality over time. Sperm count was found to be affected by age with each year of advancing age being associated with a 3.3% fall in sperm concentration. An accompanying editorial by Sherins[45] unfortunately misinterpreted this study as being concerned with men selected as sperm donors, rather than potential donors, and thus raised concerns about selection bias that were not well founded. Numerous other groups have published data proposing a secular trend in semen quality amongst normal men. Irvine *et al.*[4] later observed that the median sperm concentration fell from 98×10^6/ml among donors born before 1959 in Scotland to 78×10^6/ml amongst donors born after 1970. In a similar study, Van Waeleghem *et al.[*46] observed declines in sperm concentration from a mean of 71×10^6/ml to 58.6×10^6/ml in sperm donors of Belgium.

In contrast, a number of reports have failed to find any evidence of a secular trend in semen quality. In a study of 302 volunteer semen donors in Toulouse, France, between 1977 and 1992 no evidence of changes in semen quality with time was observed[47]. Handelsman[48] also found no evidence of any effect of year of observation or year of birth on sperm concentration, total sperm number or ejaculate volume. Later two significant reports from the USA have provided evidence of unchanging semen quality in the populations studied of Fisch *et al.[*49] and Paulsen *et al.[*50] De Mouzon *et al.[*51] have published the largest retrospective review of semen quality data. On the basis of the French national *in vitro* fertilization (IVF) register, they reviewed the results of 19,848 semen analyses from 7,714 men undergoing IVF for tubal disease, and having a normal semen analysis prior to IVF. They found a significant decrease in semen quality with later year of birth, the average sperm concentration in men born before 1939 being 92.5×10^6/ml, falling to 77.1×10^6/ml for men born after 1965. In a smaller study, Berling & Wölner-Hanssen[52] reported on semen quality in 718 semen samples submitted by infertile men from 1985 to 1995 in one Swedish centre and found no relationships with age or date of birth, although ejaculate volume seemed to decrease and normal morphology, motility and sperm penetration of hyaluronic acid polymer increased during the study period.

Most recently, a very careful reanalysis of the historical data[12] on semen quality in normal men has been published[53]. These workers used multiple linear regression models, controlling for abstinence time, age, the proportion of the sample with proven fertility, specimen collection method, study goal and geographical location to examine regional differences and the interaction between region and year of publication. Using a linear model, they found that sperm concentrations and the rate of decline in sperm concentration differed significantly across regions. They concluded that there was evidence of a decline in sperm concentrations in the USA of 1.5×10^6/ml per year, and in Europe of 3.13×10^6/ml per year, but not in non-Western countries. Results were similar when other (non-linear) models were used, and these workers concluded that their results were unlikely to be due to either confounding or selection bias[53]. Thus, the available literature on secular changes in semen quality is, at best, inconclusive. To a greater or lesser extent, all of the available data suffer from the problems of being retrospective, collected in different countries, at different times, using different methods of subject selection and recruitment and different laboratory methodology. The retrospective nature of the data means that control of important confounding variables is often imperfect, weakening the conclusions reached. More evidence is clearly needed, yet one is tempted to wonder whether the inherent difficulties in laboratory methodology, subject selection and the large number of potential confounding variables involved mean that it may never be possible to resolve the issue of secular trends in human semen quality with certainty.

Regional variations

Although the position with regard to secular changes in semen quality remains unclear, an important observation to emerge from this work is the striking regional differences that are apparent: for example, the above mentioned study by Fisch *et al.*[49], in which sperm

concentrations were highest in New York (131.5×10^6/ml), intermediate in Minnesota (100.8×10^6/ml), and lowest in California (72.7×10^6/ml). The Seattle data, with a geometric mean of 46.5×10^6/ml, is not directly comparable[50]. Within Europe, similar patterns can be observed. Semen quality in normal Finnish men would appear to be high, with a mean sperm concentration of 133.9×10^6/ml being reported[13], whereas in Paris and Edinburgh lower mean values of 98.8×10^6/ml and 104.5×10^6/ml have been reported [4,44]. In contrast, semen quality in normal men in Belgium has been reported at 66.8×10^6/ml, and in Denmark at 69.2×10^6/ml [12,46]. Whether or not there are also regional differences in the occurrence or otherwise of secular changes in semen quality is unknown[47], but it is evident that geography is a vital confounding variable which should be considered when examining such data[54]. One study reported deteriorating semen quality in a group of patients resident within the area of one water supply company, but no change in the semen of similar patients living nearby[55]. Data from the Centres d'Étude et de Conservation des Oeufs et des Spermes Humaines (CECOS)[56] has provided strong support for the existence of regional differences within France, and the recent meta-analysis by Swan *et al.*[53] noted that intraregional differences were at least as large as the mean decline in sperm concentration. It is possible that these regional differences, which might be due to ethnic, environmental or lifestyle factors, could provide a valuable tool in addressing the hypothetical causes of changes in semen quality[4]. Using time taken to achieve a pregnancy in fertile couples as a measure of fertility[57], Joffe[58] examined antenatal population and cross-sectional studies in Finland and the UK. In both comparisons, fertility was significantly greater in Finland than the UK. The author therefore concluded that 'the previously reported difference in sperm counts between Finland and elsewhere in north-west Europe (including Great Britain) is probably not artefactual'[57,58]. This along with some other reports suggest that the reported worldwide decline in semen quality is also real (Table 1).

Factors contributing reproductive health disorders and altering semen quality

The cause of these observed changes in male reproductive health remains unidentified. It is clear that lifestyle factors such as occupation[72], smoking[73], dress habits[74] and even time spent commuting[72] may be relevant. However, the hypothesis that has attracted most attention concerns exposure to environmental xeno-oestrogens during development[75]. This is now a large and complex field, reviewed recently by the Danish EPA (Danish Environmental Protection Agency)[76]. Sertoli cells play an important role in regulating the environment within the seminiferous tubules, each Sertoli cell supporting the development of a limited number of germ cells[77]. Any perturbation in the development of the reproductive system that leads to a reduction in Sertoli cell number will reduce the individual's ultimate capacity for sperm production in adult life. In most mammals, Sertoli cell replication occurs during foetal and postnatal life, Sertoli cell number becoming fixed at some stage of development. In the rat, Sertoli cell multiplication commences around 19-20 days of gestation and ceases around 15 days of postnatal life[78]. In some primates there is a rapid and substantial proliferation of Sertoli cells at the onset of puberty[79]. In man, the total number of Sertoli cells increases significantly between late foetal and pre-pubertal life, with a further increase during puberty[80]. Hence any 'window' for adverse effects on Sertoli cell multiplication may be longer in humans than in other species. The idea that exposure to 'oestrogens' may affect male reproductive development is founded on the observation that follicle-stimulating hormone (FSH) is involved in determining Sertoli cell number[81] and that oestrogens produced by Sertoli cells may keep FSH levels in check by negative feedback whilst Sertoli cell number is being determined. Hence, short-term exposure of neonatal rats to oestradiol results in a suppression of FSH levels and in consequence reductions in testicular weight and spermatogenesis in adult life, whilst exposure of rodents *in utero* to the synthetic oestrogen diethylstilboestrol (DES) results not only in reductions in testis size and spermatogenesis in adult life, but also in an increased incidence of cryptorchidism and hypospadias[82]. In a similar way, the male offspring of women exposed to diethylstilboestrol during pregnancy have an increased incidence of cryptorchidism and hypospadias at birth, and of abnormal spermatogenesis in adult life[83]. It is not clear whether they are any less fertile as a result[84]. The effect on testicular descent, and perhaps also on increase in testis cancer risk, would presumably be mediated through interference with the secretion of müllerian inhibiting substance (MIS)[85]. Testicular cancer may also be a congenital condition that becomes manifest at or after puberty[86]. Thus, the understanding of the development of the male reproductive system leads to the conclusion that exposure to exogenous oestrogens may perturb it in such a way as to give rise to the changes which appear to be emerging in human health. There is certainly concern over the growing number of chemicals that may be viewed as 'endocrine disrupters'. The Danish EPA has recently released a report raising concern over environmental chemicals with oestrogenic effects[76], whilst recent commentaries in the *Lancet[*87] and *British Medical Journal[*88] have highlighted the need for further research in this complex area. It is clear that there are chemicals in the environment which are 'oestrogenic', and which can perturb sexual development in exposed animals[89]. In mammals, it has been shown that exposure of pregnant mice to ethinyloestradiol increases the frequency of gonadal dysgenesis, cryptorchidism and testicular cancer, in association with impaired Leydig cell development and reduced Sertoli cell numbers[90] Gestational exposure of rats to xeno-oestrogens has been shown to result in reduced testicular size and sperm production[91] and we now know that exposure of pregnant sheep to xeno-oestrogens supresses foetal FSH. In an attempt to estimate the familial and genetic contributions to variation in human testicular function, Handelsman[92] has studied 11 pairs of monozygotic and 6 pairs of dizygotic twins, and observed that sperm concentration, testicular size and sex hormone binding globulin (SHBG) all had a strong familial effect, but was unable to confirm any genetic component.

CONCLUSIONS

Although the 'environmental oestrogen' hypothesis has attracted much attention, and there exist some biological data to confirm its plausibility, evidence that it is causally related to changes in human male reproductive health remains circumstantial. The evidence for secular changes in semen quality and other changes in male reproductive health is indecisive, with the exception of testicular cancer, though evidence for regional differences in male reproductive health would appear to be stronger. In both cases, association does not imply causality, and several other possible explanations require to be considered. As far as semen quality is concerned, sperm count is a poor index of fertility, and there are as yet, no data on secular changes or regional differences in sperm function, although there may be some evidence of regional differences in fertility. While the available evidence is inconclusive and circumstantial, its weight is considerable and at the very least it should raise concerns that deserve to be addressed by properly designed, coordinated and funded research. Delay may compromise the fertility and reproductive health of future generations [4,88].

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