Secular trends in monitors of reproductive hazard

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There is concern that our reproductive systems are exposed to environmental hazards. A number of potential monitors of these hazards have been proposed (reported rates of cryptorchidism, testicular cancer, hypospadias, dizygotic twinning, sperm count, ectopic pregnancy and sex ratios). To discover whether these are monitoring the same hazards, secular movements in these measures are considered here. It is suggested that the secular movements of cryptorchidism and hypospadias are insufficiently reliable to give guidance on the movements of such hazards as cause them. With one possible exception, rates have not moved in parallel and so, in general, they are not monitoring the same hazards. The exception is dizygotic twinning rates and sperm counts which may have a lagged correlation. If this is true, it may be important and throw light on the hitherto unexplained movements of both. The hazards themselves are largely unidentified, but may be presumed to include: (i) the well-publicized rise in environmental oestrogens; (ii) an increasing number of women with suboptimal oestrogens (because of dieting and arduous exercise); and (iii) hormonal consequences of these two opposing trends, e.g. an increasing number of women with suboptimal androgens (possibly accounting for the increasing rates of cryptorchidism and testicular cancer).

Introduction

There is widespread concern that the male and female human reproductive tracts are presently subject to deleterious environmental agents. Changes in rates of hypospadias, ectopic pregnancy, testicular cancer, cryptorchidism, sperm ratio and dizygotic twinning have all been adduced in this context. However, most attention has focused on changes in sperm count. All of these may be regarded as monitors of reproductive hazard. The fact that they have not all changed in parallel suggests that they are monitoring different hazards. The purpose of this note is to try to identify whether any of them are moving in parallel. This may help to indicate which of these monitors have common hazardous determinants and (possibly) to identify such determinants.

For this purpose, the recent secular movements of each monitor will be briefly reviewed. Readers seeking citations to substantiate the above comments will find them in the relevant sections.

Cryptorchidism

There have been reports that the incidence of this condition increased in England and Wales during the 1960s and 1970s (Swerdlow et al., 1983; Chilvers et al., 1984). However, Berkowitz et al. (1993) failed to find any such increase in recent decades in New York City. Moreover, there are two main reasons for questioning the reliable reporting of this condition: (i) in most cases diagnosed at birth, the testes have descended by 3 months (Berkowitz et al., 1993); and (ii) the increasing practice of orchidopexy on apparently undescended testes at younger ages (to preserve fertility) implies that some boys with retractile testes that would have descended naturally are now being operated on. So the number of orchidopexies may overestimate the number of true cryptorchids.

Hence, movements in estimated rates of cryptorchidism may not be useful as monitors of reproductive hazard. Their interest lies in the fact that cryptorchidism represents a very substantial risk factor for testicular cancer (Strader et al., 1988). This cancer has very similar risk factors as cryptorchidism (Depue et al., 1983). So it may be best to assume provisionally that both these monitors are reflecting the same hazards, although this may turn out to be false. But whereas the epidemiological data on testicular cancer invite speculation as to causes, the data on secular movements of cryptorchidism seem subject to such serious reservation as to inhibit reasonable speculation.

Testicular cancer

With few exceptions, reports have agreed that rates of this disease have been gradually increasing in the USA and Western Europe and Japan. The reported duration of the increase seems to date from when data first became available, i.e. the beginning of the century in England and Wales (Davies, 1981) and various dates from 1943 onwards for other countries of Northern Europe (Adami et al., 1994). There is one exception to this generalization; Hoff Wanderås et al. (1995), reporting on testicular cancer in Norway 1955–1992, identified a cohort effect such that the disease incidence increased in successive birth cohorts from 1916 to 1970 except for the cohort born during the Second World War. Bergström et al. (1996) confirmed this suggestion of a cohort effect in Denmark, Sweden, East Germany, Finland and Poland; they also found that Denmark and Sweden (but not the other countries) shared a
Dizygotic twinning

Of all the monitors discussed here, the dizygotic twinning rate is the one most reliably measured. Most countries publish their annual numbers of opposite sexed twin pairs and their total numbers of births. The number of dizygotic twin pairs may be presumed to be a multiple (closely approximating to 2) of the opposite sexed pairs (James, 1992). Dizygotic twinning rates have shown very substantial variation in most developed countries over the past half-century. In all European countries, and in Australia, New Zealand and Japan, there was a decline in rates during the 1960s (James, 1972). In those countries for which data were available, the decline was maternal age-specific. After 1965, the decline had apparently ceased in Bulgaria, Czechoslovakia and Hungary (James, 1982), and rates stabilized within the following 10 years in a number of other European countries, including England and Wales (James, 1986). A curious feature is that though rates in Canada fell between 1957 and 1977 (James, 1982), those in the USA were roughly stable during the same years, having fallen during 1930–1964 (Allen, 1987). Interpretation of the recent stabilized (or increasing) levels in many countries is complicated by the increasing numbers of dizygotic pairs following induced ovulation and other forms of assisted reproduction. An attempt to adjust for such factors tentatively concluded that the true dizygotic twinning rate in England and Wales and Belgium has ceased declining (James, 1995a).

The probability of a live birth dizygotic twin conception may be taken as the product of four (assumed independent) probabilities. In order, these are: $P_1$ that double ovulation occurs; $P_2$ that coitus occurs within the fertile intervals surrounding both ova; $P_3$ that both ova are fertilized; and $P_4$ that neither zygote suffers spontaneous abortion.

In principle, each of these may independently be regarded as an index of reproductive hazard. In practice, nothing seems to have been published about secular movements in $P_1$ and $P_3$ (or the analogous probabilities relating to singletons). Moreover, I have suggested that reported movements in spontaneous abortion rates are so difficult to interpret that they cannot usefully be taken as guides to the secular movements of their causes (James, 1996c). Lastly, there is evidence that mean age-adjusted coital rates vary quite substantially in time; but I have suggested that this may be in response to social, rather than health-related changes (James, 1995b). In short, although all four of the above parameters (or their singleton equivalents) are directly related to fertility, it is not known which one (or more) has caused the very substantial secular variations in dizygotic twinning rates.

Sperm counts

There have been a large number of cross-sectional studies reporting mean sperm counts. A meta-analysis suggested (on the basis of weighted linear regression) that a fall of about 50% occurred in the years 1938–1990 (Carlsen et al., 1992). However, these data are susceptible to other interpretations. In the first place, various forms of bias have been invoked to suggest that this decline was <50%, or even non-existent. The latter claim (that the decline was not real) seems implausible.
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to me, and I shall assume that a fall has occurred (at least in some places and at some times). But it remains difficult to decide whether sperm counts are still declining generally in the USA (from where most data have been published) or whether they stabilized there at some time around the beginning of the 1980s (Olsen et al., 1995). This latter interpretation is supported by data from Frisch et al. (1996) in respect of the USA as a whole, and Paulsen et al. (1996) in respect of Seattle.

Elsewhere, declines have been described that were not in synchrony with that suggested above in respect of the USA. In Paris, for instance, though there was a decline during the years 1973–1992 (Auger et al., 1995), there seems to have been no decline prior to then (Jouannet et al., 1981).

Sperm counts are also reportedly declining in Belgium (Van Waeleghem et al., 1996) though not Toulouse, France (Bujan et al., 1996).

This synopsis will conclude with two interesting recent observations: (i) in Finland there has been virtually no fall in sperm counts; they are higher there than elsewhere in Europe. Moreover, the incidence of testicular cancer and hypospadias is lower there than in other Scandinavian countries (Anonymous, 1995); (ii) Irvine et al. (1996) reported that the decline in sperm counts in Scotland seems to have been a cohort effect, suggesting that the decline was either caused by events in utero or shortly thereafter. This result of Irvine et al. (1996) has been confirmed by Mouzon et al. (1996) in respect of French donors; moreover, the data of Bujon et al. (1996) can also be interpreted in support of a cohort effect.

Ectopic pregnancy

I have previously reviewed data on this condition; there has been a continuing worldwide increase in rates of ectopic pregnancy (James, 1996b). However, more recently it has been reported that this increase has been reversed in Finland and Sweden (Mäkinen, 1996). This author noted that there were both time and cohort effects contributing to the rise in 1970–1987 in Finland and he attributed the subsequent fall to the diminishing reproductive contribution being made by the ‘baby-boom generation’ with its epidemic of gonorrhoea and subsequent pelvic inflammatory disease. These two pathologies are among the established risk factors for ectopic pregnancy and suggest physical impediment to the progress of the fertilized ovum down the tube. However, there are reasons for suspecting another class of causes of ectopic pregnancy, functional rather than structural; and I have suggested that ectopic pregnancy could result from both high and low maternal oestrogen levels (James, 1996b).

There is evidence to support this suggestion of an increasing variance in women’s oestrogen levels. Increasing numbers of women who smoke and diet and engage in demanding physical exercise would be expected to increase the proportion of women with suboptimal oestrogen levels (e.g. Skolnick, 1993). However, there are also increasing numbers of women who are obese (Kuczmarski et al., 1994); who take no exercise (Central Statistical Office, 1986); and there is increasing concern about us all being exposed to exogenous oestrogens (Sharpe and Skakkebaek, 1993; Arnold et al., 1996). The net result is that the variance of women’s oestrogen levels would be expected to have been rising in recent years.

However this multiplicity of suspected causes diminishes the utility of ectopic pregnancy rates as a monitor of reproductive hazard. Mäkinen (1996) may be correct in attributing the current decline in Scandinavia to declines in gonorrhoea and pelvic inflammatory disease. But this claim needs to be substantiated with numerical data before we can accept that this decline in pathology is alone responsible for the decline in ectopic pregnancy; a decline in suspected hormonal exposures may also have played a part.

Sex ratios

It has been proposed that offspring sex ratios are a useful indicator of male occupational reproductive hazard (James, 1994). There are reasons for suspecting low testosterone and/or high gonadotrophin levels and/or low sperm counts in categories of men who sire excesses of daughters. However, the effects of deleterious agents on the sex ratios of offspring of exposed women are not known: possibly they rise. So the fact that in England and Wales the live birth sex ratio declined almost continuously in the years 1973–1990 (Dickinson and Parker, 1996) cannot immediately be interpreted as indicative of adverse exposures. Instead, the decline may simply represent an oscillation in the stabilizing process suspected of operating on population sex ratios (James, 1995b).

Comment

It is clear from the forgoing that the female reproductive system has been subject to several different (presumably mainly hormonal) deleterious agents over the last century. The various disorders suffered by the male reproductive system (certainly hypospadias and cryptorchidism, and possibly testicular cancer and diminished sperm counts) may be due to in-utero exposures. In other words, it may be useful to think of all the above monitors as possibly reflecting adverse exposure of the female system alone; the consequences in some cases being manifested by the male system.

Secondly, there are two points to be made about rates moving in parallel, and thus possibly sharing causes: (i) one is perhaps trivial; as noted above, the risk factors for cryptorchidism and testicular cancer are similar. Moreover, the one is a very powerful risk factor for the other. So epidemiologists investigating the causes of cryptorchidism may find the literature on the epidemiology of testicular cancer more inspiring than that on cryptorchidism itself. Until recently, research tended to focus on the possibility that high maternal oestrogen levels played a causal role in these two conditions. However, low maternal testosterone levels now seem more likely, at least in regard to cryptorchidism (Key et al., 1996); (ii) the question arises whether dizygotic twinning and sperm counts are connected. If it is correct (as suggested above) that
References


the diminishing sperm count is a cohort effect, then (if there were a connection), one would expect the two rates would move in parallel but with a time lag of about a generation, from the time of gestation (ex hypothesi, the time of deleterious exposure) to the time at which the man’s sperm sample is produced.

In conformity with this suggestion, and as suggested above, dizygotic twinning declined in the USA in 1930–1964 and was roughly stable thereafter; sperm counts fell there during the 1960s and 1970s, but were apparently stable from the 1980s onwards.

Elsewhere, the dizygotic twinning decline started in the 1950s and 1960s, and ceased in many European countries after about 25 years. Cohort data from Scotland and France on sperm counts suggest a decline with date of birth in men born after 1950 or thereabouts. The present hypothesis has the appealing feature that it will be tested by the sperm counts of men born after 1975 (or thereabouts). If it is true, they should cease declining with date of birth. And if that happens, we shall again be confronted with that enduring and perplexing question: ‘what did cause the decline in dizygotic twinning rates in the US in 1930–1960 and elsewhere in 1960–1980?’
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