Human Reproduction Vol.22, No.5 pp. 1197–1199, 2007 doi:10.1093/humrep/dem020
Advance Access publication February 15, 2007

DEBATE—CONTINUED

Monitoring reproductive health in Europe: what are the best indicators?

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The Reprostat Steering Committee asks for the best monitors of reproductive health. In many European countries, some deleterious agents have caused declines over the past half-century in both dizygotic (DZ) twinning rates and sperm counts. No strong evidence suggests that these declines have reversed, though they may have ceased in some countries. Here attention is only directed at potential secular changes in the proximate biological determinants of fertility (ovulation, coitus, semen quality, fertilization, spontaneous fetal loss and 'dead time'). The most comprehensive biological monitor of reproductive health is the 'natural' DZ twinning rate (viz the rate of DZ twinning in the absence of any medical intervention around the time of conception). At present, natural DZ twins are augmented by twins produced by new techniques. So efforts should be made to estimate the annual numbers of these iatrogenic twins in each European country. Then it would be possible to follow the movements of each national natural DZ twinning rate, and thus to continue monitoring a useful measure of reproductive health that has been available in most European countries for many years. Efforts should be made to assess the sperm quality of volunteer donors in each European country.

Key words: coital rate/dizygotic twinning rate/fecundability/semen quality/sex ratio at birth

Introduction

Jahn *et al.* (2006) solicited opinion on possible practical methods of monitoring reproductive health in Europe in the future. Before responding to this request, it is useful to consider the purposes of such monitoring. There seem to be two broad categories of purpose, viz. political (or administrative) and scientific. These will be treated separately.

Political or administrative purposes

A health service has to be run and administered efficiently. For this, the service needs to be compared with itself across time and with other such services. League tables and goals within and across countries require the routine accumulation of data of the sort mentioned by Jahn *et al.* (2006), e.g. age at first child, fertility, maternal mortality and rate of induced abortion. However, there are other, quite different purposes of such monitoring. It is to such purposes that the rest of this note will be addressed.

Scientific purposes

We currently face an important question: is our reproductive health being adversely affected by endocrine disruptors (or other agents)? The reported secular movements in dizygotic (DZ) twinning rates and in sperm counts over the past half century suggest that such agents have been, and continue to be, at work. So we need to know (i) whether such effects are worsening and (ii) whether this question can be answered by the provision of routine monitoring.

Efforts to answer these questions will be offered under the headings of DZ twinning, fecundability, sex ratio, sperm concentrations, spontaneous fetal loss, coital rates and 'dead time'.

DZ twinning

The probability P of a natural DZ twin birth is given by the product of four (presumably independent) probabilities. Thus,

$$P = p_1 p_2 p_3 p_4,$$

where, p_1 is the probability that a woman will ovulate twice in a cycle, p_2 the probability that coitus occurs sufficiently frequently to ensure that there are viable sperm available to deal with both ova, p_3 the probability that both ova are fertilized and p_4 the probability that neither ovum is spontaneously aborted.

(The possibility that a DZ twin birth is the result of reduction of a higher order multiple pregnancy is ignored here.) It will be seen that each of these four probabilities is

a criterion of reproductive health. So (whether they are strictly independent or not) their product is probably a more sensitive criterion of reproductive health than any of them taken individually.

Thus, before the advent of assisted reproduction, the maternal age-specific DZ twinning rate was probably the best available indicator of reproductive health. In conformity with this notion, women who bear DZ twins are reportedly larger and taller (Corney *et al.*, 1979) and better fed (Bulmer, 1970) than control mothers of singletons or monozygotic twins. Moreover, women who bear DZ twins conceive more quickly than those who bear singletons—presumably as a consequence of high coital rates as well as hormonally mediated double ovulation (Bulmer, 1970, James, 1972). In short, women who bear (non-iatrogenic) DZ twins are a reproductive elite.

Maternal age-specific DZ twinning rates declined very substantially during the years 1960–80 in some European countries (James, 1982). This decline is the strongest available direct evidence that reproductive health was being adversely affected in Europe in those years. No explanation for this decline has been established, so renewed attempts should be made to identify the explanation. Meanwhile I suggest that it would now be worth routinely trying to estimate rates of 'natural' (non-iatrogenic) maternal-age-specific DZ twinning by adjusting the reported rates of DZ twinning for those DZ twin pairs caused by the various forms of assisted reproduction. [At present, it is estimated that more than half of all twin pregnancies are the result of assisted reproductive technologies (Van Wely *et al.*, 2006).] I attempted to estimate the frequency of iatrogenic twinning (James, 1995a) and tentatively concluded that the natural DZ twinning rate ceased declining in England and Wales at some time in the 1980s. One may provisionally infer that across the years 1960–80, many European countries were exposed to increasing levels of environmental agents (presumably endocrine disruptors) that had adverse effects on human reproductive parameters. Some time after these two decades, it seems that, in some countries, the levels of these agents stabilized and perhaps diminished. However, if the natural maternal-age-specific DZ twinning rates have not returned to their former high levels in Europe (say around 1960), one may infer that human populations here are still exposed to some measure of these adverse agents. For this reason, I suggest that *all* births following assisted reproduction should be routinely notified (by plurality and sex combination of twins) to some central data-processing agency (e.g. the National Office for Statistics). For only then will it be possible to estimate the yearly numbers of iatrogenic DZ twins and thus estimate secular changes in natural DZ twinning rates and thus assess to what extent reproductive health is being exposed to suspected adverse agents.

For practical purposes, the number of DZ twin pairs may be estimated by Weinberg's differential rule, viz. by doubling the number of opposite-sexed twin pairs. Using genetic markers, it has been shown empirically that this rule closely approximates the truth (Fellman and Eriksson, in press).

Fecundability

Fecundability (the probability of a live birth conception in a month at risk) is also a good measure of reproductive health in that it shares some of the biological determinants of DZ twinning as seen from the formula

$$F = p_1 p_2 p_3 p_4,$$

where F is the fecundability, and the four (presumably roughly independent) probabilities are p_1 the probability of ovulation, p_2 the probability that coitus occurs in the fertile interval of the ovum, p_3 the probability that the ovum is fertilized and p_4 the probability that spontaneous fetal loss does not occur.

However, in contrast to DZ twinning, fecundability is difficult to measure (Stephen and Chandra, 2006). This is so because it requires data on time-to-conception in large numbers of randomly ascertained couples wishing to achieve pregnancy. And this, in turn, requires the collaboration of large numbers of subjects concerning events that require tact, delicacy and judgement in their assessment. So, only if these difficulties are borne in mind, would it seem practical to suggest that other countries might follow the US in attempting to monitor fecundability routinely.

Sex ratio

It has become clear that sex ratios (proportions male at birth) have declined across recent decades in a number of developed countries (though not others). For instance, in their review of national live birth sex ratios over the past half-century, Parazzini *et al.* (1998) reported declines in Belgium, Bulgaria, Denmark, Finland, Germany, Greece, Hungary, the Netherlands, Poland, Portugal, Rumania, Sweden and Mexico. These authors also reported increases in sex ratios across these years in France, Ireland, Italy, Spain and Australia. Finally, in the USA, sex ratios decreased in White births and increased in Black births across the years 1969–95 (Marcus *et al.*, 1998).

To what extent can these secular changes be usefully regarded as indicators of reproductive health? There is evidence that a number of types of adverse paternal chemical and occupational exposures and of paternal illnesses are associated with low offspring sex ratios and low paternal testosterone levels (James, 2006). However, in that paper, I also adduced evidence that offspring sex ratios are significantly *high* (in contrast to controls) in association with two types of paternal pathology and nine types of maternal pathology. One may infer that routine monitoring of national sex ratios would not reliably detect reproductive (or other) pathology. This is because the effects of some forms of exposure and pathology would mask those of others. In particular, the effects (on sex ratio) of some sorts of exposure are thought to be opposite in men and women (James, 2006). This is not to deny that sex ratios, in certain well-specified conditions, may usefully indicate the effects of endocrine disruptors (viz. where the exposure status of both parents of all the offspring is known). However, without such supplementary information, interpretation of secular trends in sex ratios is problematic.

Movements in either direction may, though not decisively, suggest adverse exposures. Moreover, a stable sex ratio may mask opposing effects of adverse exposures in parents of the two sexes.

Sperm concentrations

Sperm concentrations are useful measures of sperm quality. As far as I know, I was the first to suggest that there has been a worldwide decline in sperm counts (James, 1980). However though much subsequent work has been done on the problem, agreement is not unanimous that there has been such a decline. So attempts should be made to monitor sperm counts routinely in European countries. This might be done by requiring all licensed assisted reproduction units routinely to forward data on the quality of the sperm of their volunteer donors to some central data-processing agency, e.g. in this country, the National Office for Statistics.

Spontaneous fetal loss

It would be useful to know of secular changes in rates of spontaneous fetal loss. However, the practical problems of routinely monitoring spontaneous abortion rates would seem to outweigh the benefits (James, 1996). Stillbirth rates are, of course, already subject to such monitoring.

Coital rates

Though coital rates may be thought a useful monitor of reproductive health, the interpretation of reported rates is subject to more qualification than their measurement would seem to merit. For instance, I cited reported secular changes in coital rates in the USA to support a hypothesis relating them to offspring sex ratios (James, 1995b). But I doubt if such advocacy changed many minds: this is so because changes in reported coital rates are intrinsically subject to difficulties of interpretation.

'Dead' time

For completeness, mention should be made of one last proximate determinant of fertility, namely the anovulatory interval following parturition when a woman cannot conceive, the 'temps mort' (dead time) of French mathematical demographers. If this parameter showed secular changes, so too would overall fertility. I know no data on such changes in this parameter, but it would be odd if it were immune to endocrine disruption, bearing in mind that it is extended by lactation (Henry, 1963).

Summary and conclusions

(i) It is suggested that natural DZ twinning rates may be the best overall measure of a nation's reproductive health. So efforts should be made to require fertility clinics to forward data on all their births by plurality and sex combination of twins. This would facilitate the adjustment of the reported national DZ twinning rates for those iatrogenic twins which result from the various techniques of assisted reproduction. In this way, we could derive estimates of 'natural' DZ twinning rates, and thus continue to assess reproductive health.

(ii) Reports of sperm quality from donors in fertility clinics should also be routinely made.

(iii) Apart from these two provisions, it is hard to see how routine monitoring might enable the economic assessment of secular changes in the proximate determinants of fertility.

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