Male fertility-related disorders: cause for concern or a stalking horse?

Mireille B Toledano, Paul D Nelson

Perspective on the papers by Abdullah *et al* and Nassar *et al* (see pages 576 and 580)

In this issue, Abdullah *et al* examine routine Hospital Episode Statistics (HES) from the 1990s for northern England and report a decreasing birth prevalence of cryptorchidism and orchidopexy. In addition, they report a small increase in birth prevalence of hypospadias but no change in the rate of hypospadias surgical repair (corrective procedure rates). The latter is more likely to reflect true prevalence as the vast majority of cases are referred for surgery. In contrast, Nassar *et al*, also in this issue, report on a population-based study to determine trends in hypospadias in the Australian population, 1980–2000. Data were obtained from a congenital anomaly registry (with multiple sources of notification) for aborted and still births and for live births up to 6 years old. Overall birth prevalence was found to be 3.5 over the 20-year study period with birth prevalence rates increasing significantly by 2% per annum.

Both these papers reporting contrasting trends in male fertility-related disorders are part of a wider series of publications examining the evidence for adverse trends in male reproductive health, in particular, in association with exposure to ubiquitous environmental chemicals mimicking oestrogen.

Much public interest in this body of research came from popular science, most notably Carson's *Silent spring* in 1962 warning us of the dangers posed by man-made pesticides. This was followed in 1996 by Colborn *et al*'s scientific detective story *Our stolen future*, which suggested that we were still ignoring the danger of man-made chemicals and thereby threatening our fertility and human survival. In the academic domain, these ideas were formalised into the controversial "endocrine disruptor hypothesis" notably by Skakkebaek, Sharpe and colleagues. Much evidence of chemical-hormonal activity *in vitro* is available, together with both convincing toxicological data at high doses and observational evidence of the sexuality-modifying effects of these chemicals in

wildlife. Likely candidate human outcomes for endocrine disruption include testicular cancer, decreasing sperm counts, and the congenital anomalies of cryptorchidism and hypospadias. Skakkebaek *et al* have suggested that these disorders are all related in what they term "testicular dysgenesis syndrome" and Sharp and colleagues^{2,3} have put forward putative animal models for this syndrome.

But what epidemiological evidence is available for adverse trends in congenital anomalies of the male reproductive system?

For hypospadias, several authors reported increasing trends in birth prevalence from the 1960s to the 1990s; however, recent studies from Scotland and California have cast doubt on these reports. Moreover, the contrasting articles in this issue appear simply to add to the already inconclusive evidence. Previous epidemiological studies have reported widely varying estimates of hypospadias birth prevalence. Estimates have ranged from 0.9 to 9 per 1000 male live births. The uncertainty of these figures reflects the mode and the context of ascertainment as well as true differences in different populations.

For cryptorchidism, secular trends suggested large increases in rates in Great Britain and the USA between the 1950s and the 1980s. Published data on recent trends have been scarce, although Toledano *et al*⁴ using data from HES and the General Practice Research Database (GPRD) and Abdullah *et al* suggest, in contrast, declining trends in orchidopexy rates during the 1990s in Britain. Once again, the evidence appears unclear and inconclusive.

Reported trends are often hard to interpret due to a number of factors. These include: the use of routinely collected data and their inherent inaccuracies and complexities of use and interpretation, for example, hospital activity in the UK depends not only on the underlying prevalence of disease but also on the diagnostic accuracy and

referral practice of the primary care clinician, patient-specific factors such as individual preferences, distance of residence from hospital and socio-economic class and on hospital-specific factors, such as quality of the hospital data collected, supply of hospital beds, admission policies and hospital access⁵; incomplete ascertainment by congenital anomaly registries (which varies nationally and internationally) and differences in the information they choose to collect for surveillance, for example, the exclusion of "minor anomalies" in 1990 by the UK National Congenital Anomaly Registry (NCAR) including glandular hypospadias and cryptorchidism cases, necessitating the use of orchidopexy rates from HES as a proxy for cryptorchidism prevalence; inconsistency in the methodology employed between studies and the denominator data they use, for example, Abdullah *et al* in this issue have used male live births as their denominator, whereas other studies have used total births; and, finally, the choice of inclusion criteria used both nationally and internationally for hypospadias, for example, the EUROCAT definition for hypospadias excludes glandular (mild) cases.

The epidemiological data available to answer the questions posed are therefore necessarily highly complex and difficult to interpret. Meanwhile, congenital anomalies are rare, environmental exposures of interest occur at very low levels, and we are trying to detect very small increases in risk. Unsurprisingly, the resulting body of evidence continues to be inconsistent. This inconsistency may reflect the fact that epidemiology as a tool lacks resolution to answer the question.

Whilst it is likely that hypospadias and cryptorchidism have an environmental component to their aetiology and that endocrine disturbance plays a role in the pathophysiology, it is less likely that exposure to very low concentrations of chemicals is a physiologically relevant causal factor, even where such chemicals have endocrine activity *in vitro*. Moreover, it is unlikely that current epidemiological research will provide sufficiently firm evidence of a clinically significant environmental component amenable to public health action.

As scientists, we are thus left with a highly speculative and unprovable proposition regarding the human public health relevance of endocrine disruption. The media have a subject with all the hall-mark ingredients for a continuing news story – uncertainty, disagreement between scientists (conspiracy theory) and high emotive factor, as babies are affected. We have an anxious public and no satisfactory answer for them. Public

perception of risk in this area, therefore, has the potential to become exaggerated. Moreover, media-driven public interest can lead to additional research, more equivocal data, an ever accelerating spiral of anxiety and, ultimately, public policy detrimental to health.

We discuss first the case of dichlorodiphenyl-trichloroethane (DDT) which we judge was an example of international policy driven mainly by exaggerated public anxiety and which resulted in damage to public health. Secondly, we highlight the case of chlorination disinfection by-products (DBPs) where there maybe ongoing selective interpretation of epidemiological and other evidence leading to exaggerated public perception of risk. This may drive policies which are ultimately adverse to public health.

EXAMPLE 1

DDT was the first modern pesticide developed early in World War II. Initially it was used with great effect to combat mosquitoes spreading malaria, typhus and other insect-borne human diseases, and as an agricultural insecticide. However, following Carson's *Silent spring*, there was large public outcry which eventually led to the insecticide being banned for agricultural use in the USA, and subsequently worldwide. In addition, many restrictions on the use of DDT in vector control followed, imposed by various national governments, donor countries and international aid agencies, in response to pressure from environmentalists. Such action was taken despite scientific evidence showing both a strong safety record for DDT when used in small quantities for indoor spraying in endemic regions and that, of the dozen insecticides

WHO approves as safe for house spraying, the most effective was and still is DDT. In parallel, the campaign against malaria has arguably been failing⁶ and the WHO estimates that malaria continues to afflict 300–500 million people every year and that around 1 million people die of malaria and malaria-related illness every year. Remarkably, in an important policy shift, the WHO announced last September that it was promoting the indoor use of DDT to fight malaria. Dr Arata Kochi, director of the WHO's Global Malaria Department, said "We must take a position based on the science and the data.... One of the best tools we have against malaria is indoor residual house spraying... the most effective is DDT. Extensive research and testing has... demonstrated that well-managed indoor residual spraying programmes using DDT pose no harm to wildlife or to humans".⁷

EXAMPLE 2

Chlorination has been the major disinfectant process for domestic drinking water for many years. Concern about the potential health effects of the by-products of chlorination has prompted a flurry of investigations into the possible association between exposure to these by-products and the incidence of human cancer, and more recently, with adverse birth outcomes including low birth weight, stillbirth and various congenital anomalies. These studies are looking for very small increases in risk associated with very low levels of exposure. Findings to date have been inconsistent.⁸ As with the male fertility-related disorders, however, such research has frequently made headline news, increasing fears amongst women about swimming and drinking tap water during pregnancy. Parallel with this, there have been continuous pressures on the water industry to lower DBP levels whilst trying not to compromise microbial safety in their water supply (an ever increasingly difficult task) as well as moves to use alternative primary disinfectants in water treatment plants instead of chlorine, for example, the use of ozone in some parts of Canada and Europe, with its own ozonation by-products. The latter may also carry health risks which to date have been little investigated. When assessing any potential risks associated with DBPs, however, it is essential for scientists to recognise the substantial benefits to health associated with disinfection by chlorination. The use of chlorine has virtually eliminated water-borne microbial diseases because of its ability to kill or inactivate essentially all enteric pathogenic micro-organisms, including viruses and bacteria from the human intestinal tract. We should also remember that

according to the WHO more than 1.5 billion people around the globe still do not have access to safe drinking water, and diseases associated with dirty water kill more than 25 000 people per day – more than 9 million each year – around the world.

The examples given above serve as a warning of how well-meant action and policy have had, and could have, detrimental consequences for public health. The endocrine disruptor hypothesis has all the ingredients for an environmental health scare that could lead to negative public health. We hope that scientists will carry out research mindful of the limitations of scientific methods and of the scrutiny of media, the public and politicians. Even the posing of a study question has a potential impact on public health. Resulting evidence must be weighed up and interpreted from a balanced perspective within a wider, integrated cost-benefit assessment in terms of the health of the public and society as a whole. The recent Committee on Toxicity's report on the human male reproductive system and potential chemical-induced effects⁹ offered an opportunity to embrace this wider perspective. However, we find it advocates a "more of the same" approach to investigating the endocrine disruptor hypothesis. It calls for more toxicology and epidemiology, whilst acknowledging their limitations in resolving the question, and the fact that "...a clear link between experimental data and epidemiology is still missing".⁹ We, as a community of researchers, must ask ourselves, are we moving forward this body of research or do we simply resemble the "Ascending and Descending" figures in Escher's famous lithograph? (fig 1).

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REFERENCES

- 1 Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum Reprod* 2001;**16**:972–8.
- 2 Sharpe RM, Rivas A, Walker M, et al. Effect of neonatal treatment of rats with potent or weak (environmental) oestrogens, or with a GnRH antagonist, on Leydig cell development and function

Figure 1 M.C. Escher's "Ascending and Descending" © 2007 The M.C. Escher Company-Holland. All rights reserved. www.mcescher.com.

- through puberty into adulthood. *Int J Androl* 2003;**26**:26–36.
- 3 **Sharpe R.** Hormones and testis development and the possible adverse effects of environmental chemicals. *Toxicol Lett* 2001;**120**:221–32.
 - 4 **Toledano MB, Hansell AL, Jarup L, et al.** Temporal trends in orchidopexy, Great Britain, 1992–1998. *Environ Health Perspect* 2003;**111**(1):129–32.
 - 5 **Hansell A, Bottle A, Shurlock L, et al.** Accessing and using hospital activity data. *J Public Health Med* 2001;**23**(1):51–6.

- 6 **Yamey G.** Roll Back Malaria: a failing global health campaign. *BMJ* 2004;**328**:1086–7.
- 7 **World Health Organization.** WHO gives indoor use of DDT a clean bill of health for controlling malaria. News release, September 2006. <http://www.who.int/mediacentre/news/releases/2006/pr50/en/index.html> (accessed 17 April 2007).
- 8 **Nieuwenhuijsen MJ, Toledano MB, Eaton NE, et al.** Chlorination disinfection by-products in water and their association with adverse reproductive

outcomes: a review. *Occup Environ Med* 2000;**57**(2):73–85.

- 9 **Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment.** COT meeting report on the development and function in adulthood of the human male reproductive system – potential chemical-induced effects. COT statement, November 2006. <http://www.food.gov.uk/science/ouradvisors/toxicity/statements/cotstatements2006/371075> (accessed 17 April 2007).

Management of menstruation

Manipulating growth and puberty in those with severe disability: when is it justified?

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Perspective on the paper by Albanese and Hopper (see page 629)

Albanese and Hopper have laid out a clear stepwise approach to the management of menstruation, wanted and unwanted, in girls in whom self-management is either not an option or undesirable, or where prevention of unwanted pregnancies may be in the girl's "best interests".¹ It is the use or misuse of this phrase "best interests" that can license medical practitioners to extend the nature of interventions into uncharted territory. There is no doubt that it is in the child's "best interests" to have a loving and stable home, and this is most likely to be best provided by the family. How far though should we extend clinical manipulation to achieve this end? This discussion was brought to the fore in the case of the American girl Ashley X, diagnosed with static encephalopathy,² about whom discussions with her doctors over matters concerning puberty manipulation went far beyond the standard approach and led to growth limitation with high-dose oestrogens combined with irreversible surgical interventions such as hysterectomy and mastectomy to avoid the side effects of the hormone treatment and improve quality of life. This approach has taken us into a quagmire of diametrically opposed opinions, polarised between those in support of her parents' genuine desire to achieve the best outcome for their child, and those staunch defenders of the rights of the disabled. Who is right therefore, and should the "Ashley treatment" which her parents have been advocating³ be considered for all children with severe disability? Situations such as this demand an objective examination of medical evidence but

also a clarification of our moral duties as carers and where we stand within the law.

Let us examine the facts. Ashley presented with central precocious puberty when aged 6 years, a not unusual finding in children, especially girls with major central nervous system disruption. What are the consequences of this? In children with normal cognitive functioning, early sexual maturation is usually accompanied by pronounced emotional swings and personal embarrassment resulting from the precocious physical changes of puberty causing families to beg for intervention to halt the process. Is this the same in children with reduced levels of functioning? This must be assessed individually, taking into account the carers' observations and views, and their personal situation. The inability to cope with the strong emotional surges of sex hormone secretion, or the manifestation of inappropriate explicit sexual behaviour, warrants reversible treatment with gonadotropin releasing hormone analogues. What about suppressing menstruation? Views are mixed, but in girls who have not achieved continence, families often report that menstrual periods cause little extra bother for their daughter or need for extra care. A staged and reactive approach to management is surely the most acceptable, and raises few ethical objections from any party. Surgery may need to be considered when medical treatment fails.

Why therefore such outcry at the prophylactic hysterectomy and mastectomy offered in the case of Ashley X? Well it flies in the face of moves to define judgement in this area through recent

legislation such as the Mental Capacity Act in the UK.⁴ This begins with the presumption of capacity, supporting people to make their own decisions unless proven that they cannot despite appropriate help being given. It assumes that anything done for or on behalf of people without capacity must be in their "best interests". Any consequent intervention in such circumstances should be the least restrictive of their basic rights and freedoms. Additional to this is the "Gillick test" of competence that all doctors must apply to minors below the age of 16 years to ensure that the principles of beneficence and non-maleficence are executed in each individual circumstance.⁵ An additional onus is placed therefore on those caring for under 16 year olds.⁶

A legal and moral minefield? Well not if approached piecemeal. It is clear that many children in similar circumstances are not even capable of participating minimally in decisions in respect of their own treatment. Therefore the involvement of parents is crucial and consistent with the Mental Capacity Act. However, how far does the parental exercise of authority extend, especially when the requirement is for interventions that should be the least restrictive of basic rights and freedoms? Medical therapy is often reversible, but surgery as in Ashley's case is not. Her future options are therefore more radically restricted than necessary. Here there was a very obvious conflict of interests: the options involving courses of treatment or non-treatment would affect not just her quality of life but that of her carers also. So it is more difficult to ensure that the interests of the child remain paramount when their proxy has their own interests to consider. Who therefore should exercise judgement of "best interests"? Is it the parents who have day to day responsibility, or the clinicians, hopefully furnished with objective accurate information? Are we the most advantageously placed to judge the best course of action? Even if the prevailing public view is that this treatment could be appropriate in this case, it should not necessarily lead us to conclude that similar treatment is appropriate in all cases of major disability. Individual circumstances need to be considered,