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INVITED COMMENTARY

Location, location, location—where you are born may determine your reproductive (and more general) health

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The notion that human male reproductive health has been declining in recent decades has been an issue of intense debate and media interest and a keen focus for clinical and experimental research for the past 25 or so years (Skakkebaek *et al.*, 2016). Although the research data to have emerged has largely supported and extended the evidence for declining male reproductive health, especially for sperm counts (Levine *et al.*, 2017) and testicular germ cell cancer (Gurney *et al.*, 2019), what remains unresolved is the precise cause(s) of these adverse changes. What has become clearer is that the adverse reproductive changes are likely to have their origins in early fetal life, probably in the so-called masculinization programming window identified by experimental studies in rodents (Welsh *et al.*, 2008; Sharpe, 2020), for which there is growing support from human studies (van den Driesche *et al.*, 2017; Sharpe, 2020). These developments are consistent with the testicular dysgenesis syndrome (TDS) hypothesis, first proposed 20 years ago (Skakkebæk *et al.*, 2001).

Although this new understanding has provided an important research focus, identifying what maternal factors or exposures might impact fetal testis function, especially testosterone production during the masculinization programming window, presents huge challenges. Put simply, how do you measure potential effects on the developing fetal testis at a stage (8-14 weeks' gestation) when the fetus itself is only 3.5-5cm in length and is secluded in the mother's uterus? One important, but indirect, indicator to have emerged is anogenital distance (AGD) at birth, the size of which is programmed by androgen action specifically during the masculinization programming window (Welsh *et al.*, 2008; van den Driesche *et al.*, 2017; Sharpe, 2020). However, a shorter AGD is not itself a reproductive disorder, so a more clinically relevant research focus has been to use either of two congenital male reproductive disorders, cryptorchidism and hypospadias, that are evident at birth and the occurrence of which are associated with shortened AGD in both humans (reviewed in Dean and Sharpe, 2013; Sharpe, 2020) and in experimental animal studies (Welsh *et al.*, 2008; van den Driesche *et al.*, 2017). Of the two disorders, cryptorchidism is far more common (Foresta *et al.*, 2008; Skakkebaek *et al.*, 2016) and is therefore better suited to epidemiological studies that seek to ask whether any maternal factors or exposures are associated with its occurrence.

The main focus of such epidemiological research effort has been on exposure to so-called endocrine-disrupting chemicals (EDCs), the hypothesis being that these chemicals may perturb testosterone production by the fetal testis in early gestation (Virtanen and Adamsson, 2012), one consequence of which is impaired testicular descent into the scrotum (Foresta *et al.*, 2008). In this regard, there is evidence that occupational exposure of pregnant women to certain pesticides that includes EDCs may be associated with a mildly increased risk of cryptorchidism in resulting sons (Brucker-Davis *et al.*, 2008; Virtanen and Adamsson, 2012), but evidence for a similar association in the general population, who are exposed only indirectly to pesticide contaminants in air and food, is inconsistent (Virtanen and Adamsson, 2012). Nevertheless, it was thinking along these lines that prompted a French nationwide study (Le Moal *et al.*, 2021) published in the present issue of *Human Reproduction*. This study had two main goals. First to establish if the incidence of cases of cryptorchidism requiring operative correction had changed over a 13-year period (2002–2014). Second, to use state-of-the-art spatial disease-mapping to establish if the cases of operative cryptorchidism were evenly distributed across France or showed cluster hotspots. In many respects, the results of the study confirm present thinking in that they show a 36% increase in operated cases of cryptorchidism over the 13-year period of the study and, in showing 24 hotspot clusters of such cases scattered around France, the study confirms an important role for environmental factors in determining risk of cryptorchidism.

What sets the present study apart is its nationwide scale and, as a result, its ability to provide a snapshot of the risk of a male baby having persistent cryptorchidism (i.e. requiring surgical correction) according

to where in France he was born/spent his early life; identification of an increase in cases of cryptorchidism over the short span of time of the study is icing on the cake, albeit rather alarming. There is already published evidence for regional differences in incidence of cryptorchidism in northern England (Abdullah *et al.*, 2007) southern Spain (Garcia-Rodriguez et al 1996) and in South Korea according to the degree of industrialization (Kim *et al.*, 2011), but these studies did not have the scale of the present study. As the present authors discuss at length, there are a number of limitations to the study which urge a degree of caution when interpreting the findings (Le Moal *et al.*, 2021), but these are inherent to any epidemiological study of cryptorchidism, and none of these uncertainties appear capable of undermining the main study findings. As outlined above, the question we urgently need answers to is 'what environmental factor(s) increases risk of cryptorchidism and why has this been increasing in recent times?' Does this study throw any new light on this?

First, what about the potential role of pesticide exposure? If this is important in the etiology of cryptorchidism then the identified hotspot clusters of cryptorchidism would likely be restricted to rural farming areas and/or areas of intensive agriculture, as has been reported in other studies (Garcia-Rodriguez *et al.*, 1996; Lane *et al.*, 2017). This was not the case, as only a small number of such clusters were identified and only associated with cases of bilateral cryptorchidism, which is far less common than unilateral cryptorchidism. Instead, the main finding was that clusters of cryptorchidism cases were predominantly associated with areas of previous/current heavy industry, in particular mining, smelting and metallurgical processes. Pollution, especially air pollution, in such industrialized areas has been frequently associated with increased risk of low birthweight (e.g. Pedersen *et al.*, 2013; Laurent *et al.*, 2014; Porter *et al.*, 2014; Suter *et al.*, 2019), which is the most important known determinant of cryptorchidism risk in baby boys (Jensen *et al.*, 2012). In the present study, these industrialized areas were also established as having been in economic decline and thus associated with socioeconomic deprivation. This is a particularly important observation because socioeconomic deprivation is also associated with a consistent increase in risk of preterm birth and/or small for gestational age babies (Valero de Bernabé *et al.*, 2004), and hence for cryptorchidism risk (Jensen *et al.*, 2012). Indeed, numerous aspects of poor lifelong health are associated with being born in such areas, often through their association with low birthweight or prematurity (Valero de Bernabé *et al.*, 2004; Sellstrom and Bremberg, 2006; Bergstra *et al.*, 2021).

Le Moal *et al.* (2021) rightly discuss how increased exposure to metals (e.g. lead, cadmium) or other pollutants (e.g. polychlorinated biphenyls; PCBs) in the 'industrial hotspots' might be responsible for the associated increase in risk of cryptorchidism via an endocrine-mediated mechanism. However, it needs to be also kept in mind that increased exposure to certain heavy metals (e.g. cadmium) has been associated with increased risk of low birthweight (Barn *et al.*, 2019), and similar associations have been found for exposure to PCBs and dioxin, with birthweight of male babies being more affected than females (Hertz-Picciotto *et al.*, 2005; Papadopoulou *et al.*, 2014; Vafeiadi *et al.*, 2014; Zou *et al.*, 2019). Increased exposure to another class of common pollutant, polycyclic aromatic hydrocarbons, in the proximity of industrial sites has also been associated with increased risk of preterm birth (Suter et al., 2019). Thus, it could be that exposure to industrial pollutants coupled with low socioeconomic circumstances could together increase the risk of low birthweight in baby boys (Thompson *et al.*, 2014) which in turn increases the risk of cryptorchidism (and other low birthweight-associated health problems) and might partially explain the clusters of cryptorchidism observed in the study by Le Moal *et al.* (2021). This does not exclude potential endocrine-disrupting effects of one or more of the pollutants themselves (e.g. dioxins, Vafeiadi *et al.*, 2013). Moreover, although it is theoretically possible that the mechanism(s) underlying pollutant-induction of low birthweight is secondary to an impact on androgen production by the fetal testes, the evidence from genetic males with complete androgen insensitivity syndrome shows that the higher androgen levels in male than female fetuses is not responsible for the generally higher birthweight in males (Miles *et al.*, 2010).

Some might argue that the study by Le Moal *et al.* (2021) does not take us any further forward in trying to understand the causes of cryptorchidism, and by extension testicular dysgenesis syndrome. However, it is in many respects a landmark study, for 4 reasons. First, it uses the most developed spatial monitoring statistical approaches and is thus technically front-rank. Second, it uses data for a whole country over a 13-year period. Third, it provides robust supporting evidence that environmental impacts (via the mother) on the male fetus are a very real health threat today, even in a modern developed country like France. Fourth, and in my opinion most importantly, it suggests that our recent research focus on environmental chemicals as a potential cause of cryptorchidism (and other male reproductive disorders that are increasing) may have been correct in principle but incorrect in practice. Correct because the hotspot clusters of cryptorchidism cases are clearly associated with industrialized areas that are proven to increase human exposure to numerous pollutants (Alias *et al.*, 2019; Suter *et al.*, 2019; Johnston and Cushing, 2020). Incorrect, because the main focus of research in this area over the past 20+ years has been on chemicals to which most of the population is lowly exposed via food (e.g. bisphenol A, phthalates, modern pesticides) rather than those more associated with proximity to heavy industry. Hopefully this new study will act as an important reinforcement for all of those involved in researching the causes of common male reproductive disorders at the same time as making us re-evaluate whether we have the right chemicals in primary focus.

Finally, and most importantly, the study by Le Moal *et al.* (2021) is a stark reminder that many cases of cryptorchidism are inherently preventable, if only we can identify the industrial chemical culprits, a remark that probably applies in general to the commonest male reproductive disorders. In an age of increasing couple fertility problems, this is yet another wake-up call for us all (Barratt *et al.*, 2018).

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Conflict of interest

The author declares no conflict of interest and nothing to disclose.

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