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The Early Life Influences on Male Reproductive Health

Jennifer Pontré and Roger Hart

Abstract

Increasing concern exists regarding male reproductive health worldwide. This is due to the appearance of medical reports outlining apparent adverse trends, such as a worldwide decline in total fertility rate, and an increase in testicular disorders such as testicular cancer, cryptorchidism—in parallel with a probable decline in semen quality. This is of particular concern as there is evidence to suggest that a poor sperm count is potentially associated with overall lifelong morbidity and mortality, and is effectively a predictor of lifelong health risk. This chapter examines the evidence for this decline and its potential early life causes, from in-utero exposures to childhood development.

Keywords: male reproduction health, sperm, testosterone, in-utero, phthalate, BPA

1. Introduction

Between 1986 and 1993, British physician and epidemiologist David Barker published a series of articles in the *Lancet*, proposing his hypothesis of the foetal origins of adult health and disease [1–3]. In these publications, he argued that adverse alterations in the developmental early life environment *in utero*, had potential to induce and initiate phenotypic and adaptive changes affecting an individual's responses to their later life environment, which might prove maladaptive when the early and late environments were markedly different [4, 5]. Barker's specific foetal concerns were inadequate nutrition, [6] intrauterine growth retardation, low birth weight and premature birth and their causal relationship to the origins of hypertension, coronary heart disease and non-insulin-dependent diabetes, in later life [7]. However there is now growing evidence to suggest that this 'developmental programming' and the foetal environment, which includes placental function, maternal metabolism, exposures and lifestyle factors (including maternal smoking), may influence additional systems including reproductive health and development in both males and females [5, 8].

Increasing concern exists regarding male reproductive health worldwide due to the appearance of medical reports outlining apparent adverse trends, in the context of a worldwide decline in total fertility rate (**Figure 1**) [9, 10]. This includes an increase in the incidence of the proposed 'testicular dysgenesis syndrome' [10] which encompasses a constellation of testicular disorders including testicular cancer, [11, 12] cryptorchidism and hypospadias [13]. This is in parallel with population-based evidence to suggest declining semen quality, [14] alterations in serum testosterone levels and a change in the timing of onset of male puberty [9]. Worryingly, one comprehensive review of the literature proposed that semen quality had declined by 52.4% between 1973 and 2011 among unselected men from Western countries [14]. Another recent report, published

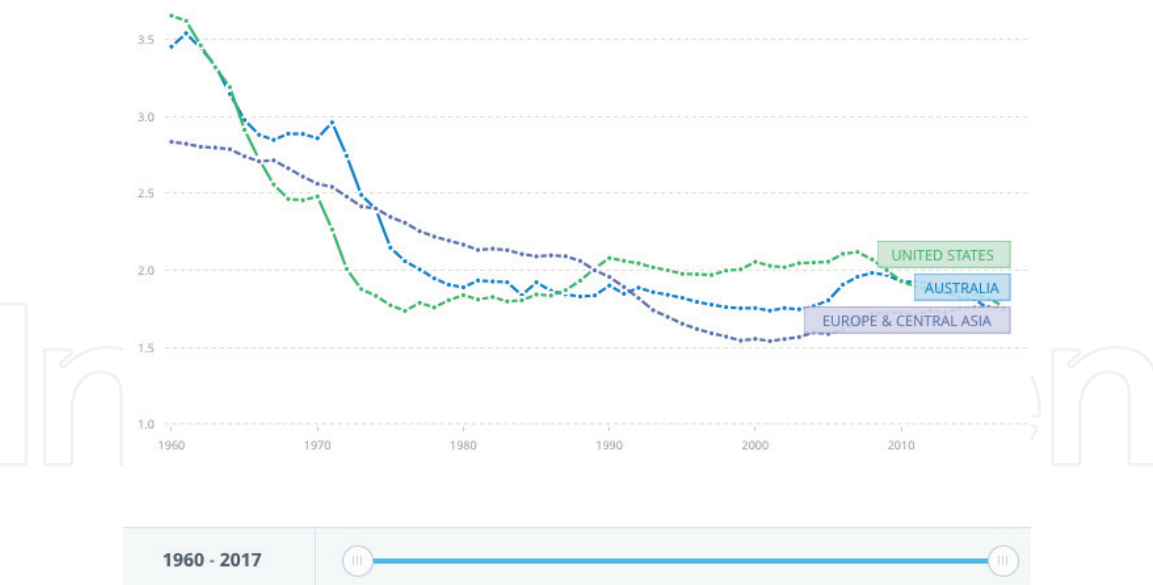


Figure 1. Total fertility rates for Australia, United States, Europe and Central Asia 1960–2017. Reprinted with permission from the World Bank: www.worldbank.org.

in 2015, found that a high proportion of healthy, unselected 20-year-old Caucasian men displayed suboptimal semen quality which did not meet the lower limit of World Health Organization reference ranges for sperm concentration, motility and morphology values [15]. These findings were echoed by a further Swiss study published in 2019 where over 60% of participants displayed suboptimal median sperm concentration [12]. Sperm count is of obvious importance in fertility and reproduction, however recent studies have now demonstrated that poor sperm count is potentially associated with overall lifelong morbidity and mortality, and is effectively a ‘canary in the mine’ marker for lifelong health risk [14, 16–18]. To elicit a greater understanding of the early life influences on these important, early determinants of male reproduction and health are therefore of great importance.

In this chapter, we present and discuss the evidence for the developmental programming of male reproductive maturation and function.

2. Male reproductive development

Male reproductive development has a long time to maturation, with onset in the embryo and completion in puberty. The critical and narrow prenatal window for the normal differentiation and growth of male reproductive tissue during which testosterone and its potent metabolite dihydrotestosterone, (DHT) masculinise the male foetus is estimated to be around 8–14 weeks of gestation [19–21]. The formation of the indifferent bipotential gonad occurs between the fourth and sixth weeks of foetal life, and male reproductive development subsequently begins when the SRY gene, encoding a ‘testis-determining factor’ on the Y chromosome stimulates the development of the primitive sex cords to form the medullary cords. Sertoli cells appear, and in the eighth week, Leydig cells appear and commence production of testosterone. In the presence of this testosterone, the mesonephric ducts develop to form the primary male genital ducts. They give rise to the efferent ductules, epididymis, vas deferens and seminal vesicles, whilst the paramesonephric ducts degenerate. Meanwhile, in the presence of DHT, the male external genitalia differentiate as the genital tubercle elongates to become the phallus and the urethral folds close over, forming the penile urethra.

The hypothalamic-pituitary-gonadal axis is active in the mid-gestational foetus, but silenced towards the end of gestation. This restraint is removed at birth, leading to reactivation of the axis and an increase in serum gonadotropin concentrations, often labelled the 'mini-puberty' [22, 23]. Testosterone concentration rises to a peak at age 1–3 months, but then falls in conjunction with the falling luteinising hormone (LH) concentration [22]. Prenatal and postnatal activation of the hypothalamic-pituitary-gonadal axis is associated with penile and testicular growth and testicular descent, and is therefore regarded as important for the development of male genitalia. These concentrations then gradually decrease towards age 6 months when there is an active inhibition of gonadotrophin-releasing hormone (GnRH) secretion, which persists throughout childhood, [22, 24] and the hypothalamic-pituitary-gonadal axis remains quiescent until puberty.

3. Male pubertal development

Male puberty marks the transitional period during which the infantile boy attains adult reproductive capacity with usual age of onset around 11.5 years.

Pubertal development of secondary sexual characteristics is initiated, at least in part, by a sustained increase in pulsatile release of GnRH from the hypothalamus. There is testicular growth as the seminiferous tubules are stimulated by follicle-stimulating hormone (FSH), and once their volume exceeds 3–4 ml pubertal onset is confirmed. Leydig cells, stimulated by LH, produce testosterone which influences penile growth and pubic hair development. Spermatogenesis occurs under the regulation of multiple endocrine and local factors [9]. Although the exact mechanisms underlying the commencement of puberty in both males and females is unclear, there is evidence for influence of a multitude of factors including genetic, environmental factors, body composition, physical fitness, nutritional and socioeconomic status, ethnicity, residence and exposure to endocrine disruptors [25]. Other important stimulatory and inhibitory pathways involving glutamate kisspeptin and the G protein-coupled receptor GPR54 exist [26, 27].

In essence, the increase of pulsatile GnRH secretion at puberty represents the cumulative effect of highly complex and intricate hypothalamic interactions that are markedly influenced by genetic factors and environmental signals [26]. An advancement in the timing of puberty has been reported worldwide over the past two decades [28]. The timing of puberty has important public health ramifications because it is related to a number of health outcomes [29]. Early puberty is potentially associated with increased risk of testicular cancer, as well as adolescent alcohol abuse, smoking, drug use, early sexual debut, sexually transmitted infections, aggressive behaviour and poor academic performance [15, 30]. These observations urge further study of the onset of puberty as a possible sensitive and early marker of the interactions between environmental conditions and genetic susceptibility that can influence physiological and pathological processes [25].

4. Potential influences of male reproductive development and pubertal development

4.1 Placental malfunction and antenatal factors

Impaired placental malfunction, which has the potential to disrupt foetal androgen production, has been theorised to affect male reproductive development, and a definite link between impaired foetal growth and reproductive function has been

established. Consequences on gonadal differentiation, sexual organ development, onset of puberty, gamete quality, hormonal status and fertility have been observed [31, 32]. Several studies have described an association between foetal growth restriction and an increased risk of male reproductive health problems, including hypospadias, cryptorchidism and testicular cancer [13, 33, 34]. In addition, twin or triplet pregnancy and preterm birth have also been shown to be associated with non-gestational-related impaired reproductive development [35]. One study demonstrated an inverse relationship between the incidence of cryptorchidism, and decreasing gestational age at birth, suggesting that premature delivery is important in view of the timing of testicular descent in foetal life [36]. A strong association between low birth weight and hypospadias has been demonstrated [37, 38].

Increasing birth weight in males has also been shown to be positively correlated with adult serum testosterone levels, however no effect on other reproductive hormone levels has been shown [39]. Adult men born with lower birth weights have, in another study, been shown to display features of hypogonadism, with reduced testicular size, lower testosterone levels and higher LH values, than controls born with appropriate weights [39]. Male children with early onset of their pubertal growth spurt are more likely to have been born underweight [40]. In a cohort of Australian men followed from birth, men born with gestational appropriate birth weights were significantly less likely to be grouped in the lowest quartile for their total motile sperm counts. Those men who were born preterm demonstrated reduced serum testosterone levels in adulthood, suggesting an adverse influence of growth restraint and prematurity on later life testicular function [41]. A prospective Danish birth cohort study of more than 2500 live born males found statistically significant associations between cryptorchidism and low birth weight, prematurity, being small for gestational age, substantial vaginal bleeding in pregnancy and breech presentation, which is in accordance with other studies [42].

4.2 Maternal medical complications of pregnancy

Abnormal maternal glucose metabolism in pregnancy may be associated with an increased risk of genital malformation for the male offspring [8, 43]. In women with gestational diabetes, the risk of delivering a male infant with cryptorchidism is increased by a factor of four compared to women without diabetes [43]. It is postulated that early growth delay of the foetus in the first trimester might play a role. This early failure of normal growth has been demonstrated even in children of diabetic mothers who are ultimately born large for gestational age [44]. The evidence is conflicting however, as no association between gestational diabetes and cryptorchidism was found in another registry-based study from Israel [45]. Maternal hypertension during pregnancy and preeclampsia are associated with hypospadias and other genital malformations, [37, 46] suggesting that placental insufficiency may play an important role in male foetal genital development.

4.3 Maternal undernutrition

The 5 month Dutch Winter Hunger Famine in 1944 gave rise to the suggestion that maternal nutrient restriction may play a role in determination of subsequent pathologic outcomes [47, 48]. This relationship has been demonstrated in several animal models [49–51]. Whilst the exact mechanism is unknown, it is theorised that maternal nutrient restriction might reprogram the development of the pituitary-adrenal axis, alter the male pituitary response to GnRH, lead to excess glucocorticoid exposure and thus exert an adverse effect on gonadal development and function [49]. This may vary according to the timing and magnitude of the

undernutrition. More studies in both humans and animals are required to further explore the effect of maternal undernutrition during the critical programming window in the foetus [50].

4.4 Maternal obesity

The prevalence of overweight and obese individuals in their reproductive years is increasing worldwide, and there is an established link between obesity and reduced fecundity in men and women [52]. Maternal obesity (and potentially paternal obesity around the time of conception) creates an adverse intrauterine environment for the developing foetus, and may have a detrimental reprogramming effect on offspring [52, 53]. Maternal obesity may alter the molecular composition of gametes, leading to epigenetic changes which impair the developmental trajectory of the resultant embryo and of future generations [32]. In male rats, maternal obesity during pregnancy and lactation has been shown to increase testicular and sperm oxidative stress leading to premature ageing of reproductive capacity [54]. In humans, one epidemiologic study reported a detrimental influence of high maternal body mass index (BMI) on the semen quality and plasma concentration of inhibin B of male offspring, [31, 52] a finding confirmed by other studies [52]. The exact processes through which maternal nutrition or maternal environment affect reproductive function in the offspring remain unclear, and may be due to an alteration of oestrogen exposure with the hormonal control of the development of the male foetal urogenital organs. Epigenetic modifications are also a clear link [31].

4.5 Maternal smoking

Exposure to cigarette smoking *in utero* has consistently been shown to negatively impact on male reproductive development, and in fact maternal smoking exposure during pregnancy may have a stronger effect on subsequent spermatogenesis than a man's own smoking in later life [8]. Reductions in median sperm output and total motile sperm are evident, and substantial [41]. One Danish cross-sectional study showed maternal smoking during pregnancy to be associated with earlier onset of puberty, lower final adult height, higher BMI, reduced testicular volume, lower total sperm count, reduced spermatogenesis-related hormones (inhibin-B and FSH) and higher free testosterone [55]. Likewise, a study of 1770 young men from the general population in Denmark, Norway, Finland, Lithuania and Estonia reported that maternal smoking during pregnancy was associated with a 20% reduction in sperm concentration [8, 56].

The effect of prenatal exposure to maternal cigarette smoke has been evaluated in another study where human gonadal cell numbers were examined by histopathological analysis following first trimester termination of pregnancy. A significant reduction in the number of germ cells and somatic cells in embryonic male (and female) gonads and the effect was dose dependent in heavy smokers [57].

4.6 Maternal gestational stress

Maternal exposure to stress in pregnancy has been shown to be a significant determinant of male reproductive development later in life. One prospective longitudinal cohort study examined this association in almost 650 males at 20 years of age. Maternal gestational stress, measured by exposure to stressful life events in early gestation was associated with lower total sperm counts, reduced number of progressive motile sperm and lower morning serum testosterone concentration. There was no effect of stressful events in late pregnancy (beyond 18 weeks'

gestation), in keeping with the proposed early foetal masculinisation programming window [19]. This is in keeping with animal models reported previously [58]. It is unclear as to the mechanism of impact, however it is theorised that alterations in cortisol levels within the critical window of programming and development of the male reproductive organs may be responsible [59].

4.7 Maternal serum oestrogens

A relationship between increasing incidence of disorders of development of the male reproductive tract, declining sperm counts and exposure to exogenous oestrogen *in utero* has been postulated for many years [53]. Animal studies have previously shown that exposure to exogenous oestrogens [60, 61] and environmental xenoestrogens [61, 62] can damage testicular function, however concern that ubiquitous and increasing global oestrogen pollution may have effect on testicular function have so far been unconfirmed by the lack of alteration in domestic animal sperm production over the past century [41, 63]. Hence this view does have its detractors [64]. The first study to formally examine the association of maternal oestrogen exposure on male reproductive development was a longitudinal cohort study of almost 400 adult males. It found that sperm output in adulthood was inversely correlated with cord serum oestradiol and oestrone [41]. Furthermore it has been reported that oestrogenic chemical exposure can also cause cryptorchidism [9]. It has been suggested that endogenous oestrogens may inhibit the hypothalamic-pituitary-gonadal axis via steroid negative feedback to reduce LH secretion, which may lead to a reduction in intra-testicular testosterone during the crucial window of development and programming in the male foetus [41]. A vegetarian diet with iron supplementation in pregnant women has been associated with a higher risk of hypospadias, perhaps due to greater exposure to phytoestrogens [37, 65].

4.8 Growth and adiposity in childhood and adolescence

Following the conclusion of the gestational period, growth and adiposity in childhood and adolescence are also important determinants of future male reproductive health. It is possible that normal growth and BMI through childhood and adolescence are associated with better adult testicular function [41]. Optimal body mass index trajectory through childhood and adolescence is associated with larger testicular volume and higher serum inhibin B and testosterone in adulthood. Rapid weight gain between birth and 24 months of age is associated with earlier onset of puberty [40]. Rapid early life weight gain has been linked to elevated insulin-like growth factor I concentrations and insulin resistance, elevated adrenal androgen concentrations, exaggerated adrenarche, obesity and consequently to concentrations of hormones such as leptin. These could all promote the activity of the GnRH pulse generator, thereby influencing the timing of puberty [40, 66]. It is unclear whether it is the predisposition to metabolic disorder that leads to later adverse testicular function or *vice versa*. However, it is probable that adverse dietary patterns exacerbate the problem, as adopting a Western dietary pattern in adolescence is well known to be linked with poor metabolic health, [67] but it is also associated with reductions in sperm concentration and serum DHT in young men [68].

Consistent height above the 50th percentile for age through childhood is associated with larger adult mean testicular volume [41]. In addition, adolescents with features of metabolic disorder at 17 years, or insulin resistance at 20 years of age, have been shown to have impaired testicular function and altered hormone levels compared to those without metabolic disorder. One study showed that men with features of metabolic risk evident at age 17 years of age had lower concentrations

of serum testosterone and inhibin B compared with those considered at low risk of metabolic disorder. Furthermore men with ultrasound evidence of non-alcoholic fatty liver disease (NAFLD) had reduced total sperm output, testosterone and inhibin B compared to men without NAFLD, when assessed at 20 years of age [69]. In analysing the data higher concentrations of systemic inflammatory markers were associated with an apparent gonadotoxic influence; with reductions in sperm output, seminal volume, sperm concentration, serum inhibin B, with increases in serum LH and FSH. Whereas, a higher concentration of systemic C-reactive protein had an apparent central negative influence on serum FSH and LH secretion inducing a central hypogonadal state with reductions in serum testosterone and seminal volume [59].

4.9 Oestrogenic endocrine disruptors: bisphenol A and phthalate exposure

A large number of ubiquitous anti-androgenic endocrine disruptors exist in increasing volumes within the environment. These chemicals interfere with the synthesis, secretion, transport, binding, action or elimination of hormones with potential adverse effects on male reproductive health. Endocrine-disrupting chemicals have been shown in animal models to decrease spermatogenic capacity and increase incidence of male infertility. In rats, exposure to anti-androgenic chemicals during the masculinisation programming window resulted in cryptorchidism, hypospadias, micropenis, short anogenital distance (a surrogate marker of androgen activity) and reduced sperm count [8, 20]. It is postulated that exposure to endocrine disruptors during the initiation of male reproductive tract development may interfere with the normal hormonal signalling and formation of male reproductive organs [70]. Of note, oestrogenic and anti-androgenic compounds are well established to induce hypospadias in humans and mice [37, 38].

Bisphenol A (BPA) has been used extensively for decades in the manufacture of polycarbonates, epoxy resins and plastics [71]. Unconjugated BPA binds to oestrogen receptors producing weak oestrogenic activity. Anti-androgenic effects are also seen. Free BPA is metabolised by the liver of the mother and foetus, and even at low environmental levels can transfer across the human placenta [72]. BPA studies on experimental animals show that effects are generally more detrimental during in utero exposure, a critical developmental stage for the embryo [73]. In vivo studies on rats showed a relationship between BPA exposure and inhibition of testicular steroidogenesis, hypogonadotropic hypogonadism, decreased sperm count and proliferation of mammary tissue [74–77].

In human studies, there is conflicting evidence for the reproductive effects of BPA. Concurrent BPA exposure has been shown to be associated with decreased sperm concentration and total sperm count, [78] increase in sperm DNA damage, [79] altered serum reproductive hormone levels and reduced semen quality [80]. However, the influences with regard to antenatal maternal BPA exposure are less evident, as a recent longitudinal cohort study of 700 healthy men evaluated stored maternal antenatal serum from a birth cohort and related total maternal BPA concentrations (as a surrogate of foetal exposure) to mature male reproductive function [71]. Whilst a small positive correlation between maternal serum BPA level and sperm concentration and motility was present, no other associations of maternal serum BPA with testicular function were observed [81]. In another review of concurrent adult exposure, whilst evidence of a link was noted in five of six included studies, no consistent relationships or trends could be observed across all studies [82].

Phthalates are another group of environmentally pervasive industrial endocrine-disrupting chemicals, some of which are potent anti-androgens, [83] which are

suspected to interfere with developmental androgen action [84]. In rats, prenatal exposure to several phthalates elicits a syndrome of genital dysmorphology in males, including incomplete testicular descent, smaller testis weight and penile size, alterations to the vas deferens and epididymis, and most notably, shortened anogenital distance [85]. Animal studies demonstrating adverse effects of phthalate exposure on semen quality, preceded those showing the same effect in humans [86]. Critical to the induction of these effects is a marked reduction in foetal testicular testosterone production at the critical window for the development of the reproductive tract normally under androgen control [85]. In infants exposed in-utero to higher concentrations of maternal phthalates there are reports of a reduction in the anogenital distance, a reproducible marker of prenatal androgenisation [83, 87]. In human adult males, the data suggests equally concerning effects, with antenatal maternal serum phthalate levels showing negative associations with testicular volume, total serum testosterone and serum FSH concentration [84]. However, it is important to state that it is more customary in the scientific literature to report urine concentrations of phthalates rather than serum. In addition to in-utero exposures, phthalate levels in breast milk have been linked to an increased LH to free testosterone ratio in male offspring at 3 months of age, suggesting testicular impairment may occur postnatally during lactation and breast feeding [9]. However, no definite association has been made between breastmilk phthalates and cryptorchidism [88, 89]. Later in adulthood, adult exposure to environmental phthalates has been linked with reductions in semen parameters in men seeking paternity [90].

Endocrine-disrupting chemicals clearly present potential for significant impact on male reproductive health related to early exposures, however further research is necessary to clarify their risk, as there are a myriad of chemicals within the environment with endocrine-disrupting properties. Their effects may be synergistic, [91] non-dose dependent and the influence of each chemical may vary according to an individual's genetic susceptibility [92].

4.10 Multigenerational and transgenerational environmental effects

There is increasing evidence to suggest that early life perturbations due to various exposures are able to exert a direct effect on the human epigenome, both in utero and in adulthood. Both multigenerational and transgenerational effects of certain environmental or lifestyle exposures are possible due to epigenetic dysregulation and inheritance in germ cells [62, 93]. These epigenetic effects include DNA methylation, histone post-translational modifications and non-coding RNAs [93]. As shown in **Figure 2**, these two phenomena differ depending on whether the affected generation had direct exposure to the original endocrine disruptor or not. If a pregnant mother (designated as the filial or F0) is exposed to an adverse stimulus, her child (F1) may be affected as a consequence of direct exposure to the same stimulus *in utero*. Because the germ cells of the F1 offspring are developing throughout gestation, their children (F2) are also directly exposed. Effects seen in the F2 generation are therefore multigenerational. In contrast, effects observed in the F3 generation that had no direct exposure would be transgenerational [93].

Numerous exposures described above, including endocrine disrupters and other lifestyle-related factors such as smoking, diet and stress may affect the male reproductive health of future generations. DNA methylation is perhaps the best known mechanism of epigenetic gene modification, and a direct effect of some environmental factors on DNA methylation has been demonstrated in experimental studies in animal models [9]. In a rat model, gestational exposure to endocrine disruptors led to heritable effects in second and third generation offspring, [94] including decreased spermatogenic capacity and increased incidence of male infertility [95].

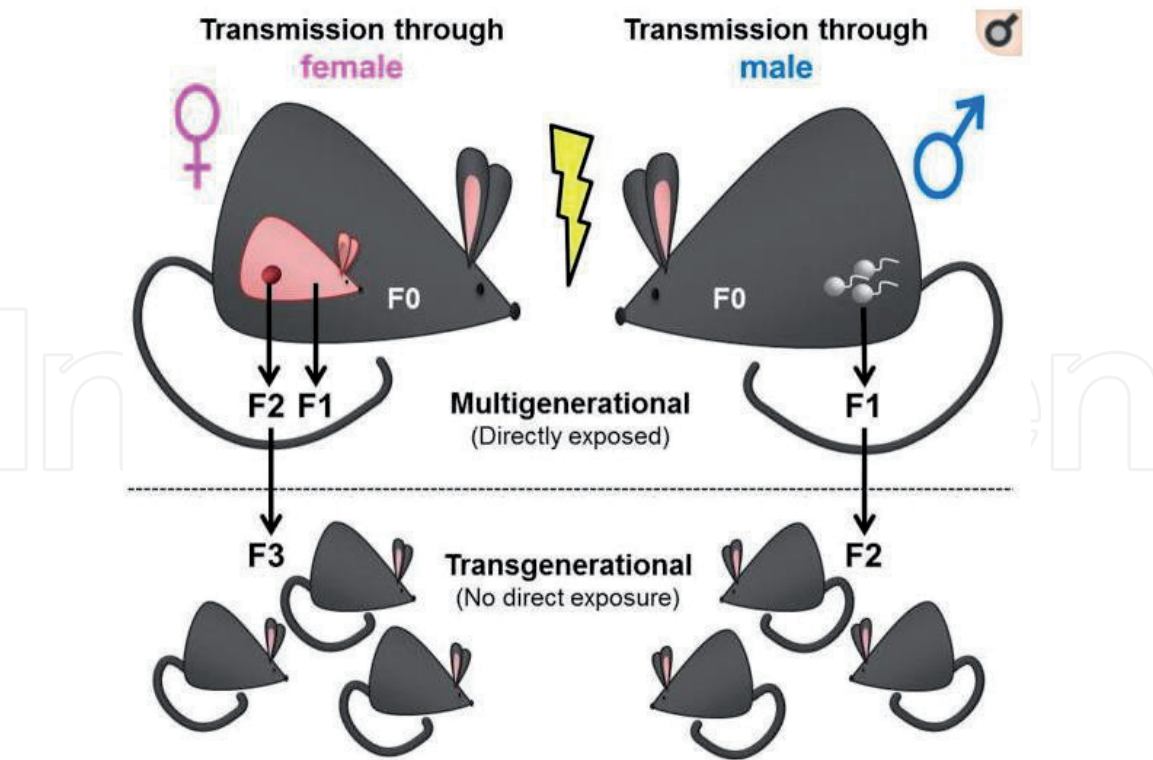


Figure 2.
Multigenerational and transgenerational effects. Reprinted with permission from Elsevier. © Xin et al. [93].

Although no human data exist to attest to this, this exciting and evolving area of research requires further work to validate findings.

5. Conclusion

There is a growing body of clear and compelling evidence for the early life origins of male reproductive health (**Figure 3**). Considering the central role the

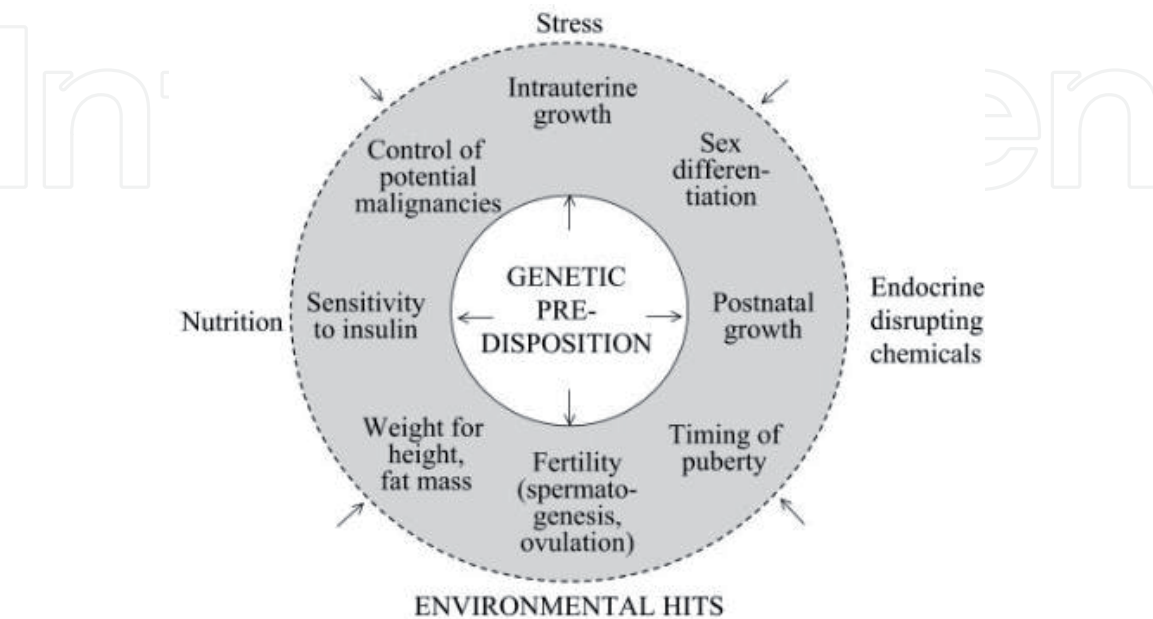


Figure 3.
Early determinants of male reproductive health. Reprinted with permission from Oxford university press. © Parent et al. [25].

reproductive hormones have in male sex differentiation, it is more than reasonable to suspect the involvement of factors that affect the production and the action of androgens during crucial windows of foetal development. However, although this developmental programming begins *in utero*, there is further convincing evidence for the effect of additional postnatal influences in early and later life. The specific mechanisms through which these associations exert their effect are as yet poorly understood. Disorders of male reproduction are clearly on the rise worldwide, and this escalation is predicted to only increase exponentially given the current obesity epidemic and the increasing impact of humans on the environment. Therefore, given the significant disease burden expected to result from declining male reproductive health, attention to further research and public health policy in this area is of the utmost importance. In addition, given the evidence for a significant number of maternal exposures and behaviours, public health measures and education focusing on maternal health are of obvious importance.

Conflict of interest

Professor Roger Hart is a shareholder in Western IVF and has received educational sponsorship from Merck, MSD, Ferring pharmaceuticals and Bayer.

Author details

Jennifer Pontré^{1,2} and Roger Hart^{1,2,3,4*}

1 King Edward Memorial Hospital, Perth, Western Australia, Australia

2 Fertility Specialists of Western Australia, Bethesda Hospital, Claremont, Western Australia, Australia

3 Fertility Specialists South, Applecross, Western Australia, Australia

4 Division of Obstetrics and Gynaecology, King Edward Memorial Hospital, University of Western Australia, Perth, Western Australia, Australia

*Address all correspondence to: roger.hart@uwa.ed.au

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