Human Reproduction Update, Vol.28, No.3, pp. 346–375, 2022
Advance Access Publication on February 21, 2022 https://doi.org/10.1093/humupd/dmac005

human reproduction update

Early programming of reproductive health and fertility: novel neuroendocrine mechanisms and implications in reproductive medicine

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Submitted on October 31, 2021; resubmitted on December 29, 2021; editorial decision on January 22, 2022

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BACKGROUND: According to the Developmental Origins of Health and Disease (DOHaD) hypothesis, environmental changes taking place during early maturational periods may alter normal development and predispose to the occurrence of diverse pathologies later in life. Indeed, adverse conditions during these critical developmental windows of high plasticity have been reported to alter the offspring developmental trajectory, causing permanent functional and structural perturbations that in the long term may enhance disease susceptibility. However, while solid evidence has documented that fluctuations in environmental factors, ranging from nutrient availability to chemicals, in early developmental stages (including the peri-conceptional period) have discernible programming effects that increase vulnerability to develop metabolic perturbations, the impact and eventual mechanisms involved, of such developmental alterations on the reproductive phenotype of offspring have received less attention.

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OBJECTIVE AND RATIONALE: This review will summarize recent advances in basic and clinical research that support the concept of DOHaD in the context of the impact of nutritional and hormonal perturbations, occurring during the periconceptional, fetal and early postnatal stages, on different aspects of reproductive function in both sexes. Special emphasis will be given to the effects of early nutritional stress on the timing of puberty and adult gonadotropic function, and to address the underlying neuroendocrine pathways, with particular attention to involvement of the Kiss1 system in these reproductive perturbations. The implications of such phenomena in terms of reproductive medicine will also be considered.

SEARCH METHODS: A comprehensive MEDLINE search, using PubMed as main interface, of research articles and reviews, published mainly between 2006 and 2021, has been carried out. Search was implemented using multiple terms, focusing on clinical and preclinical data from DOHaD studies, addressing periconceptional, gestational and perinatal programming of reproduction. Selected studies addressing early programming of metabolic function have also been considered, when relevant.

OUTCOMES: A solid body of evidence, from clinical and preclinical studies, has documented the impact of nutritional and hormonal fluctuations during the periconceptional, prenatal and early postnatal periods on pubertal maturation, as well as adult gonadotropic function and fertility. Furthermore, exposure to environmental chemicals, such as bisphenol A, and maternal stress has been shown to negatively influence pubertal development and gonadotropic function in adulthood. The underlying neuroendocrine pathways and mechanisms involved have been also addressed, mainly by preclinical studies, which have identified an, as yet incomplete, array of molecular and neurohormonal effectors. These include, prominently, epigenetic regulatory mechanisms and the hypothalamic Kiss1 system, which likely contribute to the generation of reproductive alterations in conditions of early nutritional and/or metabolic stress. In addition to the Kiss1 system, other major hypothalamic regulators of GnRH neurosecretion, such as γ-aminobutyric acid and glutamate, may be targets of developmental programming.

WIDER IMPLICATIONS: This review addresses an underdeveloped area of reproductive biology and medicine that may help to improve our understanding of human reproductive disorders and stresses the importance, and eventual pathogenic impact, of early determinants of puberty, adult reproductive function and fertility.

Key words: early programming / nutrition / peri-conceptional stage / gestational stage / perinatal stage / kisspeptins / neuroendocrine mechanisms / puberty / fertility

Introduction: developmental origins of health and disease—a reproductive perspective

It is widely accepted that disease risk may be rooted in early life. Numerous epidemiological and experimental studies have demonstrated that an organism's phenotype is shaped by the environmental conditions present in critical periods of development, including the periconceptional, prenatal and early postnatal stage. Seminal studies from Barker *et al.* (1993a,b) in the 90s pioneered the establishment of an association between disorders in embryo development and increased risk for disease in later life (Osmond *et al.*, 1993; Barker *et al.*, 1993a,b). These studies laid the foundation of the so-called Developmental Origins of Health and Disease (DOHaD) hypothesis, which proposes that early life environment has a prominent influence on later health of the developing organism. In this context, initial epidemiological studies reported associations among an adverse intrauterine environment, body weight at birth and increased incidence of cardiovascular diseases in adulthood (Osmond *et al.*, 1993; Barker *et al.*, 1993a), suggesting that environmental fluctuations taking place during the pre- and perinatal stage alter the normal development of offspring and predispose to the occurrence of cardiovascular pathologies in later life. In a more general perspective, the DOHaD hypothesis proposes that adverse environmental conditions during these critical developmental windows of high plasticity would alter the offspring developmental trajectory, causing permanent structural and functional changes that in the long term may enhance the susceptibility to develop diseases. This programming plasticity is physiologically relevant, as it endows the developing organism with a mechanism to acclimate to the intrauterine environment, which usually reflects the external environmental conditions, thus facilitating adaptation of the fetus to an eventual relatively adverse environment after birth. Yet, when the intrauterine and the postnatal milieu are substantially different, for example, as pertains to nutrient supply, such adaptive responses may negatively influence health of the offspring and enhance chronic disease risk in later stages of development.

In the last three decades, a multitude of human and animal studies have complemented and consolidated Barker's initial findings. Of note, the DOHaD hypothesis initially focused mainly on metabolic adaptations. In fact, it is now well established that early fluctuations in environmental factors, such as nutrient availability, hormonal milieu, environmental chemicals or stress during the periconceptional, prenatal or the early postnatal stage, may induce programming effects, leading to increased vulnerability to develop non-communicable diseases in offspring, such as obesity, type 2 diabetes and cardiovascular diseases (Catalano *et al.*, 2009; Fall, 2013; Horta *et al.*, 2015; Li *et al.*, 2016a; Philips *et al.*, 2017; Almeida *et al.*, 2019; Mossa *et al.*, 2019; Burgueno *et al.*, 2020; Facchi *et al.*, 2020). Yet, early adverse events have been also shown to impact bodily functions other than metabolic homeostasis, although characterization of these has lagged somewhat behind.

In this context, early-life adversity has also been shown to disrupt reproductive development and function, with an impact on pubertal maturation, as well as gonadotropic function and fertility in adulthood (Savabieasfahani *et al.*, 2006; Dupont *et al.*, 2012; Witham *et al.*, 2012; Sanchez-Garrido *et al.*, 2013; Chadio and Kotsampasi, 2014; Khorram *et al.*, 2015; Wang *et al.*, 2018; Brauner *et al.*, 2019; Mossa *et al.*, 2019). Among the potential early modifiers, maternal malnutrition during pregnancy and lactation is considered a key factor influencing the

reproductive health of progeny (Sloboda et al., 2009; Dupont et al., 2012; Sanchez-Garrido et al., 2013; Chadio and Kotsampasi, 2014; Khorram et al., 2015; Wang et al., 2018). This deleterious impact of an adverse maternal nutritional environment on the offspring's reproductive phenotype may be the result of altered programming of essential reproductive neuroendocrine pathways, which are susceptible to rewiring during these early stages of development, when environmental conditions are unfavorable (Evans et al., 2016). Another important factor that may contribute to modulating reproductive function in the offspring is the fact that gametogenesis occurs during the gestational phase. Hence, the maternal intrauterine environment may affect gamete production and quality in the offspring and may compromise fertility in adulthood. This gonadal impact of the intrauterine milieu may also cause transgenerational effects, thus leading to transmission of developmentally programmed traits to subsequent generations via epigenetic mechanisms (Cardoso et al., 2015; Aiken et al., 2016; Deodati et al., 2019). Interestingly, the parental periconceptional environment also plays an important role in determination of the metabolic and reproductive phenotype of the offspring, as recognized in recent years (McPherson et al., 2014; Lane et al., 2015; Brix et al., 2019). In this sense, inadequate parental nutrition prior to conception has been associated with an increased risk of developing metabolic and reproductive perturbations in the offspring (McPherson et al., 2014; Lane et al., 2015; McPherson et al., 2016; Li et al., 2016a; Watkins et al., 2018; Bellver and Mariani, 2019; Brix et al., 2019). Although the mechanisms underpinning the intergenerational transmission of non-genetic traits from parents to offspring remain to be fully elucidated, convincing evidence suggests that epigenetic processes may be the primary mechanism involved (Wei et al., 2015; Schagdarsurengin and Steger, 2016; Watkins et al., 2018; Franzago et al., 2019; Guo et al., 2019).

Despite the progress in this area, information about early determinants of puberty and reproductive health is still fragmentary and not always cohesive. Here, we review recent advances in basic and clinical research addressing the impact of nutritional, hormonal and environmental fluctuations during the periconceptional, fetal and early postnatal stages on different aspects of reproductive maturation and function in offspring of both sexes; particular attention is paid to the potential underlying neuroendocrine mechanisms that may be involved in reproductive abnormalities caused by adverse conditions in early life.

Periconceptional programming of reproductive function and fertility

Numerous studies during the last few years have demonstrated the importance of parental lifestyle around the time of conception for offspring health. The periconceptional period is an important developmental window that encompasses a series of relevant reproductive processes, such as gamete maturation and fertilization, as well as implantation and early gastrulation of the embryo. Environmental fluctuations during this period, as a consequence of suboptimal parental lifestyle habits, may perturb the gamete and/or zygote microenvironment, and induce metabolic, structural, functional and epigenetic changes that may reprogram offspring development and enhance disease risk throughout their lifetime. Alterations in the nutritional and metabolic milieu during this period, ranging from maternal obesity to undernutrition, have been linked to increased incidence of cardiometabolic, immune and neurological diseases in offspring (Fleming et al., 2018). Moreover, periconceptional perturbation of the metabolic milieu has been shown also to adversely influence the reproductive health and fertility of progeny. In this section, we summarize the main reproductive abnormalities observed in the offspring whose progenitors were exposed to an unfavorable nutritional/metabolic environment around the peri-conceptional period, and we discuss potential mechanisms linking maternal and paternal metabolic status around conception with reproductive health of the progeny.

Maternal effects

The maternal environment around conception has a prominent impact on the developmental program of the offspring. Nutritional quality during this stage has been shown to influence the adult phenotype of progeny, resulting in an increased incidence of metabolic and reproductive disturbances. Maternal malnutrition during the periconceptional period may induce changes in the oocyte and early embryo, and modify the resetting of the epigenome that occurs prior to gastrulation (Fig. 1). Such modification of the epigenome may alter gene expression patterns in the offspring, which may, in part at least, enhance susceptibility to diseases throughout their lives. Maternal obesity is the most representative example that illustrates the potential detrimental effects that an inadequate nutritional/metabolic milieu around conception may have on the progeny. Maternal obesity is known to have a negative influence on fertility and pregnancy outcomes. Obesity induces changes in the composition of follicular fluid, increasing the concentration of lipids, glucose and metabolic hormones and modifying protein content (Robker et al., 2009; Bou Nemer et al., 2019; Liu et al., 2020). These changes contribute to diminished oocyte quality and may negatively affect mitochondrial structure and function (Igosheva et al., 2010; Wu et al., 2015), as well as altering placental function (Altmae et al., 2017) and the epigenome of the developing organism; perturbations that may attenuate the developmental potential of the embryo (Fig. 1).

Since in conditions of maternal obesity the developing organism is persistently exposed to an adverse metabolic environment during the periconceptional, gestational and early postnatal (lactation) stages, experimental studies have been essential to discern the impact that maternal obesity may have on offspring health during these developmental windows, and to explore the underlying mechanisms linking maternal nutritional status at a specific developmental stage to later-life disease risk in the offspring. In this regard, preclinical studies based on embryo transfer technology have demonstrated that maternal obesity around conception impacts epigenetic regulation and impairs insulin signaling in different metabolic tissues (Nicholas et al., 2013a,b) and hepatic lipid metabolism (Nicholas et al., 2014) in the offspring. Interestingly, maternal weight loss during the periconceptional period also altered those intracellular pathways, suggesting that the offspring epigenome is especially sensitive to maternal metabolic status during this developmental stage (Nicholas et al., 2013a,b, 2014). In any event, the long-term detrimental effects of maternal obesity may not derive solely from impaired nutritional conditions, but may also be related to the state of chronic, low-grade inflammation caused by maternal overweight, which has been suggested

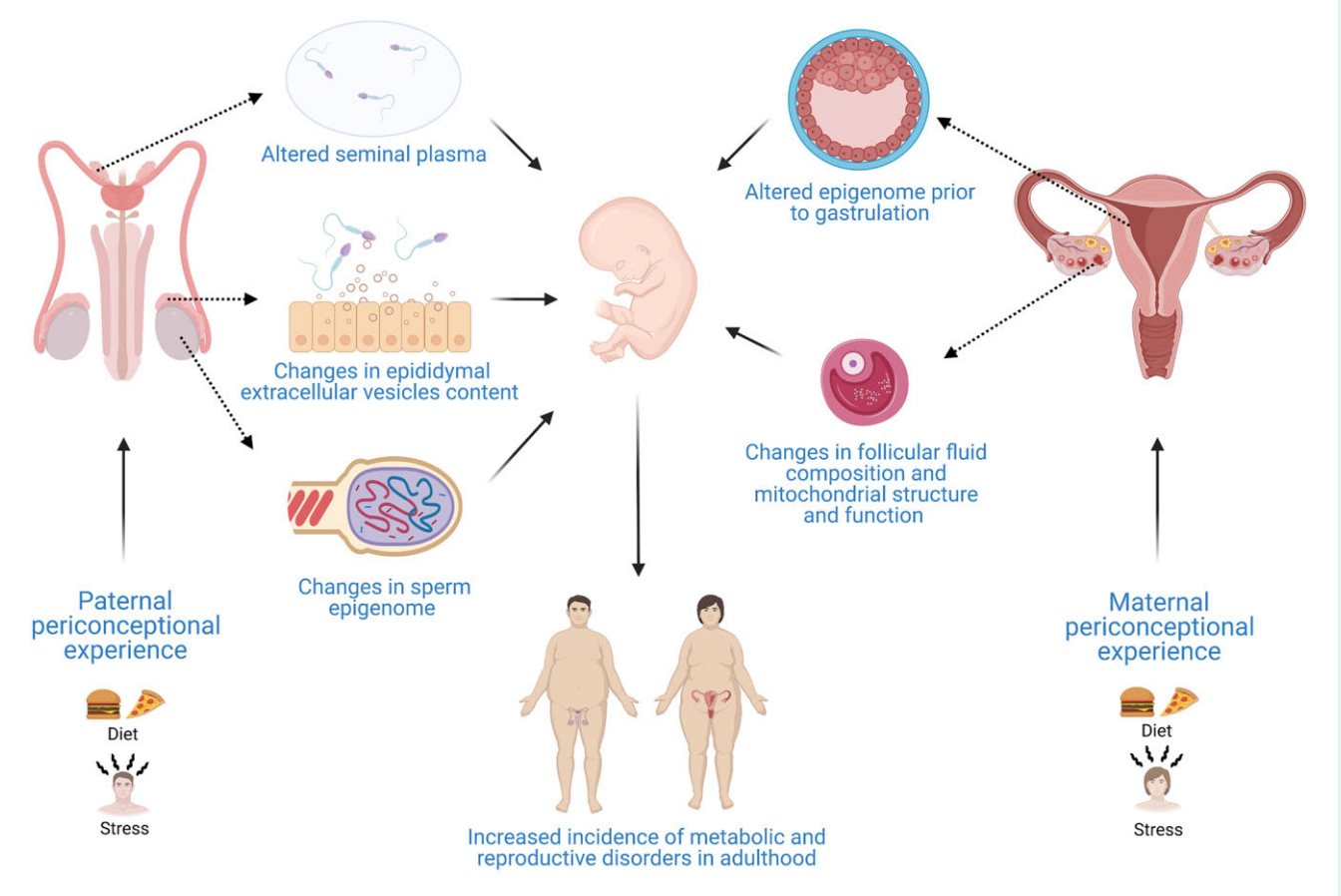

Figure 1. Periconceptional programming of reproductive function. A schematic is presented of the potential mechanisms that may underlie the impact of environmental fluctuations during the periconceptional period on adult reproductive function in the offspring. The paternal environment around conception has been reported to alter seminal plasma composition and induce changes in the sperm epigenome and epididymal extracellular vesicle content; perturbations that may lead to the development of reproductive disorders in adult offspring. Similarly, the maternal environment around conception has also been shown to alter the epigenome of the developing offspring and the composition of follicular fluid; changes that may also compromise the correct development of the embryo and increase the occurrence of reproductive abnormalities in adulthood. Figure created with BioRender (San Francisco, CA, USA).

to impact on maternal, fetal and/or placental inflammatory profiles, thereby influencing fetal programming and susceptibility to later disease (Pantham *et al.*, 2015).

While the consequences of maternal obesity or weight loss before pregnancy or during the peri-conceptional period on metabolic phenotype of the offspring have been well characterized in human and animal studies (Hochner *et al.*, 2012; Jaquiery *et al.*, 2012; Nicholas *et al.*, 2013a,b, 2014; Oostvogels *et al.*, 2014; Tan *et al.*, 2015; Bridgman *et al.*, 2018; Schellong *et al.*, 2020), the impact of changes of maternal body weight on the reproductive profile of progeny has received little attention. In mice, maternal exposure to a high-fat diet (HFD) during the periconceptional, gestational and lactation stage has been associated with abnormal oocyte growth and development in adult offspring (Cheong *et al.*, 2014). Yet, since maternal exposure to HFD comprised three different developmental windows, this study was unable to unveil the specific impact that maternal HFD exposure around conception may have on the reproductive traits of the offspring. This issue was addressed in a recent experimental study in rats, in which the animals were fed an obesogenic diet in the pre-pregnancy stage (10 weeks before pregnancy) and then switched to the control diet during pregnancy and lactation (Kalem *et al.*, 2018). This study confirmed the deleterious impact that consumption of an HFD during the pregestational period has on ovarian function of the progeny, which was demonstrated by the reduced number of primordial follicles detected in ovaries from adult female offspring (Kalem *et al.*, 2018). In addition to this detrimental effect on ovarian reserve of the offspring, periconceptional maternal obesity also altered endometrial receptivity in females, and testicular size and testosterone release in male offspring (Kalem *et al.*, 2018). In humans, longitudinal studies have demonstrated associations among maternal pre-pregnancy obesity, gestational weight gain and the timing of puberty in the progeny, with sons and daughters from women who were obese during the periconceptional stage exhibiting precocious puberty (Lawn *et al.*, 2018; Brix *et al.*, 2019). Of note, reciprocal embryo transfer studies in mice allowed dissection of the impact of an obesogenic diet before versus during pregnancy on fetal and placental growth, as well as on

metabolic features in the offspring. These analyses showed that, while pre-gestational HFD exposure impaired fetal and placental growth, HFD exposure during gestation was needed to evoke persistent body weight excess and glucose intolerance in adulthood (Sasson et al., 2015). Whether the same phenomenon applies also to reproductive traits is yet to be defined.

Periconceptional maternal undernutrition, as well as restriction in the protein content of the diet, have also been associated with reproductive abnormalities in the offspring. In sheep, maternal undernutrition before pregnancy-induced metabolic perturbations, mostly in adult male offspring, and altered gonadal weights in both sexes, with males exhibiting larger testes and females smaller ovaries (Jaquiery et al., 2012). Another study in sheep reported an increase in the oocyte population in 30-day-old female offspring from mothers undernourished around conception (Abecia et al., 2014). On the other hand, restrictions in protein content of the maternal diet during the periconception, gestation and lactation stages have also been associated with a significant reduction in the ovarian reserve of primordial follicles in offspring (Winship et al., 2018). These findings suggest that gonadal function of the developing offspring is particularly sensitive to changes in nutrient availability and composition during the periconceptional period.

Paternal effects

The paternal nutritional status around conception is also a potential determinant of the metabolic and reproductive health of offspring. While this possibility was largely neglected for decades, in recent years an array of experimental studies has assessed the impact of paternal environmental fluctuations around conception on the offspring's phenotype. The pioneering work by Ng et al. (2010) demonstrated for the first time that periconceptional paternal obesity may reprogram the metabolic health of the progeny in rats, inducing β-cell dysfunction in F1 female offspring. This non-genetic intergenerational transmission of metabolic disease risk from fathers to offspring has also been demonstrated by others, who have not only confirmed the detrimental impact of paternal diet-induced obesity but also the deleterious consequences of other nutritional challenges around conception, such as protein restriction and under-nutrition, which may have an impact on the cardiometabolic health of subsequent generations (Fullston et al., 2013; Watkins and Sinclair, 2014; Masuyama et al., 2016; McPherson et al., 2016; Watkins et al., 2018; Eberle et al., 2020). Of note is that paternal nutritional status around the periconceptional period has also been shown to influence reproductive health and fertility of the progeny. Thus, paternal obesity has been associated with subfertility and diminished gamete function in offspring of both sexes, with the effects being transmitted even to the second generation (Fullston et al., 2012). Another preclinical study reported defects in sperm motility and morphology together with impaired reproductive health in male offspring born from obese fathers (McPherson et al., 2014). However, the primary outcome documented by this study was the improvement in sperm parameters and reproductive function in male offspring from obese fathers that undertook diet and exercise prior to conception (McPherson et al., 2014). These data point out that lifestyle intervention around the periconceptional stage may counteract the undesired reproductive effects of paternal obesity in subsequent generations. Our group also reported that offspring from obese fathers are more susceptible to the deleterious effects of HFD (Sanchez-Garrido et al., 2018). In our study, we demonstrated that male offspring from obese fathers fed on an HFD exhibited increased body weight, reduced LH and testosterone levels, and impaired LH responses to kisspeptin administration, when compared with the corresponding HFD controls from lean fathers. Importantly, most of the metabolic and reproductive effects induced by HFD in male offspring were not detected in females from obese fathers exposed to the same diet, with the exception of impaired LH responses to kisspeptin (Sanchez-Garrido et al., 2018). These findings suggest that paternal obesity around conception exacerbates the metabolic and reproductive perturbations in the progeny induced by an HFD, with males being more susceptible to the detrimental effects of the diet.

Regarding the potential mechanisms responsible for this paternal intergenerational transmission of non-genetic metabolic and reproductive traits, compelling evidence suggests that changes in the sperm epigenome may be the key mechanism involved (Watkins et al., 2018; Sharma, 2019); further comments on this phenomenon can be found below. Periconceptional environmental factors, such as over-nutrition, obesity or nutritional restriction, have been shown to impact the sperm epigenome, DNA integrity and other sperm parameters, which may alter the epigenetic pattern of the developing embryo, thus programming the implantation process and pregnancy (Lambrot et al., 2013; McPherson et al., 2016; Watkins et al., 2017a, 2018). In addition to epigenetic processes, changes in seminal plasma have been proposed as a potential underlying mechanism for the intergenerational transmission of paternal non-genetic traits. The seminal plasma is composed of secretions from different male glands and has been classically considered a fluid rich in nutrients and other components that provides protection to sperm and facilitates fertilization. Seminal plasma also modulates immunological and physiological processes in the endometrium, preparing the maternal intrauterine environment for proper implantation and offspring development. Recent evidence suggests that seminal fluid composition may be altered by the paternal periconceptional nutritional/metabolic status (Watkins et al., 2018; Morgan and Watkins, 2020); changes that may influence the maternal uterine environment, affect implantation and pregnancy outcomes, and program the offspring's phenotype (Watkins et al., 2018; Morgan and Watkins, 2020). It has been recently suggested that reproductive tract extracellular vesicles may also participate in the intergenerational transmission of paternal traits to the progeny (Chan et al., 2020). Extracellular vesicles take part in the intercellular communication process, allowing mobilization of biomolecules (e.g. lipids, proteins and microRNAs) between cells. There is evidence that somatic cells transfer extracellular vesicles to sperm within the epididymal lumen, and the biological content of these vesicles seems to play a role in embryonic development (Conine et al., 2018; Chan et al., 2020). It has been suggested that changes in the paternal periconceptional milieu may modify the content of the epididymal extracellular vesicles, which may induce programming effects in offspring (Chan et al., 2020). In detail, paternal stress around conception has been linked to changes in epididymal extracellular vesicle content, including changes in microRNA and protein levels, which in turn have been associated with altered offspring neuro-development and exacerbated responses to stress in adulthood (Chan et al., 2020). Yet, no studies to date have documented the programming effects induced by changes in the cargo of paternal extracellular vesicles on adult reproductive health of the progeny. In sum,

modifications of the sperm epigenome, seminal plasma composition and epididymal extracellular vesicles content may participate in the inter-generational transmission of paternal environmental experience (Fig. 1).

Fetal programming of reproductive function and fertility

An adverse intrauterine environment contributes to shaping the offspring's reproductive phenotype. Malnutrition, hormonal fluctuations and exposure to environmental chemicals during gestation have been shown to influence pubertal maturation and adult gonadotropic function in the progeny (Fig. 2).

Effects on puberty onset

Nutritional factors

The effects of maternal prenatal nutrition on offspring reproductive and metabolic phenotype have been extensively explored in preclinical models and humans. In experimental models, nutritional restriction during pregnancy has been associated with advanced puberty onset in females (Sloboda *et al.*, 2009). Yet, some studies have reported no changes in pubertal timing (Kotsampasi *et al.*, 2009b) or even a delay in females that were prenatally undernourished (Iwasa *et al.*, 2010; Gereltsetseg *et al.*, 2012; Sanchez-Garrido *et al.*, 2013). These discrepancies on the impact of prenatal nutritional perturbations on puberty onset in females may be related to the animal species used in the different studies and/or the window of exposure to nutritional restrictions during gestation, as well as the magnitude of such restrictions. In males, maternal undernutrition during pregnancy was not associated with changes in pubertal maturation in several species (Kotsampasi *et al.*, 2009a; Sanchez-Garrido *et al.*, 2013), although prenatal undernutrition and prenatal growth restriction have been shown to impair pituitary responsiveness, reduce Sertoli cell numbers (Kotsampasi *et al.*, 2009a) and delay sexual activation, as reflected by decreased testosterone levels and reduced testicular volume in male lambs undernourished during gestation (Da Silva *et al.*, 2001). In addition to undernutrition, overnutrition during pregnancy also influences pubertal maturation in the progeny. In rats, consumption of an HFD during gestation accelerates puberty onset in the female offspring (Chang *et al.*, 2008; Sloboda *et al.*, 2009; Li *et al.*, 2012; Reynolds *et al.*, 2015; Zhou *et al.*, 2019). However, the fat composition of the diet might be a critical factor determining changes in pubertal timing, since other reports have not detected changes in the onset of puberty in offspring exposed to HFD during gestation (Bellisario *et al.*, 2014).

In humans, owing to the inherent difficulty in assessing the intrauterine nutritional status of the developing fetus, birthweight is frequently used as a surrogate marker of the nutritional status of the fetus during gestation. In global terms, low birthweight is associated with maternal undernutrition during pregnancy. Some studies in different cohorts of patients have documented an advanced onset of puberty (or menarche) in girls born small for gestational age (Cooper *et al.*, 1996; Ibanez *et al.*, 2000; Verkauskiene *et al.*, 2013). Likewise, a lower expected birthweight ratio, as estimation of growth status at birth, was associated with earlier menarche (Sloboda *et al.*, 2007). A similar trend has been observed in children of both sexes born from obese or overweight mothers (Brix *et al.*, 2019). However, acceleration of pubertal maturation in children exposed to prenatal overnutrition is more frequent in girls (Deardorff *et al.*, 2013; Kubo *et al.*, 2018; Lawn *et al.*, 2018; Aghaee *et al.*, 2019). Extensive details on the impact of nutritional perturbations during gestation on the timing of puberty in boys and girls have been recently reported elsewhere (Calcaterra *et al.*, 2021).

Hormonal factors

Fluctuations in circulating hormones in the prenatal stage have been shown to affect pubertal maturation. One of the main circulating factors whose prenatal perturbation influences the metabolic and reproductive health of offspring is androgen levels. Preclinical studies in several species have documented that prenatal overexposure to androgens advance puberty onset (Wood and Foster, 1998; Witham *et al.*, 2012; Padmanabhan *et al.*, 2015) and predispose to the development of polycystic ovary syndrome (PCOS) (Ramezani Tehrani *et al.*, 2014; Cardoso and Padmanabhan, 2019; Landers *et al.*, 2020). PCOS is the most prevalent endocrine disorder in women of reproductive age and is considered the leading cause of female infertility. The cardinal manifestations of PCOS in patients are hyperandrogenism, oligo or anovulation and polycystic ovary morphology, although the hallmark feature of PCOS is androgen excess. Of note, daughters born from mothers affected with this endocrine disorder are exposed to abnormal intrauterine androgen levels, which may enhance the risk of these girls from suffering PCOS. Corroborating the role that prenatal androgen exposure has in the development of PCOS traits and its effects on pubertal timing, a preclinical study has demonstrated that overexposure to androgens during gestation causes an acceleration of puberty onset in a sheep model of PCOS (Padmanabhan *et al.*, 2015). Interestingly, concomitant prenatal administration of androgens and flutamide, an androgen receptor antagonist, prevented acceleration of the timing of puberty and ameliorated some PCOS-related traits in this model (Padmanabhan *et al.*, 2015). Whether the same acceleration of puberty occurs in humans remains debatable, but a recent controlled study failed to demonstrate overt changes in pubertal maturation in daughters of women with PCOS (Legro *et al.*, 2017). In the same vein, a prospective study did not detect a statistical association between maternal androgens, within the normal range of human pregnancy, and PCOS in adolescence (Hickey *et al.*, 2009).

Environmental factors

Prenatal exposure to endocrine-disrupting chemicals, such as phthalates, bisphenol A (BPA) or bisphenol E and S (BPA analogues), has a negative impact on pubertal maturation. These synthetic chemicals are present in our daily life as part of plastics, cans, food containers and other products. The effect of exposure to these compounds has raised concerns during recent decades, which led to implementation of a plethora of studies addressing the impact of exposure to phthalates or bisphenols on different aspects of health, including reproduction. Concerning pubertal effects, intrauterine exposure to phthalates has been associated with perturbations in the timing of pubertal maturation in both sexes. While in girls gestational exposure to phthalate derivatives tended to advance puberty onset, particularly breast development, late onset of pubertal development has been reported in

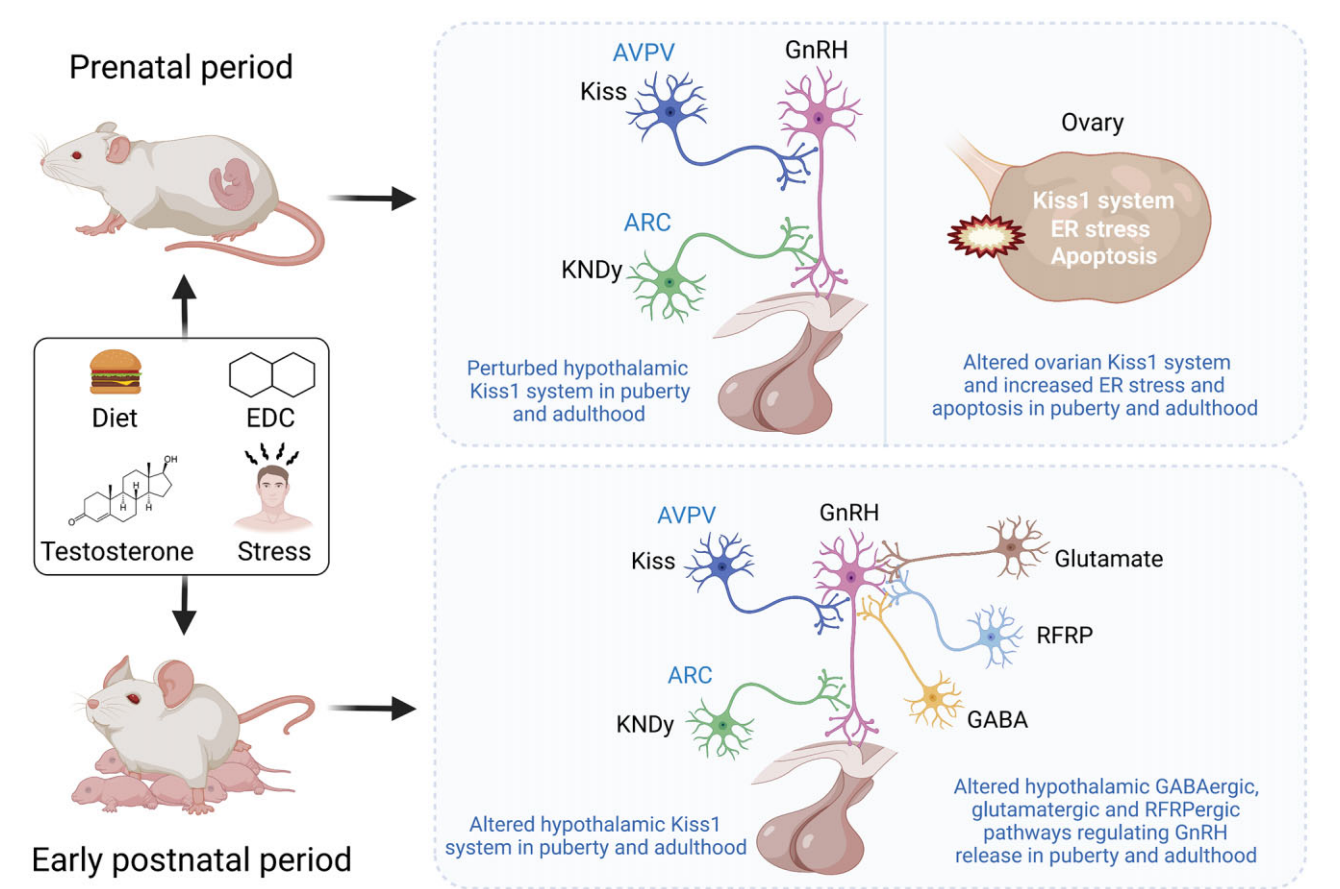

Figure 2. Fetal and postnatal programming of reproductive function. A schematic is shown of the potential mechanisms responsible for the programming effects of perinatal exposure to an array of environmental factors on pubertal maturation and reproductive function in adulthood. Environmental fluctuations during the prenatal period impact the hypothalamic Kiss1 system and impair ovarian function through perturbation of the intraovarian Kiss1 system and the increase in endoplasmic reticulum stress and follicular apoptosis at puberty and in adulthood. Early postnatal exposure to these factors also influences pubertal maturation and the reproductive profile in adulthood via modification of the hypothalamic Kiss1 system, as well as by altering GABAergic, glutamatergic and RFRP neurotransmission to GnRH neurons. ARC, arcuate nucleus; AVPV, anteroventral periventricular nucleus; EDC, endocrine disrupting chemicals; GABA, γ-aminobutyric acid; GnRH, gonadotropin-releasing hormone; KNDy, Kisspeptin, neurokinin B and dynorphin neurons; RFRP, RF amide-related peptide. For further details, see the text. Figure created with BioRender.

boys after phthalate exposure during gestation (Zhang *et al.*, 2015; Cathey *et al.*, 2020). However, these effects may vary depending on the pubertal marker considered and ethnic differences (Golestanzadeh *et al.*, 2020). The detrimental effects of intrauterine phthalate exposure on pubertal timing in females has also been demonstrated in experimental models, causing an accelerated puberty onset that is also observed in subsequent generations (Rattan *et al.*, 2018). These findings suggest that prenatal exposure to phthalate metabolites may induce transgenerational changes in pubertal maturation.

Gestational exposure to BPA affects pubertal development. The effects of BPA on puberty onset have been extensively studied in animal models and humans. In experimental models, administration of BPA during gestation has been associated with changes in pubertal timing in the offspring, which can diverge depending on the exposure period, the dose of BPA, the exposure route and the species employed in the study (Parent *et al.*, 2015). Some of these preclinical studies reported an advanced onset of puberty in female mice exposed prenatally to BPA or BPA analogues (Honma *et al.*, 2002; Nikaido *et al.*, 2004; Ruiz-Pino *et al.*, 2019; Shi *et al.*, 2019a,b); pubertal alteration that may be transmitted to subsequent generations (Shi *et al.*, 2019b). However, other studies in rodents have found no changes in pubertal timing in females prenatally exposed to BPA (Parent *et al.*, 2015). Likewise, male rodents exposed to BPA during gestation did not exhibit changes in the age of balano-preputial separation (Tinwell *et al.*, 2002), an external marker of pubertal maturation. In humans, inconsistent trends have also been observed. Some studies have reported an association between maternal serum or urinary BPA levels and an accelerated pubertal timing in girls (Watkins *et al.*, 2017b). However, there is also evidence that prenatal exposure to BPA may delay puberty onset in girls (Berger *et al.*, 2018). In the same vein, the reported effects of exposure to BPA during gestation on puberty onset in boys are also contradictory; while some reports described accelerated

pubertal development (Berger *et al.*, 2018), other studies documented reduced odds of puberty (Ferguson *et al.*, 2014). This heterogeneity of results emphasizes the need to conduct additional studies, with increased sample size, in order to assess the potential effects of prenatal exposure to BPA on the timing of puberty in both sexes.

Stress-related factors

Another factor that influences pubertal maturation in offspring is maternal stress. Initial preclinical studies addressing the role of prenatal stress as potential determinant of pubertal maturation documented a delayed puberty onset in the female offspring (Politch and Herrenkohl, 1984). Subsequent experimental studies corroborated this effect, demonstrating that prenatal exposure to glucocorticoids delays the pubertal maturation in females (Smith and Waddell, 2000). Yet, the male offspring prenatally exposed to glucocorticoids did not exhibit changes in pubertal maturation (Smith and Waddell, 2000). In humans, recent findings have suggested an association between maternal stressful life events and the age of menarche in the progeny (Brauner *et al.*, 2021). In this study, exposure to one or more stressful events during pregnancy was associated with earlier onset of puberty, as compared with the control group not exposed to stressful events during gestation. Another recent study has assessed the effects of *in utero* exposure to exogenous glucocorticoids on puberty onset in boys and girls in the context of anti-inflammatory therapies, frequently prescribed to manage specific pathologies, which can also be applied in pregnant women (Sand *et al.*, 2019). According to this study, prenatal exposure to glucocorticoids was not associated with changes in puberty onset either in boys or in girls (Sand *et al.*, 2019). Taken together, these experimental and clinical findings suggest that exposure to prenatal stress might influence the timing of puberty, particularly in females, although additional studies are required to fully assess the pubertal perturbations induced by *in utero* stress.

Effects on gonadotropic and gonadal function in adulthood

Nutritional factors

An adverse intrauterine nutritional environment may have a prominent impact on adult gonadotropic and gonadal function. In rats, maternal undernutrition during gestation reduced the number of ovarian follicles (Bernal *et al.*, 2010; Chan *et al.*, 2015), altered ovarian expression of key genes related to follicle maturation and ovulation, and increased intra-ovarian oxidative stress in adult female offspring (Bernal *et al.*, 2010). Other studies have documented that nutritional restrictions during pregnancy impaired estrous cyclicity and caused a reduction in the number of corpora lutea (Khorram *et al.*, 2015; Chan *et al.*, 2018), an increased number of atretic follicles and fewer antral follicles (Chan *et al.*, 2018) in young adult female rats. In sheep, female offspring born from dams undernourished during gestation displayed gonadotropic and gonadal alterations, whose nature depended on the developmental window in which the nutritional restriction was applied. Thus, when the nutritional challenge was applied during the first month of pregnancy, the female offspring showed increased pituitary sensitivity to GnRH, with enhanced FSH responses, and higher numbers of small follicles, whereas nutritional deprivation during mid-to-late gestation reduced the number of corpora lutea, suggesting changes in ovarian function (Kotsampasi *et al.*, 2009b). Experimental studies in guinea pigs have documented detrimental effects of early nutritional restrictions on ovarian function, with female offspring from undernourished dams exhibiting a decreased number of ovarian follicles and perturbed follicle growth (Jazwiec *et al.*, 2019). In humans, numerous reports have demonstrated associations between low birthweight, as an index of intrauterine growth restriction, and altered reproductive capacity in adult offspring; these studies were recently reviewed elsewhere (Jazwiec and Sloboda, 2019).

Males exposed to subnutrition during gestation also exhibited impaired gonadotropic and gonadal function in adulthood and, similar to that observed in females, the effects were also dependent of the timing of exposure to the nutritional restrictions. In sheep, maternal undernutrition during the first month of gestation did not cause any alteration in the gonadotropic function in adult offspring. Yet, exposure to this nutritional challenge during mid-to-late gestation led to an exacerbated gonadotropic response to GnRH administration and a reduced number of Sertoli cells in adult offspring (Kotsampasi *et al.*, 2009a). In the same vein, subsequent studies confirmed the negative impact of gestational under-nutrition on adult gonadal function in male rats, promoting a reduction in the number of Sertoli cells and changes in testicular structure (Genovese *et al.*, 2010), as well as alterations in testicular morphology and spermatogenesis, and a reduction of testicular insulin-like growth factor I (IGF-I) levels (Pedrana *et al.*, 2020).

Obesity and nutritional excess during pregnancy also has a negative impact on the reproductive phenotype of the adult offspring. Maternal obesity impairs follicle development in the offspring, promoting increased oxidative stress, lipotoxicity and compromising mitochondrial function in the oocytes (Jazwiec and Sloboda, 2019); effects that may lead to reproductive perturbations in adulthood. Prenatal exposure to an HFD is linked to reduced number of follicles (Alvarez *et al.*, 2018) and depletion of ovarian follicle reserve in adult female rats (Aiken *et al.*, 2016). On the other hand, male rats born from dams fed an HFD during gestation and lactation also exhibit reproductive derangements, including reduced circulating gonadotrophin and testosterone levels (Jacobs *et al.*, 2014) and diminished sperm production and quality (Reame *et al.*, 2014; Rodriguez-Gonzalez *et al.*, 2015).

Hormonal factors

As mentioned above, prenatal overexposure to androgens has a detrimental effect on reproductive phenotype of the offspring. The impact of prenatal androgen excess on female gonadal and gonadotropic function has been extensively studied in different preclinical models. In most species, prenatal exposure to androgens induces metabolic and reproductive traits in adult female offspring that closely resemble those observed in women with PCOS, including ovarian dysfunction, polycystic ovary morphology and/or hyperandrogenism (Abbott *et al.*, 1998; Witham *et al.*, 2012; Padmanabhan and Veiga-Lopez, 2013; Caldwell *et al.*, 2014; Cardoso *et al.*, 2015; Romero-Ruiz *et al.*, 2019). In addition, there is also evidence that prenatal androgen excess impacts the hypothalamic–pituitary–gonadal axis in female offspring, causing defects in the steroid feedback mechanisms controlling GnRH and gonadotrophin release, which promote an enhanced pituitary sensitivity to GnRH and contributes to augment circulating LH and androgens levels (Moore and Campbell, 2017; Cardoso and Padmanabhan, 2019). In humans, there is evidence that maternal hyperandrogenism during pregnancy may increase testosterone levels in daughters (Barry *et al.*, 2010) and cause PCOS-like traits in adulthood, suggesting a potential

transgenerational transmission of PCOS to the subsequent generation (Risal et al., 2019). In addition, women born small for gestational age have been shown to have significantly higher androgen levels and double the prevalence of PCOS compared to women born appropriate size for gestational age (Melo et al., 2010).

Inappropriate exposure to androgens during gestation has been associated with gonadal and reproductive abnormalities in adult male offspring. Studies in sheep have reported reduced testis size as well as sperm concentration and motility in animals exposed to androgens during fetal development (Recabarren et al., 2008; Scully et al., 2018). Similar findings were observed in rats, where prenatal exposure to androgens led to reduced testicular weight, number of Sertoli cells, testosterone levels and sperm counts in adulthood (Ramezani Tehrani et al., 2013). Of note, these gonadal and reproductive effects were highly dependent on the timing, duration and level of exposure to androgens during gestation.

Environmental factors

In utero exposure to phthalates and BPA and its derivatives has been shown to impact reproductive function in adulthood. It has been reported that female mice prenatally exposed to phthalates exhibit premature ovarian senescence, characterized by disrupted estrous cyclicity, elevated serum FSH and estradiol levels, and altered expression of key steroidogenic enzymes in the ovary (Moyer and Hixon, 2012). In addition, prenatal exposure to phthalates has been shown to reduce anogenital distance and uterine weight, as well as to induce polycystic ovary morphology, impaired estrous cyclicity and reduced fertility rates in adult female mice (Zhou et al., 2017). In males, intrauterine exposure to phthalates may compromise testicular function. Several preclinical studies have documented gonadal alterations in males exposed to phthalates during gestation, including malformed seminiferous tubules (Mahood et al., 2006), abnormal Leydig cell morphology and aggregation, and the occurrence of multi-nucleated gonocytes (Li et al., 2016b).

There is also evidence that prenatal exposure to BPA affects gonadal and gonadotropic function in adulthood. Experimental studies have demonstrated that intrauterine exposure to BPA reduces the expression of testicular steroidogenic enzymes, the number of Leydig cells, circulating testosterone levels (Ma et al., 2017) and the expression of genes related to Sertoli cell function (Tainaka et al., 2012) in adult male mice. Similarly, *in utero* exposure to BPA analogs disrupted sex steroid levels and spermatogenesis in adult male mice (Shi et al., 2018). In females, prenatal exposure to BPA affected gonadotropic function, promoting a drop in circulating FSH levels and an elevation in estradiol levels (Ma et al., 2017). Furthermore, adult females prenatally exposed to abnormal levels of BPA also displayed uterine disruption, showing a significant reduction in thickness of the uterine epithelium and disparate changes in the expression levels of the estrogen receptors (ER): ERα increased and ERβ decreased (Schonfelder et al., 2004). Similar to males, prenatal exposure to BPA analogs also had a negative impact on the gonadal and gonadotropic function in adult females, increasing serum testosterone levels, altering the expression of ovarian steroidogenic enzymes and disrupting early folliculogenesis (Shi et al., 2019a). Collectively, these results demonstrate that prenatal exposure to phthalates or BPA and its analogs negatively affects gonadal and/or gonadotropic function in adulthood in both sexes.

Stress-related factors

The effects of maternal prenatal stress on offspring reproductive health in adulthood have also been studied in both sexes. Prenatal exposure to an array of environmental stressors, including social stress, physical restraint, bright lights, exposure to heat, immersion in water or psychological stress, have been shown to disrupt gonadal and/or reproductive function in adulthood. In female rats, social stress during late pregnancy increased the number of primary follicles and increased aromatase expression in the ovary (Ashworth et al., 2016). Different prenatal stressors, such as exposure to a mixture of physical restraint, light and heat or immersion in cold water during the last week of gestation, have been associated with altered sex steroid levels (Del Cerro et al., 2015; Garcia-Vargas et al., 2019) and longer estrous cycles and reduced number of de Graaf follicles in adult female rats (Garcia-Vargas et al., 2019). In humans, a large population-based pregnancy cohort study linked exposure to psychological stress, especially during late gestation, to increased intrauterine volume and number of antral follicles in young adult females; changes that did not compromise reproductive function in these women (Bräuner et al., 2021).

In males, intrauterine stress induced by the immersion of dams in cold water resulted in increased testicular cell death and reduced circulating testosterone levels, sperm quality and fertility in adult rats (Garcia-Vargas et al., 2019). In addition, maternal immobilization during pregnancy has been associated with the occurrence of diverse testicular abnormalities in adult male rats. Animals whose mothers were immobilized in a plastic restrainer several times a day during the last week of gestation exhibited reduced anogenital distance, serum testosterone levels and Leydig cell number in adulthood (Pallares et al., 2013). On the other hand, immobilization of dams during the last 2 weeks of pregnancy also resulted in decreased LH, testosterone and testicular weight, and increased testicular cell death in adult male rats (Chen Cárdenas et al., 2013). Social stress during the third week of gestation also caused a longer anogenital distance and elevated circulating FSH levels in adult male rats, but did not alter testosterone levels or any other gonadal parameter (Ashworth et al., 2016). In humans, exposure to stressful life events during early gestation has been associated with sperm perturbations, such as reduced sperm count and motility, and reduced serum testosterone concentrations (Brauner et al., 2019). All in all, these findings indicate that the male gonadal axis may be more prone than the female axis to develop abnormalities induced by intrauterine stress, and that the period of gestational exposure to stress seems to be an important determinant of the gonadal perturbations observed in adulthood.

Contribution of the Kiss1 system

The Kiss1 system is considered an essential player in the control of puberty and reproductive function in adulthood. This system comprises two major elements: kisspeptins and their receptor, Gpr54 (Pinilla et al., 2012). Kisspeptins are a family of structurally related peptides encoded by the *Kiss1* gene. These peptides have the ability to potently stimulate GnRH and gonadotrophin secretion, playing a primary role in activation of the reproductive axis at puberty, and in regulation of gonadal function in adulthood. Kisspeptins are mostly expressed in Kiss1 neurons, which are located in two distinct hypothalamic areas, the arcuate nucleus (ARC) and the anteroventral periventricular nucleus (AVPV) (Pinilla et al., 2012). These two populations of Kiss1 neurons

mediate the negative (ARC) and positive (AVPV) feedback effects of sex steroids on GnRH/gonadotrophin release, and project mainly to GnRH neurons, where the second element of the system, Gpr54, is expressed. ARC Kiss1 neurons are sensitive to metabolic cues and are directly or indirectly targeted by metabolic hormones, such as leptin, thereby contributing to the metabolic control of reproduction (Pinilla *et al.*, 2012). In addition, a large subset of this neuronal population co-expresses the neuropeptides neurokinin B (NKB) and dynorphin, which act locally in a co-ordinates manner to modulate kisspeptin release in the same neuron, by means of stimulatory (NKB) or inhibitory (dynorphin) actions (Navarro, 2020). These neurons are named KNDy neurons and are responsible for the characteristic pattern of secretion of GnRH and gonadotrophins in a pulsatile fashion. Interestingly, the components of the Kiss1 system are also expressed in the ovary, suggesting that ovarian kisspeptin signaling may play a potential role in regulation of ovarian function (Castellano *et al.*, 2006; Gaytan *et al.*, 2009; Hu *et al.*, 2017).

Alterations in the Kiss1 system have been associated with some of the reproductive and gonadal abnormalities induced by the intrauterine perturbation of the nutritional, environmental or hormonal milieu. The delayed pubertal maturation observed in females undernourished during gestation has been linked to reduced hypothalamic Kiss1 expression in the prepubertal period (Iwasa *et al.*, 2010). Interestingly, chronic central administration of kisspeptin during this period restored the timing of pubertal maturation in these animals (Iwasa *et al.*, 2010). On the other hand, maternal obesity has been shown to advance puberty onset in the female offspring. This acceleration of pubertal maturation was associated with earlier onset of a higher LH pulse frequency in the peripubertal stage, which was related to an up-regulation of hypothalamic Kiss1 and NKB expression in the ARC (Li *et al.*, 2012). A recent study has also documented precocious onset of puberty in female rats exposed to an HFD during the prenatal and early postnatal (prepubertal) period (Kim *et al.*, 2018). These animals exhibited increased kisspeptin and NKB immunoreactivity in the ARC during the peripubertal stage (Kim *et al.*, 2018). In addition to the involvement of this central system in the acceleration of puberty associated with prenatal exposure to an obesogenic diet, a recent report has suggested a potential role of the intraovarian Kiss1 system in ovarian dysfunction observed in rats prenatally exposed to HFD. This study documented that exposure to HFD during gestation accelerated puberty onset, caused irregular cycles, and increased the number of antral and preovulatory follicles in the peripubertal period in female offspring; effects that were partially associated with augmented kisspeptin expression in the ovary (Zhou *et al.*, 2019).

On the other hand, prenatal exposure to environmental chemicals, such as BPA, has also been associated with pubertal disorders that may be mediated by a dysregulation of the Kiss1 system. In mice, perinatal exposure to low doses of BPA caused a decrease in circulating LH levels and an acceleration of puberty onset in female offspring. These effects were associated with changes in the hypothalamic Kiss1 system, characterized by an increase in the number of kisspeptin neurons in the AVPV and a decrease in the ARC (Ruiz-Pino *et al.*, 2019). As mentioned above, prenatal exposure to phthalates has also been associated with diverse reproductive abnormalities in subsequent stages of development (Zhou *et al.*, 2017). Although no mechanistic studies addressing the effects of intrauterine exposure to phthalates on the hypothalamic Kiss1 system have been reported to date, some studies have suggested that the Kiss1 system may play a role as potential mediator of the reproductive dysfunction observed after exposure to phthalates (Chen *et al.*, 2013; Yu *et al.*, 2020).

Similarly, studies conducted in different species have suggested a potential role of the Kiss1 system in driving the reproductive perturbations caused by intrauterine exposure to inappropriate levels of androgens (Witham *et al.*, 2012; Yan *et al.*, 2014; Cernea *et al.*, 2015). In female rats, prenatal androgenization increased LH pulse frequency around puberty and accelerated pubertal maturation (Yan *et al.*, 2014). Of note is that overexposure to androgens upregulated the hypothalamic expression of NKB and Kiss1 during pubertal maturation, suggesting that prenatal hyperandrogenism may precipitate activation of GnRH neurons via activation of the Kiss1 system (Yan *et al.*, 2014). In female sheep, prenatal testosterone exposure has been shown to perturb KNDy neurons in the ARC (Ahn *et al.*, 2015; Cernea *et al.*, 2015), inducing morphological changes, altering their synaptic inputs and projections to GnRH neurons, and reducing NKB receptor expression, which may be responsible for impairment in the steroid feedback mechanisms controlling GnRH and gonadotrophin release (Ahn *et al.*, 2015; Cernea *et al.*, 2015). Exposure to low androgen levels during late intrauterine development has been shown to precipitate puberty onset and cause PCOS-like symptoms in mice. Yet, studies in loss-of-function models, namely Gpr54 null mice, suggested that accelerated puberty onset observed in prenatally androgenized mice may not be mediated by changes in the Kiss1 system, since the animals lacking kisspeptin signaling also exhibited precocious puberty following prenatal exposure to androgens (Witham *et al.*, 2012). This evidence suggests that alternative neurohormonal mechanisms may be involved in the acceleration of puberty onset associated with prenatal overexposure to androgens in mice.

Contribution of other pathways

In addition to the hypothalamic Kiss1 system, gonadal mechanisms have been proposed as potential mediators of the reproductive perturbations associated with alterations of the intrauterine environment, especially in females. Nutritional deficits *in utero* have been linked to a lower birthweight as a consequence of reduced fetal growth. Female offspring exposed to this abnormal nutritional environment during gestation normally exhibit precocious puberty and ovarian alterations, including reduced ovarian reserve and premature ovarian aging. Studies in rats have reported that the reduction in the number of ovarian follicles in adulthood detected in animals undernourished prenatally may be mediated by increased follicular apoptosis caused by endoplasmic reticulum stress (Chan *et al.*, 2015). In addition to these changes, these animals exhibited a reduction in ovarian vessel density, indicative of accelerated ovarian aging; changes that were also associated with endoplasmic reticulum stress. In addition, a reduction in intraovarian antioxidant levels may be responsible for the impaired follicular function; melatonin being a potential candidate (Chan *et al.*, 2015). Another recent study, also conducted in rats, documented similar reproductive abnormalities in female offspring subjected to nutritional restrictions during gestation. In this case, young adult animals showed irregular estrous cyclicity and reduced numbers of antral follicles and corpora lutea. Similar to the previous study, the reduced number of follicles was associated with an increased apoptosis rate, reflected by an upregulation of caspase 3 expression in the ovaries of young adult

rats (Chan et al., 2018). In addition, epigenetic mechanisms are also involved in the development of reproductive alterations caused by the perturbation of the perinatal environment, as summarized in the sections below.

Early postnatal programming of reproductive function and fertility

Developmental programming is also affected by adverse conditions occurring during the early postnatal periods, which can modify reproductive disease burden later in life. The impact of such phenomena on key reproductive parameters, such as puberty and adult gonadotropic function, has been illustrated by a wealth of (mainly preclinical) studies, which are summarized below. For further details, see Fig. 2.

Effects on puberty onset

Nutritional factors

Several nutritional challenges during perinatal or early postnatal development of the offspring have been shown to induce changes in puberty and long-term reproductive dysfunctions (Jazwiec and Sloboda, 2019). Multiple studies using rodent models of neonatal overnutrition by reduction of litter size have demonstrated that postnatal overfeeding can advance pubertal onset, as reflected by earlier vaginal opening and balano-preputial separation, and accelerated attainment of reproductive capacity, evidenced by earlier occurrence of the first estrous (i.e. first ovulation) in females (Castellano et al., 2011; Sominsky et al., 2016; Wu et al., 2016; Heras et al., 2020; Stopa et al., 2021). However, other studies have shown no overt effects of early overnutrition on pubertal onset or first estrous in female rodents (Caron et al., 2012; Sanchez-Garrido et al., 2013); differences that may be related to the strain of rat or mouse and differences in the diet used in these studies. Interestingly, accelerated pubertal maturation has been consistently reported in rodents overfed during lactation and fed on HFD from weaning (Sanchez-Garrido et al., 2013) or submitted to a fat-rich diet post-weaning (Ullah et al., 2019). A maternal HFD during pregnancy and lactation has been also reported to advance the age of vaginal opening during puberty (Connor et al., 2012). Of note, female and male rats submitted to various nutritional challenges during the early postnatal period displayed differential responses in terms of puberty onset, with male rats being apparently more sensitive to changes of the early nutritional milieu (postnatal over- and under-nutrition), while females were more affected than males by prepuberal HFD (Sanchez-Garrido et al., 2013).

Evidence from preclinical models has also shown that restricted feeding during the early postnatal period has an impact on the timing of puberty and reproductive hormone levels (Castellano and Tena-Sempere, 2016). Thus, maternal food restriction during lactation and early postnatal food restriction by rearing in large litters (hence with less access to milk) have been identified as experimental paradigms for analysis of the impact of nutritional deprivation on puberty onset (Leonhardt et al., 2003; Castellano et al., 2011; Caron et al., 2012; Sanchez-Garrido et al., 2013). Severe (50%) maternal food restriction during lactation has been shown to delay puberty onset in male and female rats, by inducing a retardation of testicular growth and ovarian development (Leonhardt et al., 2003). Similarly, a maternal protein- (8–10%) or energy-restricted diet during lactation induced a delay in the onset of puberty in female pups, which displayed lower ovarian and uterus weights (da Silva Faria et al., 2004; Guzman et al., 2006). Admittedly, other protocols of maternal undernutrition during lactation, either alone or especially after combination with HFD, advanced the age of puberty onset in female rat offspring, while maternal undernutrition during pregnancy and lactation increased testicular IGF-I levels in male rats (Sloboda et al., 2009; Pedrana et al., 2020), suggesting some degree of variability in the impact of such nutritional challenge, depending on the timing, magnitude and type of diet.

Other studies have assessed the effects of early postnatal underfeeding on pubertal development using models of neonatal nutrition restriction, by increasing litter size. Such studies revealed a significant delay in pubertal onset both in male and female rodents, in some cases associated with reduced ovarian and uterine weights (Castellano et al., 2011; Caron et al., 2012; Sanchez-Garrido et al., 2013). Interestingly, the deferred puberty onset in mice from large litters was associated with an inappropriate development of axonal projections in specialized brain areas relevant for reproductive physiology, including the preoptic area (POA), showing a reduction in the density of kisspeptin fibers (Caron et al., 2012). However, other studies have described that postnatal malnutrition was not associated with delayed vaginal opening, although the day of first estrous was significantly retarded (Engelbregt et al., 2000, 2002). These conflicting findings might be related to the type of nutritional challenge, and the strain or species used. Finally, many epidemiological studies point toward an association between early obesity, adiposity and pubertal maturation in humans. High BMI in childhood is often linked to advanced pubertal onset, especially in girls, although the mechanisms underlying this association remain unclear (Lee et al., 2007; Biro et al., 2018).

Hormonal factors

There is still limited information on the effects of early postnatal overexposure to sex steroids, such as androgens, on pubertal development. To our knowledge, only one study in Sprague-Dawley female rats reported a very marked acceleration of the age of vaginal opening after exposure to a single dose of testosterone propionate on postnatal day 5: in rats neonatally injected with androgens, vaginal opening occurred around postnatal day 14, while control animals displayed canalization of the vagina around postnatal day 41 (Ongaro et al., 2015). Such scarcity in studies addressing the pubertal impact of early androgenic exposures is likely related to the fact that most of the experimental models employed to assess the effects of early postnatal exposure to androgens on gonadal function do not exhibit vaginal opening, as a consequence of androgen overload, which hampers evaluation of pubertal timing in these animals (Tyndall et al., 2012; Marcondes et al., 2015; Romero-Ruiz et al., 2019).

Environmental factors

Exposure to endocrine-disrupting chemicals during early postnatal development may also affect puberty onset. Preclinical studies have demonstrated that rodents exposed to environmentally relevant doses of BPA exhibit a disruption of the neuroendocrine mechanisms controlling puberty (Adewale et al., 2009; Fernandez et al., 2009; Losa-Ward et al., 2012; Franssen et al., 2016; Lopez-Rodriguez et al., 2019; Ruiz-

Pino *et al.*, 2019); admittedly, in some of these studies, exposures were not restricted to the early postnatal period. Thus, perinatal and early postnatal BPA exposure resulted in advanced pubertal onset in females, denoted by vaginal opening in female mice, but this acceleration was associated with a consistent suppression of circulating LH levels, indicating changes in GnRH neurosecretory activity (Ruiz-Pino *et al.*, 2019). Perturbations in pubertal timing induced by early exposure to BPA may result from changes in γ-aminobutyric acid (GABA) neurotransmission to GnRH neurons (Franssen *et al.*, 2016; Zalko *et al.*, 2016). BPA effects on neuroendocrine sexual maturation have been shown to be dose-dependent, with female rats neonatally exposed to low-dose BPA (25 ng/kg) exhibiting delayed pubertal maturation, while exposure to a high dose (5 mg/kg) caused advanced puberty (Franssen *et al.*, 2016). Of note, male rats neonatally exposed to BPA did not show changes in the age of balano-preputial separation (Nagao *et al.*, 1999; Kato *et al.*, 2006). Similarly, early life exposure to the estrogenic pesticide, dichlorodiphenyltri-chloroethane (DDT) or its metabolites (DDE or DDD) led to acceleration of GnRH secretion, associated with earlier vaginal opening in female rats (Rasier *et al.*, 2007, 2008). In addition, prepubertal rats exposed neonatally to DDT displayed reduced circulating LH levels, suggesting a potential estrogenic effect via negative feedback mechanisms during the pre-pubertal period. However, prepubertal rats exposed postnatally to DDT displayed increased GnRH pulsatility, which was associated with a premature onset of puberty, reflected by an earlier vaginal opening and advanced first estrus (Rasier *et al.*, 2007). On the other hand, a study assessed the effect of maternal DDE exposure from gestational day 1 to postnatal day 21 on offspring reproductive phenotype, and did not detect changes in pubertal timing, estrous cyclicity or circulating gonadotrophin levels (Makita, 2008). These differential effects of DDE exposure could be linked to the different routes for pesticide administration (Makita, 2008).

Neonatal exposure to phthalates has been shown also to alter pubertal development. Female rats neonatally exposed to low and high doses of di-n-butyl phthalate displayed accelerated puberty onset and increased serum estradiol levels (Hu *et al.*, 2013). Additionally, rats developmentally exposed to a mixture of selected endocrine-disrupting chemicals, that includes BPA, phthalates and DDT among others, induced multi- and transgenerational perturbations in sexual maturation and maternal care that were persistent in subsequent generations (Lopez-Rodriguez *et al.*, 2021). However, in the latter study, exposures spanned the pre-conceptional period to the end of lactation, thus hampering ability to define the specific contribution of early postnatal exposures to such transgenerational alterations.

Early life exposure to other xenoestrogenic compounds, such as the isoflavone genistein, has been associated with advanced timing of puberty in female mice (Nikaido *et al.*, 2004; Marraudino *et al.*, 2021). When genistein was administered during the gestational period, puberty onset was delayed (Levy *et al.*, 1995) but postnatal exposure caused advanced pubertal maturation in rats (Lewis *et al.*, 2003). In addition, a differential dose–response effect to early exposure to genistein has been observed in mice. While a high dose of genistein (800 mg/kg) induced defective testicular growth, a low dose (40 mg/kg) caused an increase in testicular weight and an elevation in circulating testosterone levels in pubertal males (Shi *et al.*, 2020). Altogether, these data reflect that the impact of phytoestrogens on the timing of puberty depends on multiple factors, including the type of phytoestrogen, the dose and the developmental window and duration of exposure.

Perinatal exposure to organic pollutants, such as dioxins, namely 2,3,7,8-tetrachlorodibenzodioxin (TCDD), has been documented to induce disturbances in puberty onset in rats. Early exposure to this estrogenic compound caused delayed pubertal maturation associated with a decrease in GnRH release, and a suppression of estradiol output during the estrous cycle (Shi *et al.*, 2007; Clements *et al.*, 2009; Takeda *et al.*, 2014). Conversely, exposure to other endocrine disruptors, for example perfluorinated alkyl substances, during the neonatal stage precipitated pubertal maturation in rats (Du *et al.*, 2019).

Altogether, this experimental evidence supports a tenable impact of early postnatal exposures to different endocrine disrupting chemicals (EDC) on pubertal timing. Translation of such findings to human puberty remains challenging, especially owing to difficulties in defining exposures restricted to early postnatal life, and the inherent complication of setting causal relations between exposures and phenotypic manifestations in humans. Yet, some epidemiological studies have suggested that the recent trends for changes in pubertal timing might be caused by environmental exposures (Krstevska-Konstantinova *et al.*, 2001; Aksglaede *et al.*, 2009), but whether these can be targeted to the early postnatal period remains unclear.

Stress-related factors

Several forms of early life stress, including during the early postnatal period, have been linked to alterations in puberty onset, both in animal models and humans. Models of impoverished (limited nesting/bedding) or enriched (communal nesting) environments postnatally resulted in differences in the timing of puberty. In the male offspring, rearing under impoverished conditions delayed puberty onset and reduced body weight. Conversely, male offspring from enriched nesting environments displayed advanced preputial separation linked to increased body weight (Knop *et al.*, 2019). In contrast, in female offspring, the rearing condition did not significantly alter sexual maturation or body weight (Knop *et al.*, 2019). In the same vein, another form of early life stress, caused by maternal deprivation for 1 day between postnatal days 9 and 10, advanced puberty onset in male rats while it did not affect female rat pubertal timing (Mela *et al.*, 2016). However, other studies have documented a significant delay (Manzano Nieves *et al.*, 2019) or an acceleration (Davis *et al.*, 2020) in pubertal maturation in females exposed to early life stress in the form of limited bedding/nesting. In addition, immunological stress during early stages of development has been associated with perturbations in pubertal development in females. In rats, neonatal administration of lipopolysaccharide (LPS) was linked to a significant delay in puberty onset (Knox *et al.*, 2009; Wu *et al.*, 2011). Of note, this effect was especially marked when animals were treated with LPS before postnatal day 7 (Knox *et al.*, 2009), highlighting an early critical period for postnatal programming of pubertal timing by immunological stress. Another form of neonatal stress, namely early-life maternal separation, has been shown also to impact puberty onset in a sex-specific manner (Mela *et al.*, 2016; Cowan and Richardson, 2019). Thus, a stress protocol in which female and male offspring were separated from their mother and placed in an incubator for 3 h a day from postnatal days 2 to 14 resulted in divergent trends on puberty onset, with female rats exhibiting precocious puberty and males showing delayed pubertal maturation (Cowan and Richardson, 2019). However, the other form of maternal deprivation mentioned

above, in which dams were removed between postnatal days 9 and 10, caused and advancement of puberty onset in male rats, while it did not affect female pubertal timing (Mela et al., 2016). Finally, in humans, early life stress has also been associated with perturbed pubertal development. Family stress during childhood, caused by paternal absence or stressful family relationships, has been linked to earlier pubertal maturation (Moffitt et al., 1992; Ellis and Garber, 2000; Belsky et al., 2015). Overall, results from clinical and preclinical studies suggest that the impact of early life stress on pubertal maturation is discernible but rather variable, depending on the nature of the neonatal stress, the window of exposure to the stimulus and the species and strain used in the study.

Effects on gonadotropic and gonadal function in adulthood

Nutritional factors

In rodents, several nutritional manipulations during early postnatal development have been shown to impact reproductive physiology in adulthood, although the nature and magnitude of such an impact heavily depend on the type and timing of the nutritional challenge. In this context, neonatal overfeeding has been reported to affect adult reproductive function in female rats (Sanchez-Garrido et al., 2015; Sominsky et al., 2016; Wu et al., 2016; Stopa et al., 2021). Thus, neonatal overfeeding by rearing in small litters resulted in disruption in estrous cyclicity, with a lower frequency of estrous phase and higher of diestrus, together with augmented circulating FSH levels (Sanchez-Garrido et al., 2015; Stopa et al., 2021). Maternal exposure to an HFD during pregnancy and lactation induced altered estrous cyclicity related to advanced ovarian aging (Connor et al., 2012). This altered phenotype in terms of estrous cyclicity is supported by the ovarian changes observed in postnatally overfed rats, which exhibited advanced follicle depletion in adulthood, characterized by a reduced number of primordial follicles in the follicular pool (Sominsky et al., 2016). Collectively, this evidence supports that overfeeding during the early stages of development may compromise ovarian function in adulthood.

In a similar manner, nutritional deprivation during the neonatal period has been shown to impact reproductive physiology in adulthood. Thus, evidence for post-pubertal ovarian failure and disrupted folliculogenesis was found in females that were reared with mothers submitted to dietary restriction during lactation; a phenomena that seems to induce premature ovarian aging (Faria Tda et al., 2008; Sloboda et al., 2009; Bernal et al., 2010; Chan et al., 2015). In males, maternal undernutrition by 50% food restriction during pregnancy and lactation led to persistent effects on testicular morphology and spermatogenesis in adulthood (Pedrana et al., 2020). Again, the fact that the nutritional interventions spanned the gestational and postnatal periods makes it difficult to tease apart the specific contribution of each programming window.

Hormonal factors

Experimental studies have documented that not only prenatal but also neonatal overexposure to androgens causes reproductive dysfunction in adult females, resembling traits observed in women with PCOS. In female rats, treatment with testosterone propionate within the first 5 days of life has been associated with the occurrence of metabolic, hormonal and gonadal perturbations in adulthood (Ota et al., 1983; Marcondes et al., 2015; Ongaro et al., 2015; Romero-Ruiz et al., 2019). Androgen excess during this critical stage of development has been linked to increased circulating LH and testosterone levels, altered ovarian theca-interstitial area, development of polycystic ovaries and absence of corpora lutea in adulthood (Marcondes et al., 2015). Yet, although the gonadal impact of early exposure to androgens was to some extent equivalent across the different studies, the endocrine effects were partially divergent. As an example, in several studies early overexposure to androgens did not augment circulating testosterone or LH levels in adulthood (Ongaro et al., 2015; Romero-Ruiz et al., 2019). These differential effects may be related to the rat strain employed in the study and/or the time of exposure to androgens during early development. Supporting the importance of the window of exposure to androgens, one study assessed the impact of androgen treatment during the prenatal and/or the early postnatal stage on ovarian function in adult rats (Tyndall et al., 2012). This study reported no effects on adult ovarian function when testosterone propionate was administered during the prenatal or late postnatal (from postnatal days 15 to 24) stage. Conversely, exposure to this androgenic compound during the neonatal period, from postnatal days 1 to 24, caused a PCOS-like phenotype in adulthood, characterized by overweight and gonadal dysfunction (Tyndall et al., 2012).

Environmental factors

Early postnatal exposure to endocrine disruptors, such as BPA, DDT, PCBs (polychlorinated biphenyls) and dioxins, may have negative effects on reproductive function in adulthood. In male rats, perinatal exposure to BPA induced an elevation in serum estrogen and LH levels at postnatal day 50, although testosterone levels were reduced (Bai et al., 2011). In female rodents, perinatal exposure to BPA has been shown to reduce LH secretion and alter the LH surge, the estrous cycle and sexual behavior in adulthood (Herath et al., 2001; Rubin et al., 2001; Monje et al., 2010; Xi et al., 2011).

Neonatal exposure to other endocrine disruptors, such as the biocide tributyltin, reduced ovarian weight and increased FSH levels in female rats (Makita, 2008). On the other hand, exposure to TCDD during early development caused premature reproductive senescence, characterized by endocrine disruption, altered estrous cyclicity and imprinted defects in sexual behavior in adult females (Shi et al., 2007; Takeda et al., 2014). Neonatal exposure to genistein also altered the estrous cyclicity in adult female mice, while in males it decreased testicular weight and fecal testosterone levels (Marraudino et al., 2021). Additionally, neonatal genistein exposure impaired male copulatory behavior in Long-Evans rats (Ali et al., 2020). Collectively, these data document persistent deficits in reproductive function and sexual behavior in adulthood induced by early postnatal exposure to endocrine disruptors.

Stress-related factors

Early postnatal life stressors may also impact adult reproductive function. Thus, early immunological stress induced by administration of LPS to Sprague-Dawley rats on postnatal days 3–5 perturbed adult ovarian function, causing irregular estrous cyclicity, decreased follicular reserve and increased thickness of the theca (Wu et al., 2011). A similar neonatal immunological challenge was associated with a depletion of ovarian reserve, estrous cycle irregularities, and advanced reproductive senescence in Wistar rats (Sominsky et al., 2012). In addition, neonatal

LPS exposure has been shown to impair sexual performance by altering sexual behavior. Namely, neonatal LPS increased rejection behaviors in adult females, which resulted in decreased content of sperm in the vagina of these animals (Walker *et al.*, 2011). In males, early exposure to LPS caused a reduction in circulating LH and testosterone levels during mating (Walker *et al.*, 2011). Other neonatal stressors, such as transient maternal deprivation, might induce changes in adult reproductive function or behavior in rodents (Mela *et al.*, 2016), although changes are modest and additional studies are needed to fully define the long-term reproductive impact of this form of postnatal stress.

Contribution of the Kiss1 system

Early postnatal nutritional manipulations have an impact on development of the neuronal networks involved in the regulation of reproductive function, including the Kiss1 system (Fig. 2). In models of early postnatal undernutrition in mice, delayed timing of puberty was associated with abnormal axonal projections in specialized brain areas relevant in reproductive physiology, for example the POA, which display a reduction in the density of kisspeptin fibers that persists in adulthood (Caron *et al.*, 2012). Similarly, female rats undernourished during lactation, as reared in large litters, displayed delayed pubertal development associated with a significant decrease in both hypothalamic Kiss1 mRNA levels and reduced kisspeptin immunolabeling in the ARC (Castellano *et al.*, 2011).

Early overnutrition has been shown to affect pubertal onset and reproductive function in adulthood in several experimental models (Castellano *et al.*, 2011; Stopa *et al.*, 2021). Interestingly, these effects were associated with increased body weight and higher expression levels of hypothalamic Kiss1 in peripubertal female rats, suggesting that changes in kisspeptin signaling may underlie part of such a perturbation of pubertal programming. In addition, the decreased fertility and cycling dysfunction observed in these animals in adulthood was associated with lower estradiol levels, and reduced GnRH and Kiss1 mRNA expression in the POA (Stopa *et al.*, 2021). In a similar model of early postnatal overnutrition (small litters) in female rats, which were maintained on an HFD from weaning onwards, the obese animals showed lower Kiss1 mRNA expression in the ARC and higher mRNA expression in the POA in adulthood (Sanchez-Garrido *et al.*, 2015). Collectively, data from these models show that early postnatal overfeeding promotes opposite effects on the Kiss1 system in the hypothalamus of females in puberty and adulthood. Thus, early overweight seemingly activates the hypothalamic Kiss1 system to trigger puberty onset, as seen in neonatal overfed rats, whereas in adulthood these females exhibit decreased hypothalamic Kiss1 expression, which may contribute to the reproductive deficits bound to persistent obesity.

In a similar vein, the neuronal Kiss1 system displayed changes in the number of kisspeptin projections in the hypothalamic paraventricular nucleus (PVN) in peripubertal females subjected to postnatal nutritional manipulations. Both in animals underfed or overfed during the early postnatal period, kisspeptin immunolabeling was reduced in the PVN, suggesting a perturbation of PVN kisspeptin fiber innervation associated with altered pubertal timing (Caron *et al.*, 2012; Heras *et al.*, 2020). However, the mechanisms underlying this downregulation of kisspeptin innervation in the PVN, and its implications for metabolic programming of puberty, have not been clarified yet.

The Kiss1 system is also sensitive to early postnatal exposure to endocrine disruptors, although the functional link and pathways involved in changes in kisspeptin expression and altered pubertal timing caused by exposure to these compounds remain to be fully elucidated (Roepke and Sadlier, 2021). Divergent patterns of Kiss1 expression have been reported in female mice exposed to low doses of BPA during the neonatal period, which exhibited a persistent impairment of kisspeptin neuronal maturation, with significantly increased kisspeptin expression in the AVPV, but fewer kisspeptin neurons and lower Kiss1 and Tac2 (i.e. the gene encoding NKB) expression in the ARC compared with control animals (Navarro *et al.*, 2009; Franssen *et al.*, 2014; Ruiz-Pino *et al.*, 2019). However, no changes in kisspeptin immunoreactivity in the ARC were detected in male rats neonatally exposed to different BPA doses (50 µg/kg and 50 mg/kg), although BPA exposure induced a decline in ARC kisspeptin content in pubertal and adult females (Patisaul *et al.*, 2009; Losa-Ward *et al.*, 2012). Thus, the sensitivity of the Kiss1 system to BPA exposure might be influenced by the sex and timing of exposure. In line with these findings, a study performed in female rats described a decrease in AVPV Kiss1 expression in the infantile period after neonatal exposure to BPA, whereas an increase in AVPV Kiss1 expression was detected during the pubertal transition in the offspring exposed to BPA during gestation and lactation (Bai *et al.*, 2011). In addition, gestational and lactational BPA exposure has been shown to increase kisspeptin cell number in the AVPV in adult females (Naule *et al.*, 2014). Collectively, these data suggest that perinatal exposure to BPA may disrupt the normal differentiation of ARC and AVPV Kiss1 neuronal populations, ultimately affecting pubertal timing and ovarian function.

Additional experimental studies have described the potential influence of exposure to other endocrine disruptors during early postnatal development on the hypothalamic Kiss1 system. Neonatal exposure to a high dose of dibutyl phthalate advanced puberty onset and increased Kiss1 mRNA expression in the ARC of female rats (Hu *et al.*, 2013). Neonatal exposure to high doses of genistein decreased the density of AVPV kisspeptin fibers projecting to GnRH neurons in adult female rats. This decrease in fiber innervation affected ovarian morphology and induced an anovulation-like phenotype (Bateman and Patisaul, 2008; Patisaul and Adewale, 2009; Losa *et al.*, 2011). A recent study has also documented that neonatal exposure to genistein reduces kisspeptin expression in several hypothalamic areas, including the AVPV and the ARC (Marraudino *et al.*, 2021). Exposure to other EDC during the perinatal period, such as PCBs, has been shown to reduce the number of ERα-expressing neurons and Kiss1 expression in the AVPV, as well as the number of GnRH neurons expressing c-fos, a marker of neuronal activation, in adult female offspring (Dickerson *et al.*, 2011). In addition, perinatal exposure to an immune challenge has also been shown to alter pubertal development and the expression pattern of Kiss1 mRNA: neonatal treatment with LPS caused a significant delay in puberty onset and reduced Kiss1 expression in the POA in pre-pubertal female rats (Knox *et al.*, 2009).

Contribution of other neuroendocrine pathways

In addition to the Kiss1 system, other major hypothalamic regulators of GnRH neurosecretion, such as GABA and glutamate, may be targets of developmental programming. GABA has been classically

regarded as an inhibitory signal on GnRH neurons, but excitatory actions on the GnRH network have been identified (Ojeda et al., 2006; Herbison and Moenter, 2011). A prepubertal decrease in GABAergic neurotransmission in POA seems to be required for the reactivation of GnRH release during the pubertal transition. GABA actions on GnRH neurons at puberty are also modulated by environmental/peripheral signals, such as fluctuations in metabolic cues or exposure to EDCs during critical windows of development. In this vein, the frequency of GABAergic inputs onto GnRH neurons and GnRH neuronal activity is diminished by acute fasting (Sullivan et al., 2003; Sullivan and Moenter, 2004), suggesting that GABAergic transmission onto GnRH neurons could be regulated by nutritional deficits during critical periods that could affect the pubertal timing. Early exposure to BPA may also modulate GABAergic neurotransmission, with opposite effects depending on dose and timing of exposure, that may increase (Cardoso et al., 2011; Ogi et al., 2015) or decrease (Zhou et al., 2013) GABAergic tone in adult rodents. Gestational and lactational exposure to a dose of BPA that increases GABAergic tone was associated with decreased hypothalamic GnRH release, which led to reduced FSH and testosterone levels in male rats, although circulating LH levels were not altered (Cardoso et al., 2011). In addition, a dose-dependent effect of early postnatal exposure to BPA on GABAergic tone has been described in female rats. Thus, postnatal exposure to a low dose of BPA caused delayed pubertal maturation, which was associated with higher hypothalamic GABAergic tone and slower GnRH pulsatility, whereas exposure to a high dose of BPA advanced puberty onset, seemingly via reduced GABAergic tone (Franssen et al., 2016).

On the other hand, the glutamatergic tone is known to increase in the hypothalamus before puberty. Postnatal exposure to a low dose of BPA in male rats has been shown to increase the concentration of glutamate in the brain (Zhang et al., 2019). Yet, little is known about the potential impact of such changes on modulation of the GnRH network. Neonatal exposure to other environmental chemicals, such as DDT, has been shown to increase glutamate-evoked GnRH release (Rasier et al., 2008), whereas a decrease in glutamate and GnRH release was associated with reduced LH, FSH and testosterone after perinatal exposure to BPA in prepubertal male rats (Cardoso et al., 2010). Collectively, these findings suggest an impact of EDCs on GABAergic and glutamatergic pathways regulating GnRH release.

As final note to this section, early exposure to BPA has also been shown to alter the expression of RF amide-related peptide-3 (RFRP3), identified as an inhibitory peptide of GnRH release (Tsutsui et al., 2010). Thus, neonatal administration of BPA induced a decrease in RFRP3 neurons in the dorsomedial hypothalamic nucleus, as well as in RFRP3 fiber density and their contacts with GnRH neurons in the POA, which was associated with advanced pubertal development (Losa-Ward et al., 2012).

Epigenetic mechanisms of early programming of reproductive function

While, as reviewed in previous sections, numerous clinical and preclinical studies have described the impact of adverse early life events on maturation and function of the reproductive system, and identified putative pathways (e.g. Kiss1) involved, our knowledge about the molecular mechanisms underpinning such durable effects remains incomplete. The difficulties for setting the mechanistic basis of these programming phenomena are diverse and range from the complexity to infer causative relations inherent to clinical studies to the deferred nature of many of the deleterious effects of early stressors: this hampers our ability to unambiguously define whether changes are causative or associative. However, significant progress in the area has taken place recently (Bar-Sadeh et al., 2020), led by substantial advances in characterization of the basis of early programming of metabolic function, and the recognition of novel molecular factors with key physiological roles in the control of puberty and fertility. For example, in the last decade, epigenetic regulatory mechanisms have been identified as key elements for the precise control of different aspects of reproduction, and have been pointed out as putative targets and effectors of the impact of adverse environmental conditions on early programming of the reproductive system (Bar-Sadeh et al., 2020).

Epigenetics refers to the complete set of reversible or heritable changes in gene expression/activity that occurs independent of changes in the primary nucleotide sequence, therefore altering the phenotype without changes at the genotype level (Dupont et al., 2009). Importantly, epigenetic changes can be induced by endogenous and external signals, thereby endowing the organism with an additional level of complexity that is pivotal for setting cell diversity and permitting adaptation to different environmental conditions. Epigenetic modulation of gene expression can occur in three main ways: chemical modifications of DNA, mainly methylation; posttranslational modifications of the chromatin, from methylation to acetylation of histones, among other phenomena; and modulation via non-coding (nc) RNA, of which miRNAs are the best characterized. These epigenetic mechanisms operate as connected phenomena, which functionally interact to modulate transcriptional activity and protein translation in a coordinated manner.

In the last decade, accumulating evidence has supported a role for epigenetics in the modulation of key facets of reproductive maturation and function, from sex differentiation and puberty onset to adult fertility (Semaan et al., 2012; Lomniczi et al., 2013; Piferrer, 2013; Lomniczi et al., 2015). These mechanisms are thought to include all major forms of epigenetic regulation (i.e. DNA methylation, histone modifications, ncRNAs), and to operate at different levels of the reproductive axis. Extensive recapitulation of these epigenetic phenomena is beyond the scope of this review and they have been summarized elsewhere (for example, see Aylwin et al., 2019; Bar-Sadeh et al., 2020; Vazquez et al., 2021). Yet, for the interest of the present review, it is worth stressing that epigenetic regulation of reproduction operates in all major reproductive tissues, including not only the gonads and pituitary (Eguizabal et al., 2016; Yosefzon et al., 2017) but also the hypothalamus, where epigenetic regulatory mechanisms have been described in key neuronal populations, such as GnRH neurons (Kurian et al., 2016; Messina et al., 2016) and, prominently, Kiss1 neurons. Yet, while there is no doubt that epigenetics actually plays a relevant role in control of the reproductive system, our understanding of how these mechanisms are targeted (and persistently influenced) by early adverse conditions remains limited. Some illustrative examples on key reproductive phenomena controlled by epigenetic mechanisms, which have been proven to be sensitive to early programming, will be briefly discussed in this section. For further details, see Fig. 3.

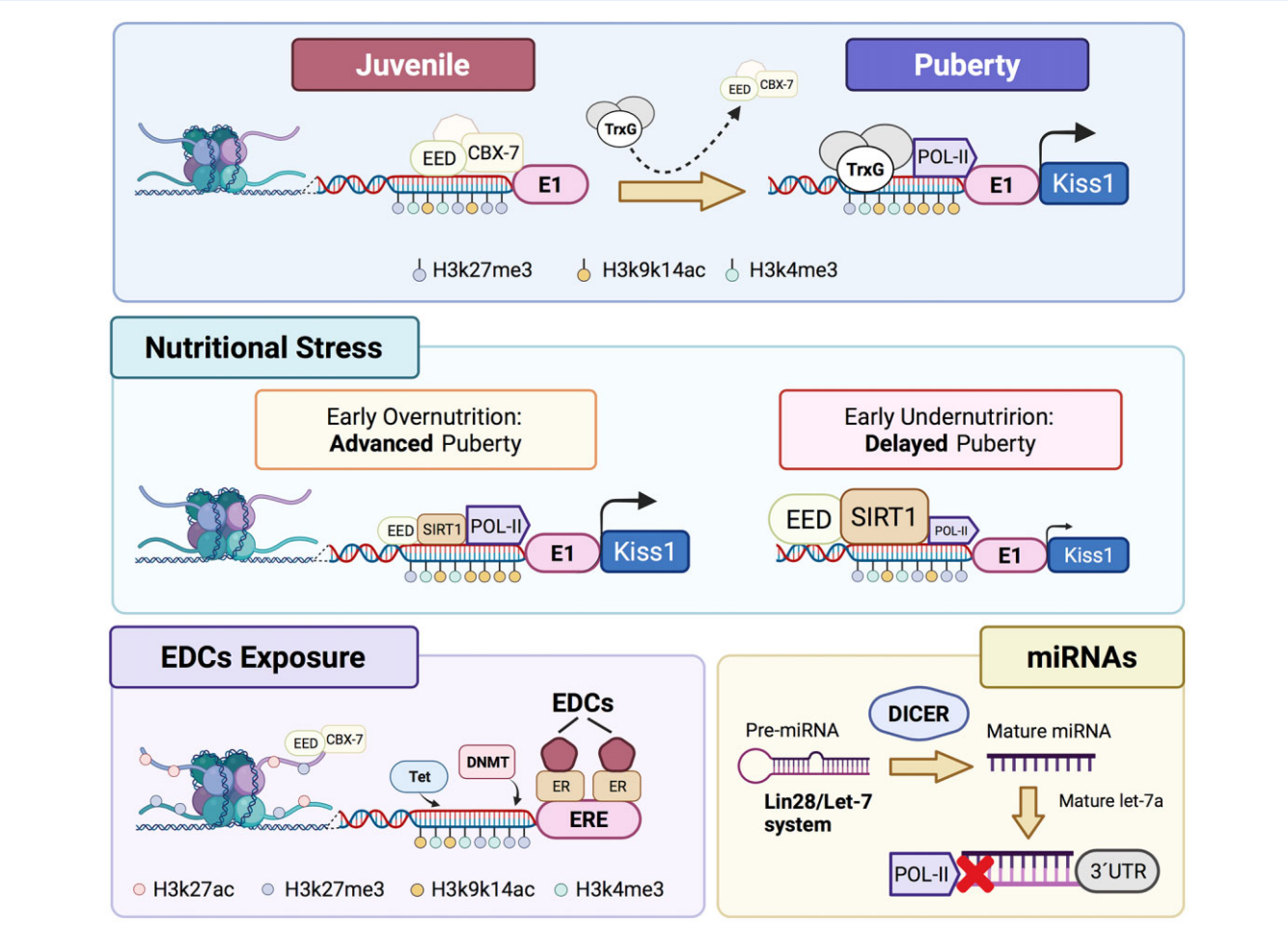

Figure 3. Epigenetic mechanisms of early programming of reproductive function. The upper panel shows the proposed roles of PcG and TrxG regulatory factors on the E1 for regulation of the pubertal transition. Activity of Kiss1 promoter is defined by the balance between PcG and TrxG regulatory components. A predominance of PcG elements during the juvenile period down-regulates Kiss1 expression, while removal of PcG factors EDD and CBX7 during pubertal transition, together with recruitment of TrxG elements at the Kiss1 promoter, changes the chromatin landscape into a permissive configuration, leading to increased Kiss1 transcription and puberty onset. The middle panel is a schematic of the epigenetic mechanisms for metabolic modulation of Kiss1 expression at puberty. Early postnatal overnutrition causes a premature eviction of the repressors, SIRT1 and EED, from the Kiss1 promoter. Conversely, early undernutrition is linked to persistence of SIRT1 and EED at the Kiss1 promoter, thereby causing suppression of Kiss1 expression. In the lower left panel, the proposed mechanism for the effects of EDCs, such as bisphenol A, on reproductive function is depicted. Besides transcriptional control via binding to sex steroid receptors, such as ER, early exposures to EDCs can also alter DNMT expression and the activity of histone acetyltransferases in the hypothalamus, and evoke changes in the subcellular location of Tet2, involved in the initiation of DNA demethylation, which modify histone tail methylation. EDCs can also affect hypothalamic expression of Kiss1 and ERα, via modulation of PcG members, EED and CBX-7. Finally, in the lower right panel, the proposed regulation by neonatal exposures to androgens or estrogens of the miRNA pathway, Lin28/Lin28B, as putative modulator of puberty, is depicted. CBX-7, chromobox protein homolog 7; DNMT, DNA methyltransferase; E1, kiss1 promoter; EDCs, endocrine disrupting chemicals; EED, embryonic ectoderm development; ER, estrogen receptor; Erα, estrogen receptor alpha; PcG, polycomb Group; SIRT1, sirtuin 1; Tet2, tet methylcytosine dioxygenase 2; TrxG, trithorax Group. Figure created with BioRender.

One facet of reproductive maturation that has been recently shown to be exquisitely controlled by an epigenetic regulatory mechanism is puberty. Preclinical studies from Lomniczi *et al.* (2013) have documented that pubertal timing is finely controlled by the reciprocal interplay between two groups of epigenetic regulators, of a repressive and activator nature, that acting mainly on Kiss1 neurons in the ARC regulate in a very precise manner Kiss1 expression during puberty. On the one hand, members of the Polycomb Group (PcG) of gene repressors (Grossniklaus and Paro, 2014), namely, embryonic ectoderm development (EED) and CBX7, have been shown to down-regulate Kiss1 expression during the early juvenile period, but owing to methylation of their promoters such a repressive action is lifted during the pubertal transition, thereby leading to a switch in chromatin configuration, that enhances Kiss1 expression, as a key driver of puberty (Lomniczi *et al.*,

2013). On the other hand, these repressive actions of PcG are opposed by the activity of members of the Trithorax group (TrxG), which act as activators of gene expression. Thus, the TrxG elements, mixed-lineage leukemia 1 (MLL1) and MLL3, have been shown operate at the level of the Kiss1 promoter, to enhance Kiss1 expression at puberty (Toro et al., 2018) (Fig. 3). Other factors potentially contributing to this epigenetic regulation of Kiss1 and puberty are KDM6B, a histone demethylating enzyme that removes the repressive mark caused by methylation of histone 3 (H3) at k27 (Wright et al., 2021), and CHD7, which is a member of the TrxG family; for the latter, genetic inactivation of CHD7 in humans has been associated with central hypogonadism (Kim et al., 2008), therefore suggesting a putative function of this epigenetic regulator in human reproduction.

While the above evidence supports a role of epigenetics in the control of puberty, whether (and if so, how) early stressors may influence such epigenetic regulatory mechanisms to modulate pubertal timing is largely unstudied. However, our recent work has disclosed that early (postnatal) nutritional stress can influence a member of the Sirtuin family, SIRT1, as novel regulator of pubertal timing, which acting mainly in Kiss1 neurons in cooperation with EED can epigenetically repress Kiss1. SIRT1 is a NAD^+-dependent deacetylase, with capacity to operate on multiple targets, including histones and p53 (Nogueiras et al., 2012; Giblin et al., 2014). SIRT1 acts as a cell energy sensor, whose activation takes place in conditions of energy insufficiency (Nogueiras et al., 2012). Our recent data in murine models demonstrated that SIRT1, operating in ARC Kiss1 neurons, contributes to pubertal modulation by early nutritional cues. Interestingly, our expression and functional studies not only pointed out that SIRT1 is a repressor of Kiss1, which becomes evicted from the Kiss1 promoter during normal pubertal transition, but also showed that in models of accelerated puberty caused by early-onset obesity owing to overfeeding during lactation and postweaning, hypothalamic SIRT1 protein content in general, and in Kiss1 neurons in particular, is decreased and such a reduction permits a change in the chromatin landscape at the Kiss1 promoter, that ultimately enhances Kiss1 expression and accelerates puberty (Vazquez et al., 2018). These data indicate that early nutritional conditions, such as postnatal obesity, can influence pubertal timing via modulation of SIRT1-dependent epigenetic mechanisms. Admittedly, however, since our model of early overfeeding did not tease apart the impact of postnatal (i.e. lactation) versus postweaning overweight, the precise window for such programming effect cannot be defined on the basis of these data. Our studies documented that not only early overnutrition but also undernutrition influenced this SIRT1/Kiss1 system, so that prepubertal subnutrition enhanced SIRT1 content in the hypothalamus and Kiss1 neurons, and resulted in a protracted repressive interaction between SIRT1 and the Kiss1 promoter that seemingly contributes to delay puberty in conditions of an energy deficit (Vazquez et al., 2018) (Fig. 3). Whether early postnatal undernutrition, for example by rearing in large litters which is known to suppress Kiss1 expression and pubertal timing (Castellano et al., 2011), operates via modulation of hypothalamic SIRT1 awaits further investigation.

Not only nutritional challenges but also environmental chemical stressors, such as EDC, have been proposed to affect reproductive function via modulation of epigenetic mechanisms (Fig. 3). This is illustrated by the case of BPA, which has been shown to cause epigenetic modifications, such as changes in DNA methylation, histone modifications and/or variations in miRNA levels, in rodents and humans (Faulk et al., 2016; Sabry et al., 2019; Qin et al., 2020). Moreover, BPA exposure during gestation disrupted the expression levels of the DNA methyltransferases DNMT1 and DNMT3A in the cortex and hypothalamus of juvenile offspring, perturbing the expression levels of ERs as well as sexual behavior in mice (Kundakovic et al., 2013). Likewise, administration of BPA during the neonatal period resulted in hypermethylation of the promoters of ERα and ERβ in the rat testis, with a discernible impact on spermatogenesis and fertility (Doshi et al., 2011). Furthermore, BPA was able to increase the activity of histone acetyltransferases, which caused an elevation in the level of histone acetylation in zebrafish embryos and spermatozoa (Lombo et al., 2019). The long-term effects of BPA on the epigenetic mechanisms operating in key hypothalamic populations governing the reproductive axis remain largely unexplored, but experimental studies demonstrated that BPA can change the subcellular location of Tet2, a member of the ten-eleven translocation (Tet) family of enzymes which initiate DNA demethylation, in GnRH neurons and caused changes in the level of methylation of histone 3 at the GnRH promoter in mice (Kurian et al., 2016). On the other hand, a recent study has documented that exposure to a mixture of 13 different EDC, including BPA, can affect (in a transgenerational manner) pubertal timing, which was delayed, and the expression of key genes for pubertal control, including Kiss1 and ERα, via mechanisms putatively involving repressors of the PcG acting at the hypothalamus (Lopez-Rodriguez et al., 2021). This evidence, obtained in rats, highlights the capacity of EDC to induce far-reaching epigenetic reprogramming of reproductive maturation, with the potential to affect multiple generations.

Finally, other epigenetic mechanisms, including miRNA-regulatory pathways, have been recently shown to participate in the precise control of reproductive maturation and function, acting at central, for example in the control of GnRH and Mkrn3 (Sangiao-Alvarellos et al., 2013; Messina et al., 2016; Heras et al., 2019), and peripheral, for example at the pituitary and testis (Gaytan et al., 2013; Wang et al., 2015), levels. However, the capacity of adverse early life conditions to persistently influence miRNA pathways remains largely unknown but fragmentary evidence strongly suggests this is likely the case. Thus, neonatal exposure to high levels of estrogen or androgen in female rats persistently altered the expression ratios of members of the miRNA family, let-7, and their binging protein, Lin28, at the time of puberty, suggesting persistent programming effects on this pubertal regulatory module (Sangiao-Alvarellos et al., 2013). On the other hand, early prenatal stress in mice has been shown to cause perturbed masculinization in the second-generation male offspring, via the paternal lineage and through a mechanism of epigenetic-mediated perturbation of normal programming involving persistent changes in the brain levels of several miRNAs, such as miR-322, miR-574 and miR-873 (Morgan and Bale, 2011). As mentioned in previous sections, the mechanisms whereby periconceptional paternal stress can induce durable, even transgenerational effects, in the progeny are multiple and can include changes in epididymal sperm caused by the influence of the miRNA cargo of reproductive tract extracellular vesicles; a phenomenon that has been shown to cause long-lasting programming effects (Chan et al., 2020).

Implications of disorders of early programming for reproductive medicine

While compelling evidence supports the view that developmental programming affects different aspects of reproductive maturation and function later in life, proving causative associations between early adverse life events and phenotypic reproductive changes remains a major challenge, especially as it pertains to human studies. The same difficulty applies to defining the underlying mechanisms for deferred reproductive disruption caused by early adversity, which in many cases, especially in clinical studies, can only be inferred based on phenomenological studies. All these features have hampered the application of DOHaD principles in reproductive medicine, regarding the prevention, diagnosis and eventual treatment of human reproductive disorders. Some of these hurdles for further progress in the area have been nicely summarized recently, in a review by Bar-Sadeh *et al.* (2020). This work emphasized the importance of integral experimental approaches, in which big-data analyses from clinical studies, targeting ideally large populations, could provide the basis, in a reverse-translation manner, for cellular and animal studies addressing specific mechanisms, which may lead to molecular studies (e.g. targeting specific epigenetic regulatory pathways), in order to provide further insight into the clinical data. This integral approach would help to establish causative associations and illuminate new strategies for the prevention, prognosis, and diagnosis of various reproductive pathologies.

A paradigmatic example in this context is exposures to EDC in humans, and their impact on maturation and function of the reproductive axis. Numerous studies have documented human population exposures to multiple EDC, including exposures during early critical periods, such as gestation or peri-conception (Haggerty *et al.*, 2021). Furthermore, solid clinical evidence has suggested an association between early or transgenerational EDC exposures and various reproductive disorders in both sexes. However, establishing definitive causal connections between these pathologies and exposures to specific EDC has remained elusive in many cases. Hence, the combination of preclinical and clinical studies appears crucial to identify and strengthen causative associations, allowing us to apply precautionary principles even before a definitive demonstration of the mechanistic basis or the causal relation between early exposures and specific reproductive phenotypes in humans. This precautionary principle is especially relevant in the context of DOHaD as, in most cases, phenotypic manifestations occur in a deferred manner and the underlying mechanisms are solidly wired, well before clinical symptoms become detectable.

In any event, recognition of DOHaD principles, and their importance in human pathophysiology, opens new scenarios for reproductive medicine, both in terms of prevention and intervention. Regarding prevention, realization of the particular sensitivity of the reproductive system to early stressors calls for attention in the implementation (and follow-up) of ART; an area of reproductive medicine that has witnessed astonishing progress in recent decades. Undoubtedly, advances in technologies applied to ART have been phenomenal over the last years and have permitted substantial improvements in the procedures and their safety, so that ART protocols are currently endowed with rather modest risks. Different clinical and experimental studies have stressed the importance of environmental conditions during IVF practice on later health outcomes, therefore recognizing the requirement to precisely control all potential stressors during the periconceptional window of vulnerability (Gardner and Kelley, 2017; AljahdAli *et al.*, 2020), as they may result in reprogramming of the embryo epigenome and set phenotype trajectories later in life. Published examples provide details on the interest of DOHaD in this *very active* area of reproductive medicine (Roy *et al.*, 2017; Rinaudo and Adeleye, 2018).

Reproductive health can be also affected by metabolic disorders, given the close connection between the neuroendocrine systems governing reproductive maturation and function, and metabolic homeostasis (Manfredi-Lozano *et al.*, 2018). Hence, preventing alterations of developmental programming leading to metabolic perturbations may also help the prevention of reproductive disorders. This is epitomized by changes in pubertal timing, whose prevalence (at least as it pertains to the age of thelarche in girls) is increasing in different geographic areas and may have deleterious consequences for different health outcomes later in life. Solid genetic and epidemiological evidence has linked pubertal timing with diabetes risk or child obesity (Elks *et al.*, 2010; Perry *et al.*, 2014; Reinehr and Roth, 2019). While this connection is partially set by common genetic pathways (Elks *et al.*, 2010), it may be also rooted in early developmental perturbations, which might be preventable to some extent by acting on environmental conditions (nutrition, stress, chemicals) during the periconceptional, gestational and early postnatal periods.

On the other hand, recognition of DOHaD principles may open options for better diagnosis and eventual intervention of reproductive diseases. While such a possibility is still far from clinical practice, some fragmentary evidence suggests that this could be the case in highly prevalent reproductive disorders, such as PCOS. As mentioned in previous sections, a putative causal factor for PCOS is early exposure to androgen excess in females, which contributes to generation of the reproductive and metabolic manifestations of the syndrome later in life. Recent evidence has documented that women suffering from PCOS display persistently altered patterns of methylation in the promoters of multiple genes in blood, of which several, such as tet methylcytosine dioxygenase 1 (TET1), roundabout guidance receptor 1 (ROBO1), cyclin-dependent kinase inhibitor 1A (CDKN1A), histidine decarboxylase (HDC) and insulin-like growth factor binding protein like 1 (IGFBPL1), were hypomethylated. Similar patterns of hypomethylation were also found in the ovarian tissue of a mouse PCOS-like model (Mimouni *et al.*, 2021). Admittedly, since methylation is a tissue-dependent process, changes in methylation profiles in blood cells do not necessarily reflect ovarian changes in methylation in women with PCOS, but these findings set the scene for the use of such altered methylation signatures for the molecular diagnosis of PCOS, in line with recent efforts using other epigenetic factors, such as miRNAs (Romero-Ruiz *et al.*, 2021). Even more interestingly, these epigenetic changes may contribute to the transgenerational inheritance of PCOS, since treatment of PCOS mice with the donor of methyl groups, S-adenosyl-methionine, was capable to reverse the major neuroendocrine and metabolic defects of this model (Mimouni *et al.*, 2021). These findings set the basis for 'epigenetic' treatments of common reproductive disorders, with potential transgenerational effects.

Conclusions and future perspectives

In the last three decades, since the inception of the DOHaD hypothesis, a wealth of experimental and clinical data has shown that early environmental conditions can profoundly and persistently influence later developmental trajectories, which shape not only adult physiology but also predisposition to disease. While the initial data gathered by Barker and co-workers focused mostly on early metabolic programming, compelling evidence has now demonstrated that key aspects of reproductive maturation and function, ranging from pubertal timing to adult fertility, can be also profoundly influenced by early environmental factors, so that adverse life events during these sensitive windows can perturb later reproductive phenotypes in the progeny. While this contention makes good biological sense, given the proven organizing influence of endogenous (and exogenous) sex steroids on relevant aspects of reproductive maturation such as sexual differentiation, recognition of the whole set of far-reaching developmental influences of a wide range of conditions, from malnutrition to different forms of stress, has substantially expanded our understanding of reproductive physiology and pathophysiology.

Although this 'reproductive' facet of DOHaD is now well set, several aspects of such developmental programming remain ill-defined and are likely to attract attention and research interest in coming years. First, as stressed in previous sections, while phenomenological associations are well defined, unraveling of the mechanistic basis for the reproductive impact of early life adversity is incomplete, especially as it pertains to human disease, and will require additional efforts for integral approaches, combining big-data analyses in large populations and experimental studies in suitable cellular and animal models. Efforts in this front may not only help to solve at last the ongoing debate on the actual risk posed by environmental EDC exposures on human health but also will clarify the basis for the worrying trends toward rapid deterioration of human reproduction in multiple countries, which is possibly a multifactorial phenomenon, caused by chemical exposures and other environmental factors, whose interplay (and mechanisms of action) needs further investigation.

In the same vein, while DOHaD studies have mostly focused, for obvious biological reasons, on maternal exposures, growing and convincing evidence points out that the paternal factor is also an important variable, which has remained neglected for decades. In this context, the accumulating experimental and clinical data strongly suggest that consideration (and potential intervention) should also be given to the paternal environment, especially during the pre- and peri-conceptional period (Soubry, 2018), stressing the need for more in-depth analyses of the putative roles of fathers in the transmission of environmental signals, from obesity to stress or pollutants, to their offspring. Indeed, recent studies on developmental programming have emphasized the need to consider pre-/periconception in its entirety, with both maternal and paternal factors included (Stephenson *et al.*, 2018). This will ultimately improve our understanding of the basis of human reproductive disorders and widen our repertoire of preventive measures, for example regarding public health policies, which need to be applied to both parents.

Although DOHaD studies have mostly focused on the early developmental periods, including peri-conceptional, gestational and early postnatal stages, compelling evidence points out that other sensitive maturational periods are susceptible of environmental programming, with durable consequences on later health. A paradigmatic example is puberty, which is not only influenced by earlier developmental events but also is shaped by concurrent environmental inputs, from nutrition to EDC (Avendano *et al.*, 2017). Importantly, various studies have identified a pubertal *organizational* period, which seems to be especially important in setting socio-sexual behaviors in a long-term manner, according to rodent studies (Cross *et al.*, 2020). Whether the same applies to humans is yet to be defined, but perturbations in the timing of puberty, either earlier or later pubertal timing, have been associated with a number of adverse health outcomes, both in women and men, including different types of cancers and cardiometabolic diseases, as well as reproductive, musculoskeletal, gastro-intestinal and neurocognitive conditions (Day *et al.*, 2015). Hence, puberty and adolescence can be regarded as a vulnerable period, also from the DOHaD perspective, in which prevention strategies may help to reduce disease burden later in life (Bay *et al.*, 2016). Importantly, some of the adaptative changes occurring during puberty might be protective against adverse phenotypes, as suggested by the fact that selective post-pubertal feeding with an HFD has been shown to be more deleterious on specific metabolic traits (such as liver steatosis) than life-long HFD exposure in Swiss Webster mice (Glavas *et al.*, 2021). This is possibly a reflection of specific adaptative responses during puberty, with capacity to more efficiently buffer the impact of adverse metabolic conditions. Whether the same may apply to some reproductive traits awaits future investigations.

Finally, recognition of the influence of DOHaD on reproduction opens new avenues and opportunities for reproductive medicine, in terms of prevention, diagnosis and even treatments, whose exploitation in human clinics is still in its infancy. Some of these have been briefly summarized in a previous section of this review, and range from potential 'epigenetic' therapies, whose basis has been experimentally set for PCOS very recently, to improved protocols for implementation and follow-up of ART. All in all, efforts in this front involving integral research approaches, combining preclinical and clinical studies, will not only illuminate fundamental aspects of human physiology but also will be instrumental in substantially changing how we approach common reproductive disorders and medical practice in the near future.

Data availability

This is a narrative review based on published data. Accordingly, specific data sharing is not applicable to this article as no new datasets were generated or analyzed during the current study.

Acknowledgements

The authors are indebted with the members of their research team at the Physiology Section of the University of Cordoba and IMIBIC, who actively participated in the generation of some experimental data discussed herein.

Authors' roles

M.A.S.-G. and M.T.-S. designed the review, reviewed the literature, wrote the manuscript and designed some figures. D.G.-G. performed literature research, wrote the manuscript and designed some figures. All authors critically reviewed the complete manuscript and approved the final version.

Funding

The work from the authors' laboratory summarized in this article was supported by grants BFU2017-83934-P and PID2020-118660GB-I00 (to M.T.-S.; Agencia Estatal de Investigación, Spain; co-funded with EU funds from FEDER Program); project PIE14-00005 (to M.T.-S.; FlexiMet, Instituto de Salud Carlos III, Ministerio de Sanidad, Spain); Projects P12-FQM-01943 and P18-RT-4093 (Junta de Andalucía, Spain), Project PI-0358-2018-FIB (to M.A.S.-G.; FIBICO); and EU research contract GAP-2014-655232. CIBER is an initiative of Instituto de Salud Carlos III (Ministerio de Sanidad, Spain).

Conflict of interest

All authors declare no conflict of interest.

Disclosure statement

The authors have nothing to disclose in relation to the contents of this work.

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