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REVIEW

The role of early life nutrition in programming of reproductive function

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Accumulating evidence suggest that the concept of programming can also be applied to reproductive development and function, representing an ever expanding research area. Recently issues such as peri- or even preconceptional nutrition, transgenerational effects and underlying mechanisms have received considerable attention. The present chapter presents the existed evidence and reviews the available data from numerous animal and human studies on the effects of early life nutritional environment on adult reproductive function. Specific outcomes depend on the severity, duration and stage of development when nutritional perturbations are imposed, while sex-specific effects are also manifested. Apart from undernutrition, effects of relative overnutrition as well as the complex interactions between pre- and postnatal nutrition is of high importance, especially in the context of our days obesity epidemic. Mechanisms underlying reproductive programming are yet unclear, but may include a role for epigenetic modifications. Epigenetic modulation of critical genes involved in the control of reproductive function and potential intergenerational effects represent an exciting area of interdisciplinary research toward the development of new nutritional approaches during pre- and postnatal periods to ensure reproductive health in later life.

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Introduction

It is now well established that the phenotype of an individual can be driven by *in utero* environmental conditions. This has given rise to the concept of the 'developmental origins of health and disease' (DOHaD) hypothesis, which implies that a stimulus or insult acting during critical periods of growth and development may result in permanent alteration of the structure, physiology and metabolism of the offspring. Maternal nutritional status has been recognized as a prominent cause of programming. To date such nutritional programming effects have been largely characterized in terms of susceptibility to non-communicable diseases and there have been outstanding reviews that summarize the existed evidence and provide background on the developmental origin of cardiovascular disease, insulin resistance and type-2 diabetes, obesity and metabolic syndrome.[1–3]

As reproductive axis and its hormonal control systems are largely established in fetal life, they represent a target for developmental programming. Therefore, in the last years the DOHaD approach has been extended to encompass programming of reproductive axis and function and related data have been presented in recently published reviews.[4–6] Specific outcomes depend on the severity, duration and stage of development when nutritional perturbations are imposed, while sex-specific effects are also manifested. Apart from undernutrition, effects of relative overnutrition, as well as the complex interactions between pre- and postnatal nutrition is of high importance, especially in the context of our days obesity epidemic.

To date the majority of data refer to the effects of undernutrition imposed during early or mid to late gestation, but it has recently been recognized that peri- and even preconceptional period may represent one of the most critical developmental windows, characterized by dynamic changes affecting future phenotype.[7] The most widely used animal models in developmental programming studies have been rodents and sheep. Although rodents offer significant advantages with respect to their short gestation period and availability of molecular tools, sheep studies provide power for translation to human pregnancy, as sheep has the advantage of a long gestation period, enabling targeting of specific developmental windows and produces a fetus comparable in size to humans.

The present review critically presents the existed evidence and reviews the available data from numerous animal experimental and human retrospective cohort studies, on the effects of early life nutritional environment on reproductive axis development and adult reproductive function. Mechanisms underlying reproductive programming and transgenerational effects are also presented.

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Early life nutrition and programming of puberty onset

Neuroendocrine control mechanisms

From a neuroendocrine perspective, puberty is the reactivation of the gonadotropin-releasing hormone (GnRH) secretory system, leading to a sustained increase in pulsatile GnRH release, which stimulates the release of gonadotrophins and in turn gonadal activity.[8] Several neurotransmitters and neuromodulators have been shown to control pulsatile GnRH release, among them kisspeptin plays a significant role in puberty. In fact humans with mutation in the kisspeptin receptor GPR54 exhibit delayed puberty, not puberty at all or precocious puberty.[9–11] Following the recognition of its fundamental role in puberty onset, this peptide is now recognized as an essential endogenous regulator of the GnRH system.[12] Although mechanisms leading to the timing of puberty differ between species, in that a gonadal steroid-independent mechanism is operative at the pubertal transition in primates (decreased tonic inhibition), whereas gonadal steroid-dependent mechanisms (decreased sensitivity to estradiol negative feedback) are involved in rodents and sheep,[13] it is now well recognized that both GnRH and kisspeptin neurons are major regulators of the preovulatorty GnRH surge in rat, sheep and human.[14–16] The most consistent population of kisspeptin neurons identified across different mammalian species is the group located in the arcuate (ARC) nucleus (infundibular nucleus in humans), but kisspeptin cell bodies have also been identified in the preoptic hypothalamic region.[17] Moreover, strong evidence suggest that the overall organization of the of the kisspeptin neuronal system in mammals is fairly consistent, and direct anatomical projections to GnRH neurons, at the level of both cell bodies and terminals are a common feature in mammals.[18]

A tight coupling between energy homeostasis and puberty onset is well recognized and metabolic signals play a significant role in puberty.[19] However, in addition to postnatal nutrition, accumulating evidence indicate that nutrition during pregnancy is also an important determinant for postnatal hypothalamic regulation and subsequent function. Maternal malnutrition can influence puberty and later fertility through changes in hypothalamic circuits controlling reproduction and in most species studied so far the distribution pattern of GnRH neurons is already established before birth.[20] There is strong evidence to suggest that direct metabolic regulation of the GnRH secretory activity is via KiSS-1/GRP54 system, because GRP54 receptors are present on GnRH neurons,[21] implying that this hormone operates as a neuroendocrine conduit for conveying metabolic information onto brain reproductive centers (likely, GnRH neurons), thereby contributing to the well-known coupling between body energy status and puberty onset.[22,23] Moreover, in studies investigating the effects of maternal care on the programming of hypothalamo–pituitary–gonadal (HPG) axis, a role of kisspeptin neurons in mediating these effects has been suggested, as low licking/grooming rats exhibit an earlier vaginal opening, indicative of puberty onset, compared with high LG offsprings.[24,25]

Animal experimental data

Maternal protein restriction during pregnancy and/or lactation has been reported to delay puberty onset in both male and female progeny, in rats.[26,27] A role for kisspeptin in mediating this effect is highly likely, as the delay in vaginal opening in undernourished rats was accompanied by significantly lower hypothalamic *Kiss1* mRNA expression.[28] Recently its role was further confirmed in studies implying nutritional perturbations during postnatal period (to mimic conditions of metabolic disturbance during late gestation in humans), in which maternal underfeeding resulted in a decrease in Kp-positive neurons in the ARC nucleus, whereas overfeeding caused accelerated puberty onset and higher expression levels of *Kiss1* mRNA in the anterior periventricular area of the hypothalamus of the offspring.[29] Opposite effects have also been reported, with maternal undernutrition resulting in an advanced attainment of puberty, but a reduction in progesterone levels in later life, whereas offspring exposed to maternal high-fat diet during pregnancy and lactation exhibited earlier puberty onset and enhanced ovarian function, as evident by higher progesterone levels.[30] The reasons for these contrasting results are not clear, but it appears that in rats lactation period is more critical in determining a delay in puberty onset, since in these artricial species significant maturation occurs early in life.

In sheep, moderate maternal undernutrition was not detrimental to the onset of puberty (defined as first ovulation) in female lambs,[31] but in males experienced placentally mediated fetal growth restriction, a delay in puberty onset and sexual activation, as measured by mean testosterone concentration and testis size, was detected.[32] Studies from our laboratory involving sheep offspring underfed *in utero* during two developmental windows, early (0–30) and mid to late (30–100) days of gestation, revealed no differences in the timing of endocrine puberty compared with normal fed ones, further strengthening the role of critical body weight for the onset of sexual maturation.[33,34]

Collectively, early nutritional perturbations exert sex- and window of exposure-specific effects on the attainment of sexual maturity in offspring. The severity, as well as the duration of the insult, may also affect the outcome and most importantly an interplay between pre- and postnatal nutrition may be a significant determinant of the timing of puberty onset. The impact of early nutrition on puberty onset and the potentially associated health problems represents an issue of translational interest, especially in case of overfeeding, given the rising incidence of gestational and childhood obesity in human.

Human epidemiological data: the role of birth body weight

In humans, birth weight (BW) was used as a proxy for fetal development, since small weight at birth may arise from maternal undernutrition or reduced nutrient delivery to the fetus due to different placental insufficiency.

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A secular trend toward an earlier age at menarche was documented during the last decades, both in United States and Europe.[35–37] On the other hand, growing evidence is accumulated on the relationship between early life events and an increased risk of premature adrenarche, early puberty and associated fertility problems. To this respect, early life events and particular weight at birth have been reported to affect sexual maturation and a number of excellent reviews summarize the existed evidence.[38,39] Data on the relationship between BW and age at menarche are controversial, possibly because of the heterogeneity in the study designs. Cohort studies in United Kingdom,[40] Spain[41] and Israel[42] reported an association between low BW and timing of puberty or menarche, suggesting an effect of BW *per se*, but others have pointed out that an interplay between low BW or accelerated weight gain in infancy is more important in determining the timing of puberty. In particular, the significance of the interaction between pre- and postnatal nutrition has nicely been highlighted in studies demonstrated that both lower BW combined with higher body mass index during childhood predict early age at menarche.[43] In addition, in both boys and girls a relatively low BW and rapid weight gain between birth and 24 months were independently associated with an earlier age in onset of puberty.[44] Similarly, data from a large sample of young adult men highlighted that the rate of weight gain from birth to 6 months of age, coincident with early postnatal critical period for HPG axis development in human, predicts early maturation and higher testosterone levels, although the contribution of the prenatal nutrition has not been ruled out.[45] In children born small, but gaining weight rapidly central and total adiposity has been reported to increase,[46] thus, elevated insulin-like growth factor-1 (IGF1) concentrations and insulin resistance, as well as higher leptin levels following rapid infancy weight could contribute to the trigger for earlier pubertal development, by promoting the activity of the GnRH pulse generator.[47] Treatment of low BW girls with metformin, an antibiatetic drug, resulted in a delay in their pubertal development up to menarche along with a decrease in leptin and IGF1 levels.[48,49] All together the above data point out that the higher incidence of early menarche in low BW girls reflects alterations of the adipoinsulinar axis, thus linking early growth restrictions, postnatal adiposity and reproductive development. However, more detailed data on pre- and postnatal growth are required in order to evaluate the complex interactions between size at birth, infancy growth trajectory and timing of sexual maturation, especially when considering the association of pre- and postnatal interactions to the later onset of metabolic disease.[50]

Early life nutrition and programming of the reproductive axis development and function

Animal models represent important tools for investigating the DOHaD hypothesis. However, there are a number of limitations, which makes extrapolation back to human questionable. Highlighting the key differences between rat, sheep and human with respect to reproductive maturation will help to better understand and interpret the data presented in this review. Normal ovarian development during embryogenesis determines the fertility and reproductive capacity later in life.[51] Important landmarks of ovarian development are similar between precocious (human, sheep) and altricial species (rat), however, variations exist in the timing of each step (Fig. 1). Primordial germ cells (PGCs) migrate to the gonadal ridge at about 12–13 days post coitum (dpc) in rat,[52] whereas in sheep and human migration occur at about 3 and 5 weeks of gestation, respectively.[52,53] Shortly after the sex-specific differentiation of the gonad, PGCs start transforming into oogonia increasing steadily in number, until they enter meiosis, becoming oocytes.[54] Onset of meiosis occurs at 15.5 dpc in rat,[55] whereas in sheep and human at

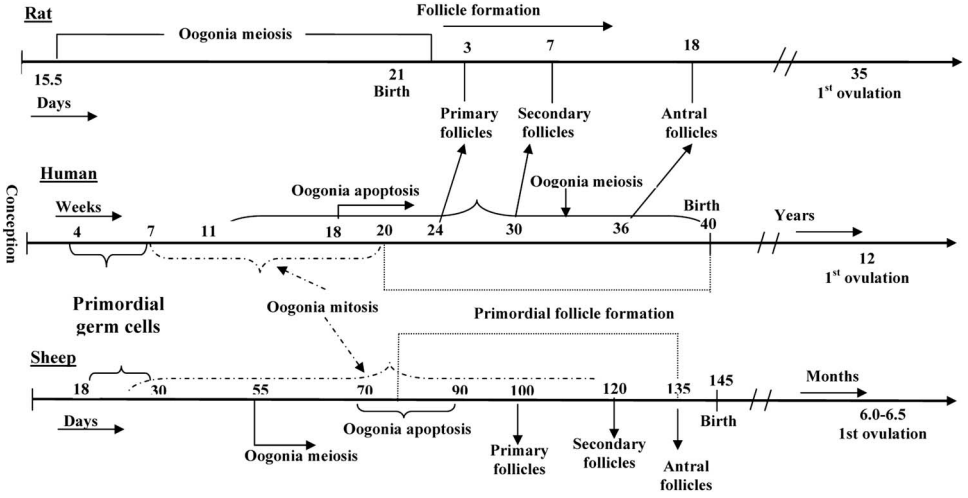

Fig. 1. Milestones of ovarian development in rat, sheep and human.

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weeks 8 and 11–12, respectively.[56,57] As a consequence of initiation of meiosis, multiplication is prohibited and the store of female gametes is set definitively at that stage of life. Initial folliculogenesis represents the last step of ovarian differentiation. It takes place during the fetal life in human (20 weeks to birth),[58] in sheep (11–14 weeks)[56] and within the first week of postnatal life in rat.[59] In human and sheep, the recruitment of resting primordial follicles into the growing follicle population starts in fetal life and it is only after puberty that cyclic increases in serum gonadotropins stimulate the antral follicles to become preovulatory follicles during each menstrual cycle in human and estrus cycle in sheep. In contrast, in rats, the majority of follicles form and are recruited to grow after birth and the first wave of follicles develop intro antral follicles over the next 3 weeks.[60] Puberty or first estrus occurs around day 34 in rat, whereas in sheep at ~6 months of age, depending on breed and season. In both human and rodent species follicle growth continues until the primordial follicle population is depleted.[61]

Unlike oogenesis in females, whose oocyte population is determined at birth, in males spermatogonia act as stem cells and constantly divide to produce gametes spermatogenesis relies on the establishement of a normal adult Sertoli cell number, as they are the primary determinant of sperm production capacity in adulthood.[62] It is now well accepted that Sertoli cells proliferate during two periods in life, fetal and neonatal and in peripubertal period in all species.[63] Therefore, cell proliferation in the embryonic and early postnatal periods is crucial for establishing the mature adult size of the testis and maintains a sufficient population of sperm-producing Sertoli cells during adulthood.

Animal experimental data

Studies restricted to fetal or/and neonatal life

Evidence in males supports a negative impact of early life undernutrition on testicular structure and function. Maternal undernutrition imposed during both gestation and lactation or during lactation in rats led to drastic reduction in gonadal weight and structure in progeny, indicating a potential influence on later reproductive function.[27] Indeed, exposure to low-protein diet (LPD) during gestation reduced sperm count and influenced male's ability to impregnate female rats in the F_1 male offspring.[64] In sheep, data on males are controversial and range from no effects in fetal testis weight and Sertoli cell number after nutritionally mediated placental growth restriction,[65] to 20% reduction in the number of Sertoli cells in newborn lambs undernourished *in utero*.[66] Sertoli cells could provide a target for programming, as their number per testis is the most important factor that determines the ceiling of sperm production and output.[67] On the other hand, maternal undernutrition in early gestation in sheep led to increased expression of steroidogenic acute regulatory protein (StAR) mRNA in the fetal testes, and increased plasma testosterone concentrations.[68] A number of data also indicate effect of maternal undernutrition on the fetal hypothalamo–pituitary axis function. In particular, in male sheep fetus maternal undernutrition has been shown to influence the pituitary response to GnRH challenge[69] and altered pituitary sensitivity has also been observed in 55-day-old lambs, born to mothers undernourished from 30 days of gestation to term.[70]

In rat, offspring of dams undernourished during gestation and/or lactation exhibited impaired folliculogenesis, reflected by a greater number of small size antral follicles and reduced number of large size graafian follicles[27] or impaired follicular maturation.[71] A significant reduction in all types of follicles (primordial, secondary, antral) along with changes in key ovarian gene expression and increased ovarian oxidative stress has been demonstrated in ovaries of rats born to dams undernourished during specific developmental windows.[72] On the other hand, prenatal exposure to high-fat nutrition and exposure from weaning alters estrous cyclicity in adult rats, exhibiting also prolonged or persistent estrus.[73] These results clearly indicate that adverse effects can be manifested at both ends of nutritional spectrum.

In sheep, oogonial meiosis and follicular development were found to be delayed in fetuses undernourished during early gestation, indicating that undernutrition imposed even before differentiation of the ovary can compromise subsequent follicular development.[31] Maternal undernutrition has been reported to affect the rate of cell atresia causing a delay in the fetal germ cell degeneration,[74] whereas later studies pointed out to the changes in apoptosis-regulating genes, thus altering the balance of apoptosis and proliferation in the developing follicles and surrounding ovarian cells, leading to reduced follicle number postnatal.[75]

Effects persisting in adulthood

The studies mentioned above are mostly limited to the late gestation fetus or young animals. However, it is well accepted that alterations in the developmental process of the HPG axis generally are perceived only at puberty or in adult reproductive life[76] and more likely after the gonadal feedback is set up.[33] This is also the case with the reproductive consequences of early glucocorticoid or androgen exposure, which are only evident after puberty, when many of the sex-linked differences in developmental programming appear for the first time with the onset of gonadal steroidogenesis.[77] A number of studies have been set up in our laboratory to examine the effects of maternal undernutrtion, during different developmental windows on adult reproductive axis and function, as early perturbations could be of significance only if long-lasting effects are considered. In male sheep, maternal undernutrition during the first month of pregnancy did not affect pituitary response to GnRH in 10-month-old offspring, but when it was imposed during mid to late gestation (30–100 days) resulted in an enhanced luteinizing hormone (LH) and follicle-stimulating hormone (FSH) response and increased basal FSH levels.[34] In addition, undernutrition

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during this specific window resulted in reduced seminiferous tubule diameter and decreased number of Sertoli cells, accompanied by a higher proportion of cells with apoptotic nucleus in the testes of the offspring, indicating a direct gonadal effect.[78] Lower Sertoli cell number and changes in testicular structure have also been reported recently for adult rats born to dams undernourished during gestation and lactation.[79]

Female sheep offspring, born to mothers undernourished during the 1st month of gestation exhibited an enhanced pituitary sensitivity in terms of FSH response and were also presented with an increased number of small follicles, whereas maternal undernutrition from mid to late pregnany resulted in decreased number of corpora lutea in their ovaries.[33] Immunohistochemical studies showed a significantly lower number of Ki67 immunoreactive cells, whereas TUNEL staining did not reveal any differences in the number of apoptotic granulosa cells of graafian follicles in both groups animals undernourished from mid to late gestation.[78] Thus, an early exposure to feed restriction may alter the central/peripheral FSH regulation and consequently higher FSH response in these animals may be associated with an attenuated feed back signal on the pituitary, mainly from inhibin. In addition, the lower number of corpora lutea detected in these animals may potentially affect the establishment of pregnancy, since corpus luteum provide steroid hormonal support essential for the establishment and maintenance of early pregnancy,[80] explaining probably the increased embryonic loss reported in ewes undernourished as fetuses.[81,82] Taking together, the above data point out to window-of-exposure and sex-specific effect of undernutrition on hypothalamo–pituitary axis function and gonadal development.

In a separate sheep model of intrauterine growth retardation (IUGR), involving overnourished adolescent ewes, more compelling reductions in the size of the ovarian follicular pool of female offspring was reported.[83] There is now compelling evidence to suggest that in both overnourished and undernourished ovine pregnancies, fetuses experience a period of nutrient restriction as a result of alterations in placental delivery of maternal nutrients, making similar *in utero* reallocations of energy and nutrients to favor organs and tissues, critical to survival, at the expense of other organs and tissues of lesser significance to maintain competitive fitness.[84]

Human studies: the role of birth body weight

Studies examining the follicular growth in normal and growth restricted human fetuses reported either a reduction in the volume percentage of follicles in the growth-restricted fetuses or no difference between groups.[85,86] In a number of studies, involved adolescent girls born small for gestational age (SGA) reduced ovarian and uterine size and a low ovulation rate, accompanied by elevated serum FSH levels have been reported.[87–89] However, as treatment with metformin induced ovulation and normalize both abdominal fat and lean body mass, it is more likely that reduced ovulation is a secondary effect, due to deranged metabolism, accompanied by hyperinsulinism, central adiposity and dyslipidemia.[90]

Regarding males, results on long-term effects of IUGR on the HPG function are controversial. Reduced testicular volume, along with lower testosterone and higher LH levels were detected in males born SGA, indicating a different setup of the HPG axis with a tendency to hypogonadism in the SGA subjects.[91] These results, with increased levels of gonadotropins, are similar to those in females, pointing out a peripheral partial insensitivity to gonadotropins.[92] A permanent disturbance in the steroid biosynthesis with elevated levels of estradiol, dihydrotestosterone and inhibin B was observed in SGA males, that could be part of the explanation to testicular dysgenesis syndrome.[93] However, data from a prospective study in adolescent men found no differences for testicular volume or the secretory pattern of gonadotrophins between (SGA) and adequate for gestational age (AGA) males.[94] Overall, despite the methodological inadequacies of individual study results, accumulating evidence from animal and human studies points toward a subtle impairment of both Sertoli and Leydig cell function caused by perinatal growth restriction, probably associated with increased risk of male reproductive health.[95]

Do effects translate into compromised fertility?

A common finding among studies in rodents, sheep and humans is the disrupted follicular development following maternal feed restriction. As it is well documented that effects on oocyte number will determine the span of female reproductive life, these effects are most likely to impact on subsequent fertility. Therefore, it is of significant importance to determine if this prenatal compromise in the development of reproductive axis translates into any significant functional deficit in subsequent reproductive performance and particular fertility, representing the main outcome of reproductive function. Follow-up studies of historical cohort of Dutch famine women, based on a number of fertility markers such as age at first pregnancy, completed family size and interpregnancy interval do not support a detrimental effect on fertility of women exposed to famine *in utero*.[96,97] The same authors also demonstrated no association between BW and fertility of both men and women and, furthermore, although subjects born SGA were more insulin resistant than AGA ones, yet no evidence of any relation between insulin resistance and reduced fertility was observed. A French cohort study also reported no evidence of any relation between BW and fertility of both men and women.[98] Regarding effects on the onset of menopause in women, most studies do not provide evidence of an association between size at birth and age at menopause,[99] whereas others reported a U-shaped relationship between BW and time of menopause.[100] Studies in sheep also indicate that apart from small size at birth, large size is also associated with lower fertility.[101] In the same species, a bout of maternal nutrient restriction from early to

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mid gestation resulted in marked reduction in the fertility of the offspring, in association with decreased progesterone concentrations in maternal blood.[102] In males conflicting results have been reported, ranging from no effect of BW on semen quality[103] to a significant association between BW and testosterone levels, independent from adult weight.[104] Moreover, previous studies reported lower BW in subfertile men of unknown etiology, supporting the concept of *in utero* programming across the range of BW.[105] Although experimental and epidemiological data link the BW to postnatal adverse effects, it is also apparent that programming effects may be expressed in the absence of any changes in BW.[106] It is also widely accepted that the catch-up growth that follows *in utero* growth restriction, underlies many of the adverse effects occurring during adulthood,[107,108] and more importantly in case of mismatch between the predicted and actual mature environment, as has been proposed for metabolic outcomes.[109] The impact of catch-up growth on fertility in humans, however, is largely unknown, but it certainly complicates interpretation of the effects of nutrient restriction during pregnancy *per se* on physiological function in the offspring. Whether associations documented in experimental and epidemiological studies between early life nutrition history and later reproductive outcomes reflect a developmental impairment or an adaptive capacity to adjust reproductive strategy is still uncertain and a matter of debate.[110,111] Data from Polish women provide support for predictive adaptive theory,[112] as differences in nutritional status at birth showed to predict ovarian sensitivity, as determined by estradiol levels, to energetic stress in adulthood. In particular, women with a high ponderal index (PI) at birth did not exhibit ovarian steroidogenesis suppression to moderate levels of physical activity, whereas women who had a lower PI at birth showed ovarian suppression in association with moderate energetic stress. As it is nicely pointed out by Kuzawa and Quin,[113] outcomes related to physiologic and endocrine systems are more prone to developmental plasticity paradigm and propose that apart from documented downstream effects, the study of the regulatory changes that underline them is crucial in distinguishing between developmental impairment or a regulatory adjustment in system settings. However, from a life history perspective, these adaptations would optimize lifetime resource allocation, enhance survival, and maintain fitness.[114]

Periconceptional nutrition and the impact of obesity

The periconceptional period is recently gaining a crucial role to programming since it is characterized by extensive reorganization of cellular phenotype during oocyte maturation, fertilization and embryonic genome activation.[7] Oocyte acquires developmental competence mainly during the terminal steps of folliculogenesis and meiotic maturation and it depends on the establishment of a fruitful molecular dialog between the oocyte and surrounding follicular cells.[115] Changes to the immediate environment surrounding oocytes, probably resulting from nutritionally induced changes in hormone and metabolite levels can alter the pattern of genes expressed by ovarian follicles, impacting immediate and longer-term development.[116] On the other hand, as oocyte quality influences early embryonic, fetal and postnatal development[117] it is widely accepted that oocyte development represents a critical feature in developmental programming hypothesis. Moreover, preimplantation embryo has been shown to be sensitive to environmental perturbations with long-term consequences.[118] The vital role of periconceptional nutrition has been highlighted in studies involved in diet manipulation of donor animals.[119–121] In particular, studies in sheep clearly indicate that both under and overfeeding during pre-mating period result in reduced oocyte quality and embryonic development.[122] Interestingly, short-term underfeeding before conception influenced the expression of a number of genes related to oocyte metabolic activity. However, factors such as time of nutritional treatment, composition of the diet and most importantly duration of nutritional manipulation determine final outcomes.[123]

Increasing evidence also suggest that obesity negatively impact the developmental competence of the oocyte, affecting its ability to be fertilized and support embryo development.[124] Animal models of induced obesity represent a nice example of how nutritional status before conception affects subsequent oocyte quality and embryonic development. In the diet-induced obesity mouse model, an increase in apoptotic cells has been detected in the preovulatory ovarian follicles leading to smaller oocytes displaying decreased maturation, reduced blastocyst survival rates and abnormal embryonic cellular differentiation.[125] Increased apoptosis in the preovulatory follicles and decreased oocyte maturation along with increased placental IGF2r expression and smaller pups have been reported in similar models of induced obesity before conception.[126] Ovarian regulation disturbances may also be due to higher concentration of IGF1 in obese conditions, which has been reported to decrease embryo quality, by increasing the levels of apoptosis and impairing cell allocation at the blastocyst stage.[127] Recently results from an intriguing experiment, elegantly outlined a role of compromised mitochondrial activity and impaired antioxidant capacities in mediating the adverse effects of obesity on reproductive outcomes.[128]

Apart for female obesity, there is now mounting evidence to suggest that male obesity is also implicated in reducing fertility and impaired reproductive outcomes. Paternal obesity at the time of conception showed compromised gamete health in F1 offspring, increased oxidative stress in male offspring and changes to mitochondrial function in female offspring,[129] indicating a role for paternal transmission of diminished reproductive health to future generations. There is now accumulating evidence to support that obese condition and over rich diet disturbs ovarian regulation and function, causing fertility perturbations as well as adverse developmental

programming into adulthood. The most well characterized effects are associated with metabolic and behavioral outcomes in adult life,[126,130–132] but data related to reproductive outcomes are almost missing. Intervention studies with follow-up of the offspring will help in clarifying the role of obesity or overfeeding before and during pregnancy in causing adverse reproductive outcomes in the offspring.

Underlying mechanisms: the role of epigenetics

The way through which environmental insults, such as nutrition contribute to the onset of later detrimental outcomes likely involves a complex interaction between the maternal environment, placental changes, and epigenetic programming of the embryo. However, the mechanisms through which early life events are transmitted to the target organs are complex and still poorly understood. They may include structural changes, altered cell proliferation/apoptosis, changes in hormone levels and receptor abundance. Maternal endocrine milieu is crucial in mediating the effects of nutrition, as hormones can directly or through changes in placenta phenotype act on the fetal tissues to alter cell growth and differentiation, consequently affecting their function later in life.[133,134] Endocrine programming has recently been highlighted as mediating such effects, since undernutrition disrupts a wide range of endocrine pathways, including HPG axis, resulting in long-term effects on offspring's health.[135] The effects on fetal endocrine development may be mediated, at least in part, by exposure of the developing fetal organs to altered circulating or tissue concentrations of glucocorticoids[136] and prenatal nutrient restriction has been shown to alter HPA axis function in young and adult offspring, suggesting that HPA programming may be a common outcome of prenatal environmental challenge.[137–141] However, direction of changes depends on developmental step and age of the offspring.[136,139] Molecular mechanisms underlying the effects of glucocorticoids probably include epigenetic changes in target gene promoters, including the GR,[142] thus affecting persistently glucocorticoid signaling in certain tissues. Pituitary gonadotrophs,[143] as well as ovary,[144] are all glucocorticoid targets in the adult. Furthermore, the coexistence of progesterone, estrogen and the type II glucocorticoid receptor reported in the ovine preoptic area and ARC nucleus, further support a role for glucocorticoids in mediating effects on reproductive axis, suggesting that all three steroids may influence the activity of the same neurons to modulate both reproductive and stress axes.[145] Together these data provide strong evidence that glucocorticoids represent an important developmental trigger and that their effects are mediated at the level of DNA methylation.[146]

Epigenetic modulation of gene transcription provides the most plausible mechanism through which fetal nutrient supply can alter gene expression in the developing fetus, leading to later permanent effects. There have been outstanding reviews on how the concept of epigenetics has been applied to the developmental programming hypothesis, mainly related to metabolic and cardiovascular outcomes.[147–151] Regarding epigenetic mechanisms underlying programming of reproductive function evidence comes from the field of assisted reproductive technologies (ARTs). Studies on reproductive outcomes after *in vitro* fertilization strongly support the well-recognized concept that alteration of biochemical and biophysical conditions at conception and during early embryonic life associated with ARTs, may result in changes in epigenetic processes and lead to short- and long-term effects on development and health.[152,153] Although a variety of mechanisms may associate preimplantation environment with future developmental changes, the aberrant expression of imprinted genes has been proposed to play a significant role.[154,155] Several studies have identified changes in imprinted gene expression throughout the development associated with culture composition during the preimplantation period when the DNA methylation pattern may be sensitive to environmental conditions.[156,157] DNA methylation and histone modifications have been implicated as the most prominent process to alter gene expression and which can be altered by the availability of amino acids or micronutrients during pregnancy.[158–160] Interestingly, similar alterations in the expression of the imprinted genes *H19* and *IGF2* has also been reported to occur in fetal sheep due to maternal LPD during the preimplantation period.[161] Given that maternal undernutrition can lead to alteration in steroid hormone levels,[162,163] this may in turn affect *H19* and/or *IGF2* gene expression. Fowden and Forhead[164] highlighted the potential role of hormones as epigenetic signals in determining the phenotypical outcome of environmental cues acting during intrauterine development, as hormones signal the type, severity and duration of the environmental cue to the developing feto-placental tissues.

Studies have also shown that a high number of genes in the blastocyst exhibit sexual dimorphism with an extensive transcriptional regulation led by the sex chromosomes, both for *in vivo* and *in vitro*-derived embryos and that changes in postnatal growth induced by a maternal LPD at the time of conception, may be resulted partly from the sex-specific programming of imprinted gene expression within the preimplantation embryo itself.[165] The sex-specific effects observed for several programming outcomes, as a result to early nutritional perturbations, could also be explained in the light of the well-documented sexual dimorphism in environmental epigenetic programming. As dimorphic genes' expression might be under the control of sex-specific epigenetic marks, environmental factors, including nutrition, can influence, in a sex-specific manner these flexible epigenetic marks, mainly during critical windows of development.[166] The concept of epigenetic modulation underlying sexual dimorphism is further enhanced by recent results showing that both promoters of androgen and estrogen receptor genes, and the expression of their target genes, are regulated by epigenetic mechanisms.[167]

There is now strong evidence to support that environmental influences including maternal nutrition during embryonic and early life development can permanently alter epigenetic gene

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regulation, which in turn can result in imprinting and reprogramming of the epigenome, impacting on detrimental reproductive outcomes in later life.

Transgenerational effects

One of the most crucial features of developmental programming is that epigenetic modifications may be expressed in subsequent generations. Accumulating evidence from studies in humans and animal models support nongenomic transmission between generations of induced phenotypic traits mainly associated with metabolic programming and disease risk.[168] Insights into transgenerational effects related to reproductive systems come from studies with endocrine disrupting chemicals (EDCs). For example, exposure of pregnant rats to the endocrine disruptor vinclozolin caused decreased spermatogenic capacity in the F1 generation that was transferred through the male germline to the fourth generation.[169] Results from a number of elegant experiments by Gore[170] investigating the effects of prenatal EDCs exposure on reproductive neuroendocrine functions in two generations, clearly indicate that perinatal EDCs impact reproductive neuroendocrinology function at several levels, by exerting detrimental effects on neuroendocrine circuits including GnRH neurons and their regulatory inputs and altering reproductive behaviors. In particular, F2 adult females exhibited suppressed progesterone and LH concentrations on proestrus, whereas males and females from both generations showed altered expression of neuroendocrine genes in the preoptic area of the hypothalamus. More interestingly, they showed trangenerational effects of EDCs on reproductive systems, probably including neuroendocrine targets. The way through which EDCs can induce epigenetic transgenerational phenotypes is probably a nice paradigm of how nutritional perturbations during preconception might also, through germline reprogramming, impact on subsequent generations' reproductive function. Given the fact that endocrine disrupting compounds can act as hormone agonists or antagonists and that nutritional mediated hormonal alterations act probably as imprinting factors, it is of interest to examine if similar mechanisms operate in mediating effects of early life nutrition on neuroendocrine circuits governing reproduction or on any other features of the reproductive axis. Both nutritional perturbations and exposure to EDCs can affect hormonal regulation and metabolic pathways. Indeed, hormones and nutritional components can both directly activate receptors or modulate pathways responsible for gene expression control. Thus, as it has been stated recently, 'The developmental disruption effects associated with nutrients and environmental chemicals are likely two sides of the same coin and epigenetic regulatory pathways are likely sites for effects of both nutrient and environmental toxicant effects'.[171]

There is also emerging evidence for transgenerational transmission down the paternal line.[172] Female progeny of obese males demonstrated subfertility phenotypes that were transmitted to both sexes of the F2 generation via F1 males and to F2 males via the F1 maternal lineage.[173] The altered sperm epigenome observed in obese males epigenome via increased acetylation[174] and differential microRNA content[175] probably implies transgenerational epigenetic inheritance. Epigenetic modifications, due to fetal EDCs exposure have also been shown to pass up to four generations of offspring via the male germline, linked to altered sperm epigenome.[176,177]

Conclusions and future implications

Epigenetic modulation of critical genes involved in the control of reproductive function and potential intergenerational effects represent an exciting area of interdisciplinary research toward development of new nutritional approaches during pre- and postnatal periods to ensure reproductive health in later life. The challenge will be to determine whether interventions can prevent, or modify, these effects, thereby resulting in a healthier start to life and optimizing both later metabolic and reproductive outcomes. In between, there are emerging areas of critical interest including the extension of studies of the nutritional environment of the early embryo to include a better understanding of the impact of the perturbations of the environment of the gametes and embryo during both physiological process and a range of ARTs on reproductive health of next generations. Although the existence of sexually dimorphic phenotypes is rather obvious, the mechanisms that underlie this process still remain a matter of interest. Finally, the contribution of paternal lineage to the intergenerational transmission of detrimental outcomes and especially of a decline in fertility remains to be elucidated.

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Conflicts of Interest

None.

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