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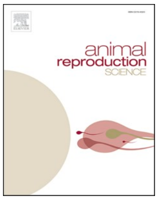

Maternal nutrition and fetal imprinting of the male progeny

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ABSTRACT

The global population as well as the demand for human food is rapidly growing worldwide, which necessitates improvement of efficiency in livestock operations. In this context, environmental factors during fetal and/or neonatal life have been observed to influence normal physical and physiological function of an individual during adulthood, and this phenomenon is called fetal or developmental programming. While numerous studies have reported the impact of maternal factors on development of the female progeny, limited information is available on the potential effects of fetal programming on reproductive function of the male offspring. Therefore, the objective for this review article was to focus on available literature regarding the impact of maternal factors, particularly maternal nutrition, on reproductive system of the male offspring. To this end, we highlighted developmental programming of the male offspring in domestic species (i.e., pig, cow and sheep) as well as laboratory species (i.e., mice and rat) during pregnancy and lactation. In this sense, we pointed out the effects of maternal nutrition on various functions of the male offspring including hypothalamic–pituitary axis, hormonal levels, testicular tissue and semen parameters.

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1. Introduction

The concept of developmental programming, which refers to the effect of environmental factors during fetal and/or neonatal life on normal physical and physiological function of an individual during adulthood, was initially popularized by David Barker (Hales and Barker, 2001, Barker, 2003, Barker, 2004, Reynolds et al., 2010, Wathes, 2022). Developmental programming is also called fetal programming or fetal imprinting (Johnston et al., 2008). Numerous studies demonstrated the role of developmental processes in the health and disease of various organs and bodily systems in human, particularly in metabolic and cardiovascular conditions, over the recent decades (Gluckman et al., 2005, Mcmillen and Robinson, 2005, Giussani and Davidge, 2013, Padmanabhan et al., 2016). In this context, maternal undernutrition or over-nutrition during pregnancy and lactation could alter the development of organs and impair prenatal and neonatal growth (Ji et al., 2017). In addition, David Barker suggested that the origins of some chronic diseases could be related to how fetuses respond to their early intrauterine environment, a concept now widely referred to as the "fetal origins of adult disease"(Barker, 1995).

Among several environmental factors, maternal plane of nutrition is considered as a major culprit for alteration in developmental programming of the offspring (Ahmadi et al., 2017, Jahangirifar et al., 2019). Maternal nutrition during embryonic, fetal and suckling periods can cause short- and long-term consequences for the progeny (McCoski et al., 2021). The resultant structural and functional changes may increase susceptibility of the offspring to diseases and alter its reproductive performance (Weller et al., 2016). The majority of data refer to the effects of undernutrition imposed during early or mid to late gestation. Also, it has been recognized that even preconceptional period may be one of the critical developmental windows for programming of the offspring (Chadio and Kotsampasi, 2014).

Maternal malnutrition can influence puberty and later fertility through changes in hypothalamic properties controlling reproduction. These negative effects of maternal malnutrition on the offspring could materialize during early pregnancy because development of hypothalamic neurons including those secreting GnRH initiates from early fetal period. Moreover, in studies investigating the effects of maternal care on the programming of hypothalamic–pituitary–gonadal (HPG) axis, kisspeptin neurons contributed to mediation of these effects. Because low licking/grooming (LG) rats exhibited an earlier vaginal opening, an indicator of puberty onset,

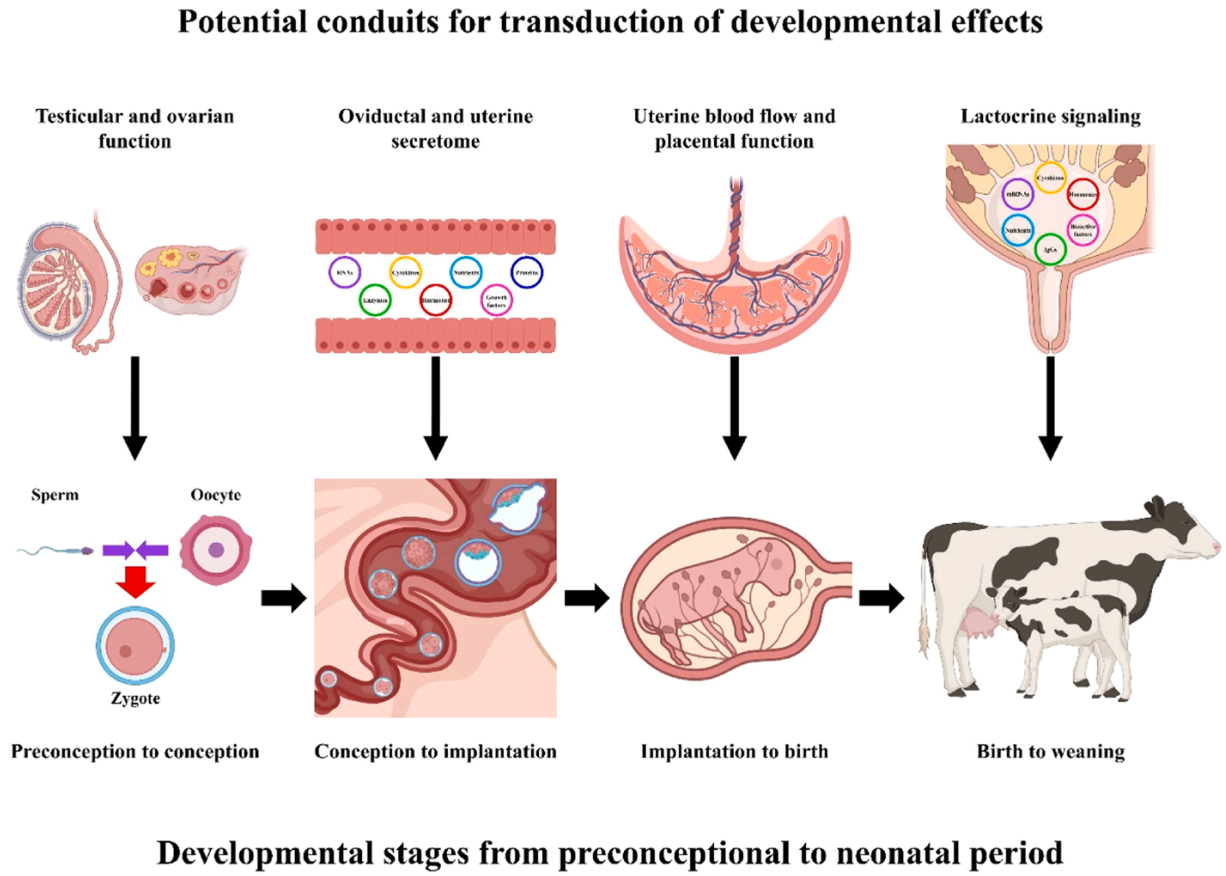

Fig. 1. Various stages of offspring development from preconceptional to neonatal period, and the potential conduits for the influence of developmental effects during different developmental stages. Herein, it is worth mentioning that bovine fetus and neonate were used to simply present a schematic diagram and these stages and mechanisms can be true in other species as well. Created with BioRender.com.

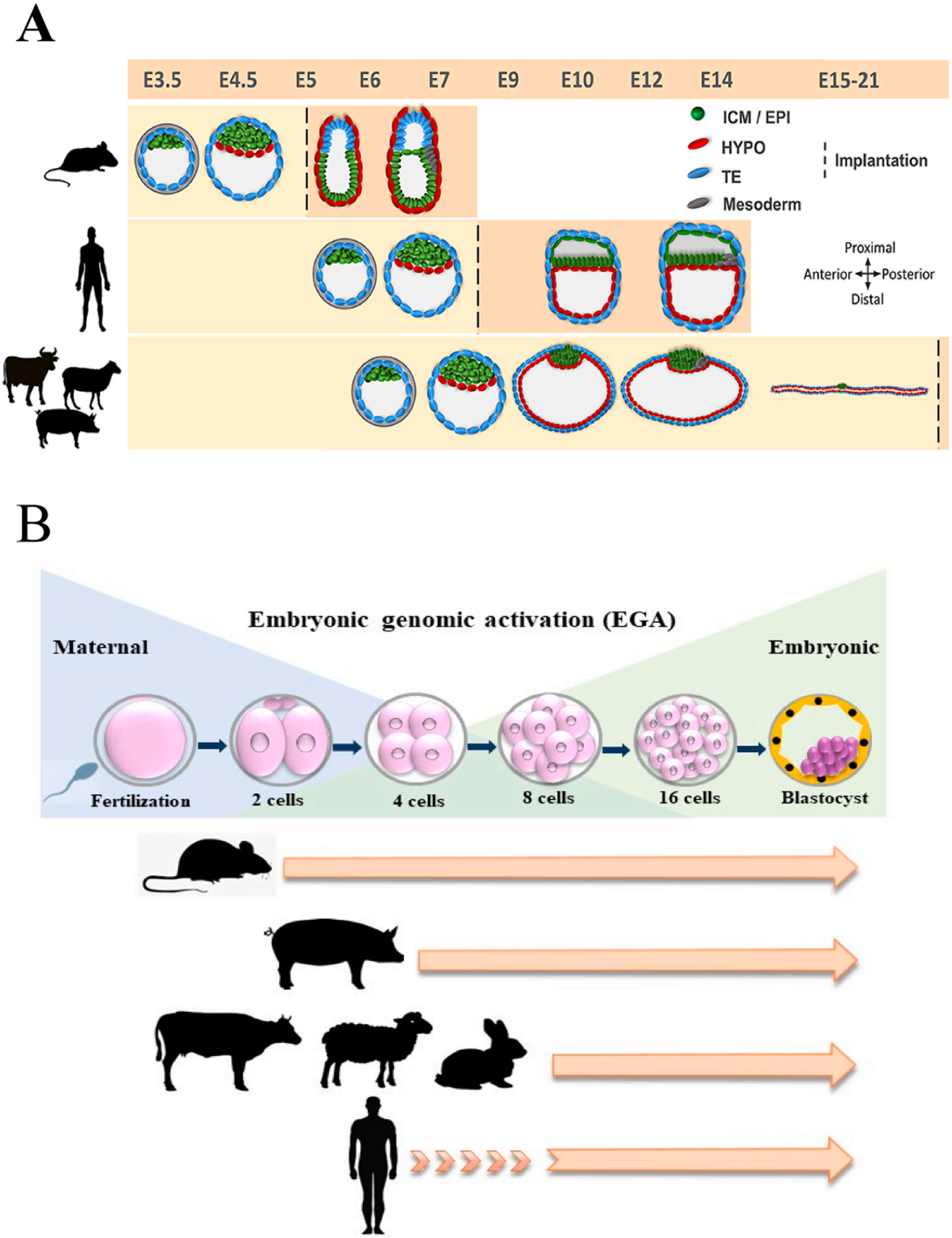

Fig. 2. Comparative developmental and **embryonic genomic activation** (EGA) timeline among mice, humans, and farm ungulates. (**A**) Different cell lineages are indicated. Embryo development in humans and farm ungulates is delayed compared to mice. Implantation occurs after blastocyst hatching in mice and humans, while in farm ungulates it occurs following conceptus elongation. Mouse epiblast develops in a cup shape after the blastocyst stage, while in humans and farm ungulates, it forms a flat embryonic disc. (**B**) EGA begins at two cells in mice and four cells in pigs. In sheep, cows, and rabbits, EGA starts at eight cells. In macaques and humans, EGA occurs between four and eight cells. E: embryonic day; ICM: inner cell mass; EPI: epiblast; HYPO: hypoblast; TE: trophectoderm. Part A of the figure is adapted and permitted by Frontiers.

compared with high LG offspring (Chadio and Kotsampasi, 2014).

The interaction of genetics and environment, which is so-called as nature, and nurture, is the foundation for health and disease. Exposure of the mother to a disadvantageous environment, particularly imbalance diet, during pregnancy not only influence the placenta and fetus, but may also impact the epigenetics of germ cells forming during fetal development, thereby perpetuating the negative effect transgenerationally (Wathes, 2022). The greatest epigenetic plasticity takes place during gamete maturation and embryogenesis, and the consequences can last for part of or whole life of the exposed generation, and even be transmitted to subsequent generations (Bianconi et al., 2018a, Chadio and Kotsampasi, 2014). The developmental repercussions of early life exposures and corresponding epigenetic mechanism have been elaborated by Sánchez-Garrido et al. (2022); however, limited data is available on the developmental effects of maternal nutrition on the male offspring in livestock.

It has been shown that fertility of the offspring is programmed by maternal factors (Cameron, 2011). In other words, the reproductive performance of animals during adulthood is determined, at least in part, by a variety of exogenous factors during different stages of development. With respect to the effect of maternal under-nutrition on growth and development of the reproductive organs (e.g., hypothalamus, pituitary, and gonads) in the offspring, it is not only a matter of exposure and time of exposure is of importance (Rhind et al., 2001; Lugarà et al., 2022). In this context, several studies in different species have focused on malnutrition and little information exists on applying strategies revolving around use of supplements for mothers in the case of nutritional deficiency (Ghasemi et al.).

While the majority of studies focused on female offspring (Mossa et al., 2013, Cushman et al., 2014, Akbarinejad et al., 2017, Akbarinejad et al., 2018, Akbarinejad et al., 2019, Tenley et al., 2019; Makiabadi et al., 2022; Shourabi et al., 2022; Sadeghi et al., 2023, Bafandeh et al., 2023, Makiabadi et al., 2023; Akbarinejad and Cushman, 2024; Cushman et al., 2024; Harati et al., 2024; Mobedi et al., 2024), the inevitable roles of maternal and uterine environmental factors on male offspring performance and growth has not received as much attention. It is reasonable to speculate that reproductive development of males is also affected by maternal nutrition. This could occur at hypothalamic-pituitary axis via the alternation of signaling pathways and hormonal secretions or at the level of the gonads via changes in gene expression, testicular morphology and semen quality. Given the potential role of developmental factors in productive and reproductive performance of the male animal as well as the growing demand for food in human (Henchion et al., 2021), it appears that studying developmental programming in the male offspring warrants serious consideration. Accordingly, we summarized the ontogeny of the offspring and the factors affecting developmental programming of the male reproductive system in livestock and labratory animals in the current review article.

2. Various developmental stages of the offspring

As aforementioned, the dam plays a critical role in processes revolving around developmental programming of the offspring, and in this regard, the causes could be the individual characteristics of the dam or the environmental factors surrounding and affecting the dam (Velazquez et al., 2023, Reynolds et al., 2023). Yet the mechanisms whereby the offspring is influenced during various developmental stages, including pre-conceptional, zygotic, embryonic, fetal and neonatal, may be different (Velazquez et al., 2023, Reynolds et al., 2023) (Fig. 1). In brief, the ontogeny of the offspring initiates from the formation and development of corresponding gametes (i.e., oocyte and sperm) which form the zygote upon fertilization and syngamy (Molè et al., 2020). Further, embryonic period begins by commencement of cell divisions in the zygote, which leads to organogenesis and initiation of fetal period (Perez-Gomez et al., 2021) (Fig. 2A). Speaking of the zygote and early embryo, it is worth mentioning that the process of transitioning from oogenetic to embryonic genomic activation (EGA) is commonly referred to as the maternal-to-zygotic transition (MZT) (Halstead et al., 2020). This is a crucial process that occurs during early embryonic development and encompasses two closely synchronized events, including EGA and destruction of maternal gene transcripts (Tadros and Lipshitz, 2009). The initiation of EGA in mammalian embryos varies across species. In mice, EGA commences at two-cell stage, while in pigs, it occurs at four-cell stage. In sheep, cows, and rabbits, EGA begins at the eight-cell stage. In macaques and humans, EGA takes place between four-cell and eight-cell stage (Fig. 2B) (Tadros and Lipshitz, 2009). Thus, the zygote and early embryos are transcriptionally inactive and depends on molecular products produced by the oviduct and uterus for their vital functions in rodents, lagomorphs, ungulates, and primates (Perez-Gomez et al., 2021, Bastos et al., 2022) (Fig. 1).

Following EGA, the embryo gradually becomes independent of maternal transcriptome and proteome, but it still requires maternal nutritional supply. Concomitant with cellular divisions of inner cell mass (ICM) and initiation of organogenesis, ICM as well as trophectoderm contribute to development of extra-embryonic membranes and trophoblastic layer, which would eventually form the placenta (Rivera-Perez and Hadjantonakis, 2014). During this period, the embryo is nourished via uterine secretions after EGA to attachment to uterus, and afterwards, the embryo and further the fetus are nourished through the placenta (Rivera-Perez and Hadjantonakis, 2014) (Fig. 1). In this regard, there is temporal variation among different species as in rodents and primates, the blastocyst initiates attachment and implantation shortly after hatching; however, in ruminants (bovine and ovine), the blastocyst remains in the uterus for several days before undergoing rapid elongation (Imakawa et al., 2018). Accordingly, the time lag between EGA and nourishment from placenta varies among different species, which leads to species-specific physical and biochemical interactions between the dam and offspring during early life (Lanman and Seidman, 1977, Rivera-Perez and Hadjantonakis, 2014, Kojima et al., 2014, Lonergan et al., 2016, Imakawa et al., 2018, Loide et al., 2018, Walls et al., 2022). After placentation, placenta is the major conduit for transfer of oxygen and nutrients from maternal bloodstream to fetal circulation throughout gestation up until parturition, and placenta plays a pivotal role in developmental programming of the offspring (Reynolds et al., 2023) (Fig. 1). Upon parturition, the development programming of neonate could still be influenced by the dam since lactocrine signals could have short- and long-term effects on the offspring (Bartol et al., 2008, Bartol et al., 2013; Bagnell and Bartol, 2019a, 2019b; Fischer-Tlustos et al. 2021) (Fig. 1).

3. Testis development in boar, bull, ram, mice and rat

In addition to development of the whole body of an individual, the development of testis as the male gonad is of importance as far as the developmental programing of male reproduction is concerned. In this context, the temporal development of testicular tissue differ among various species and knowledge of this specific temporal pattern in each species is necessary because it is not always a matter of exposure to a stressor, and in some cases, it is a matter of time of exposure to a stressor considering the critical window of testicular development in the fetus. Hence, we summarized the temporal pattern of testicular development in some species in this section.

3.1. Boar

In porcine, the expression of sex-determining region Y (SRY) gene persists for an extended duration of approximately three weeks. The duration of expression continues for a period exceeding two weeks subsequent to the initial manifestation of Sertoli cell differentiation, which occurs on day 28 following coitus in pigs. The testicular isoform has been observed to exhibit activity, as the presence of oestrone sulphate was initially identified in male pig fetuses at day 31 following coitus. The prenatal steroidogenic pathway exhibits notable variations in pigs as compared to other mammalian species. Furthermore, the investigation examined the presence of 3β-hydroxysteroid dehydrogenase (3β-HSD) expression in the gonads of male, female, and intersex fetuses on days 50 and 70 post-coitus (Pailhoux et al., 2001). The gestational (114 d) and neonatal (21 d after birth) periods are two critical phases in swine production (Ji et al., 2017). The last 30 days of gestation is the most active period of fetal development during which piglets obtain about two-thirds of their birthweight (Jainudeen and Hafez, 1993, Ullrey et al., 1965). This increase in size is due to active periods of hyperplasia in most tissues. This is true for the testes and mitosis of Sertoli cells is high at 70 days after conception and continues to increase for the remainder of gestation. The development of reproductive organs begins prenatally and continues postnatally during suckling. In boars, Sertoli cell mitotic activity remains high, and in gilts, granulosa and endometrial cells begin to acquire the biochemical response elements that regulate adult reproduction (Flowers, 2023).

3.2. Bull and ram

The bovine gonad develops into a recognizable structure at around 41 days of gestation. The scrotum develops from the gonad over the course of the subsequent three to four months of gestation. The testes are small and solid structures that are made up of cords of undifferentiated gonocytes at birth. Between the ages of 7 and 10 months, there is a dramatic increase in testicular size. Bulls enter puberty between the ages of 32–44 weeks old depending on breed. This coincides with the completion of the process by which spermatogonia evolve from primary and secondary spermatocytes to rounded and elongated spermatid, and eventually spermatozoa. The bovine testis develops from a thickening of coelomic epithelium on the medioventral side of the mesonephros. During embryonic development, the genital ridges are invaded by primordial germ cells that travel from the yolk sac to the dorsal aorta and the ventral mesonephric tubules. These cells make an amoeboid journey to the genital ridges. These cells manifest in the bovine gonadal ridge during day 26 of gestation. Early gamete precursor cells are large, round, and rich in alkaline phosphatase and glycogen. They have integrated with the other epithelial cells in the bovine embryo's coelomic epithelium by day 28 (Lodhi et al., 2000).

In ovine, the emergence of the genital ridges occurs during the 20th day of gestation. At 20 days of gestation in sheep, the gonad remains in a primordial state, exhibiting complete bipotentiality and identical characteristics regardless of the XX or XY genotype. The activation of the SRY gene occurs in a specific fraction of somatic XY cells during the day 23 of gestation in sheep (Heidari et al., 2023). The sheep exhibits a rapid increase in the number of somatic and germ cells within the testes throughout fetal development, namely before day 100 of gestation. This proliferation is characterized by a fast rate of cell division without concurrent cell differentiation. Moreover, it has been observed that fetal stem cells in sheep undergo a minimum of eight mitotic divisions, with six of these divisions taking place prior to day 110 of gestation. During the period from day 110 of gestation to birth, there is a decrease in the replication of stem cells (SC), which then increases once again after birth (Giffin, 2015). It is necessary to point out that among farm animals, it seems that numerous studies focused on the ovine maternal nutrition effects on the offspring fertility (Chadio and Kotsampasi, 2014; Mossa et al., 2018).

3.3. Mice and rat

Epigenesis is the mode of germline determination in many mammalian species, including mice and humans. Primordial germ cells (PGCs) are the first cells that develop along the germ line. The fate of the embryo's PGCs is established before gastrulation in both humans (often during the second week after conception) and mice (particularly on embryonic day 6–7) (Extavour and Akam, 2003). To develop a functional gonad, PGCs need to be translocated from the yolk sac endoderm to the embryo proper, and the somatic precursors of the gonad need to multiply and form the GRs, the primordia of the eventual testis or ovary. PGCs are reincorporated into the embryo approximately a week after specification outside of the embryo, when the embryonic disc folds and the region of the yolk sac containing PGCs gives rise to the hindgut and the midgut. Therefore, PGCs are isolated cells among endodermal cells of the primitive hindgut and midgut epithelium in proximity to the aorta. These events occur during the fourth week of embryonic development, well before GRs are formed (Mäkelä et al., 2019). In murine, the initial population of PGCs migrates towards the developing gonadal region at E 10.5 (Dudley et al., 2007). Subsequently, a majority of the PGCs successfully establish themselves within the gonadal ridge by E 13.5 (Roelen and Chuva De Sousa Lopes, 2022). The Y chromosome exerts its influence via the SRY gene, which initiates the process of testis differentiation in the initially undifferentiated genital ridges that would otherwise develop into ovaries. In addition, it should be noted that the activation of the SRY gene in XX gonads leads to the differentiation of testicular tissue (Wilhelm et al., 2007).

The testis contains several distinct cell lineages, with the germ cells, Sertoli cells, and Leydig cells being the most significant ones. During prenatal development, Sertoli cells are the initial cell type to undergo differentiation within the gonad anlage (Magre and Jost, 1991, França et al., 2016). Large cells exhibit adhesion to one another and enclose the germ cells, also known as gonocytes, so constituting the seminiferous cords. The procedure takes place throughout the period of 13.5–14.5 days post-conception (dpc) in rats and from 11.5 to 12.5 dpc in mice. Subsequently, it should be considered that Sertoli cells undergo continued proliferation until day 16 post-partum (dpp) in rats and 17 dpp in mice, at which point the Sertoli cell population is conclusively established. In the stage of adulthood, the process of spermatogenesis relies on the quantity and quality of Sertoli cells, which are essential for the structural support required for the maturation of germ cells (Vergouwen et al., 1991). Leydig cells differentiate in the interstitial space after Sertoli cells have completed their initial differentiation. Expression of 3β-HSD in the fetal rat testis begins at 14.5 dpc, while testosterone production begins at 15.5 dpc. Testosterone production in mice begins about 12.5 days post-conception. While this cell type may remain into adulthood in the rat, in the mouse its functional activity subsides throughout late fetal and neonatal life. Another population of Leydig cells (i.e. adult Leydig cells) starts to differentiate from 15 dpp in the rat whereas in the mouse they replace the fetal cells between 5 and 15 dpp. Adult Leydig cells deviate both morphologically and physiologically from their prenatal counterparts (Migrenne et al., 2012). Altogether, more attention should be given to testis development in mice and rats during lactation period and before weaning that was ignored in some studies on the maternal nutrition effects on the offspring.

Table 1
Effects of maternal diet manipulation during gestation on male offspring birth weight.

	Maternal diet manipulation	Time/ duration/gestation phase	Effects on birth Weight
Pig			
Dwyer et al. (1994)	Over-nutrition	From day 25–80 of Gestation	↑
Bontempo et al. (2004)	Supplement (Conjugated linoleic acid)	From late pregnancy and continued throughout lactation	↔
Corino et al. (2009)	Supplement (Conjugated linoleic acid isomers)	From 7 days before parturition and ending 7 days postpartum, or until weaning	↑
Chen et al. (2019)	Supplement (Short-chain fatty acids)	From day 85 of gestation to 21 day of lactation	↔
Hasan et al. (2019)	Supplement (Resin acid-enriched composition contains free fatty acid)	One week before farrowing	↔
Nguyen et al. (2020)	Supplement (Low n6:n3 ratio fatty acid)	From day 28 of gestation until the end of lactation	↑
Lugarà et al. (2022)	Supplement (Spirulina: a blue-green algae)	During 9 weeks pre-gestation until the end of lactation	↔
Wang et al. (2022)	Supplement (Sildenafil)	Different stages of gestation: Day 0–110, 0–30, 80–110 and 30–110	↑
Cattle			
Sullivan et al. (2009)	Dietary protein (high & low level)	Different stages of gestation: first and second trimesters of gestation	↑
Mossa et al. (2013)	Nutrient restricted (to 60% of maintenance)	From 11 days before artificial insemination up to day 110 of gestation	↔
Cushman et al. (2014)	Nutrient restricted (to 75%, 100% and 125% of maintenance)	Different stages of gestation: Second & third trimester	↔
Mohrhauser et al. (2015)	Negative energy status (80% of the energy requirements)	From ~ 100 to ~ 190 days of gestation	↓
Weller et al. (2016)	Over-nutrition	Mid- and late gestation	↔
Batistel et al. (2017)	Supplement (Amino acid)	During late pregnancy	↑
Copping et al. (2018)	Dietary protein (high & low level)	From 60 days before conception to 23 days post conception and first trimester	↔
Noya et al. (2019)	Under-nutrition (65% of the energy requirements)	During first third of gestation	↔
Alharthi et al. (2021)	Body condition score (BCS); high BCS ≥ 3.75	During late-pregnancy	↓
Long et al. (2021)	Nutrient restricted (70% of the energy requirements)	From 158 days of gestation to parturition	↓
Sheep			
Deligeorgis et al. (1996)	Under-nutrition (60% of the energy requirements)	From 30 day of pregnancy to parturition	↓
Da Silva et al. (2001)	Over-nutrition	During the first 100 days of pregnancy	↓
Rae etal, (2002) a	Under-nutrition (50% of the energy requirements)	From mating to 119 days of gestation	↔
Lutz et al. (2006)	Nutrient restricted (50% of the energy requirements)	From days 28–78 of gestation	↔
Kotsampasi et al. (2009)	Under-nutrition (50% of the energy requirements)	From day 0–30 or 31–100 days of gestation	↔
Mossa et al. (2018)	Supplement (Starch)	From mating to parturition or for the last 75 days of gestation	↔

↑: Increase of birth weight, ↓: Decrease of birth weight, ↔: Not significantly changed

4. Swine maternal nutrition and male offspring

Previous studies evaluated the effect of nutrients in the maternal diet on sow reproduction, and piglet survival and performance (Blavi et al., 2021, Ji et al., 2017) and without seriously considering investigation of parameters related to reproductive performance of the male offspring.

4.1. *Effects of maternal nutrition on function of HPG axis*

The activation of the hypothalamic-pituitary (HP) axis is critical for the initiation and maintenance of reproductive cycles in swine and is influenced by a number of parameters, such as nutrition, metabolism, and gonadal steroids (Garcia et al., 2020, Marín-García and Llobat, 2021). Moreover, it has established that the initiation of puberty in gilts are metabolically gated (Zhao et al., 2021). Interestingly, Thorson et al. reported that short-term (10 days) negative energy balance induced reduced frequency and increased amplitude of Luteinizing hormone (LH) pulses in ovariectomized gilts (Thorson et al., 2018).

4.2. *Effects of IUGR on male offspring*

Intrauterine growth restriction (IUGR) is a typical challenge in pork industry and adverse effects of IUGR can be carried for up to three generations. So, IUGR and its effect on reproductive performance of offspring is an exciting area for research and industry (Ji et al., 2017). In domestic species such as swine, the number of offspring born is an important economic trait, and the components of litter size (ovulation rate, embryonic survival, and uterine capacity) can be influenced by genetic selection (Foxcroft et al., 2006). Nevertheless, pigs exhibit the highest rates of embryonic mortality, IUGR, and neonatal mortality among livestock mammals. These problems are exacerbated by a variety of factors encountered at different levels of swine production, including extreme ranges of environmental temperatures, feed hygiene and safety, suboptimal nutrition, and disease, which implicate the importance of maternal nutrition with regard to future performance of male piglets (Ji et al., 2017).

Low birth weight has been suggested as a consequence of IUGR and low birth weight was associated with unfavorable sperm parameters (Table 1). Previously, it was reported that boars raised in litters of six or less piglets ($\leq$6 piglets/litter) reached puberty sooner and produced more sperm per ejaculate compared with boars raised in litters of nine or more piglets ($\geq$9 piglets/litter) (Flowers). Furthermore, Estienne and Harper reported that adult boars with a birth weight of $<$ 1.3 kg had lower sperm concentrations and less total sperm per ejaculate than adult boars with a birth weight of $>$ 1.8 kg. In addition, both testicular development and adult reproductive performance are compromised in boars with low birthweights (Estienne and Harper, 2010). Therefore, identification of mechanisms regulating fetal testes development and prenatal factors influencing postnatal boar fertility is critical to help improve pork production and swine industry (Stenhouse et al., 2022). In particular, the maternal uterine status during gestation is a key factor for optimal materno-fetal communication, and thus, for variables such as litter size, number of piglets born alive, birth weight of piglets and neonatal growth of piglets (Wang et al., 2022).

4.3. *Effects of maternal nutrition on testicular development and sperm production*

Recently, in a comprehensive review, it was pointed out that appropriate feeding strategies during early life could increase piglet performance and welfare around weaning (Blavi et al., 2021), which may affect the future reproductive performance of boars as well. Intriguingly, Flowers (2023) suggested that birthweight and immunocrit levels exhibited positive relationship with total sperm per ejaculate in boar. In this regard, both testicular development and adult reproductive performance are compromised in boars with low birthweights. Previously, a series of studies in swine have also demonstrated that maternal nutrition during gestation had a crucial role in piglet birthweight that low birth weight was primarily associated with a reduced number of secondary muscle fibers (Dwyer et al., 1994, Handel and Stickland, 1987). In pregnant pigs, supplementation with n-3 polyunsaturated fatty acids (PUFA) increased the number of embryos and the total number of piglets born (live and/or stillborn), and led to prolongation of gestation. Yet other studies found no effect of n-3 PUFA on piglet birth weight, although positive effects on piglet vitality and pre- and post-weaning growth have been reported (Tanghe and De Smet, 2013).

Birth weight is a good indicator of the degree of intrauterine growth restriction, and it has a positive correlation with the size of the testicular development and sperm production as well (Flowers, 2015). Alterations in the composition of the diet consumed by pregnant swine have been shown to increase average birth weight and reduce the incidence of runts (Ashworth, 2013). Almeida et al. (2013) focused on birth weight [high (range 2.0–2.2 kg) and low (range 0.8–1.0 kg)] and its impacts on testicular development in boar. For 8-day piglets, testicular weight and volume, gonadossomatic index (GSI), and Sertoli cell number per testis were dramatically lower in low-birthweight piglets. At 8 months of age, testicular weight and volume and spermatid number per testis were lower in low-birthweight piglets. However, in 8-day-old and 8-month-old boars, seminiferous cord (SC) diameter and Sertoli cell number per cross section of SC were similar in high- and low-birthweight piglets (Almeida et al., 2013). Similarly, Auler et al. (2017) reported that testicles of boars weighing 2.0 kg at birth were 16% heavier and contained 53% more spermatids at 8 months of age compared with those weighing 1.0 kg. Also, boars with birthweights of 2.0 kg consistently produced more sperm compared with their littermates that weighed 1.0 kg and this difference increased with age (Flowers, 2023). Pietruszka et al. (2017) showed the male piglets in the group with greater birthweight, when compared with the group with lower birthweight, had heavier bodyweight when they were 21, 28, 63 and 180 days old, larger testes and semen volume, greater sperm concentration and total number of sperm in the semen and a longer ejaculation time. Altogether, previous studies focused on the importance of birth weight (Almeida et al., 2013) and testis size (Sanglard et al., 2019) which confirmed the critical roles of these parameters on the male offspring performance. As a practical guide, a diet containing 14% crude protein (CP) for feeding pregnant swine during the entire period of gestation is currently used in some farms and is also recommended by some extension agents, but such a gestation diet is not optimum for porcine embryonic survival (Ji et al., 2017). Hence, it seems that birthweight can be a proper parameter for estimation of male offspring reproductive capability (Flowers, 2023). However, we need more investigations with additional sperm functional tests to support this hypothesis.

Several studies have reported that the addition of fatty acids (FAs) to the daily feed rations of sows during late pregnancy and/or lactation could reduce body weight loss during lactation, shorten the weaning-to-estrus interval, and increase the fat content of colostrum and milk which may affect the male offspring (Chen et al., 2019). Fatty acids have antibacterial and anti-inflammatory effects, and can enhance immunity and prevent the occurrence of sow reproductive diseases (Chen et al., 2019). During late pregnancy, adequate energy intake as well as the composition of ration seem to be of key importance in supporting the physiology of farrowing and colostrum quality (Peltoniemi et al., 2019). Numerous studies reported that some FAs (conjugated linolenic, n-3 and oleic acids) supplemented in gestating and lactating diets can improve sow colostrum immunoglobulins, piglet performance, average daily gain and weaning weight (Bontempo et al., 2004, Corino et al., 2009, Hasan et al., 2019, Yao et al., 2012). In addition, a low dietary n-6: n-3 ratio improved weaning survival rate, suckling piglets' weight gain, and total n-3 FAs in colostrum and milk (Nguyen et al., 2020).

4.4. *Effects of Colostrum and litter size on male offspring*

Colostrum intake is perhaps the most critical neonatal event for newborn piglets due to its effects on their immediate survival and subsequent development. Hence, the importance of colostrum in programming reproductive development is probably one of the most exciting opportunities for both basic and applied research for improvement of lifetime productivity (Flowers, 2023). In this regard, Bartol et al. (2008) were the first to propose the "Lactocrine hypothesis" which states that non-nutritional compounds in milk play critical roles in the organization and subsequent development of key response elements in reproductive organs. In neonatal boars, colostrum intake stimulated Sertoli cell proliferation and the activity of several genes associated with development of male reproductive tract. More recently, the relationship between immunocrits at 36 h postnatally in neonatal boars and their adult sperm production was reported (Flowers, 2023). At 18 months of age, there was a strong positive correlation ($r = 0.798$; $p \leq 0.001$) between immunocrit and total sperm per ejaculate, and boars with the highest immunocrits produced 20 billion more sperm per ejaculate than those with the lowest immunocrits. Birthweight was used as a covariate in the statistical analyses so these preliminary results reflected the effects of colostrum intake that were corrected for differences in birthweight. Furthermore, preweaning growth depends on lactation strategy and positive relationships between preweaning growth and adult fertility also were observed in boars. For instance, training success (100% vs. 68.8%) and average total sperm per ejaculate (70 vs. 60 billion) were higher in those that nursed in litters of ≤ 7 compared with their counterparts that nursed in litters of ≥ 10. Several Computer-Assisted Semen Analysis (CASA) variables, including percentage of motile sperm and average curvilinear velocity, were consistently elevated in ejaculates from boars weaned from small litters. Thus, it appears that litter-of-origin variables influence the fertilization competence of sperm, albeit in a relative sense (Almeida et al., 2013).

All in all, birthweight, immunocrit, weaning age, and weaning weight had a positive relationship with lifetime productivity, while the number of pigs at birth and during nursing had a negative association with adult reproductive function in boars (Blavi et al., 2021, Flowers, 2023). Therefore, the selection of best parameters/indices for birth weight, immunocrits and preweaning effects on testicular developments are suggested. Nonetheless, the impact of birth weight on male piglet sexual performance, sexual hormones, age at puberty, libido, and semen quality are required to be further investigated.

5. Bovine and ovine maternal nutrition and male offspring

Worldwide, beef cattle and sheep production systems rely largely on forage-based diets as the source for majority of their nutritional requirements. However, seasonal variations in forage quality and quantity frequently affect nutrient utilization and animal performance by inadequate dietary intake, including energy and protein (McCoski et al., 2021), and this phenomenon should be considered in studies on ruminants.

5.1. *Effects of maternal nutrition on offspring endocrine functions*

Scrotal size can change based on nutritional status, breeding season, and age of the animal; thus, it seems logical that maternal nutrition during testes development (beginning on day 41 and 31 post-fertilization in bull and ram embryos, respectively) can also impact testes size and weight (McCoski et al., 2021). Structural effects on gonadal development could be a result of either direct effects of nutrition on the gonads or through altered function of hypothalamic-pituitary axis. The anterior pituitary gland produces hormones that regulate growth (growth hormone: GH), metabolic function (thyroid-stimulating hormone: TSH), stress response (adrenocorticotropic hormone: ACTH) and reproductive function (luteinizing hormone: LH, follicle-stimulating hormone: FSH, prolactin: PRL). It has been recognized that in sheep, the effects of maternal nutrition on reproductive performance could be mediated through changes in hypothalamic activity and secretion of gonadotrophin releasing hormone (GnRH) or in the pituitary response to GnRH, either of which could affect circulating gonadotrophin profiles (Kotsampasi et al., 2009, Chadio and Kotsampasi, 2014). It is surprising to note that 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 LH and FSH response and increased basal FSH levels. In addition, undernutrition 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, which collectively indicated the direct effect of maternal undernutrition on development of gonads (Kotsampasi et al., 2009).

Previously, the cross-talk between function of fetal hypothalamic–pituitary axis and maternal undernutrition in sheep was reported (Rae et al., 2002b). In particular, in male sheep fetus, maternal undernutrition has been shown to influence the pituitary response to GnRH challenge, and altered pituitary sensitivity has also been observed in 55-day-old lambs born to mothers undernourished from 30 days of gestation to term (Deligeorgis et al., 1996).

Under adverse intrauterine conditions, the fetus could permanently modify some endocrine functions to ensure its own survival (Noya et al., 2019). The structure, physiology and metabolism of different organs and systems could be modified, leading to detrimental postnatal metabolic changes (Mossa et al., 2015) and predisposing offspring to cardiovascular, metabolic and endocrine diseases in later life (Ford and Long, 2011). In the first trimester of gestation, cows experience a negative energy balance, which means that the fetus have to adapt its metabolism to a poor uterine environment. In most of the cases, these fetal adaptive mechanisms were irreversible with consequences in postnatal life, highlighting the crucial role of maternal nutrition during the first stages of gestation (Mohrhauser et al., 2015).

Recent studies in cows have shown that maternal nutritional restriction during the first half of gestation altered the proportion of somatotropes within the fetal anterior pituitary and, in post-natal life, enhanced the ACTH/cortisol response during stress as well as decreased plasma concentrations of progesterone in the females (Long et al., 2021). Results of the study by Long et al. (2021) indicated that nutrient restriction during late gestation led to a reduced number of growth hormone-positive cells (somatotropes) in the pituitaries of heifer offspring. Previous studies have identified a decreased proportion of somatotropes in the pituitary of fetal lambs when mothers were suffering from nutritional restriction during mid-gestation (Lutz et al., 2006). In cattle, balanced nutrition during pre-weaning and post-weaning stages of male calves had a significant impact on testicular steroidogenesis and gonadotropins releasing hormone, contributing to regulation of the bull fertility (Singh et al., 2018). Such variation in prenatal nutrition has been shown to affect both testicular development and circulating gonadotrophins in the prepubertal bull (Sullivan et al., 2009). Fetal programming is the concept that expression or function of inherited genes is altered by external stimulus during pre- and perinatal development. Uniquely, this phenomenon has been observed in beef heifers in response to maternal nutrient restriction during pregnancy with effects on fetal growth as well as skeletal muscle and pancreas function (Long et al., 2021). Maternal nutritional restriction during gestation has been shown to decrease postnatal growth rates in sheep (Sartori et al., 2020) and cattle (Funston et al., 2010) progeny.

5.2. *Effects of maternal nutrition on puberty, testicular development and sperm production*

Maternal nutritional restriction decreased birthweight, testes weight and number of Sertoli cells in lambs (Kotsampasi et al., 2009), which was related to altered secretion of hormones and expression of genes in testis (Teixeira et al., 2007). Therefore, it was hypothesized that birthweight could play a key role in programming of the reproductive axis and subsequent reproductive capacity in the offspring. It is becoming more evident that different nutrients (or their lack) can cause epigenetic changes through different mechanisms (Chavatte-Palmer et al., 2018) (Table 1). Intriguingly, vast of the variations in size at birth in ruminants is determined by the intrauterine environment rather than the fetal genome (Wathes, 2022). In male calves, Sertoli cells begin to proliferate between 40 and 50 days post conception and play a crucial role in gonad development during fetal life and in postnatal spermatogenesis (Copping et al., 2018). It was suggested that protein insufficiency may impact testicular development in a cell-specific manner in bull (McCoski et al., 2021). The key findings were that the low protein dietary treatment in nulliparous heifers altered reproductive development of their male progeny in the early post-pubertal period as reflected by differences in reproductive hormones, testicular cytology and sperm production with a subsequent delay in reaching puberty (Copping et al., 2018). Low protein of maternal diet culminated in lower concentration of FSH at 330 and 438 days of age and decreased sperm quality in the male offpring. In this study, an in utero low protein diet increased the age at which bulls reached puberty considering the motility, morphology and concentration of spermatozoa observed in the ejaculate (Copping et al., 2018).

Late-gestation represents an important period in fetal development due to the rapidly increasing nutritional requirements of the fetus. During this period in dairy cattle, circulating nutrients and blood variables can directly alter placental and fetal metabolism; therefore, maintenance of maternal body condition in late-gestation is an important factor for optimal fetal development (Batistel et al., 2017). For instance, nutritional restriction during late-gestation reduced growth of calves (Alharthi et al., 2021) and it was shown by low birth weight in male calves, which further affected concentration of sexual hormones and postnatal growth rates. In addition, maternal undernutrition during pregnancy followed by ad libitum access to nutrients during postnatal life could induce postnatal metabolic disruptions in multiple species (Long et al., 2021).

Using a model of overfed pregnant ewes, lambs with normal and low birth weights were compared (Da Silva et al., 2001), and it was revealed that both testicular volume and testosterone concentrations decreased in low birth weight male lambs between 28 and 35 weeks of age and the seasonal increase in testosterone concentrations occurred later in low birth weight male lambs. Da Silva et al. (2001) pointed out that moderate maternal undernutrition was not detrimental to the onset of puberty in female lambs (determined by monitoring time of the first ovulation), but fetal growth restriction due to placental dysfunction led to delayed onset of puberty in the male offspring (determined by monitoring testosterone concentration and testicular size). Yet studies of Chadio's team involving sheep offspring underfed in utero during two developmental windows, early (days 0–30 of gestation) and mid to late (days 30–100 of gestation), revealed no differences in the timing of endocrine puberty compared with normal fed ones (Kotsampasi et al., 2009).

5.3. *Effects of maternal over-nutrition on male offspring*

Maternal overnutrition is an undertreated issue in ruminants. Bull fetuses exposed to maternal overnutrition experienced a decrease in expression of steroidogenic acute regulatory protein (*StAR*), hydroxysteroid 17-Beta dehydrogenase 3 (*HSD17β3*), insulin-like growth factor 1 (IGF1), IGF2, and IGF1 receptor (IGF1R), genes involved in testes development and steroidogenesis (Weller et al., 2016). In particular, IGF1 is produced by Leydig and Sertoli cells, and IGF1R is found on germ and somatic cells of the testis (McCoski et al., 2021). Also, bull calves exposed to over-supplementation during gestation had a tendency to have a smaller tubular diameter than those exposed to reduced protein levels (Sullivan et al., 2010). These findings compliment a later report of reduced seminiferous tubule length and diameter, and a reduced percentage of testicular tissue made up of seminiferous tubules in calves exposed to overnutrition (Weller et al., 2016).

6. Murine maternal nutrition and male offspring

While studies on farm animals almost focused on maternal undernutrition effects on male offspring, studies on rat and mice investigated other aspects of the effect of maternal nutrition on the offspring, including the effects of nutritional supplements and unfavorable components. Although nutritional requirements as well as genetic potential have been well documented for livestock species, these figures are not comprehensively defined for the laboratory animals. In addition, the initial stages of development of reproductive organs occur before birth in swine, bovine and ovine; however, part of developmental of reproductive organs in rodents occurs during lactation. These differences in biological and developmental process between farm and laboratory animals make extrapolation form one category to the other difficult. Moreover, these differences may lead to observation of discrepancies in findings of studies focusing on farm animals versus studies focusing on laboratory animals. Regardless, studies have shown preconceptional, embryonic, fetal and suckling periods could be the critical biological windows as far as developmental programming of the male offspring is concerned.

6.1. *Undernutrition*

Maternal undernutrition during both gestation and lactation or during lactation only in rats led to a drastic reduction in gonadal weight and structure in the progenies (Chadio and Kotsampasi, 2014). Maternal undernutrition decreases sperm production in the male offspring probably through modulation of IGF1. IGF1 is a paracrine factor produced by a number of tissues, including the testis where it plays a role in proliferation and development of stem cells and germ cells and testicular differentiation (Pedrana et al., 2020). Maternal protein restriction (feeding 10% protein *vs.* feeding 20% protein to control animals) during the lactation period could affect offspring phenotype in several ways. Male offspring from protein-restricted dams had lighter body weight, delayed testicular descent and lower concentrations of LH and testosterone (Zambrano et al., 2006, Rodríguez-González et al., 2020). Muranishi et al. (2022) showed mothers fed with a low-protein diet during gestation and lactation produced male offspring with normal sperm morphology, concentration, and motility but with diminished fertility during adulthood. Particularly, in contrast to control, sperm from these offspring showed a remarkable lower capacity to fertilize oocytes when copulation occurs early in the estrus cycle relative to ovulation, due to an altered sperm capacitation (Muranishi et al., 2022). In the study by Torres et al. (2021), a mild food restriction (15%) during gestation exerted programming effects on the litter, delayed physical and neurobiological development and affected reproductive parameters (i.e., advanced onset of puberty in the female and poorer reproductive physiology in male and female pups during adulthood). During adulthood, these pups showed a significant decrease in sperm quality compared to control pups (Torres et al., 2021).

6.2. *Nutrient Supplementations*

It has been shown that consumption of n-6 FAs has dramatically increased over recent decades. n-6 FA are considered as essential FA and believed to be required for synthesis of a plethora of endogenous components playing pivotal role for normal function of several organs. However, excessive consumption of n-6 FA favors pro-thrombotic and pro-inflammatory mechanisms and could contribute to pathogenesis of various conditions including atherosclerosis, obesity, and diabetes (Blasbalg et al., 2011). These conditions would be aggravated when over-consumption of n-6 FA is accompanied by under-consumption of n-3 FA since n-6:n-3 balance would be of utmost importance for proper regulation of various pathways, systems and organs, especially it has curial roles in maternal nutrition (Ghasemi et al.). Among various categories of cells present in the body, three types of cells, including neurons, retina rod outer segments, and male gamete, have been recognized for possessing plasma membranes enriched in n-3 PUFAs (De Vriese and Christophe, 2003). Uniquely, prior to birth, all of the Docosahexaenoic acid (C22:6 omega 3; DHA) accumulated in the fetal brain must originate from n-3 FA in the maternal diet *via* placental transfer (Innis, 2005). Although numerous studies evaluated FA supplementation in maternal diet and confirmed the effects of various FAs on offspring's brain and vision, little information exists regarding the effects of maternal nutrition on the male offspring reproductive organs. On the other hand, one of the concerns with n-3 PUFAs is the fact that these FAs could easily be oxidated due to the susceptibility of their double bonds in the chain, culminating in rancidification and generation of unfavorable components. As a result, antioxidants, including vitamin E, are used to protect n-3 PUFAs supplements from rancidity so as to maintain their beneficial impacts (Nateghi et al., 2019). However, to our knowledge, the question of whether supplementing maternal diet with PUFA source with and without vitamin E affects male offspring semen quality alongside with brain function has not been addressed (Ghasemi et al.).

For the first time, we investigated offspring's testis and brain response to maternal nutrition in mice. We indicated feeding mice mothers with fish oil (n-3 PUFAs) and vitamin E during pregnancy and lactation could increase sperm motility parameters in the offspring. In vitamin E group, seminiferous tubules diameter, seminiferous epithelium thickness and Leydig cell numbers were positively influenced by maternal diet (Ghasemi et al.). A similar approach was underway to investigate relationships between maternal diet supplementation with PUFA and Vitamin E and their adult sperm production. Testes cells length, width and weight was lower in offspring that their mothers fed fish oil without Vitamin E during prenatal period. Vitamin E consumption during postnatal period improved these parameters. Spermatogonia, spermatocytes, spermatids, Sertoli cells and Leydig cells were increased in groups consumed fish oil with vitamin E as compared to the control group (Zare Ebrahim Abad et al., 2017).

Excessive intake of all essential nutrients is associated with adverse effects, but in the case of n-3 PUFAs, few health risks are ascribed to this condition, albeit long-term consequences remain unclear. Excess in n-3 PUFAs leads to the impairment of several physical developmental parameters in the lactating offspring and delays growth in length over the lactation and post-weaning periods (Bianconi et al., 2018a). Lactation could be considered as a more susceptible period to the harmful effects of an increased maternal consumption of n-3 PUFAs (Church et al., 2008). This phenomenon could be due to the fact that changes induced by diet in the FAs profile of maternal milk are less compensated in the excessive than in the deficient situation, because the fat mobilization from maternal adipose tissue could maintain milk FA composition (Bianconi et al., 2018a). In this context, the importance of antioxidant levels should be considered when we focus on the proper levels of n-3 PUFAs in experiments since physiological response to dietary PUFAs depends on antioxidant content in diet. Perhaps, dietary antioxidant content could alter the optimum levels of n-3 PUFAs which suggested in previous studies (Nateghi et al., 2019). Therefore, more attention should be given to dietary antioxidant levels in interpretation of findings of studies on maternal nutrition, in which the impact of antioxidants was not considered.

6.3. *Overnutrition*

Maternal consumption of diets high in fat and sucrose during pregnancy augmented the risk of infertility in the male offspring (Bianconi et al., 2018b), particularly in the offspring prenatal consumption of these diets continued during postnatal period (Mao et al., 2018). A growing number of animal studies have shown that maternal high-fat diet intake could adversely affect offspring's ovarian physiology by inducing oxidative stress, apoptosis, and changing the expression of some genes. In this regard, the effect of maternal high-fat diet on female offspring depends not only on diet composition, fat content, feeding stage but also on the selected animal species (Wei et al., 2023). Male rats were shown to have reduced fertility due to increased oxidative stress levels exerted by maternal overnutrition and obesity. Sperm are especially susceptible to reactive oxygen species (ROS) because they lack cytoplasmic antioxidant enzymes and have high levels of membrane PUFA. Moreover, oxidative stress in sperm can increase DNA damage and apoptosis and affect sperm quality (Rodríguez-González et al., 2015). It seems that testis is more susceptible to oxidative stress than ovary and the negative effects of high fat diet may be amplified in male offspring. Finally, the source of fat (Saturated or unsaturated fatty acids) in the high-fat diet and the amount of antioxidants in basic diet should be considered and mentioned.

6.4. *Unfavorable components*

The typical Western diet, commonly consumed by pregnant mothers, contains high amounts of the trans FAs (TFA) and advanced glycation end products (AGEs). While the negative effects of maternal TFA on offspring metabolic health was reported and high TFA levels during pregnancy seemed to be associated with lower birth weight in human (Ren et al., 2021), the effects of TFA on male offspring fertility is an undertreated issue. It was hypothesized that TFAs may block the placental transfer of omega-3 (n−3) FAs to the fetus or disrupt their metabolism (Cohen et al., 2011). Recently, the paternal TFA and vitamin E diet effects on rat offspring's semen quality and peroxisome proliferator-activated receptors (PPARs) expression was reported by our team (Khamehiee et al., 2021). It is surprising to note that TFA intake in paternal diet may have negative effects on reproductive system of the offspring while vitamin E may not alter these effects.

AGEs, a heterogenous group of products formed by the reaction between proteins and reducing sugars, can form endogenously due to non-enzymatic reactions or by exogenous sources such as diet. One of the exogenous sources of AGEs are foods experiencing high thermal processing (Mouanness and Merhi, 2022). Maternal exposure to high dietary AGEs during pregnancy could predispose mice offspring to metabolic disturbances later in life; for example, prenatal exposure to high dietary AGEs have been shown to predispose the male offspring to weight gain and to metabolic alterations (Csongová et al., 2018). When Wistar rat mothers were fed diet high in simple sugars and saturated fats, the offspring testicles smaller and testosterone production decreased. Intriguingly, sperm analysis results were not altered. All negative effects on reproductive functions were more apparent in groups fed diet high in simple sugars and saturated fats during the preconceptional period (Kalem et al., 2018). It was proposed that high saturated fats in diet with high simple sugars may increase the probability of production of AGEs (Emami et al., 2023). In addition, there is evidence indicating the importance of AGEs in oxidative stress and inflammation (Darmishonnejad et al., 2024), which accentuates the potential critical roles of AGEs in maternal nutrition and male offspring, and warrants further studies.

7. Broader implications and future research

There is compelling evidence for the effects of developmental processes on health and reproduction of the offspring considering the studies on both farm and laboratory animals. Yet more studies that investigate sex-dependent mechanisms and epigenetic modifications in models of developmental programming are needed in order to examine maternal, paternal and transgenerational contributions. The use of farm animal models to identify mechanisms that cause or contribute to developmental programming (whether negative or positive) can address the questions in both biomedical and agricultural sciences (Hammer et al., 2023). Experiments associated with the effect of maternal nutrition are interdisciplinary research, and undernutrition, overnutrition, nutritional supplementation and conception of unfavorable components are four major approaches in studies pertaining to the effect of maternal nutrition on the male offspring. In this context, further research is required to investigate the effects of fetal imprinting on hormones, testis tissue, semen parameters, and reproductive function of male offspring. It is a putative mechanism in mammalian species that in response to maternal malnutrition, the fetus will alter its metabolism to preferentially store consumed calories as fat for future utilization during periods of hardship (Symonds et al., 2004). Nutrition during early pregnancy could have more subtle effects on organ and tissue development with potential long-term consequences, whereas nutrition during later pregnancy mostly impacts fetal and carcass growth (Noya et al., 2019). Moreover, the mechanisms whereby environmental insults such as malnutrition contribute to incidence of later detrimental outcomes likely involve a complex interaction among maternal environment, placental changes, and epigenetic programming of the offspring. However, the pathways through which the effect of early life events are mediated to the target organs are complex and still poorly understood. They may include structural changes, alterations in cell proliferation/apoptosis, changes in secretion of hormones and regulation of receptors (Chadio and Kotsampasi, 2014).

Furthermore, we need reliable tests and indices when we talk about studies related to developmental programming of the male offspring fertility. For instance, in some maternal nutrition studies, male offspring had normal sperm morphology, concentration, and motility, but diminished fertility. Therefore, more attention should be given to sperm potential for fertility as well as sperm functional tests, which might have not considered in some of previous studies investigating the effects of maternal nutrition on reproduction of the male offspring.

Not only there is a growing body of evidence supporting negative effects of AGEs on human fertility (Zhu et al., 2020) but also, prenatal exposure to a diet elevated in AGEs causes deficits in prenatal growth, pubertal onset, and reproductive organ development in female mice (Merhi et al., 2020). Meanwhile, limited information exists to explain the role of AGEs and AGEs receptors in the relationship between maternal nutrition and male offspring in murine model. Whether these findings can be extrapolated to humans remains to be determined by future studies.

Eventually, it is worth noting that in studies revolving around developmental programming of male reproduction, we should consider the temporal pattern of male reproductive tract development in each individual species. Because all species do not necessarily have the similar temporal development of male reproductive tract and time of exposure is of importance with regard to some stressors. Therefore, findings from one species should be carefully extrapolated to another species.

CRediT authorship contribution statement

Zahrasadat Ghasemi: Writing – original draft, Conceptualization. **AliReza Alizadeh Moghadam Masouleh:** Study design, Supervision, Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Leila Rashki Ghaleno:** Writing – original draft, Project administration, Conceptualization. **Vahid Akbarinejad:** Writing – review & editing, Project administration, Conceptualization. **Mojtaba Rezazadeh Valojerdi:** Study design, Writing – review & editing, Project administration, Methodology, Conceptualization. **Abdolhossein Shahverdi:** Study design, Writing – review & editing, Project administration, Conceptualization.

Declaration of Competing Interest

The authors have no conflict of interest to disclose.

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