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REVIEW

Intra-uterine programming of future fertility

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Abstract

The developmental origins of health and disease (DOHaD) shows that a relationship exists between parental environment at large, foeto-placental development and the risk for the offspring to develop non-transmittable disease(s) in adulthood. This concept has been validated in both humans and livestock. In mammals, after fertilization and time spent free in the maternal reproductive tract, the embryo develops a placenta that, in close relationship with maternal endometrium, is the organ responsible for exchanges between dam and foetus. Any modification of the maternal environment can lead to adaptive mechanisms affecting placental morphology, blood flow, foetal-maternal exchanges (transporters) and/or endocrine function, ultimately modifying placental efficiency. Among deleterious environments, undernutrition, protein restriction, overnutrition, micronutrient deficiencies and food contaminants can be outlined. When placental adaptive capacities become insufficient, foetal growth and organ formation is no longer optimal, including foetal gonadal formation and maturation, which can affect subsequent offspring fertility. Since epigenetic mechanisms have been shown to be key to foetal programming, epigenetic modifications of the gametes may also occur, leading to inter-generational effects. After briefly describing normal gonadal development in domestic species and inter-species differences, this review highlights the current knowledge on intra-uterine programming of offspring fertility with a focus on domestic animals and underlines the importance to assess transgenerational effects on offspring fertility at a time when new breeding systems are developed to face the current climate changes.

KEYWORDS
developmental origins of health and disease, fertility, gametes, gonads, large animals

1 | INTRODUCTION

Epidemiological studies in humans and experimental studies in model and domestic animals (Chavatte-Palmer et al., 2016; Smith et al., 2014; Wei et al., 2023; Zambrano et al., 2021) have shown that maternal malnutrition (reduced or in excess) and/or its metabolic consequences in the mother, during the periconceptional and gestational windows of vulnerability, can alter the health of male or female offspring, including effects on reproductive functions. These metabolic alterations may also be associated with reproductive disorders through changes in energy metabolism and nutrient signalling, noticeably insulin resistance (Bridge-Comer et al., 2019). Insulin, for example, influences many features of ovarian development and function, affecting steroidogenesis,

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regulation of luteinizing hormone (LH) receptors, insulin receptors, ovarian growth and follicle development (Poretsky et al., 1999). Thus, the effects of maternal diet and more broadly of its environment have been observed on the health of the offspring but also on gonadal differentiation and the development of the reproductive system, from the foetal stage (Chavatte-Palmer et al., 2014; Dupont et al., 2011). These effects are observed in both sexes, although sex-related differences in outcome are often observed (Bridge-Comer et al., 2019; Tarrade et al., 2015). Effects on puberty, gamete quality, fertility or hormonal balance of individuals in adulthood have also been demonstrated in humans and animal models (Sánchez-Garrido et al., 2022).

Domestic animals are also affected by these effects. This review summarizes the current knowledge in mammalian livestock and indicates the knowledge-gaps related to the programming of fertility in domestic animals. These are particularly of importance in a global context of climate change, when new farming strategies (new feedstuff, peri-urban farming, etc) are being explored. The molecular mechanisms for transgenerational effects on fertility, known to be epigenetic modifications, are so far little explored in domestic animals and will not be discussed here.

2 | GONADAL DEVELOPMENT IN MAMMALS

In all vertebrates, the testis and the ovary develop from the same embryonic primordium. At different moments of its development, which vary according to the species, this primordium engages in male or female differentiation according to its genetic heritage (determination of the genetic sex). In mammals, the gonads are formed during intrauterine life in the first half of gestation with great variations depending on the species (9.5–10 days post-conception in the mouse; 24 days in the sheep and 30 days in humans). The development of the ovary involves two crucial stages: meiosis of the oocytes and the formation of the follicles (functional unit of the ovary). There is a time lag between male and female differentiation (see (INSERM, 2011; Rosenfield et al., 2008), with ovarian differentiation in all mammals occurring later than testicular differentiation, which should be considered when selecting exposure windows (Figure 1). In males, steroidogenesis begins during foetal life in all species, whereas in females, its initiation varies according to species. Thus, species with active steroidogenesis during foetal life (ruminants, equines, lagomorphs, human species) may be more sensitive to the effects of, for example, endocrine disruptors.

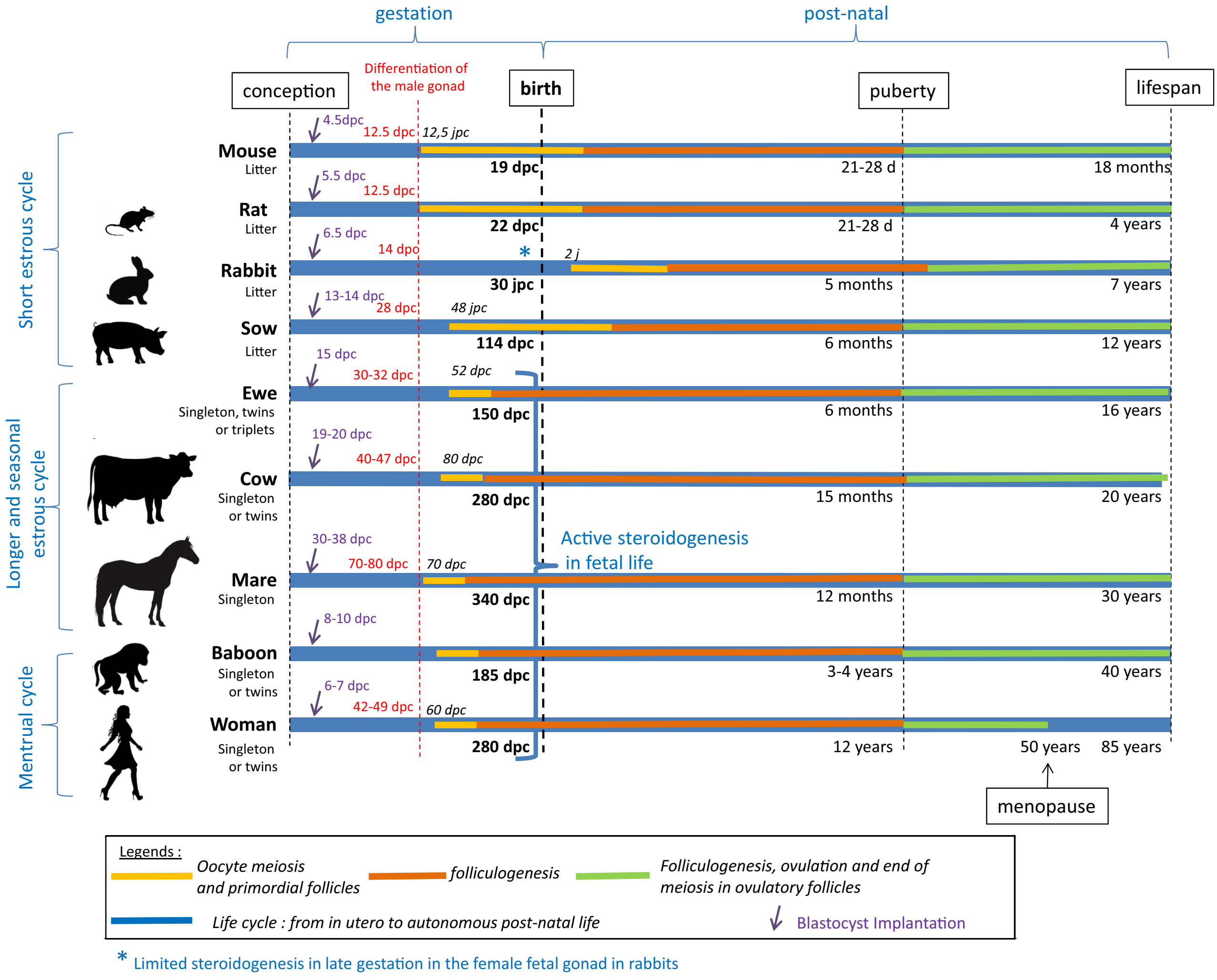

FIGURE 1 Comparison between physiological events during gestation in model and domestic species and humans.

In females of most major mammalian species, the oocyte pool is complete before birth, established during foetal life from the primordial follicle pool. It represents the female's supply of fertilizable oocytes throughout her life (INSERM, 2011). Although oocyte meiosis begins during gestation in rodents and the sow, it continues after birth in these species. Folliculogenesis begins in the ovary during foetal life in the female, sheep, and mare, but only early in postnatal life in rodents and rabbits (Chavatte-Palmer et al., 2014). In addition, oestrogens, that play an important role in controlling ovarian differentiation, are secreted from the ovary during foetal life in non-rodent mammals, whereas there is no ovarian steroidogenesis during foetal life in the mouse. Despite these differences, rodents are often used as models in reproductive toxicology.

In males, the testes are essential endocrine regulators of foetal masculinization and male development and are themselves subject to hormonal regulation during gestation. Data from the literature suggest that in most mammalian species, testicular function goes through a period of independent development before the foetal hypothalamic–pituitary-gonadal axis develops around mid-gestation. This independent pituitary phase coincides with the most critical period of foetal masculinization. Thereafter, the foetal testes appear to become pituitary-dependent as Leydig cell function declines and Sertoli cell numbers increase. The two most common mammalian species used in this type of study (rodents and primates) represent special cases of this general pattern, with parturition occurring at a less mature state in rodents compared to primates (O'Shaughnessy & Fowler, 2011). In rodents, in contrast to primates, Sertoli cells proliferate before and after birth to coordinate testicular development. They stop dividing at puberty, with no possibility of renewal. In addition, in rodents, the hormonal function of the testes starts early, before the pituitary phase, related to foetal development, whereas in primates, the testes will depend on placental gonadotropin released during the pituitary phase.

In mammals, adult Sertoli cell numbers have been shown to be strongly correlated with both adult testicular size and sperm production, and alterations in their development have a direct impact on other testicular cells such as Leydig cells (and foetal germ cells, leading to fertility disorders in adulthood (Shah et al., 2021; Sharpe et al., 2003).

Considering the species differences described previously, the transposition of physiological results from humans or animal models (rodents) to domestic animals is not always straightforward. In any case, the quantity of primordial follicles in the foetal ovary is fixed and defined for the entire reproductive life of the female, whereas in the male, spermatogenesis produces gametes continuously from puberty to senescence. Thus, any quantitative alteration of the germ cells that occurs very early in the female will be irreversible and may have very long-term effects (20–30 years) on fertility whereas in males, long-term effects are more likely to be due to qualitative alterations occurring during in utero testicular development.

3 | FACTORS AFFECTING OFFSPRING FERTILITY

The many factors shown to affect offspring fertility are presented in Figure 2.

4 | MATERNAL UNDERNUTRITION DURING PREGNANCY AND OFFSPRING FERTILITY

Most studies based on epidemiological data in humans and experimental work in rodents, ruminants and pigs indicate small but significant effects of maternal undernutrition on offspring gonadal development, steroidogenesis, age at puberty, plasma concentrations of gonadotropins and inhibin B, folliculogenesis in females and Sertoli cell numbers in males and females (Chadio & Kotsampasi, 2014; Chavatte-Palmer et al., 2014; Dupont et al., 2019; Gonzalez-Bulnes et al., 2013; Pedrana et al., 2020; Teleken et al., 2020).

In high-yielding dairy cattle, where insemination and fertilization are concomitant with the negative energy balance associated with early lactation, epidemiological studies have demonstrated a transgenerational effect of maternal lactation on offspring lactation performance (Gonzalez-Recio et al., 2012) with additional effects on offspring fertility being reported in female offspring from lactating cows (Wathes, 2012).

In males, depending on breed and nutritional conditions, small testicular size and reduced Sertoli cell numbers are usually observed

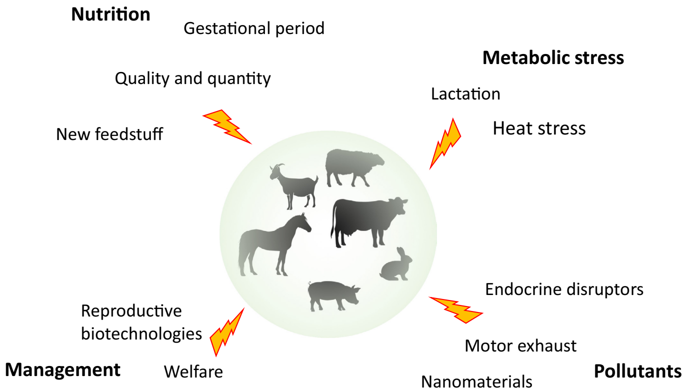

FIGURE 2 Schematic representation of different factors that may affect domestic animals' offspring fertility.

(Bridge-Comer et al., 2019). Puberty is generally delayed both in sheep and cattle (Da Silva et al. 2001, Copping et al., 2018). Additionally, in sheep, altered pituitary responsiveness has been observed after maternal undernutrition in lambs of both sexes (Kotsampasi, Balaskas, et al., 2009; Kotsampasi, Chadio, et al., 2009). In particular, feeding ewes 50% of maintenance requirements from 14 days before until 7 days after conception or conception to 30 days resulted in the birth of lambs that displayed an increased number of oocytes or follicles in their ovaries (Abecia et al., 2014; Chadio & Kotsampasi, 2014).

In conclusion for this part, contrasting effects on gonadal development have been observed in male and female sheep and cattle offspring depending on the timing and duration of the undernutrition period as well as the genetic background of the animals.

Protein restriction during foetal life in rodents has been used to induce premature ageing of reproductive functions, illustrated in rats by impaired oestrous cycles (Guzmán et al., 2006; Zambrano et al., 2014). More recently, in mice, it has been shown that a low-protein maternal diet during gestation programmes a low ovarian reserve in the offspring (Winship et al., 2018).

In beef heifers, protein restriction applied shortly before conception and during the first 110 days of gestation (period of proliferation of the number of oocytes and follicles in the foetal ovary) does not affect birth weight, growth or carbohydrate metabolism of calves; however, ovarian follicular reserve and plasma anti-Müllerian hormone (AMH) concentrations are reduced while plasma FSH are increased in female offspring (Mossa et al., 2013). These elevated plasma FSH concentrations would be explained by a reduced number of antral follicles and thus a reduced feedback of oestradiol to the pituitary gland.

A comparison of maternal protein and energy restriction in beef heifers in the peri- (−60 to 23 days post-conception [dpc]) and post-conceptional (24–98 dpc) periods demonstrated that although offspring birthweight was not affected by any of the treatments, adult bull offspring semen quality (sperm count, motility, morphology) was significantly affected by maternal nutrition, in particular restriction in the periconceptional period, despite no difference in testicular weight (Copping et al., 2018).

While it is known that caloric restriction in cows and sheep will alter ovarian development and the number of follicles in the offspring (Chavatte-Palmer et al., 2014; Mossa et al., 2013), supplementation with metabolizable protein at the end of gestation in cows and sheep will improve the fertility of the offspring and accelerate puberty (Sullivan et al., 2009; Van Emon et al., 2015), which is of economic interest to the industry.

5 | MATERNAL EXCESS NUTRITION DURING PREGNANCY AND OFFSPRING FERTILITY

Given the growing number of overweight and obese people, particularly among women of childbearing age, and the easy access to and often lower price of highly processed foods rich in fats and sugars, the incidence of excessive maternal and postnatal caloric intake is henceforth more common in humans than undernutrition (Bridge-Comer et al., 2019). In humans, excess nutrition in early life has been associated with increased incidence of cardio-metabolic disease in adulthood, increased incidence of obesity and its comorbidities, and is linked to a number of reproductive dysfunctions such as polycystic ovary syndrome (PCOS), anovulation and precocious puberty (Kubo et al., 2016). In animal models, early puberty has been described in the offspring of obese or fat rodents and rabbits, with prolonged or persistent oestros and follicular atresia in females (Aiken et al., 2016; Léveillé et al., 2014) while a decrease in testicular size and testosterone secretion was observed in rabbit male offspring with no effect on sperm concentration, sperm DNA integrity and sperm membrane composition (Dupont et al., 2014). These results may be linked to the reduced birth weight and placental vascularization observed in this model (Tarrade et al., 2013), since intrauterine growth retardation is also described as an exacerbating factor in terms of offspring fertility (Bridge-Comer et al., 2019). Similar results have been reported in rats, where male offspring born to dams fed a cafeteria-type or high-fat diet have reduced plasma testosterone concentrations and epididymal weight, with variable sperm counts (Jacobs et al., 2014; Mao et al., 2018), associated with an increase in oxidative stress in their reproductive system (Rodríguez-González et al., 2015), linked to a decline in antioxidant defence mechanisms (Bautista et al., 2017).

In domestic animals, data are scarce on the effects of maternal excess nutrition but excess nutritional intake could also have a deleterious effect on offspring fertility (Weller et al., 2016). Using the obese adolescent ewe model, the group of J. Wallace showed that maternal excess nutrition during pregnancy was often associated with intra-uterine growth retardation (IUGR), with increased pituitary LHβ expression in the female IUGR foetuses in late gestation (131 days) (Da Silva et al., 2002) but earlier (103 days) (Da Silva et al., 2003). Total ovarian follicular numbers were reduced both in IUGR and normally grown female foetuses in the high maternal nutrition group at both gestational ages, but testicular seminiferous cord development and Sertoli cell numbers were not affected in males (Da Silva et al., 2002, 2003). In horses, low-key inflammation in foals has also been reported in relation to maternal obesity (Robles et al., 2018). Feeding mares with excess concentrated feeds rich in carbohydrates has been associated with earlier testicular maturation in their male offspring, but the effect on onset of puberty was not studied (Robles et al., 2017).

Excess fat deposition in females is associated with increased maternal plasma leptin concentrations and leptin resistance that may affect placental function and subsequent offspring development (Tessier et al., 2013). In particular, maternal obesity impairs the physiological plasma leptin peak in the neonatal offspring, both in rodents and sheep (Bouret, Caron, et al., 2008; Long et al., 2011). The neonatal leptin peak has been shown to promote organ maturation, including the hypothalamus, in rodents and domestic animals (Attig et al., 2011, 2013; Bouret & Simerly, 2006). In rodents, maternal obesity affects offspring hypothalamic neuronal development and induces leptin resistance in the arcuate nucleus of the hypothalamus (Bouret, Gorski, et al., 2008; Vogt et al., 2014). So far, in cattle, recent work failed to demonstrate effects of maternal body condition score on offspring leptin surge. While most research on the role of the early leptin surge has focused on its effect on offspring appetite control (Kirk et al., 2009), the programming of neuronal hypothalamic maturation through endoplasmic reticulum stress may also affect sexual function through effects on GnRH or Kisspeptin neurons (Bouret, Caron, et al., 2008; Guimiot et al., 2012; Lucaccioni et al., 2021), which may contribute to the altered fertility reported in offspring from obese dams. Interestingly, in leptin-resistant Iberian pigs with high plasma leptin concentrations, both maternal undernutrition or excess nutrition during pregnancy were associated with excess fat deposition and earlier puberty in female offspring compared to controls, although only those that were underfed during pregnancy had reduced prolificacy (reduced litter size) in their first gestation (Gonzalez-Bulnes et al., 2013).

6 | MATERNAL EXPOSURE TO ENVIRONMENTAL POLLUTANTS

There is increasing concern in humans about the role of endocrine disruptors and the foetus is particularly sensitive to exposure to chemical substances (Barouki et al., 2012). Indeed, in humans, reduced fertility due to reduced sperm production, reproductive tract obstruction, inflammation and sexual disorders, has been associated in males to prenatal exposure to chemical substances present in our environment during mammalian germ cell development (Berlioux et al., 2022; Maurice et al., 2018; Sharpe, 2010). In females, reproductive development, fertility and the onset of menopause have been shown to be affected by endocrine disruptors (De Souza et al., 2022; Fowler et al., 2012). Both in males and females, endocrine disruptors can also affect mini-puberty in humans (Lucaccioni et al., 2021). In addition, the human population is also exposed to numerous endocrine disruptors as well as other environmental stressors, commonly referred to as the exposome (Haug et al., 2018). For example, associations between prenatal exposure to phthalates and synthetic phenols (PSP, used in a variety of everyday consumer products) and health outcomes have been described, affecting child growth, with inconsistent data concerning body mass index, metabolic and cardiovascular traits and sex-specific responses. Of particular interest for this review, an association has been reported between in utero exposure to phthalates and the period of sexual maturation in both sexes, being dependent on the period of PSP exposure during foetal life for boys (Watkins et al., 2014, 2017).

The extent of domestic animals' exposure to pollutants and endocrine disruptors warrants exploration. Sheep exposure to pasture fertilized using biosolid fertilizers (also referred to as sludge, processed from human sewage) induce sex-specific changes in maternal metabolome (Thangaraj et al., 2023) and affect offspring sexual development. Interestingly, foetal testicular development is more affected by transient exposure of the pregnant dams during pregnancy compared to continuous exposure (Lea et al., 2022). Observed effects included reduced testicular and adrenal mass, together with low birth weight, as well as reduced ano-genital distance and plasma testosterone concentrations in males (Lea et al., 2022). In ewe lambs, masculinizing effects are observed, and the ovarian reserve is reduced with most important effects observed when dams are exposed in mid- and late gestation (Lea et al., 2016).

Exposure to particulate matter and nanomaterials also raise concern in humans (Hougaard et al., 2015). In mice, maternal exposure to diesel exhaust at concentrations close to human exposure was shown to affect male offspring spermatogenesis (Yokota et al., 2021) with intergenerational (F1) and transgenerational (F2) effects on daily sperm production (Kyjovska et al., 2013). In rabbits, although maternal exposure to similar concentrations did not affect testicular nor ovarian development, the offspring sperm DNA fragmentation rate was three-fold higher than in control males (Bourdon et al., 2018). Female fertility per se was not affected, but second generation placental function and lipid metabolism were disturbed (Rousseau-Ralliard et al., 2019; Valentino et al., 2016). Domestic animals may be particularly exposed as nanomaterials are included as feed additives in livestock nutrition (Pandey et al., 2023; Reddy et al., 2020; Szacawa et al., 2021) and as farm vehicles are mostly using diesel fuel. Studies are needed to evaluate the impact of nanomaterials and air pollution in livestock on offspring fertility.

In conclusion, although largely unexplored in farm animals, livestock oral or airborne exposure to environmental pollutants may affect overall fertility, and perhaps also product quality, especially in the case of peri-urban farming.

7 | OTHER ENVIRONMENTAL EFFECTS: A NEED FOR EVALUATION

With the current and upcoming changes in the global climate, pregnant women and children are recognized as very vulnerable (Chalupka et al., 2023). Similar causes and effects may also be observed in domestic animal. Heat stress, for example, becomes a concern worldwide, not only in countries close to the equator. Whereas it is known to affect sperm production and embryo development, concerns are currently raised for its effects on feto-placental development and offspring fertility and production, as demonstrated in dairy cattle (Cattaneo et al., 2022).

In addition, the need for new feedstuff to replace current feeds that are either imported, or no longer available, is increasing. Most new feeds are evaluated for their nutritional contents, safety for the animals they will be given to and the potential effects on production are evaluated. Nevertheless, many nutritional compounds used in animal feedstuff are known to have epigenetic effects (Chavatte-Palmer et al., 2018) and it will be important to monitor offspring fertility when these new compounds are fed to animals used for reproduction. For example, maize silage, forage and rough feed in ruminants are recommended to reduce carbon footprint (Wilkinson & Garnsworthy, 2017). This increase in dietary fibres reduces the proportion of methionine and lysine in the duodenum (Lean et al., 2018). Methionine is a key element of the one-carbon (1C) metabolism that provides methyl groups for de novo synthesis and/or methylation of purines and pyrimidines (DNA methylation) but also biogenic amines, proteins, and phospholipids. Dietary methionine contents during the periconceptional period affects embryo/fetal gene expression and methylation patterns as well as post-natal growth performance although so far, to our knowledge, effects on offspring fertility have not been explored (Acosta et al., 2016; Peñagaricano et al., 2013; Silva et al., 2021; Syring et al., 2023). As another example, micronutriment supplementation is often used in the post-partum period in dairy cattle. Although one study did not evidence effects of supplementation with a commercially available supplement on maternal PBMC (Peripheral Blood Mononuclear Cell) methylation (Gasselin et al., 2020), caution should be applied when herbal supplements with unknown or known epigenetic effects (Bozkurt et al., 2012; Wu et al., 2023) are administered to animals during reproductive cycles (Cui et al., 2022; El-Zaher et al., 2021; Japheth et al., 2021).

Finally, in humans and model animals, mental stress due to early life stress such as parental separation or trauma, as well as chronic stress, are known to affect offspring development and behaviour with a wide variety of symptoms, mostly related to anxiety and behaviour (Jawaid et al., 2021). Although a direct effect on fertility has not been reported, altered behaviour in domestic animals will impair the possibility to use these animals for breeding and thus affect reproduction.

8 | ARTIFICIAL REPRODUCTIVE TECHNOLOGIES

The use of ability of artificial reproductive technologies (ART), in particular embryo technologies, is increasing very rapidly in domestic animals worldwide (Viana, 2022). In livestock systems where the main aim is the propagation of animals with high genetic merit, it is important that offspring fertility is not affected by technology. So far, it has been shown that cattle offspring fertility is not affected by artificial insemination (Marrella et al., 2021) nor by the collection and transfer in recipient dams of in vivo produced embryos (MOET) (Baruselli et al., 2018; Bonilla et al., 2014). Interestingly, a slight improvement in fertility, as measured by number of services per conception, was reported in IVF-derived cattle compared to MOET (Mullaart et al., 2021). In cloned cattle, where an increased age at puberty was reported in cloned heifers, but oestrous cycle length, number of follicular waves and hormonal profiles were not different from AI-conceived controls and their capacity to achieve and maintain pregnancy to term was not affected (Enright et al., 2002; Heyman et al., 2004; Panarace et al., 2007; Wang et al., 2011; Watanabe & Nagai, 2008). Similarly, there was no detrimental effect of cloning on offspring fertility in pigs (Adachi et al., 2014; Kawarasaki et al., 2017; Shi et al., 2020, 2022; Williams et al., 2006).

In conclusion, altogether, the currently available information indicates that livestock offspring born after embryo technologies are fertile (Velazquez et al., 2023), although other phenotypic characters such as growth and/or metabolism may be affected in offspring.

9 | PATERNAL ENVIRONMENT

The programming role of the paternal environment has been revealed in the past decade, with effects of paternal nutrition or exposure to environmental disruptors being reported in their offspring for several generations (Oshio et al., 2020; Soubry, 2018a, 2018b). Briefly, genome-wide erasure and re-apposition of DNA methylation take place during pregnancy in the foetal male primordial germ cells and pro-spermatogonia, with different timing relative to conception in mice and cattle (Kiefer et al., 2021). This is an important window of epigenetic plasticity that can be altered by gestational conditions, with modifications of the sperm methylome that in mice have been shown to affect subsequent offspring fertility (Lambrot et al., 2013) and metabolism (Martinez et al., 2014). In sheep, maternal undernutrition during pregnancy was shown to alter the DNA methylation landscape and the functional parameters of spermatozoa (Toschi et al., 2020). In cattle, the sperm methylome is affected by neonatal nutrition (Perrier et al., 2020) but further studies are needed to evaluate prenatal effects.

10 | CONCLUSION

Altogether, the data presented here demonstrate that many environmental factors may affect offspring fertility in domestic animals. It must be emphasized, however, that many effects may be missed with domestic animals that are not necessarily kept in farms for very long, nor long enough to observe deleterious effects on their health and fertility due to their early environment. Nevertheless, these effects might be present and passed on to subsequent generations. It is thus important to consider that long term, transgenerational effects of new breeding practices aiming at reducing the environmental impact of farming, such as peri-urban farming, using new, more sustainable feedstuff, reducing the use of antibiotics in a One Health perspective and exploring the use of natural products such as herbs or essential oils as alternatives, improving the durability of feedstuff using nanoparticles, etc... should be assessed before they are largely implemented. They should also be studied directly in the species of interest, as gonadal development is very different in terms of timing, but also because placental response to maternal environment varies between domestic species and primates or rodents.

AUTHOR CONTRIBUTIONS

PCP, ACT and DRR have discussed the contents of the paper. PCP has written the first draft of the paper, ACT and DRR have read and corrected the paper. DRR has designed Figure 1. PCP has designed Figure 2.

CONFLICT OF INTEREST STATEMENT

None of the authors have any conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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