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The mammalian preimplantation embryo: its role in the environmental programming of postnatal health and performance

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ABSTRACT

During formation of the preimplantation embryo several cellular and molecular milestones take place, making the few cells forming the early embryo vulnerable to environmental stressors than can impair epigenetic reprogramming and controls of gene expression. Although these molecular alterations can result in embryonic death, a significant developmental plasticity is present in the preimplantation embryo that promotes full-term pregnancy. Prenatal epigenetic modifications are inherited during mitosis and can perpetuate specific phenotypes during early postnatal development and adulthood. As such, the preimplantation phase is a developmental window where developmental programming can take place in response to the embryonic microenvironment present *in vivo* or *in vitro*. In this review, the relevance of the preimplantation embryo as a developmental stage where offspring health and performance can be programmed is discussed, with emphasis on malnutrition and assisted reproductive technologies; two major environmental insults with important implications for livestock production and human reproductive medicine.

Keywords: preimplantation embryo; developmental programming; nutrition; reproductive biotechnologies.

1. Introduction

The mammalian preimplantation embryo represents a critical developmental stage where cellular and molecular milestones not experienced by somatic cells take place. Fertilisation results in the formation of the zygote, a totipotent cell with the capacity to generate all the

cells of the body in a specific temporal and spatial sequence that ultimately leads to development of a fertile adult individual (Condic, 2014). The acquisition of totipotency requires extensive epigenetic remodelling of the parental chromatin in the single cell zygote (Cantone and Fisher, 2013; Clift and Schuh, 2013). In simple terms, epigenetic remodelling involves molecular modifications that do not alter the DNA sequence but influence transcription to regulate gene expression that promotes correct cellular differentiation, dosage compensation, genomic imprinting, genome structure maintenance, and other epigenetically controlled events necessary for normal development (Youngson and Morris, 2013). The epigenetic remodelling during the first divisions of the early embryo is critical for embryonic genome activation (EGA). In general, EGA involves a minor and a major wave of transcription. In humans, major EGA occurs around the 4- and 8-cell stage (Braude et al., 1988; Vassena et al., 2011; Leng et al., 2019) but signs of embryonic transcription have been detected at the 1-cell stage (Asami et al., 2022). In cattle, the major EGA also takes place around the 4- and 8-cell stage (Kues et al., 2008; Jiang et al., 2014), whereas in mice it occurs around the 2-cell stage (Aoki, 2022). Some studies indicated that the major EGA in bovine embryos takes place between the 8- and 16-cell stages (Misirlioglu et al., 2006; Graf et al., 2014), but this seems to be associated with the origin of embryos, as *in vitro*-produced embryos were used in those studies, highlighting the need to use *in vivo*-produced embryos to establish reference embryo developmental parameters (Jiang et al., 2014). A timely occurrence of EGA determines to a great extent the progression to the blastocyst stage, a sphere-like structure with a hollow fluid-filled cavity (i.e., blastocoel) where founder cell lineages are established (Canovas and Ross, 2016; Ross and Sampaio, 2018; Paonessa et al., 2021; Sun et al., 2021). As such, during blastocyst formation, several transcription factors need to be expressed in a species-specific pattern to allow the formation of the inner cell mass (ICM) and the trophectoderm (TE) (Carreiro et al., 2021; Pérez-Gómez et al., 2021; Aguila et

al., 2022). The ICM contains the epiblast and primitive endoderm while the TE is comprised of a single layer of polarised cells surrounding the ICM (Polar TE) and blastocoel (Mural TE). The epiblast gives rise to the foetus, and the trophectoderm and primitive endoderm contribute to the formation of extra-embryonic tissues such as the placenta and yolk sac (Bedzhov et al., 2014; White et al., 2018) (Fig. 1).

Importantly, the few cells (around 50-400 cells by the time the blastocyst stage is reached, depending on the species) involved in this developmental stage are vulnerable to environmental stressors that can affect early embryo development via dysregulation of epigenetic reprogramming and controls of gene expression that can cause embryo demise (i.e., early pregnancy loss) (Paonessa et al., 2021; Zhu et al., 2021). However, the preimplantation embryo possesses a significant developmental plasticity that promotes full-term pregnancy (Velazquez, 2015; Coticchio et al., 2021; Sharpley et al., 2021), and given that prenatal epigenetic modifications are inherited during mitosis and can perpetuate specific phenotypes during early postnatal development and adulthood (Gabory et al., 2011; Fleming et al., 2018; Wang and Ibeagha-Awemu, 2021), the preimplantation period is a developmental window where developmental programming can be exerted. Developmental programming can be defined as the ability of environmental factors during prenatal or early postnatal development to induce permanent physiological, metabolic, and epigenetic alterations that in turn influence health status and increase risk of disease in an individual (Sutton et al., 2016). This notion is the base for the Developmental Origins of Health and Disease (DOHaD) concept (Hoffman et al., 2017; Suzuki, 2018). Indeed, experimental models and epidemiological studies in several species (e.g. humans, rodents, and livestock species) have shown that various environmental challenges including, but not limited to, malnutrition (i.e., over- and undernutrition), assisted reproductive technologies (ART), endocrine-disrupting chemicals, and heat stress have the capacity to influence embryo

development resulting in long-term consequences for postnatal life (Jacobs et al., 2017; Fleming et al., 2018; Velazquez et al., 2019; Fleming et al., 2021; Ghaffari, 2022; Plante et al., 2022; Beilby et al., 2023). Different environmental conditions can alter the nature and severity of programming changes across species with embryo sex being a consistent variable in response (Heras et al., 2016; Hansen et al., 2016; Fleming et al., 2021). In this review, we focus on the relevance of the preimplantation embryo (before hatching from the zona pellucida) as a developmental phase where offspring health and performance can be programmed, with emphasis on two major environmental insults, malnutrition and ART, which have important implications for livestock production and human reproductive medicine.

2. Induction of altered developmental programming by malnutrition in mammalian preimplantation embryos

Once fertilisation takes place in the oviduct, the zygote will go through several cell divisions, entering the uterus at the morula stage (or early blastocyst stage, depending on the species) ultimately developing into the blastocyst stage. The components of the oviductal and uterine fluid directly influence the development of the free-floating preimplantation embryo, which possesses an array of sensors to detect changes in the microenvironment of the reproductive tract. In turn, the preimplantation embryo activates molecular and metabolic adaptations to cope with challenges such as nutrient deficits or excesses (Velazquez, 2015). The long-term effects of undernutrition exposure during the preimplantation period were first demonstrated in rodents, where pregnant female rats were fed with a low protein diet exclusively from embryonic day (E) 0.5 to E4.25 (i.e., from the zygote to the blastocyst stage). This nutritional challenge resulted in offspring with enhanced body weight gain

during the first 5 weeks of postnatal life along with increased blood pressure until 11 weeks postnatally, especially in male offspring (Kwong et al., 2000). This preimplantation model of protein undernutrition was subsequently applied in mice (i.e., protein restriction exclusively from E0.5 to E3.5, from the zygote to the blastocyst stage), where body weight gain and blood pressure were also higher in offspring derived from a low protein *in vivo* microenvironment, but in this case the effect was more noticeable in female offspring as exposed males did not show changes in body weight gain (Watkins et al., 2008). This undernutrition model also showed that a low protein intake during just preimplantation development can induce a decreased formation of neural stem cells during foetal development that in turn can alter behaviour and memory in adult offspring (Gould et al., 2018). In addition, this maternal dietary model also resulted in poor bone mineral density especially in males, indicating dysfunction across multiple body organs (Lanham et al., 2021).

Further research with this mouse model revealed that protein restriction decreased concentrations of insulin in maternal blood and branched-chain amino acids (BCAA) in uterine luminal fluid (ULF) around the time of blastocyst formation (Eckert et al., 2012). Moreover, an embryo transfer study revealed that mouse blastocysts exposed *in vitro* to these same BCAA and insulin deficits from the 2-cell stage and up to the time of blastocyst formation resulted in the birth of offspring with enhanced body weight gain and increased blood pressure during early postnatal development, highlighting the ability of BCAA and insulin deficits during the preimplantation period to induce altered phenotypes during postnatal life (Velazquez et al., 2018).

However, the developmental competence of the preimplantation embryo not only relies on the conditions present in the oviduct and uterus, but also on the microenvironment surrounding oocyte development before fertilisation (Velazquez and Fleming, 2013a). As

such, undernutrition during the so called periconceptional period can induce changes in preimplantation embryos with long-term consequences during postnatal life (Fleming et al., 2018). There are several periconceptional models with different time frames before and after conception, but models covering oocyte maturation, and the preimplantation period (i.e., before hatching from the zona pellucida) allow to delineate the effects imposed in the preimplantation embryo from those exerted post-hatching and post-implantation (Padhee et al., 2015). Accordingly, in an embryo transfer sheep model of periconceptional undernutrition it was found that vitamin B12, folate and methionine restriction from 8 weeks before until 6 days after fertilisation resulted in the production of blastocysts that when transferred into well-fed embryo recipients produced offspring with increased body fatness that displayed insulin resistance and high blood pressure. These effects were sex-specific as they were present mainly in males (Sinclair et al., 2007). In an *in vivo* periconceptional model where sheep were fed with 70% of maintenance requirements from 28 days before to 7 days after mating, an impaired glucose tolerance was observed in resultant male lambs at 10 weeks of age (Smith et al., 2010). Interestingly, feeding ewes 50% of maintenance requirements from 14 days before until 7 days after conception resulted in the birth of lambs that displayed an increased number of oocytes in their ovaries at 1 month of age (Abecia et al., 2014). However, it remains unknown if this nutritional effect will influence reproductive performance after puberty.

Overnutrition can also cause changes in preimplantation embryos with long-term repercussions. For instance, a meta-analysis of over 100 animal studies from five mammalian species (rats, mice, sheep, pigs and non-human primates) indicated that offspring from obese mothers displayed higher body weight, adiposity, and blood pressure along with increased concentrations of triglycerides, cholesterol, glucose, and insulin (Menting et al., 2019). The contribution of the preimplantation embryo in this adverse programming seems to be

significant as embryo transfer studies found that mouse blastocysts derived from obese embryo donors resulted in dysregulation of imprinting, metabolic, and mitochondrial genes in placental tissue (McPherson et al., 2015). Embryo transfer experiments at the zygote stage using a model of rabbit does fed with a high fat-high cholesterol diet showed that pre-conceptional exposure to the diet was sufficient to disturb feto-placental fatty acid homeostasis at term, but with no effect on foetal weight or placental efficiency (Rousseau-Ralliard et al., 2021). In a rabbit model of maternal hyperglycaemia derived from induction of severe type 1 diabetes 7 days prior to conception, day 4 embryos (blastocyst stage) transferred to control dams were growth retarded, hyperglycaemic and dyslipidemic at term compared to controls (Rousseau-Ralliard et al., 2019). Finally, adverse programming in the preimplantation embryo to maternal undernutrition does not depend upon inherent obesity since in its absence, high-fat diet can alter mouse offspring metabolism and neurogenesis (Ojeda et al., 2023).

In ruminant embryo transfer models, it was reported an increased body fat mass (Rattanatray et al., 2010), altered expression of hepatic miRNAs involved in insulin signalling (Nicholas et al., 2013b), and dysregulated abundance of proteins involved in glucose transport and glycogen synthesis in skeletal muscle (Nicholas et al., 2013a) of four months old lambs derived from embryos produced in sheep fed with 170% maintenance energy requirements for four months before to 7 days after conception. Moreover, ewes fed with 150% of their maintenance requirements for 17 days prior and 6 days after insemination gave birth to lambs that had heavier ovaries and neck thymus at five days of age (Kleemann et al., 2015). However, it remains to be determined whether these organ alterations will affect future reproductive performance and immune activity.

But what are the molecular and cellular perturbations induced by malnutrition during preimplantation embryo development? The effects of malnutrition on the quality of

preimplantation embryos is usually analysed by examining the ability of oocytes or early embryos to reach the blastocyst stage during *in vitro* culture or by *in vitro* exposure to metabolites and metabolic hormones at levels that try to resemble in *vivo* conditions of malnutrition during the periconceptional period, especially in cases of overnutrition (e.g. lipotoxic microenvironments) (reviewed in Velazquez, 2015; Broughton and Moley, 2017; Leroy et al., 2023). However, embryos produced in *in vivo* models can provide a more natural profile of the alterations induced by malnutrition. As such, alterations observed in murine blastocysts formed *in vivo* during maternal protein restriction include reduced mTORC1 signalling, altered cell allocation (Eckert et al., 2012), and enhanced endocytosis (Sun et al., 2014). The latter is considered a compensatory mechanism to increase histotrophic nutrition during episodes of protein deprivation and can be induced *in vitro* by deficient BCAA availability, especially isoleucine (Caetano et al., 2021). There is also evidence of deficiencies in MAP kinase signalling associated with increased apoptosis, and in glycolysis affecting energy metabolism in embryonic stem cell lines derived from maternal protein restricted ICMs (Khurana et al., 2023).

On the other hand, murine blastocysts formed *in vivo* during maternal overnutrition displayed increased apoptosis levels (Fabian et al., 2017) and downregulation of genes involved in glucose and lipid uptake, (Bermejo-Alvarez et al., 2012). The latter is believed to be a protective mechanism against excessive nutrient uptake by the preimplantation embryo (Bermejo-Alvarez et al., 2012). In rabbits, a high fat and cholesterol diet induced an overexpression of adipophilin in embryos at the time of EGA (16-20 cell stage) (Picone et al., 2011) but reduced adipophilin expression at the blastocyst stage (Tarrade et al., 2013), demonstrating the rapid and dynamic adaptation of the embryo to maternal environmental conditions, with sex-dependent long-term effects in the feto-placental unit and offspring. Similar to the mouse undernutrition models discussed above, the rabbit model of induced

maternal diabetes also leads to changes in blastocyst mTORC1 signalling at an early stage of developmental programming (Gürke et al., 2016). In cattle, a decreased expression of proteins involved in stress response and growth factor binding was observed in blastocysts from obese cows (Velazquez et al., 2011). In high yielding dairy cows, the negative energy balance induced by early lactation activates the mTOR pathway, tumor protein p53 and autophagy in blastocysts together with methylation changes in genes involved in energy and lipid metabolism (Chaput and Sirard, 2020). However, more mechanistic studies in blastocysts from *in vivo* models of malnutrition are needed, especially at the protein and metabolomic level.

All the above-mentioned alterations in embryos and offspring are derived from maternal exposure, however, some perturbations can be aggravated or induced solely by the paternal lineage. For example, murine embryos produced by obese fathers and non-obese mothers and then transferred into well-fed surrogate mothers resulted in a decreased copy number of mtDNA in foetal liver, a phenotype not observed in offspring from embryos produced in obese mothers mated with non-obese males (McPherson et al., 2015). Moreover, in the same study, the altered placental gene expression observed in foetuses from embryos produced by obese mothers, was further exacerbated when both parents were obese (McPherson et al., 2015). This highlights the known contribution of the paternal side in developmental programming associated with malnutrition and other environmental insults (Reviewed by (Hur et al., 2017; Eberle et al., 2020; Watkins et al., 2020).

In humans, it is difficult to illustrate a direct role of malnutrition around the time of blastocyst formation on postnatal phenotypes as experimental induction of malnutrition cannot be performed for obvious ethical reasons. Nevertheless. epidemiological studies have shown that individuals that are conceived during episodes of undernutrition had a higher risk

of developing cardiovascular and metabolic disease (e.g., hypertension) in adulthood. which has been associated with epigenetic alterations (reviewed by (Fleming et al., 2018).

Overall, there is good evidence in mice and livestock species indicating that malnutrition around the periconceptional period can result in the formation of preimplantation embryos with the potential of producing offspring with altered phenotypes during postnatal life (Fig. 1). However, no clear *in vivo* evidence is available indicating that preimplantation embryos produced under conditions of malnutrition result in the production of animals with impaired reproductive capacity. Notwithstanding, programming of reproductive capacity most probably will be induced by environmental challenges, including malnutrition, during later stages of embryonic development and/or during foetal formation, where developmental milestones such as germ cell generation, oogonia/gonocyte differentiation, and ovaries/testes development takes place (Velazquez and Fleming, 2013b; Chavatte-Palmer et al., 2014; Chadio and Kotsampasi, 2019; Cushman and Perry, 2019). Here, it is relevant to mention that developmental programming studies analysing the effects of maternal malnutrition on reproductive performance do not usually test the capacity of the resultant offspring to actually deliver progeny. This is especially true for farm animal studies where usually only endpoints that indicate reproductive potential are tested (e.g., number of ovarian follicles, testes size, semen quality, concentrations of reproductive hormones, and age at puberty) (Sinclair et al., 2016b).

3. Induction of altered developmental programming by ART in mammalian preimplantation embryos

The aim of ART is the production of healthy offspring using techniques that interfere with the normal biological pathways of reproductive-related events and/or structures related to

folliculogenesis, ovulation, fertilisation, and preimplantation embryo development (Velazquez, 2008). *In vitro* generation of gametes via embryonic stem cells or induced pluripotent stem cells (iPSC) to generate a viable preimplantation embryo is also becoming part of the ART toolbox (Zhang et al., 2020; Gauthier-Fisher et al., 2022). The use of ART for human reproductive medicine has been increasing during the last decades, with over 8 million children born via *in vitro* fertilisation (IVF) (Fauser, 2019). However, this estimate does not include children conceived by other ART such as ovulation induction and intrauterine insemination. In the cattle industry, the production of calves *via* transfer of embryos produced by superovulation and artificial insemination (AI) (i.e., multiple ovulation and embryo transfer [MOET]) is being steadily superseded by the use of *in vitro* embryo production (IVEP) in some countries (Ferré et al., 2020; Viana, 2022). In domestic species, IVEP usually involves *in vitro* maturation (IVM), IVF, and *in vitro* embryo culture (IVEC), whereas in humans IVM is less used, and IVF is generally applied to *in vivo* matured oocytes followed by IVEC. Some ART such as intracytoplasmic sperm injection (ICSI) are increasing in popularity in human reproductive medicine (Glenn et al., 2021) while others have potential applications for livestock production, conservation biology, and biomedicine but are at simulation/experimental level (e.g., iPSC, surrogate sire technology) or their use is banned in some countries (e.g. somatic cell nuclear transfer) (Stanton et al., 2019; Zhang et al., 2020; Galli and Lazzari, 2021; Bolton et al., 2022; Mueller and Van Eenennaam, 2022).

3.1. Impact of ART on birth weight

Since the 1990's research has been carried out in cattle to try to elucidate the consequences of ART, especially in offspring produced via IVEP. A common phenotype found in calves produced via IVF or reproductive cloning is a high birth weight (Table 1), a

feature also reported in pigs (París-Oller et al., 2021), and sheep (Walker et al., 1992; Thompson et al., 1995) offspring produced via IVF. Experiments in cattle found that the increased birth weight associated with IVEP was alleviated by culturing *in vitro*-produced zygotes in the oviduct of sheep (Behboodi et al., 1995; Lazzari et al., 2002), but studies in sheep have shown that this practice is not always effective at normalising birth weight (Holm et al., 1996), indicating that oocyte maturation and fertilisation are sensitive events with the potential to induce long-term phenotypes in offspring. Nevertheless, it seems that provision of an *in vivo* environment during preimplantation embryo development can sometimes ameliorate foetal overgrowth induced by *in vitro* conditions, and this could partially explain why some studies did not find differences in birth weight between calves produced by MOET and AI or natural breeding (King et al., 1985; van Wagtendonk-de Leeuw et al., 2000; Lazzari et al., 2002; Baruselli et al., 2021). However, some studies did not find an increase in birth weight in IVF calves when compared to natural breeding (Givens et al., 2006) or AI controls (Otoi et al., 1996; Agca et al., 1998; Chavatte-Palmer et al., 2002; Jacobsen et al., 2003; Rérat et al., 2005; Rasmussen et al., 2013; Bonilla et al., 2014; Kannampuzha-Francis et al., 2015; Lopes et al., 2020). The contrasting results could be related to statistical limitations such as low sample size, or not controlling for bulls used and important maternal features in embryo recipients affecting birth weight such as, age at first calving, parity, milk production (Wathes, 2022) and progesterone concentrations (Rabaglino et al., 2023). Indeed, contrasting results regarding birth weight associated to IVF have been reported within the same research group (Breukelman et al., 2004; Breukelman et al., 2005). Alternatively, it could be also due to the type of culture medium used in different studies. Accordingly, within IVF-produced calves, differences in birth weight can be induced by the composition of the culture medium during IVEC (Moore et al., 2007; Bonilla et al., 2014; Tríbulo et al., 2017), a scenario also observed in sheep (Thompson et al., 1995; Mara et al., 2015), mice (Fernández-

Gonzalez et al., 2004; Donjacour et al., 2014; Velazquez et al., 2018) and humans (Kleijkers et al., 2016).

However, variations in the composition of culture media do not always affect birth weight in cattle (Thompson et al., 1998; Jacobsen et al., 2002; Gómez et al., 2017; Amaral et al., 2022a) and humans (Zandstra et al., 2015), and some believe that differences in birth weight in humans attributed to different culture media are the result of confounding factors difficult to control in human studies (Rieger, 2017; Sunde et al., 2017; Thompson et al., 2017). Moreover, although recent data showed that IVF-conceived children had a higher risk of presenting macrosomia at birth (Yu et al., 2022), the majority of human studies have found that the effect of *in vitro* microenvironments during preimplantation embryo development seem to be associated with a low birth weight (reviewed by Schroeder et al., 2022), in contrast with the high birth weight usually found in cattle produced by IVF (Beilby et al., 2023). Nevertheless, birth weights below the normal range of AI controls have been reported in IVF (Bonilla et al., 2014) and somatic cell nuclear transfer (SCNT) calves (Meirelles et al., 2010). The effect of ART on birth weight of mice is challenging to analyse due to difficulties in controlling for possible effects of litter size, and as such, differences in birth weight have been reported between mice produced by natural breeding and IVEP, in some (Le et al., 2013; Donjacour et al., 2014; López-Cardona et al., 2015) but not all studies (Watkins et al., 2007).

3.2. Impact of ART on postnatal development

Although an increased body weight gain during postnatal life has been reported in IVEP-derived cattle (Table 1), some studies did not find this feature (Jacobsen et al., 2003; Bonilla et al., 2014). The available evidence also indicates that physiological, haematological, and

biochemical profiles do not seem to be substantially affected during postnatal life in calves produced via IVEP (Jacobsen et al., 2000a; Sangild et al., 2000; Bertolini et al., 2004; Rérat et al., 2005; Givens et al., 2006; Rasmussen et al., 2013; Lopes et al., 2022; Saito et al., 2022). Similarly, calves produced by SCNT seem to have a similar growth trajectory when compared with animals produced by AI or natural breeding (Wells et al., 2004; Tian et al., 2005; Yonai et al., 2005; Watanabe and Nagai, 2008; Konishi et al., 2011; Wang et al., 2011). A comparison of 7–9-year-old sheep produced by SCNT with 6-year-old sheep produced by MOET revealed no differences in glucose metabolism, blood pressure, and signs of degenerative joint disease (Sinclair et al., 2016a). However, in the above-mentioned cattle studies, analyses have been carried out in the first weeks after birth or at the most during the first years of life, as such long-term analyses are difficult to produce in cattle due to long gestation periods, i.e. around 270-290 days (Andersen and Plum, 1965; Vieira-Neto et al., 2017), and postnatal development to adulthood, where cattle usually achieve mature size around 4 years of age (Duplessis et al., 2015). In current dairy systems lifespan of cows from birth to culling is around 4.5-6 years, but natural life expectancy of cattle is around 20 years (De Vries and Marcondes, 2020; Hoffman and Valencak, 2020; Vredenberg et al., 2021), making it challenging to truly evaluate long-term effects of ART or any other environmental challenge during the normal lifespan of cattle in commercial settings. Hence, rodent models can be a practical model to examine development and health from birth to adulthood, and even senescence, due to their short lifespan (Azzu and Valencak, 2017). As such, studies in mice have revealed that preimplantation embryos produced by ART can result in the birth of offspring with growth, cardiovascular, metabolic, and behavioural alterations in adulthood (Table 2). Mouse models have also showed that asynchronous embryo transfer (i.e., transfer of *in vivo*-produced blastocyst to the oviduct) results in the production of mice with high birth weight, decreased body weight gain and blood pressure during postnatal development when

compared to offspring produced by natural breeding (López-Cardona et al., 2015). This highlights the relevance of the microenvironment in the reproductive tract for programming of the preimplantation embryo. Of note, embryo transfer studies in mice have revealed that absence of seminal fluid in the reproductive tract after mating leads to the birth of offspring with increased body weight gain, adiposity, and blood pressure, along with insulin resistance, especially in males (Bromfield et al., 2014). This is associated with the capacity of the seminal fluid to modulate expression of embryotrophic genes in oviduct and uterus in mice and other species, including cattle (Bromfield et al., 2014; Ibrahim et al., 2019; Morgan and Watkins, 2020). In cattle, the use of AI results in very low exposure to seminal fluid due to dilution of ejaculates for commercial purposes. Although it is clear the seminal fluid is not necessary to achieve pregnancy, seminal fluid may influence postnatal phenotypes as suggested by the increased birth weight of calves born from cows treated with an infusion of seminal fluid following AI with sexed semen (Ortiz et al., 2019). The postnatal effects of the use of sexed semen, which is now a common practice in cattle production, so far have been little explored.

In humans, growth and both metabolic and cardiovascular health have been reported to be affected in ART-conceived (i.e., IVF and ICSI) children, but later in life these effects seem to be ameliorated. The available evidence also seems to indicate that cognitive development in children is not affected by the use of ART (reviewed by Velazquez et al., 2019; Hart and Wijs, 2022; Schroeder et al., 2022). It is pertinent to consider that children born via ART usually come from families with high economic income and education (Barbuscia et al., 2019; Goisis et al., 2020), which might help to alleviate the risks derived from ART and might partially explain the contrasting results observed during postnatal development of ART-conceived children. However, given that the oldest ART-conceived humans are still in their 40s, the health monitoring of this population must continue to ensure the application of

ART is compatible with healthy ageing (Velazquez et al., 2019). This long-term monitoring is especially relevant when considering that leucocyte telomere length seems to be shorter in ART-conceived children, particularly when pregnancy is achieved with transfer of blastocysts, suggesting that extended duration of *in vitro* embryo culture can affect telomere elongation during preimplantation development (Wang et al., 2022a). Shortening of telomeres in leucocytes has been associated with development of cardiovascular disease and risk of developing specific types of cancer (Giaccherini et al., 2021; Zheng et al., 2022).

All the aforementioned postnatal effects were found in the F1 generation, and hence a relevant question is whether postnatal phenotypes derived from developmental programming during the preimplantation period induced by ART will also affect the F2 generation. Studies in mice have revealed that hypertensive IVF-derived males (F1) mated with females produced by natural breeding produced F2 male offspring with increased blood pressure, indicating intergenerational transmission of altered vascular function (Rexhaj et al., 2013). Females were not analysed in the latter study. Similarly, male mice with glucose intolerance derived from blastocysts produced under suboptimal *in vitro* culture conditions (by adding foetal calf serum) transmitted this phenotype to two subsequent generations. Interestingly, this transgenerational effect was only observed in males (Calle et al., 2012). Data from rabbits showed that MOET embryos subjected to cryopreservation produced offspring that displayed a low body weight gain up to the third generation when compared to natural breed offspring, indicating a transgenerational effect (Garcia-Dominguez et al., 2020a). However, there is a lack of information on the possible intergenerational and transgenerational effects of ART in mammals (Chavatte-Palmer and De Schauwer, 2023). But overall, there is good evidence that preimplantation embryos produced via ART can result in the birth of offspring with altered phenotypes during postnatal development (Fig. 2).

3.3. Anatomical abnormalities associated with ART

In cattle, pregnancy loss is high after embryo transfer of *in vitro*-produced embryos, especially with cloned embryos (Hill, 2014; Ealy et al., 2019). Furthermore, in some cases, abnormalities during pregnancy can arise when transferring preimplantation embryos produced by IVF or cloning, resulting in the production of offspring with malformations and/or macrosomia that can lead to neonatal mortality. In ruminants, the so-called large offspring syndrome (LOS), is a congenital overgrowth syndrome that has been reported in calves and lambs produce by IVEP or cloning (Young et al., 1998; Hill, 2014). Mortality in this case is associated with enlargement of internal organs (e.g., heart, liver), macroglossia, musculoskeletal abnormalities, pulmonary disease, and other abnormalities that ultimately results in a decreased ability to stand up, feed, and breathe (Meirelles et al., 2010; Smith et al., 2012; Chen et al., 2013; Hill, 2014; Li et al., 2019). In pigs, the incidence of malformations and neonatal death is also high in IVEP-derived offspring when compared to AI controls (Schmidt et al., 2015; Ao et al., 2020; Chen et al., 2022), but offspring data available are mainly from cloned or transgenic pigs. The phenotypic deviations observed in offspring produced via IVF are associated with several placental and foetal abnormalities linked to epigenetic alterations in the preimplantation embryo (reviewed by El Hajj and Haaf, 2013; Urrego et al., 2014; Duranthon and Chavatte-Palmer, 2018; Rivera, 2020; Siqueira et al., 2020; Chen et al., 2022; Schroeder et al., 2022). Similarly, in cloned animals, abnormalities have been associated with aberrant epigenetic reprogramming of the donor nucleus in reconstructed embryos (Wang et al., 2020).

3.4. Culture medium is not the only inductor of altered phenotypes during postnatal life

The phenotypic alterations reported in offspring derived from *in vitro* environments are by far the clearest example of how the preimplantation embryo can determine the expression of phenotypes during postnatal life. Exposure to culture medium is certainly an environmental insult, as current culture media formulations are not able to mimic the *in vivo* physiological profiles (i.e., nutrients, growth factors, metabolic hormones, metabolites, antioxidants, etc.) present in the ovarian follicle and both oviductal and uterine fluid during oocyte maturation and preimplantation embryo development, respectively. Indeed, studies in cattle have shown that *in vitro* embryo production under different media conditions alters embryo gene expression in a sex-dependent manner (Heras et al., 2016). Moreover, the longer the embryo spends in culture medium, the more affected are embryo gene expression, development (Enright et al., 2000; Rizos et al., 2008) and DNA methylation (Salilew-Wondim et al., 2018). Moreover, duration of embryo culture following IVF in mice prior to transfer to recipients results in differing effects on metabolic and cardiovascular health in male offspring (Aljahdali et al., 2020). However, besides culture medium, there are several other environmental challenges that the oocyte, sperm, and the resultant preimplantation embryo are exposed to during *in vitro* procedures with the potential to affect postnatal development (Feuer and Rinaudo, 2012; Urrego et al., 2014; Ramos-Ibeas et al., 2019). Indeed, in rabbits it has been found that embryo cryopreservation *per se* can induce changes in birth weight, body weight gain, and organ weight in the resultant offspring (Garcia-Dominguez et al., 2020b). Similarly, recent retrospective analyses in humans reported that embryo cryopreservation had the largest impact on birth weight and increased the risk of being born large for gestational age (Anav et al., 2019; Pontesilli et al., 2021; Gullo et al., 2022).

Other *in vitro* procedures such as embryo biopsy have also the potential to induce developmental programming during the preimplantation period as shown by the increased body weight gain and impaired memory skills observed in mouse offspring derived from

biopsied embryos in comparison with non-biopsied IVEP control embryos (Yu et al., 2009; Sampino et al., 2014). Similarly, increased body weights were observed from 4 to 10 weeks after birth in mice derived from oocyte spindle transfer technology when compared to IVF controls (Shiina et al., 2019). There is also evidence suggesting that procedures endured by the spermatozoa can exert long-term effects on the offspring. For instance, a retrospective study indicated that *in vitro* preimplantation bovine embryos produced with sexed sperm was associated with decreased milk production in the resultant offspring (Siqueira et al., 2017). Nevertheless, a recent retrospective analysis comparing AI-derived cows produced with either conventional or sexed sperm did not find differences in milk production, and it was suggested that detrimental effects of sexed sperm might be sire-specific and/or exacerbated by the use of other ART such as sperm cryopreservation before the sexing procedure (Maicas et al., 2020).

3.5. Can altered phenotypes induced by ART be ameliorated?

Animal ART models have shown that modification of culture media may be able to alleviate some of the altered phenotypes induced by *in vitro* microenvironments during preimplantation embryo development. For example, the addition of melatonin during IVEC prevented the development of blood pressure (Rexhaj et al., 2015) and glucose intolerance (Jia et al., 2022) observed in mice produced via IVEP. The latter effect was associated with restored hepatic expression of Fbxl7, a gene with important roles in apoptosis, cell proliferation, mitochondrial function, cancer development and protection against glucose-induced cell injury (Ni et al., 2021; Wang et al., 2022b). The use of reproductive (i.e., from the oviduct and uterus) fluids during IVEC seems to be able to promote DNA methylation changes in *in vitro*-derived porcine blastocysts similar to *in vivo* counterparts (Canovas et al.,

2017), leading to the production of pigs with physiological profiles partially resembling those of AI controls during postnatal development (París-Oller et al., 2022). In cattle, the addition of reproductive fluids during IVEC ameliorated alterations in DNA methylation in muscle and blood of IVF-derived calves (Li et al., 2022), but a clear effect on postnatal growth was not observed (Lopes et al., 2022). The use of reproductive fluids during IVEC has also been tested in humans, but enough data to confirm any beneficial effects in the resultant offspring are not available yet (Canha-Gouveia et al., 2021).

3.6. Is reproductive capacity affected in ART-derived offspring?

The ability of ART-derived offspring to reproduce successfully is a requisite for successful application of ART, especially in livestock systems where the main aim is the propagation of animals with high genetic merit for production of animal products for human consumption. Although cattle sired by AI are usually used as control group, strictly speaking AI is part of the ART toolbox. A study comparing cattle sired by AI or natural breeding did not find differences in reproductive performance (Marrella et al., 2021). Some evidence suggests that the reproductive performance of cattle derived from preimplantation embryos produce by IVEP does not seem to be impaired. For instance, age at first service and calving have been found to be similar between IVF and AI offspring (Bonilla et al., 2014; Baruselli et al., 2021). Another study used cattle produced by MOET as control counterparts and reported no difference in the interval from calving to first insemination in IVF-derived cattle. Interestingly, this study observed a slight improvement in services per conception in IVF-derived cattle (Mullaart et al., 2021). In contrast, recent studies found that the interval from first service to conception (Lafontaine et al., 2023b) and the incidence of cystic ovarian follicles (Lafontaine et al., 2023a) was higher in IVF-derived cows compared to cattle

produced by MOET and AI. However, it is not clear if the altered ovarian phenotype is a direct result of IVEP or the consequence of the high milk production expected in elite cows produced via IVF (Lafontaine et al., 2023a). It is also relevant to consider that these retrospective studies rely on the analysis of reproductive variables that can be affected by farm management practices and technical issues (e.g., oestrous detection method, semen straws handling, etc.), and as such they reflect more the reproductive efficiency needed to maximise farm profits rather than ability to reproduce *per se*.

A similar scenario has been reported in cloned cattle, where an increased age at puberty was reported in SCNT 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; Wang et al., 2011; Watanabe, 2013). Nevertheless, from a livestock product point of view this finding is relevant as late onset of puberty is not compatible with a low age at first calving needed to achieve a good lifetime productivity in dairy cattle systems (Wathes et al., 2014). Cloned heifers and cows also seem to have a similar ability to produce preimplantation embryos either by MOET or IVEP when compared to AI-conceived controls (Polejaeva et al., 2014). Regarding bull performance, cloned bulls seem to produce semen of acceptable quality in AI centres (Panarace et al., 2007). Similarly, no detrimental effects on reproductive performance have been associated with cloning in pigs (Williams et al., 2006; Adachi et al., 2014; Kawarasaki et al., 2017; Shi et al., 2020; Shi et al., 2022).

As previously mentioned, embryo biopsy was sufficient to alter body weight and memory in mice, however, reproductive capacity was not affected (Yu et al., 2009). In contrast, male mice derived from zygotes produced by superovulation that were cultured *in vitro* up to the blastocyst stage before embryo transfer displayed a lower spermatozoa motility and decreased capacity to achieve pregnancy compared to males produced by natural mating

(Calle et al., 2012). Similarly, compared to controls produced by natural breeding, male mice produced by ICSI showed a decreased number of spermatozoa, and a lower pregnancy rate following natural mating (Ramos-Ibeas et al., 2014). Currently, the use of ICSI to alleviate infertility in domestic species is limited compared to other species (e.g., humans), and in livestock species is usually applied for production of transgenic animals (Salamone et al., 2017), but future applications in some domestic animals (e.g., horses) may increase if efficacy improves (Benammar et al., 2021; Briski and Salamone, 2022). The efficacy of ICSI in cattle is low (Unnikrishnan et al., 2021; Briski and Salamone, 2022) and hence, to the best of the authors' knowledge, ICSI-derived offspring data are not available in the specialised literature examining the long-terms effects of ICSI in this species.

Interestingly, in humans it was reported that young male adults conceived via ICSI displayed a low sperm concentration and motility compared to controls born after natural conception (Belva et al., 2016). In a more recent study, a higher risk of puberty disorders was present in boys and girls conceived by IVF and ICSI compared to spontaneously conceived children. Furthermore, risk of puberty disorders was higher for ICSI-conceived children (Klemetti et al., 2022). However, it remains to be determined if ART-conceived individuals with these reproductive impairments are unable to reproduce. Indeed, given that the main use of ART in humans is to alleviate infertility (Serour and Serour, 2021), a relevant concern is the possibility that ART such as IVF can facilitate the propagation of infertility to the resultant offspring (Hanevik et al., 2016). In cattle, the application of ART usually relies on the use of oocyte and embryo donors that are reproductively competent, but given that the use of IVEP has been suggested as a strategy to produce offspring from infertile cattle (Gamarra et al., 2022), this possibility should be explored (Velazquez, 2008).

Overall, the existing evidence suggests that preimplantation embryos from livestock species derived from IVF or reproductive cloning produce offspring that is capable to

reproduce, but some evidence indicates that from a productivity point of view, certain reproductive variables might be affected. On the other hand, experimental data indicates that ART-derived murine embryos can produce male offspring with impaired capacity to reproduce. In humans, no clear evidence is available to suggest that ART-conceived individuals possess a decreased capacity to reproduce.

3.7. How quickly are preimplantation embryos programmed during in vitro development?

In *in vivo* models it is difficult to determine the precise time during the preimplantation period where programming of the early embryo can take place. However, *in vitro* models are suitable to test different exposure times to identify susceptible developmental stages. For example, *in vitro*-produced mouse blastocysts exposed to palmitic acid (i.e., as a model of lipotoxicity) for 30 hours before embryo transfer resulted in the birth of pups that were smaller at postnatal day 18, but by day 50 they were heavier than control counterparts (Jungheim et al., 2011). Manipulation of the redox state of mice zygotes with pyruvate or lactate for 10-15 h and transfer at the 2-cell stage was sufficient to produce offspring with decreased postnatal growth rate, with a more marked effect in offspring derived from embryos treated with pyruvate (Banrezes et al. 2011). Exposure for 4 h to medium capable to alter calcium oscillations during fertilization in ICSI-derived zygotes or 2 -cell embryos resulted in the birth of female mice with increased body weight gain, and in both sexes a smaller brain weight was observed (Ozil et al., 2017). The sex-specific differences can be attributed to the sexual dimorphism already demonstrated at the blastocyst stage (Gutiérrez-Adán et al., 2006; Bermejo-Alvarez et al., 2008), including the response to IVEC conditions (Tan et al., 2016; Taqi et al., 2019).

In dairy cattle, embryos treated with colony-stimulating factor 2 (CSF2) for two days, starting around the time of compaction (five days after IVF), produced offspring with increased body weight gain during the first 13 month of age compared to IVEP calves derived from non-treated embryos (Kannampuzha-Francis et al., 2015). However, this enhanced body growth associated with CSF2 supplementation during IVEC was not replicated in *Bos indicus* cattle and it was suggested that breed susceptibility to CSF2 and/or differences on husbandry practices between studies might have contribute to these contrasting results (Estrada-Cortés et al., 2021a). Bovine zygotes exposed *in vitro* to choline for 7 days resulted in the production of calves with increased birth weight that were heavier at 205 days of age (Estrada-Cortés et al., 2021b). Tríbulo et al. (2017) reported that supplementation of culture medium from day 5 to 7 after IVF (i.e., during the morula to the blastocyst stage transition) with CSF2 and Dickkopf WNT Signaling Pathway Inhibitor 1 (DKK1) alone or in combination generated blastocysts that produced calves with decreased birth weight. The low birth weight was observed regardless of the inclusion of CSF2 during IVEC (Tríbulo et al., 2017). Interestingly, an increased birth weight was observed in calves derived from embryos treated with (DKK1) from day 5 to 7.5 after IVF (Amaral et al., 2022b). Amaral et al. (2022b) suggested that these contrasting results were due to the inclusion of serum during IVEC in the study by Tríbulo et al. (2017). However, another study by the same group testing long-term effects of DKK1 in conjunction with serum supplementation did not find any effect on birth weight (Amaral et al 2022a). Hence the role of DKK1 as a modulator of birth weight in cattle remains unclear.

In mice it has been found that embryo transfer *per se* (i.e., immediate transfer of embryos into surrogate mothers following collection from the reproductive tract) was enough to increase birth weight and decreased blood pressure during postnatal life along with presentation of anxiety-like behaviour (López-Cardona et al., 2015). Interestingly, immediate

embryo transfer of *in vivo*-derived blastocysts produced by superovulation resulted in the birth of murine offspring with increased body weight gain postnatally (Watkins et al., 2007), a feature that was not observed when blastocysts for immediate embryo transfer were produced by natural breeding (López-Cardona et al., 2015). This highlights the effects that superovulatory treatments can exert during the preimplantation period, including epigenetic alterations in embryos and changes in the reproductive tract that ultimately can disrupt normal preimplantation embryo development (reviewed by Marshall and Rivera, 2018).

4. Conclusions

There is no clear indication in livestock species and humans that offspring reproductive capacity is affected by challenges associated with malnutrition and ART around the time of blastocyst formation, but evidence indicates that developmental milestones can be affected (e.g., birth weight and body weight gain). However, experimental evidence in mice has shown that ART-derived offspring can display impaired capacity to reproduce. Although the postnatal phenotypes are not always replicated among species, there is substantial evidence indicating that developmental alterations during postnatal life can be primed during the preimplantation period. From a practical point of view the preimplantation embryo cannot be seen in isolation, but as a critical prenatal developmental window that can contribute substantially to the programming of postnatal health and performance.

Establishment of healthy pregnancies is still a concern that needs to be addressed in livestock produced via IVEP, especially when using SCNT as this represents not only a problem of economic relevance but also an important animal welfare issue that needs to be resolved if we want to increase public acceptance of ART.

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Figure legends

Figure 1. During preimplantation embryo development (before hatching from the zona pellucida) several cellular and molecular milestones can be affected by environmental factors, including malnutrition. The cellular and molecular landscape of the blastocyst will be affected by the nutritional microenvironment present in the ovary and reproductive tract (i.e., maternal malnutrition) and by the spermatozoa quality and epigenetic status derived from the nutritional milieu present in testicles and accessory sex glands. Although malnutrition can lead to embryo demise, the preimplantation embryo possesses a great capacity for plasticity to deal with environmental challenges to promote pregnancy to term. However, this developmental trade-off can lead to expression of altered phenotypes during postnatal life (see text for details). *The developmental stage of embryonic genome activation is species-dependant.

Figure 2. Assisted reproductive techniques (ART) can affect the *in vivo* milieu in which preimplantation embryos develop (e.g., superovulatory treatments and lack of uterine priming with seminal fluid). *In vitro* microenvironments and procedures in gametes and embryos will also affect the cellular and molecular landscape of the resultant preimplantation embryo, which can result in the birth of offspring with altered phenotypes during postnatal development (see text for details). Dotted lines just intend to clarify the pathway. *In vitro* maturation (IVM), *in vitro* fertilisation (IVF), *in vitro* embryo culture (IVEC), somatic cell nuclear transfer (SCNT), intracytoplasmic sperm injection (ICSI), embryo transfer (ET), artificial insemination (AI). Model based on ruminant and rodent models.

Table 1. Phenotypic changes and risk of mortality during postnatal life in cattle offspring derived from embryo production technologies.

Type of ART	Control	Type of ET	Main outcome (sex affected)	Reference
IVM, IVF, IVEC (*n*=8)	AI (*n*=74)	Fresh	↑ Birth weight (♂)[A] ↑ Neonatal mortality	(Behboodi et al., 1995)
IVM, IVF, IVEC (*n*=39)	AI (*n*=28)	Fresh	↑ Birth weight (♂♀)[B] ↑ Body weight gain (♂♀)	(Sinclair et al., 1995)
ECNT, OVS (*n*=418) MOET (*n*=4687)	AI/NB (*n*=8,925)	Fresh, F-T	↑ Birth weight (♂♀) ↑ Body weight gain (♂♀)[C]	(Wilson et al., 1995)
IVM, IVF, IVEC (*n*=559) ECNT, OVS (*n*=126) MOET (*n*=45)	AI (*n*=496,160)	Fresh, F-T	↑ Birth weight (♂♀) ↑ Neonatal mortality[D]	(Kruip and den Daas, 1997)
IVM, IVF, IVEC (*n*=12)	MOET (*n*=6)	Fresh, F-T	↑ Birth weight (♂)[E] ↑ Heart size	(McEvoy et al., 1998)

IVM, IVF, IVEC (*n*=550)	AI (*n*=2,502)	Fresh, F-T	↑ Birth weight (♂♀) ↑ Neonatal mortality	(van Wagtendonk-de Leeuw et al., 1998)
IVM, IVF, IVEC (*n*=17)	AI (*n*=85)	Fresh, F-T	↑ Birth weight (♂♀)[F]	(Jacobsen et al., 2000b)
IVM, IVF, IVEC (*n*=376)	MOET (*n*=998)	F-T	↑ Birth weight (♂♀) ↑ Neonatal mortality	(Numabe et al., 2000)
IVM, IVF, IVEC (*n*=147)	MOET (*n*=121)	Fresh, F-T	↑ Birth weight (♂♀) ↑ Neonatal mortality[G]	(Numabe et al., 2001)
IVM, IVF, IVEC (*n*=1,219) MOET (1,058)	AI (*n*=6,482)	Fresh, F-T	↑ Birth weight (♂♀)	(van Wagtendonk-de Leeuw et al., 2000)
IVM, IVF, IVEC (*n*=25) MOET (*n*=27)	AI (*n*=169)	Fresh, F-T	↑ Birth weight (♂♀)	(Yang et al., 2001)
IVM, IVF, IVEC (*n*=9)	MOET (*n*=6)	Fresh	↑ Birth weight (♂♀)[B]	(Bertolini et al., 2002)
SCNT, IVEC (*n*=16) IVM, IVF, IVEC (*n*=20)	AI (*n*=176)	Fresh	↑ Birth weight (♂♀)[H]	(Chavatte-Palmer et al., 2002)
IVM, IVF, IVEC (*n*=33) IVM, IVF, OVS (*n*=34)	AI (*n*=24) MOET (*n*=63)	F-T	↑ Birth weight (♂♀)[I]	(Lazzari et al., 2002)
IVM, IVF, IVEC (*n*=54)	MOET (*n*=26)	Fresh, F-T	↑ Birth weight (♂♀)	(Martínez et al., 2002)
IVM, IVF, IVEC (*n*=4)	AI(*n*=20)	Fresh	↑ Birth weight (♂♀)	(Sakaguchi et al., 2002)
IVM, IVF, IVEC (*n*=59)	MOET (*n*=53)	Fresh, F-T	↑ Birth weight (♂♀)	(Breukelman et al., 2005)
IVM, IVF, IVEC (*n*=18)	MOET (*n*=9)	Fresh	↑ Birth weight (♂♀)[J]	(Park et al., 2005)
IVM, IVF, IVEC (*n*=11)	AI (*n*=8)	F-T	↑ Body weight gain (♂♀)	(Rérat et al., 2005)

IVM, IVF, IVEC (*n*=23)	AI/NB (*n*=55)	Fresh	↑ Birth weight (♂)	(Camargo et al., 2010)
IVM, IVF, IVEC (*n*=80)	AI (*n*=20)	Fresh	↑ Birth weight (♂♀)	(Pimenta-Oliveira et al., 2011)
IVM, IVF, IVEC (*n*=73)	AI (*n*=22)	Fresh, F-T	↑ Risk of mortality(♀)[K]	(Bonilla et al., 2014)
IVM, IVF, IVEC (*n*=1651) MOET (*n*=432)	AI (*n*=3,465)	Fresh, F-T	↑ Birth weight (♀)[L] ↑ Body weight gain (♀)[M] ↑ Risk of mortality(♀)[M] ↓ Milk production(♀)[M]	(Siqueira et al., 2017)
IVM, IVF, IVEC (*n*=17)	AI (*n*=8)	F-T	↑ Neonatal mortality	(Lopes et al., 2020)
MOET (*n*=609)	NB (*n*=510)	Fresh, F-T	↑ Birth weight (♂♀) ↑ Body weight gain (♂♀)	(Martínez et al., 2021)
IVM, IVF, IVEC (*n*=460) MOET (*n*=740)	AI (*n*=3,489)	Fresh, F-T	↑ Birth weight (♀)[N]	(Baruselli et al., 2021)
IVM, IVF, IVEC (*n*=213)	AI (*n*=60)	Fresh, F-T	↑ Birth weight (♂♀)	(Crowe et al., 2023)

IVM=*in vitro* maturation, IVF= *in vitro* fertilisation, IVEC= *in vitro* embryo culture, MOET= multiple ovulation plus AI and embryo transfer (ET), ECNT=embryonic cell nuclear transfer, OVS=*in vivo* culture in sheep oviduct, SCNT=somatic cell nuclear transfer, AI=artificial insemination, NB=natural breeding, *n*=number of calves, Frozen-thawed= F-T.

[A]No female calves were produced.

[B]Difference was observed only in single ET calves, not in twin ET calves.

[C]ECNT, OVS vs MOET and AI/NM.

[D]Only in IVM, IVF, IVEC and ECNT, OVS calves.

[E]Only males were analysed.

[F]Differences were found only when serum was used in culture medium, and when embryos were cryopreserved before ET.

[G]Only when embryos were exposed to cumulus cells during IVEC.

[H]Only in SCNT calves

[I]Only in IVM, IVF, IVEC calves

[J]In the *in vitro* group 18 and 24h IVM were used, differences were found only in the 24 h IVM group.

[K]only female calves were analysed.

[L]in the *in vitro* group conventional and sexed semen was used, and only female calves were analysed. No difference in birth weight between MOET and AI calves.

[M]Differences were found only in animals produced with sexed semen.

[N]only female calves were analysed, and no difference in birth weight were found between MOET and AI calves.

Table 2. Phenotypic changes during postnatal life in mouse offspring derived from embryo production technologies.

Mouse Strain	Type of ART	Control	Type of ET	Main phenotypic outcome (sex affected)	Reference
B6C3F1	MO, SCNT, IVEC (*n*=5)	NB (*n*=15)	Fresh	↑ Body weight gain (♀)[A]	(Tamashiro et al., 2000)
B6D2F1	MO, SCNT, IVEC (*n*=12)	NB (*n*=7)	Fresh	↓ Life span (♂)[B]	(Ogonuki et al., 2002)
B6C3F1	MO, SCNT, IVEC (*n*=9) IVEC (*n*=7)	NB (*n*=7)	Fresh	↑ Birth weight (♀)[A] ↑ Body weight gain (♀)[A] ↑ Body fat deposition (♀)[A] ↑ Increased insulin and leptin levels (♀)[A]	(Tamashiro et al., 2002)
129Sv x B6*	NB, IVEC (*n*=99)	NB-ET (*n*=36)	Fresh	Impaired spatial memory (♂♀)	(Ecker et al., 2004)

(CBA x B6) x MF1	MO-NB, IVEC (*n*=52) MOET (*n*=48)	NB (*n*=154)	Fresh	↑ Body weight gain (♂♀)[C]	(Watkins et al., 2007)
CD1 and B6D2F1	MO, ICSI, IVEC (*n*=103)	NB (*n*=47)	Fresh	↑ Body weight gain (♀) ↑ incidence of pneumonia (♀) Presence of anxiety-like behaviour (♀) Impaired memory (♀)	(Fernández-Gonzalez et al., 2008)
B6C3F1	MO, IVF, IVEC (*n*=22) MO, ICSI, IVEC (*n*=24) MO, SCNT, IVEC (*n*=9)	NB (*n*=18)	Fresh	↑ Birth weight (♂♀) ↑ Body weight gain (♀)[D] ↑ leptin levels (♀)[D] Glucose intolerance (♀)[E]	(Scott et al., 2010)
B6 x CBA	MO-NB, IVEC (*n*=45)	NB (*n*=15)	Fresh	Glucose intolerance (♂)	(Calle et al., 2012)
B6	MO, IVF, IVEC (*n*=51)	NB, IVEC-ET (*n*=51)	Fresh	↑ Birth weight (♂♀)	(Le et al., 2013)
FVB	MO, IVF, IVEC (*n*=10-74)	NB (*n*=10-73)	Fresh	↑ Blood pressure (♂)[B] ↓ Life span(♂)[B,F]	(Rexhaj et al., 2013)
B6	MOET-2 cells (*n*=10) MO, IVF, IVEC (*n*=10) MO, ICSI, IVEC (*n*=10)	NB(*n*=10)	Fresh	Altered fatty acid composition in liver and adipose tissue (♂)[B]	(Wang et al., 2013)
B6	MO, IVF, IVEC (*n*=6-28) MOET (*n*=6-23)	NB-ET (*n*=6-28)	Fresh	↓ Birth weight (♀) Glucose intolerance (♀)[F]	(Chen et al., 2014a)
B6	MO, IVF, IVEC (*n*=6-26) MOET (*n*=6-28)	NB-ET(*n*=6-21)	Fresh	↓ Birth weight (♂)[B] Glucose intolerance (♂)[E,B]	(Chen et al., 2014b)
CF1 x B6D2F1/J	MO, IVF, IVEC (*n*=54)	MOET (*n*=36)	Fresh	↑ Body weight gain (♂)[G] Glucose intolerance (♂)[G]	(Donjacour et al., 2014)

B6	MO, IVF, IVEC (*n*=58)	MOET (*n*=32)	Fresh	↓ Body weight gain (♂♀)[G] ↓ Birth weight (♀)[H] ↑ Body weight gain (♀)[H] ↑ Body fat deposition (♀)[H]	(Feuer et al., 2014)
CD1	NB-ET (*n*=175)	NB (*n*=23)	Fresh	↑ Birth weight (♂♀)[I]	(López-Cardona et al., 2015)
B6	MO, IVF, IVEC (*n*=50)	NB (*n*=57)	Fresh	↑ Birth weight (♂♀)	(Strata et al., 2015)
ICR	MO, IVF, IVEC (*n*=67)	MOET (*n*=72)	Fresh	↑ Body weight gain (♂)	(Tan et al., 2016)
FVB	MO, IVF, IVEC (*n*=47)	NB (*n*=28)	Fresh	↑ Body weight gain (♂)[B]	(Cerny et al., 2017)
B6	MO, ICSI, IVEC (*n*=20) IVM, ICSI, IVEC (*n*=20)	NB (*n*=20)	Fresh	↑ Body weight gain (♂♀)	(Wang et al., 2017)
B6	MO, IVF, IVEC (*n*=12) MO, ICSI, IVEC (*n*=12) IVM, ICSI, IVEC (*n*=10)	NB, IVEC-ET (*n*=16)	Fresh	↑ Heart and kidney size (♂♀)[J] ↑ Cholesterol levels (♂)[J] ↑ Blood pressure (♀)[K]	(Le et al., 2019)
CD1	MO, IVF, IVEC (*n*=10) MO, ICSI, IVEC (*n*=10)	NB (*n*=10)	Fresh	Reduced immune response after vaccination (♂)[B]	(Ahmadi et al., 2020)
B6 x CBA	MOET-2 cells (*n*=45) MOET-BL (*n*=47) MO, IVF, IVEC-2 cell (*n*=61) MO, IVF, IVEC-BL (*n*=42)	NB (*n*=80)	Fresh	↑ Body weight gain (♂♀) ↑ Blood pressure (♂♀) Glucose intolerance (♂♀)[L]	(Aljahdali et al., 2020)
CD1	MOET-2 cells (*n*=27) MOET-BL (*n*=30)	NB (*n*=103)	Fresh	↑ Body fat deposition (♀) Glucose intolerance (♂)[M]	(Anisimova et al., 2020)

	MO-NB, IVEC (*n*=23)				
CD1	MO, ICSI (*n*=36)	NB (*n*=37)	Fresh	↑ Body weight gain (♂♀) Impaired learning (♂♀) and memory (♀)	(Lewon et al., 2020)
B6	MO-NB (*n*=12) MOET-2 cells (*n*=12) MO, IVF, IVEC-2 cell (*n*=12)	NB (*n*=12)	Fresh	↑ susceptibility to cerebral ischemia-reperfusion injury(♂)^{E,B} Impaired locomotor coordination (♂)^{E,B}	(Li et al., 2020)
CF1 x B6SJL	MO, IVF, IVEC (*n*=17-25)	NB (*n*=29-35)	Fresh	↑ Birth weight (♂♀) ↑ Body weight gain (♀) ↑ Cholesterol levels (♀) ↑ Triglycerides and insulin levels (♂) ↑ Body fat deposition (♂)	(Narapareddy et al., 2021)
B6D2F1	MO, IVF, IVEC (*n*=167)	NB (*n*=75-117)	Fresh F-T	↑ Birth weight (♂♀) ↑ Body weight gain (♂)^{F} Glucose intolerance (♂)^{N}	(Qin et al., 2021)
B6 x DBA2	MO, IVF, IVEC (*n*=6-8)	MOET (*n*=6-8)	Fresh	↑ Body weight gain (♂)^{B} Glucose intolerance (♂)^{B}	(Jia et al., 2022)
FVB	MO, IVF, IVEC (*n*=6-10)	NB (*n*=6-10)	Fresh	↑ Blood pressure (♂)^{B}	(Meister et al., 2022)
B6	MO, IVF, IVEC (*n*=12-25)	NB (*n*=11-26)	Fresh	↑ Body weight gain (♂)^{B} ↑ hepatic lipid accumulation (♂)^{B} Glucose intolerance (♂)^{B}	(Bo et al., 2023)

*129Sv=129S6/SvEvTac and B6=C57BL/6J, NB=natural breeding (offspring or embryos produced with non-superovulated females), IVM=*in vitro* maturation, IVF= *in vitro* fertilisation, IVEC= *in vitro* embryo culture, MOET= multiple ovulation (MO) plus natural

breeding and embryo transfer (ET), ICSI=intracytoplasmic sperm injection, SCNT=somatic cell nuclear transfer, BL=Blastocyst, *n*=number of mice (in some studies the number varies per test/outcome analysed), Frozen-thawed= F-T.

[A]Only females were analysed.

[B]Only males were analysed.

[C]Main difference was observed with the MO-NB, IVEC group

[D]Difference only observed with the SCNT group. Only females were produced in the SCNT group.

[E]Difference only observed with the MO, IVF, IVEC group

[F]Observed when *in vitro*-produced offspring was fed with a high fat diet.

[G]In the *in vitro* group they compare oxygen tension during embryo culture (20% vs 5%) and addition of amino acids. Difference found with medium not supplemented with amino acids and under 20% oxygen.

[H]Difference found with 5% oxygen and addition of amino acids.

[I]Difference was associated with asynchronous embryo transfer (i.e., transfer of blastocysts to the oviduct).

[J]Except in offspring derived from the MO, IVF, IVEC group.

[K]Only in the IVM, ICSI, IVEC group.

[L]Except in females derived from the MO, IVF, IVEC-BL group.

[M]Except in the MOET-BL group.

[N]Only observed in offspring derived from embryos that were frozen-thawed.

Fig 1

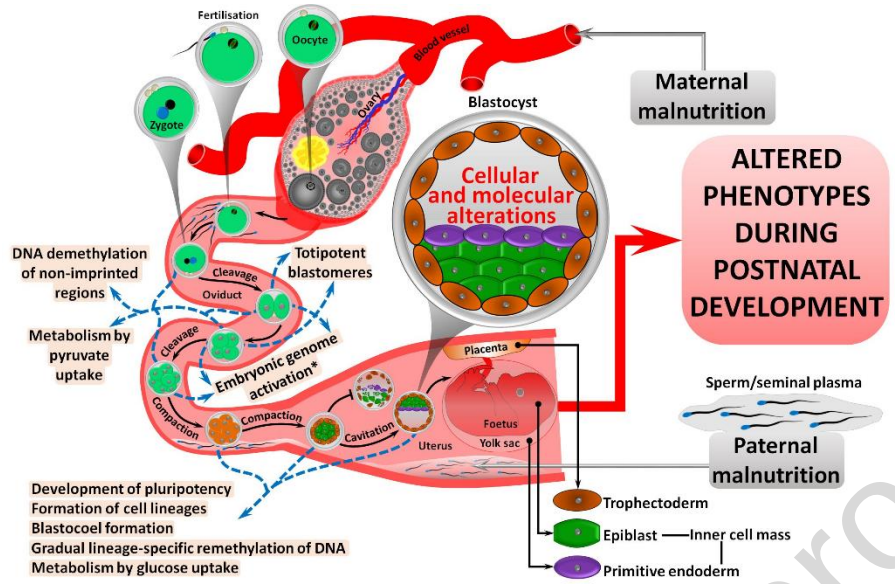
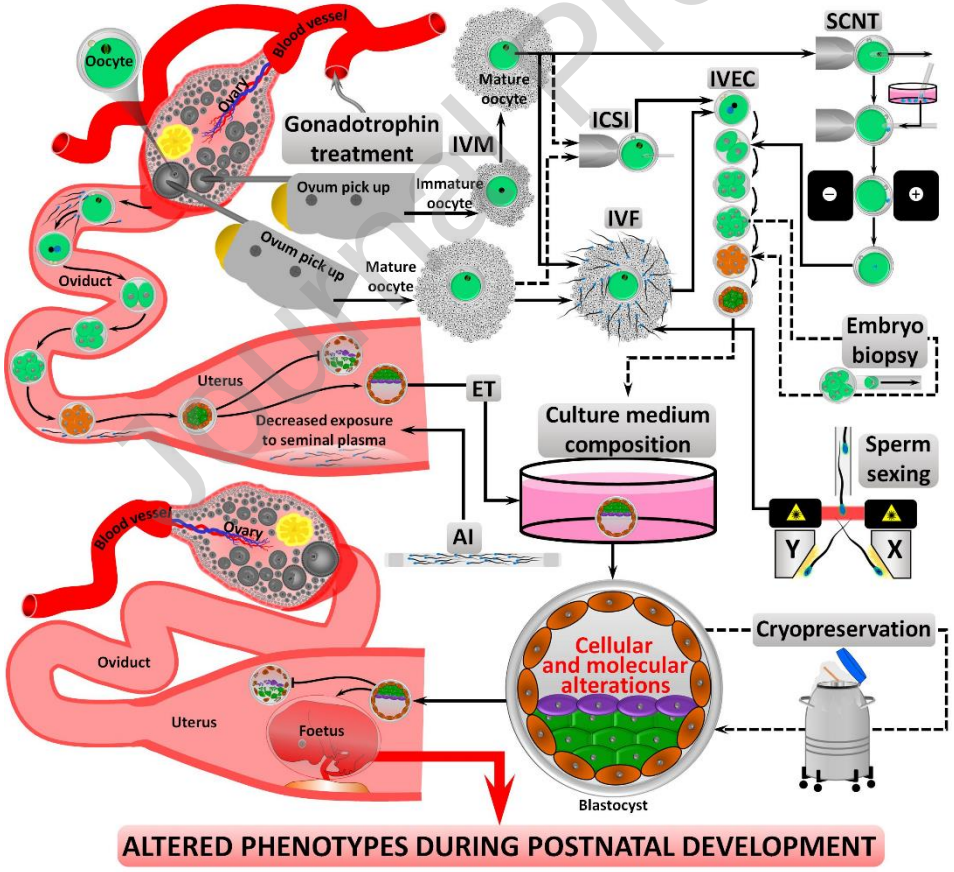


Fig 2



CRediT author statement

Miguel A. Velazquez: Conceptualization, Writing - Original Draft, Writing - review & editing. **Abdullah Idriss:** Writing - Original Draft. **Pascale Chavatte-Palmer:** Writing - review & editing. **Tom P Fleming:** Writing - review & editing.

Competing Interest statement

The authors declare no conflict of interest.

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Highlights:

- Preimplantation embryos are vulnerable to environmental stressors
- Developmental plasticity of preimplantation embryos promotes full-term pregnancy
- Postnatal health and performance can be programmed in the preimplantation period.