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25 years after Dolly: update on long term effects of embryo biotechnologies

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Abstract

Since the announcement of the birth of Dolly, the world's first mammal produced by cloning, it was demonstrated for the first time that somatic cells could be reprogrammed to produce a whole individual. This represented a considerable change in paradigm in the field of embryo technologies both in humans and animals which led to an intense burst of research on nuclear transfer but also on the establishment of pluripotency and the directed edition of the genome. As such, induced pluripotent cells and gene editing tools, the best-known being CRISPR-Cas9, are now available to the scientific community. Nevertheless, cloning was associated with important developmental abnormalities in a variable proportion of pregnancies, raising concern about the long-term effects of embryo technologies at a time when the concept of the developmental origins of health and disease had emerged, together with a better understanding of the underlying epigenetic modifications. The focus of this article is to review current knowledge on long term effects of artificial reproduction technologies in mammals, leading to globally reassuring information although differences are present and caution remains necessary taking the current increasing number of *in vitro* produced ruminant and equine embryos into account and their potential intergenerational consequences.

Keywords

Periconception, ART, programming, IVF, ICSI, cryopreservation

1. Introduction

Since the announcement of the birth of Dolly, the world's first mammal produced by cloning (Wilmut et al., 1997), it was demonstrated for the first time that somatic cells could be reprogrammed to produce a whole individual. This represented a considerable change in paradigm in the field of embryo technologies both in humans and animals (Alberio & Wolf, 2021; Sinclair, 2021).

Somatic cell nuclear transfer (SCNT) technology has been successful in both small and large ruminants and today, SCNT offspring have been produced in at least 25 species (*List of Animals That Have Been Cloned*, n.d.). It is a useful tool for farm animal breeding and research, production of transgenic animals for biomedical purposes, and conservation of endangered species. Current transgenic cattle in which certain gene functions are gained or suppressed, include those producing valuable pharmaceutical proteins in their milk; for example, cows overexpressing casein, or cattle where the prion protein is not expressed so that they are considered safe for human consumption. Recent genome editing technologies, such as zinc-finger nucleases, transcription activator-like effector nucleases, and CRISPR-Cas9, have been successfully adapted for applications in cattle and small ruminants. These technologies can be used directly on the zygote genome, thus bypassing the need to genetically engineer somatic cells and then perform SCNT.

Nevertheless, in the late 90's and early 2000's, around the time when Dolly was born, the high occurrence of developmental aberrations associated with the *in vitro* production of ruminant embryos (large offspring syndrome or LOS) hampered the progress of Animal Reproductive technologies (ART) applications to livestock production (Sinclair et al., 2000). These abnormalities were particularly spectacular in cloned animals (Chavatte-Palmer et al., 2002;

Constant et al., 2006; Lee et al., 2004; Young et al., 1998), suggesting that they might result from a cumulative effect of embryo technologies, as shown in mice (de Waal et al., 2015).

Nowadays, the major aberrations observed in *in vitro* produced (IVP) offspring have been largely reduced with the refinement of embryo culture (Galli et al., 2014) and the removal of serum and coculture in culture conditions as it was shown to be deleterious in mice (Fernández-Gonzalez et al., 2004).

The worldwide production of IVP embryos is, however, increasing rapidely, with more than 1.1 million bovine embryos being produced *in vitro* yearly (Viana, 2021). Recently, unformal reports on the birth of IVP bovine offspring with gestational abnormalities, such as increased size offspring and large placentas, have become more common, prompting recent research on the prenatal diagnosis (Rivera et al., 2022) and epigenetic etiology (Rivera, 2020) of the syndrome in bovine. Thus, it is appropriate to consider to which extent pre- and post-natal survival, health and wellbeing is affected in IVP-derived livestock embryos.

2. The developmental origins of health and disease and embryo production

The early stages of mammalian embryonic development are reported to be particularly sensitive to alterations in the microenvironment (Fleming et al., 2018). An adverse *in vivo* maternal or *in vitro* "periconceptional" environment will not only affect early embryo development but may have distinct long-term effects as well, giving rise to the concept of the "developmental origins of health and disease" (DOHaD) (Duranthon & Chavatte-Palmer, 2018; Van Eetvelde et al., 2017). The DOHaD hypothesis states that adaptive changes, as response to environmental stressors like maternal undernutrition for example, may alter physiology and metabolism to ensure that the growth of the offspring matches the prevailing nutrient

availability (Barker et al., 2010). These adaptive measures, however, may induce sustained changes in the phenotype and may affect postnatal growth, long-term health, metabolism, disease susceptibility (including diabetes, obesity, and cardio-vascular dysfunction), and productivity of the offspring (Gluckman et al., 2010).

in vitro -produced embryos face various potential environmental stressors such as culture medium composition, medium pH, culture oil, oxygen tension, temperature variations during manipulation, light exposure, shear stress associated with repeated pipetting, nonphysiological hormonal stimulation, and so on — all factors that might individually or interactively affect embryo development and the health, growth, and development of *in vitro* -conceived offspring (Duranthon & Chavatte-Palmer, 2018; Fleming et al., 2018; Galli et al., 2014; Lazzari et al., 2020; Niederberger et al., 2018). The underlying molecular mechanisms of cellular memory affecting gene expression are commonly referred to as epigenetic marks (Jammes et al., 2011). Epigenetic modifications in IVP embryos compared to *in vivo* produced controls are often considered as a proxy for abnormal programming, although post-implantation development and placental adaptations may modulate initial embryonic insults (Tarrade et al., 2015). In addition, despite the potential detection of epigenetic perturbations, adverse effects of early developmental programming may not be detected until advanced post-natal age. A clear post-natal or transgenerational phenotype should be observed to confirm the concerns raised by initial epigenetic modifications, which is often lacking in both livestock and human studies, due to obvious practical and also ethical limitations.

3. Livestock embryo production

In bovine and equine, embryos are either collected *in vivo* at the blastocyst stage by flushing the uterus of a donor animal after artificial insemination (AI) or produced *in vitro* after ovum pick-up (OPU), *in vitro* maturation (IVM) of oocytes, fertilization, and embryo culture to the blastocyst stage. Despite the large number of bovine IVP embryos produced worldwide and the constant improvement of IVM, fertilization, and embryo culture procedures over the past two decades, IVP of bovine embryos remains non-optimal compared with production of embryos *in vivo* (Ealy et al., 2019; Hansen, 2020). Finally, although cloned embryos are made using oocytes collected from slaughterhouse ovaries, IVM and subsequent steps are required. The following paragraphs focus on the known epigenetic and phenotypic effects of techniques used for large animal reproductive technologies.

3.1. Bovine

3.1.1. Superovulation

Oocyte growth in bovine and equine occurs over several months, during which the oocyte undergoes serial structural and epigenetic modifications that are required for normal embryonic development after fertilization. Because of the prolonged nature of this process, oocytes are particularly sensitive to environmental challenges, especially in the final phase of growth, in which the maternal imprinted genes are methylated in a size-specific manner (Anckaert & Fair, 2015a). Indeed, increasing methylation of a representative panel of five maternally methylated genes was observed during the growth phase of bovine oocytes (O'Doherty et al., 2012).

Since the early 1980s, multiple ovulation and embryo transfer (MOET) has been used in farm animals to increase the diffusion of cow genetics and has been widely successful (Viana, 2021). Nevertheless, superovulation regimens might compromise or at least interfere with the imprinted status of matured oocytes in bovine (Chu et al., 2012; Fair, 2010), as has been shown in mice (Anckaert & Fair, 2015b; Sullivan-Pyke et al., 2020). Both the number and developmental quality of embryos produced following ovulation induction may be affected (Gad et al., 2011; Hansen, 2020), either through the recruitment of oocytes from follicles of different qualities or due to different endometrial receptivity (Forde et al., 2012; Mansouri-Attia et al., 2009). Indeed, cellular and metabolic activity is increased in blastocysts collected from superovulated heifers compared to those that developed in the oviduct of unstimulated animals (Gad et al., 2011; Gad, Hoelker, et al., 2012). In addition, in mice, superovulation alone was shown to alter fetal and placental growth and placental gene expression (Mainigi et al., 2014).

3.1.2. *In vitro* production

So far, the little data available on effects of IVM on gene expression show little aberrant methylation in the metaphase II oocyte (Anckaert & Fair, 2015b; Lu et al., 2018). After fertilization, however, the embryo culture affects embryo gene expression.

The transcriptome of IVP blastocysts produced from *in vitro* matured oocytes recovered from slaughtered cows evidenced several hundred differentially expressed genes compared to that of blastocysts developed *in vivo* from superovulated and artificially inseminated cows (Gad, Schellander, et al., 2012; Heras et al., 2016). Notably, genes involved in lipid metabolism were found differentially expressed, which is in line with the accumulation of lipid droplets in IVP

embryos. Sexually dimorphic responses to IVP were also observed, indicating that male and female embryos respond differently to their environment, as already shown in culture conditions (Bermejo-Alvarez et al., 2010).

The embryonic genome activation period (8 cell stage in bovine) appears the most sensitive to environmental changes (Gad, Hoelker, et al., 2012). The deleterious effects of the time the embryo spent in the culture medium were reported on embryo gene expression and subsequent development (Enright et al., 2000; Rizos et al., 2008). Subsequently, others analyzed DNA methylation in embryos produced from *in vitro* matured, *in vitro* fertilized oocytes and *in vitro* cultured embryos until the zygote, 4-cell, 16 cell stage and subsequently developed *in vivo* (Salilew-Wondim et al., 2018). The longer the *in vitro* culture period, the higher the number of differentially DNA methylated regions compared to *in vivo* developed embryos, with an even distribution among chromosomes. Methylation patterns, however, were not directly related to the differences in gene expression, probably due to the complex relationship between methylation and gene expression, depending on the genomic region where methylation occurs or on the fact that DNA methylation is only one among several epigenetic marks that affects gene expression.

In other species, IVP was also shown to alter embryo and/or feto-placental methylation, as reviewed elsewhere (Anckaert & Fair, 2015b; Duranthon & Chavatte-Palmer, 2018; Heber & Ptak, 2021).

It is challenging to monitor the long-term effects on the health of IVP calves because of the organization of the bovine industry. As animals are generally culled at a few years of age, only clinically visible effects observed in young animals are reported. To date, and since the removal of serum and co-culture from embryo culture conditions that were shown to be related to the occurrence of LOS , adverse neonatal and adult health outcomes associated

with IVP embryos are not much reported by the bovine industry, although an increase in birth weight is still observed (Hansen, 2020; Rivera et al., 2022), associated with high levels of morbidity and mortality among IVP embryo-derived ruminant offspring (Bonilla et al., 2014b; Rivera, 2020; Sinclair et al., 2000). Commonly observed phenomena include increases in placenta, body and organ size, perturbations in growth rate, cardiovascular function and glucose homeostasis regulation (Hansen & Siqueira, 2017). Production characteristics, carcass weight, and fertility do not seem affected by IVP, although it has been suggested that milk yield tends to be lower in cows born after IVP using reverse X-sorted semen compared with IVP controls (Hansen & Siqueira, 2017). Not only did these females produce less milk, but milk fat and milk protein contents were also decreased (Bonilla et al., 2014a; Hansen & Siqueira, 2017). In males, in a highly managed situation, no effect of IVP was observed on semen production of 1-year-old bulls or on embryo production results in 1-year-old females (van Wagtendonk-de Leeuw, 2006) although recent data demonstrate up-regulation of the hypothalamus-pituitary-gonadal axis and differences in the expression of genes involved in energy regulation between IVP and control male calves (Rabaglino et al., 2021, 2022). Epigenetic and transcriptomic markers of the IVP or *in vivo* origin were identified in the calves' white blood cells (Rabaglino et al., 2021).

In view of the numerous placental (de Waal et al., 2015; Donjacour et al., 2014; Mann et al., 2004) and long term effects of *in vitro* production and embryo culture reported in model species (Donjacour et al., 2014; Fernández-Gonzalez et al., 2008; Feuer et al., 2014; Narapareddy et al., 2021; Rexhaj et al., 2013; Ventura-Juncá et al., 2015), more studies on adult IVP offspring are still required.

As a positive note, the group of Pilar Coy in Spain has recently reported that the addition of reproductive fluids collected from the oviduct and the uterus reduced the phenotypic

differences between *in vitro* and *in vivo* derived offspring in cattle and porcine (Lopes et al., 2022; París-Oller et al., 2021, 2022), thus providing new avenues to reduce long term effects of ART in domestic animals.

3.2. Small ruminants

In sheep, IVP has been reported to delay development during early gestation: IVP sheep conceptuses were smaller than controls between d 20 and 28 of development; that is, the phase when exponential growth occurs in sheep embryos (Ptak et al., 2013). Indeed, the proteomic analysis of ovine IVP embryos shows clear differences with *in vivo* embryos (Passos et al., 2022). Around the time of implantation, early fetal cardiovascular development is altered in IVP embryos, reflected in pericardial and placental hemorrhage compared with naturally conceived conceptuses (Fidanza et al., 2014). Subsequently, compromised placental development resulted in the birth of growth retarded lambs (Fidanza et al., 2014). In these IVP conceptuses, abnormalities in global DNA methylation of the placenta were demonstrated (Reynolds et al., 2013), which are most probably related to reduced DNA methyltransferase 1 (DNMT1) expression and enzyme activity observed at the time of implantation (Ptak et al., 2013). Indeed, implantation might be an important bottleneck for the development of IVP embryos, as illustrated by the fact that conceptuses that did not survive showed impaired DNMT1 expression, whereas those that continued past this bottleneck showed normal DNMT1 expression (Ptak et al., 2013).

3.3. Horses

In horses, in contrast to most domestic animals but similar to humans, mare or stallion subfertility is the main indication for the use of ART (Benammar et al., 2021; Hinrichs, 2018). Because of the poor development so far using *in vitro* fertilization, intra-cytoplasmic sperm injection (ICSI) is the main technology used, which has not been associated with obvious developmental abnormalities in equidae (Clérico et al., 2020; Heras et al., 2017; Hinrichs, 2018; Valenzuela et al., 2018). Nevertheless, there is a general agreement regarding, first, the link between sperm DNA fragmentation and male infertility, and second, the possibility of inadvertently microinjecting a DNA-damaged sperm during ICSI, resulting in worse embryo quality and lower reproductive results, as well as the future animal's health (Fernández-Gonzalez et al., 2008). So far, epidemiological data in humans taking into consideration both IVF and ICSI does not demonstrate differences due to the use of ICSI or IVF on child's health (Pontesilli et al., 2021).

4. Other embryo manipulations

4.1. Embryo biopsy

With the development and simplification of whole genome sequencing, embryo biopsy is currently used to predict genetic value at the embryo stage in order to obtain rapid genetic improvement (Sirard, 2018). In ruminants, in a global comparison in pregnancy rates at 30 and 60 d after transfer of biopsied *vs* non-biopsied *in vivo*-produced embryos, those biopsied at the morula stage (D7) resulted in lower pregnancy rates compared with non-biopsied blastocysts (de Sousa et al., 2017; Naitana et al., 1996). No significant differences between

biopsied and control IVP embryos were observed when pregnancy rates were compared (de Sousa et al., 2017). In horses, for morulae and early blastocysts, pregnancy rates are reported similar between biopsied and non-biopsied embryos (Hinrichs & Choi, 2012; Riera et al., 2019; Seidel et al., 2010).

4.2. Cryopreservation of embryos

In the view of the reported increased birthweight of children born after IVP and embryo cryopreservation in humans (Anav et al., 2019; Raja et al., 2022; Shapiro et al., 2016), particular concern exists for long term effects after cryopreservation.

In cattle, when grade I embryos are used, frozen IVP embryos have similar pregnancy rates as conventional ET embryos (Ferré et al., 2020).

In horses, the cryopreservation of *in vivo* produced blastocysts requires that the large blastocoele is collapsed before vitrification (Hinrichs, 2020; Wilsher et al., 2021). In contrast, IVP and *in vivo* produced late morulas can be frozen successfully both by slow freezing or vitrification (Hinrichs, 2020).

For small ruminants, the cryopreservation of *in vivo* produced embryos was shown to affect blastocyst gene expression, with a more pronounced effect of vitrification compared to slow freezing (Brair et al., 2020), resulting in similar lambing rate in some studies but increased lamb weight at 2 months in the vitrified group (dos Santos-Neto et al., 2017; Figueira et al., 2019; Khunmanee et al., 2020). Reduced cryotolerance has been observed after ovine IVP, with an 10% reduction in lambing rates decrease after transfer of frozen-thawed *in vivo*-produced embryos *vs* 10-20% for frozen-thawed IVP blastocysts (Romão et al., 2015). More recently, lambing rates and birthweights were reported to be similar between IVP and *in vivo*

conceived embryos, although embryo survival rate varied between <10% to 37.7% after cryopreservation, depending on the methodology used (dos Santos-Neto et al., 2017).

4.3. Cloning

Cloning efficiency remains low in domestic animals with <10% success for obtaining a live and healthy offspring after embryo transfer (Akagi et al., 2014; Heyman et al., 2002; Panarace et al., 2007), with a very large variation between cell lines. Nevertheless, the initial doubts about clone adult health due to the short telomeres and the potential early ageing of Dolly the sheep have not been confirmed (Corr et al., 2017; Miyashita et al., 2011; Sinclair, 2021; Sinclair et al., 2016). In horses, the use of mesenchymal stem cells as nuclear donors was shown to improve the health of foals at birth (Olivera et al., 2018). Moreover, the use of epigenetic modificators (H3K9me3 demethylase Kdm4d mRNA and treatment with histone deacetylase inhibitor trichostatin A) after nuclear transfer using fibroblasts enabled the birth of cloned macaque monkeys, which had not been possible before (Liu et al., 2018). In any case, once the neonatal period is over, cloned animals that appear healthy become undistinguishable from controls produced by conventional method (P. Chavatte-Palmer et al., 2004; P. M. Chavatte-Palmer et al., 2009; Miyashita et al., 2011; Panarace et al., 2007; Schauwer & Chavatte-Palmer, 2020) and their commercialization for human consumption has been allowed by the FDA in the United States.

5. Conclusion

This literature review shows that since Dolly and the onset of the Large Offspring Syndrome in IVP ruminant embryos, current data in domestic animals suggest little long-term effects of IVP. Nevertheless, most studies show that embryo gene expression is affected by embryo technologies, but they do not analyze epigenetic modifications nor adult offspring health, let alone trans- or inter-generational consequences. Since production animals are not growing old, long term effects may be missed and epigenetic modifications may affect subsequent generations. In addition, in view of the evolution of breeding practice due to global warming and increased exposure to pollutants and endocrine disruptors, multiple insults may result in more pronounced effects after IVP, calling for more attention and long-term follow-up of individuals born after IVP and their offspring.

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