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The effects of Assisted Reproductive Technologies on genomic imprinting in the placenta

Eric A. Rhon-Calderon[a], Lisa A. Vrooman[a], Laren Riesche[a,b], Marisa S. Bartolomei[a,*]

[a] Epigenetics Institute, Department of Cell and Developmental Biology, University of Pennsylvania Perelman School of Medicine, Smilow Center for Translational Research, 3400 Civic Center Blvd, Bldg 421, Philadelphia, PA, 19104-6058, USA

[b] Department of Family and Community Health, Claire M. Fagin School of Nursing, University of Pennsylvania, Philadelphia, PA, USA

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ABSTRACT

The placenta is a complex and poorly understood organ, which serves as the connection between the mother and the developing fetus. Genomic imprinting, defined as a regulatory process resulting in the expression of a gene in a parent-of-origin-specific manner, plays an important role in fetal development and placental function. Disturbances that occur during the establishment and maintenance of imprinting could compromise the placenta and fetus, and ultimately, offspring health. Assisted Reproductive Technologies (ART) have been widely used to overcome infertility, however experimental studies have shown that ART procedures affect placentation and the expression of imprinted genes. Here we briefly review the role of imprinted genes in placental development and the evidence from mouse and human studies suggesting ART disrupts imprinted gene regulation in the placenta.

1. Introduction

Assisted Reproductive Technologies (ART) are non-coital methods of conception used to treat infertility and achieve a pregnancy involving the *in vitro* manipulation of gametes and/or embryos. This includes *in vitro* fertilization (IVF) and intracellular sperm injection (ICSI) [1]. The use of ART to overcome infertility problems has helped many couples, accounting for up to 8 million births worldwide and it is expected that the number of ART births will increase as more couples postpone having children or infertility arises on a more regular basis due to changes in lifestyle or exposure to environmental factors, such as endocrine disruptors [2]. While ART has been proposed to be safe, it is associated with multiple adverse health outcomes for mothers and babies, including pregnancy-induced hypertension, gestational diabetes, placenta abruption, preterm birth, low-birth weight and perinatal mortality [2]. It is postulated that these outcomes may be due to alteration in the epigenetic landscape of DNA, especially in the placenta. Epigenetics encompasses multiple chemical reactions and processes that modify and regulate gene activity without affecting the underlying DNA sequence. Ultimately, epigenetic modifications make the genome more dynamic and are influenced by genetic variability and environmental factors such as ART [2–4]. One of the most well studied epigenetic marks is DNA methylation, the addition of a methyl group directly on a cytosine base. This epigenetic mark plays role in genomic imprinting, a phenomenon in mammals that regulates gene expression in a parent-of-origin-specific manner [5]. Multiple genes are imprinted and importantly, they have known functions in fetal growth and development [2]. In this review, we discuss what is currently known about genomic imprinting in the placenta and the effect of ART on this epigenetic phenomenon in animal models and humans.

2. Placenta

The placenta is a temporary organ that regulates growth and development of the embryo during gestation. One of its major functions is to control nutrient and gas exchange between the developing embryo and its mother. In 1937, Harland Mossman defined the placenta as “any intimate apposition or fusion of the fetal organs to the maternal (or paternal) tissues for physiological exchange” [6]. The Mossman definition applies not only to mammalian placentas, but also to any structure that is involved in the exchange of nutrients between the maternal side and the developing embryo. The placenta has two major functions, according to Wooding and Burton: 1) maximize fetal nutrient and oxygen acquisition from the mother, and 2) minimize immunological rejection by the maternal immune system [7].

Placental insufficiency is a term that refers to progressive deterioration in placental function that compromises the transplacental transfer of nutrients to the fetus [8]. This deterioration in placenta

* Corresponding author. Epigenetics Institute, Department of Cell and Developmental Biology, University of Pennsylvania Perelman School of Medicine, 9-123 Smilow Center for Translational Research, University of Pennsylvania, 3400 Civic Center Blvd, Bldg 421, Philadelphia, PA, 19104-6058, USA.
E-mail address: bartolom@pennmedicine.upenn.edu (M.S. Bartolomei).

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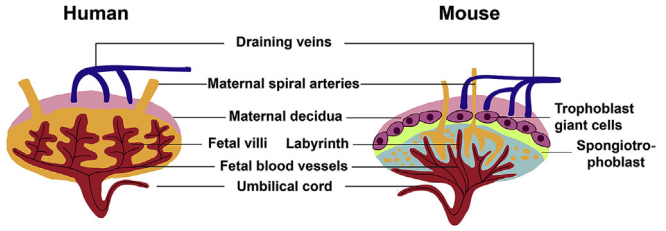

Fig. 1. Comparison of the human and mouse placenta structures. The mature utero-placental unit in humans consists of two layers: 1) Outer maternal layer, which includes the decidua and the maternal vasculature (yellow and pink) and 2) Inner layer or villous tree, which contains the placenta vasculature where nutrient exchange from the maternal to fetal blood occurs (red); while the mouse placenta consists of three layers: 1) Outer maternal layer, which includes the decidua and the maternal vasculature (yellow and pink), 2) A middle region, or junctional zone where the trophoblast giant cells are present (dark pink), and 3) Inner layer or labyrinth layer, which contains the placenta vasculature (red).

exchange is responsible for the reduction in fetal growth (fetal growth restriction or FGR), which is present in up to 60% of placental insufficiency cases. FGR is considered the second most frequent cause of perinatal death after prematurity and its occurrence has major impacts on the fetus and placenta with consequences on cardiovascular, metabolic, and neurological development up to adulthood [9].

The placenta is common to all mammals and while its function is conserved, its structure varies. Because human placental tissue is only available from term pregnancies or some miscarriages, its research use is limited. However, the use of animal models such as mouse has increased our knowledge of how different genes, diseases, toxins, or other factors can impact the health of extraembryonic tissues in different stages of development [10]. Human and mouse placentas are comprised of three major layers (Fig. 1): 1) An outer maternal layer includes the decidual cells of the uterus as well as the maternal vasculature that brings blood to and from the implantation site, 2) A middle "junctional" region that attaches the fetal placenta to the uterus and contains the trophoblast cells that invade the uterine wall, and 3) an inner layer, composed of highly branched villi that form the placental villi in humans or the labyrinth layer in mice, which functions in nutrient exchange [11]. In both mouse and human placenta, the fetal trophoblast cells erode through the maternal endothelium. As a result, the fetal trophoblast cells are immersed in maternal blood. This type of placentation in which maternal blood is in direct contact with the fetal chorion (trophoblast) is called hemochorial placentation, which is more efficient in nutrient transfer compared to the other types of placentation. Human and mouse placentas present some differences; while the trophoblast cells in both species penetrate and invade the endometrium only in humans will it continue into the myometrium. In the mouse, the yolk sac plays the major role in feto-maternal exchange and only later in gestation is this role taken over by the placenta. In contrast, in humans, the placenta is the main source of exchange from early stages and the yolk sac is largely vestigial [12]. Placentas are characterized also for their endocrine function; human placentas are the major producer of Human Chorionic Gonadotropin (hCG) and estrogen, characteristics that are absent in rodents [13]. The labyrinth zone of the mouse placenta has three layers of trophoblast that separate the maternal blood from the fetal blood vessels: the cytotrophoblast and two layers of syncytiotrophoblast, while in the human placenta there is only one layer: the syncytiotrophoblast, which is maintained by the underlying cytotrophoblasts [65]. Although human and mouse placentas differ in some details, they still share cell morphology and molecular mechanisms involved in placental development [10].

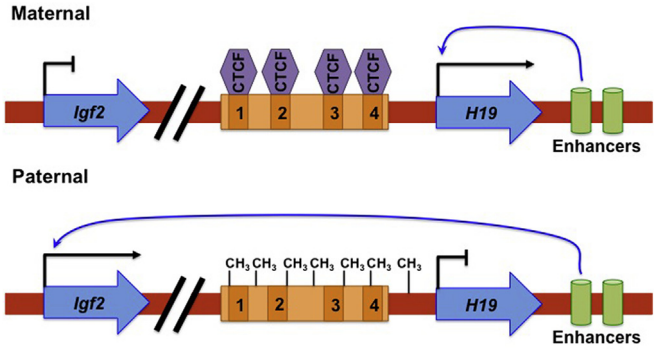

Fig. 2. Example of an imprinted locus using the insulator model of imprinting: *H19/Igf2*. Regulation of imprinted expression at the mouse *H19/Igf2* locus, which has a known role in placental growth, with DNA methylation status and gene expression depicted. Arrows at genes denote active status while arrows pointing right to left denote interaction between the enhancer and gene promoters. See Ref. [35] for details. Note that other imprinted loci use alternate methods of regulation, including regulation by long non-coding RNAs.

3. Genomic imprinting

Genomic imprinting is an epigenetic phenomenon where a small number of genes are expressed in a parent-of-origin-specific manner in mammals. The parental-specific expression is regulated by epigenetic marks, such as DNA methylation and/or histone modifications that are allele-specific. These marks are established during gametogenesis and maintained throughout life for most imprinted loci [14,15]. Imprinted genes reside in clusters throughout the genome, regulated by imprinting control regions (ICRs) [16] that exhibit allele-specific DNA methylation (Fig. 2). These ICRs are methylated in a sex-specific manner during gametogenesis and this methylation is maintained after fertilization when most of the genome is being reprogrammed (Fig. 3). The ICRs also serve as either methylation-sensitive insulators (Fig. 2) or promoters for long non-coding RNAs [14,15]. To date more than 130 imprinted genes have been discovered in mice compared to at least 70 that have been discovered in humans, some of these are imprinted only in the placenta. The embryonic and extraembryonic tissues from mouse and human share an extensive number of imprinted genes, some of which are summarized in Table 1. Errors in the epigenetic status of several imprinted loci can adversely influence embryonic growth and development.

The imprinting of most of these genes is conserved in the placental mammals that have been investigated. The majority of imprinted genes in mouse are largely conserved with respect to methylation status and allelic expression in human although there are some exceptions [17]. In the case of primordial germ cells (PGCs) both human and mouse undergo an erasure of DNA methylation during the early stages of embryonic development, but in humans the retention of the maternal DNA methylation is higher than in mouse [17] (Fig. 3). The gamete methylation profiles in human and mouse are remarkably similar. The protection of DNA methylation at ICRs is required in both mouse and human, but the epigenetic modifiers implicated in this maintenance have evolved distinct roles between species [17]. For example, while global epigenetic marks are similar in mature sperm from mouse and human, *de-novo* DNA methylation might differ. Mice express DNMT3C which is involved in DNA methylation, while in humans this enzyme is not present [17].

4. Imprinted genes and placental development

A number of imprinted genes are highly expressed in placenta and are important for its development. These genes are involved in the growth, morphology, and nutrient transfer capacity of the placenta and, thereby, control the nutrient supply for fetal growth [18]. Transgenic

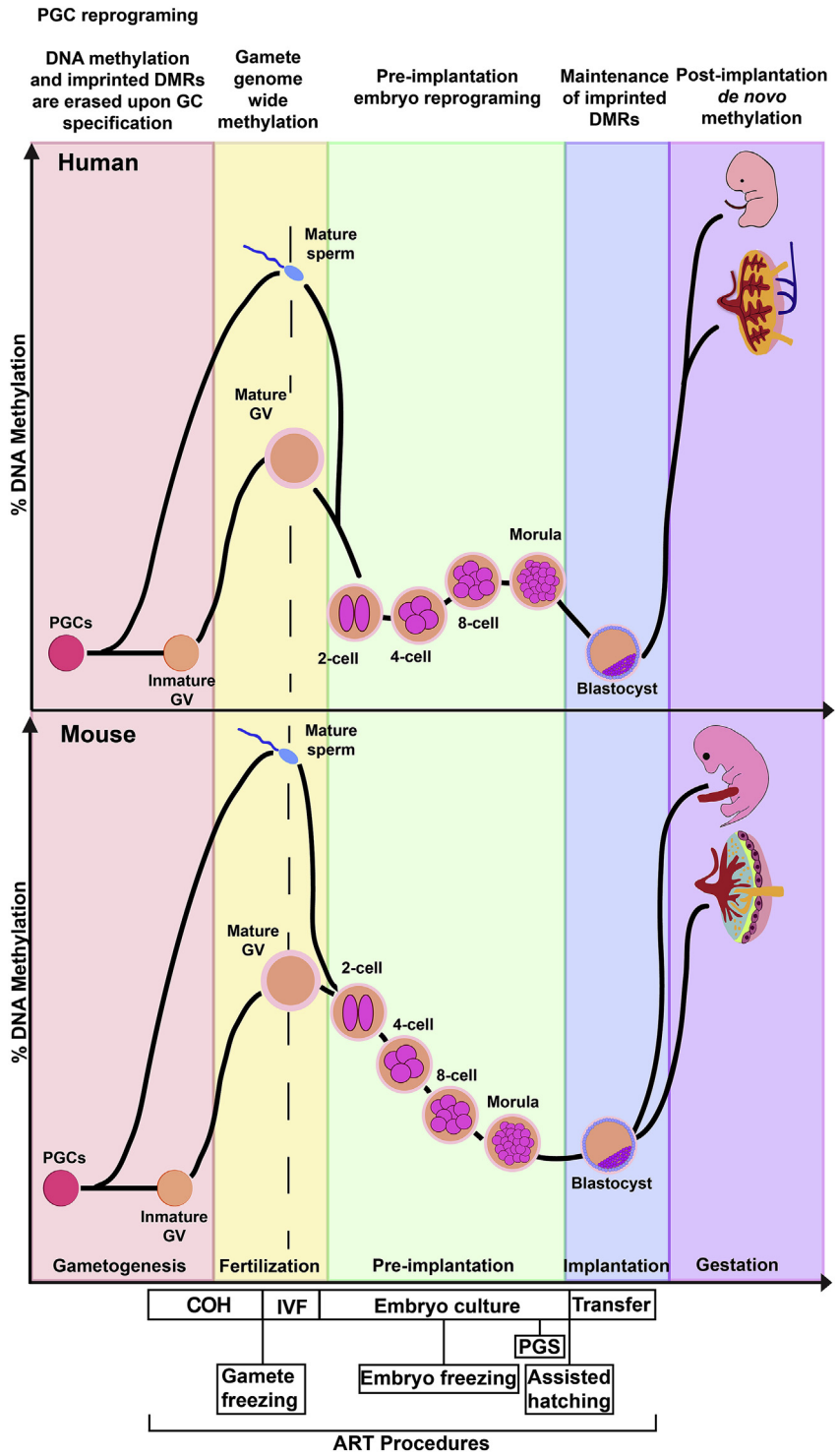

Fig. 3. Epigenetic reprogramming in humans and mouse: changes of DNA methylation during gametogenesis, fertilization, and embryo development. Relative level of DNA methylation is shown on the Y axis. ART procedures take place during normal DNA methylation reprogramming. COH: Controlled ovarian hyperstimulation, IVF: *In vitro* Fertilization, PGS: Preimplantation genetic sampling, PGC: Primordial germ cells, GV: Germinal vesicle, GC: Germinal cells, DMR: Differentially methylated regions. See Refs. [23,36,37] for more details.

mouse models have demonstrated roles for imprinted genes in placental function and fetal growth. For example *Ascl2, Phlda2* and *Peg10* are indispensable for proper placental morphology and function. *Igf2* has been shown to be involved in nutrient regulation as well as placental size and morphology [19]. Imprinted genes and their function in placental development have been the subject of many in depth reviews: see the review by Tunster et al. [20] and Nelissen et al. [19]. The most well studied imprinted genes with known roles in placental development are summarized in Table 1.

The proper regulation of imprinted genes in the placenta is essential, with aberrant regulation associated with abnormalities. Given the function of the placenta in maternal-fetal cross talk and production of hormones and growth factors, aberrant genomic imprinting in the placenta can have adverse impacts on embryonic growth and

Table 1
Examples of imprinted genes with significant functions in mammalian development.

Imprinted gene	Active allele	Specie identify	Primary Function	Associated pathologies in placenta or fetal growth	Reference
H19	Maternal	Human Mouse	Encodes an abundant RNA. Negative regulator of embryonic growth	IUGR SGA Pre-eclampsia	[38]
Igf2r	Maternal	Mouse	IGF2R protein binds to IGF2 and clears it from the circulation without transmitting a growing signal. It also has an intracellular trafficking function	IUGR SGA	[39]
Kcnq1	Maternal	Human Mouse	Expressed in multiple fetal tissues, and biallellic expression in adult heart. It encodes a voltage-sensitive potassium channel	IUGR	[40]
Cdkn1c	Maternal	Human Mouse	Active in fetal tissues. Encodes a kinase inhibitor that regulates cell proliferation	IUGR SGA	[41]
Phlda2	Maternal	Human Mouse	Encodes a Pleckstrin homology domain protein involved in the restriction of the spongiotrophoblast	IUGR SGA Low birth weight	[42]
Ube3a	Maternal	Human	Encodes a protein ligase that mediates the degradation of p53	–	[43]
Wt1	Maternal	Human	Encodes for WT1 protein involved in the development of the gonads and kidneys	IUGR	[44]
Mash-2 or Ascl2	Paternal	Mouse	Encodes a transcription factor that participates in the development of the spongiotrophoblast in the placenta	Several structure anomalies	[45]
Peg10	Paternal	Human	Development of spongiotrophoblast	IUGR	[46,47]
Igf2	Paternal	Human Mouse	Mitogen function in embryonic and extraembryonic tissues. Also, has an anti-apoptotic function	IUGR SGA Low birth weight	[48]
Ins1 and *Ins2*	Paternal	Mouse	Expressed in yolk sac, encodes for a hormonal regulator that also acts as growth factor	–	[49,50]
Kcnq1ot1	Paternal	Human Mouse	Expressed in embryonic and extraembryonic tissues, encodes an RNA that regulates normal growth and development. Also regulates the function of maternal *Kcnq1*	SGA	[51]
Mest/Peg1	Paternal	Human	Expressed in fetal tissues and regulates growth and maternal behavior	IUGR Low birth weight	[52]
Peg3	Paternal	Human Mouse	Expressed in placenta and other tissues, such as brain. Regulates placental and fetal growth, and maternal behavior	IUGR	[52]
Snrpn	Paternal	Human Mouse	Expressed in fetal and adult tissues. Encodes a splicing factor	IUGR	[53]
Xist	Paternal	Mouse	Expressed in placenta. X-linked gene that encodes a non-translated RNA involve in X-chromosome inactivation, inherited by female offspring	–	[54]
miR-675	Maternal	Human Mouse	Signaling the end of placental growth	Placental growth alteration	[55]
Rtl1	Paternal	Mouse	Maintenance of placental capillaries	–	[56]
Slc22a3	Maternal	Mouse	Mono-amine uptake to the embryo through the placenta	IUGR SGA	[57]
Dlk1	Paternal	Human	Regulate maternal-fetal interaction	IUGR	[58,59]
Plagl1 or Zac	Paternal	Human	Placental and fetal development	IUGR	[58,59]
Meg3	Maternal	Human	Regulates placental growth	IUGR	[58,59]
C19mc	Paternal	Human	Role in placental biology and maternal adaptation to pregnancy	Pre-eclampsia	[60,61]
DNMT1	Paternal	Human	Maintenance of imprints during cleavage	IUGR	[62,63]
Grb10	Maternal (trophoblast)	Human Mouse	Negative regulator of growth	Disproportionate placental and fetal overgrowth	[64]

IUGR: Intrauterine growth restriction, SGA: Small for gestational age, -: non placenta pathology described.

development and could explain low birth weight children as well as adult-onset diseases that originate in utero [21]. These pathologies, which have an increased incidence in humans, can be understood and predicted from murine models. These models have shown that low birth weight, programming of metabolic diseases in the adult, plus some complications of pregnancy, such as pre-eclampsia and gestational diabetes, result from fetuses and placentas carrying abnormal genomic imprinting [20].

5. Effect of ART on imprinted genes in the placenta

As mentioned above work from various laboratories has shown that ART is associated with health risks for mothers and fetuses such as stillbirth, preterm birth, intrauterine growth restriction (IUGR), abnormal placentation, and other pregnancy complications [9]. ART-conceived children have shown a loss of DNA methylation at ICRs and a higher incidence of rare epigenetic disorders such as Beckwith-Wiedemann syndrome, and Angelman syndrome [22]. Additional studies have found that ART procedures may increase imprinting disorders, mainly because the different procedures used during ART, such as superovulation, embryo transfer, and *in vitro* culture may cause alterations in the DNA methylation patterns in oocytes and embryos [23]. Indeed, ART procedures and manipulations take place during critical epigenetic reprogramming, leading to aberrations in genomic imprinting that may compromise normal development of the placenta and subsequently the fetus in animal models, such as mouse, and humans (Fig. 3).

Studies specifically examining the effect of ART on placenta development in humans have shown that alterations in DNA methylation may cause deregulation of gene expression. However, the nature of human studies makes it hard to rule out the influence of infertility status and other confounding factors. Further, the number of samples analyzed was small and the assays may be limited to a small number of imprinted genes. Sakian et al. studied placentas conceived from IVF and ICSI procedures in humans, and although they did not observe alterations in the placental or fetal weight, they reported alterations in gene expression in *H19* and *IGF2* which they suggest was due to a loss of imprinting on the paternal allele [24]. Katari et al. demonstrated that

compared to placentas from naturally-conceived human pregnancies, ART-conceived placentas have an increase in gene expression of *MEST* and *SERPINF1,* a decrease in gene expression of *COPG2* and *NNAT,* a loss of methylation in *GRB10, MEST, PEG3, SERPINF1* and *SCL22A2,* no changes in the methylation or expression of *DLK1, GNAS*, *H19* and *KCNQ1OT1*. Because these genes are involved in the development and differentiation of adipocytes, insulin signaling and obesity, upregulation of these genes in the placenta could suggest increased risk of metabolic syndrome in adulthood [25]. An additional study by Shi et al. reported alterations in the methylation patterns of the *IGF2/H19* ICR in placentas from three children conceived by ART. Nevertheless, these children appeared healthy. They hypothesized that the methylation perturbation was due to imprinting errors in the gametes or errors that occur during embryo culture [26]. Rancourt et al. reported that *PEG1* was hypomethylated with no significant difference in the gene expression, while *H19* was hypomethylated and its gene expression was increased in placentas of successful pregnancies from ovulation induction or IVF [27]. Finally, Nelissen et al. observed that DNA methylation was reduced in *H19* and *PEG1* in IVF/ICSI human placentas and the gene expression of *H19* and *PHLDA2* was significantly increased in the IVF/ICSI group, but they did not observe significant differences in body weight of the analyzed children [4,19]. While some of these alterations may be due to ART procedures it is possible that theses epigenetic changes may be a reflection of the underlying infertility of the couple. Kobayashi et al. and Hanna et al. showed that the sperm and the oocyte methylation patterns could be altered prior fertilization, which could impact in gene expression affecting the offspring [17,28]. Other studies of imprinted DMRs in humans have shown that there are no differences between spontaneous and ART-conceived samples [29]. One of these studies found that even with a small difference in methylation associated with the type of conception there were no changes in gene expression [27,29].

Due to confounding factors in human ART studies, animal studies have proven to be critical in determining the effects of ART. The vast majority of animal studies have shown that embryo culture and procedures used in ART can alter epigenetic gene regulation and cause placental and fetal abnormalities. In large animal studies, sheep and/or cattle that are derived from *in vitro* embryo culture with or without cloning procedures often present with an overgrowth syndrome and sheep with large offspring syndrome had reduced expression and abnormal methylation of the *Igf2r* gene [30].

The use of mouse models to test the effect of ART procedures in placentation and development has increased, allowing more insight into why placental abnormalities and loss of imprinting occur with these procedures. Doherty et al. studied the effect of two different culture media on the expression of *H19* and *Snrpn* after culture of mouse embryos from the 2-cell to the blastocyst stage, concluding that Whitten's medium caused a demethylation of the paternal allele and biallellic expression of *H19* while KSOM medium did not affect the normal methylation and expression of *H19,* for both media *Snrpn* was unaffected [31]. Khosla et al. showed that the supplementation of culture medium with fetal bovine serum altered the expression and methylation of three imprinted genes involved in the growth and development of the embryo and placenta (*H19*, *Igf2* and *Grb10*), leading to aberrant development [32]. Fortier et al. reported a loss of methylation and biallelic expression of *H19*, increased expression of *Igf2,* loss of imprinting in *Snrpn* and no changes in the expression or methylation pattern of *Kcnq1ot1* in placenta following superovulation with or without embryo transfer. These results suggest that superovulation affects both maternal and paternal alleles with compromised oocyte quality and interference of imprinting maintenance during preimplantation development [32]. De Waal et al. showed that superovulation, oxygen level during embryo culture, and IVF could induce morphological and epigenetic alterations in the placenta by disturbing the DNA methylation of the ICR of the *H19/Igf2*, *Snrpn*, *Peg3* and *Kcnq1ot1* loci [33,34]. Taken together, work to optimize ART procedures may decrease adverse outcomes, by minimizing the occurrence of placental abnormalities and epigenetic aberrations.

6. Conclusions

The placenta is a complex organ that regulates nutrient exchange between the developing embryo and its mother. Its functions are determined, in part, by epigenetic reprograming events that will not only regulate gene expression during development but also may be involved in the pathogenesis of some syndromes. Because the placenta is a sensitive organ that plays an important role in maternal-fetal interactions, dysregulation by ART may impact fetal growth and development. ART procedures can affect the placenta by altering methylation patterns of imprinted genes, consequently affecting their expression, likely because some of the procedures take place during gametogenesis and embryonic reprogramming. The use of animal models has shown the direct relationship between ART procedures and imprinting disorders. The use of imprinted genes as biomarkers for placental alteration may facilitate screening and prediction for future health outcomes in the ART-conceived children.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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