ISSN 1062-3604, Russian Journal of Developmental Biology, 2020, Vol. 51, No. 6, pp. 356–376. © Pleiades Publishing, Inc., 2020.
Russian Text © The Author(s), 2020, published in Ontogenez, 2020, Vol. 51, No. 6, pp. 417–439.

REVIEWS

The Effect of Embryo Culture on Ontogenesis of Mammalian Offspring

S. V. Ranneva[a, b], E. Yu. Brusentsev[a], T. N. Igonina[a], D. S. Ragaeva[a], I. N. Rozhkova[a], N. I. Ershov[a], A. L. Levinson[c], and S. Ya. Amstislavsky[a, b, *]

[a] *Institute of Cytology and Genetics, Siberian Branch, Russian Academy of Sciences, Novosibirsk, 630090 Russia*
[b] *Novosibirsk National Research State University, Novosibirsk, 630090 Russia*
[c] *Novosibirsk Center of Reproductive Medicine, Novosibirsk, 630037 Russia*
**e-mail: amstis@yandex.ru*

Received February 25, 2020; revised June 16, 2020; accepted June 19, 2020

Abstract—A review of data about the impact of assisted reproductive technologies, mainly in vitro culture of preimplantation embryos, on pre- and postnatal development is presented. Specificities of the influence of nutrient media on the development of the embryo and the formation of fetuses are considered. Special attention is paid to the long-term effects in offspring that is born after the application of these procedures.

Keywords: assisted reproductive technologies, in vitro culture, preimplantation embryo, fetus, ontogenesis, epigenetics, long-term effects

DOI: 10.1134/S1062360420060077

INTRODUCTION

Assisted reproductive technologies (ART) have been used in medicine to overcome infertility for more than 40 years (Steptoe and Edwards, 1978; Berntsen et al., 2019). According to the international glossary, the term "ART" refers to any in vitro manipulation with human oocytes, spermatozoa, or embryos for reproduction, including the cultivation of embryos in vitro (Zegers-Hochschild et al., 2017). The fundamental processes of genome epigenetic reprogramming, which occur at the stage of gamete maturation and early embryonic development of mammals, coincide with some stages of ART, in particular, with the cultivation of embryos in artificial media (Reik et al., 2001). Meanwhile, the nutrient media in which mammalian embryos develop in vitro differ in qualitative and quantitative composition from the intrauterine environment of the oviducts and uterus, in which early prenatal development occurs in vivo (Summers and Biggers, 2003; Aguilar and Reyley, 2005). In addition, embryos in in vitro culture lack signaling molecules (hormones, cytokines, growth factors) from the reproductive tract (Makieva et al., 2018). This can be solved by adding appropriate components, including the liquid medium of the oviduct and uterus, to the culture medium, as well as by coculturing embryos with autologous endometrial cells (Canovas et al., 2017; Le Saint et al., 2019). However, during cultivation, embryos are exposed to various factors, such as pH fluctuations, high oxygen concentration, changes in osmolality, etc. (Sunde, 2019). These factors can lead to violations of natural reprogramming processes, specifically the absence of demethylation, or, on the contrary, aberrant methylation of loci that are not normally methylated, and phenotypic abnormalities, in particular, an increased risk of diseases associated with genomic imprinting disorders in offspring (Mani et al., 2020).

Currently, data about the health of children born after the use of ART are being collected (Berntsen et al., 2019; Ramos-Ibeas et al., 2019; Sunde, 2019). Children that are conceived using ART are more likely to be born prematurely, and they are also more likely to have a reduced birth body weight (Hayashi et al., 2012). However, at present, there is no clear answer to the question as to whether this is an effect of the application of ART or a consequence of infertility and the age of the parents (Hayashi et al., 2012; Sunkara et al., 2019). Therefore, the study of the influence of in vitro culture and other stages of ART on the ontogenesis and phenotypic characteristics of offspring in the postnatal period is extremely important. The first chapter of our review is devoted to the historical aspects of the development of media for the cultivation of human and animal embryos as well as the current state of this problem. In the following chapters, we focused on the impact of certain stages of ART associated with in vitro fertilization (IVF) and embryo culture on the pre- and postnatal development of the mammalian organism. Considering more complex protocols, including cryopreservation of gametes and embryos, as well as preimplantation genetic diagnostics, is beyond the scope of this review.

OPTIMIZATION OF CULTURAL SYSTEMS

The liquid content of mammalian oviducts and the uterus provides the necessary conditions for oocytes, sperm movement, fertilization, and early development of embryos (Aguilar and Reyley, 2005; Aviles et al., 2010). The natural nutrient medium of the female genital tract contains many different compounds that come into it through the blood or are synthesized by epithelial cells of the reproductive tract (Leese, 1988). Important components of the natural medium of the oviducts and uterus are K^+, Na^+, Ca^{2+}, Mg^{2+}, Cl^-, energy substrates (lactate, pyruvate, glucose), a variety of amino acids, proteins, prostaglandins, and steroid hormones and growth factors, such as insulin-like growth factor of the first type IGF-1, epidermal growth factor EGF, granulocyte-macrophage colony-stimulating factor GM-CSF (Aguilar and Reyley, 2005). The list of embryotropic factors that are secreted by epithelial cells of the reproductive tract is still not precisely defined and is growing every year (Aviles et al., 2010). To ensure the development of preimplantation embryos in vitro, it is important to use solutions with correctly selected components in optimal concentrations as well as the most acceptable gas composition of the atmosphere in which this process is carried out.

Development of Culture Media for in vitro Cultivation of Mammalian Preimplantation Embryos

When creating nutrient media, researchers use two main approaches: "back-to-nature," when trying to make the composition of components and their concentrations as close as possible to those of the reproductive pathways, and "let embryo choose," when their composition is selected empirically (Summers and Biggers, 2003; Brusentsev et al., 2014). Currently, the most popular media for in vitro cultivation of preimplantation embryos of laboratory animals are: KSOM, KSOMaa, HECM, mR1ECM, G1/2, SOF, CZB (Summers and Biggers, 2003; Brusentsev et al., 2014; Finger et al., 2015; Belli et al., 2019). The composition of these nutrient media is shown in Table 1. The nutrient media that were very popular in the cultivation of laboratory animal embryos in the past, in particular, the M16 medium that was developed in 1971, are currently rather of historical interest (Summers and Biggers, 2003) and are not included in the table. Some of the culture media presented in Table 1 consists of a minimal number of necessary substances selected according to the "let embryo choose" principle, such as KSOM (K+ simplex optimized medium), which contains 11 ingredients (the number of ingredients is 12 with the addition of serum albumin). Despite the small number of components, this medium is balanced in their concentrations and is optimally suited for the development of early mouse embryos (Summers and Biggers, 2003; Brusentsev et al., 2014). However, for other mammalian species, more component-rich versions of this medium, in particular, KSOMaa, which has 32 components because of the addition of amino acids, are often used (Biggers et al., 2000; Summers, 2014; Belli et al., 2019).

In some animal embryo culture media, 5–15% of bovine (cattle) or other mammalian serum is added (Han and Niwa, 2003; Amstislavsky et al., 2018). Also, to optimize the medium, reproductive fluids (follicular, from oviduct, or uterus) could sometimes be added. For example, in an experiment on the cultivation of early pig embryos, the addition of these components not only improves the quality of developing blastocysts but also corrects epigenetic changes caused by the application of ART (Canovas et al., 2017). Another approach to optimize the nutrient medium is to add osmolites, such as serum albumin (Summers and Biggers, 2003; Brusentsev et al., 2014; Brusentsev et al., 2018) or its synthetic analogs, in particular, polyvinyl alcohol PVA (Cozzi et al., 2010; Brusentsev et al., 2014). Free amino acids are used as a resource for plastic metabolism (Cozzi et al., 2010).

Overcoming the Two-Cell Block of Development of Rodent Preimplantation Embryos

For a long time, a two-cell block of development was a problem for the cultivation of early, from the zygote stage, rodent (mice, hamsters, rats) embryos (Schini and Bavister, 1988; Lawitts and Biggers, 1991; Miyoshi et al., 1994). Numerous attempts to overcome the block included modifying the composition of the media by changing the concentrations of some basic components—NaCl, KCl, $NaHCO_3$, KH_2PO_4, pyruvate, glucose—as well as adding additional components, such as ethylenediaminetetraacetic acid (EDTA) and glutamine (Chatot et al., 1990). Using the simplex method, which allowed optimizing the concentration of components of the culture medium, John Biggers and his colleagues created the simplex optimized medium, SOM (Lawitts and Biggers, 1991; Summers, 2014). Cultivation in this medium allowed for not only overcoming the two-cell block of mouse embryo development but also obtaining a high percentage of blastocysts (Lawitts and Biggers, 1991). Subsequently, the SOM medium was modified and given the name KSOM, that is, the SOM medium enriched with potassium (Lawitts and Biggers, 1993). Researchers have shown successful development of mouse embryos up to the blastocyst stage in a modified mKSOM medium enriched with glucose (Biggers and McGinnis, 2001). It was also found that the presence of phosphates in the KSOM medium in the case of mouse embryos causes a block in the development of only a small group of zygotes that are sensitive to this component (Biggers and McGinnis, 2001).

Meanwhile, the negative effect of the presence of phosphates in the culture medium on the development of hamster (Schini And Bavister, 1988) and rat (Miyoshi et al., 1994) embryos was shown. Hamster

Table 1. Composition of some synthetic culture media most commonly used for in vitro cultivation of preimplantation embryos of laboratory animals

Components	Name of the nutrient medium (concentration of components mM excluding footnotes)									
	KSOM[3]	KSOMaa[4,6]	$KSOM_g$aa[5]	HECM[2]	mR1ECM[7]	G1.2/2.2[4]		SOF[1]	SOFaa[6]	CZB[4]
NaCl	95.0	95.0	95.0	98.0	110.0	90.1	90.1	107.7	107.7	81.3
KCl	2.5	2.5	2.5	3.2	3.2	5.5	5.5	7.2	7.2	4.7
$CaCl_2$	1.7	1.7	1.7	2.0	2.0	1.8	1.8	1.7	1.2	1.7
$MgCl_2$	–	–	–	0.5	0.5	–	–	0.5	0.5	–
$MgSO_4$	0.2	0.2	0.2	–	–	1.0	1.0	–	–	1.2
$NaHCO_3$	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.1	25.1	25.0
KH_2PO_4	0.4	0.4	0.4	–	–	–	–	1.2	1.2	1.2
NaH_2PO_4	–	–	–	–	–	0.3	0.3	–	–	–
Sodium lactate	10.0	10.0	10.0	10.0	10.0	10.5	5.9	3.3	3.3	31.3
Sodium pyruvate	0.2	0.2	0.2	0.5	0.5	0.3	0.1	0.3	0.4	0.3
Glucose	0.2	0.2	5.56	–	7.5	0.5	3.2	1.5	–	–
Glutamine	1.0	1.0	1.0	1.0	0.1	0.5	–	–	–	1.0
Taurine	–	–	–	7.0	–	–	–	–	–	–
EDTA	0.01	0.01	0.01	–	–	0.01	–	–	–	0.1
Inositol	–	–	–	–	–	–	0.01	–	–	–
Nicotinamide	–	–	–	–	–	–	0.08	–	–	–
Pantothenate	–	–	–	–	–	–	0.004	–	–	–
Pyridoxine	–	–	–	–	–	–	0.005	–	–	–
Riboflavin	–	–	–	–	–	–	0.0003	–	–	–
Thiamine	–	–	–	–	–	–	0.003	–	–	–
Folic acid	–	–	–	–	–	–	0.002	–	–	–
Choline chloride	–	–	–	–	–	–	0.007	–	–	–
SA[a]	1.0*	3.0*	1.0*	–	4.0*	2.0*	2.0*	32*	8*	5.0*
PVA[b]	–	–	–	1.0*	–	–	–	–	–	–
NEAA[c]	–	1.0#	1.0#	2.0#	2.0#	2.0#	2.0#	–	2.0#	–
EAA[d]	–	0.5#	0.5#	1.0#	1.0#	1.0#	1.0#	–	1.0#	–

[a] Serum albumin, [b] polyvinyl alcohol, [c] nonessential amino acids, [d] essential amino acids; * mg/mL, # % (v/v); [1] Tervit et al., 1972; [2] Schini and Bavister, 1988; [3] Lawitts and Biggers, 1993; [4] Gardner et al., 2004; [5] Biggers et al., 2005; [6] Sagirkaya et al., 2006; [7] Cozzi et al., 2010.

embryo culture medium (HECM), which is free of phosphates was designed for the cultivation of hamster embryos (Table 1). Ten modifications of this medium have been designed so far (Seshagiri and Vani, 2019). Based on HECM, a specialized rat one-cell embryo culture medium (R1ECM) was designed for the cultivation of rat embryos (Table 1). Embryos of some rat lines were successfully cultured using this medium (Miyoshi et al., 1994; Brusentsev et al., 2015). Meanwhile, a modification of the KSOM medium for the cultivation of rat embryos without any phosphates and with the addition of taurine, glycine, glutamate, and alanine (KSOM-R) was recently designed (Nakamura et al., 2016). It has been shown that rat embryos develop faster in the KSOM-R medium than in mR1ECM (Men et al., 2020).

Optimal Media for Cultivation of Preimplantation Embryos of Different Mammalian Species

To date, there is no universal culture medium on which embryos of preimplantation stages of all mammalian species can be cultured in vitro. Nevertheless, great progress has been made in optimizing culture media in the laboratory animal embryos' cultivation experiments (Summers and Biggers, 2003; Brusentsev et al., 2014; Summers, 2014). Currently, early embryos of mammals, such as mustelids (Amstislavsky et al., 2012), cats (Herrick et al., 2007; Amstislavsky et al., 2018; Brusentsev et al., 2018), canines (Lindeberg et al., 1993; Luvoni et al., 2006), cattle (Sugimura et al., 2012), etc., have been successfully cultivated. When cultivating mammalian embryos, it is necessary to take into

account their species specificity (Amstislavsky et al., 2012) since significant differences are observed in the in vitro development of embryos of even so closely related rodent species as mice (Summers and Biggers, 2003; Brusentsev et al., 2015), rats (Miyoshi et al., 1995; Han and Niwa, 2003; Brusentsev et al., 2015; Igonina et al., 2019), and hamsters (Schini and Bavister, 1988; Amstislavsky et al., 2015; Brusentsev et al., 2015). When selecting the concentrations of components of nutrient media, in particular, pyruvate, the species specifics are also taken into account. For example, pig embryos are rich in lipid granules, their needs differ from mouse embryos with a low content of intracellular lipids (Bradley and Swann, 2019).

Early embryos of mice (Belli et al., 2019), rats (Men et al., 2020), cattle (Nedambale et al., 2004), rabbits (Liu et al., 1996), sheep (Aghaz et al., 2016), pigs (Machaty et al., 1998), and camels (Yaqoob et al., 2017) have been effectively developed on KSOM (mKSOM, KSOMaa, and KSOM-R) media. HECM medium and HECM-based R1ECM medium have been used for the cultivation of developing murine (Brusentsev et al., 2015), hamster (Amstislavsky et al., 2015; Brusentsev et al., 2015; Seshagiri and Vani, 2019), rat (Miyashi et al., 1995; Iganina et al., 2019), and macaque (Zhau et al., 2006) embryos of early stages. Other "candidate media for universality," in which preimplantation embryos of various mammalian species can be successfully cultured in vitro, can be proposed, for example, G1/2, SOF, and CZB. The G1/2 or G1.2/2.2 medium is used for the cultivation of mouse (Finger et al., 2015), horse (Choi et al., 2003a), cattle (Lane et al., 2003), goat (Hosseini et al., 2015), and pig (Swain et al., 2001) embryos. Various modifications of the SOF medium (SOFaa, SOF1/2, etc.) are used for in vitro culture of embryos of cattle (Nedambale et al., 2004), sheep (Mara et al., 2014), goat (Hosseini et al., 2015), lama (Trasorras et al., 2014), dog (Rodrigues et al., 2004), and cat (Sanan-muang et al., 2011). Embryos of early stages of mouse (Chatot et al., 1990), horse (Choi et al., 2003b), goat (Izquierdo et al., 1999), pig (Pollard et al., 1995), and ferret (Li et al., 2001) develop on the CZB medium. However, no matter how balanced the artificial culture medium for in vitro cultivation of preimplantation embryos, it still remains suboptimal, in particular, because the development of embryos in vivo, as mentioned earlier, is affected by various hormones and growth factors (Aguilar and Reyley, 2005).

The inclusion of individual growth factors or a combination of them in the culture medium in vitro improves early embryonic development and increases the proportion of implantable embryos (Kawamura et al., 2012; Brusentsev et al., 2014). Several studies indicate an acceleration in the development of mammalian preimplantation embryos when growth factors such as IGF-1 (Kozhevnikova et al., 2017), EGF (Brusentsev et al., 2015), GM-CSF (Amstislavsky et al., 2015), etc., as well as a combination of several growth factors, are added (Kawamura et al., 2012). Human chorionic gonadotropin (HCG), beta-endorphin, insulin, and other hormones also have a stimulating effect on the development of mammalian embryos in vitro (Brusentsev et al., 2014; Dinopoulou et al., 2016).

Effect of Physical and Chemical Parameters of Cultivation on the Development of Mammalian Preimplantation Embryos in vitro

Conditions such as temperature, humidity, pH of the culture medium, and the composition of the gas mixture maintained in laboratory CO_2 incubators can significantly affect the development of embryos (Brusentsev et al., 2014). The main rule of the embryological laboratory is to maintain the stability of the environment where embryos are cultured in vitro: it is necessary to minimize the number of manipulations and observations of embryological material outside the CO_2 incubator to reduce stress for the cleaving embryos (Miller, 2014).

Temperature control, as well as humidity control in the CO_2 incubator, is most important for the culture system since developing embryos are very sensitive to temperature changes (Miller, 2014). At the moment, the most optimal temperature for maintaining the development of early embryos outside the body is considered to be approximately 37°C (Swain et al., 2016) and the most optimal humidity is approximately 90% (Higdon et al., 2008). It should also be taken into account that the temperature is unevenly distributed in each specific CO_2 incubator, and there are "cold" and "hot" zones where the temperature may differ (Miller, 2014).

The most important indicator for maintaining the development of preimplantation embryos outside the mother's body is the pH of the culture medium (Brusentsev et al., 2014). Components of culture media and the composition of the gas mixture incubator should, thus, be selected providing a pH in the range of 7.2–7.4 (Brusentsev et al., 2014). The main component of the nutrient medium which regulates this parameter is sodium bicarbonate, which is usually added to the medium at a concentration of 25 mM (Brusentsev et al., 2014). The incubator maintains the pH at the desired level due to its constant content of 5–7% CO2 (Higdon et al., 2008).

The optimal composition of the gas mixture has a great influence on the effectiveness of preimplantation embryo cultivation in vitro (Brusentsev et al., 2014). The gas composition in the incubator often contains 5% CO_2 and 95% air (Higdon et al., 2008). In vivo, mammalian embryos are in an environment where the oxygen content is 2.5 or more times lower than in the atmosphere (Fischer and Bavister, 1993; Menezo et al., 2013). It has been shown that a high O_2 content impairs the development of embryos, leads to an

increase in the frequency of mitochondrial disorders and high levels of reactive oxygen species and can also affect the processes of chromosome divergence (Menezo et al., 2013; Belli et al., 2019). In the experiment, it was shown that reducing the oxygen content in the gas mixture from 20 to 5% when culturing mouse embryos significantly improves their development (Belli et al., 2019). In addition, some evaporating organic compounds (styrene, formaldehyde, glutaraldehyde, toluene), as well as micro-organisms in the laboratory air, can have a negative impact on the process of embryo cultivation (Miller, 2014).

In vitro Cultivation of a Preimplantation Human Embryo

The results of studies obtained on various animal species are also taken into account when creating media for in vitro cultivation of human embryos (Brusentsev et al., 2014). Great progress has been made in optimizing culture media used in medicine (Youssef et al., 2015). The development of two-stage (sequential) media, as well as the transition to a single-stage protocol (single media) (Morbeck et al., 2014, 2017) are very important for human in vitro embryo culture. The composition of some branded nutrient media which are used today in reproductive medicine is shown in Table 2.

The two-step method was designed by researchers using the "back-to-nature" approach to maximize the approximation of cultivation conditions to the natural conditions of an environment with changing composition (Gardner, 1998; Gardner and Lane, 2014). In relation to in vitro cultivation of early human embryos, the following two stage culture media have been developed: (1) G1/2 from Vitrolife, Sweden; (2) QACM/QABM from CooperSurgical (SAGE), Denmark; (3) SICM/SIBM from Cook, United States; (4) IVC1/IVC3 from InVitroCare, United States; (5) ISM1/BA from CooperSurgical (Origio), Denmark (Morbeck et al., 2014). Later, using the "let embryo choose" approach, researchers developed single-stage culture media that are suitable for both early and later stages of development (Morbeck et al., 2017). These media include: (1) Global from CooperSurgical (LifeGlobal), Denmark; (2) CSC from FUJIFILM Irvine Scientific, Japan; (3) G-TL from Vitrolife, Sweden; (4) 1-Step from CooperSurgical (Origio), Denmark (Morbeck et al., 2017). Such media allow for less manipulation of embryos and, thus, minimize the likelihood of damages (Dieamant et al., 2017).

Similar to in vitro culture media for mammalian preimplantation embryos, the addition of certain hormones and growth factors to increase the effectiveness of ART is also used in clinics (Ziebe et al., 2013). Taking into account the complex cascade of molecular interactions between the endometrium and the embryo (Makieva et al., 2018), a different approach, namely cocultivation of embryos with autologous endothelial cells of the endometrium, was applied to optimize culture systems (Le Saint et al., 2019). In a recent clinical study, it was shown that this method of cultivation significantly increases the percentage of obtaining blastocysts of good quality compared to the traditional method (Le Saint et al., 2019). However, this approach is technically complex and expensive, which makes it difficult to implement in clinical practice.

SPECIFIC FEATURES OF MAMMALIAN PREIMPLANTATION EMBRYOS' DEVELOPMENT in vitro AND EFFECT ON SUBSEQUENT ONTOGENESIS

Five decades ago, at the very beginning of the history of embryo cultivation of laboratory animals, it was shown that the development of preimplantation mouse embryos in vitro is significantly slower than their development in vivo (Bowman and McLaren, 1970). However, it should be noted that such results were obtained under conditions that are not most favorable for cultivation: using nutrient solutions that were originally developed for growing somatic cells, not embryos, with unbalanced concentrations of components and in the absence of CO_2 incubators. In some studies, in particular, in the study of Schwarzer et al., it was found that in vitro mouse embryos developed even better than in vivo; an increase in the frequency of blastocyst formation and the implantation index were indicators of this improvement (Schwarzer et al., 2012). Also, the influence of the culture medium on the embryo transcriptome and the number of cells in blastocysts were studied in this work, and it was concluded that the procedure of embryo extraction with subsequent embryo transfer reduces the quality of embryos and changes their transcriptome (Schwarzer et al., 2012). It was previously shown that such routine manipulations with embryos lead to aberrant expression of certain imprinted genes in embryonic and extra-fetal tissues in the postimplantation period (Rivera et al., 2008). Interestingly, embryo pipetting activates stress-sensitive MAPK8/9 kinases that affect cell proliferation and are involved in the induction of apoptosis (Xie et al., 2007). Researchers suggest that epigenetic defects observed during embryo transfer may be the result of the activation of stress-sensitive MAP kinases (Rivera et al., 2008).

During in vitro cultivation, the accumulation of ammonium due to the decay of unstable L-glutamine affects embryo development (Biggers et al., 2004; Men et al., 2020). In modern versions of KSOM, more stable dipeptides, such as L-alanine-L-glutamine (AlaGln) and L-glycine-L-glutamine (GlyGln), are often used instead of L-glutamine to reduce the accumulation of ammonium) (Biggers et al., 2004). Interestingly, the percentage of developing blastocysts drops rapidly with this replacement (Gln $\rightarrow$ AlaGln/GlyGln) in case of rat embryos' culturing, in contrast to murine embryos culturing (Men et al., 2020). The authors

Table 2. Composition of some synthetic culture media most commonly used for in vitro cultivation of human preimplantation embryos

Components	Name of the nutrient medium (concentration of the components mM, with the exception of footnotes)													
	G1/2[1,3]		QACM/QABM[1]		SICM/SIBM[1]		IVC1/IVC3[1,3]		ISM1/BA[1]		Global[1,2]	CSC[1,2]	G-TL[2]	1-Step[2]
Calcium	1.1	1.1	2.2	2.2	1.1	1.1	2.1	1.9	1.8	1.4	1.6	1.9	1.0	2.1
Phosphorus	0.3	0.3	–	0.3	0.2	0.4	–	0.3	0.3	1.1	0.2	0.2	0.3	0.3
Potassium	5.8	5.8	4.7	4.9	4.8	5.0	4.6	4.9	8.4	5.3	2.8	2.8	5.5	2.9
Chlorine	124.0	127.0	118.0	113.0	122.0	121.0	107.0	108.0	116.0	114.0	108.0	112.0	106.0	112.0
Sodium	152.0	149.0	132.0	132.0	140.0	136.0	142.0	143.0	131.0	144.0	138.0	138.0	137.0	132.0
Magnesium	1.7	1.7	1.8	1.8	1.5	1.5	0.2	0.2	0.9	0.8	0.2	0.8	1.6	1.8
Ferrum	–	3.0**	1.0**	2.0**	11.0**	9.0**	5.0**	5.0**	9.0**	57.0**	–	4.0**	–	–
Selenium	–	–	–	–	3.0**	3.0**	–	–	4.0**	4.0**	–	–	–	–
Aluminum	1.0**	1.0**	18.0**	21.0**	1.0**	1.0**	2.0**	6.0**	5.0**	16.0**	1.0**	–	–	–
Chrome	0.1**	0.2**	0.2**	0.2**	0.3**	0.3**	0.7**	0.9**	0.2**	1.2**	0.4**	0.7**	–	–
Cobalt	0.3**	0.2**	0.2**	0.2**	0.3**	0.2**	0.2**	0.2**	0.5**	0.6**	0.1**	0.2**	–	–
Manganese	0.5**	0.6**	3.6**	3.6**	0.5**	0.5**	0.6**	0.6**	1.4**	0.8**	0.4**	0.8**	–	–
Glucose	0.5	3.4	0.1	2.8	0.3	3.1	–	2.7	1.0	1.0	0.2	0.5	1.0	0.2
Citrate	0.080	0.080	–	0.200	–	–	–	0.200	0.020	0.003	–	0.020	0.010	–
Octanate	–	–	–	–	–	–	–	–	–	–	0.7	0.3	0.3	0.4
Lactate	10.8	6.0	3.9	3.9	1.8	1.8	10.1	9.4	3.2	2.4	4.9	5.7	10.0	4.4
Pyruvate	0.3	0.1	0.5	0.1	0.4	0.3	0.1	0.1	2.0	0.2	0.2	0.3	0.6	0.2
Arginine	–	360.0#	–	313.0#	25.0#	252.0#	–	590.0#	138.0#	124.0#	278.0#	292.0#	324.0#	336.0#
Cysteine	–	54.0#	–	54.0#	2.0#	32.0#	–	9.0#	42.0#	38.0#	32.0#	34.0#	26.0#	28.0#
Histidine	–	121.0#	–	102.0#	8.0#	86.0#	–	188.0#	99.0#	54.0#	76.0#	80.0#	89.0#	90.0#

Table 2. (Contd.)

Components	Name of the nutrient medium (concentration of the components mM, with the exception of footnotes)													
	G1/2[1,3]		QACM/QABM[1]		SICM/SIBM[1]		IVC1/IVC3[1,3]		ISM1/BA[1]		Global[1,2]	CSC[1,2]	G-TL[2]	1-Step[2]
Isoleucine	–	249.0#	–	209.0#	17.0#	169.0#	–	388.0#	147.0#	208.0#	182.0#	199.0#	215.0#	204.0#
Leucine	–	265.0#	–	227.0#	18.0#	182.0#	–	408.0#	158.0#	217.0#	177.0#	188.0#	204.0#	206.0#
Lysine	–	260.0#	–	223.0#	18.0#	174.0#	–	417.0#	148.0#	179.0#	154.0#	168.0#	182.0#	182.0#
Methionine	–	63.0#	–	56.0#	4.0#	43.0#	–	100.0#	89.0#	54.0#	44.0#	50.0#	54.0#	54.0#
Phenylalanine	–	125.0#	–	106.0#	8.0#	86.0#	–	200.0#	90.0#	104.0#	79.0#	83.0#	91.0#	92.0#
Threonine	–	242.0#	–	210.0#	18.0#	172.0#	–	374.0#	81.0#	211.0#	162.0#	176.0#	184.0#	204.0#
Tryptophan	–	30.0#	–	28.0#	2.0#	22.0#	–	51.0#	100.0#	21.0#	18.0#	20.0#	21.0#	23.0#
Tyrosine	–	114.0#	–	100.0#	12.0#	114.0#	–	186.0#	70.0#	91.0#	69.0#	75.0#	80.0#	83.0#
Valine	–	256.0#	–	224.0#	17.0#	179.0#	–	428.0#	356.0#	225.0#	163.0#	174.0#	200.0#	196.0#
Alanine	148.0#	151.0#	–	–	135.0#	135.0#	–	136.0#	338.0#	124.0#	46.0#	48.0#	63.0#	38.0#
Asparagine	126.0#	129.0#	112.0#	124.0#	88.0#	84.0#	–	113.0#	73.0#	104.0#	42.0#	46.0#	40.0#	36.0#
Aspartate	–	–	93.0#	104.0#	81.0#	85.0#	–	95.0#	6.0#	578.0#	42.0#	43.0#	12.0#	58.0#
Glutamate	–	–	–	–	90.0#	87.0#	–	103.0#	1.0#	102.0#	40.0#	41.0#	–	49.0#
Glutamine	–	–	–	–	30.0#	26.0#	–	–	778.0#	–	–	–	10.0#	36.0#
Glycine	135.0#	141.0#	119.0#	131.0#	6647.0#	4815.0#	–	121.0#	1760.0#	701.0#	42.0#	44.0#	185.0#	48.0#
Proline	112.0#	113.0#	93.0#	103.0#	85.0#	80.0#	–	99.0#	82.0#	96.0#	55.0#	60.0#	126.0#	66.0#
Serine	127.0#	130.0#	107.0#	123.0#	92.0#	89.0#	–	109.0#	96.0#	113.0#	40.0#	42.0#	96.0#	46.0#
Taurine	131.0#	–	122.0#	120.0#	6489.0#	6380.0#	–	–	296.0#	–	–	–	48.0#	–
SA[a]	4.0*	4.0*	5.0*	5.0*	5.0*	5.0*	4.0*	1.0*	5.0*	5.0*	10.0*	5.0*	5.0*	5.0*

[a] Serum albumin, * mg/L, ** μg/L, # μM; [1] Morbeck et al., 2014; [2] Morbeck et al., 2017; [3] Tarahomi et al., 2019.

explain these negative effects by the incorrectly selected concentration of dipeptides, which is suitable only for murine embryos, and the possible inability of rat embryos to effectively utilize these substances due to the low affinity of their dipeptidases (Men et al., 2020). For the case of rat embryo culture, other ways to avoid the accumulation of ammonium are proposed, such as replacing the culture medium with a new one every 24 h (Nakamura et al., 2016), or increasing its volume (Men et al., 2020).

Conditions of in vitro culture of mammalian embryos affect the velocity of their development, which is manifested in changes in the number of cells in blastocysts, as well as disturbances of gene expression and fetal development (Mani and Manigi, 2018; Ramos-Ibeas et al., 2019). The effect of cultivation on the epigenome, as well as on postimplantation development of the fetus, is described in more detail in the following subsections. Thus, the expression of a large number of cytokines supporting the development of early embryos is shown in the human endometrium (Kawamura et al., 2012). Recent data suggest that in vitro cultivation of preimplantation embryos is accompanied by changes in the expression of certain genes (Sunde, 2019).

Effect of in vitro Culture on Changes in Gene Expression in Preimplantation Embryos of Laboratory Animals

To date, data from the researches on embryos of various mammalian species indicate significant changes in the gene-expression pattern because of the usage of ART (de Waal et al., 2014). However, most studies have examined the cumulative effect of ART on the phenotype and gene expression but not on the individual stages (de Waal et al., 2014; Feuer et al., 2016). Also, studies on mice have shown a significant effect of interline differences on the results of embryo cultivation (de Waal et al., 2014).

In the paper on the influence of various stages of in vitro procedures on the state of the transcriptome of blastocysts and adult descendants, it was shown that it is the conditions of cultivation and, first of all, the concentration of oxygen that provoke the greatest deviations in gene expression in mouse blastocysts (Feuer et al., 2016). At the same time, each combination of the studied procedures is characterized by its unique expression profile associated with different signaling and metabolic pathways (Feuer et al., 2016).

The greatest attention of researchers is focused on the effects of ART on epigenetic regulation of gene expression and, in particular, on violations of genomic imprinting during early embryo development (Market-Velker et al., 2010). In the context of the culture medium composition as a factor of cultivation, the study on mice, in which five commercial culture media (KSOMaa, Global, HTF, P1/MB, and G1.5/G2) are compared in parallel to the poorest Whitten's media and in vivo conditions, can be considered as one of the most significant studies (Market-Velker et al., 2010). Analysis of methylation and expression of three imprinted loci, *H19*, *Peg3*, and *Snrpn*, when embryos were cultured to the blastocyst stage showed that both paternal (*H19*) and maternal (*Peg3* and *Snrpn*) imprinting occurs in cases of all six media, although to different degrees, which allowed us to rank the media by proximity to in vivo conditions (Market-Velker et al., 2010).

Large-scale changes in the embryo's DNA methylation and gene expression profiles as a result of cultivation were shown using full-genomic methods. Thus, using RNA-seq and PBAT-seq, it was shown that pig embryo culturing in comparison with in vivo conditions leads to changes in methylation patterns and gene expression associated with reprogramming, imprinting, and cell development (Canovas et al., 2017). Moreover, an addition of the contents of the reproductive pathways to the culture system resulted in less-pronounced deviations in gene expression and epigenome at the blastocyst stage, which is due, in particular, to the prevention of demethylation of the *IGF2R* locus directly associated with large offspring syndrome (Canovas et al., 2017).

In a mouse model, the combined effect of in vitro fertilization and embryo culture on transcriptome and epigenome of extraembryonic and placental tissues was investigated using RNA-seq and MeDIP-seq, and 409 genes were identified whose expression was altered according to hypo- or hypermethylation of their promoters in response to in vitro procedures (Tan et al., 2016). The identified genes are functionally related to the formation of the cytoskeleton, the development of blood vessels and organs, and the metabolism of the entire body. It was also shown that the degree of genome hypomethylation in cattle embryos is more pronounced with the increase of the duration of in vitro culture (Salilew-Wondim et al., 2015).

Effect of in vitro Culture on Changes in the Gene Expression Profile and Epigenome of Human Embryos

A significant influence of the culture medium composition on the gene expression profile was also shown on human embryos (Kleijkers et al., 2015). In particular, it was found that the cultivation of early human embryos in a fairly simple HTF medium compared to the rich multicomponent Vitrolife G5 Plus medium leads to significant changes in the expression of 951 genes at the blastocyst stage, most of which are associated with apoptosis, protein degradation, metabolism, and cell cycle control, which, in particular, leads to a twofold decrease in the frequency of successful implantation (Kleijkers et al., 2015). It is obvious that the stage of development of the embryo and the age of the donor play a significant role in the observed changes in the transcriptome when comparing the above-mentioned culture media (Mantikou

et al., 2016). However, this result was quite expected, since the HTF medium is designated for maturation of oocytes and for fertilization. The comparison of the influence of media that are designed for embryo culture from the zygote stage to the moment of embryo transfer to the uterus on the transcriptome of blastocysts of the same class could be much more interesting; however, due to ethical regulations, such studies are difficult to conduct. Morbeck et al. conducted detailed studies of the composition of CSC, Global, G-TL, and 1-Step culture media used in reproductive medicine (Morbeck et al., 2017). These media have been shown to be significantly different in pyruvate, lactate, and amino acid composition (Morbeck et al., 2017). Moreover, it was found that the composition of media, as well as the concentration of oxygen, significantly affects the percentage of blastocyst development (Morbeck et al., 2017).

It is worth noting that these studies emphasize the pronounced stochasticity of observed changes in the embryonic transcriptome and epigenome, which may also reflect the significant influence of other biological factors on the systems of regulation of gene expression in early embryos in addition to the conditions of their cultivation (Mani and Mainigi, 2018; Ramos-Ibeas et al., 2019). The influence of various culturing factors on the embryo epigenome is described in more detail in the corresponding review papers (Mani and Mainigi, 2018; Ramos-Ibeas et al., 2019).

Effect of in vitro Culture of Early Mammalian Embryos on Their Postimplantation Development

Conditions of fertilization and early preimplantation development of an embryo in vivo and in vitro are significantly different from each other (Summers and Biggers, 2003). Various components of culture media and other culturing factors can disrupt the formation of blastocysts, cause a decrease in the number of cells in the internal cell mass, and changes in gene expression that can subsequently affect the course of pregnancy (Ramos-Ibeas et al., 2019). In particular, after the IVF procedure followed by the cultivation of preimplantation mouse embryos on such culture media as KSOMaa and Whitten's, the frequency of miscarriages increases (Delle Piane et al., 2010). However, it was shown in another study that there was no increased frequency of miscarriages after culturing mouse embryos according to the 13 most common recent clinical protocols (Schwarzer et al., 2012). Moreover, some protocols showed a decrease in this rate (Schwarzer et al., 2012). Also, in different mammalian species, after the application of ART, including in vitro cultivation, fetal growth restriction is observed at the early stages of pregnancy; however, there is a significant increase in placenta size and acceleration of fetal development at its later stages (Delle Piane et al., 2010; Bloise et al., 2012, 2014). This compensatory increase in placental size in response to intrauterine growth retardation in fetuses after the ART application probably provides additional support to the fetus (Bloise et al., 2014).

Contradicting data were obtained about the effect of ART, and, particular, in vitro culture, on changes in the level of apoptosis in the placenta when culturing murine embryos (Raunig et al., 2011; Bloise et al., 2012). Some researchers showed an increase in apoptosis after IVF procedures or intracytoplasmic sperm injection (ICSI) (Raunig et al., 2011), while others did not find such a change (Bloise et al., 2012). The association of ART with changes in the placental transcriptome in mice (Delle Pianne et al., 2010; Fauque et al., 2010), as well as a decrease in blood vessel density in cattle (Miles et al., 2005), was also shown. Based on the above, it can be concluded that the effects of ART, in particular during in vitro culture, on the preimplantation embryo, have an impact on the further prenatal development of the fetus and, as other studies show, may have long-term consequences in postnatal ontogenesis in animals (Duranthon and Chavatte-Palmer, 2018; Sunde, 2019).

Effect of in vitro Culture of Human Embryos on Their Postimplantation Development

The effect of ART on postimplantation development was also shown for humans, with deviations similar to those found in animals, in particular, there was intrauterine fetal growth retardation, a compensatory increase in placental size, and the likelihood of microcalcinations in some cases (Joy et al., 2012; Haavaldsen et al., 2012; Nelissen et al., 2013). However, the frequency of spontaneous abortions with ART generally remained the same as after natural conception, although data, including concomitant factors of maternal age, etc., are not sufficient to make a clear conclusion (Bloise et al., 2014). Newborns conceived using ART are more likely to be born prematurely and have a low birth body weight compared to those conceived naturally (Pandey et al., 2012; Wennerholm et al., 2020). Perinatal mortality and congenital abnormalities are also significantly more common in such cases than in spontaneous pregnancy (Pandey et al., 2012).

Several papers are devoted to comparing the effect of different embryo culture protocols currently used in the clinic on intrauterine development and perinatal outcomes (Zandstra et al., 2015). However, only five of 11 papers on this topic showed that media of different manufacturers can affect a child's body weight at birth, and six showed no effect (Zandstra et al., 2015).

Thus, the qualitative and quantitative composition of the culture medium intended for in vitro cultivation of embryos of different mammalian species, including humans, as well as other conditions, such as partial oxygen pressure, can influence the effectiveness of preimplantation embryo development. Researches in this area are still relevant and need to be continued.

EFFECT OF ART ON POSTNATAL DEVELOPMENT OF MAMMALIAN OFFSPRING

According to the hypothesis of "Developmental Origins of Health and Disease," certain disorders in adult organisms depend on the conditions of their prenatal development, in particular, on the mother's nutrition and, consequently, the embryo during pregnancy (Barker, 2007). The current understanding of this hypothesis also concerns periods of preimplantation development and implantation (Fleming et al., 2015). In this regard, the nutrient medium used for in vitro fertilization and cultivation can have a very significant impact on embryos' early development (Sunde et al., 2019).

Animal studies show that the metabolism of adults depends on the conditions of the preimplantation stage of their development. IVF and in vitro cultivation of early embryos can lead to the transformation of the pathways of the growth and development of the organism, and disruption of murine lipid and carbohydrate metabolism at the later stages of ontogenesis (Bloise, 2014; Duranthon and Chavatte-Palmer, 2018). Thus, small changes in the ratio of pyruvate to lactate in the culture medium affect mitochondrial activity in zygotes and have long-term effects on the birth weight of offspring and further postnatal growth in mice (Banrezes et al., 2011). According to the results of another study, culturing murine embryos in a suboptimal Whitten's medium with 20% oxygen content in the gas mixture resulted in increased postnatal growth in males, reduced glucose tolerance, and an enlarged left ventricle of the heart, whereas no changes were observed in offspring under optimal culture conditions (KSOMaa and 5% O_2) (Donjacour et al., 2014). At the same time, there is evidence that the application of both suboptimal Whitten's medium and optimal KSOMaa medium for murine embryo culture resulted in changes in the postnatal growth pathways, fat accumulation, increased hyperglycemia, and impaired pancreatic function in adults (Feuer et al., 2014). Also, IVF and ICSI procedures with murine embryos in CZB medium lead to carbohydrate metabolism disorders; the offspring had a higher birth weight and decreased glucose tolerance as well as increased insulin resistance (Scott et al., 2010). The results about birth weight obtained in this study contradict the results of some studies on humans, in which it was shown that children conceived using ART have a lower birth weight than children after natural conception (Wennerholm and Bergh, 2020). This contradiction can be explained by the fact that, unlike the situation in humans, the size of murine litter mice can significantly decrease after ART, and, because of this, the fetuses receive more nutrients; also, young and healthy females are used for experiments to carry pregnancies, while people with reproductive problems are patients of the ART clinics.

IVF and embryo culture in vitro can cause some changes in the development and functioning of the cardiovascular system. In vitro culture of mouse embryos, starting from the two-cell stage, led to increased blood pressure associated with increased activity of the angiotensin-converting enzyme in the blood serum of 27-week-old females (Watkins et al., 2007). In another study, endothelial dysfunction and elevated arterial blood pressure (BP) in male mice were obtained after the use of ART and it was accompanied by changes in the methylation of the promoter of the gene encoding eNOS in the aorta, and it was correlated with reduced expression of eNOS in blood vessels and reduced synthesis of NO (Rexhaj et al., 2013). However, the use of Whitten's suboptimal medium resulted in a decrease in systolic pressure in male mice (Donjacour et al., 2014). It was shown that in vitro cultivation of preimplantation embryos of hypertensive rats of the ISIAH line in the mR1ECM medium led to the mitigation of arterial hypertension parameters of animals of this line (Igonina et al., 2019). These divergences in results may be related to differences in experimental design, blood pressure measurement methods, and genetic characteristics of laboratory animals.

Also, various behavioral abnormalities in postnatal ontogenesis are found in mice born after the use of ART methods (Ecker et al., 2004; Fernandez-Gonzalez et al., 2004). When in vivo fertilized embryos were incubated in KSOM with the addition of 10% fetal serum, the delay in incisor eruption and maturation of motor activity of offspring in the early postnatal period of development, as well as deterioration of long-term memory at the age of 21 days, reduced anxiety at 5 months of age and was followed by its increase at the age of 15 months (Fernandez-Gonzalez et al., 2004). Adult mice born after in vivo fertilization and cultivation in KSOM and Whitten's media showed reduced anxiety, decreased spatial memory, and increased locomotor activity at the age of 4–5 months (Ecker et al., 2004). However, offspring obtained after using HTF medium to culture mouse embryos to the blastocyst stage did not demonstrate any changes in learning ability (Li et al., 2011).

Thus, studies on laboratory models make it possible to evaluate the effects of ART procedures on long-term health and postnatal phenotype. However, it is important to note that the effects of the culture medium on laboratory animals may vary depending on the genetic model chosen for the study, the age at which the effects are studied, and the sex of the offspring.

IMPACT OF ART ON POSTNATAL HUMAN DEVELOPMENT

Treatment of infertility in humans using ART methods includes the following main stages: ovarian stimulation, obtaining oocytes and spermatozoa,

IVF/ICSI, embryo culture in vitro, and embryo transfer. All these procedures can potentially affect the developing embryo and, consequently, the future health of the child. Also, these methods work in a complex, which must be taken into account when interpreting the effects of individual stages of ART. Infertility and related diseases of the parents (Jaques et al., 2010; Hayashi et al., 2012), maternal age (Kahveci et al., 2018; Pinheiro et al., 2019), and hormonal stimulation of the ovaries (Klemetti et al., 2010; Labarta et al., 2014) may have additional effects on the offspring's health. The question of the interaction of all these factors and their relation to negative effects on children's health is still open.

It should also be noted that there is still no universal "standard protocol" for IVF and in vitro culture of preimplantation embryos in reproductive medicine. Different laboratories around the world use different culture media for performing ART procedures (Sunde, 2019). By analyzing the phenotype of children born after embryo culture in vitro in different commercial media, some researchers find a significant effect of this factor (Dumoulin et al., 2010; Kleijkers et al., 2015), while others find no differences (Ziebe et al., 2013). Contradictory results are due to the extreme complexity of interpreting clinical data; it is difficult to standardize the study conditions, in particular, because the quantitative composition of the components of most commercial media used in the clinic is not provided by the manufacturer (Tarahomi et al., 2019). However, there are studies illustrating significant differences in the compositions of some commercial media (Morbeck et al., 2017; Tarahomi et al., 2019).

Perinatal Characteristics

Researches on ART effects on humans focuses primarily on pregnancy and live birth rates. Children conceived using ART are slightly more likely to be born prematurely and have a low weight for gestational age as well as an increased risk of congenital malformations (D'Angelo et al., 2011; Pinborg et al., 2013; Sunkara et al., 2019). Initially, it was thought that this may be associated with multiple pregnancies, but these risks have also recently been confirmed compared to naturally conceived and single pregnancies (Pandey et al., 2012; Wennerholm and Bergh, 2020). The increased risks of adverse perinatal outcomes after the use of ART methods seem to be associated with multiple factors (Sunkara et al., 2019). Some studies indicate that adverse perinatal outcomes are associated with patient subfertility (Jaques et al., 2010; Hayashi et al., 2012) and parental age (Kahveci et al., 2018; Pinheiro et al., 2019). However, differences in perinatal outcomes between spontaneous and ART-assisted pregnancies are significant even after excluding the influence of these factors (Pinborg et al., 2013), which may indicate the contribution of manipulations during ART procedures.

In particular, ovarian stimulation, a necessary stage of ART, can affect negatively perinatal outcomes, even if it is used in women before natural conception (Klemetti et al., 2010; D'Angelo et al., 2011; Labarta et al., 2014). One of the approaches is to compare natural and ART-derived pregnancies in the same woman. Such studies show an increased risk of premature birth after application of ART compared to natural conception (Pinborg et al., 2013); therefore, factors related to hormonal stimulation and/or ART methods may also play an important role. A German-British group of scientists have conducted an interesting work that analyzed a group of women who gave birth to their first child after ICSI and the second child after applying this procedure or as a result of natural conception (Ludwig et al., 2008). There were no significant differences in the duration of pregnancy or in the weight of newborns in both groups (Ludwig et al., 2008). Another study by the same researchers showed an increase in the frequency of cryptorchidism in boys born after ICSI compared with naturally conceived ones (Ludwig et al., 2009a). However, no significant differences were found for other health indicators, including neurological abnormalities, motor skills, emotional development, and intelligence (Ludwig et al., 2009a, 2009b).

Epigenetic Impairments

The use of ART methods is associated with a potentially sensitive period of epigenetic reprogramming to environmental influences. Thus, the first wave of demethylation-remethylation occurs during gametogenesis and the second during preimplantation development (Zacchini et al., 2019). Analysis of the levels of methylation of certain genes in the placenta showed that differences in DNA methylation in children conceived naturally and using ART appeared regardless of the presence of parental infertility (Song et al., 2015). Epigenetic changes that are likely related to in vitro culture have also been observed in human gametes and embryos (El Hajj and Haaf, 2013). Gene expression in preimplantation embryos has been shown to vary depending on the culture medium used for IVF and subsequent in vitro culture (Kleijkers et al., 2015). However, another study concluded that the global gene expression profile in a human embryo is more influenced by factors such as the stage of embryo development and maternal age rather than the tested medium and culture conditions (Mantikou et al., 2016).

ART-associated changes in DNA methylation are found in the differentially methylated regions (DMR) that are imprinted during gametogenesis and embryonic development (Hiura et al., 2014). According to a meta-analysis by Lazaraviciute at al., genomic imprinting diseases, a group of rare congenital disorders, occur more frequently after IVF use (Lazaraviciute et al., 2014). It was found that ART application is

associated with a higher probability of developing diseases caused by genomic imprinting disorders, such as Beckwith-Wiedemann syndrome (BWS), Angelman, Prader–Willi, and Silver–Russell syndromes (Hattori et al., 2019). However, in clinical practice, this does not matter much. For example, BWS remains an extremely rare disease even with a tenfold increase in risk in children born after the use of ART (Mussa et al., 2017).

One of the factors associated with the disruption of genomic imprinting is male subfertility. A meta-analysis of 24 studies showed significant hypomethylation of the imprinted *H19* gene as well as hypermethylation of *SNRPN* and *MEST* in the spermatozoa of men with idiopathic infertility compared to fertile control (Santi et al., 2017). Another factor that may influence epigenetic reprogramming in oocytes is a hormonal induction of ovulation (Sato et al., 2007; Marshall and Rivera, 2018). However, human oocyte studies are limited due to a small amount of material and lack of suitable control, taking into account age and general impairments in oogenesis. Oocytes of ages GV and MI obtained from subfertile women as a result of hormonal ovarian stimulation have been shown to have increased methylation of the *H19* gene and loss of methylation in the *PEG1* gene (Sato et al., 2007). In addition, the influence of maternal age on the epigenome must be taken into account since late reproductive age is known to be associated with aberrant global DNA methylation in oocytes and embryos (Marshall and Rivera, 2018). A study by Hiura et al. found cellular mosaicism in the methylation levels in children with genomic imprinting diseases conceived using ART, suggesting that these changes occur during the first cell divisions during embryo culture in vitro (Hiura et al., 2014). Thus, it is still unknown when genomic imprinting errors occur and what factors predispose to epigenetic changes. However, there is a clear association between the use of ART and specific imprinting disorders.

Metabolic Syndrome

Prerequisites for the occurrence of cardiovascular abnormalities in humans conceived using ART, as well as diseases associated with metabolic disorders, have been noted since the DOHaD hypothesis was applied to the preimplantation period (Fleming et al., 2015, 2018). For more than 40 years, the state of the cardiovascular system has been studied in ART-derived people at different ages: in children, adolescents, and young adults (Ceelen et al., 2008; Scherrer et al., 2012; Guo et al., 2017; Meister et al., 2018; Halliday et al., 2019). In one of the first studies in children of prepubertal age (12 years), a small but significant increase in systolic arterial blood pressure (SAP) was found in children after ART (109 ± 11 mm Hg) compared to that in naturally conceived children (105 ± 10 mm Hg) and also of diastolic arterial blood pressure (DAP) in children born with ART (61 ± 7 mm Hg) compared to that in naturally conceived children (59 ± 7 mm Hg) (Ceelen et al., 2008). It is worth noting that a group of children born from subfertile parents was used as a control in this study, so, the influence of the parental factor of infertility was excluded (Ceelen et al., 2008). However, although blood pressure indicators were increased, they remained within the normal range for children of this age (Ceelen et al., 2008).

Guo et al. performed a meta-analysis of blood pressure data, including a group of 872 children conceived in IVF-ICSI procedures and 3034 children conceived naturally from ten clinical studies, and found a small but significant weighted average difference of 1.88 mmHg for systolic arterial blood pressure and 1.52 mmHg for diastolic arterial blood pressure (Guo et al., 2017). However, the rate of heterogeneity in the groups was quite high. Meanwhile, this indicator decreased significantly when the authors of the meta-analysis stratified the samples by year of birth. This revealed an interesting feature: children born in 1990–1999 had a significant increase in both SAP (3.75 mm Hg) and DAP (2.70 mm Hg) in contrast to the group of children born in 2000–2009 (0.186 mm Hg was a difference for SAP and 0.19 mm Hg was a difference for DAP). Further, the authors evaluated the contribution of factors of younger age and the predominant number of children conceived using ICSI in 2000–2009 but did not find their influence. The authors suggested that improvements in ART programs over time, including ovulation stimulation protocols and embryo culture conditions, contributed to the leveling of differences in blood pressure between groups (Guo et al., 2017).

This review also provides a meta-analysis of metabolic parameters, such as fasting insulin levels, glucose levels, and lipid profile, in children conceived using ART. Also, research data on the body mass index (BMI), which is one of the diagnostic criteria for metabolic syndrome, were combined and analyzed (Guo et al., 2017). A meta-analysis of seven studies showed that children conceived with IVF/ICSI ($n = 477$) had higher fasting insulin levels compared to naturally conceived children ($n = 185$) but did not change glucose levels or insulin resistance index (Guo et al., 2017). A meta-analysis of data from five studies showed that children born as a result of ART ($n = 332$) had statistically lower levels of low-density lipoproteins compared to children born as a result of natural fertilization ($n = 1701$), while the level of high-density lipoproteins did not differ between the groups. Thus, children after ART had a more favorable lipid profile (Guo et al., 2017). Data from 14 studies that reported BMI (the total number was 1914 children after IVF-ICSI and 3881 naturally conceived children) were combined and analyzed in the same review: it turned out that there was no difference in this indicator between the groups (Guo et al., 2017).

Interesting results were presented in a recent paper, the authors of which analyzed the levels of proprotein convertase subtilisin/Kexin type 9 (PCSK9), an important component of lipid homeostasis, in the blood plasma of children conceived using ART ($n = 73$) and naturally conceived ($n = 73$) (Vlachopoulos et al., 2019). PCSK9 levels have been shown to increase with age (within 2 years, from eight to ten) in children born after ART, while, they decrease, on the contrary, in naturally conceived children (Vlachopoulos et al., 2019). Increasing levels of PCSK9 lead to a gradual deterioration of the lipid profile in these children, which leads to an increased risk of cardiovascular diseases (Vlachopoulos et al., 2019). The results of this study highlight the role of lipid metabolism indicators as early indicators of hidden cardiometabolic disorders concerning the conception method (Vlachopoulos et al., 2019). However, it is worth noting that the number of analyzed cases was small, and the contribution of additional factors was not taken into account. To make a clear conclusion, further studies with a large sample size are needed.

In addition to blood pressure indicators, researchers studied structural and functional features of the cardiovascular system in children conceived using ART (Scherrer et al., 2012; Valenzuela-Alcazar et al., 2013; Von Arx et al., 2015). One of these studies shows signs of both systemic and pulmonary endothelial dysfunction during the prepubertal period (Scherrer et al., 2012). It was later shown that changes affect not only blood pressure and vascular function but also the structure of the heart (Valenzuela-Alcazar et al., 2013; Von Arx et al., 2015). Signs of heart and vascular remodeling were found in fetuses and infants conceived using ART (Valenzuela-Alcazar et al., 2013). It is known that fetal heart remodeling is associated with intrauterine growth retardation and, consequently, low fetal body weight, nevertheless, differences between groups in this study were significant even after excluding children with low birth weight from the study (Valenzuela-Alcazar et al., 2013). Thus, the authors suggested that the differences were directly related to the use of ART rather than perinatal factors (Valenzuela-Alcazar et al., 2013). Recently, the same group of researchers showed that the detected differences persist until the age of 3 years (Valenzuela-Alcazar et al., 2019).

However, the question of differences at later life stages is still debatable: some researchers report about left ventricular dysfunction in 4–5-year-old children (Zhou et al., 2014; Liu et al., 2015), while others have found right ventricular dysfunction in 12-year-old children, which is manifested only in stressful conditions (Von Arx et al., 2015). In a recent study, adolescent children with an average age of 16.5 years were tested for signs of endothelial dysfunction and blood pressure monitoring (Meister et al., 2018). It is worth noting that this work examined the same cohort of children as in the previous study using the same methods; the samples were aligned by birth weight and gestational age, none of the mothers of children from these samples had pregnancy complications that could contribute to deviation from the normal parameters of the cardiovascular system (Scherrer et al., 2012). It turned out that the signs of systemic endothelial dysfunction in children remained approximately the same after 5 years (Meister et al., 2018). Moreover, eight of 52 children in the ART group already met the criteria for first-degree arterial hypertension (blood pressure > 130/80 mm Hg) at this age. It should be noted that this study excluded premature babies and those with low birth weight. However, the limitations in this work were the relatively small sample size (54 people in the ART group and 40 in the control group) as well as the fact that all children were patients of the same clinic (Meister et al., 2018). In contrast to this study, young people (22–35 years old) in Australia in the ART group (193 people) and the control group (86 people) did not show any abnormalities in the parameters of the cardiovascular system (Halliday et al., 2019).

Because the samples in clinical studies are heterogeneous due to the influence of a huge number of factors, the contribution of which is often impossible to take into account in the human population, it is difficult to estimate the impact of ART at this stage and, even more, at the stage of embryo cultivation. However, we should pay more attention to the state of health and monitor the state of the cardiovascular system in people conceived using ART. Many of the identified signs, although they are within the normal range for these ages, are predictive criteria for diseases in the future. The mechanisms underlying such deviations are still unclear, but we can assume that one of the reasons may be specific changes in gene expression patterns in blood pressure regulation systems if we take into account research on laboratory models (Wang et al., 2018).

Thus, data on the health status of children born after a standard set of ART procedures, usually consisting of IVF or ICSI, followed by in vitro culture and embryo transfer have currently been accumulated. Some children were found to have ART-associated abnormalities in the cardiovascular, nervous, and other systems of the body; they have higher systolic and diastolic blood pressure, glucose levels (Ceelen et al., 2008), and insulin levels in the blood (Guo et al., 2017), decreased peripheral insulin sensitivity (Chen et al., 2014), and a higher risk factor for diabetes (Kettner et al., 2016). They also may experience changes in cognitive abilities and intelligence (Sandin et al., 2013; Liu et al., 2017).

Central Nervous System Disorders

Although many studies have tried to establish a causal relationship between the usage of ART and the occurrence of neurological disorders in children (Klemetti et al., 2006; Maimburg and Vaeth, 2007; Kallen et al., 2010; Sandin et al., 2013; Liu et al., 2017), only a few of these studies have found arguments for its existence. In particular, contradictive results were

obtained when trying to find the relationship between the usage of ART and the incidence of cerebral palsy (Klemetti et al., 2006; Kallen et al., 2010). One study showed an increased risk of this pathology after IVF use (Klemetti et al., 2006), but another study found no statistically significant effect of this factor among single pregnancies; however, researchers showed a higher risk of developing cerebral palsy when carrying twins (Kallen et al., 2010).

Conflicting results were also obtained for autistic spectrum disorders (ASD) (Maimburg and Vaeth, 2007; Lehti et al., 2013; Sandin et al., 2013; Liu et al., 2017). Research on a relatively small sample (976 people) from Denmark, for the period 1990–1999, has found a 59% reduction in the risk of autism in children after ART compared to those conceived naturally (Maimburg and Vaeth, 2007). A more recent study with an analysis of the medical records of 16582 children from Finland (born between 1991 and 2005) found no significant effect of IVF on the incidences of ASD (Lehti et al., 2013). However, there was a significant association of this procedure with Asperger's syndrome in boys (Lehti et al., 2013). It is important to note that studies related to the investigation of the effect of ART on health, in particular on the development of the nervous system of offspring, are heterogeneous in design (Rumbold et al., 2017); for example, mixed groups of IVF/ICSI children who were not separated by the method of conception can be used (Pinborg et al., 2003).

One of the first studies with separate groups by the method of conception (IVF or ICSI) was conducted in Sweden on a large sample of more than 2.5 million people born in 1982–2007 (Sandin et al., 2013). In this study, a slight increase in the risk of developing ASD, as well as mental retardation, was found in children conceived using the more invasive method ICSI compared with those conceived using traditional IVF (Sandin et al., 2013). Later, this result was confirmed in the study of the effects of ART application in US clinics (Kissin et al., 2015). The authors found that 0.9% of children after ICSI and 0.6% after IVF were born with this diagnosis (Kissin et al., 2015). In other studies, researchers found no differences in neurological functions and cognitive abilities in children after IVF/ICSI and single pregnancy (Place and Englert, 2003; Ponjaert-Kristoffersen et al., 2004, 2005; Belva et al., 2007; Leunens et al., 2008; Wagenaar et al., 2008). In a Belgian study of a sample of 66 children conceived with ICSI, 52 children after IVF, and 59 control children, there were no significant differences when comparing these groups with each other at the age of 3 and 5 years in verbal skills and IQ but only when taking into account the level of parental education (Place and Englert, 2003). Later, another group of researchers from Belgium also found no significant differences in neurological indicators in children aged 8 years born after ICSI (n = 150) compared to naturally conceived children (n = 147) except for minor changes in balance and diadochokinesis tests, which the ART group performed slightly worse (Belva et al., 2007). However, ICSI conceived children performed better in the fingertip touch test (Belva et al., 2007). In an international study based on a sample from three countries, when comparing preschool children born after ICSI (300 people) and naturally conceived (260 people), there were also no differences in the results of the Wechsler test (Ponjaert-Kristoffersen et al., 2004). Later, the same group, based on the research on the sample of 5-year-old children from five European countries, 511 after ICSI, 424 after IVF, and 488 in control, showed that the method of conception (IVF or ICSI) does not affect the child's intellectual development (Ponjaert-Kristoffersen et al., 2005). However, the authors clarify that factors such as the age and education of the mother may affect the cognitive development of children born with ART compared to naturally conceived children (Ponjaert-Kristoffersen et al., 2005). Later, the same group found that 8-year-old children from the ART group born in Belgium (n = 151) had a higher IQ than the control group (n = 153); the authors attribute this to their mothers' higher level of education (Leunens et al., 2006). However, these children's intellectual development indicators leveled off after 2 years, which may also be due to a weakening of the mother's influence (Leunens et al., 2008). In Dutch research conducted on a sample of 8–18-year-old schoolchildren, the effect of IVF children's cognitive abilities was studied (Wagenaar et al., 2008). As a result, there were no significant differences between IVF groups (n = 233) and control groups (n = 233) in academic performance and mental abilities (Wagenaar et al., 2008). British scientists have shown that children born as a result of ART at the age of 3 and 5 years had higher indicators of verbal abilities compared to those naturally conceived; however, this difference leveled by the age of 11 (Barbuscia and Mills, 2017). The data from the presented papers show that, in human society, social factors in the family play a more important role in the formation of cognitive abilities in a child than the possible influence of the ART procedure.

In 2017, the first meta-analysis, which included three population-based studies and eight case-control studies conducted on a heterogeneous sample of more than eight million children over the period 2006–2015, was published; this meta-analysis confirmed the association of ART use with a slight increase in the risk of ASD in offspring (Liu et al., 2017). Studies analyzed were conducted in Europe (four studies), in America (four studies), and in Asia (three studies). Studies included in this meta-analysis evaluated the influence of either ART as a whole or IVF or ICSI separately. Thus, the results of the meta-analysis showed that the use of ART can lead to an increase in the frequency of ASD in children. A reliable link between ART and the risk of developing ASD has also been shown for European countries as well as for the Asian population. The

authors of the meta-analysis suggest that manipulation with gametes and embryos, hormonal stimulation, freezing and culturing of embryos, and other ART procedures can lead to the possible epigenetic changes that are at the heart of the identified phenomenon (Liu et al., 2017). However, to confirm this hypothesis, it is necessary to conduct a molecular genetic analysis of embryos obtained in vitro (Liu et al., 2017).

This literature review shows that the data on the effect of ART on the development of CNS disorders in humans are very contradictory and difficult to interpret. Also, the maternal factor, the health status and age of the parents, and their level of education play an important role in the postnatal life of the child (Ponjaert-Kristoffersen et al., 2005; Barbuscia and Mills, 2017). Therefore, to assess the impact of certain reproductive procedures on perinatal outcomes correctly, it is necessary to exclude the influence of negative maternal factors (Sunkara et al., 2019). For a better understanding of the impact of these technologies on the offspring's body, experimental animal models have been created (Ramos-Ibeas et al., 2019).

CONCLUSIONS

Thus, there are quite a lot of papers that attempt to establish a link between the application of ART and developmental changes in both prenatal and postnatal ontogenesis. Currently, there is a variety of culture media for in vitro cultivation of preimplantation mammalian embryos, including human embryos. The qualitative and quantitative composition of these media can have a significant impact on the pre- and postimplantation development of embryos. Although most infants are healthy after ART, some studies show that these procedures can affect both perinatal outcomes and the long-term health of these children (Duranthon and Chavatte-Palmer, 2018). Moreover, some studies establish the relationship between ART and various diseases of the central nervous system in humans. However, the results of these studies are still very controversial. Since the interpretation of medical data is difficult due to accompanying disorders of the parents, differences in the protocols, and other factors that are difficult to account for; all this creates motivation to set up experiments on laboratory animals.

ACKNOWLEDGMENTS

We thank the Center for Genetic Resources of Laboratory Animals Shared-Access Center and the Shared Center for Microscopic Analysis of Biological Objects, Institute of Cytology and Genetics, Siberian Branch, Russian Academy of Sciences, Novosibirsk, Russia.

FUNDING

The reported study was funded by Russian Foundation for Basic Research, project no. 20-015-00162, as well as a budget project of the Institute of Cytology and Genetics, Siberian Branch, Russian Academy of Sciences, project no. 0259-2019-0003-C-01.

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflict of interest.

This article does not contain any studies involving animals or human participants performed by the authors.

AUTHOR CONTRIBUTIONS

S.V. Ranneva and E.Yu Brusentsev are responsible for preparing the section Optimization of Cultural Systems as well as preparing tables; D.S. Ragaeva and N.I. Ershov are responsible for preparing the section Specific Features of Mammalian Preimplantation Embryos' Development in vitro and Effect on Subsequent Ontogenesis. T.N. Igonina, I.N. Rozhkova, and A.L. Levinson are responsible for preparing the section Effect of Art on Postnatal Development of Mammalian Offspring. S.Ya. Amstislavsky participated in the writing of all sections and carried out the general editing of the article.

REFERENCES

Adamson, G.D., de Mouzon, J., Chambers, G.M., et al., International Committee for Monitoring Assisted Reproductive Technology: world report on assisted reproductive technology, 2011, *Fertil. Steril.*, 2018, vol. 110, no. 6, pp. 1067–1080.

Aghaz, F., Hajarian, H., and Karami Shabankareh, H., In vitro culture medium (IVC) supplementation with sericin improves developmental competence of ovine zygotes, *Reprod. Biol.*, 2016, vol. 16, no. 1, pp. 87–90.

Aguilar, J. and Reyley, M., The uterine tubal fluid: secretion, composition and biological effects, *Anim. Reprod.*, 2005, vol. 2, no. 2, pp. 91–105.

Amstislavsky, S., Lindeberg, H., and Luvoni, G., Reproductive technologies relevant to the genome resource bank in Carnivora, *Reprod. Domest. Anim.*, 2012, vol. 47, no. 1, pp. 164–175.

Amstislavsky, S., Brusentsev, E., Kizilova, E., et al., Embryo cryopreservation and in vitro culture of preimplantation embryos in Campbell's hamster (*Phodopus campbelli*), *Theriogenology*, 2015, vol. 83, no. 6, pp. 1056–1063.

Amstislavsky, S., Brusentsev, E., Kizilova, E., et al., Sperm cryopreservation in the Far-Eastern wildcat (*Prionailurus bengalensis euptilurus*), *Reprod. Dom. Anim.*, 2018, vol. 53, no. 5, pp. 1219–1226.

D'Angelo, D.V., Whitehead, N., Helms, K., Barfield, W., and Ahluwalia, I.B., Birth outcomes of intended pregnancies among women who used assisted reproductive technology, ovulation stimulation, or no treatment, *Fertil. Steril.*, 2011, vol. 96, no. 2, pp. 314–320.

Von Arx, R., Allemann, Y., Sartori, C., et al., Right ventricular dysfunction in children and adolescents conceived by assisted reproductive technologies, *J. App. Phys.*, 2015, vol. 118, no. 10, pp. 1200–1206.

Aviles, M., Gutierrez-Adan, A., and Coy, P., Oviductal secretions: will they be key factors for the future ARTs?, *Mol. Hum. Reprod.*, 2010, vol. 16, no. 12, pp. 896–906.

Banrezes, B., Sainte-Beuve, T., Canon, E., et al., Adult body weight is programmed by a redox-regulated and energy-dependent process during the pronuclear stage in mouse, *PLoS One*, 2011, vol. 6, no. 12. e29388.

Barbuscia, A. and Mills, M.C., Cognitive development in children up to age 11 years born after ART—a longitudinal cohort study, *Hum. Reprod.*, 2017, vol. 24, pp. 1–7.

Barker, D.J., The origins of the developmental origins theory, *J. Intern. Med.*, 2007, vol. 261, no. 5, pp. 412–417.

Belli, M., Zhang, L., Liu, X., et al., Oxygen concentration alters mitochondrial structure and function in in vitro fertilized preimplantation mouse embryos, *Hum. Reprod.*, 2019, vol. 34, no. 4, pp. 601–611.

Belva, F., Henriet, S., Liebaers, I., et al., Medical outcome of 8-year-old singleton ICSI children (born > or = 32 weeks' gestation) and a spontaneously conceived comparison group, *Hum. Reprod.*, 2007, vol. 22, no. 2, pp. 506–515.

Berntsen, S., Soderstrom-Anttila, V., Wennerholm, U.B., et al., The health of children conceived by ART: "the chicken or the egg?," *Hum. Reprod. Update*, 2019, vol. 25, no. 2, pp. 137–158.

Biggers, J.D. and McGinnis, L.K., Evidence that glucose is not always an inhibitor of mouse preimplantation development in vitro, *Hum. Reprod.*, 2001, vol. 16, no. 1, pp. 153–163.

Biggers, J.D., McGinnis, L.K., and Raffin, M., Amino acids and preimplantation development of the mouse in protein-free potassium simplex optimized medium, *Biol. Reprod.*, 2000, vol. 63, no. 1, pp. 281–293.

Biggers, J.D., McGinnis, L.K., and Lawitts, J.A., Enhanced effect of glycyl-L-glutamine on mouse preimplantation embryos in vitro, *Reprod. Biomed. Online*, 2004, vol. 9, no. 1, pp. 59–69.

Biggers, J.D., McGinnis, L.K., and Lawitts, J.A., One-step versus two-step culture of mouse preimplantation embryos: is there a difference?, *Hum. Reprod.*, 2005, vol. 20, no. 12, pp. 3376–3384.

Bloise, E., Lin, W., Liu, X., et al., Impaired placental nutrient transport in mice generated by in vitro fertilization, *Endocrinology*, 2012, vol. 153, pp. 3457–3467.

Bloise, E., Feuer, S.K., and Rinaudo, P.F., Comparative intrauterine development and placental function of ART concept: implications for human reproductive medicine and animal breeding, *Hum. Reprod. Update*, 2014, vol. 20, no. 6, pp. 822–839.

Bowman, P. and McLaren, A., Cleavage rate of mouse embryos in vivo and in vitro, *J. Embryol. Exp. Morphol.*, 1970, vol. 24, no. 1, pp. 203–207.

Bradley, J. and Swann, K., Mitochondria and lipid metabolism in mammalian oocytes and early embryos, *Int. J. Dev. Biol.*, 2019, vol. 63, pp. 93–103.

Brusentsev, E.Yu., Igonina, T.N., and Amstislavsky, S.Ya., Traditional and modern approaches to culture of preimplantation mammalian embryos in vitro, *Russ. J. Dev. Biol.*, 2014, vol. 45, no. 2, pp. 53–65.

Brusentsev, E.Yu., Igonina, T.N., Abramova, T.O., et al., Cryopreservation, in vitro culture and transfer of preimplantation embryos in Djungarian hamster (*Phodopus sungorus*), *Reprod. Dom. Anim.*, 2015, vol. 50, pp. 677–683.

Brusentsev, E.Yu., Igonina, T.N., Rozhkova, I.N., Ragaeva, D.S., and Amstislavsky, S.Ya., Effects of growth factors during in vitro culture of mouse and rat embryos, *Russ. J. Genet.: Appl. Res.*, 2016, vol. 6, no. 4, pp. 378–383.

Brusentsev, E., Kizilova, E., Mokrousova, V., et al., Characteristics and fertility of domestic cat epididymal spermatozoa cryopreserved with two different freezing media, *Theriogenology*, 2018, vol. 110, pp. 148–152.

Canovas, S., Ivanova, E., Romar, R., et al., DNA methylation and gene expression changes derived from assisted reproductive technologies can be decreased by reproductive fluids, *Elife*, 2017, vol. 6, pp. 1–24.

Ceelen, M., van Weissenbruch, M.M., Vermeiden, J.P.W., et al., Cardiometabolic differences in children born after in vitro fertilization: follow-up study, *J. Clin. Endocrinol. Metab.*, 2008, vol. 93, no. 5, pp. 1682–1688.

Chatot, C.L., Lewis, J.L., Torres, I., and Ziomek, C.A., Development of 1-cell embryos from different strains of mice in CZB medium, *Biol. Reprod.*, 1990, vol. 42, no. 3, pp. 432–440.

Chen, M., Wu, L., Zhao, J., et al., Altered glucose metabolism in mouse and humans conceived by IVF, *Diabetes*, 2014, vol. 63, no. 10, pp. 3189–3198.

Choi, Y.H., Love, C.C., Varner, D.D., Love, L.B., and Hinrichs, K., Effects of gas conditions, time of medium change, and ratio of medium to embryo on in vitro development of horse oocytes fertilized by intracytoplasmic sperm injection, *Theriogenology*, 2003a, vol. 59, nos. 5–6, pp. 1219–1229.

Choi, Y.H., Chung, Y.G., Walker, S.C., Westhusin, M.E., and Hinrichs, K., In vitro development of equine nuclear transfer embryos: effects of oocyte maturation media and amino acid composition during embryo culture, *Zygote*, 2003b, vol. 11, no. 1, pp. 77–86.

Cozzi, J., Wang, E., Jacquet, C., et al., Procedures for somatic cell nuclear transfer in the rat, *Methods Mol. Biol.*, 2010, vol. 597, pp. 137–150.

Delle Piane, L., Lin, W., Liu, X., et al., Effect of the method of conception and embryo transfer procedure on mid-gestation placenta and fetal development in an IVF mouse model, *Hum. Reprod.*, 2010, vol. 25, pp. 2039–2046.

Dieamant, F., Petersen, C.G., Mauri, A.L., et al., Single versus sequential culture medium: which is better at improving ongoing pregnancy rates? A systematic review and meta-analysis, *JBRA Assist. Reprod.*, 2017, vol. 21, no. 3, pp. 240–246.

Dinopoulou, V., Drakakis, P., Kefala, S., et al., Effect of recombinant-LH and hCG in the absence of FSH on in vitro maturation (IVM) fertilization and early embryonic development of mouse germinal vesicle (GV)-stage oocytes, *Reprod. Biol.*, 2016, vol. 16, no. 2, pp. 138–146.

Donjacour, A., Liu, X., Lin, W., Simbulan, R., and Rinaudo, P.F., In vitro fertilization affects growth and glucose metabolism in a sex-specific manner in an outbred mouse model, *Biol. Reprod.*, 2014, vol. 90, no. 4, p. 80.

Dumoulin, J.C., Land, J.A., Van Montfoort, A.P., et al., Effect of in vitro culture of human embryos on birth-

weight of newborns, *Hum. Reprod.*, 2010, vol. 25, no. 3, pp. 605–612.

Duranthon, V. and Chavatte-Palmer, P., Long term effects of ART: what do animals tell us?, *Mol. Reprod. Dev.*, 2018, vol. 85, no. 4, pp. 348–368.

Ecker, D.J., Stein, P., Xu, Z., et al., Long-term effects of culture of preimplantation mouse embryos on behavior, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, vol. 101, no. 6, pp. 1595–1600.

Fauque, P., Mondon, F., Letourneur, F., et al., In vitro fertilization and embryo culture strongly impact the placental transcriptome in the mouse model, *PLoS One*, 2010, vol. 5. e9218.

Fernandez-Gonzalez, R., Moreira, P., Bilbao, A., et al., Long-term effect of in vitro culture of mouse embryos with serum on mRNA expression of imprinting genes, development, and behavior, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, vol. 101, no. 16, pp. 5880–5885.

Feuer, S.K., Liu, X., Donjacour, A., et al., Use of a mouse in vitro fertilization model to understand the developmental origins of health and disease hypothesis, *Endocrinology*, 2014, vol. 155, no. 5, pp. 1956–1969.

Feuer, S., Liu, X., Donjacour, A., et al., Common and specific transcriptional signatures in mouse embryos and adult tissues induced by in vitro procedures, *Reproduction*, 2016. pii: REP-16-0473.

Finger, B.J., Harvey, A.J., Green, M.P., and Gardner, D.K., Combined parental obesity negatively impacts preimplantation mouse embryo development, kinetics, morphology and metabolism, *Hum. Reprod.*, 2015, vol. 30, no. 9, pp. 2084–2096.

Fischer, B. and Bavister, B.D., Oxygen tension in the oviduct and uterus of rhesus monkeys, hamsters and rabbits, *Reproduction*, 1993, vol. 99, no. 2, pp. 673–679.

Fleming, T.P., Velazquez, M.A., and Eckert, J.J., Embryos, DOHaD and David Barker, *J. Dev. Orig. Health. Dis.*, 2015, vol. 6, no. 5, pp. 377–383.

Fleming, T.P., Watkins, A.J., Velazquez, M.A., et al., Origins of lifetime health around the time of conception: causes and consequences, *Lancet*, 2018, vol. 391, no. 10132, pp. 1842–1852.

Gardner, D.K., Changes in requirements and utilization of nutrients during mammalian preimplantation embryo development and their significance in embryo culture, *Theriogenology*, 1998, vol. 49, no. 1, pp. 83–102.

Gardner, D.K., Lane, M., and Watson, A.J., *A Laboratory Guide to the Mammalian Embryo*, Oxford: University Press, 2004.

Gardner, D.K. and Lane, M., Mammalian preimplantation embryo culture, *Methods Mol. Biol.*, 2014, vol. 1092, pp. 167–182.

Guo, X.Y., Liu, X.M., Jin, L., et al., Cardiovascular and metabolic profiles of offspring conceived by assisted reproductive technologies: a systematic review and meta-analysis, *Fertil. Steril.*, 2017, vol. 107, no. 3, pp. 622–631.

Haavaldsen, C., Tanbo, T., and Eskild, A., Placental weight in singleton pregnancies with and without assisted reproductive technology: a population study of 536,567 pregnancies, *Hum. Reprod.*, 2012, vol. 27, pp. 576–582.

El Hajj, N. and Haaf, T., Epigenetic disturbances in in vitro cultured gametes and embryos: implications for human assisted reproduction, *Fertil. Steril.*, 2013, vol. 99, no. 3, pp. 632–641.

Halliday, J., Lewis, S., Kennedy, J., et al., Health of adults aged 22 to 35 years conceived by assisted reproductive technology, *Fertil. Steril.*, 2019, vol. 112, no. 1, pp. 130–139.

Han, M.S. and Niwa, K., Effects of BSA and fetal bovine serum in culture medium on development of rat embryos, *J. Reprod. Dev.*, 2003, vol. 49, no. 3, pp. 235–242.

Hattori, H., Hiura, H., Kitamura, A., et al., Association of four imprinting disorders and ART, *Clin. Epigenetics*, 2019, vol. 11, no. 1, p. 21.

Hayashi, M., Nakai, A., Satoh, S., and Matsuda, Y., Adverse obstetric and perinatal outcomes of singleton pregnancies may be related to maternal factors associated with infertility rather than the type of assisted reproductive technology procedure used, *Fertil. Steril.*, 2012, vol. 98, no. 4, pp. 922–928.

Herrick, J.R., Bond, J.B., Magarey, G.M., et al., Toward a feline-optimized culture medium: impact of ions, carbohydrates, essential amino acids, vitamins, and serum on development and metabolism of in vitro fertilization-derived feline embryos relative to embryos grown in vivo, *Biol. Reprod.*, 2007, vol. 76, no. 5, pp. 858–870.

Higdon, H.L., 3rd, Blackhurst D.W., Boone W.R. Incubator management in an assisted reproductive technology laboratory, *Techniques and Instrumentation*, 2008, vol. 89, no. 3, pp. 703–710.

Hiura, H., Okae, H., Chiba, H., et al., Imprinting methylation errors in ART, *Reprod. Med. Biol.*, 2014, vol. 13, no. 4, pp. 193–202.

Hosseini, S.M., Hajian, M., Ostadhosseini, S., et al., Contrasting effects of G1.2/G2.2 and SOF1/SOF2 embryo culture media on pre- and post-implantation development of non-transgenic and transgenic cloned goat embryos, *Reprod. Biomed. Online*, 2015, vol. 31, no. 3, pp. 372–383.

Igonina, T.N., Ragaeva, D.S., Petrova, O.M., et al., Effects of in vitro culture at the preimplantation embryo stage on early development and hypertension in ISIAH rats, *Hypertens. Pregnancy*, 2019, vol. 38, no. 4, pp. 208–216.

Izquierdo, D., Villamediana, P., and Paramio, M.T., Effect of culture media on embryo development from prepubertal goat IVM-IVF oocytes, *Theriogenology*, 1999, vol. 52, no. 5, pp. 847–861.

Jaques, A.M., Amor, D.J., Baker, H.W., et al., Adverse obstetric and perinatal outcomes in subfertile women conceiving without assisted reproductive technologies, *Fertil. Steril.*, 2010, vol. 94, no. 7, pp. 2674–2679.

Joy, J., Gannon, C., McClure, N., and Cooke, I., Is assisted reproduction associated with abnormal placentation?, *Pediatr. Dev. Pathol.*, 2012, vol. 15, pp. 306–314.

Kahveci, B., Melekoglu, R., Evruke, I.C., and Cetin, C., The effect of advanced maternal age on perinatal outcomes in nulliparous singleton pregnancies, *BMC Preg. Child*, 2018, vol. 18, no. 1, p. 343.

Kallen, A.J., Finnstrom, O.O., Lindam, A.P., et al., Cerebral palsy in children born after in vitro fertilization. Is the risk decreasing?, *Eur. J. Paediatr. Neurol.*, 2010, vol. 14, no. 6, pp. 526–530.

Kasterstein, E., Strassburger, D., Komarovsky, D., et al., The effect of two distinct levels of oxygen concentration

on embryo development in a sibling oocyte study, *J. Assisted Reprod. Genet.*, 2013, vol. 30, no. 8, pp. 1073–1079.

Kawamura, K., Chen, Y., Shu, Y., et al., Promotion of human early embryonic development and blastocyst outgrowth in vitro using autocrine/paracrine growth factors, *PLoS One*, 2012, vol. 7, no. 11. e49328.

Kettner, L.O., Matthiesen, N.B., Ramlau-Hansen, C.H., et al., Fertility treatment and childhood type 1 diabetes mellitus: a nationwide cohort study of 565,116 live births, *Fertil. Steril.*, 2016, vol. 106, no. 7, pp. 1751–1756.

Kissin, D.M., Zhang, Y., Boulet, S.L., et al., Association of assisted reproductive technology (ART) treatment and parental infertility diagnosis with autism in ART-conceived children, *Hum. Reprod.*, 2015, vol. 30, no. 2, pp. 454–465.

Kleijkers, S.H., Eijssen, L.M., Coonen, E., et al., Differences in gene expression profiles between human preimplantation embryos cultured in two different IVF culture media, *Hum. Reprod.*, 2015, vol. 30, no. 10, pp. 2303–2311.

Klemetti, R., Sevon, T., Gissler, M., and Hemminki, E., Health of children born as a result of in vitro fertilization, *Pediatrics*, 2006, vol. 118, no. 5, pp. 1819–1827.

Klemetti, R., Sevon, T., Gissler, M., and Hemminki, E., Health of children born after ovulation induction, *Fertil. Steril.*, 2010, vol. 93, no. 4, pp. 1157–1168.

Kozhevnikova, V.V., Igonina, T.N., Brusentsev, E.Yu., et al., Comparison of preimplantation development of OXYS and WAG rat embryos in vivo and in vitro, *Vavilov. Zh. Genet. Selekts.*, 2017, vol. 21, no. 7, pp. 810–815.

Labarta, E., Bosch, E., and Pellicer, A., Impact of ovarian stimulation with gonadotrophins on embryo aneuploidy, *Hum. Reprod. Update*, 2014, vol. 20, no. 6, p. 964.

Lane, M., Gardner, D.K., Hasler, M.J., and Hasler, J.F., Use of G1.2/G2.2 media for commercial bovine embryo culture: equivalent development and pregnancy rates compared to co-culture, *Theriogenology*, 2003, vol. 60, no. 3, pp. 407–419.

Lawitts, J.A. and Biggers, J.D., Overcoming the 2-cell block by modifying standard components in a mouse embryo culture medium, *Biol. Reprod.*, 1991, vol. 45, no. 2, pp. 245–251.

Lawitts, J.A. and Biggers, J.D., Culture of preimplantation embryos, *Methods Enzymol.*, 1993, vol. 225, pp. 153–164.

Lazaraviciute, G., Kauser, M., Bhattacharya, S., Haggarty, P., and Bhattacharya, S., A systematic review and meta-analysis of DNA methylation levels and imprinting disorders in children conceived by IVF/ICSI compared with children conceived spontaneously, *Hum. Reprod. Update*, 2014, vol. 20, no. 6, pp. 840–852.

Leese, H.J., The formation and function of oviduct fluid, *J. Reprod. Fertil.*, 1988, vol. 82, pp. 843–856.

Lehti, V., Brown, A.S., Gissler, M., et al., Autism spectrum disorders in IVF children: a national case-control study in Finland, *Hum. Reprod.*, 2013, vol. 28, no. 3, pp. 812–818.

Leunens, L., Celestin-Westreich, S., Bonduelle, M., Liebaers, I., and Ponjaert-Kristoffersen, I., Cognitive and motor development of 8-year-old children born after ICSI compared to spontaneously conceived children, *Hum. Reprod.*, 2006, vol. 21, no. 11, pp. 2922–2929.

Leunens, L., Celestin-Westreich, S., Bonduelle, M., Liebaers, I., and Ponjaert-Kristoffersen, I., Follow-up of cognitive and motor development of 10-year-old singleton children born after ICSI compared with spontaneously conceived children, *Hum. Reprod.*, 2008, vol. 23, no. 1, pp. 105–111.

Li, Z.Y., Jiang, Q.S., Zhang, Y.L., Liu, X.M., and Engelhardt, J.F., Successful production of offspring after superovulation and in vitro culture of embryos from domestic ferrets (*Mustela putorius furos*), *Reproduction*, 2001, vol. 122, no. 4, pp. 611–618.

Li, L., Le F., Wang L.Y. et al. Normal epigenetic inheritance in mice conceived by in vitro fertilization and embryo transfer, *J. Zhejiang. Univ. Sci. B*, 2011, vol. 12, no. 10, pp. 796–804.

Lindeberg, H., Jalkanen, L., and Savolainen, R., In vitro culture of silver fox embryos, *Theriogenology*, 1993, vol. 40, no. 4, pp. 779–788.

Liu, Z., Foote, R.H., and Simkin, M.E., Effect of amino acids and alpha-amanitin on the development of rabbit embryos in modified protein-free KSOM with HEPES, *Mol. Reprod. Dev.*, 1996, vol. 45, no. 2, pp. 157–162.

Liu, H., Zhang, Y., Gu, H., et al., Association between assisted reproductive technology and cardiac alteration at age 5 years, *JAMA Pediatr.*, 2015, vol. 169, no. 6, pp. 603–605.

Liu, L., Gao, J., He, X., et al., Association between assisted reproductive technology and the risk of autism spectrum disorders in the offspring: a meta-analysis, *Sci. Rep.*, 2017, vol. 7, p. 46207.

Ludwig, A.K., Katalinic, A., Jendrysik, J., et al., Spontaneous pregnancy after successful ICSI treatment: evaluation of risk factors in 899 families in Germany, *Reprod. Biomed. Online*, 2008, vol. 17, no. 3, pp. 403–409.

Ludwig, A.K., Katalinic, A., Thyen, U., et al., Physical health at 5.5 years of age of term-born singletons after intracytoplasmic sperm injection: results of a prospective, controlled, single-blinded study, *Fertil. Steril.*, 2009a, vol. 91, no. 1, pp. 115–124.

Ludwig, A., Katalinic, A., Thyen, U., et al., Neuromotor development and mental health at 5.5 years of age of singletons born at term after intracytoplasmatic sperm injection ICSI: results of a prospective controlled single-blinded study in Germany, *Fertil. Steril.*, 2009b, vol. 91, no. 1, pp. 125–132.

Luvoni, G.C., Chigioni, S., and Beccaglia, M., Embryo production in dogs: from in vitro fertilization to cloning, *Reprod. Domest. Anim.*, 2006, vol. 41, no. 4, pp. 286–290.

Machaty, Z., Day, B.N., and Prather, R.S., Development of early porcine embryos in vitro and in vivo, *Biol. Reprod.*, 1998, vol. 59, no. 2, pp. 451–455.

Maimburg, R.D. and Vaeth, M., Do children born after assisted conception have less risk of developing infantile autism?, *Hum. Reprod.*, 2007, vol. 22, no. 7, pp. 1841–1843.

Makieva, S., Giacomini, E., Ottolina, J., et al., Inside the endometrial cell signaling subway: mind the gap(s), *Int. J. Mol. Sci.*, 2018, vol. 19, no. 9, p. 2477.

Mani, S. and Mainigi, M., Embryo culture conditions and the epigenome, *Semin. Reprod. Med.*, 2018, vol. 36, pp. 211–220.

Mani, S., Ghosh, J., Coutifaris, C., et al., Epigenetic changes and assisted reproductive technologies, *Epigenetics*, 2020, vol. 15, nos. 1–2, pp. 12–25.

Mantikou, E., Jonker, M.J., Wong, K.M., et al., Factors affecting the gene expression of in vitro cultured human preimplantation embryos, *Hum. Reprod.*, 2016, vol. 31, no. 2, pp. 298–311.

Mara, L., Sanna, D., Casu, S., Dattena, M., and Munoz, I.M., Blastocyst rate of in vitro embryo production in sheep is affected by season, *Zygote*, 2014, vol. 22, no. 3, pp. 366–371.

Market-Velker, B.A., Fernandes, A.D., and Mann, M.R., Side-by-side comparison of five commercial media systems in a mouse model: suboptimal in vitro culture interferes with imprint maintenance, *Biol. Reprod.*, 2010, vol. 83, no. 6, pp. 938–950.

Marshall, K.L. and Rivera, R.M., The effects of superovulation and reproductive aging on the epigenome of the oocyte and embryo, *Mol. Reprod. Dev.*, 2018, vol. 85, no. 2, pp. 90–105.

Meister, T.A., Rimoldi, S.F., Soria, R., et al., Association of assisted reproductive technologies with arterial hypertension during adolescence, *J. Am. Col. Card.*, 2018, vol. 72, no. 11, pp. 1267–1274.

Men, H., Stone, B.J., and Bryda, E.C., Media optimization to promote rat embryonic development to the blastocyst stage in vitro, *Theriogenology*, 2020, vol. 151, pp. 81–85.

Menezo, Y., Lichtblau, I., and Elder, K., New insights into human pre-implantation metabolism in vivo and in vitro, *J. Assist. Reprod. Genet.*, 2013, vol. 30, no. 3, pp. 293–303.

Miles, J.R., Farin, C.E., Rodriguez, K.F., Alexander, J.E., and Farin, P.W., Effects of embryo culture on angiogenesis and morphometry of bovine placentas during early gestation, *Biol. Reprod.*, 2005, vol. 73, pp. 663–671.

Miller, K., Optimizing Culture Conditions, in *Culture Media, Solutions, and Systems in Human ART*, Quinn, P., Ed., Cambridge Univ. Press, 2014, ch. 17.

Miyoshi, K., Funahashi, H., Okuda, K., et al., Development of rat one-cell embryos in a chemically defined medium: effects of glucose, phosphate and osmolarity, *J. Reprod. Fertil.*, 1994, vol. 100, pp. 21–26.

Miyoshi, K., Abeydeera, L.R., Okuda, K., and Niwa, K., Effects of osmolarity and amino acids in a chemically defined medium on development of rat one-cell embryos, *J. Reprod. Fertil.*, 1995, vol. 103, no. 1, pp. 27–32.

Morbeck, D.E., Krisher, R.L., Herrick, J.R., et al., Composition of commercial media used for human embryo culture, *Fertil. Steril.*, 2014, vol. 102, no. 3, pp. 759–766. e9.

Morbeck, D.E., Baumann, N.A., and Oglesbee, D., Composition of single-step media used for human embryo culture, *Fertil. Steril.*, 2017, vol. 107, no. 4, pp. 1055–1060. e1.

Mussa, A., Molinatto, C., Cerrato, F., et al., Assisted reproductive techniques and risk of Beckwith–Wiedemann syndrome, *Pediatrics*, 2017, vol. 140, no. 1. pii: e20164311.

Nakamura, K., Morimoto, K., Shima, K., et al., The effect of supplementation of amino acids and taurine to modified KSOM culture medium on rat embryo development, *Theriogenology*, 2016, vol. 86, no. 8, pp. 2083–2090.

Nedambale, T.L., Dinnyes, A., Groen, W., et al., Comparison on in vitro fertilized bovine embryos cultured in KSOM or SOF and cryopreserved by slow freezing or vitrification, *Theriogenology*, 2004, vol. 62, nos. 3–4, pp. 437–449.

Nelissen, E.C., Dumoulin, J.C., Daunay, A., et al., Placentas from pregnancies conceived by IVF/ICSI have a reduced DNA methylation level at the H19 and MEST differentially methylated regions, *Hum. Reprod.*, 2013, vol. 28, pp. 1117–1126.

Pandey, S., Shetty, A., Hamilton, M., Bhattacharya, S., and Maheshwari, A., Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis, *Hum. Reprod. Update*, 2012, vol. 18, no. 5, pp. 485–503.

Pinborg, A., Loft, A., Schmidt, L., and Andersen, A.N., Morbidity in a Danish national cohort of 472 IVF/ICSI twins, 1132 non-IVF/ICSI twins and 634 IVF/ICSI singletons: health-related and social implications for the children and their families, *Hum. Reprod.*, 2003, vol. 18, no. 6, pp. 1234–1243.

Pinborg, A., Wennerholm, U.B., Romundstad, L.B., et al., Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis, *Hum. Reprod. Update*, 2013, vol. 19, no. 2, pp. 87–104.

Pinheiro, R.L., Areia, A.L., Mota Pinto, A., and Donato, H., Advanced maternal age: adverse outcomes of pregnancy, a meta-analysis, *Acta. Med. Port.*, 2019, vol. 32, no. 3, pp. 219–226.

Place, I. and Englert, Y., A prospective longitudinal study of the physical, psychomotor, and intellectual development of singleton children up to 5 years who were conceived by intracytoplasmic sperm injection compared with children conceived spontaneously and by in vitro fertilization, *Fertil. Steril.*, 2003, vol. 80, no. 6, pp. 1388–1397.

Pollard, J.W., Plante, C., and Leibo, S.P., Comparison of development of pig zygotes and embryos in simple and complex culture media, *J. Reprod. Fertil.*, 1995, vol. 103, no. 2, pp. 331–337.

Ponjaert-Kristoffersen, I., Tjus, T., Nekkebroeck, J., et al., Psychological follow-up study of 5-year-old ICSI children, *Hum. Reprod.*, 2004, vol. 19, no. 12, pp. 2791–2797.

Ponjaert-Kristoffersen, I., Bonduelle, M., Barnes, J., et al., International collaborative study of intracytoplasmic sperm injection-conceived, in vitro fertilization-conceived, and naturally conceived 5-year-old child outcomes: cognitive and motor assessments, *Pediatrics*, 2005, vol. 115, no. 3, pp. e283–e289.

Ramos-Ibeas, P., Heras, S., Gomez-Redondo, I., et al., Embryo responses to stress induced by assisted reproductive technologies, *Mol. Reprod. Dev.*, 2019, vol. 86, no. 10, pp. 1292–1306.

Raunig, J.M., Yamauchi, Y., Ward, M.A., and Collier, A.C., Placental inflammation and oxidative stress in the mouse model of assisted reproduction, *Placenta*, 2011, vol. 32, pp. 852–858.

Reik, W., Dean, W., and Walter, J., Epigenetic reprogramming in mammalian development, *Science*, 2001, vol. 293, no. 5532, pp. 1089–1093.

Rexhaj, E., Paoloni-Giacobino, A., Rimoldi, S.F., et al., Mice generated by in vitro fertilization exhibit vascular dysfunction and shortened life span, J. *Clin. Invest.*, 2013, vol. 123, no. 12, pp. 5052–5060.

Rivera, R.M., Stein, P., Weaver, J.R., et al., Manipulations of mouse embryos prior to implantation result in aberrant expression of imprinted genes on day 9.5 of development, *Hum. Mol. Genet.*, 2008, vol. 17, no. 1, pp. 1–14.

Rodrigues, B.A., Santos, L.C., and Rodrigues, J.L., Embryonic development of in vitro matured and in vitro fertilized dog oocytes, *Mol. Reprod. Dev.*, 2004, vol. 67, no. 2, pp. 215–223.

Rumbold, A.R., Moore, V.M., Whitrow, M.J., et al., The impact of specific fertility treatments on cognitive development in childhood and adolescence: a systematic review, *Hum. Reprod.*, 2017, vol. 32, pp. 1489–1507.

Sagirkaya, H., Misirlioglu, M., Kaya, A., et al., Developmental and molecular correlates of bovine preimplantation embryos, *Reproduction*, 2006, vol. 131, no. 5, pp. 895–904.

Le Saint, C., Crespo, K., Bourdiec, A., et al., Autologous endometrial cell co-culture improves human embryo development to high-quality blastocysts: a randomized controlled trial, *Reprod. Biomed. Online*, 2019, vol. 38, no. 3, pp. 321–329.

Salilew-Wondim, D., Fournier, E., Hoelker, M., et al., Genome-wide DNA methylation patterns of bovine blastocysts developed in vivo from embryos completed different stages of development in vitro, *PLoS One*, 2015, vol. 10, no. 11. e0140467.

Sananmuang, T., Tharasanit, T., Nguyen, C., Phutikanit, N., and Techakumphu, M., Culture medium and embryo density influence on developmental competence and gene expression of cat embryos, *Theriogenology*, 2011, vol. 75, no. 9, pp. 1708–1719.

Sandin, S., Nygren, K.G., Iliadou, A., et al., Autism and mental retardation among offspring born after in vitro fertilization, *JAMA*, 2013, vol. 310, pp. 75–84.

Santi, D., De Vincentis, S., Magnani, E., and Spaggiari, G., Impairment of sperm DNA methylation in male infertility: a meta-analytic study, *Andrology*, 2017, vol. 5, no. 4, pp. 695–703.

Sato, A., Otsu, E., Negishi, H., Utsunomiya, T., and Arima, T., Aberrant DNA methylation of imprinted loci in superovulated oocytes, *Hum. Reprod.*, 2007, vol. 22, no. 1, pp. 26–35.

Scherrer, U., Rimoldi, S.F., Rexhaj, E., et al., Systemic and pulmonary vascular dysfunction in children conceived by assisted reproductive technologies, *Circulation*, 2012, vol. 125, no. 15, pp. 1890–1896.

Schini, S.A. and Bavister, B.D., Two-cell block to development of cultured hamster embryos is caused by phosphate and glucose, *Biol. Reprod.*, 1988, vol. 39, no. 5, pp. 1183–1192.

Schwarzer, C., Esteves, T.C., Arauzo-Bravo, M.J., et al., ART culture conditions change the probability of mouse embryo gestation through defined cellular and molecular responses, *Hum. Reprod.*, 2012, vol. 27, no. 9, pp. 2627–2640.

Scott, K.A., Yamazaki, Y., Yamamoto, M., et al., Glucose parameters are altered in mouse offspring produced by assisted reproductive technologies and somatic cell nuclear transfer, *Biol. Reprod.*, 2010, vol. 83, no. 2, pp. 220–227.

Seshagiri, P.B. and Vani, V., Enabling hamster embryo culture system: development of preimplantation embryos, *Methods Mol. Biol.*, 2019, vol. 2006, pp. 45–61.

Song, S., Ghosh, J., Mainigi, M., et al., DNA methylation differences between in vitro- and in vivo-conceived children are associated with ART procedures rather than infertility, *Clin. Epigenetics*, 2015, vol. 7, p. 41.

Steptoe, P.C. and Edwards, R.G., Birth after the reimplantation of a human embryo, *Lancet*, 1978, vol. 312, p. 366.

Sugimura, S., Akai, T., Hashiyada, Y., et al., Promising system for selecting healthy in vitro-fertilized embryos in cattle, *PLoS One*, 2012, vol. 7, no. 5, pp. 1–12.

Summers, M.C. and Biggers, J.D., Chemically defined media and the culture of mammalian preimplantation embryos: historical perspective and current issues, *Hum. Reprod. Update*, 2003, vol. 9, no. 6, pp. 557–582.

Summers, M.C., A brief history of the development of the KSOM family of media, *Hum. Fertil.*, 2014, vol. 17, suppl. 1, pp. 12–16.

Sunde, A., Embryo culture and phenotype of the offspring, *In Vitro Fertil.*, 2019, pp. 877–889.

Sunkara, S.K., Chinta, P., and Kamath, M.S., Perinatal outcomes following assisted reproductive technology, *J. Hum. Reprod. Sci.*, 2019, vol. 12, pp. 177–181.

Swain, J.E., Bormann, C.L., and Krisher, R.L., Development and viability of in vitro derived porcine blastocysts cultured in NCSU23 and G1.2/G2.2 sequential medium, *Theriogenology*, 2001, vol. 56, no. 3, pp. 459–469.

Swain, J.E., Carrell, D., Cobo, A., et al., Optimizing the culture environment and embryo manipulation to help maintain embryo developmental potential, *Fertil. Steril.*, 2016, vol. 105, no. 3, pp. 571–587.

Tan, K., Zhang, Z., Miao, K., et al., Dynamic integrated analysis of DNA methylation and gene expression profiles in in vivo and in vitro fertilized mouse post-implantation extraembryonic and placental tissues, *Mol. Hum. Reprod.*, 2016, vol. 22, no. 7, p. 485.

Tarahomi, M., Vaz, F.M., van Straalen, J.P., et al., The composition of human preimplantation embryo culture media and their stability during storage and culture, *Hum. Reprod.*, 2019, vol. 34, no. 8, pp. 1450–1461.

Tervit, H.R., Whittingham, D.G., and Rowson, L.E., Successful culture in vitro of sheep and cattle ova, *J. Reprod. Fertil.*, 1972, vol. 30, no. 3, pp. 493–497.

Trasorras, V., Baca Castex, C., Alonso, A., et al., First llama (*Lama glama*) pregnancy obtained after in vitro fertilization and in vitro culture of gametes from live animals, *Anim. Reprod. Sci.*, 2014, vol. 148, nos. 1–2, pp. 83–89.

Valenzuela-Alcaraz, B., Crispi, F., Bijnens, B., et al., Assisted reproductive technologies are associated with

cardiovascular remodeling in utero that persists postnatally, *Circulation*, 2013, vol. 128, no. 13, pp. 1442–1450.

Valenzuela-Alcaraz, B., Serafini, A., Sepulveda-Martinez, A., et al., Postnatal persistence of fetal cardiovascular remodelling associated with assisted reproductive technologies: a cohort study. *BJOG*, 2019, vol. 126, no. 2, pp. 291–298.

Vlachopoulos, C., Kosteria, I., Sakka, S., et al., PCSK9 and Lp(a) levels of children born after assisted reproduction technologies, *J. Assist. Reprod. Genet.*, 2019, vol. 36, no. 6, pp. 1091–1099.

de Waal, E., Mak, W., Calhoun, S., et al., In vitro culture increases the frequency of stochastic epigenetic errors at imprinted genes in placental tissues from mouse concept produced through assisted reproductive technologies, *Biol. Reprod.*, 2014, vol. 90, no. 2, p. 22.

Wagenaar, K., Ceelen, M., van Weissenbruch, M.M., et al., School functioning in 8- to 18-year-old children born after in vitro fertilization, *Eur. J. Pediatr.*, 2008, vol. 167, no. 11, pp. 1289–1295.

Wang, Q. and Zhang, Y., Le, F., et al., Alteration in the expression of the renin-angiotensin system in the myocardium of mice conceived by in vitro fertilization, *Biol. Reprod.*, 2018, vol. 99, no. 6, pp. 1276–1288.

Watkins, A.J., Platt, D., Papenbrock, T., et al., Mouse embryo culture induces changes in postnatal phenotype including raised systolic blood pressure, *Proc. Natl. Acad. Sci. U. S. A.*, 2007, vol. 104, no. 13, pp. 5449–5454.

Wennerholm, U.B. and Bergh, C., Perinatal outcome in children born after assisted reproductive technologies, *Ups. J. Med. Sci.*, 2020, pp. 1–9.

Xie, Y., Wang, F., Puscheck, E.E., and Rappolee, D.A., Pipetting causes shear stress and elevation of phosphorylated stress-activated protein kinase/jun kinase in preimplantation embryos, *Mol. Reprod. Dev.*, 2007, vol. 74, no. 10, pp. 1287–1294.

Yaqoob, S.H., Saadeldin, I.M., Swelum, A.A.-A., and Alowaimer, A.N., Optimizing camel (*Camelus dromedarius*) oocytes in vitro maturation and early embryo culture after parthenogenetic activation, *Smal. Rum. Res.*, 2017, vol. 153, pp. 81–86.

Youssef, M.M., Mantikou, E., van Wely, M., et al., Culture media for human pre-implantation embryos in assisted reproductive technology cycles, *Cochrane Database Syst. Rev.*, 2015, no. 11, p. CD007876.

Zacchini, F., Sampino, S., Stankiewicz, A.M., Haaf, T., and Ptak, G.E., Assessing the epigenetic risks of assisted reproductive technologies: a way forward, *Int. J. Dev. Biol.*, 2019, vol. 63, pp. 217–222.

Zandstra, H., Van Montfoort, A.P., and Dumoulin, J.C., Does the type of culture medium used influence birthweight of children born after IVF?, *Hum. Reprod.*, 2015, vol. 30, no. 3, pp. 530–542.

Zegers-Hochschild, F., Adamson, G., David Dyer, S., et al., The international glossary on infertility and fertility care, 2017, *Hum. Reprod.*, 2017, vol. 32, no. 9, pp. 1786–1801.

Zhou, Q., Yang, S.H., Ding, C.H., et al., A comparative approach to somatic cell nuclear transfer in the rhesus monkey, *Hum. Reprod.*, 2006, vol. 21, no. 10, pp. 2564–2571.

Zhou, J., Liu, H., Gu, H.T., et al., Association of cardiac development with assisted reproductive technology in childhood: a prospective single-blind pilot study, *Cell. Physiol. Biochem.*, 2014, vol. 34, no. 3, pp. 988–1000.

Ziebe, S., Loft, A., Povlsen, B.B., et al., A randomized clinical trial to evaluate the effect of granulocyte-macrophage colony-stimulating factor (GM-CSF) in embryo culture medium for in vitro fertilization, *Fertil. Steril.*, 2013, vol. 99, pp. 1600–1609.

Translated by A. Ermakov