Reproductive Toxicology 68 (2017) 72–84

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Can assisted reproductive technologies cause adult-onset disease? Evidence from human and mouse

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ARTICLE INFO

Article history:
Received 7 April 2016
Received in revised form 15 July 2016
Accepted 22 July 2016
Available online 26 July 2016

Keywords:
Assisted reproductive technologies
In vitro fertilization
Chronic disease
Hypertension
Diabetes
Epigenetics
Mouse

ABSTRACT

Millions of children have been born worldwide though assisted reproductive technologies (ART). Consistent with the *Developmental Origins of Health and Disease* hypothesis, there is concern that ART can induce adverse effects, especially because procedures coincide with epigenetic reprogramming events. Although the majority of studies investigating the effects of ART have focused on perinatal outcomes, more recent studies demonstrate that ART-conceived children may be at increased risk for postnatal effects. Here, we present the current epidemiological evidence that ART-conceived children have detectable differences in blood pressure, body composition, and glucose homeostasis. Similar effects are observed in the ART mouse model, which have no underlying infertility, suggesting that cardiometabolic effects are likely caused by ART procedures and not due to reasons related to infertility. We propose that the mouse system can, consequently, be used to adequately study, modify, and improve outcomes for ART children.

1. Introduction

The *Developmental Origins of Health and Disease* (DOHaD) hypothesis posits that environmental stresses or exposures during development can increase the risk of disease later in life. The first compelling evidence for the existence of DOHaD in humans comes from epidemiological studies showing that nutritional state during prenatal development increases the risk for metabolic syndromes and cardiovascular disease [1]. At the center of the DOHaD hypothesis is the concept of developmental plasticity, in which the biological pathways that govern prenatal development are not fixed. This developmental plasticity, which allows for phenotypic changes in the fetus in response to environmental stress, may be beneficial if the stress is within normal range [2]. Adaptive response mechanisms during development may allow offspring to be better suited to the environment in which they will be born. In contrast, phenotypic changes that result from stresses outside the normal range or from exposures that humans have not evolved defenses against are likely non-adaptive and may lead to adverse effects. With respect to human development, assisted reproductive technologies (ART) are an example of extreme 'exposures', requiring the in vitro handling of gametes and embryos in a synthetic culture environment.

Well-over 5,000,000 babies have been born worldwide via ART [3]. ART and its many associated procedures are constantly changing to fit the needs of patients [4] (Fig. 1). The two most common types of ART are conventional in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), which are accompanied by controlled ovarian hyperstimulation (COH), oocyte retrieval, embryo culture, and embryo transfer procedures. Recent technological advancements have led to the availability of several additional procedures, including the cryopreservation of gametes/embryos, preimplantation genetic diagnosis/screening (PGD/PGS), and others. Even with the successful implementation of these technologies, ART is associated with a number of complications, including a higher risk of congenital anomalies, hypertensive disorders of pregnancy, disorders of the placenta, preterm birth, low birth weight, perinatal mortality and small size for gestational age, imprinting disorders, among other problems presenting at birth, as well as later onset problems [5–8]. Animal models of ART

Abbreviations: ART, assisted reproductive technologies; DOHaD, developmental origins of health and disease; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; COH, controlled ovarian hyperstimulation; PGD/PGS, preimplantation genetic diagnosis or screening; ICRs, imprinting control regions; BMI, body mass index; FMD, flow mediated dilation; IMT, carotid intima-media thickness; MPI, myocardial performance index; TSH, thyroid stimulating hormone; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; SO, superovulation; ET, embryo transfer.

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http://dx.doi.org/10.1016/j.reprotox.2016.07.015
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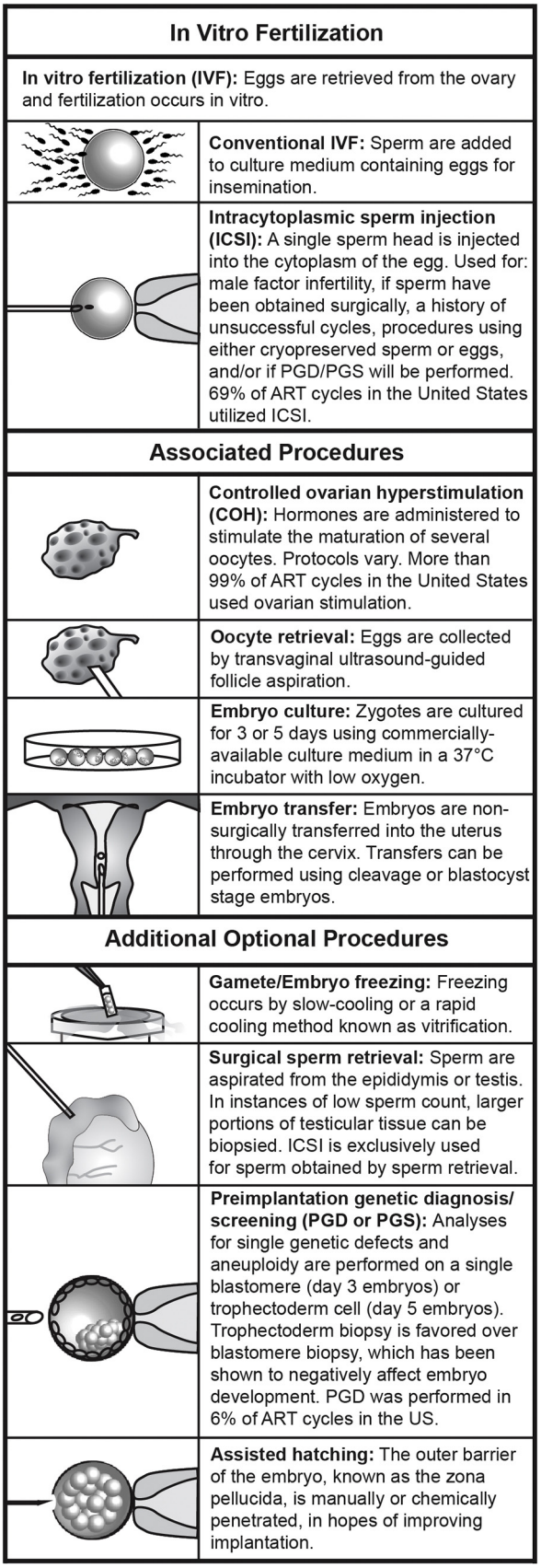

Fig. 1. ART and its associated procedures. A brief description of the different modes of ART (IVF and ICSI) and associated procedures.

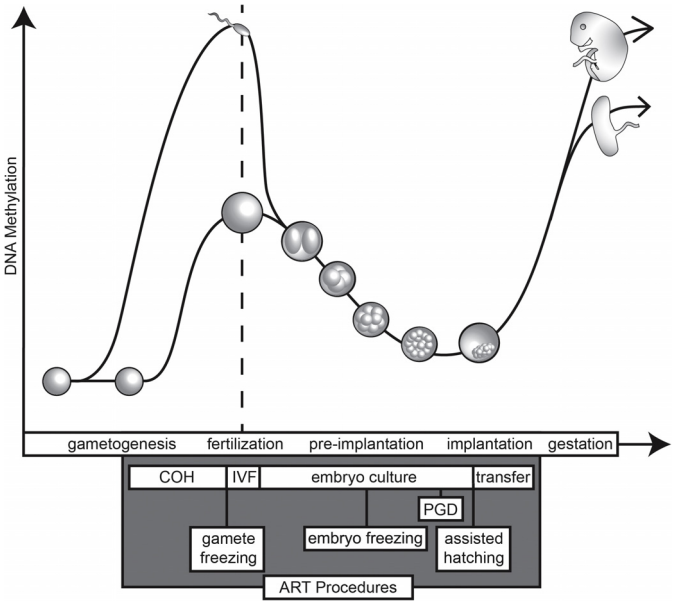

Fig. 2. The timing of ART procedures coincides with dynamic DNA methylation changes in gametes and embryos. Controlled ovarian hyperstimulation (COH) allows the maturation of several immature oocytes. DNA methylation is acquired during this period of oocyte maturation. Fertilization and pre-implantation embryo development occur in vitro with commercially available culture media at 37 °C and low oxygen conditions. Following fertilization, there is both active and passive demethylation of the paternal and maternal genomes, respectively, in the embryo. Embryo culture and transfer coincide with this demethylation. DNA methylation acquisition occurs promptly in the postimplantation embryo. DNA methylation levels in the extraembryonic tissues are relatively hypomethylated compared to levels in the embryo. IVF = in vitro fertilization; PGD = pre-implantation genetic diagnosis.

with no underlying infertility, can exhibit analogous complications that have been described in ART children, suggesting that ART procedures are the source of these complications rather than reasons associated with infertility [9]. In this review, we discuss how ART procedures may impact epigenetic reprogramming coinciding with embryonic development and summarize the current epidemiological and experimental evidence suggesting ART procedures result in adverse postnatal cardiometabolic outcomes. It is important to consider how ART procedures may affect long-term health in offspring given the number of babies that are born using ART each year.

2. Periconception as a critical window

Notably, the procedures used in ART take place at times when maximal epigenetic reprogramming is occurring, including during female gametogenesis and immediately after fertilization. Reprogramming of the epigenome is critical to gametogenesis and early embryonic development, involving the erasure and reestablishment of DNA methylation and alterations of histone posttranslational modifications, which are essential to reset the gene expression patterns necessary for germ cell maturation. Following fertilization, the epigenome introduced by the gametes must again be reset to establish the pluripotency that is required for development of embryonic lineages. Fig. 2 depicts the changes in DNA methylation that occur during reprogramming of the germline and early embryo. Although it is well known that histone post-translational modifications are also dynamically reprogrammed at this time [10], much more information exists regarding DNA methylation changes because single nucleotide resolution on small numbers of cells has, until recently, been more robust for DNA methylation profiling. Thus, for the sake of this review, we will focus on DNA methylation. In this section, we briefly describe the vast