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In Vitro fertilization and adverse obstetric and perinatal outcomes

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ABSTRACT

Most IVF-conceived children are healthy, but IVF has also been associated with adverse obstetric and perinatal outcomes as well as congenital anomalies. There is also literature suggesting an association between IVF and neurodevelopmental disorders as well as potentially long-term metabolic outcomes. The main driver for adverse outcomes is the higher risk of multiple gestations in IVF, but as the field moves toward single embryo transfer, the rate of multiple gestations is decreasing. Studies have shown that singleton IVF pregnancies still have a higher incidence of adverse outcomes compared to unassisted singleton pregnancies. Infertility itself may be an independent risk factor. Animal models suggest that epigenetic changes in genes involved in growth and development are altered in IVF during the hormonal stimulation and embryo culture. Further animal research and prospective human data are needed to elucidate the mechanisms by which IVF may contribute to adverse outcomes and to decrease risks.

Introduction

Infertility affects 7.5 million women in the United States and approximately 1 in 8 couples have trouble conceiving or sustaining a pregnancy.[1] Assisted reproductive technologies (ART) are used to treat infertility and include hormonal medications that stimulate the ovulation of one or more oocytes, intrauterine insemination (IUI) in which a processed sample of sperm is instilled into the uterine cavity directly, and *in vitro* fertilization (IVF). IVF is a particularly successful treatment for infertility. IVF involves ovarian stimulation with gonadotropin hormones, followed by retrieval of oocytes under sedation with subsequent fertilization by sperm in the laboratory, and development of embryos in culture prior to transfer into the uterus (Fig. 1).

Since the birth of Louise Brown in 1978, over 5 million children have been conceived via IVF[2,3] and children conceived after IVF now account for 1.6% of births in the United States.[1] IVF may also be combined with intracytoplasmic sperm injection (ICSI), which is a technique for fertilization of the oocyte in the laboratory by directly injecting a single sperm into the cytoplasm of the oocyte (Fig. 1F). Since its development in the early 1990s for the treatment of male infertility, ICSI has gained popularity and, in 2012, ICSI accounted for 93.3% of IVF cycles with male factor infertility and 66.9% of IVF cycles without male factor infertility.[4] Embryos produced after IVF or ICSI may be transferred to the uterus during the same cycle of hormonal stimulation (fresh embryo transfer) or they may be cryopreserved and later thawed prior to transfer (frozen/thawed transfer) in a later cycle with more physiologic hormonal levels.

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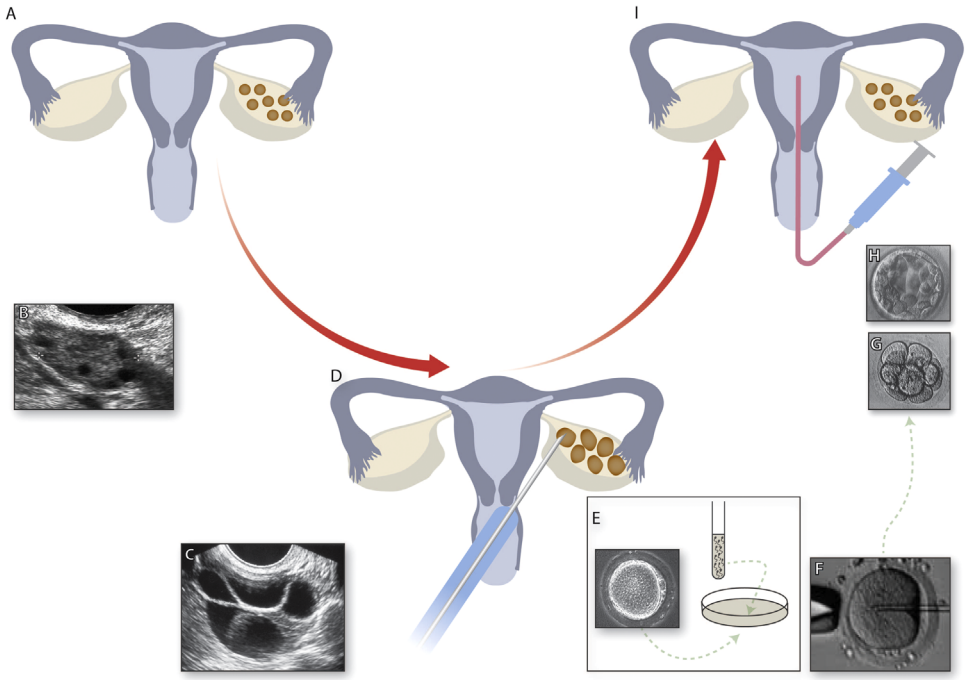

Fig. 1 – The IVF process. (A) Cartoon showing the normal female reproductive system. (B) Transvaginal ultrasound image of unstimulated ovary showing small antral follicles. Ovaries are stimulated by daily gonadotropin injections resulting in the growth of multiple ovarian follicles. (C) Transvaginal ultrasound image of a stimulated ovary with multiple growing follicles. Estradiol is produced as follicles grow and mature. (D) When follicles reach a certain size, oocytes (eggs) are retrieved from the follicles under transvaginal ultrasound guidance under sedation. Oocytes and sperm are combined in the laboratory either by (E) conventional insemination by combining the sperm and oocytes in a dish in the laboratory or by (F) intracytoplasmic sperm injection (ICSI). Embryos are cultured for 3 days (8-cell embryo (G)) to 5 days (blastocyst-stage embryo (H)). (I) A selected embryo is then transferred into the uterus and excess good-quality embryos are cryopreserved.

While the majority of IVF-conceived children are healthy, IVF has been associated with an increased risk of adverse obstetric and perinatal outcomes including hypertensive disorders of pregnancy, preterm labor (PTL) and preterm delivery (PTD), and low birth weight (LBW).[5,6] IVF pregnancies have also been associated with congenital anomalies, imprinting disorders, and neurodevelopmental disorders.[7–9] Furthermore, there is literature that shows that LBW infants are not only at increased risk for adverse neonatal outcomes, but are also at increased risk for adverse metabolic outcomes throughout life including obesity, hypertension, and diabetes.[10–16] Many of these outcomes can be attributed to an increased risk of multiple gestations with ART, however, with the increasing use of single embryo transfer, multiple pregnancies have been significantly reduced.[17,18] Still, there are conflicting data on whether singleton IVF pregnancies have similar or more adverse outcomes compared to unassisted singleton pregnancies.[19–24] This review will examine available data on the association between IVF, with or without ICSI (IVF/ICSI), and adverse perinatal as well as long-term health outcomes and help determine the epidemiological drivers of these outcomes.

Hormonal and epigenetic alterations in IVF

In IVF, the oocytes and embryos are exposed to supraphysiological levels of estradiol, which is produced by the ovaries in response to injectable gonadotropins. Vascular endothelial growth factor (VEGF) levels also become elevated in humans and mice after ovarian stimulation and may have a negative impact on placentation.[25,26] Furthermore, both female and male gametes are manipulated during oocyte retrieval and embryo culture, exposing gametes and embryos to an altered environment at the earliest and, perhaps, most susceptible period. These alterations of the gamete environment may potentially promote changes that lead to adverse perinatal outcomes. The mechanism(s) by which adverse outcomes arise from manipulations of the gamete environment are unknown and likely multifactorial, but epigenetic modification of genes responsible for growth and development may play a role. In fact, animal studies have demonstrated that even in the absence of infertility, procedures and techniques utilized during IVF/ICSI may result in epigenetic changes that lead to long-term changes in neurodevelopment, growth, and metabolism in offspring (Fig. 2).[25,27–29]

Epigenetics involves molecular mechanisms such as DNA methylation and/or histone modification of chromatin that lead to changes in gene expression and phenotypic characteristics. Imprinting is an epigenetic phenomenon in which genes are expressed by parent-of-origin. Epigenetic adaptations to a stressful intrauterine or embryo culture environment likely lead to long-term effects as shown in several human and animal studies.[30,31] Embryo culture conditions have been shown to alter the expression of the imprinted mouse gene *H19*, which is a regulator of growth.[32] Expression