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REVIEW

# Health outcomes of children born after IVF/ICSI: a review of current expert opinion and literature



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**Abstract** The Sixth Evian Annual Reproduction (EVAR) Workshop Group Meeting was held to evaluate the impact of IVF/intracytoplasmic sperm injection on the health of assisted-conception children. Epidemiologists, reproductive endocrinologists, embryologists and geneticists presented data from published literature and ongoing research on the incidence of genetic and epigenetic

abnormalities and congenital malformations in assisted-conception versus naturally conceived children to reach a consensus on the reasons for potential differences in outcomes between these two groups. IVF-conceived children have lower birthweights and higher peripheral fat, blood pressure and fasting glucose concentrations than controls. Growth, development and cognitive function in assisted-conception children are similar to controls. The absolute risk of imprinting disorders after assisted reproduction is less than 1%. A direct link between assisted reproduction and health-related outcomes in assisted-conception children could not be established. Women undergoing assisted reproduction are often older, increasing the chances of obtaining abnormal gametes that may cause deviations in outcomes between assisted-conception and naturally conceived children. However, after taking into account these factors, it is not clear to what extent poorer outcomes are due to the assisted reproduction procedures themselves. Large-scale, multicentre, prospective epidemiological studies are needed to investigate this further and to confirm long-term health consequences in assisted-conception children. 

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**KEYWORDS:** assisted reproduction, imprinting disorders, intracytoplasmic sperm injection, infertility, IVF, children outcome

## Introduction

Assisted reproduction treatment has advanced significantly since the first IVF infant born over 30 years ago (Stephens and Edwards, 1978). An estimated 3.75 million births have resulted from assisted conceptions (ESHRE, 2010), incorporating techniques such as intracytoplasmic sperm injection (ICSI; Palermo et al., 1992) and testicular sperm extraction (TESE; Devroey et al., 1994). Within Europe and countries such as Turkey and Russia, 493,184 treatment cycles were reported in 2007, with a 7.6% increase compared with 2006 (de Mouzon et al., 2012). Most treatment cycles (55.7%) were performed in France, Germany, Spain, the UK and Italy (de Mouzon et al., 2010, 2012). A trend towards increased use of ICSI has been observed worldwide (Nyboe Andersen et al., 2008, 2009).

Considering this increase, it is important to assess the potential health risks in assisted-conception children. Debate continues about whether identified risks are attributable to assisted reproduction techniques or to intrinsic parental characteristics affecting gamete quality and fertility.

The age-related diminution of the quality and fertility of oocytes is key in assisted reproduction: a high proportion of human oocytes have chromosome abnormalities and this increases with maternal age (Balasch and Gratacós, 2012; Cheung et al., 2011; Fragouli et al., 2011b; Johnson and Tough, 2012; Pellestor et al., 2003). Despite this, childbearing at advanced reproductive age is increasingly common in developed countries. Reasons include extended time at university, advancing professional careers, contraception, late meeting of the partner, incorrect information concerning progress in assisted reproduction technologies and desire for a second child after a late first pregnancy or second marriage (Lamarque et al., 2007). In the Netherlands, mean maternal age at fertility clinic intake increased by 3.7 years over two decades, from 27.7 years in 1985 to 31.4 years in 2008 (de Graaff et al., 2011). This demographic shift toward later conception has resulted in the proportion of women over 35 years at intake almost quadrupling from 7.9% to 31.2%. As more women delay childbearing until later in life, the quantity as well as the quality of oocytes obtained is reduced. In addition, unfavourable health outcomes to both mother and child are increased (Glasser et al., 2011).

Assisted reproduction treatment involves manipulating several steps in human reproduction, including hormones

to down-regulate pituitary function and stimulate the ovary for supernumerary oocyte production, in-vitro maturation of oocytes, direct injection of immature spermatozoa into oocytes, in-vitro culture of preimplantation embryos before transfer to the uterus and cryopreservation of either gametes or embryos (Zegers-Hochschild et al., 2009a,b). A large body of literature has investigated whether these procedures have the potential to alter normal gamete and embryo development and affect the health of assisted-conception children.

Of particular concern is the possibility of genomic imprinting disorders in assisted-conception children due to disturbances in the establishment and maintenance of imprinting during gametogenesis, fertilization and embryonic development (Amor and Halliday, 2008; Owen and Segars, 2009). According to the 'developmental origins of adult disease' hypothesis, prenatal conditions may change organ development and function in developing organisms (Barker, 1995). The resulting physiological, metabolic and endocrine changes can be persistent and may predispose children to increased susceptibility to disease in later life. It remains to be seen whether assisted reproduction procedures affect the epigenetic processes that occur during critical points in early embryonic development and result in long-term health consequences.

This paper provides an overview of the published literature on the incidence of genetic abnormalities and congenital malformations in assisted-conception children versus naturally conceived children and gives insights on potential differences. Collecting and interpreting data from epidemiological studies of assisted-conception children is challenging, due to a lack of uniformity of clinical definitions and differences in data collection methods. These are also highlighted in this review. The Sixth Evian Annual Reproduction (EVAR) Workshop Group Meeting was held in Evian, France in April 2011 to discuss prenatal, neonatal and long-term outcomes in assisted-conception children. It provided a unique opportunity for the faculty to present and discuss the latest scientific information on these issues. The outcomes of previous EVAR meetings have been published (Devroey et al., 2009; Diedrich et al., 2007, 2011; Fauser et al., 2008, 2011). Here are reported the opinions of the EVAR Workshop Group 2011 on the safety and impact of fertility techniques in assisted-conception children and the potential causes of deviations in genetic abnormalities.

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