Impact if In vitro Fertilization on Children’s Health: A Literature Review

Maria A. Karalexi, Marios K. Georgakis, and Eleni Th. Petridou
Department of Hygiene, University of Athens, Greece

Abstract
Indisputable are the benefits of assisted reproductive technology (ART), including in vitro fertilization (IVF) for subfertility treatment. These technologies have been increasingly adopted, albeit concerns regarding potential short- and long-term consequences on children’s health. We aimed to review previous relevant publications on a topic of major public health concern. IVF pregnancies seem to be associated with increased perinatal morbidity, including prematurity, multiple births, low birth weight and congenital malformations, as well as, neonatal mortality. Regarding long-term outcomes, IVF has been significantly associated with increased risk for cerebral palsy, mainly attributed to prematurity, whereas the neurodevelopmental outcome does not seem to be affected. IVF is also related to exposure to high stress levels; yet, the so far findings about cardiometabolic consequences remain controversial. More robust seem to be the results for certain rare malignancies, including retinoblastoma/ hepatoblastoma, and specific childhood acute leukemia subtypes. It is not clear whether the effect of IVF on the epigenetic profile can be attributed to the underlying subfertility or the procedure itself. In conclusion, IVF increases the incidence of premature and high-risk newborn, whereas pre-implantation diagnostic techniques can be used to reduce the likelihood of transmission of genetic diseases. Future epidemiologic and basic research is anticipated to more meticulously assess the long-term consequences as the cohort of IVF children is growing and to assist informed choices for subfertile couples.

INTRODUCTION
The first successful pregnancy by in vitro fertilization (IVF) was realized by P. Steptoe and R. Edwards in 1978; since then, assisted reproductive technologies (ART) have grown to encompass methods used to achieve pregnancy by artificial means during which handling of eggs and sperm occurs [1]; of note are the introduction of intra-cytoplasmic sperm injection (ICSI) pertaining to male subfertility, the cryopreservation of human embryos, and the pre-implantation genetic testing (Pre-implantation Genetic Diagnosis, PGD), which enables the prenatal diagnosis of genetic diseases [2]. Currently, more than five million “test tube babies” have been born worldwide; specifically, in the Western world, an estimated 1% of children born annually are conceived by ART [3], whereas in some European countries including Sweden, IVF pregnancies account for approximately 5% of all births [4,5].

Despite the indisputable benefits of IVF techniques in terms of subfertility treatment, their rapid spread has raised emerging scientific concerns about the potential short- and long-term adverse outcomes on both maternal and childhood health [6,7]. Although the results of several published studies are controversial, IVF pregnancies have been associated with perinatal complications, including mortality, abnormal placental growth, preterm delivery and low birth weight [7,8]. Additionally, long-term consequences of IVF have been reported, including neurodevelopmental disorders, cardiometabolic diseases and carcinogenesis [9-11].

We opted to summarize published evidence on short- and long-term outcomes of IVF on children’s health, also encompassing studies which assess the potential confounding effect of subfertility on the reported associations. 4. Methods

Relevant published scientific articles were sought in Medline database up to March 31st 2016, using combinations of the following MeSH terms: “IVF”, “in vitro fertilization”, “ICSI”, “intracytoplasmic sperm injection”, along with “adverse health outcomes”, “perinatal outcome”, “cancer”, “neurodevelopment deficits”, and “congenital malformations”. Eligible were considered studies exploring the association of IVF with risk of short- and long-term complications in the offspring.

RESULTS

Short-term outcomes
Perinatal complications: Results from three meta-analyses
have shown an increased risk of perinatal complications among children conceived by IVF, including: approximately 3 times increased risk for prematurity (Risk Ratio, RR: 2.99, 95% Confidence Intervals, CI: 1.54-5.80) [13]; 70% increase of low birth weight risk (RR: 1.70, 95% CI: 1.50-1.92), 40% for small for gestational age birth (RR: 1.40, 95% CI: 1.15-1.71), and 55% for cesarean delivery (RR: 1.54, 95% CI: 1.44-1.66) (Table 1) [12]. In addition, compared to naturally conceived, IVF newborn are more likely to require admission in Neonatal Intensive Care Units (RR: 1.27, 95% CI: 1.16-1.40) and 68% more likely to suffer any type of perinatal morbidity (RR: 1.68, 95% CI: 1.11-2.55) [12].

In recent studies [14], the risk of any complication following IVF was estimated to double compared to that of non-IVF pregnancies, whereas there also seems to be an incremental risk according to the degree of subfertility and type of fertility treatment performed [15]. Indeed, different perinatal outcomes stem from embryo transfer in a fresh or cryo-preserved IVF treatment performed [16]. In particular, births following fresh double embryo transfer (DET) have shown a 58% increased risk of perinatal mortality [16].

In addition, compared to births following fresh single embryo transfer (SET, DET) have shown a 58% increased risk of perinatal mortality [16]. In particular, births following fresh double embryo transfer (SET, DET) have shown a 58% increased risk of perinatal mortality.

In Table 1, we summarize the findings from various studies that have evaluated the risks associated with IVF. These studies have employed different designs, including cohort studies and meta-analyses, and have assessed a variety of outcomes, such as perinatal mortality, low birth weight, prematurity, and congenital malformations. The studies included in this table were conducted in different countries, such as Australia, Denmark, the United States, and Spain, and the sample sizes range from 15 to 306,995 births.

**Table 1: Descriptive characteristics of selected (cohort and meta-analyses) studies on the association of in vitro fertilization (IVF) with perinatal complications.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Study period</th>
<th>Sample size (N)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marino, 2014</td>
<td>Australia</td>
<td>Cohort</td>
<td>1986-2002</td>
<td>306,995 births/5,949 IVF pregnancies</td>
<td>IVF/perinatal mortality (OR: 1.82, 95% CI: 1.34-2.28); low birth weight (OR: 1.98, 95% CI: 1.77-2.20); prematurity (OR: 2.30, 95% CI: 1.82-2.90); neonatal death (OR: 2.04, 95% CI: 1.27-3.26)</td>
</tr>
<tr>
<td>Helmerhost, 2004</td>
<td>-</td>
<td>Meta-analysis</td>
<td>-</td>
<td>25 studies</td>
<td>ICSI with fresh-embryo transfer/low birth weight (OR: 1.96, 95% CI: 1.52-2.52); prematurity (OR: 1.63, 95% CI: 1.24-2.15); neonatal death (OR: 2.54, 95% CI: 0.91-7.06)</td>
</tr>
<tr>
<td>Jackson, 2004</td>
<td>-</td>
<td>Meta-analysis</td>
<td>-</td>
<td>15 studies (12,283 IVF/1.9 million natural pregnancies)</td>
<td>IVF/perinatal mortality (OR: 2.20, 95% CI: 1.60-3.00); prematurity (OR: 2.00, 95% CI: 1.70-2.20); low birth weight (OR: 1.80, 95% CI: 1.40-2.20)</td>
</tr>
<tr>
<td>McDonald, 2005</td>
<td>-</td>
<td>Meta-analysis</td>
<td>-</td>
<td>19 studies</td>
<td>ICSI/prematurity (&lt;33 gestation weeks, OR: 2.99, 95% CI: 1.54-5.80); very low birth weight (&lt;1500g, OR: 3.78, 95% CI: 4.29-5.75); small for gestational age (OR: 1.59, 95% CI: 1.20-2.11)</td>
</tr>
<tr>
<td>Wisborg, 2010</td>
<td>Denmark</td>
<td>Cohort</td>
<td>1989-2006</td>
<td>20,080 single births</td>
<td>IVF-ICSI/same size increased risks between children of subfertile women conceived naturally and children conceived by IVF</td>
</tr>
<tr>
<td>Cooper, 2011</td>
<td>US</td>
<td>Cohort</td>
<td>1999-2009</td>
<td>1246 fertile/461 subfertile women (natural, IVF, and OS conception)</td>
<td>IVF/same size increased risks of low birth weight between children of sub-fertile women conceived naturally and children conceived by IVF</td>
</tr>
<tr>
<td>Qin, 2016</td>
<td>-</td>
<td>Meta-analysis</td>
<td>-</td>
<td>50 cohort studies</td>
<td>IVF/prematurity (RR: 2.12, 95% CI: 1.73-2.59); low birth weight (RR: 1.61, 95% CI: 1.49-1.75); perinatal mortality (RR: 1.64, 95% CI: 1.41-1.90); congenital malformation (RR: 1.37, 95% CI: 1.29-1.45)</td>
</tr>
</tbody>
</table>

**Abbreviations:** OR: Odds Ratio; RR: Risk Ratio; CI: Confidence Intervals; IVF: In Vitro Fertilization; ICSI: Intracytoplasmic Sperm Injection; OS: Ovarian Stimulation; NICU: Neonatal Intensive Care Unit.

Relatively few studies have focused on the risk for...
chromosomal aberrations following IVF. Nonetheless, significant concerns have risen pointing to a 5% increased risk among children conceived using sperm from infertile males with the ICSI procedure compared to the 0.5% risk in the general population [26]; it is possible that this technique eliminates the power of “natural selection” of the most appropriate spermatozoon [27]. Interestingly, this effect of ICSI has been reported to be proportionally related to the sperm concentration and motility [26]; it is possible that this technique eliminates the power of “natural selection” of the most appropriate spermatozoon [27].

Of interest is the potential effect of IVF on gene imprinting in the developing fetus [29]. The majority of published studies have examined DNA methylation in children conceived by IVF, but results remain conflicting. Beckwith-Wiedemann and Angelman syndromes are the most extensively studied imprinting disorders and multiple reports have been published on IVF-conceived children suffering these disorders [30,31]; yet, given the rarity of these entities, the absolute risk appears to be low and practically negligible at a population level.

**Long-term outcomes**

**Neurodevelopmental disorders:** Neurodevelopmental outcomes of children born after spontaneous and IVF pregnancies seem to be rather comparable [32,33] as presented in (Table 2). There is scarce evidence for a low magnitude increased risk for mental delay among children born after ovulation stimulation [33]; yet, it is unknown whether this risk relies on parental factors associated with infertility. Likewise, the reported increased risk for epilepsy [33] or mental disorders, such as aggression and depression [34] in children born after IVF, might be attributed to the concomitant prematurity or low birth weight. Of note, in a large Swedish cohort study [28,158 IVF and 2,417,886 naturally conceived children] [35], IVF pregnancies were not associated with any autistic spectrum disorder. This study pointed, however, to a statistically significantly increased risk for Attention Deficit Hyperactivity Disorder (ADHD) among IVF children (Odds Ratio, OR: 1.18, 95% CI: 1.03-1.36). Nonetheless, when examining specific techniques, compared with classic IVF, ICSI has been associated with an elevated risk for autistic spectrum disorders (OR: 4.60, 95% CI: 2.14-9.88) and mental retardation [OR: 2.35, 95% CI: 1.01-5.45] [10]. Likewise, results from a large size meta-analysis showed a statistically significant association of IVF with developmental disorders and ADHD; yet, the significant between-study heterogeneity should be acknowledged [32]. A more recent meta-analysis, however, revealed only a higher risk for cerebral palsy among children born after IVF [32].

Conversely, worth noting is the higher quality of parental care in IVF versus naturally conceived children, which has been consistently reported to positively affect their long-term care in IVF versus naturally conceived children, which has been consistently reported to positively affect their long-term care in IVF versus naturally conceived children, which has been consistently reported to positively affect their long-term care in IVF versus naturally conceived children, which has been consistently reported to positively affect their long-term care in IVF versus naturally conceived children, which has been consistently reported to positively affect their long-term

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Study period</th>
<th>Sample size (N)</th>
<th>OR (95%CI)</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stromberg, 2002 [54]</td>
<td>Sweden</td>
<td>Cohort</td>
<td>1982-1995</td>
<td>5,680 IVF/11,360 naturally conceived</td>
<td>4.00 (1.90-8.30)</td>
<td>age, sex, place of residence</td>
</tr>
<tr>
<td>Hvidtjorn, 2009 [32]</td>
<td>Denmark</td>
<td>Cohort</td>
<td>1984-1997</td>
<td>9,056 IVF/1,417,166 naturally conceived</td>
<td>1.50 (1.10-2.15)</td>
<td>none</td>
</tr>
<tr>
<td>Stromberg, 2002 [54]</td>
<td>Denmark</td>
<td>Cohort</td>
<td>1995-2003</td>
<td>33,139 IVF/555,828 naturally conceived</td>
<td>1.13 (0.97-1.31)</td>
<td>multiple</td>
</tr>
<tr>
<td>Hvidtjorn, 2009 [32]</td>
<td>-</td>
<td>Meta-analysis</td>
<td>-</td>
<td>8 studies</td>
<td>inconsistent results</td>
<td>significant heterogeneity</td>
</tr>
<tr>
<td>Stromberg, 2002 [54]</td>
<td>-</td>
<td>Meta-analysis</td>
<td>-</td>
<td>30 studies</td>
<td>inconsistent results</td>
<td>significant heterogeneity</td>
</tr>
<tr>
<td>Stromberg, 2002 [54]</td>
<td>-</td>
<td>Meta-analysis</td>
<td>-</td>
<td>9 studies (19,462 IVF/432,950 naturally conceived)</td>
<td>2.18 (1.7-2.77)</td>
<td>significant heterogeneity</td>
</tr>
<tr>
<td>Stromberg, 2002 [54]</td>
<td>-</td>
<td>Meta-analysis</td>
<td>-</td>
<td>2,623,517 cohort/6,225 IVF</td>
<td>1.81 (1.52-2.13)</td>
<td>duration of subfertility</td>
</tr>
<tr>
<td>Stromberg, 2002 [54]</td>
<td>-</td>
<td>Meta-analysis</td>
<td>-</td>
<td>3,617 IVF/90,203 births</td>
<td>2.30 (1.12-4.73)</td>
<td>preterm birth, multiplicity</td>
</tr>
</tbody>
</table>

**Table 2:** Descriptive characteristics of selected (cohort and meta analyses) studies on the association of in vitro fertilization (IVF) with neurodevelopmental complications.

**Abbreviations:** OR: Odds Ratio; CI: Confidence Intervals; IVF: In Vitro Fertilization
cognitive and mental well-being [36-38]. Specifically, compared to adopted and spontaneously conceived, parents of IVF children are more likely to comply in follow-up programs, are more emotionally tied to the child and superior are also parental-childhood relationships [39].

Cardiometabolic complications: Many reports have suggested a forthcoming risk of metabolic complications for children born after IVF; this seems to be explained by the hypothesis of suboptimal embryo/fetal cellular stress conditions predisposing to adult cardiometabolic pathologies. Accumulating evidence suggests that fetal and placental growth kinetics is considered important features predicting postnatal health. Indeed, a recent systematic review has depicted an association of IVF with abdominal obesity and overall obesity, particularly among females [11]. In addition, several studies have pointed to increased levels of serum triglycerides, higher rates of subclinical hypothyroidism and rise in mean systolic and diastolic blood pressure among IVF children, whereas increased levels of fasting glucose, circulating adiponectin and insulin resistance are not yet well documented [40,41]. As the number of children born after IVF grows, it is also considered important to investigate the potential impact of IVF on atherosclerosis and cardiovascular morbidity.

Malignancies: Synthesis of findings on the association of IVF in a recent meta-analysis comprising 25 studies [42] showed statistically significantly increased risks for rare childhood cancers, such as retinoblastoma (RR: 1.62; 95% CI: 1.12-2.35), central nervous system tumors (RR: 1.88; 95% CI: 1.02-3.46), neuroblastoma (RR: 4.04; 95% CI: 1.24-13.18) and hematological malignancies (RR: 1.59; 95% CI: 1.32-1.91); likewise, positive results were yielded on the association of IVF with hepatitis (RR: 9.20, 95% CI: 2.10-31.50) [43] and Langerhans cell histiocytosis (RR: 3.20, 95% CI: 1.40-7.30) [44].

Robust, overall, seem also to be the positive but of lower magnitude findings on the association with childhood acute leukemia (RR: 1.67, 95% CI: 1.02-2.73) [45], albeit a null association was derived from a British study, likely attributed to methodological shortcomings [46,47]. The association of IVF with risk of childhood leukemia seems to meet several causality criteria as it concerns a certain type of the disease (acute lymphoblastic leukemia, ALL), is more evident among younger age groups and is particularly linked to the ovarian stimulation technique (RR: 2.60, 95% CI: 1.60-4.30) [48]. Likewise, in a Greek-Swedish study, the magnitude of risk increased from approximately 2.5 to 4 times in children with ALL aged ≥3.8 and <2 years, respectively, reflecting the putatively intrauterine origin of the disease [9].

COMMENT

In the approximately four decades following the birth of the first IVF baby, innovations in the technique have overcome numerous seemingly insurmountable barriers to allow couples the chance to childbearing. Major advances during the first decade of its implementation allowed wider accessibility of IVF. In the ensuing decade, the introduction of ICSI and other relevant techniques led to major breakthroughs in the area of male infertility. More recently, the advent of FPG allowed couples with sex-linked diseases and numerous genetic disorders to have children free of the condition. Efforts continue to focus on potential ways to increase the success of IVF using PGD for aneuploidy screening. Finally, improving the efficiency of oocyte cryopreservation and of ovarian tissue transplantation is expected to provide alternative options to women who choose to delay childbearing. Despite these major technological advances, the thriving population, currently grown to more than five million IVF children worldwide, has raised considerable scientific concerns about the potential adverse effects of the technique, as reflected in the more than 2,500 relevant publications.

Most of the reported short-term effects on the health of children born after IVF are well-documented. Nonetheless, the magnitude of the impact of the underlying infertility on the associations observed, as well as the potentially divergent effect of the different IVF technologies merit further investigation. Specifically, IVF children seem to be at increased risk for prematurity, low birth weight and other perinatal complications partly attributed to the increased risk of IVF-related multiple pregnancies. Intriguing is, however, the lower risk of perinatal complications reported for specific assisted reproduction techniques, such as ICSI. Regardless of the IVF technique, recent findings suggest that IVF embryos may be susceptible to epigenetic modifications, possibly responsible for the observed direct and late effects [49].

Regarding the potential long-term complications of IVF children, results from published studies indicate that their physical, cognitive, social and emotional development does not seem to differentiate from those conceived naturally. The only exception possibly pertains to an increased risk of neurological complications, such as cerebral palsy, potentially attributed to the common coexistent prematurity. Growing scientific interest exists, however, regarding the potential endocrine disorders, including the metabolic syndrome, whereas significant seems to be the impact of IVF on the epigenetic profile of children [29]. Lastly, recent studies have intensively focused on the potential impact of IVF on cancer development, as it constitutes the second most common cause of death in childhood following injuries. Methodological issues should be acknowledged regarding studies on childhood cancer, notably the rare and evolving exposure (IVF technology) along with the rare outcome (cancer); moreover, detailed primary data regarding the technique necessary to quantify the explored association may not be readily available in many countries. The current study aimed to merely review and synthesize published results, which point, however, to a robust positive association of IVF with some rare childhood malignancies and specific subtypes of acute leukemia.

In conclusion, IVF is worldwide recognized as one of the few fields of medicine enjoying major popular growth and sustained advances despite the accumulating evidence that IVF children may be at increased risk of perinatal complications and chromosomal anomalies compared to children naturally conceived; our understanding of the potential long-term health effects of the technique is rather immature. Therefore, an increased awareness of these potential issues is crucial, whereas intense efforts should be devoted to follow the long-term impact of IVF technologies as the oldest IVF child is turning 37 years. Future epidemiologic and basic research on the underlying pathophysiology are anticipated.
in order to assess the long-term consequences and distinguish the potential risk factors which are exclusively associated with IVF from those resulting from the concomitant parental infertility in order to assist informed choices.

REFERENCES
