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Title: Long-term follow-up of ICSI-conceived offspring compared with IVF-conceived offspring: A systematic review of health outcomes beyond the neonatal period

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Abstract

Background: The use of ICSI has increased significantly worldwide, often chosen instead of IVF, yet long-term health outcomes are unknown and health differences between ICSI and IVF conceptions have not been comprehensively assessed.

Objective: A systematic review of health outcomes of ICSI-conceived offspring beyond the neonatal period compared to IVF-conceived offspring.

Design: PubMed, OVID Medline/Embase, Informit, Web of Science and Proquest databases were searched on 9 November 2016 for studies reporting on health outcomes in ICSI-conceived offspring beyond 28 days after birth.

Main outcomes measure(s): Physical and psychosocial health.

Results: The search strategy yielded 2781 articles; 2539 were not relevant or did not meet inclusion criteria and 137 were duplicates. 105 full-text papers were evaluated further and 34 satisfied the inclusion criteria. Studies comparing ICSI- and IVF-conceived children suggest their neurodevelopment is comparable. Growth and aspects of physical health are also similar, however studies are few and limited to childhood. ICSI-conceived children may be at increased risk of autism and intellectual impairment. No difference in risk of childhood cancer was reported in one study.

Conclusion: The neurodevelopment of ICSI-conceived children appears comparable to those of IVF conception, however data relating to neurodevelopmental disorders, growth, physical health and childhood cancer are inconclusive. Further research into health outcomes in adolescence and adulthood is required before conclusions can be drawn about the long-term safety of ICSI compared to IVF. Until then, ICSI might be better reserved for its original intended use, male-factor infertility.

Key words: intra-cytoplasmic sperm injection / ICSI / follow-up / children / offspring

Introduction

Assisted Reproductive Technology (ART) has advanced significantly since the first *in vitro* fertilization (IVF) conceived baby was born in 1978. By 2013, an estimated 5 million births worldwide had resulted from assisted conception (Adamson *et al.*, 2013), and at present 1.5 million ART cycles are performed and 350,000 babies born worldwide each year (European IVF-Monitoring Consortium

(EIM) *et al.*, 2016). Intra-cytoplasmic sperm injection (ICSI) has been in clinical use since 1992, initially only for management of male factor infertility (Palermo *et al.*, 1992). As it is proven as an efficient method of fertilization, bypassing the process of natural sperm selection, it is now frequently used in cases of mild male factor infertility, unexplained infertility and fertilization failures. The percentage of ART procedures involving ICSI has escalated globally from 47.6% in 2000 to 66% in 2010 and exceeds 90% in some jurisdictions (Mansour *et al.*, 2014; Dyer *et al.*, 2016). With this increased usage, the need to understand any potential adverse effects on ICSI-conceived offspring is imperative.

Most of the literature on IVF and ICSI conceptions has focused on neonatal and obstetric outcomes with evidence of greater neonatal morbidity, obstetric complications and congenital malformations compared to spontaneous conceptions (Hansen *et al.*, 2005; Pandey *et al.*, 2012; Wen *et al.*, 2012; Hansen *et al.*, 2013; Qin *et al.*, 2015). A population-based study from Australia found a significantly reduced risk of birth defects in IVF- compared to ICSI-conceived infants, suggesting treatment effects specific to ICSI or male infertility factors may explain the association (Davies *et al.*, 2012). However, two meta-analyses demonstrated no difference in risk of congenital malformations between IVF and ICSI conception (Lie *et al.*, 2005; Wen *et al.*, 2012), and another meta-analysis, focused on genitourinary malformations, including hypospadias and cryptorchidism, also showed no significant difference on review of only higher quality studies (Massaro *et al.*, 2015).

The limited research involving ART-conceived adolescents and young adults suggests some physiological differences in their physical health (e.g. higher blood pressure) compared to spontaneously conceived (SC) peers (Wilson *et al.*, 2013). Their psychosocial outcomes, however, appear similar (Wilson *et al.*, 2011) and most IVF-conceived children develop into healthy young adults (Halliday *et al.*, 2014). No studies have yet compared health outcomes between ICSI- and IVF-conceived adolescents or young adults.

The purpose of this manuscript is to systematically review the available evidence on health outcomes in ICSI-conceived offspring beyond the neonatal period. In view of the increasing usage of ICSI over conventional IVF worldwide, and therefore the importance of examining health differences between these methods of conception, only studies directly comparing health outcomes between ICSI- and IVF-conceived children will be included.

Methodology

A literature search of online databases including PubMed, OVID Medline/Embase, Informit, Web of Science and Proquest was performed on 9 November 2016. Searches were performed for all study types published in the English language using relevant MeSH headings and key words: ("sperm injections, intracytoplasmic/" OR "ICSI" OR "intra-cytoplasmic sperm injection" OR "intracytoplasmic sperm injection") AND ("child" OR "children" OR "offspring" OR "adolescent*" OR "follow" OR "follow-up"). Articles were screened by title and abstract for information on the health and development of ICSI-conceived offspring beyond the neonatal period, defined as 28 days after birth. Full-text articles were then assessed for eligibility. Multiple papers from the same center and/or authors were reviewed in detail to determine whether the most recent publication was an accumulation of cases from earlier studies; if so then only the most recent publication was included for analysis.

Inclusion criteria were established prior to the literature search and included original studies that were either case-control or cohort studies, and reported on health outcomes in ICSI-conceived offspring beyond the neonatal period, compared to IVF-conceived offspring. Studies were excluded if they presented grouped data on IVF- and ICSI-conceived offspring, not allowing for extraction of ICSI data. Studies reporting on perinatal and later outcomes were included, but only data relating to health beyond the neonatal period were extracted for analysis. Studies focused on offspring of fathers with a known genetic cause of infertility, such as Klinefelter's syndrome or Y chromosome microdeletions were excluded. Meta-analyses, systematic reviews and case reports were also omitted from our analysis. Studies of contention were few and differences resolved by consensus. We reviewed the reference lists of all meta-analyses and systematic reviews meeting criteria to identify additional potential references.

Data were extracted by standard form from all studies according to PRISMA guidelines (Moher *et al.*, 2015). Recorded information included first author, year of publication, location, study design, sample sizes of study population and control group, plurality and gestation, age of offspring at assessment, outcome measures, methodology, confounders considered by the authors, key results, and strengths and limitations of the study. Descriptive statistics were performed using Microsoft Excel (Version 10.11.6, Microsoft Corporation, Redmond, WA, USA).

Results

A PRISMA flow diagram outlining the review process is presented in Figure 1. The search strategy yielded 2781 articles. Of these, 2539 were not relevant or did not meet inclusion criteria and 137 were duplicates. One hundred and five full-text papers were evaluated further and 34 satisfied the inclusion criteria. Of the 71 eliminated papers, 28 reported on ICSI- compared to SC offspring and 8 reported on ICSI-conceived offspring without a SC or IVF-conceived control group.

A further 35 papers were eliminated; 15 were excluded as they presented group data on IVF- and ICSI-conceived offspring that did not allow extraction of ICSI data (Pinborg *et al.*, 2003; Carson *et al.*, 2010; Hvidtjørn *et al.*, 2010; Zhu *et al.*, 2010; Carson *et al.*, 2011; Hvidtjørn *et al.*, 2011; Zachor and Ben Itzchak, 2011; Woldringh *et al.*, 2011b; Shimada *et al.*, 2012; Bay *et al.*, 2013; Lehti *et al.*, 2013; Carson *et al.*, 2013a; 2013b; Kuiper *et al.*, 2015; Pontesilli *et al.*, 2015), six were review articles (Leslie, 2004; Middelburg *et al.*, 2008; Hvidtjørn *et al.*, 2009; Woldringh *et al.*, 2010; Conti *et al.*, 2013; Ilioi and Golombok, 2015), four were commentaries or letters (Sutcliffe *et al.*, 1998; Vogt, 1999; Foresta and Ferlin, 2001; Painter and Roseboom, 2007), three presented group data on fertility treatments (Shelton *et al.*, 2009; Bay *et al.*, 2014a; 2014b), two studies did not report health outcomes beyond the neonatal period (Bonduelle *et al.*, 1999; Guo *et al.*, 2013), two studies reported on the same outcomes in the same cohort of children published previously (Bonduelle *et al.*, 1996a; 1996b), one was an editorial (Niederberger, 2005), one was a case report (Xiao *et al.*, 2009), and one paper reported group data on children born after subzonal insemination and ICSI (Bonduelle *et al.*, 1994).

Neurodevelopment

Twenty-four studies published between 1995 and 2016 (median 2006) reporting on neurodevelopment in ICSI- compared to IVF-conceived offspring at a median age (range) of 4.5 years (2 months to 7.5 years) were identified; fourteen included SC infants as an additional control group (Table I). Median sample sizes (range) were 120 (15-525), 132 (22-1153) and 85 (29-37897) for ICSI-, IVF- and SC groups, respectively. All studies assessed neurocognitive development using a range of tools, e.g., the Bayley Scales of Infant Development, Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R), and McCarthy Scales of Children's Abilities. Many studies also evaluated behavioral and psychological outcomes, and family relationships, and performed general physical and neurological examinations.

Five studies raised concerns about neurodevelopment, including an early prospective review by Bowen *et al.* (1998) of 89 one-year old ICSI-conceived children who were compared with IVF- and SC children and scored lower on the Bayley mental development index (ICSI 95.9, IVF 101.8, SC 102.5, $p<0.0001$). Similar results were observed when restricting analyses to singletons (ICSI 97.0, IVF

102.7, SC 103.2, p=0.002) and twins (ICSI 92.0, IVF 99.6, SC 100.6, p=0.03). A significantly higher proportion of ICSI-conceived children also had developmental delay, which remained significant after excluding fathers with unskilled occupations (ICSI 16%, IVF 1%, SC 1%, p<0.0001).

A study from Iran found a greater number of ICSI-conceived infants with delayed babbling compared to IVF-conceived infants of 9 months of age (Noori *et al.*, 2012).

Utilizing the Danish National Birth Cohort, Zhu *et al.* (2009) used maternal questionnaires to compare developmental progress of 18-month-old singletons of fertile couples (time to pregnancy (TTP) ≤12 months), infertile couples who conceived naturally (TTP >12 months) and couples who underwent infertility treatment. The ART group overall, which included children born after ICSI, IVF, intrauterine insemination and hormonal therapy, had a slight delay in motor and cognitive development compared to children born to infertile couples who conceived naturally (OR 1.24, 95% CI 1.01-1.53), and ICSI-conceived children had the highest risk of delay for most milestones compared to the other ART treatments.

Knoester *et al.* (2007) found higher parent reported problem behavioral scores in 81 ICSI-conceived girls aged 5 to 8 years compared to 81 IVF-conceived girls (mean difference (MD) 8, 95% CI 3-14; p<0.05), although overall problem behavioral scores and prevalence of behavioral disorders were similar between ICSI- and IVF-conceived children. No differences in parenting stress or child quality of life, as determined from child and parent questionnaires were found.

A German study reported significantly lower intelligence quotient (IQ) scores (94.1 vs 102.0, p=0.005) and higher rates of delayed cognitive development (23.5% vs 2.9%, p=0.011) in 34 ICSI-conceived children compared to 35 IVF-conceived children at 5 and 10 years of age, although the IQ of the ICSI group still fell within the normal range (Goldbeck *et al.*, 2009).

In contrast the remaining 19 studies found no significant differences in neurodevelopment between ICSI-and IVF-conceived children (Bonduelle *et al.*, 1995; 1998; Van Golde *et al.*, 1999; Bonduelle *et al.*, 2003; Leslie *et al.*, 2003; Place and Englert, 2003; Squires *et al.*, 2003; Barnes *et al.*, 2004; Papaligoura *et al.*, 2004; Ponjaert-Kristoffersen *et al.*, 2005; Sutcliffe *et al.*, 2005; Wennerholm *et al.*, 2006; Knoester *et al.*, 2007; Palermo *et al.*, 2008; Knoester *et al.*, 2008b; Xing *et al.*, 2011; Schendelaar *et al.*, 2014; Xing *et al.*, 2014; Punamäki *et al.*, 2016). A few also stratified male infertility by individual semen parameters, and found no association between presence or nature of paternal sperm abnormalities and delayed development (Bonduelle *et al.*, 2003; Leslie *et al.*, 2003; Wennerholm *et al.*, 2006). One group reported a higher proportion of children at risk of delayed development if conceived with ejaculated sperm (11.5%, 55/478) compared to surgically retrieved sperm (2.8%, 2/71; p<0.001), but this finding was unexplained (Palermo *et al.*, 2008).

Insert table I.

Neurodevelopmental disorders

Three studies utilizing population-based registry data published between 2004 and 2015 (median 2013) have reported on neurodevelopmental disorders, including rates of cerebral palsy, mental retardation and autistic spectrum disorders (ASD) (Pinborg *et al.*, 2004b; Sandin *et al.*, 2013; Kissin *et al.*, 2015) (Table II).

The first, a retrospective review in Denmark, compared 1560 ICSI-conceived singletons and twins aged 2 to 7 years to 4718 IVF-conceived singletons and twins, and 10,239 SC twins matched for age, sex, plurality and gestational age (Pinborg *et al.*, 2004b). Similar rates of cerebral palsy and mental retardation were observed in ICSI- and IVF-conceived children. There was a non-significant trend towards these problems being more evident in ICSI-conceived twins than IVF-conceived twins (OR 1.3, 95% CI 0.6-3.0), yet the converse was seen in singletons (OR 0.5, 95% CI 0.2-1.2). Adjusted odds ratios of neurological sequelae, cerebral palsy and mental retardation were the same in twins after assisted conception and SC twins.

A more recent retrospective review in the USA of 27,901 ICSI- and 13,753 IVF-conceived infants from birth until 5 years of age found a higher incidence of ASD in ICSI-conceived singletons (adjusted hazard risk ratio [aHRR] 1.65, 95% CI 1.08-2.52) and multiples (aHRR 1.71, 95% CI 1.10-2.66) (Kissin *et al.*, 2015). This difference remained significant when ICSI was used without male factor infertility (aHRR 1.57, 95% CI 1.18-2.09) or after non-surgical semen collection (aHRR 1.41, 95% CI 1.09-1.81).

A third study, using registry data in Sweden, facilitated by mandatory developmental assessments at well-child care clinics, prospectively followed 10,718 ICSI-conceived offspring derived from ejaculated sperm, 796 ICSI-conceived offspring from surgically extracted sperm, 19,445 IVF-conceived offspring and 2,510,166 SC offspring from 1 to 28 years of age to determine diagnoses of ASD and mental retardation (Sandin *et al.*, 2013). ICSI and IVF conceptions were further divided according to fresh or frozen embryo use. Overall an increased risk of mental retardation, defined as an IQ lower than 70 plus limitations in adaptive behavior, was observed in ICSI- compared to non-ICSI conceived offspring (RR 1.51, 95% CI 1.10-2.09), but was not significant when restricted to singletons (RR 1.50, 95% CI 0.98-2.29). Compared with IVF conceptions using fresh embryos, a significantly increased risk of ASD (RR 4.60, 95% CI 2.14-9.88) and mental retardation (RR 2.35, 95% CI 1.01-5.45) was associated with ICSI conceptions using surgically extracted sperm and fresh embryos. An elevated risk of mental retardation (RR 1.47, 95% CI 1.03-2.09) was also observed following ICSI conceptions using ejaculated sperm and fresh embryos. When restricting analyses to singleton births, only the risk of mental retardation after ICSI using ejaculated sperm and fresh embryos (RR 1.60, 95% CI 1.00-2.57) or frozen embryos (RR 2.36, 95% CI 1.04-5.36) were significant. Subgroup analysis of ICSI-conceived offspring according to the source of sperm revealed an increased risk of ASD in the surgically extracted sperm group compared to the ejaculated sperm group (RR 3.29, 95% CI 1.58-6.87), however this was no longer significant when analysis was restricted to singletons (RR 0.73, 95% CI 0.10-5.30). Compared with SC offspring, those born after any procedure had a significantly increased risk of mental retardation (RR 1.18, 95% CI 1.01-1.36); the risk of ASD was similar (RR 1.14, 95% CI 0.94-1.39). For both outcomes, risk estimates were not statistically significant when restricting analyses to singletons.

Insert table II.

Growth

Three studies published between 2006 and 2011 (median 2010) examined growth at a median age of 3.5 (1.5-6) years (Table III). Median sample sizes of ICSI-, IVF- and SC groups were 201 (68-330), 158 (67-347) and 851 (70-5059), respectively.

Head circumference, height and weight were similar at every time point in a prospective cohort of 166 ICSI-, 143 IVF- and 173 SC singletons who were followed from birth until 12 years of age (Basatemur *et al.*, 2010). Measurements for height and weight were obtained from medical records at birth, physical examination at 4-5 years of age, and parent questionnaires at 7-9 and 10-12 years of age.

In a larger prospective cohort of 330 ICSI- and 347 IVF-conceived singletons, with an additional cross-sectional control group of 5059 SC singletons, no significant differences in weight were recognized between ICSI- and IVF-conceived children from 1 month to 4 years of age at multiple time points (Woldringh *et al.*, 2011a). Results of IVF and ICSI combined groups compared to the SC group were also similar.

Another study examined anthropometric measurements and serum growth factors in a prospective infant and cross-sectional child cohort of ICSI- (236 infants, 68 children), IVF- (173 infants, 67 children) and SC (1530 infants, 70 children) offspring (Kai *et al.*, 2006). No significant differences in weight from 3 months to 3 years (infant cohort), and weight and insulin-like growth factor-1 and insulin-like growth factor binding protein-3 levels at 5 years (child cohort), were reported between ICSI- and IVF-conceived children.

Insert table III.

General physical health

Three studies published between 2004 and 2008 (median 2005) assessed general physical health at a median age of 5 (4.5-6.5) years (Table IV). Median sample sizes of ICSI-, IVF- and SC groups were 540 (87-2117), 437 (81-6406) and 538 (85-10239), respectively.

A retrospective review of general health, growth and medical care utilization of 81 ICSI- and 81 IVF-conceived singletons aged 5 to 8 years found overall outcomes to be similar (Knoester *et al.*, 2008a).

In a multicenter cohort of 5 year old singletons born after at least 32 weeks of gestation, ICSI- and IVF-conceived children had significantly increased rates of childhood illness, requirements for surgery and medical therapy, and hospital admissions compared to age-matched SC peers; however no significant differences were found between ICSI- and IVF-conceived children (Bonduelle *et al.*, 2005).

Data on hospital care utilization was recorded in a retrospective Danish cohort of ICSI- and IVF-conceived offspring (Pinborg *et al.*, 2004a). In this study, registry data were reviewed for hospital admissions, outpatient appointments and operations in 2117 ICSI- and 6406 IVF-conceived singletons and multiples, and 10,239 SC twins. No differences were found in hospitalizations or surgical procedures between ICSI- and IVF-conceived children. Similar risk of hospitalization and a surgical procedure was observed in ICSI and IVF twins combined, and SC twins.

Insert table IV.

Childhood cancer

A study undertaken in Israel followed 9,042 ART- and 211,763 SC children for a median of 10.6 years and 9.3 years, respectively to determine the risk of cancer (Lerner-Geva *et al.*, 2016) (Table IV). Linkage with the Israel National Cancer Registry was used to determine diagnoses with a total of 21 cases identified in the ART group (2.2 per 10,000 person-years) and 361 in the SC group (1.8 per 10,000 person-years). An upward trend in the overall adjusted cancer risk (RR 1.42, 95% CI 0.85-2.37), and a significantly increased risk for retinoblastoma (RR 6.18, 95% CI 1.22-31.2) and renal tumours (RR 3.25, 95% CI 1.67-6.32) was found in the ART group compared to the SC group. No difference in risk was observed between ICSI- and IVF-conceived children in subgroup analysis (OR 0.76, 95% CI 0.32-1.81).

Discussion

Utilization of ICSI rather than conventional IVF in cases of non-male-factor infertility continues across all regions, although is most widespread in the Middle East, despite evidence demonstrating no advantage over IVF in terms of clinical outcome (Bhattacharya *et al.*, 2001; Mansour *et al.*, 2014). This systematic review of 34 studies demonstrates that more research is required before firm conclusions can be drawn about the long-term safety of ICSI compared to conventional IVF. Studies to date have predominantly focused on neurodevelopment during infancy and childhood with reassuring results, however data on neurodevelopmental disorders, growth, general physical health and childhood cancer are limited or inconclusive, and require further investigation. Evaluation of health in adolescence and adulthood is needed, as well as studies focusing on relevant health outcomes in these age groups, such as metabolic and reproductive endpoints. Importantly, there is potential for epigenetic modifications induced by the ICSI procedure, the consequences of which may not become apparent until later in life, necessitating a much longer follow up of offspring than has occurred to date. Current evidence is inadequate but suggests the ICSI technique itself could be at least partly responsible for any adverse health effects in offspring; underlying paternal infertility, however, is likely to contribute and further research separating these factors is necessary.

This review found 24 studies of ***neurodevelopment*** and concludes that ICSI-conceived offspring are similar to their IVF-conceived counterparts in this regard. Only five studies raised concern; two of which had important methodological limitations (Bowen *et al.*, 1998; Noori *et al.*, 2012). In one, although demographic differences were considered in the analyses and groups were matched for parental age, parity and plurality, there was lack of adjustment for parent education, primary language spoken at home and maternal occupation, as well as an absence of blinding, use of cryopreserved embryos in the ICSI group and insufficient power (Bowen *et al.*, 1998). These limitations were highlighted by the same authors in a follow-up study at 5 years (Leslie *et al.*, 2003). A cross-sectional review of prelinguistic behavior in 9-month-old infants by Noori *et al.* (2012) had insufficient power, did not adjust for confounders in statistical analyses, and lacked obstetric and neonatal health data, and information regarding parent educational level and socio-economic status.

Goldbeck *et al.* (2009) reported significantly lower IQ scores in ICSI- compared to IVF-conceived 5 and 10-year old children, however this was a particularly small study with poor statistical power. Knoester *et al.* (2008) also documented a lower IQ in similarly aged ICSI- compared to IVF-conceived infants, but this finding did not reach statistical significance, and larger studies have demonstrated no differences using a wider range of cognitive measures (Leslie *et al.*, 2003; Place and Englert, 2003; Ponjaert-Kristoffersen *et al.*, 2005; Xing *et al.*, 2014). The sample size was also too small to draw firm conclusions on differences in problem behaviors between ICSI- and IVF-conceived girls, as reported in another study by Knoester *et al.* (2007). Furthermore, this latter finding contradicts results of a larger study showing no differences in behavior between ICSI- and IVF-conceived children aged 5 years, who were assessed using the same tool (Barnes *et al.*, 2004).

The evaluation of development in 18 month-old ICSI- and IVF-conceived children by Zhu *et al.* (2009) suggested that infertility treatment, especially ICSI, might be associated with a slight delay in some early developmental milestones rather than underlying parental infertility. This is supported by other studies that have evaluated developmental outcomes according to paternal semen characteristics and shown no evidence of deleterious consequences in children of fathers with severe sperm abnormalities (Bonduelle *et al.*, 2003; Leslie *et al.*, 2003; Wennerholm *et al.*, 2006).

A number of studies have reported on ***neurodevelopmental disorders*** including ASD, cerebral palsy and intellectual disability among ART-conceived infants with inconsistent results (Hvidtjørn *et al.*, 2010; Zachor and Ben Itzchak, 2011; Shimada *et al.*, 2012; Bay *et al.*, 2013; Lehti *et al.*, 2013). Studies specifically investigating the association of ICSI use with these diagnoses have also been inconclusive and a potential mechanism is yet to be proposed.

An increased risk of ASD and mental retardation in children born following ICSI using surgically extracted sperm and fresh embryo transfers compared to children of IVF conception and fresh embryo transfers was reported in a Swedish population based study; risk of mental retardation was also elevated following ICSI conception using ejaculated sperm (Sandin *et al.*, 2013). Only an increased risk of mental retardation after ICSI using ejaculated sperm remained significant, however, after restricting analyses to singletons births. These results must be interpreted with caution; information on parent educational level and socio-economic status was missing, some outcomes were based on small numbers, and confidence intervals were often wide and close to unity. Subgroup analysis according to cause of male infertility would have strengthened this study. One of the largest population-based datasets on ART found a higher incidence of ASD in ICSI- compared to IVF-conceived infants, which remained significant when ICSI was used without male factor infertility and with non-surgical method of sperm collection, again suggesting the ICSI procedure itself may be responsible (Kissin *et al.*, 2015). This finding may be flawed, as enrolment at the developmental services registry, which was used to obtain diagnoses of ASD, was voluntary and therefore the biases attributable to missing data cannot be excluded. Conversely, a registry based study from Denmark found similar rates of intellectual disability, cognitive developmental delay and cerebral palsy in ICSI- and IVF-conceived children (Pinborg *et al.*, 2004b).

Studies examining ***growth*** have demonstrated no significant differences between ICSI- and IVF-conceived children. Important limitations of Basatemur's study include its reliance on parental measurement of height and weight, small sample size, poor response rate during follow-up, and inability to control for parental height (Basatemur *et al.*, 2010). In Woldringh's cohort, parents reported on the weight of the ICSI and IVF groups, introducing potential reporting bias (Woldringh *et al.*, 2011a). By measuring serum growth factors, Kai's study provided a more extensive evaluation of growth, however it was limited by a small sample size in the child cohort and an inability to obtain blood samples from all children (Kai *et al.*, 2006).

The three studies that have compared aspects of ***general physical health***, such as childhood illnesses, requirement for surgical interventions and medical therapies, and hospitalizations, provide no evidence of adverse outcomes in the ICSI group.

The etiology of ***childhood cancer*** remains largely unclear, but may involve the early stages of fetal development (Hargreave *et al.*, 2013). Epigenetic mechanisms contribute to carcinogenesis in humans (Hargreave *et al.*, 2013), and therefore epigenetic modification of gene expression induced by ART procedures or as a result of poor gametes, in the context of parental infertility, may play a role in childhood cancer. The largest meta-analysis has previously documented an increased risk for cancers, in particular hematological, neural and solid cancers among ART-conceived children

(Hargreave *et al.*, 2013). An Israeli study investigated this more recently and demonstrated a non-significant increase in the overall cancer risk in ART compared to SC children (Lerner-Geva *et al.*, 2016). Specific types of cancer were increased, but the risk estimates were based on small numbers and may have been due to chance. There was no difference in childhood cancer risk between ICSI- and IVF-conceived children. It is difficult to draw any conclusions from this study due to limited follow-up and its retrospective design.

Given the increasing and often unnecessary use of ICSI worldwide, and its potential broad health consequences on future generations, further research efforts are paramount. A greater understanding of the health implications will enhance couple counseling prior to ART, improve clinical practice, and encourage further research into male infertility and fertility preservation options. Knowledge about the contribution of individual risk factors, including components of the ICSI procedure will enable modification and avoidance of potential harm. Therefore, until further research can demonstrate long-term safety, we suggest that ICSI be reserved for its original intended use, male-factor infertility.

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Author's contributions: S.C. designed the review and conducted the literature search, analysis, interpretation of literature and preparation of manuscript. J.H. assisted with design, study selection, analysis and interpretation of literature. R.M. and M.O. contributed to analysis and interpretation of literature.

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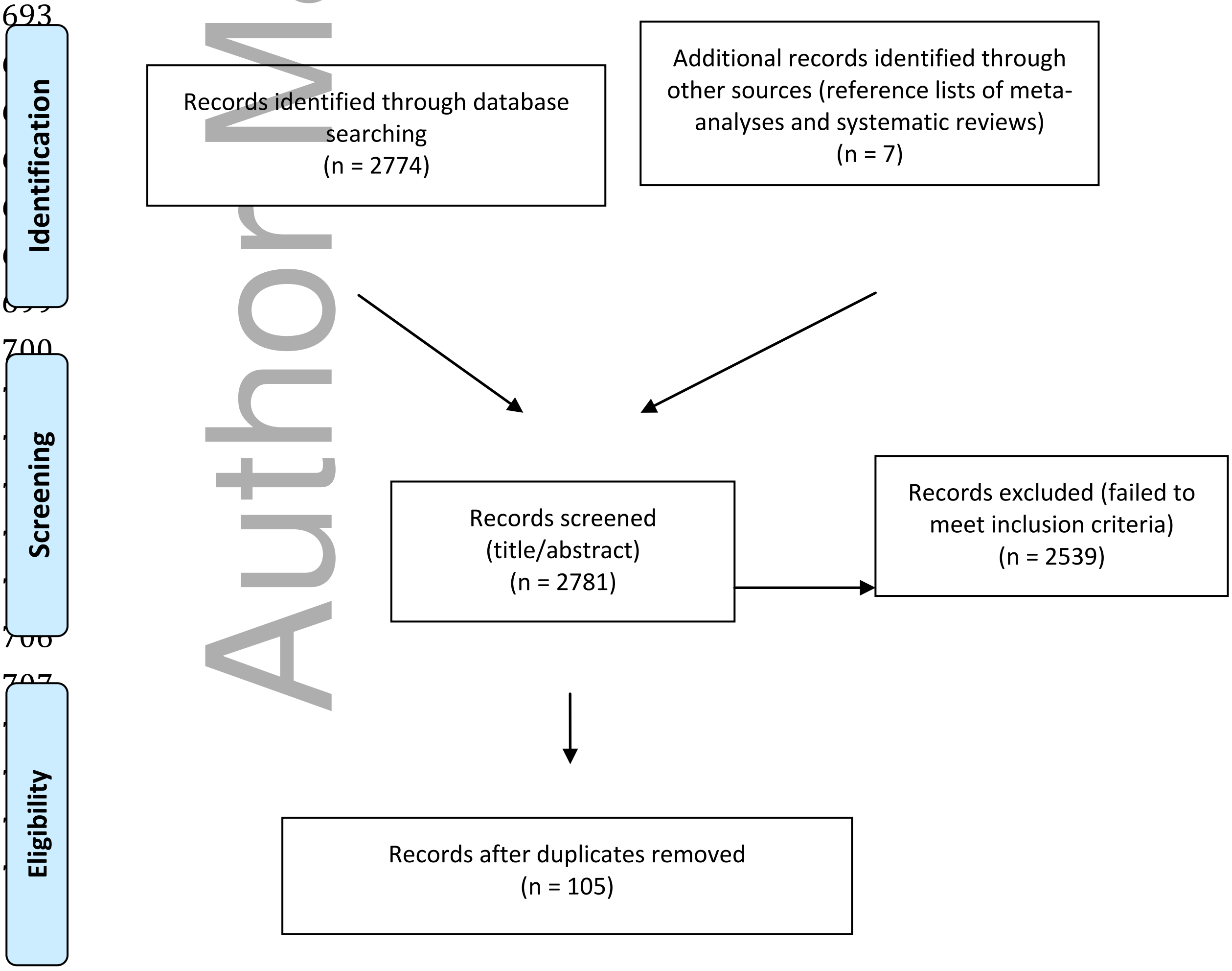
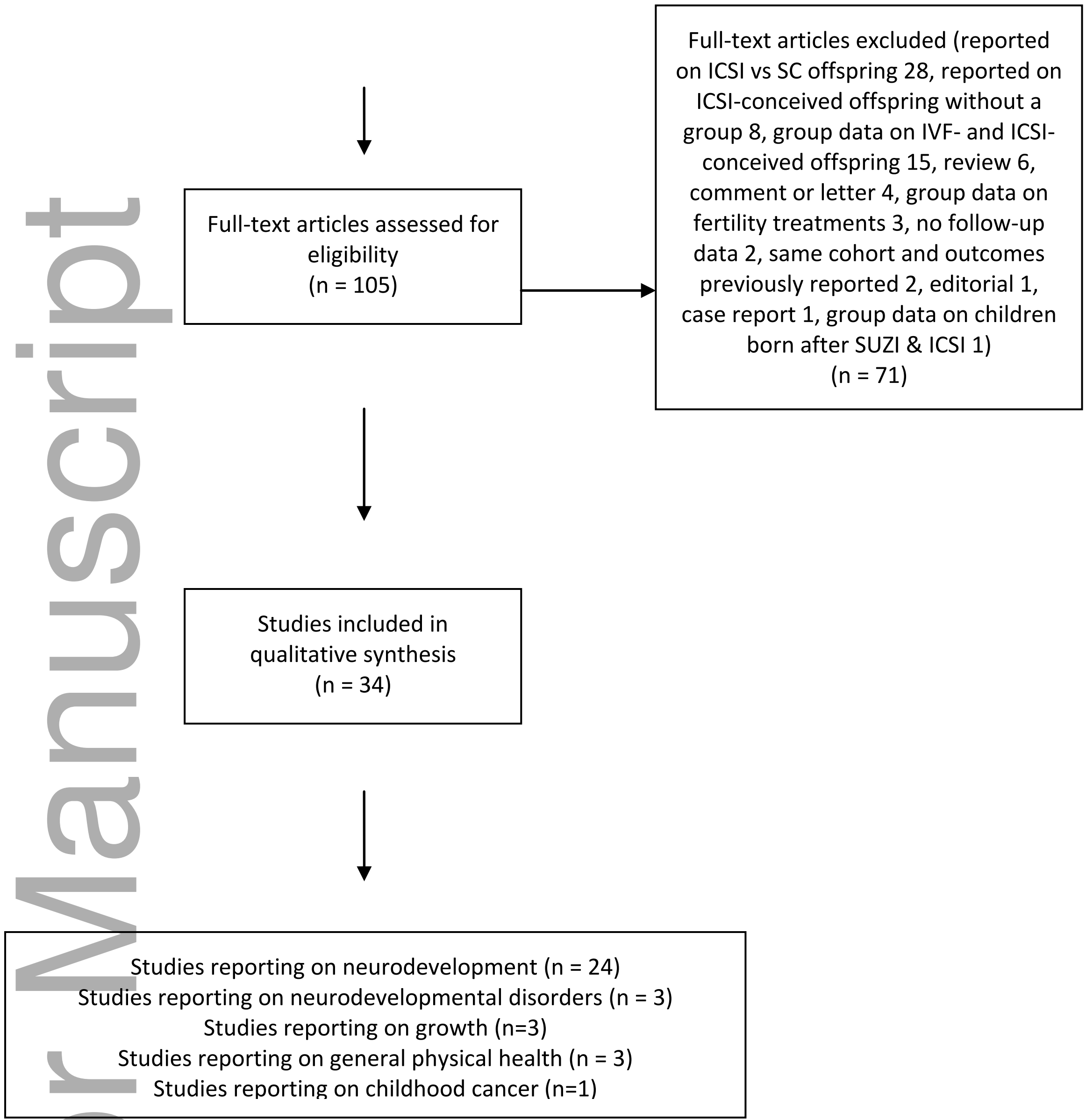
Figures





Supplementary figure 1: PRISMA four-phase flow diagram of search yield, screening and inclusion steps(Moher *et al.*, 2009)

Tables

Please see attached tables.

Table I. Studies reporting on neurodevelopment in ICSI- and IVF-conceived offspring

Authors, year, location	Research design and study population	Age	Outcome measures	Key results
Barnes *et al.* 2004, Belgium, Denmark, Greece, Sweden & UK	Cross-sectional cohort: 484 ICSI-, 403 IVF- and 502 SC offspring; singletons; ≥32 wks	5 yrs	WPPSI-R & subsets from MSCA; Bene-Anthony FRT; McDevitt & Carey temperament questionnaire; CBCL; PSI Short Form; physical examination	No significant differences in total temperament, psychomotor development or behavior of children between groups; no differences in children's feelings towards parents between groups
Bonduelle *et al.* 1995, Belgium	Prospective cohort: 120 ICSI- and 126 IVF-conceived offspring; singletons & multiples; any gestation	2 mth	Parent interviews; physical examination & developmental milestones	One child with abnormal neurological development & one with abnormal psychomotor examination in ICSI group; no significant differences between groups
Bonduelle *et al.* 1998, Belgium	Prospective cohort: 201 ICSI- and 131 IVF-conceived offspring; singletons & multiples; ≥20 wks; same cohort as Bonduelle 1995	2 yrs	BSID-II (mental scale only)*	No significant differences in overall mental development between groups; lower scores in multiples vs singletons; no difference between ICSI & IVF multiples
Bonduelle *et al.* 2003, Belgium	Prospective cohort: 439 ICSI- (378 singletons, 61 twins) and 207 IVF-conceived (138 singletons, 69 twins) offspring; singletons & twins; any gestation; same cohort as Bonduelle 1998	2 yrs	Parent questionnaires; BSID-II (mental scale)*	No difference in development between ICSI & IVF singletons or twins or children overall; no difference in Bayley score in relation to paternal sperm characteristics
Bowen *et al.* 1998, Australia	Prospective cohort: 89 ICSI-, 84 IVF- and 80 SC offspring; singletons and multiples; any gestation	1 yr	Parent questionnaires; physical examination & BSID-II at 1 yr*	Mean Bayley MDI lower in ICSI vs IVF & SC groups (95.9 vs 101.8 & 102.5, p<0.0001); higher rate of delayed development (MDI<85) at 1 yr in ICSI vs IVF & SC group (17 vs 2 & 1%, p<0.0001); persisted after exclusion of unskilled fathers (16% ICSI, 1% IVF, 1% SC; p<0.0001)
Goldbeck *et al.* 2009, Germany	Retrospective cohort: 34 ICSI- (20 at 5 yr, 14 at 10 yr) and 35 IVF-conceived (21 at 5 yr, 14 at 10 yr) offspring; singletons; ≥34 wks	5 & 10 yrs	Parent interviews; K-ABC	Lower IQ scores in ICSI vs IVF group (94.1 vs 102.0, p=0.005); greater % borderline delayed cognitive development in ICSI vs IVF group (23.5% vs 2.9%, p=0.011) – seen at 5 yr & 10 yr; IQ of ICSI group still in normal range (mean 98.2; SD 12.2)
Knoester *et al.* 2007a, Holland	Cross-sectional cohort; 81 ICSI-, 81 IVF- and 85 SC offspring; singletons; ≥37 wks	5-8 yrs	Standardized neurological examination with a focus on minor neurological dysfunction (MND)	No difference in neuromotor outcome between ICSI & IVF children (MND prevalence 66.3 vs 61.3%, PR 1.08; 95% CI 0.83-1.29)
Knoester *et al.* 2007b, Holland	Prospective cohort: 81 ICSI- vs 81 IVF-conceived, 87 ICSI- vs 85 SC offspring; singletons; any gestation; same cohort as Knoester 2007a	5-8 yrs	Parent questionnaire including CBCL, PSI & two QOL questionnaires (Dux25 & TACQOL); child questionnaire (Dux25 child form)	No significant differences in behavioral disorders between ICSI & IVF; higher behavior problem scores in ICSI girls vs IVF girls on CBCL (MD 8, p<0.05); no difference between groups in QOL scores rated by children & adults
Knoester *et al.* 2008, Holland	Prospective cohort: 83 ICSI- vs 83 IVF-conceived, 86 ICSI- vs 85 SC offspring; singletons; any gestation; same cohort as Knoester 2007a & b	5-8 yrs	Parent questionnaire; IQ measured using the RAKIT (short form)	Lower non-significant adjusted mean IQ in ICSI vs IVF group (adjusted MD 3.6, 95% CI -0.8-8.0); mean IQ of ICSI group in normal range (mean RAKIT IQ 103).
Leslie *et al.* 2003, Australia	Prospective and cross-sectional cohorts: 97 ICSI- (73 prospective, 24 cross-sectional), 80 IVF- (prospective) and 110 SC (60 prospective, 50 cross-sectional) offspring; singletons and multiples; any gestation	5 yrs	Assessment using WPPSI-R	No difference in mean full-scale IQ between groups (ICSI: 110 +/- 18, IVF: 111 +/- 13, SC: 114 +/- 13, p=0.21); no difference in % children with delayed cognitive development between groups (ICSI: 5.2%, IVF: 2.5%, SC: 0.9%, p=0.18); mean three IQ scales in normal range for all groups; no association between IQ & presence or nature of any abnormality in paternal sperm
Noori *et al.* 2012, Iran	Cross-sectional cohort: 129 ICSI- and 22 IVF-conceived offspring; plurality unknown; ≥37 wks	9 mths	Parent questionnaires to assess speech & language using ELM-2	Higher number of infants with delay in babbling in ICSI vs IVF group (40.9% vs 23.2%, no p value provided)
Palermo *et al.* 2008, USA	Prospective cohort: 553 ICSI- and 264 IVF-conceived offspring at 3 yrs, 102 ICSI- and 56 SC offspring at 5 yrs; singletons (3 & 5 yrs) and multiples (5 yrs); any gestation	3 & 5 yrs	Developmental assessment at 3 yrs using parent questionnaires including ASQ; IQ at 5 yrs using WPSSI-R; motor development using PDMS; physical examination*	No difference in development between ICSI & IVF children at 3 yrs; subgroup analysis showed more children at risk of developmental delay if ejaculated sperm used for ICSI compared with surgically retrieved sperm (11.5 vs 2.8%, p<0.001)
Papaligoura *et al.* 2004, Greece	Retrospective cohort: 15 ICSI-, 26 IVF- and 29 SC offspring; singletons & twins; any gestation	1 yr	BSID-II; parent interview to compare psychological effects of ICSI & IVF	No significant difference in mental development between groups (MDI: ICSI 101.4, IVF 95.7, SC 98.9, p=0.44; PDI: ICSI 94.1, IVF 85, SC 90.7, p=0.25)

Place *et al.* 2003, Belgium	Prospective cohort: 66 ICSI-, 52 IVF- and 59 SC offspring; singletons; ≥37 wks	9 mth - 5 yr	Maternal interview; parent questionnaire; pediatrician questionnaire; assessments at 9 & 18 months using revised Brunet-Lezine scale; assessments at 3 & 5 yrs using WPPSI-R*	No significant differences in health problems, surgical interventions & hospitalizations between groups; mean IQs significantly lower in ICSI & IVF groups vs SC group at 3 yrs (ICSI 94.1, IVF 91.7, SC 103.9, p=0.007) but no longer significant after adjusting for levels of parent education in multivariate analyses (p=0.102); no difference in mean IQs between groups at 5 years
Ponjaert-Kristofferson *et al.* 2005, Belgium, Denmark, Greece, Sweden, UK	Retrospective & prospective cohorts: 511 ICSI-, 424 IVF- and 488 SC offspring; singletons, ≥32 wks	5 yrs	WPPSI-R & MSCA Motor Scale; physical examination; FRT; parent questionnaire on parental mental health, family functioning & child's socio-emotional development	No differences between groups in cognitive (VIQ, PIQ or FSIQ) or motor function; in subgroup of firstborn children with maternal age at birth of 33-45 yrs, SC group had better VIQ & FSIQ scores than ICSI & IVF groups, but differences <1 IQ point (e.g. mean VIQ: 109.44 vs 108.75 & 108.46, p<0.05)
Punamaki *et al.* 2016, Finland	Prospective cohort: 255 ART (IVF & ICSI) vs 278 SC offspring; 164 IVF- vs 76 ICSI-conceived offspring; singletons; any gestation	7-8 yrs	Mental health - PRS of BASC; social development- Assertion-dimension of parent version of SSRS & Excluded by Peers-dimension of CBS; cognitive developmental - parental questionnaire (FTF)	No difference in mental health or developmental outcomes between ICSI & IVF groups; overall no difference in mental health or cognitive & social development between ART & SC children
Schendelaar *et al.* 2014, Holland	Prospective cohort: 67 ICSI- (extracted from IVF groups), 22 COH-IVF conceived, 27 MNC-IVF conceived and 79 SC from subfertile couples; singletons; any gestation	4 yrs	Neurological examination according to Hempel (NOS, fluency score, prevalence of complex MND)	No difference in fluency score, NOS & prevalence of complex MND between ICSI & IVF group; no difference between children of subfertile parents & fertile group
Squires *et al.* 2003, USA	Prospective cohort: 141 ICSI- and 144 IVF-conceived offspring; singletons & multiples; any gestation	4 mth-4 yrs	Parent questionnaires; ASQ to assess development at 4- & 6-month intervals	No significant difference in risk of developmental delay in ICSI vs IVF groups (11.7 vs 8.0%, p=0.07)
Sutcliffe *et al.* 2005, UK, Belgium, Denmark, Sweden, Greece	Prospective cohort: 525 ICSI-, 425 IVF- and 523 SC offspring; singletons; ≥32 wks	5 yrs	MSCA (Motor Scale) and additional 2 items (comb & spoon) to assess left handedness; parent questionnaire	No difference in observed handedness between ICSI, IVF & SC groups
Van Golde *et al.* 1999, Spain	Retrospective cohort: 120 ICSI- and 132 IVF-conceived offspring; singletons & multiples; any gestation	0-18 mth	Parent interviews; physical examination including national Catalan developmental scale by a pediatrician at 3-month intervals*	No significant differences between ICSI & IVF groups for physical &/or mental development (total developmental problems 3.4% ICSI vs 2.4% IVF)
Wennerholm *et al.* 2006, Belgium, Denmark, Greece, Sweden, UK	Retrospective cohort: 492 ICSI- (epididymal or testicular 38, sperm conc $<1x10^6$/ml 62, sperm conc 1-$5x10^6$/ml 84, sperm conc 5-$20x10^6$/ml 133, sperm conc $>20x10^6$/ml 175) and 265 IVF-conceived (sperm conc $<20x10^6$/ml 31, sperm conc $>20x10^6$/ml 234) offspring; singletons; ≥32 wks	5 yrs	Measurement of height & weight; WPPSI-R	No significant difference in growth & cognitive development between ICSI & IVF children; no difference according to paternal sperm concentration
Xing *et al.* 2011, China	Retrospective cohort: 86 ICSI- and 165 IVF-conceived offspring; singletons & multiples; any gestation	4-6 yrs	Infants-Junior Middle School Students' Social-Life Abilities Scale by interview (132-item questionnaire)	No significant difference between ICSI & IVF groups for communication, self-dependence, locomotion, work skills, socialization, self-management & total scores
Xing *et al.* 2014, China	Cross-sectional cohort: 178 ICSI- (87 singletons, 91 twins) and 388 IVF-conceived (175 singletons, 213 twins) offspring; singletons & twins; any gestation	4-6 yrs,	Parent questionnaires; C-WISC (subscales: perceptional reasoning, verbal learning, spatial orientation & speed, verbal fluency)	No difference in all IQ items between preterm singletons & twins of IVF or ICSI conception
Zhu *et al.* 2009, Denmark	Prospective cohort: 309 ICSI-, 1153 IVF-, 1029 IUI-conceived, 818 HT-conceived, 37897 SC with TTP <12 mths (fertile couples) and 4351 SC with TTP>12 mths (infertile couples) offspring; singletons; any gestation	18 mth	Parent questionnaire on 12 developmental milestones at 18 months	Slight delay in cognitive development in ART vs SC infertile group (OR 1.24, 95% CI 1.01-1.53); highest RR of delay in ICSI group vs IVF, IUI & HT groups; increased risk of severe developmental delay in ART group overall vs SC children of fertile couples (OR 2.26, 95% CI 0.72-7.08); no difference between children of untreated infertile couples & fertile couples (OR 0.84, 95% CI 0.19-3.66)

*Also reported perinatal and/or obstetric outcomes and/or congenital malformations, shaded rows represent studies showing significant differences between ICSI- and IVF-conceived children

ABC: Assessment Battery for Children, ASQ: Ages and Stages Questionnaire, BSID-II: Bayley Scales of Infant Development (2nd edition), BASC: Behavioral Assessment System for Children, CBCL: Child Behavior Checklist, CBS: child behavior scale, COH-IVF: controlled ovarian hyperstimulation IVF, DAS: Dyadic Adjustment Scale, DQ: developmental quotient, Dux25: Dutch Children TNO AZL Quality of Life Questionnaire, ELM-2: Early Language Milestone Scale-2, FRT: Family Relations Test, FSIQ: full-scale IQ, FTF: Five to Fifteen, HT: hormone treatment, IUI: Intrauterine insemination, K-ABC: Kaufman-Assessment Battery for Children, MaCA: major congenital anomalies, MDI: mental development index, MNC-IVF: modified natural cycle IVF, MD: mean difference, MND: minor neurological dysfunction, MSCA: McCarthy Scales of Children's Abilities, NOS: neurological optimality score, PRS: Parent Rating Scales, PDMS: Peabody Developmental Motor Scales, PIQ: performance IQ; PR: prevalence ratio, PSI: parenting stress index, QOL: quality of life, RAKIT: Revised Amsterdam Child Intelligence Test, SSRS: Social Skills Rating System, TACQOL: TNO AZL Child Quality of Life questionnaire, TTP: time to pregnancy, VABS: Vineland Adaptive Behavior Scale, VIQ: verbal IQ, WISC-R: Wechsler Intelligence Scale for Children-Revised, WPPSI-R: Wechsler Preschool and Primary Scales of Intelligence-Revised

Table II. Studies reporting on neurodevelopmental disorders in ICSI- and IVF-conceived offspring

Author, year, location	**Research design and study population**	**Age**	**Outcome measures**	**Key results**
Kissin *et al.* 2015, USA	Retrospective cohort: 27,901 ICSI- and 13,753 IVF-conceived offspring; singletons & multiples; any gestation	0-5 yrs	Review of medical records & registry data for demographics, obstetric history, fertility treatment, perinatal data; review of Developmental Services registry for annual incidence of autism diagnosis	Higher incidence of autism in ICSI singletons vs IVF singletons (aHRR 1.65, 95% CI 1.08-2.52) & ICSI multiples vs IVF multiples (aHRR 1.71, 95% CI 1.10-2.66); remained significant when ICSI used without male factor infertility (aHRR 1.57, 95% CI 1.18-2.09) or non-surgical semen collection (aHRR 1.41, 95% CI 1.09-1.81)
Pinborg *et al.* 2004, Denmark	Retrospective cohort: 1560 ICSI- (1149 singletons, 411 twins), 4718 IVF- (3456 singletons, 1262 twins) and 10,239 SC (all twins) offspring; any gestation; same cohort as Pinborg 2004 (table IV)	2-7 yrs	Review of registry data for obstetric outcomes, neurological & psychiatric diagnoses including CP, mental retardation, severe mental developmental disturbances & retarded psychomotor development	Similar rate of neurological sequelae in ICSI vs IVF children overall (OR 0.9, 95% CI 0.5-1.6); OR 1.3 (95% CI 0.6-3.0) for neurological sequelae in ICSI twins vs IVF twins & OR 0.5 (0.2-1.2) for ICSI singletons vs IVF singletons; no difference in prevalence of CP
Sandin *et al.* 2013, Sweden	Prospective cohort: 10,718 ICSI-conceived offspring using ejaculated sperm (9241 fresh embryo, 1477 frozen embryo), 796 ICSI-conceived offspring using surgically extracted sperm (628 fresh embryo, 168 frozen embryo), 19,445 IVF-conceived offspring (16,668 fresh embryo, 2777 frozen embryo) and 2,510,166 SC offspring; singletons & multiples; any gestation	1.5-28 yrs	Review of registry data & parent interviews for fertility history & treatment, obstetric & perinatal data, ASD diagnosis; medical & developmental screening at 4 yrs	Compared with IVF using fresh embryos, significant increase in risk for: - ASD after ICSI using surgically extracted sperm with fresh embryos (RR 4.60, 95% CI 2.14-9.88); not evident in singletons (RR 0.95, 0.13-7.09) - Mental retardation after ICSI using surgically extracted sperm with fresh embryos (RR 2.35, 1.01-5.45); not evident in singletons (RR 0.70, 0.10-5.16) - Mental retardation after ICSI using ejaculated sperm with fresh embryos (RR 1.47, 1.03-2.09), also present in singletons (RR 1.60, 1.00-2.57) - Mental retardation in singletons after ICSI using ejaculated sperm with frozen embryos (RR 2.36, 1.04-5.36) Increased risk of ASD in surgically extracted sperm group vs ejaculated (RR 3.29, 1.58-6.87), not significant when restricted to singletons (RR 0.73, 0.10-5.30); increased risk for mental retardation after ICSI vs no ICSI (RR 1.51, 1.10-2.09), similar in singletons (RR 1.50, 0.98-2.29)

aHRR: adjusted hazard risk ratio, ASD: autistic spectrum disorder, CP: cerebral palsy, SC: spontaneously conceived

Table III. Studies reporting on growth in ICSI- and IVF-conceived offspring

Authors, year, location	Research design and study population	Age	Outcome measures	Key results
Basatemur *et al.* 2010, UK	Prospective cohort: 166 ICSI-, 143 IVF- and 173 SC offspring; singletons; ≥32 wks; same cohort as Bonduelle 2005 (table IV)	0-12 yrs	Review of clinic records for birth measurements; height & weight measured by pediatrician at 4-5 yrs; height & weight at 7-9 yrs & 10-12 yrs from parent questionnaires (response rate 60% ICSI/IVF groups, 44% SC group)	No significant differences in HC, height & weight between groups at any time point
Kai *et al.* 2006, Denmark	Prospective infant cohort: 236 ICSI-, 173 IVF-, 1530 SC offspring; singletons & multiples; ≥32 wks Cross-sectional child cohort: 68 ICSI-, 67 IVF-, 70 SC offspring; singletons; ≥32 wks	Infant cohort: 3 mth-3 yr Child cohort: 5 yr	Parent questionnaires on parental height; anthropometric measurements (height, weight, HC, AC, BMI, fat folds) at birth, 3, 18, 36 (infant cohort) & 60 months (child cohort); non-fasting blood samples for serum IGF-1 & IGFBP-3 at 3 months (60% ICSI, 63% IVF, 67% SC) & 5 yrs (78% ICSI, 82% IVF, 84% SC)*	No differences in anthropometrical measurements between ICSI & IVF children & controls in either cohort; no significant differences in IGF-1 or IGFBP-3 at 3 & 5 yrs between ICSI & IVF groups
Woldringh *et al.* 2011, Holland	Prospective and cross-sectional cohorts: 330 ICSI- & 347 IVF-conceived offspring (prospective), 5059 SC offspring (cross-sectional); singletons; ≥37 wks	1 mth-4 yrs	Parent questionnaires including questions about weight at 1, 3, 4, 12 & 18 mths & 2, 3 & 4 yrs; weight measurements by local doctor in SC group at similar intervals	No significant difference in weight from 1 month to 4 years between ICSI & IVF groups

*Also reported perinatal and/or obstetric outcomes and/or congenital malformations
AC: abdominal circumference, BMI: body mass index, HC: head circumference, SC: spontaneously conceived

Table IV. Studies reporting on general physical health and childhood cancer in ICSI- and IVF conceived offspring

Authors, year, location	**Research design and study population**	**Age**	**Outcome measures**	**Key results**
General physical health				
Bonduelle *et al.* 2005, Belgium, UK, Denmark, Sweden, Greece	Cross-sectional cohort: 540 ICSI-, 437 IVF- and 538 SC offspring; singletons; ≥32 wks; same cohort as Barnes 2004 (table III)	5 yrs	Parent interview; physical examination including anthropometric data, visual acuity & pure tone audiometry*	Compared to SC group, ICSI & IVF children more likely to have significant childhood illness (74% ICSI, 77% IVF, 57% SC; p<0.001), need surgery (24% ICSI, 22% IVF, 14% SC; p<0.001) esp. genitourinary surgery (5% ICSI, 3% IVF, 1% SC; p=0.005), require medical therapy (11% ICSI, 9% IVF, 5% SC; p<0.001) & be admitted to hospital (31% ICSI, 28% IVF, 20% SC; p<0.001); no difference in physical examination between groups; no difference in outcomes between countries
Knoester *et al.* 2008, Holland	Retrospective cohort: 81 ICSI- and 81 IVF-conceived offspring, 87 ICSI- and 85 SC offspring; singletons; any gestation	5-8 yrs	Parent questionnaire; physical examination including biometrical data & vision*	Higher rate of physical therapy in IVF vs ICSI group (OR 2.6, 95% CI 1.0-6.6); unexplained increased frequency of vomiting in IVF vs ICSI group; no difference in general health, growth or hospitalizations between ICSI & IVF or SC groups
Pinborg *et al.* 2004, Denmark	Retrospective cohort: 2117 ICSI- offspring (1282 singletons, 835 twins), 6406 IVF-offspring (3848 singletons, 2558 twins) and 10239 SC twins; any gestation; same cohort as Pinborg 2004 (table II)	2-7 yrs	Review of registry data for hospital admissions, mean number of days in hospital, outpatient appointments, diagnoses & operations performed	No difference in hospitalizations & surgical procedures between ICSI & IVF children; no difference in hospitalizations & surgical procedures between IVF/ICSI twins & SC twins
Childhood cancer				
Lerner-Geva *et al.* 2016, Israel	Retrospective cohort: 9,042 ART vs 211,763 SC children, ICSI vs IVF (numbers not disclosed in study); singletons & multiples; any gestation	9-11 yrs	Cancer diagnoses via linkage with the Israel National Cancer Registry	Elevated risk for overall cancer in ART vs SC group, but not statistically significant after adjustment for maternal & infant characteristics (RR 1.42, 95% CI 0.85-2.37); significantly increased risk for retinoblastoma (RR 6.18, 95% CI 1.22-31.2) & renal cancer (RR 3.25, 95% CI 1.67-6.32) in ART group but small numbers; no difference in risk of cancer between ICSI & IVF (OR 0.76, 95% CI 0.32-1.81)

*Also reported perinatal and/or obstetric outcomes and/or congenital malformations
SC: spontaneously conceived