Impact of male factor infertility on offspring health and development

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Monitoring the safety of intracytoplasmic sperm injection (ICSI) has been impeded by uncertainties regarding the extent to which offspring health is influenced by paternal characteristics linked to male infertility or the processes that ICSI treatment entails. Few studies examining long-term health and developmental outcomes in children conceived with ICSI have considered the influence of paternal infertility adequately. In the available literature, large population-based studies suggest underlying male factors, and the severity of male factor infertility, increase the risk of mental retardation and autism in offspring, as does the ICSI procedure itself, but these findings have not been replicated consistently. Robust evidence of the influence of male factors on other health outcomes is lacking, with many studies limited by sample size. Nevertheless, emerging evidence suggests children conceived with ICSI have increased adiposity, particularly girls. Further, young men conceived with ICSI may have impaired spermatogenesis; the mechanisms underlying this remain unclear, with inconclusive evidence of inheritance of Y chromosome microdeletions. The current inconsistent and often sparse literature concerning the long-term health of children conceived with ICSI, and the specific influence of male infertility factors, underscore the need for concerted monitoring of children conceived with this technique across the lifespan. With the rapid expansion of use of ICSI for non-male factors, sufficiently large studies that compare outcomes between groups conceived with this technique for male factors versus non-male factors will provide critical evidence to elucidate the intergenerational impact of male infertility. (Fertil Steril® 2019;111:1047–53. ©2019 by American Society for Reproductive Medicine.)

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Male factor infertility is defined as one or more abnormal semen parameters detected on semen analysis or the presence of inadequate sexual or ejaculatory function (1). Among couples seeking treatment for infertility, male factors are the sole cause in approximately 20% of cases and implicated in a further 30% to 40% in combination with female factors (2–5).

Common semen abnormalities include low semen volume (oligospermia, ≤1.5 ml), low sperm concentration (oligozoospermia, ≤15 million spermatozoa/ml), decreased sperm motility (asthenozoospermia, total motility ≤40% or <32% progressive motile spermatozoa), and abnormal sperm morphology (teratozoospermia, ≤4% normal forms) (6). The degree of male infertility is typically classified as severe when there is a sperm concentration less than 5 million per milliliter (severe oligozoospermia) or no sperm in the ejaculate (azoospermia) (7).

The introduction of intracytoplasmic sperm injection (ICSI) into assisted reproductive technology (ART) in 1992 heralded a breakthrough in the treatment of severe male factor infertility. Prior to that, couples with this type of infertility often faced a poor prognosis with conventional in vitro fertilization (IVF), which is reliant on optimal numbers and functioning of sperm for fertilization. In contrast, ICSI involves the direct injection of a single spermatozoon into the oocyte via micromanipulation techniques, using either ejaculated sperm or, in the case of azoospermia, microsurgically extracted sperm from the epididymis or testis.

The use of ICSI has enabled many couples worldwide to achieve their desire for a biological child. Nevertheless, there have been ongoing concerns about the health and developmental outcomes of children conceived by this technique, as the use of a single spermatozoon bypasses the processes of natural sperm selection occurring in normal fertilization.

A primary concern is the potential for transmission of genetic disorders to the child. Men with severe oligozoospermia or azoospermia have an increased risk of genetic abnormalities including karyotypic chromosomal abnormalities, Y-chromosome microdeletions and cystic fibrosis gene mutations, and can also have sperm that are chromosomally

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TABLE 1

Summary of research examining paternal infertility requiring treatment with ICSI on long-term health and developmental outcomes in offspring.

Outcome	Summary
Cognitive outcomes	The severity of male factor infertility does not appear to influence cognitive development in early childhood among children conceived with ICSI, however, many studies are limited by sample size and the potential for ICSI by itself to influence cognitive outcomes requires clarification.
Neurodevelopmental disorders	Several large population-based studies report modest increases in risks of mental retardation and autism in children conceived with ICSI. There are conflicting findings concerning the specific contribution of male factor infertility to these elevated risks.
Growth, adiposity, and cardiometabolic health	There is evidence that children conceived with ICSI have accelerated postnatal growth and may be at risk of increased adiposity, particularly girls. The specific influence of male factor infertility on these outcomes remains unknown, and studies are limited by small sample size.
Male infertility	Men conceived with ICSI may have impaired spermatogenesis, which could be due to either inherited or non-inherited factors. This requires confirmation in larger studies.

Note: ICSI = intracytoplasmic sperm injection.

Rumbold. Health of children born to men with infertility. Fertil Steril 2019.

abnormal even when there is no detectable genetic defect (7–9). Genetic factors have also recently been linked to abnormalities in sperm morphology and function (10).

A second concern is the potential introduction of epigenetic modifications, with diverse consequences for offspring health and development (11, 12). Epigenetic alterations may occur because of parental characteristics related to infertility or directly from the laboratory processes involved in ICSI required to create and manipulate embryos (13).

Several reviews of the literature pertaining to long-term health and developmental outcomes of children conceived with ICSI have now been undertaken (14–17). These reviews identify possible increased risks of certain neurodevelopmental disorders, as well as impaired cardiometabolic and reproductive health profiles among children conceived with ICSI. However, the pattern of elevated risks is not consistent across all studies. In addition, uncertainties remain about whether any increases in risk are due to infertility itself or to aspects of the treatment.

Discerning the impact of these various factors has been difficult in historical cohorts of ICSI-conceived children, where the use of ICSI has occurred exclusively for severe male infertility. Typically, children in these cohorts have been compared with either children conceived spontaneously or those conceived with conventional IVF; in both instances, the parental health profiles of the comparison groups are considerably different to the ICSI group, and the treatment modality tends to be inextricably linked to the type of infertility experienced.

However, the past two decades have witnessed a rapid rise in the use of ICSI for mild male factor infertility, non-male factors, and fertilization failures (18), such that it is now the predominant mode of ART conception in many countries. While this may not be prudent given the unknown risks (19), it does mean that it is now possible to examine outcomes among children conceived with ICSI with stratification for type and severity of infertility, including specific sperm parameters. This is important not only for counselling individual couples about long-term risks associated with an infertility diagnosis, but also for identifying the treatment factors that could be modified to promote offspring health.

Here we review the literature concerning the long-term outcomes of children conceived with ICSI, where attempts have been made to distinguish the specific influence of male factor infertility (and severity) from ICSI treatment-related factors. We focus on outcomes related to cognitive development, neurodevelopmental disorders, growth and metabolic health, and male infertility (Table 1).

COGNITIVE OUTCOMES

There is now a substantial pool of studies examining cognitive outcomes in children conceived with ICSI. A recent systematic review of this literature (14) found that most studies were subject to methodological limitations, with less than a third of studies rated as high quality. Among high quality studies the results were conflicting, with some evidence of lower intelligence quotient (IQ) scores among children conceived with ICSI relative to spontaneously conceived children and IVF children, while other studies reported comparable outcomes between these groups.

We identified seven studies that examined cognitive outcomes among children conceived with ICSI with stratification for specific paternal sperm parameters. In a study of 208 singleton children aged 1 to 2 years of age, Sutcliffe and colleagues (20) reported no differences in mean scores on the Griffiths Mental Development Scales between children conceived to oligozoospermic men and those conceived to men with other sperm abnormalities or other indications for ICSI. The findings were replicated by the same group in a study of 58 singleton ICSI children of the same age (21), with the authors concluding that the severity of the father's sperm defect did not significantly influence infant neurodevelopmental outcomes. Similarly, in a subset of 439 ICSI children (including twins) aged 24 to 28 months, Bonduelle et al. (22) found no difference in the mean scores on the Bayley Scales of Infant Development when stratified by sperm

parameters, including severe oligozoospermia, as well as indicators of sperm motility and morphology.

In a study of older children by Leslie and colleagues (23), including 97 ICSI-conceived children aged 5 years of age, comparisons were made with peers conceived with conventional IVF or spontaneously. There were no overall differences in mean IQ between these groups, however, the distribution of IQ was shifted to the left among ICSI children, such that 5.2% had an IQ <85 compared with 2.5% and 0.9% of IVF and spontaneous conception groups. Although this was not statistically significant, the findings raise concern about possible intellectual impairment in the ICSI group. Most relevant to the focus of this review, within the subgroup of ICSI-conceived children, mean IQ was not different between children stratified by the type of paternal defect, and the IQ of children whose father had a triple sperm defect was not significantly different from that of children whose fathers had normal sperm.

These findings are in agreement with Wennerholm and colleagues (24) who examined cognitive outcomes in five year-old singleton children born after 32 weeks and conceived with ICSI (n=492) and IVF (n=265) in five European countries. Within the ICSI group, mean IQ scores were similar across all sperm concentration levels, and when the source of sperm was epididymal or testicular compared with ejaculated sperm. Similarly, in the IVF group, IQ scores were similar between children of fathers with a sperm count <20 and ≥20 million per ml.

Two further studies examining the influence of the source of sperm reported that cognitive outcomes were superior in the group of children conceived with surgically extracted sperm. In a Dutch study, mental development scores on the Bayley scales were higher in 148 singleton children aged 2 years and conceived from epididymal sperm in comparison with Dutch age matched reference scores (25). However, this could be due to confounding as the authors did not adjust for maternal education, which was higher in the ICSI group. Further, in a study of three year-old children, Palermo and colleagues (26) found offspring conceived with surgically extracted sperm were less likely to be classified as developmentally at risk than those conceived from ejaculated sperm using the Ages and Stages Questionnaire (2.8% vs. 11.5%, $P<.001$). These anomalous findings warrant further exploration, and may be subject to bias, as few details were provided about the establishment of this cohort.

Collectively these studies suggest that among children conceived with ICSI, the severity of male factor infertility does not appear to influence cognitive development in early childhood. However, studies of cognitive outcome in adolescents and adulthood are lacking. A key limitation of the existing literature is the small sample size of the ICSI group overall (<500 across all studies), and in each strata of sperm parameter, including the 'normal' sperm comparison group. Therefore, these studies only have adequate statistical power to detect large differences between groups and null findings cannot be viewed as reassuring. Existing studies are also subject to bias arising from incomplete follow up arising from attrition, and selection bias due to exclusion of multiple births reviews (14–16). In addition, while these studies suggest cognitive outcomes are comparable between children conceived by ICSI for severe and less severe sperm defects, the inconsistent findings in the general literature concerning outcomes of ICSI children means that the potential for ICSI by itself to influence cognitive outcomes still requires clarification.

In summary, large appropriately designed population-based studies, for whom the indications for infertility treatment are well characterized, and with a sufficiently sized comparison group of children conceived with ICSI for non-male factor indications are needed to clarify both the influence of male factor infertility and ICSI on cognitive outcomes.

NEURODEVELOMENTAL DISORDERS

A recent systematic review examined the influence of ICSI on neurodevelopmental disorders and found conflicting findings with regard to the risks of mental retardation and autism among children conceived with ICSI relative to those conceived with conventional IVF (15).

We identified four large population registry studies that specifically examined the contribution of male factor infertility to neurodevelopmental disorders in these groups. The largest of these studies, undertaken by Sandin and colleagues (27) in Sweden, involved 10,718 children conceived with ICSI, 19,445 children conceived with IVF, and 2,510,166 spontaneously conceived children born between 1982 and 2007 and followed for an average of 10 years. In this study, the risk of mental retardation was heightened in children conceived with any ART (relative risk [RR] 1.18, 95% confidence interval [CI] 1.01–1.36), and particularly elevated in those conceived with ICSI relative to IVF (RR 1.51, 95% CI 1.10–2.09). When the source of sperm was examined, relative to conventional IVF (with fresh embryo transfer cycles), the risk of mental retardation was greatest in those conceived with ICSI using surgically extracted sperm and fresh embryo transfer cycles (RR 2.35, 95% CI 1.01–5.45, $P=.05$) and remained elevated in those conceived with ICSI using ejaculated sperm and fresh embryo cycles (RR 1.47, 95% CI 1.03–2.09). Further, children conceived with ICSI using ejaculated sperm and frozen embryo cycles also had an elevated risk (RR 2.36, 95% CI 1.04–5.36). The findings were robust to adjustment for parental age, parental psychiatric history, child age, and birth year. However, when confined to singletons, the association for ICSI and surgically extracted sperm lost statistical significance, most likely reflecting a loss of statistical power.

Irrespective of mode of conception, the overall comparison of use of surgically extracted versus ejaculated sperm revealed an elevated risk of mental retardation in the surgical group although this was not statistically significant (RR 1.67, 95% CI 0.73–3.79), except in the subgroup born preterm (RR 3.31 95% CI 1.18–9.31). While risks are elevated, the absolute frequency of mental retardation in these groups was low. Nevertheless, the findings suggest that severe male infertility, requiring surgical sperm extraction, contributes to an increased risk of mental retardation in offspring. Importantly, treatment factors, including ICSI and embryo cryopreserva-

In the same study, the risk of autism was examined and found to be increased in children conceived with ICSI using surgically extracted sperm and fresh embryo cycles relative to conventional IVF (RR 4.60, 95% CI 2.14–9.88). These findings were not significant in the sub analyses of singleton births, again, possibly reflecting a loss of statistical power. Comparing children conceived with surgically extracted sperm with those conceived with ejaculated sperm (using either conventional IVF or ICSI), there was an increase in risk associated with surgical extraction (RR 3.29 95% CI 1.58–6.87), suggesting the severity of paternal infertility is an important contributor to risk of autism.

Kissin and colleagues (28) examined diagnosis of autism within the first five years of life in 42,383 children conceived with ART (1997–2006), and reported an overall increase in risk of autism when ICSI was used over conventional IVF, which was present in both singletons (hazard ratio [HR] 1.65, 95% CI 1.08–2.52) and multiple births (HR 1.71, 1.10–2.66), after adjusting for parental age, infant sex, and pregnancy and birth outcomes. Importantly, a diagnosis of male infertility was not associated with an increased risk of autism, when results were stratified by type of infertility (male/non-male) and method of semen collection. For example, relative to children conceived with IVF (without ICSI), the association between autism and ICSI was stronger among children conceived with ICSI for non-male factors (HR 1.57, 95% CI 1.18–2.09) and using ejaculated sperm (HR 1.41, 95% CI 1.06–1.81), and attenuated and no longer statistically significant in children conceived with ICSI for male factor infertility (HR 1.23, 95% CI 0.92–1.64) and using surgically collected semen (HR 1.22, 95% CI 0.65–2.31). A diagnosis of male factor infertility thus appears to be a very broad classification, lacking precision as an exposure variable. This should be borne in mind throughout this review.

Two further studies contrast with the findings of both of these prospective cohorts. In a large Danish study of mental disorders (autism, mental retardation, and conduct disorders) in over 33,000 children conceived with fertility treatment born between 1995 and 2003, there was no increased risk of any disorder in children conceived with ICSI, or separately for children conceived with either IVF or ICSI for male factor infertility, when compared with spontaneously conceived controls (29). In addition, Hvidtjorn and colleagues (30) found no increased risk of autism in children conceived with either IVF or ICSI with a male infertility diagnosis, relative to spontaneously conceived controls.

In relation to other neurodevelopmental disorders, several studies have now examined the risk of cerebral palsy in ART children (31), however, we identified only one study that stratified outcomes according to the type of infertility. In that study, the risk of cerebral palsy was not elevated in those conceived with IVF or ICSI for male factor infertility relative to other causes, nor when ICSI was compared with conventional IVF, however the number of cases of cerebral palsy was small (32).

In summary, several large population registry studies report modest increases in risks of mental retardation and autism in children conceived with ICSI. However, these findings have not been replicated consistently, and there are conflicting results concerning the specific contribution of male factor infertility to the elevated risk. Possible explanations for the inconsistent findings include differences in the diagnosis and recording of male factor infertility, in the length of follow up of children, or in the ascertainment of neurodevelopmental disorders. For example, one study (28) utilized a database established to manage support services for affected families, which therefore may reflect more severe cases of neurological impairment. Nevertheless, given the severity of these outcomes, further investigation of neurodevelopmental disorders among children conceived with ICSI is warranted, with well-defined indications for treatment.

GROWTH, ADIPOSITY AND CARDIOMETABOLIC HEALTH

There have been longstanding concerns about the growth of ART children overall, given the established excess of preterm birth and low birth weight in this group (33) and the emerging evidence from animal and human studies suggesting that specific IVF and ICSI components can induce epigenetic modifications in genes that affect fetal growth (12, 34). Concerns extend to the risk of obesity and poor cardiometabolic health in later life, which in the general population are elevated in children born small who then have accelerated postnatal growth, possibly as a result of enduring effects of epigenetic reprogramming (35).

There remains a paucity of studies examining patterns of childhood growth in children conceived with ICSI. In a recent systematic review and meta-analysis of studies of childhood growth in singletons (age range 1–28 years, median 5 years), children conceived with ICSI were found to have similar weight and height to those conceived spontaneously (17). In several of the included studies, comparable childhood weight was observed in the ICSI and spontaneous conception groups, despite ICSI children having lower birth weights, indicating a higher rate of postnatal growth in this group. Additional analyses by age group indicated that accelerated growth occurred predominantly before 5 years of age. The influence of type of infertility was not explored in any of these studies. In addition, few studies examined growth beyond preschool age, and many of these studies were subject to potential bias arising from low participation rates.

We identified only one study that examined the influence of sperm parameters on growth in children conceived with ICSI (24). In that study of singleton children born at greater than 32 weeks gestation, the height and weight at age 5 years did not differ substantively in the ICSI (n=492) or IVF (n=265) groups when stratified by the source of sperm or sperm concentration.

A small number of studies have reported measures of adiposity, blood pressure and insulin resistance in children conceived with ICSI. Most of this literature comprises repeated observations of a Belgium cohort of singleton ICSI-conceived children born after 32 weeks gestation undertaken by Belva and colleagues (36–38). In this cohort, at age 8 years ICSI-conceived children had higher systolic and diastolic blood pressure than spontaneously conceived controls

(37), but this difference was not sustained at subsequent follow up at 14 years of age (38).

Further, at the 14 year follow up, the group reported that body composition measurements were higher in ICSI-conceived girls, indicating susceptibility to central, peripheral and total adiposity, and both ICSI conceived-males and females with more advanced pubertal development had more peripheral adiposity (39). At 18 to 22 years of age, there were comparable rates of cardiometabolic risk factors, including mean concentrations of total cholesterol, triglycerides, insulin, HOMA-IR, and blood pressure between the ICSI and spontaneous conception groups (36). The exception was that young men conceived with ICSI were more likely to have low high-density lipoprotein cholesterol concentration than male controls (19.6% vs. 5.6%).

Within this cohort, the use of ICSI occurred predominantly for male factor infertility, however, the possible influence of semen factors on the outcomes of interest was not explicitly examined. In addition, the small sample size (the original cohort comprised 439 children at 2 years of age) and low participation rate at each follow up point (e.g. 30% of the eligible ICSI cohort participated at 18 years of age), mean the findings could be subject to bias.

We identified one further large population registry study that examined the risk of type 1 diabetes in children conceived with IVF or ICSI, stratified by type of infertility (40). This group found no elevated risk of this condition among children conceived with IVF or ICSI relative to spontaneous conceptions, nor among those conceived to parents with recorded male factor infertility (irrespective of mode of conception).

In summary, among the few studies that have examined growth and cardiometabolic factors, there is evidence that ICSI children experience accelerated postnatal growth, and may be at risk of increased adiposity, particularly girls. The specific influence of male factor infertility on these outcomes remains unknown.

MALE INFERTILITY

Whether the use of ICSI perpetuates male infertility in offspring has been a central concern since the introduction of this technique. However, efforts to understand this have been hampered by a lack of knowledge about the role of genetic and epigenetic factors in idiopathic male infertility. The relative youth of the ICSI-conceived population, with the oldest children now just beginning to enter their peak reproductive years, is also an impediment. Before adulthood, there is often large variability in hormonal parameters at any given age, reflecting considerable variation in maturation rates of children.

Despite this, a small number of prospective studies have examined hormonal profiles in male children conceived with ICSI. Mau Kai and colleagues (41) examined neonatal testicular function at 3 months of age, and found the 87 male infants conceived with ICSI for male factors had a 23% to 27% reduction in serum testosterone and free serum testosterone, and a 60% reduction in luteinizing hormone to testosterone ratio compared with infants conceived spontaneously. There was no difference in these parameters when male infants conceived with IVF for female factors were compared with spontaneously conceived peers.

In the cohort established in Belgium by Belva and colleagues, described earlier, at 8 years of age there was no difference in concentrations of inhibin B or antimüllerian hormone, both indicators of Sertoli-cell function, among boys conceived with ICSI compared with spontaneously conceived peers (42) or in subsequent follow up at 14 years of age (43). Salivary testosterone concentration was comparable between these groups at 14 years (44). Within the group conceived with ICSI, there were no clear differences in the concentration of inhibin B, antimüllerian hormone, or salivary testosterone for boys born to fathers with severe oligozoospermia versus those without, although these subgroups were small (n=38 and n=20, respectively).

When the Belgium cohort was assessed at age 18–22 years, there was evidence of reduced semen quality among men conceived with ICSI (45), with the overall median sperm count, median total sperm count and total motile sperm count being half that of their spontaneously conceived peers. This finding was robust to adjustment for key confounders such as age, BMI, abstinence period, genital malformation, and time to analysis. Other parameters, including sperm morphology, total motility, progressive motility and volume were not appreciably different between the groups. When assessed against World Health Organization reference values, ICSI-conceived men (n=54) were more than twice as likely to have a sperm concentration <15 million per ml (OR 2.7, 95% CI 1.1–6.7), an extremely low sperm concentration (<5 million per ml) (OR 2.6, 95% CI 0.6–10.7) and below-reference (<4% normal) sperm morphology rates (OR 2.3, 95% CI 0.7–7.9), although the latter two comparisons were not statistically significant. ICSI men were also three to four times more likely to have inhibin B levels below the 10th percentile and FSH levels above the 90th percentile in comparison with spontaneously conceived peers, however the differences were of borderline statistical significance (46).

Among the ICSI-conceived men, 72% were born to fathers with a sperm concentration <15 million per ml (48% had <5 million per ml). There was no strong correlation between paternal sperm parameters and the sperm parameters of their sons, except for total sperm count, which was only weakly negatively correlated (45). Further paternal severe oligozoospermia did not increase the likelihood of the son having a low sperm concentration.

In the same cohort, eight men conceived with ICSI had extremely low sperm counts (<5 million per ml), and of these, six were tested for Y chromosome deletions, with no abnormalities detected in any participants. These findings suggest that Y chromosome deletions, either inherited or de novo mutations, were not responsible for the reduced sperm quality seen in ICSI sons.

Nevertheless, two subsequent studies provide some evidence of inherited Y chromosome deletions in sons conceived with ICSI. In a study of 87 infertile men and 47 sons, Katagiri and colleagues (8) detected Y chromosome microdeletions in 3.4% of the fathers and 2.1% of their sons; among the children, none were de novo deletions. Further, in a smaller study

of 44 ICSI-conceived sons, a partial microdeletion was present in one son and also detected in his father (26).

In summary, among the few studies that have examined reproductive outcomes among male children conceived with ICSI, there is some evidence of impaired spermatogenesis. The reasons for this remain obscure. There is some evidence of transmission of Y-chromosome microdeletions in sons, however, this was not consistently found. Nevertheless, this does not rule out the possibly of other genetic causes or the transmission of epimutations related to paternal characteristics or treatment factors.

Across all the studies, the number of ICSI-conceived children was small, and all relied on a single blood or semen sample. This may limit the reliability of findings, particularly the semen analysis, as sperm concentration and volume can fluctuate significantly within the same individual in response to physiological and environmental stressors. Therefore, while the existing studies provide important first evidence of impaired fertility among offspring, the findings require confirmation in larger studies.

CONCLUSION

Current knowledge of the implications of male factor infertility for the long-term health of the offspring has been clouded by an inability to separate out the influence of infertility from its treatment, namely ICSI. Evidence from recent large population-based registry studies suggests that both severe male factor infertility and the use of ICSI may contribute to a small increase in risk of mental retardation and autism in offspring, however there are inconsistent findings about the relative contribution of these factors. There is a much smaller literature examining other health outcomes, particularly in the period beyond early childhood. Nevertheless, the emerging evidence of changes in body composition during adolescence, particularly among girls conceived with ICSI, and the presence of sperm abnormalities in adult males conceived with ICSI, warrant further investigation. The specific contribution of paternal factors to these outcomes remains unclear.

With the rapid expansion in use of ICSI for non-male factor infertility, it will be increasingly possible to discern the effects of paternal characteristics and treatment factors on childhood outcomes. This will require sustained investment in population registries and in longitudinal clinical studies to support comprehensive follow up and achieve sufficient sample sizes. Unpacking these relationships will also necessitate continued efforts to standardize the evaluation and reporting of semen parameters (47), comprehensive characterization of indications for infertility treatment, and the careful construction of appropriate control groups. Comparison of outcomes among children conceived with ICSI for male factors versus ICSI for non-male factors, matched for other treatment processes (e.g. cryopreservation) will provide critical information to draw reliable conclusions about the contribution of male infertility on the life-long health of offspring. In view of the suggestive evidence that ICSI may directly contribute to risks, the avoidance of ICSI when conceived with less invasive treatment accentuates this imperative.

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