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Child health: is it really ART that we need to be concerned about?

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Abstract

Concerns remain about the health of children conceived by infertility treatment. Studies to date have predominantly not identified substantial long-term health effects after accounting for plurality, which is reassuring given the increasing numbers of children conceived by infertility treatment worldwide. However, as technological advances in treatment arise, ongoing studies remain critical for monitoring health effects. To study whether the techniques used in infertility treatment cause health differences, however, remains challenging due to identification of an appropriate comparison group, heterogeneous treatment, and confounding by the underlying causes of infertility. In fact, the factors that are associated with underlying infertility, including parental obesity and other specific male and female factors may be important independent factors to consider. As such, the following review will summarize key methodological considerations in studying children conceived by infertility treatment including the evidence of associations between underlying infertility factors and child health.

Keywords

child health; IVF; confounding; epidemiology

INTRODUCTION

The health of children conceived with assisted reproductive technologies (ART) has always been of concern to couples considering infertility treatments and for health practitioners. Worldwide, the number of births conceived by ART continues to climb.^{1–3} As of 2015, ART contributed to 1.7% of all births in the United States (US).² Almost all ART procedures

performed in the US are *in vitro* fertilization (IVF), of which 69% included intracytoplasmic sperm injection (ICSI).² Though other types of fertility treatment, including ovulation induction (OI) and intrauterine insemination (IUI), are commonly used as the first line of treatment, less data has been gathered to track their trends over time. Estimates of births conceived with non-ART treatments range from 3–7%.⁴

There have been numerous reviews published on the topic of child health after conception by infertility treatment, including one published last year in the current journal⁵ and our own focused on cardio-metabolic health.⁶ Hence, the current review is not intended to exhaustively review the existing literature in this area. However, in brief, evidence suggests that babies conceived by ART are born earlier and smaller than their peers, which lead to concerns for neurodevelopmental and other long-term health outcomes given the evidence from developmental origins of health and disease research. Nevertheless, in general we^{7,8} and others have found no major differences in development or growth in early childhood after accounting for plurality. Longer term studies are needed, as well as studies with a substantial group of children conceived by non-ART treatments. Less investigated are early signs of developmental differences such as fetal growth and placental development.⁹ Specific techniques and treatment effects such as embryo culture media and oocyte vitrification also continue to be evaluated.

The goal of the present review is to discuss the epidemiologic hurdles to studying the health impact of conception by infertility treatment, including how perhaps the reasons for infertility may drive independent health effects long-term. Under the developmental origins of health and disease paradigm, specific conditions, such as maternal obesity, may lead to long-term offspring health risks ranging from obesity to neurodevelopmental delay. These conditions are also related to the risk of infertility. As such, we will also review common risk factors for male and female infertility and discuss potential impacts on developmental programming in order to address how best to investigate whether ART itself possesses risks to child health.

EPIDEMIOLOGIC RESEARCH INTO HEALTH OF CHILDREN CONCEIVED BY INFERTILITY TREATMENT

There are some unique methodological considerations for studying children conceived by infertility treatment. Table 1 summarizes the considerations below which are discussed in greater detail.

Population Considerations

Couples undergoing infertility treatment comprise a unique study population, making it challenging to choose the correct comparison group in epidemiologic studies. Many studies investigating health effects of children conceived by infertility treatment have utilized a group of children conceived spontaneously as a comparison. An inherent problem with using a comparison group of children conceived spontaneously is that it becomes difficult to discern whether the adverse health outcomes potentially observed in the offspring are a result of the infertility treatment, or rather the underlying infertility that indicated treatment.

If the study question is to examine the effect of infertility treatment on the risk of health outcomes, comparisons should be made between children spontaneously conceived and children conceived through treatment, either both derived from fertile couples or both from infertile couples. The former strategy may be unethical and the latter may be untenable. Hence, other strategies are necessary.

One such strategy is to compare health of children conceived with ART against children conceived by subfertile couples in the same clinic who did not go on to use ART as a method. The Millennium Birth Cohort, for example, examined children who were conceived by subfertile couples. They did not find any differences between the ART (n=101) and the subfertile (n=485) groups with regards to childhood behavioral difficulties at 5 and 7 years of age.¹⁰ In a separate investigation using the same cohort, the researchers found that subfertility was associated with risk of asthma in children along with the ART group.¹¹ Some difficulties in using this strategy include not having equal sample sizes of children followed, and residual confounding, as couples who undergo ART may likely have more severe infertility than subfertile couples which remain a source of unclear bias. For rare outcomes, a combination of large registry data may be necessary. One such large retrospective cohort in Massachusetts found that use of ART and diagnosed subfertility were both associated with higher prevalence of birth defects compared to spontaneous conceptions.¹² Their definition of subfertility may more represent that of resolved infertility, as it included a past indication of infertility treatment but not in the current cycle.¹² Such a definition may provide a closer counterfactual comparison to remove underlying infertility rather than no conception after 12 months of trying, but may also have the limitation of misclassification for any current fertility treatment use missed from documentation or a change in partner. Nevertheless, it is an important strategy to keep in mind for trying to disentangle underlying infertility from findings on treatment effects.

Apart from underlying infertility, population comparability is also challenged by the socioeconomic gap between couples who can afford infertility treatment for conception and couples in the general population. According to data from 2014, the average cost of one fresh ART cycle in the US has been estimated as \$13,548 US dollars, which may be a substantial proportion of annual household income in the general population.¹³ Until recently, ART was not part of mandated health insurance coverage, and as a result, those seeking treatment for infertility were of higher socioeconomic background, limiting the generalizability of findings from the epidemiologic studies to the general population. Since the 1980's, 14 states in the US have passed laws mandating the insurance coverage of infertility treatments. As insurance coverage for these treatments has become more widely available for a broader population, there is increasing heterogeneity in the socioeconomic background of children born to ART treatments. Despite increased availability of treatment, evidence suggests that racial and economic disparities persist even in mandated states, perhaps due to lack of access and awareness of treatments.¹⁴ As such, efforts should be made in future epidemiologic studies to evaluate long-term outcomes children conceived by infertility treatment among socioeconomically and racially heterogeneous populations, and also consider whether the study population is paying for treatment out-of-pocket.

Heterogeneous treatments

Adding to the difficulties of separating specific treatment effects from confounding by underlying infertility is that the selection of treatment options is a revolving process. Treatment selection primarily depends on the factors related to infertility diagnosis and the patients' response to specific types of treatment. When treatment fails, a more aggressive protocols may be used. Grouping all ART together creates a heterogeneous exposure group. Studies are now beginning to separate the types of hormonal treatment used for ovarian stimulation to better investigate specific long-term health effects. One such study using large registry data found that progesterone treatment rather than other hormonal exposures, increased autism risk.¹⁵

Other studies have also evaluated the effects of ICSI as it is becoming increasingly common for the treatment of male factor infertility. In fact, its use in the US has increased from 36.4% in 1996 to 76.2% in 2018, with the largest increase among cycles without male factor infertility.¹⁶ The safety of ICSI has been questioned due to reports suggesting an increase in congenital anomalies in children who were conceived with ICSI.^{17–19} The majority of studies utilize registry data to capture these rare outcomes.^{16,18–21} As infertility may be a risk factor for birth defects, studies comparing ICSI to the general population do not properly address the risk of the ICSI procedure itself.^{19,22–24} For example, the indication for ICSI is an important factor, as male factor infertility has been associated with an elevated risk of congenital malformations. A cohort of 1,586 patients undergoing prenatal invasive screening after ICSI found that abnormal fetal karyotypes were increased in fetuses conceived after ICSI in comparison to the general population (1.4 versus 0.3 to 0.4%). Of the inherited anomalies experienced in the ICSI population, 17 of 22 were due to a structural anomaly in the father. In addition, de novo mutations were increased for semen concentration less than $20 \times 10^6/\text{ml}$.²⁵ The higher rate of genitourinary defects in male infants conceived with ICSI implicates that male factor infertility is likely an independent contributing factor.¹⁸

Evolving technologies

Ongoing surveillance and research are also required to keep up with the technological advances being made in infertility treatment. In 2013, the American Society for Reproductive Medicine (ASRM) announced that oocyte cryopreservation was no longer considered experimental.²⁶ Vitrification is the technique of cryopreservation that solidifies the cell and extracellular environment into a glass-like state without the formation of ice.²⁷ Due to this recent change, no childhood studies have been conducted but short-term perinatal outcomes have been examined. A prospective case control study compared pregnancy outcomes of previously vitrified oocytes from egg donors to fresh autologous oocytes.²⁸ There was no significant difference between the gestational age at delivery or birth weight.²⁸ However, this study potentially selected on the highest achievable outcomes, as the donor population is consistently young and healthy. More studies are needed to assess clinical outcomes in the general population. An observational cohort study found that embryo quality was not impacted by use of cryopreserved oocytes. However, morphokinetic studies did show that embryo development was delayed after use of cryopreserved oocytes. It is unknown if this may translate to pregnancy or neonatal outcomes.²⁹

Another recent change in practice is that transfer of day 5 embryos has been advocated by ASRM to decrease the risk of multiple gestations and allow selection of the highest quality embryo.³⁰ The development of the embryo to the blastocyst stage provides an additional competence measure, as the activation of the embryonic genome occurs at the 8-cell stage.³¹ Blastocysts transfers are reported to result in higher live birth rates in comparison to cleavage stage embryos in good prognosis patients.³² It is suggested that increased implantation rates are a result of improved endometrial synchronization.^{32,33} However, good prognosis patients are more likely to be selected for a day 5 transfer as they are more likely to have a greater number of embryos available for transfer. A randomized study including women who were less than 37 years of age had a higher pregnancy rate after embryo transfer on day 5 compared to day 3 (35.6% vs 23.7%).³⁴ A retrospective study found that in patients less than age 40, live birth rates per initiated cycle were significantly higher after transfer of single blastocyst versus cleavage-stage embryo (37.8% vs 31.3%).³⁵ A retrospective clinical study found that with increasing age, patients were less likely to develop an embryo to the blastocyst stage. However, this was likely due to the decrease number of oocytes retrieved. Patients, regardless of age, achieved similar pregnancy rates per blastocyst transferred.³⁶

Extended culture of embryos to day 5 may be associated with adverse pregnancy outcomes. A total of 12,712 singleton births recorded in the Canadian ART Register database were reviewed to identify the impact on obstetric outcomes. Day 5 embryo transfer was associated with an increased risk of preterm birth in day 5 versus day 3 embryo transfer (odds ratio [OR] 1.32, 95% confidence interval [CI] 1.17–1.49).³⁷ A retrospective review of Society for Assisted Reproductive Technology (SART) 2004–2006 data found an increased risk of preterm delivery in singleton pregnancies after day 5 transfer compared with day 3 transfer (18.6% vs 14.4 %; adjusted OR 1.39, 95% CI 1.29–1.50).³⁸ These findings were also consistent for donor recipient patients and patients who were considered to have a good prognosis. A meta-analysis also reported that day 5 embryo transfers were associated with an increase in congenital anomalies in comparison to cleavage stage embryos (OR 1.29, 95% CI 1.03–1.62).³⁹ A retrospective registry study reviewing 4,819 singleton births after blastocyst transfers, 25,747 cleavage-stage transfers and nearly 2 million spontaneous conceptions found no increase in birth defects. However, perinatal mortality and risk of placental complications were higher in blastocyst transfers.⁴⁰ Blastocyst transfer may impact child development as well. A randomized control study found that the type of culture media was associated with birth weight and growth during the first 2 years of life.⁴¹ Culture media has been shown to influence expression of genes critical for embryo development in animal studies.⁴² Future studies are necessary to determine the impact of blastocyst transfer on the development of the fetus and throughout the lifetime of the individual. Such changes in techniques also drive the necessity for ongoing surveillance.

EPIDEMIOLOGIC CUNUNDRUM: ART VS. UNDERLYING INFERTILITY

Apart from population and technological considerations, underlying infertility has been a source of confounding giving rise to questions regarding whether associations observed with child health are truly due to treatment effects. Parental health has an impact on child outcomes beginning at delivery.⁴³ Despite a wealth of research into developmental programming from maternal pregnancy conditions, fewer studies have focused on pre-

conceptional health and how infertility risk factors of both partners may play a role. Part of the difficulties lie in measuring participants prior to pregnancy as well as accuracy of participant reported diagnoses of some of the infertility disorders. Below summarizes the evidence for factors which children's health has been investigated, including parental age, parental obesity, dietary intake, thyroid function, depression, and other female gynecologic conditions.

Parental age

Advanced maternal age (≥ 35 years) increases risks of pregnancy and neonatal complications.^{44–46} It can also increase risks of chromosomal abnormalities. Based on increasing rates of preterm delivery and other adverse neonatal outcomes, one anticipates higher risks of adverse long-term outcomes. However, risks of long-term impact on childhood growth and development from advanced maternal age may be modified by postnatal circumstances. Women of older age at childbirth tend to have better socioeconomic status and it is difficult to tease apart those benefits conferred. Indeed, in a study of children from five birth cohorts in low to middle income countries, stunting at 2 years of age (OR 0.64; 95% CI 0.54–0.77) and failure to complete secondary schooling (OR 0.59; 95% CI 0.48–0.71) were both protected by advanced maternal age as compared to children of mothers of 20–25 years of age.⁴⁷ A retrospective cohort study tried to tackle the question of longer term outcomes by using hospital data linking 200,000 deliveries in Israel and their outcomes through 18 years of age.⁴⁸ They did not identify clear differences in risk of childhood morbidities (i.e., central nervous system/brain, lymphoma, leukemia) related to maternal age at 35–39 (hazard ratio [HR] 1.06; 95% CI 0.76–1.48) or even at 40–50 years (HR 0.73; 95% CI: 0.36–1.46) when compared to 20–34 years.⁴⁸ Yet, other studies have observed high risks of childhood cancers including retinoblastoma and leukemia with increasing maternal age.⁴⁹ Further complicating the impact of maternal age in ART is the use of donor or autologous oocytes and the unclear comparison group in those cases. Live-birth rates decline with increasing maternal age in ART but this is particularly true for autologous cycles rather than for donor cycles.⁵⁰ Hence, the maternal age effects are suspected to be due to decreasing oocyte quality over time, but aside from short-term outcomes, the impact of maternal age over the life-course may be counterbalanced by positive socioeconomic influences with older age, particularly in terms of childhood growth and development although perhaps less so for risks of cancer.

Paternal age may also play a role that sometimes is difficult to isolate from the effects of maternal age as couples tend to have correlated age. For example, the Childhood Leukemia International Consortium identified increased risks of acute lymphoblastic leukemia associated with advanced paternal age with mixed results for advanced maternal age, owing to the collinearity of the age information.⁵¹ Accumulating evidence suggests, however, that paternal age and indeed paternal risk factors in general, may be important to assess. A very comprehensive systematic review of this evidence was published on paternal factors.⁵² The authors located the most articles for investigations into paternal age, with much fewer for other aspects (i.e., obesity, smoking) due to fewer studies with paternal information. For short-term outcomes, they found “little or no difference” in rates of preterm, low birth weight or small-for-gestational age due to advanced paternal age. A very slight increase in

stillbirths (with low evidence) and in birth defects (with moderate evidence) was also observed. For longer term outcomes, paternal age has been related to risks for autism⁵³ but evidence of other psychiatric disorders is lacking. Little evidence suggested increased risks for childhood cancer, obesity, or diabetes.⁵²

Parental Obesity

About a third of all US adults are obese (BMI ≥ 30), making it a critical concern. Male and female obesity increases risk of infertility. For females, obesity is associated with anovulation, miscarriage and longer time to pregnancy. The impact of adiposity is primarily hypothesized to be through hormonal disruption as adipose tissue is endocrinologically active. For males, increases in DNA fragmentation and epigenetic effects have been observed and are beginning to be further elucidated. Few studies have investigated childhood outcomes related to paternal BMI.⁵² In the short-term, paternal height rather than BMI is associated with birthweight. In terms of long-term effects, the Upstate KIDS Study observed that paternal obesity (BMI ≥ 30) was associated with increased odds of failing the personal-social domain of the Ages and Stages Questionnaire (ASQ), rated by parents at 4, 8, 12, 18, 24, 30, and 36 months of age.⁵⁴ Although this association was not strong, it was independent of maternal BMI. In fact, maternal obesity was associated with failing the fine motor domain. Severe parental obesity (BMI ≥ 35 in both parents) was additionally associated with failing the problem-solving domain. Findings from Suren and colleagues using data from MoBa, a large birth cohort from Norway, has also demonstrated a stronger, linear association between paternal BMI rather than maternal BMI with risk of developing autism.⁵⁵

As the role of epigenetics have come to be demonstrated, however, empirical evidence suggests that the paternal contribution goes beyond traditional heridity.^{56,57} In 2015, scientists from INSERM demonstrated in a clever experiment that sperm/testis RNA from male mice fed a western diet injected into one-cell embryos of control parents fed standard diets, lead to progeny with higher weight and altered glucose tolerance.⁵⁸ They further identified two microRNAs (i.e., miR-19b and miR-29a) to be particularly dysregulated in male mice fed western diets. Specifically, miR-19b micro-injection increased offspring body weight. Apart from miRNA, other small piwi RNA (piRNA) or transfer RNA (tRNA) are also suspected to play a role.⁵⁶

Many more studies have investigated the role of maternal obesity on short- and long-term outcomes in child health. Pre-pregnancy BMI is also associated with pregnancy complications such as gestational diabetes and preeclampsia which in turn lead to neonatal complications such as preterm delivery and suboptimal fetal growth (i.e., macrosomia or growth restriction). Apart from the observed associations in Upstate KIDS mentioned above, other studies have also identified maternal obesity as a risk factor for a range of neurodevelopmental outcomes.⁵⁹

Dietary factors: Vitamin D

Moreover, obesity is tied to energy balance, dietary intake, and micronutrient metabolism. For instance, obese individuals are more likely to have low circulating concentrations of 25-hydroxy vitamin D [25(OH)D] since the lipid soluble vitamin is sequestered by adipose

tissue. Vitamin D's potential link with fertility is suggested by evidence that its receptor is prevalent on both male and female reproductive tissues in rodent models.⁶⁰ In one study, female rats deficient in vitamin D experienced a 75% reduction in fertility.⁶¹ Investigations in humans have largely focused on pregnancy outcomes of women undergoing ART. As recently reviewed by Pacis et. al., vitamin D deficient women [25(OH)D<20ng/mL] have a lower percent implantation and clinical pregnancy per embryo transfer compared with vitamin D sufficient [25(OH)D ≥30ng/mL] women.⁶²

Maternal vitamin D levels, in turn, have been investigated with regards to child health. Gestational and cord blood 25(OH)D concentrations have been associated with neurodevelopmental outcomes, such as mental or psychomotor development, among infants and toddlers in most,^{63–68} but not all,⁶⁹ studies. In early childhood, low 25(OH)D concentrations from gestational or newborn samples have been related to externalizing symptoms,⁷⁰ attention deficit hyperactivity disorder (ADHD)-like symptoms^{70–72} and autism diagnosis.^{73–75} Interestingly, no association between gestational or cord blood 25(OH)D and lifetime ADHD diagnosis has been detected.^{76,77} In middle childhood and early adolescence, gestational 25(OH)D has been inversely associated with language ability⁷⁸ and verbal fluency.⁷⁹ However, it is unclear if the associations detected between 25(OH)D and markers of infant development translate into other cognitive or behavioral problems later in life since, with one exception,⁶⁹ no relation between low 25(OH)D concentrations and measures of cognitive ability (i.e., IQ or scholastic achievement)^{68,70,77,80} or behavior problems^{68,69,77,78,80,81} in middle childhood or adolescence has been found. Nutritional studies remain difficult to conduct. Unlike vitamin D, many other factors such as protein intake or even caloric consumption, are not well captured by biomarkers. Self-report is also limited. Future epidemiologic studies of maternal nutrition may leverage on new technologies such as metabolomics.

Polycystic Ovarian Syndrome (PCOS)

PCOS is a complex endocrine disorder affecting 5–16% of women.^{82–84} It is the most common identifiable cause of infertility, and is characterized by menstrual irregularities, hyperandrogenism, polycystic ovaries, and frequently, obesity and insulin resistance.⁸² PCOS is a strongly heritable disorder, with studies suggesting that over 70% of PCOS is linked to genetic causes.^{85,86} Mothers with PCOS are at higher risk of numerous pregnancy complications, including gestational diabetes, pregnancy-induced hypertension, preeclampsia, pre-term birth, and infant mortality, which may all influence offspring health.^{87,88} Women with PCOS may be hyperandrogenic during pregnancy, and endocrine function during pregnancy may impact fetal development. While these changes do not appear to impact infant growth patterns, accumulating evidence suggests that *in utero* exposure to a hyperandrogenic environment is associated with neurodevelopmental disorders in offspring.^{89–94} In the Upstate KIDS Study, maternal PCOS was associated with higher risks of developmental delays in several domains, particularly among girls.⁸⁹ This finding has been supported by several large studies in Europe using administrative data, which have found associations between maternal PCOS and/or elevated fetal testosterone and higher risks of autism, ADHD and pervasive developmental disabilities.^{90–92,95–99}

As with studies of potential health effects of IVF on offspring, studies of PCOS face several methodological challenges. PCOS is a heterogeneous condition with diagnostic criteria that have changed over time, and identification of true cases may be challenging. As PCOS is associated with higher risks of depression and mental health disorders, there has been some concerns that maternal mental health may confound the relationship between PCOS and offspring neurodevelopment, despite a lack of evidence that maternal mental health conditions cause PCOS. A large recent study in the United Kingdom addressed this concern by comparing offspring of women with PCOS to offspring of mothers without PCOS with similar mental health history, finding that PCOS was associated with higher risk ADHD and autism regardless of maternal mental health history.⁹² A second concern is that PCOS may be more frequently diagnosed in women pursuing fertility treatment, which in the US is expensive and may reflect a population with higher socioeconomic status (SES). In these cases, lower SES women with PCOS may be underrepresented in some studies if study selection is conditional on pursuit of fertility treatment. This could lead to greater misclassification of PCOS status by SES among a control or non-PCOS reference population compared to a case or PCOS-positive group in research studies. Due to potential associations of SES with PCOS and neurodevelopment, statistical adjustment for SES is an important consideration. However, despite concerns about misclassification of PCOS by SES, the consistency of estimates across different countries and health systems where diagnosis of PCOS may be less related to SES – such as European countries with national healthcare systems – suggests that associations between PCOS and neurodevelopmental disorders are less likely to be wholly attributable to SES or country-specific patterns of diagnosis. The hypothesis that maternal PCOS may increase risk for offspring neurodevelopment is also supported by animal models, which indicate that a PCOS-like phenotype in mothers can have a host of metabolic and developmental implications for offspring.¹⁰⁰ Studies that show a relationship between fertility treatment and offspring health, particularly neurodevelopment, should consider the role of PCOS and other causes of infertility.

Thyroid function

Hypothyroidism affects 2–4% of reproductive-age individuals and is most often caused by thyroid autoimmunity.¹⁰¹ Thyroid hormones including thyroid stimulating hormone (TSH), thyroxine (T4) and triiodothyronine (T3) exert direct and indirect effects on normal ovarian function and may thus be relevant for female infertility. For example, granulosa cells contain T3 binding sites and serum levels of T3 and T4 have been shown to correlate with follicular fluid levels of these hormones.¹⁰² Thyroid hormones may also act indirectly on the hypothalamic-pituitary-ovarian axis via suppression of sex hormone-binding globulin (SHBG) activity and elevation of thyrotropin-releasing hormone (TRH).¹⁰³ Specifically, decreased binding activity of SHBG may increase free testosterone and estradiol, resulting in elevated androstenedione and estrone.

It is currently unclear whether the effects of thyroid hormones on sex steroid hormone levels and menstrual cycle length are sufficient to influence female fertility, as epidemiologic studies evaluating hypothyroid and infertility are scarce and conflicting. A cross-sectional study of women ages 18–39 reported significantly higher TSH levels among women with unexplained infertility as compared to controls (1.95 versus 1.66 mIU/L; $P = 0.0003$).¹⁰⁴

Moreover, twice as many women with unexplained infertility had TSH levels ≥ 2.5 mIU/L as compared to controls ($P < 0.05$). These findings are consistent with those of Poppe et al, who observed significantly higher mean TSH levels among 197 infertile women presenting at a fertility clinic as compared to 100 parous women (1.7 ± 0.8 versus 1.2 ± 0.7 mIU/L; $P = 0.05$).¹⁰⁵ The association was particularly strong for women experiencing ovulatory disorder infertility as compared to control women (1.9 ± 0.9 versus 1.2 ± 0.7 mIU/L; $P = 0.003$). The presence of thyroid peroxidase antibodies (TPO-Abs) was also associated with 2.5 times the odds (95% CI 1.02–5.12) of infertility as compared to no TPO-Abs. In a more recent prospective study of euthyroid women, preconception subclinical hypothyroidism, as defined by TSH ≥ 2.5 mIU/L, was not associated with time to pregnancy, pregnancy loss, or live birth among healthy fecund women.¹⁰⁶ The presence of TPO-Abs antibodies was also not associated with any of these outcomes in that population.

Hypothyroidism seems to be related to disruption of ovarian function and menstrual cycle disturbance, which may subsequently lead to subfertility and indication for infertility treatment. Collectively, the existing evidence suggests that overt hypothyroidism is positively associated with infertility, whereas subclinical hypothyroidism is not, though there is much debate about the relevant cut-point for differentiating the two.¹⁰⁷ Furthermore, it is largely unknown what the joint effects of hypothyroidism, infertility and ART treatment may have on the health outcomes of the offspring. Future studies should carefully consider these joint effects in well-designed prospective cohort studies.

Thyroid hormones are essential for growth and development of all organs during the fetal period and later. In the brain, they act through nuclear receptors and regulate gene expression influencing neurogenesis, neuronal migration, neuronal and glial cell differentiation, myelination, and synaptogenesis.^{108–111} During the first weeks of gestation when the fetal thyroid gland is not fully functional, inadequate thyroid hormones in the mother can also be detrimental because the fetus solely relies on maternal transfer of hormones for growth and development.¹¹² Even though substantial physiological alteration occurs in thyroid function of pregnant women to maintain the need of the mother and fetus, thyroid dysfunction is a common clinical problem during pregnancy.¹¹³ If it remains undetected or inadequately treated, maternal overt hypothyroidism results in cognitive impairments in the offspring, even in the absence of neonatal hypothyroidism.¹¹⁴ Neuroimaging studies of children born to hypothyroid mothers have shown that brain morphological abnormalities may persist as the child ages despite maternal treatment.^{115,116} In view of this evidence, guidelines recommend treatment of overt hypothyroidism during pregnancy to prevent adverse outcomes in both mother and child.^{117,118}

In recent years, emerging evidence from epidemiological studies suggests that milder forms of thyroid hormone insufficiency during gestation are also associated with suboptimal cognitive and behavioral outcomes in children. Subclinical hypothyroidism which is defined as high levels of TSH with T4 within the gestational age-specific normal range is associated with a reduction in children's IQ.¹¹⁴ Differences in mental development and neuropsychological functioning have been reported in children born to women with subclinical hypothyroidism compared to euthyroid women.^{119,120}

Children born to women with isolated hypothyroxinemia (T4 values below the 2.5th or 5th percentile with TSH within the normal range) are at increased risk of suboptimal cognitive function¹²¹, language delay¹²², ADHD symptoms and other behavioral problems,^{123–126} autistic symptoms,^{127,128} motor function and executive function,¹²⁴ and schizophrenia.¹²⁹ One neuroimaging study reported an association of maternal hypothyroxinemia with smaller grey matter and cortex volumes and larger cerebellar white matter volumes in children at age 6 years.¹³⁰ Null associations have been reported as well.¹³¹

Grounded on convincing evidence from observational studies,^{121–125,127–130} two randomized clinical trials have examined the benefit of treatment on cognitive function in the children of women who underwent thyroid screening in early pregnancy and had mild thyroid insufficiency.^{132,133} However, the trials have failed to demonstrate expected benefits of treatment and improvement in children's IQ. Nonetheless, some speculate that the null findings are attributed to late interventions (after week 12 of gestation) or potential overtreatment.^{134,135} Considering the lack of strong evidence on the association between milder forms of hypothyroidism and infertility, it is unlikely that subclinical hypothyroidism or hypothyroxinemia explain the potential impact of ART on the offspring's neurodevelopment. Overt hypothyroidism in women, however, should be considered in studies of ART and child neurodevelopment.

Parental depression

Empirical evidence suggests that there is an association between depression and infertility.¹³⁶ For instance, a cross-sectional study in Hungary found that infertile women had significantly higher depression scores than their fertile counterparts (14.94 vs. 8.95, $p < 0.0001$).¹³⁷ Similarly, a Polish study found higher mean depression scores associated with infertility among women (8.5 vs. 5.2, $p < 0.0001$).¹³⁸ Men, although less studied, are not exempt to depressive symptoms associated with infertility.¹³⁹ Methodological limitations, including the cross-sectional design, small sample size, lack of appropriate comparison groups, and inadequate adjustment for confounding (particularly with history of depression) present a challenge in determining whether depression is a predictor or a consequence of infertility.¹⁴⁰

Experiencing depressive mood over time may have a negative influence on the regulation of reproductive hormones in male and female, or it may give rise to conditions such as obesity which in turn affects fertility.¹⁴¹ However, it is less clear whether infertility can be the underlying factor for depressive mood versus a cause of infertility. Given limitations of the literature, more methodologically rigorous studies are needed for a thorough understanding of the etiological direction of the association between depression and infertility. In particular, examining the timing of depression onset, duration, and history during the preconception period may improve the understanding of this relationship. Information on the timing and nature of depression may enable reproductive health researchers to establish a timeline for development of depression with respect to fertility status for couples.

Irrespective of the mode of conception, parental psychological health may negatively impact child outcomes. Perinatal depression (depression during pregnancy and postpartum period) particularly has a negative influence on infant and child development.^{142,143} Various studies

have shown that children born to women experiencing perinatal depression are at a higher risk for experiencing adverse behavioral and developmental outcomes including preterm birth¹⁴⁴, externalizing and internalizing behaviors^{145,146}, poor growth¹⁴⁷, and reduced cognitive functioning.¹⁴⁸ Fathers are also at risk for experiencing perinatal depression¹⁴⁹, though research on fathers' depression status during this time period is scarce^{150,151} and its effect on child outcomes is unclear. Several studies suggest fathers' perinatal depression is associated with children's adverse emotional status^{152,153} however a more recent study found that this relationship is mediated by maternal depression and couple conflicts.¹⁵⁴

Depression during the perinatal period may be an indication of a more chronic condition with an onset in the preconception period. However, studies examining the onset, frequency, and duration of depression during preconception period are limited. Furthermore, despite accumulating evidence on the presence of perinatal depression in fathers^{155,151}, the literature on this topic including predictors of this condition—specifically the timing and the history of depression—and its association with infertility and child outcomes is very limited and remain important to assess.

Other female infertility factors

Aside from the aforementioned conditions indicated for infertility treatment, little is known about the long-term health outcomes of children conceived by ART to women with other conditions associated with infertility, such as endometriosis and fibroids. Endometriosis is associated with infertility, and accounts for up to 40% of all infertility causes among couples seeking treatment.¹⁵⁶ Importantly, endometriosis is associated with an inflammatory milieu.¹⁵⁷ Women with endometriosis undergoing ART experience a reduced rate of fertilization,¹⁵⁶ thought to be caused by excessive local production of pro-inflammatory cytokines including interleukins and tumor necrosis factor-alpha (TNF- α). In line with the inflammation hypothesis, women with endometriosis are at increased risk of hypertension and cardiovascular disease, indicating long-term health consequences associated with inflammation beyond just the reproductive years.^{158,159} Uterine fibroids occur in up to 70% of women and are also associated with infertility.¹⁶⁰ Some have hypothesized that inflammation may also play a role in the pathogenesis of uterine fibroids, and women with fibroids appear to experience higher cardiovascular risk.¹⁶¹ Because inflammation is associated with adverse pregnancy and child health outcomes, future epidemiologic studies should evaluate long-term child health outcomes among those conceived with ART by mothers with uterine fibroids and endometriosis.

Note on Impact of Confounding

Despite the long list of possible related conditions reviewed above, a note must be made that the bias from confounding is dependent on its strength of association with the outcome of interest as well. It is usually best to draw a causal diagram¹⁶² depicting the model one wants to estimate associations for and determine which are true confounders and which may be mediators of associations (e.g., preterm delivery) that need not be adjusted for, or may require more specific types of analyses. Figure 1 shows an example of a conceptual diagram for examining the association between ART and the outcome of neurodevelopment. One can adjust for BMI, underlying infertility and socio-demographics (i.e., age, race, education) to

adequately control for the confounders listed. In this case, even if underlying infertility does not directly impact neurodevelopment in some way, due to its association with upstream factors, its adjustment would remain a possible option for controlling for confounding of these other factors (e.g., thyroid function) that might not be well captured in a specific study but are known to lead to neurodevelopmental issues.

However, even if there is no information collected on some of the indicators of infertility treatment in a specific study, the impact of confounding by indication for each specific research question can be estimated using bias analyses.¹⁶³ Such analyses may then help evaluate whether the missing confounding information would or would not have impacted the associations found in the study. Following the recommended reporting guidelines such as STROBE for observational research¹⁶⁴, unadjusted estimates should also be published along with models with successive adjustment models to better evaluate the impact of covariate adjustment. In addition, causal evidence for the confounders are required. For the above factors, many of which have been understudied, the true estimates of associations along with biological underpinnings between them and child health remain unclear. Further research is necessary to provide better estimates for bias analyses.

Conclusion

In sum, the evidence accumulated on the health of children after conception by ART (and less so for non-ART treatments) suggest that they are largely similar in development and growth as their peers. However, given the heterogeneity and continuing advancements of ART procedures, ongoing research and surveillance that tackles the existing methodological challenges is essential. Even if fertility treatment techniques themselves may not cause marked differences in long-term health, attention should also be given to understanding the impact of the causes of infertility including both male and female factors.

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References

1. Calhaz-Jorge C, De Geyter C, Kupka MS, et al. Assisted reproductive technology in Europe, 2013: results generated from European registers by ESHRE. *Human Reproduction* 2017;32(10):1957–1973 [PubMed: 29117383]
2. Sunderam S, Kissin DM, Crawford SB, et al. Assisted Reproductive Technology Surveillance - United States, 2015. *MMWR: Surveillance Summaries* 2018;67(3):1–28
3. Kushnir VA, Barad DH, Albertini DF, Darmon SK, Gleicher N. Systematic review of worldwide trends in assisted reproductive technology 2004–2013. *Reproductive Biology and Endocrinology* 2017;15(1):6 [PubMed: 28069012]
4. Schieve LA, Devine O, Boyle CA, Petrini JR, Warner L. Estimation of the contribution of non-assisted reproductive technology ovulation stimulation fertility treatments to US singleton and multiple births. *American Journal of Epidemiology* 2009;170(11):1396–1407 [PubMed: 19854803]
5. Zore T, Wang ET. Perinatal and Childhood Outcomes Associated with Infertility. *Seminars in Reproductive Medicine* 2017;35(3):304–310 [PubMed: 28658715]
6. Yeung EH, Druschel C. Cardiometabolic health of children conceived by assisted reproductive technologies. *Fertility and Sterility* 2013;99(2):318–326 [PubMed: 23312226]

7. Yeung EH, Sundaram R, Bell EM, et al. Examining Infertility Treatment and Early Childhood Development in the Upstate KIDS Study. *JAMA Pediatr* 2016;170(3):251–258 [PubMed: 26746435]
8. Yeung EH, Sundaram R, Bell EM, et al. Infertility treatment and children's longitudinal growth between birth and 3 years of age. *Human Reproduction* 2016;31(7):1621–1628 [PubMed: 27165624]
9. Rifouna MS, Reus AD, Koning AH, et al. First trimester trophoblast and placental bed vascular volume measurements in IVF or IVF/ICSI pregnancies. *Human Reproduction* 2014;29(12):2644–2649 [PubMed: 25336709]
10. Carson C, Redshaw M, Sacker A, Kelly Y, Kurinczuk JJ, Quigley MA. Effects of pregnancy planning, fertility, and assisted reproductive treatment on child behavioral problems at 5 and 7 years: evidence from the Millennium Cohort Study. *Fertility and Sterility* 2013;99(2):456–463 [PubMed: 23158833]
11. Carson C, Sacker A, Kelly Y, Redshaw M, Kurinczuk JJ, Quigley MA. Asthma in children born after infertility treatment: findings from the UK Millennium Cohort Study. *Human Reproduction* 2013;28(2):471–479 [PubMed: 23223378]
12. Liberman RF, Getz KD, Heinke D, et al. Assisted Reproductive Technology and Birth Defects: Effects of Subfertility and Multiple Births. *Birth Defects Res* 2017;109(14):1144–1153 [PubMed: 28635008]
13. Kissin DM, Boulet SL, Jamieson DJ, Surveillance ftART, Team R. Fertility treatments in the United States: improving access and outcomes. *Obstetrics and Gynecology* 2016;128(2):387–390 [PubMed: 27399992]
14. Jain T. Socioeconomic and racial disparities among infertility patients seeking care. *Fertility and Sterility* 2006;85(4):876–881 [PubMed: 16580368]
15. Davidovitch M, Chodick G, Shalev V, et al. Infertility treatments during pregnancy and the risk of autism spectrum disorder in the offspring. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2018;86:175–179 [PubMed: 29864450]
16. Boulet SL, Mehta A, Kissin DM, Warner L, Kawwass JF, Jamieson DJ. Trends in use of and reproductive outcomes associated with intracytoplasmic sperm injection. *JAMA* 2015;313(3):255–263 [PubMed: 25602996]
17. Rimm AA, Katayama AC, Diaz M, Katayama KP. A meta-analysis of controlled studies comparing major malformation rates in IVF and ICSI infants with naturally conceived children. *Journal of Assisted Reproduction and Genetics* 2004;21(12):437–443 [PubMed: 15704519]
18. Bonduelle M, Wennerholm UB, Loft A, et al. A multi-centre cohort study of the physical health of 5-year-old children conceived after intracytoplasmic sperm injection, in vitro fertilization and natural conception. *Human Reproduction* 2005;20(2):413–419 [PubMed: 15576393]
19. Davies MJ, Moore VM, Willson KJ, et al. Reproductive technologies and the risk of birth defects. *New England Journal of Medicine* 2012;366(19):1803–1813 [PubMed: 22559061]
20. Kissin DM, Zhang Y, Boulet SL, et al. Association of assisted reproductive technology (ART) treatment and parental infertility diagnosis with autism in ART-conceived children. *Human Reproduction* 2015;30(2):454–465 [PubMed: 25518976]
21. Ludwig M, Katalinic A. Malformation rate in fetuses and children conceived after ICSI: results of a prospective cohort study. *Reproductive Biomedicine Online* 2002;5(2):171–178
22. Wen SW, Leader A, White RR, et al. A comprehensive assessment of outcomes in pregnancies conceived by in vitro fertilization/intracytoplasmic sperm injection. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2010;150(2):160–165
23. Ombelet W, Peeraer K, De Sutter P, et al. Perinatal outcome of ICSI pregnancies compared with a matched group of natural conception pregnancies in Flanders (Belgium): a cohort study. *Reproductive Biomedicine Online* 2005;11(2):244–253 [PubMed: 16168226]
24. Lambert RD. Safety issues in assisted reproductive technology: aetiology of health problems in singleton ART babies. *Human Reproduction* 2003;18(10):1987–1991 [PubMed: 14507811]
25. Bonduelle M, Van Assche E, Joris H, et al. Prenatal testing in ICSI pregnancies: incidence of chromosomal anomalies in 1586 karyotypes and relation to sperm parameters. *Human Reproduction* 2002;17(10):2600–2614 [PubMed: 12351536]

26. Mature oocyte cryopreservation: a guideline. *Fertil Steril* 2013;99(1):37–43 [PubMed: 23083924]
27. Rienzi L, Gracia C, Maggiulli R, et al. Oocyte, embryo and blastocyst cryopreservation in ART: systematic review and meta-analysis comparing slow-freezing versus vitrification to produce evidence for the development of global guidance. *Hum Reprod Update* 2017;23(2):139–155 [PubMed: 27827818]
28. Seshadri S, Saab W, Exeter H, et al. Clinical outcomes of a vitrified donor oocyte programme: A single UK centre experience. *Eur J Obstet Gynecol Reprod Biol* 2018;225:136–140 [PubMed: 29709727]
29. Cobo A, Coello A, Remohi J, Serrano J, de Los Santos JM, Meseguer M. Effect of oocyte vitrification on embryo quality: time-lapse analysis and morphokinetic evaluation. *Fertil Steril* 2017;108(3):491–497.e493 [PubMed: 28865549]
30. Blastocyst culture and transfer in clinical-assisted reproduction: a committee opinion. *Fertil Steril* 2013;99(3):667–672 [PubMed: 23714439]
31. Gosden RG. Oogenesis as a foundation for embryogenesis. *Mol Cell Endocrinol* 2002;186(2):149–153 [PubMed: 11900888]
32. Blake DA, Farquhar CM, Johnson N, Proctor M. Cleavage stage versus blastocyst stage embryo transfer in assisted conception. *Cochrane Database Syst Rev* 2007(4):Cd002118
33. Glujovsky D, Farquhar C, Quinteiro Retamar AM, Alvarez Sedo CR, Blake D. Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology. *Cochrane Database Syst Rev* 2016(6):Cd002118
34. Zech NH, Lejeune B, Puissant F, Vanderzwalmen S, Zech H, Vanderzwalmen P. Prospective evaluation of the optimal time for selecting a single embryo for transfer: day 3 versus day 5. *Fertil Steril* 2007;88(1):244–246 [PubMed: 17292362]
35. De Vos A, Van Landuyt L, Santos-Ribeiro S, et al. Cumulative live birth rates after fresh and vitrified cleavage-stage versus blastocyst-stage embryo transfer in the first treatment cycle. *Hum Reprod* 2016;31(11):2442–2449 [PubMed: 27619768]
36. Shapiro BS, Richter KS, Harris DC, Daneshmand ST. Influence of patient age on the growth and transfer of blastocyst-stage embryos. *Fertil Steril* 2002;77(4):700–705 [PubMed: 11937119]
37. Dar S, Librach CL, Gunby J, Bissonnette F, Cowan L. Increased risk of preterm birth in singleton pregnancies after blastocyst versus Day 3 embryo transfer: Canadian ART Register (CARTR) analysis. *Hum Reprod* 2013;28(4):924–928 [PubMed: 23349411]
38. Kalra SK, Ratcliffe SJ, Barnhart KT, Coutifaris C. Extended embryo culture and an increased risk of preterm delivery. *Obstet Gynecol* 2012;120(1):69–75 [PubMed: 22914393]
39. Dar S, Lazer T, Shah PS, Librach CL. Neonatal outcomes among singleton births after blastocyst versus cleavage stage embryo transfer: a systematic review and meta-analysis. *Hum Reprod Update* 2014;20(3):439–448 [PubMed: 24480786]
40. Ginstrom Ernstad E, Bergh C, Khatibi A, et al. Neonatal and maternal outcome after blastocyst transfer: a population-based registry study. *Am J Obstet Gynecol* 2016;214(3):378.e371–378.e310 [PubMed: 26928152]
41. Kleijkers SH, van Montfoort AP, Smits LJ, et al. IVF culture medium affects post-natal weight in humans during the first 2 years of life. *Hum Reprod* 2014;29(4):661–669 [PubMed: 24549211]
42. Rizos D, Loneragan P, Boland MP, et al. Analysis of differential messenger RNA expression between bovine blastocysts produced in different culture systems: implications for blastocyst quality. *Biol Reprod* 2002;66(3):589–595 [PubMed: 11870062]
43. Buck Louis GM, Bell E, Xie Y, Sundaram R, Yeung E. Parental health status and infant outcomes: Upstate KIDS Study. *Fertility and Sterility* 2018;109(2):315–323 [PubMed: 29338856]
44. Roustaei Z, Vehvilainen-Julkunen K, Tuomainen TP, Lamminpää R, Heinonen S. The effect of advanced maternal age on maternal and neonatal outcomes of placenta previa: A register-based cohort study. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2018;227:1–7
45. Leader J, Bajwa A, Lanes A, et al. The Effect of Very Advanced Maternal Age on Maternal and Neonatal Outcomes: A Systematic Review. *Journal of Obstetrics and Gynaecology Canada Journal d'Obstétrique et Gynécologie du Canada* 2018

46. Johnson JA, Tough S, Sogc Genetics C. Delayed child-bearing. *Journal of Obstetrics and Gynaecology Canada Journal d'Obstétrique et Gynécologie du Canada* 2012;34(1):80–93
47. Fall CH, Sachdev HS, Osmond C, et al. Association between maternal age at childbirth and child and adult outcomes in the offspring: a prospective study in five low-income and middle-income countries (COHORTS collaboration). *Lancet Glob Health* 2015;3(7):e366–377 [PubMed: 25999096]
48. Interat M, Wainstock T, Sheiner E, Kapelushnik J, Fischer L, Walfisch A. Advanced maternal age during pregnancy and the risk for malignant morbidity in the childhood. *European Journal of Pediatrics* 2018;177(6):879–886 [PubMed: 29629497]
49. Yip BH, Pawitan Y, Czene K. Parental age and risk of childhood cancers: a population-based cohort study from Sweden. *International Journal of Epidemiology* 2006;35(6):1495–1503 [PubMed: 17008361]
50. Luke B, Brown MB, Wantman E, et al. Cumulative birth rates with linked assisted reproductive technology cycles. *New England Journal of Medicine* 2012;366(26):2483–2491 [PubMed: 22738098]
51. Petridou ET, Georgakis MK, Erdmann F, et al. Advanced parental age as risk factor for childhood acute lymphoblastic leukemia: results from studies of the Childhood Leukemia International Consortium. *European Journal of Epidemiology* 2018
52. Oldereid NB, Wennerholm UB, Pinborg A, et al. The effect of paternal factors on perinatal and paediatric outcomes: a systematic review and meta-analysis. *Human Reproduction Update* 2018;24(3):320–389 [PubMed: 29471389]
53. Sandin S, Schendel D, Magnusson P, et al. Autism risk associated with parental age and with increasing difference in age between the parents. *Molecular Psychiatry* 2016;21(5):693–700 [PubMed: 26055426]
54. Yeung EH, Sundaram R, Ghassabian A, Xie Y, Buck Louis G. Parental Obesity and Early Childhood Development. *Pediatrics* 2017;139(2)
55. Suren P, Gunnes N, Roth C, et al. Parental obesity and risk of autism spectrum disorder. *Pediatrics* 2014;133(5):e1128–1138 [PubMed: 24709932]
56. Chen Q, Yan W, Duan E. Epigenetic inheritance of acquired traits through sperm RNAs and sperm RNA modifications. *Nat Rev Genet* 2016;17(12):733–743 [PubMed: 27694809]
57. Schagdarsurengin U, Steger K. Epigenetics in male reproduction: effect of paternal diet on sperm quality and offspring health. *Nat Rev Urol* 2016;13(10):584–595 [PubMed: 27578043]
58. Grandjean V, Fourre S, De Abreu DA, Derieppe MA, Remy JJ, Rassoulzadegan M. RNA-mediated paternal heredity of diet-induced obesity and metabolic disorders. *Scientific Reports* 2015;5:18193 [PubMed: 26658372]
59. Sanchez CE, Barry C, Sabhlok A, et al. Maternal pre-pregnancy obesity and child neurodevelopmental outcomes: a meta-analysis. *Obesity Reviews* 2018;19(4):464–484 [PubMed: 29164765]
60. Johnson JA, Grande JP, Roche PC, Kumar R. Immunohistochemical detection and distribution of the 1,25-dihydroxyvitamin D3 receptor in rat reproductive tissues. *Histochem Cell Biol* 1996;105:7–15 [PubMed: 8824901]
61. Halloran BP, Deluca HF. Effect of vitamin D deficiency on fertility and reproductive capacity in the female rat. *J Nutr* 1980;110:1573–1580 [PubMed: 7400847]
62. Pacis MM, Fortin CN, Zarek SM, Mumford SL, Segars JH. Vitamin D and assisted reproduction: should vitamin D be routinely screened and repleted prior to ART? A systematic review. *J Assist Reprod Genet* 2015;32(3):323–335 [PubMed: 25547950]
63. Hanieh S, Ha TT, Simpson JA, et al. Maternal vitamin D status and infant outcomes in rural Vietnam: a prospective cohort study. *PLoS One* 2014;9(6):e99005 [PubMed: 24967813]
64. Zhu P, Tong SL, Hao JH, et al. Cord blood vitamin D and neurocognitive development are nonlinearly related in toddlers. *J Nutr* 2015;145(6):1232–1238 [PubMed: 25878203]
65. Morales E, Guxens M, Llop S, et al. Circulating 25-hydroxyvitamin D3 in pregnancy and infant neuropsychological development. *Pediatrics* 2012;130(4):e913–920 [PubMed: 22987876]

66. Chi M, Zhu L, Zhang Z, et al. The relationship between maternal serum vitamin D levels and infant neurodevelopment and anthropometry: a prospective observational study. *J Nutr Sci Vitaminol* 2018;64:161–167 [PubMed: 29710034]
67. Tylavsky FA, Kocak M, Murphy LE, et al. Gestational Vitamin 25(OH)D Status as a Risk Factor for Receptive Language Development: A 24-Month, Longitudinal, Observational Study. *Nutrients* 2015;7(12):9918–9930 [PubMed: 26633480]
68. Darling AL, Rayman MP, Steer CD, Golding J, Lanham-New SA, Bath S. Association between maternal vitamin D status in pregnancy and neurodevelopmental outcomes in childhood: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Br J Nutr* 2017;117:1682–1692 [PubMed: 28697816]
69. Keim SA, Bodnar LM, Klebanoff MA. Maternal and cord blood 25(OH)-vitamin D concentrations in relation to child development and behaviour. *Paediatr Perinat Epidemiol* 2014;28(5):434–444 [PubMed: 24938425]
70. Daraki V, Roumeliotaki T, Koutra K, et al. High maternal vitamin D levels in early pregnancy may protect against behavioral difficulties at preschool age: the Rhea mother-child cohort, Crete, Greece. *Eur Child Adolesc Psychiatry* 2018;27(1):79–88 [PubMed: 28685401]
71. Mossin MH, Aaby JB, Dalgard C, Lykkedegn S, Christesen HT, Bilenberg N. Inverse associations between cord vitamin D and attention deficit hyperactivity disorder symptoms: A child cohort study. *Aust N Z J Psychiatry* 2017;51(7):703–710 [PubMed: 27694636]
72. Morales E, Julvex J, Torrent M, et al. Vitamin D in Pregnancy and Attention Deficit Hyperactivity Disorder-like Symptoms in Childhood. *Epidemiology* 2015;26:458–465 [PubMed: 25867115]
73. Chen J, Xin K, Wei J, Zhang K, Xiao H. Lower maternal serum 25(OH) D in first trimester associated with higher autism risk in Chinese offspring. *J Psychosom Res* 2016;89:98–101 [PubMed: 27663117]
74. Wu DM, Wen X, Han XR, et al. Relationship Between Neonatal Vitamin D at Birth and Risk of Autism Spectrum Disorders: the NBSIB Study. *J Bone Miner Res* 2018;33(3):458–466 [PubMed: 29178513]
75. Fernell E, Bejerot S, Westerlund J, et al. Autism spectrum disorder and low vitamin D at birth: a sibling control study. *Mol Autism* 2015;6(3)
76. Gustafsson P, Rylander L, Lindh CH, et al. Vitamin D Status at Birth and Future Risk of Attention Deficit/Hyperactivity Disorder (ADHD). *PLoS One* 2015;10(10):e0140164 [PubMed: 26509435]
77. Strom M, Halldorsson TI, Hansen S, et al. Vitamin D measured in maternal serum and offspring neurodevelopmental outcomes: a prospective study with long-term follow-up. *Ann Nutr Metab* 2014;64(3–4):254–261 [PubMed: 25300268]
78. Whitehouse AJ, Holt BJ, Serralha M, Holt PG, Kusel MM, Hart PH. Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development. *Pediatrics* 2012;129(3):485–493 [PubMed: 22331333]
79. Veena SR, Krishnaveni GV, Srinivasan K, et al. Association between maternal vitamin D status during pregnancy and offspring cognitive function during childhood and adolescence. *Asia Pac J Clin Nutr* 2017;26(3):438–449 [PubMed: 28429909]
80. Gale CR, Robinson SM, Harvey NC, et al. Maternal vitamin D status during pregnancy and child outcomes. *Eur J Clin Nutr* 2008;62(1):68–77 [PubMed: 17311057]
81. Laird E, Thurston SW, van Wijngaarden E, et al. Maternal vitamin D status and the relationship with neonatal anthropometric and childhood neurodevelopmental outcomes: results from the Seychelles Child Development Nutrition Study. *Nutrients* 2017;9(1235)
82. Dumesic DA, Oberfield SE, Stener-Victorin E, Marshall JC, Laven JS, Legro RS. Scientific Statement on the Diagnostic Criteria, Epidemiology, Pathophysiology, and Molecular Genetics of Polycystic Ovary Syndrome. *Endocrine Reviews* 2015;36(5):487–525 [PubMed: 26426951]
83. Lauritsen MP, Bentzen JG, Pinborg A, et al. The prevalence of polycystic ovary syndrome in a normal population according to the Rotterdam criteria versus revised criteria including anti-Mullerian hormone. *Human Reproduction* 2014;29(4):791–801 [PubMed: 24435776]
84. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Human Reproduction* 2010;25(2):544–551 [PubMed: 19910321]

85. Kuijper EA, Vink JM, Lambalk CB, Boomsma DI. Prevalence of polycystic ovary syndrome in women from opposite-sex twin pairs. *Journal of Clinical Endocrinology and Metabolism* 2009;94(6):1987–1990 [PubMed: 19351727]
86. Vink JM, Sadrzadeh S, Lambalk CB, Boomsma DI. Heritability of polycystic ovary syndrome in a Dutch twin-family study. *Journal of Clinical Endocrinology and Metabolism* 2006;91(6):2100–2104 [PubMed: 16219714]
87. Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Human Reproduction Update* 2006;12(6):673–683 [PubMed: 16891296]
88. Doherty DA, Newnham JP, Bower C, Hart R. Implications of polycystic ovary syndrome for pregnancy and for the health of offspring. *Obstetrics and Gynecology* 2015;125(6):1397–1406 [PubMed: 26000511]
89. Bell GA, Sundaram R, Mumford SL, et al. Maternal polycystic ovarian syndrome and early offspring development. *Human Reproduction* 2018;33(7):1307–1315 [PubMed: 29668891]
90. Kosidou K, Dalman C, Widman L, et al. Maternal polycystic ovary syndrome and the risk of autism spectrum disorders in the offspring: a population-based nationwide study in Sweden. *Molecular Psychiatry* 2015
91. Kosidou K, Dalman C, Widman L, et al. Maternal Polycystic Ovary Syndrome and Risk for Attention-Deficit/Hyperactivity Disorder in the Offspring. *Biological Psychiatry* 2016
92. Berni TR, Morgan CL, Berni ER, Rees DA. Polycystic Ovary Syndrome Is Associated With Adverse Mental Health and Neurodevelopmental Outcomes. *Journal of Clinical Endocrinology and Metabolism* 2018;103(6):2116–2125 [PubMed: 29648599]
93. Palomba S, Marotta R, Di Cello A, et al. Pervasive developmental disorders in children of hyperandrogenic women with polycystic ovary syndrome: a longitudinal case-control study. *Clinical Endocrinology* 2012;77(6):898–904 [PubMed: 22612600]
94. Bell GA, Sundaram R, Mumford SL, et al. Maternal polycystic ovarian syndrome and offspring growth: the Upstate KIDS Study. *Journal of Epidemiology and Community Health* 2018
95. Auyeung B, Baron-Cohen S, Ashwin E, Knickmeyer R, Taylor K, Hackett G. Fetal testosterone and autistic traits. *British Journal of Psychology* 2009;100(Pt 1):1–22 [PubMed: 18547459]
96. Auyeung B, Taylor K, Hackett G, Baron-Cohen S. Foetal testosterone and autistic traits in 18 to 24-month-old children. *Molecular Autism* 2010;1(1):11 [PubMed: 20678186]
97. Hines M. Prenatal endocrine influences on sexual orientation and on sexually differentiated childhood behavior. *Frontiers in Neuroendocrinology* 2011;32(2):170–182 [PubMed: 21333673]
98. Hu M, Richard JE, Maliqueo M, et al. Maternal testosterone exposure increases anxiety-like behavior and impacts the limbic system in the offspring. *Proceedings of the National Academy of Sciences of the United States of America* 2015;112(46):14348–14353 [PubMed: 26578781]
99. Manson JE. Prenatal exposure to sex steroid hormones and behavioral/cognitive outcomes. *Metabolism: Clinical and Experimental* 2008;57 Suppl 2:S16–21
100. Puttabyatappa M, Cardoso RC, Padmanabhan V. Effect of maternal PCOS and PCOS-like phenotype on the offspring's health. *Molecular and Cellular Endocrinology* 2016;435:29–39 [PubMed: 26639019]
101. Poppe K, Velkeniers B, Glinde D. The role of thyroid autoimmunity in fertility and pregnancy. *Nature Clinical Practice: Endocrinology & Metabolism* 2008;4(7):394–405
102. Wakim AN, Polizotto SL, Buffo MJ, Marrero MA, Burholt DR. Thyroid hormones in human follicular fluid and thyroid hormone receptors in human granulosa cells. *Fertility and Sterility* 1993;59(6):1187–1190 [PubMed: 8495763]
103. Krassas GE. Thyroid disease and female reproduction. *Fertility and Sterility* 2000;74(6):1063–1070 [PubMed: 11119728]
104. Orouji Jokar T, Fourman LT, Lee H, Mentzinger K, Fazeli PK. Higher TSH Levels Within the Normal Range Are Associated With Unexplained Infertility. *Journal of Clinical Endocrinology and Metabolism* 2018;103(2):632–639 [PubMed: 29272395]
105. Poppe K, Velkeniers B. Thyroid disorders in infertile women. *Annales d'Endocrinologie* 2003;64(1):45–50

106. Plowden TC, Schisterman EF, Sjaarda LA, et al. Subclinical Hypothyroidism and Thyroid Autoimmunity Are Not Associated With Fecundity, Pregnancy Loss, or Live Birth. *Journal of Clinical Endocrinology and Metabolism* 2016;101(6):2358–2365 [PubMed: 27023447]
107. Brabant G, Beck-Peccoz P, Jarzab B, et al. Is there a need to redefine the upper normal limit of TSH? *European Journal of Endocrinology of the European Federation of Endocrine Societies* 2006;154(5):633–637
108. Lavado-Autric R, Auso E, Garcia-Velasco JV, et al. Early maternal hypothyroxinemia alters histogenesis and cerebral cortex cytoarchitecture of the progeny. *Journal of Clinical Investigation* 2003;111(7):1073–1082 [PubMed: 12671057]
109. Cuevas E, Auso E, Telefont M, Morreale de Escobar G, Sotelo C, Berbel P. Transient maternal hypothyroxinemia at onset of corticogenesis alters tangential migration of medial ganglionic eminence-derived neurons. *European Journal of Neuroscience* 2005;22(3):541–551 [PubMed: 16101736]
110. Bernal J. Thyroid hormones and brain development. *Vitamins and Hormones* 2005;71:95–122 [PubMed: 16112266]
111. Kester MHA, Martinez de Mena R, Obregon MJ, et al. Iodothyronine Levels in the Human Developing Brain: Major Regulatory Roles of Iodothyronine Deiodinases in Different Areas. *The Journal of Clinical Endocrinology & Metabolism* 2004;89(7):3117–3128 [PubMed: 15240580]
112. Morreale de Escobar G, Obregon MJ, Escobar del Rey F. Role of thyroid hormone during early brain development. *European Journal of Endocrinology of the European Federation of Endocrine Societies* 2004;151 Suppl 3:U25–37
113. Korevaar TIM, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. *Nature Reviews: Endocrinology* 2017;13(10):610–622 [PubMed: 28776582]
114. Haddow JE, Palomaki GE, Allan WC, et al. Maternal Thyroid Deficiency during Pregnancy and Subsequent Neuropsychological Development of the Child. *New England Journal of Medicine* 1999;341(8):549–555 [PubMed: 10451459]
115. Lischinsky JE, Skocic J, Clairman H, Rovet J. Preliminary Findings Show Maternal Hypothyroidism May Contribute to Abnormal Cortical Morphology in Offspring. *Frontiers in Endocrinology* 2016;7:16 [PubMed: 26941710]
116. Samadi A, Skocic J, Rovet JF. Children born to women treated for hypothyroidism during pregnancy show abnormal corpus callosum development. *Thyroid* 2015;25(5):494–502 [PubMed: 25780811]
117. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid* 2017;27(3):315–389 [PubMed: 28056690]
118. De Groot L, Abalovich M, Alexander EK, et al. Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism* 2012;97(8):2543–2565
119. Smit BJ, Kok JH, Vulsma T, Briet JM, Boer K, Wiersinga WM. Neurologic development of the newborn and young child in relation to maternal thyroid function. *Acta Paediatrica* 2000;89(3):291–295 [PubMed: 10772276]
120. Li Y, Shan Z, Teng W, et al. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25–30 months. *Clinical Endocrinology* 2010;72(6):825–829 [PubMed: 19878506]
121. Ghassabian A, El Marroun H, Peeters RP, et al. Downstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal IQ and brain morphology in school-age children. *Journal of Clinical Endocrinology and Metabolism* 2014;99(7):2383–2390 [PubMed: 24684462]
122. Henrichs J, Bongers-Schokking JJ, Schenk JJ, et al. Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. *Journal of Clinical Endocrinology and Metabolism* 2010;95(9):4227–4234 [PubMed: 20534757]

123. Ghassabian A, Bongers-Schokking JJ, Henrichs J, et al. Maternal thyroid function during pregnancy and behavioral problems in the offspring: the generation R study. *Pediatric Research* 2011;69(5 Pt 1):454–459 [PubMed: 21471776]
124. Andersen SL, Andersen S, Liew Z, Vestergaard P, Olsen J. Maternal Thyroid Function in Early Pregnancy and Neuropsychological Performance of the Child at 5 Years of Age. *Journal of Clinical Endocrinology and Metabolism* 2018;103(2):660–670 [PubMed: 29220528]
125. Modesto T, Tiemeier H, Peeters RP, et al. Maternal Mild Thyroid Hormone Insufficiency in Early Pregnancy and Attention-Deficit/Hyperactivity Disorder Symptoms in Children. *JAMA Pediatr* 2015;169(9):838–845 [PubMed: 26146876]
126. Oostenbroek MHW, Kersten RHJ, Tros B, Kunst AE, Vrijkotte TGM, Finken MJJ. Maternal hypothyroxinaemia in early pregnancy and problem behavior in 5-year-old offspring. *Psychoneuroendocrinology* 2017;81:29–35 [PubMed: 28411411]
127. Roman GC, Ghassabian A, Bongers-Schokking JJ, et al. Association of gestational maternal hypothyroxinemia and increased autism risk. *Annals of Neurology* 2013;74(5):733–742 [PubMed: 23943579]
128. Levie D, Korevaar TIM, Bath SC, et al. Thyroid Function in Early Pregnancy, Child IQ, and Autistic Traits: a Meta-analysis of Individual-participant Data. *Journal of Clinical Endocrinology and Metabolism* 2018
129. Gyllenberg D, Sourander A, Surcel HM, Hinkka-Yli-Salomaki S, McKeague IW, Brown AS. Hypothyroxinemia During Gestation and Offspring Schizophrenia in a National Birth Cohort. *Biological Psychiatry* 2016;79(12):962–970 [PubMed: 26194598]
130. Korevaar TIM, Muetzel R, Medici M, et al. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. *The Lancet Diabetes & Endocrinology* 2016;4(1):35–43
131. Pääkkilä F, Männistö T, Hartikainen A-L, Suvanto E. Maternal Thyroid Function During Pregnancy and the Child's Linguistic and Sensory Development in the Northern Finland Birth Cohort 1986. *Frontiers in Endocrinology* 2018;9:127 [PubMed: 29632517]
132. Lazarus JH, Bestwick JP, Channon S, et al. Antenatal Thyroid Screening and Childhood Cognitive Function. *New England Journal of Medicine* 2012;366(6):493–501 [PubMed: 22316443]
133. Casey BM, Thom EA, Peaceman AM, et al. Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. *New England Journal of Medicine* 2017;376(9):815–825 [PubMed: 28249134]
134. Brent GA. The Debate over Thyroid-Function Screening in Pregnancy. *New England Journal of Medicine* 2012;366(6):562–563 [PubMed: 22316450]
135. Korevaar TIM, Chaker L, Peeters RP. Improving the clinical impact of randomised trials in thyroidology. *Lancet Diabetes Endocrinol* 2017
136. Fassino S, Abbate-Daga G, Amianto F, Leombruni P, Boggio S, Rovera GG. Temperament and character profile of eating disorders: a controlled study with the Temperament and Character Inventory. *International Journal of Eating Disorders* 2002;32(4):412–425 [PubMed: 12386906]
137. Lakatos E, Szigei JF, Ujma PP, Sexty R, Balog P. Anxiety and depression among infertile women: a cross-sectional survey from Hungary. *BMC Women's Health* 2017;17(1):48 [PubMed: 28738833]
138. Drosdzol A, Skrzypulec V. Depression and anxiety among Polish infertile couples--an evaluative prevalence study. *J Psychosom Obstet Gynaecol* 2009;30(1):11–20 [PubMed: 19308778]
139. Yang B, Zhang J, Qi Y, Wang P, Jiang R, Li H. Assessment on Occurrences of Depression and Anxiety and Associated Risk Factors in the Infertile Chinese Men. *Am J Mens Health* 2017;11(3):767–774 [PubMed: 28413943]
140. Greil AL. Infertility and psychological distress: a critical review of the literature. *Social Science and Medicine* 1997;45(11):1679–1704 [PubMed: 9428088]
141. Bhongade MB, Prasad S, Jiloha RC, Ray PC, Mohapatra S, Koner BC. Effect of psychological stress on fertility hormones and seminal quality in male partners of infertile couples. *Andrologia* 2015;47(3):336–342 [PubMed: 24673246]

142. Guxens M, Tiemeier H, Jansen PW, et al. Parental psychological distress during pregnancy and early growth in preschool children: the generation R study. *American Journal of Epidemiology* 2013;177(6):538–547 [PubMed: 23436897]
143. Lampard AM, Franckle RL, Davison KK. Maternal depression and childhood obesity: a systematic review. *Preventive Medicine* 2014;59:60–67 [PubMed: 24291685]
144. Jarde A, Morais M, Kingston D, et al. Neonatal outcomes in women with untreated antenatal depression compared with women without depression: A systematic review and meta-analysis. *JAMA Psychiatry* 2016;73(8):826–837 [PubMed: 27276520]
145. Kingston D, Kehler H, Austin MP, et al. Trajectories of maternal depressive symptoms during pregnancy and the first 12 months postpartum and child externalizing and internalizing behavior at three years. *PloS One* 2018;13(4):e0195365 [PubMed: 29652937]
146. Vafai Y, Steinberg JR, Shenassa ED. Maternal postpartum depressive symptoms and infant externalizing and internalizing behaviors. *Infant Behavior & Development* 2016;42:119–127 [PubMed: 26800212]
147. Park H, Sundaram R, Gilman SE, Bell G, Louis GMB, Yeung EH. Timing of Maternal Depression and Sex-Specific Child Growth, the Upstate KIDS Study. *Obesity (Silver Spring)* 2018;26(1):160–166 [PubMed: 29090856]
148. van der Waerden J, Bernard JY, De Agostini M, et al. Persistent maternal depressive symptoms trajectories influence children's IQ: The EDEN mother-child cohort. *Depression and Anxiety* 2017;34(2):105–117 [PubMed: 27603172]
149. Kim P, Swain JE. Sad dads: paternal postpartum depression. *Psychiatry (Edgmont)* 2007;4(2):35–47
150. O'Brien AP, McNeil KA, Fletcher R, et al. New Fathers' Perinatal Depression and Anxiety-Treatment Options: An Integrative Review. *Am J Mens Health* 2017;11(4):863–876 [PubMed: 27694550]
151. Paulson JF, Bazemore SD. Prenatal and postpartum depression in fathers and its association with maternal depression: a meta-analysis. *JAMA* 2010;303(19):1961–1969 [PubMed: 20483973]
152. Takehara K, Suto M, Kakee N, Tachibana Y, Mori R. Prenatal and early postnatal depression and child maltreatment among Japanese fathers. *Child Abuse Negl* 2017;70:231–239 [PubMed: 28633058]
153. Ramchandani P, Stein A, Evans J, O'Connor TG, team As. Paternal depression in the postnatal period and child development: a prospective population study. *Lancet* 2005;365(9478):2201–2205 [PubMed: 15978928]
154. Gutierrez-Galve L, Stein A, Hanington L, Heron J, Ramchandani P. Paternal depression in the postnatal period and child development: mediators and moderators. *Pediatrics* 2015;135(2):e339–347 [PubMed: 25560437]
155. Cameron EE, Sedov ID, Tomfohr-Madsen LM. Prevalence of paternal depression in pregnancy and the postpartum: An updated meta-analysis. *Journal of Affective Disorders* 2016;206:189–203 [PubMed: 27475890]
156. Fadhlou A, Bouquet de la Jolinerie J, Feki A. Endometriosis and infertility: how and when to treat? *Front Surg* 2014;1:24 [PubMed: 25593948]
157. Mu F, Harris HR, Rich-Edwards JW, et al. A Prospective Study of Inflammatory Markers and Risk of Endometriosis. *American Journal of Epidemiology* 2018;187(3):515–522 [PubMed: 28992341]
158. Mu F, Rich-Edwards J, Rimm EB, Spiegelman D, Forman JP, Missmer SA. Association Between Endometriosis and Hypercholesterolemia or Hypertension Novelty and Significance. *Hypertension* 2017;70(1):59–65 [PubMed: 28559401]
159. Mu F, Rich-Edwards J, Rimm EB, Spiegelman D, Missmer SA. Endometriosis and Risk of Coronary Heart Disease. *Circulation: Cardiovascular Quality and Outcomes* 2016;9(3):257–264 [PubMed: 27025928]
160. Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. *BJOG: An International Journal of Obstetrics and Gynaecology* 2017;124(10):1501–1512 [PubMed: 28296146]

161. Uimari O, Auvinen J, Jokelainen J, et al. Uterine fibroids and cardiovascular risk. *Human Reproduction* 2016;31(12):2689–2703 [PubMed: 27733532]
162. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999;10(1):37–48 [PubMed: 9888278]
163. Fox MP, Lash TL. On the Need for Quantitative Bias Analysis in the Peer-Review Process. *American Journal of Epidemiology* 2017;185(10):865–868 [PubMed: 28430833]
164. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *International Journal of Surgery (London, England)* 2014;12(12):1495–1499

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Figure 1.
Conceptual Diagram for Examining the Association between Use of Assisted Reproductive Technologies (ART) and Offspring Neurodevelopment.

Table 1.**Key Methodological Considerations in Studying Children Conceived by Infertility Treatment**

Challenges with studies on ART	Primary concerns
Selection of appropriate populations	<ul style="list-style-type: none"> • Using children conceived spontaneously as a comparison poses challenges in discerning whether differences are due to the treatment procedures or the underlying infertility • Socio-economic differences in couples who undergo infertility treatment and the general population may limit comparability, and future studies should seek to evaluate differences in socio-economically and racially diverse populations
Confounding	<ul style="list-style-type: none"> • Studies may be confounded by a number of factors, and perhaps most importantly underlying infertility • Other factors to consider include: thyroid function, BMI, age, race, SES, nutrition, environment, mental health, health of both parents
Study design	<ul style="list-style-type: none"> • Lack of RCTs • Lack of long follow-up in cohort studies
Representativeness	<ul style="list-style-type: none"> • Comparison between studies is often challenging due to protocol heterogeneity in treating infertility (ovarian stimulation, ICSI, ART) and evolving technologies and techniques • Technological advances in techniques make any findings today not necessarily relevant for future children conceived by more advanced techniques