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Assisted Reproductive Technologies and Children's Neurodevelopmental Outcomes

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Abstract

Initial reports suggested that children conceived with assisted reproductive technologies (ART) may be at increased risk for a spectrum of developmental disabilities. Evolving evidence suggests that some of the early risks may have been overstated when not taking plurality of birth or gestational age at delivery into consideration, since both are independent risk factors for neurodevelopmental disabilities arising from alterations in structure and function or limitations in activities. Continued research is needed to overcome lingering data gaps in light of the equivocal literature for many neurodevelopmental disabilities relative to ART, increasing utilization of services and changes in the clinical management of infecund couples such as the adoption of natural cycles or *in vitro* maturation treatment options. Population-based cohorts with longitudinal assessment of the multifaceted nature of neurodevelopment across critical and sensitive windows is paramount for the development of empirically based guidance for clinical and population health.

Keywords

Assisted reproductive technology; children; epidemiology; neurodevelopment; impairments

Introduction

Children conceived using assisted reproductive technology (ART) represent currently about 1.4% of live births in the United States, but greater than 3% of live births in Connecticut, District of Columbia, Massachusetts, New Jersey, and New York (1). These percentages are likely to increase as treatment continues to advance and services become covered by health insurance. Of note is the additional percentage of births that are assisted by other infertility treatments such as ovulation stimulation by administration of clomiphene citrate (e.g., Clomid®), alone or in combination with gonadotropins (e.g., follicle-stimulating hormone [FSH]), and intrauterine insemination. The impact of ART on population health is notable, including in the United States, largely as a reflection of the greater percentage of multiple

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births (47% vs. 3%), preterm births (33% vs. 12%) and low birth weight (LBW: 32% vs. 8%) infants conceived with ART in comparison with the general birth population, respectively (1). These percentages vary tremendously across states with notable upper bounds. For example, 48% of ART births in Puerto Rico were LBW (< 2,500 g) in comparison with 26% in Massachusetts, while preterm births (< 37 wk) varied from 47% in Wyoming to 21% in Vermont.

Given that infants conceived with ART are more likely to be born preterm, small-for-gestational age (SGA, < 10th percentile for reference) or as multiples relative to children conceived without treatment, they represent a population at risk for mortality and morbidity, including a spectrum of neurodevelopmental disabilities (NDDs) (2). Questions remain, however, whether the disabilities or developmental differences can be attributed to the infertility treatment and/or underlying parental impaired fecundity, multiple gestation, or unmeasured environmental factors. There have been a number of follow-up studies of children born from ART addressing their neurodevelopmental status, which have been reviewed exhaustively (3-10), as practitioners have looked for answers and information for counseling expectant couples. Evidence on the long-term effects of infertility treatments remains equivocal, with the main criticisms of existing studies being that they frequently do not account for birth plurality and/or chorionicity if twins are even included, have small sample sizes, are rarely able to characterize the infertility treatment protocols except broadly, rely on clinic-based populations, inadequate selection of comparison children, or failure to account for known determinants of growth and development.

In practicality, the root causes of NDDs may not matter to expectant couples, but the answer has implications for treatment and obstetrical management. At the population level, NDDs carry tremendous socioeconomic costs and contribute heavily to the global burden of disease, given the higher associated mortality and long-term disability for children born early or with reduced size (11). In fact, the U.S. President's Council on Bioethics called for improved monitoring of infertility treatments and outcomes and long-term longitudinal studies to assess child health concerns for better informed decision-making on the part of practitioners and parents (12).

This paper reviews the available data regarding the neurodevelopmental status of children conceived with ART in comparison with children conceived without such treatment. For purposes of this paper, we define ART as the manipulation of gametes or embryos external to the body for purposes of establishing a pregnancy (13). Further, we utilize the conceptual framework of the International Classification of Functioning, Disability and Health that defines a disability as difficulty with any or all of the three interrelated areas of function: 1) impairments, defined as problems in body function or alterations in body structure (e.g., blindness, paralysis); 2) activity limitations, defined as difficulties in executing activities (e.g., eating, walking); and 3) participation restriction, defined as problems with involvement in any aspect of life (e.g., employment discrimination) (11). This paper addresses impairments (i.e., autism, cerebral palsy, intellectual disability, sensory impairments) and activity limitations (e.g., attention and hyperactivity, communication, motor, verbal), but not participation restriction. Since many authors focus on multiple neurodevelopmental outcomes using validated diagnostic instruments, we refer to activity limitations as attention and other neurodevelopmental outcomes. We begin the paper with a short review of ART and perinatal outcomes, given that they are associated with NDDs in general followed by a succinct review of the recent literature for specific NDDs. Other important outcomes such as birth defects and cardiovascular health are discussed in accompanying papers in this issue. We conclude with a discussion of the methodologic limitations underlying lingering data gaps, and offer key research strategies aimed at advancing our knowledge.

Adverse Perinatal Outcomes

It has been well established that infertility treatment and ART are associated with an increased risk of obstetrical complications and adverse perinatal outcomes. In a review of 17 matched control studies published from 1985-2002, Helmerhorst and colleagues (10) reported that after ART, singletons were at significantly increased risk for very preterm (< 32 wk) and moderately preterm delivery (32-36 wk), small-for-gestational age (SGA) birth, and perinatal mortality with relative risks ranging from 1.40 (95% confidence interval [CI]: 1.15, 1.71) for SGA to 3.27 (CI: 2.03, 5.28) for very preterm delivery. Cesarean delivery and neonatal intensive care unit (NICU) admissions were also increased, and the eight non-matched studies that were reviewed showed similar patterns (10).

In contrast to singletons, ART-conceived twins were not at increased risk for either very preterm delivery or preterm delivery and SGA in comparison with twins conceived without ART (10). In fact, ART twins were reported to have a 40% reduction in risk of perinatal mortality (0.58, CI: 0.44, 0.77), compared with twins conceived spontaneously. However, unlike the findings for singletons, which have been replicated and confirmed in a number of meta-analyses and population-based studies (14-20), the picture for twins is more complicated and less established (10, 21, 22). Specifically, ART twins are much more likely to be dichorionic, dizygotic pairs, and therefore twins conceived spontaneously are an inappropriate comparison group, since monochorionic pairs who are likely to have worse outcomes are included in the comparison. Using as the comparison 4,097 unlike-sex, spontaneously-conceived twin pairs (in other words, no monochorionic, monozygotic pairs) the perinatal outcomes for 700 ART twin pairs in Western Australia, surveyed from 1994-2000, showed that adverse outcomes were indeed increased with ART (22). The odds of very preterm delivery was 2.5 (CI: 1.6, 3.7) and moderately preterm delivery was 1.9 (CI: 1.3, 2.2), with very low birth weight (VLBW: < 1,500g) and moderately low birth weight (1,500-2,499 g) showing comparable increased risk. Twins conceived by ART were also more likely to be delivered by emergency cesarean, have longer birth admissions, and more frequent hospitalizations in the first three years of life than spontaneously conceived twins (22).

Finally, although less abundant, there is now some evidence suggesting that ovulation stimulation apart from ART may be associated with poor fetal growth. Comparing among live born singleton infants conceived with ART, with ovulation stimulation medications, and spontaneously in a sample of 16,748 births in six States under surveillance by the Pregnancy Risk Assessment Monitoring System (PRAMS), D' Angelo and colleagues (19) corroborated that singleton infants conceived with ART are at risk for preterm delivery and SGA birth, with adjusted odds ratios (AOR) of 1.91 (CI: 1.31, 2.80) for preterm delivery and 1.98 (CI: 1.21, 3.24) for SGA. Singleton infants conceived with ovulation stimulation were not at risk of preterm delivery but were at risk of SGA (AOR: 1.71, CI: 1.09, 2.69). On the other hand, this study did not show effects of the different treatments for multiple births. This is probably for two reasons: first, there were too few twins or triplets in the treatment groups (n=285) and twins in the reference (n=176) for meaningful comparison; and second, the reference was all spontaneously conceived twins, including an unknown number of monochorionic pairs, which would have attenuated the difference among the groups in terms of outcomes. In sum, the available weight of evidence to date supports a shortened gestation and lighter birth size for ART-conceived infants in comparison with infants conceived without such treatment.

Neurodevelopmental Impairments

Little is known about the etiologic determinants of NDDs making it difficult to specify statistical models inclusive of relevant variates and known/potential confounders. With increasing support for the early origins of health and disease hypothesis (23), delineating peri-conceptional and *in utero* influences on human development becomes essential for understanding association studies focusing on ART and children's development. Further complicating our understanding is recognition of possible trans-generational exposures that may affect parents' fecundity and offspring's development reflecting a shared etiology (24, 25). Such data are absent and, therefore, we focus on research that is assessing ART and children's development.

Autism

Concern has arisen as to whether children conceived by ART may be at increased risk of autism and the autism spectrum disorders (ASD), again either from a treatment effect or because of parental characteristics, such as older parental age. Studies from Scandinavia (Finland, Denmark, Sweden), either case-control or retrospective cohort studies, with autism diagnosed from discharge registers have been inconsistent in their findings, but so far have been reassuring (26-28). An early Swedish study looking at births from 1984-1997 (26), showed an increased risk of ASD with infertility treatment, though the findings did not achieve significance (OR: 1.35, CI: 0.86, 2.11). Among Finnish births from 1996-1999 (27), ART was not associated with an increased risk for behavioral disorders usually diagnosed in childhood or adolescence, including ASD, among singletons (OR: 1.05, CI: 0.57, 1.91). On the other hand, a higher but insignificant increased risk for these disorders was observed for twins (OR: 3.05, CI: 0.70, 13.29). Finally, a Danish study (28) of children born from 1995-2000 after assisted conception (IVF or ovulation induction) observed a moderately decreased risk of ASD for twins (OR: 0.82, CI: 0.23, 2.95). In the United States, Grether and colleagues (29) reported no increased risk of ASD (AOR: 0.99; CI: 0.67, 1.50) among 349 singleton cases born between 1995-1998 in Northern California who were compared with 1,847 control children in relation to parental infertility using various indicators. A significantly increased risk was observed for twins (OR: 3.9, CI: 1.2, 13). These findings for twins appear to corroborate the results of the Finnish Study (27), but it is important to note that the Grether and colleagues (29) analysis was based only on 21 twin cases and 54 twin controls.

Cerebral Palsy

While earlier, smaller studies with short follow-up intervals tended to report null findings for both *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) techniques, a number of large, primarily Scandinavian population-based cohort studies based on registry data have reported a significant increase in risk of cerebral palsy (CP) for IVF children as compared to those spontaneously conceived (5, 26, 27, 30-34). The later studies are prospective cohorts and obtained neurological outcome data from physical examination, medical or hospital records and/or registry records. In general, they found about a twofold increased risk in cerebral palsy with IVF or ICSI that is explained to some extent, but not all, by preterm delivery and multiple births (34). However, with the number of twin births from ART decreasing over time in Scandinavia, the rates of cerebral palsy have likewise decreased (35).

Similarly, a recent study by Davies and colleagues (36) from South Australia, 1986-2002, looked at cerebral palsy in the context of birth defects incidence in a cohort of 308,974 births, of which 6,163 were from assisted conception (i.e., IVF and ICSI). These authors were able to adjust for a number of parental and fetal factors, including maternal age, parity,

fetal sex, year of birth, maternal race/ethnicity, maternal country of birth, maternal conditions of pregnancy, maternal smoking, socioeconomic status, and maternal and paternal occupation, but did not adjust for timing of delivery (i.e., very preterm or preterm). In the adjusted models, there was an increased risk of cerebral palsy overall (AOR: 2.66, CI: 1.79, 3.94), with the effect being larger for singletons from assisted conceptions (AOR: 2.22, CI: 1.35, 3.63), than for twins (AOR: 1.39, CI: 0.69, 2.77) (36).

Researchers continue to assess the relation between ART and CP in the context of other aspects of parental infertility. The Danish National Birth Cohort (1997-2003) was used to assess if the increased risk of cerebral palsy noted with ART was due to the effect of ART treatment or parental infertility. Zhu and colleagues (34) identified cases of CP through the Danish registry among children ages 4 years or older, and looked at outcomes in relation to time-to-pregnancy (TTP: 0-2, 3-5, 6-12, > 12 months), infertility treatment (IVF, ICSI, other), and whether or not the pregnancy was planned. In the total cohort of 90,203 children, 165 cases (0.18%) of cerebral palsy were identified, and there was no association between TTP and the risk of cerebral palsy. While subfecundity was not associated with cerebral palsy, after adjusting for preterm delivery and multiple birth, there was a more than twofold risk associated with ART (adjusted Hazard Ratio (aHR): 2.30, CI: 1.12, 4.73).

Investigators have attempted to synthesize original research using a weight of evidence approach for assessing ART and CP. Specifically, a recent meta-analysis of 19,462 children conceived with IVF reported a twofold increased odds of CP. However, the authors identified important methodologic limitations that impact a more complete understanding of the association (6). These limitations included limited sample sizes particularly for rare outcomes such as CP, little to no information on other aspects of couples' fecundity and specific aspects of ART and other infertility related treatment, such as ovulation stimulation.

Intellectual Disability

Little is known if and how ART may affect the developing brain, and there have been virtually no studies that have followed ART fetuses by ultrasound to delivery to chart the development of the brain. Following initial reports suggesting that ICSI children were at significantly increased risk for developmental delay in comparison to IVF and naturally conceived children, recent evidence suggests comparable mental development. A review summarizing nine previous studies involving 969 ICSI children and 828 controls (343 IVF, 485 naturally conceived) concluded that most ICSI-conceived children had normal mental development, but that maternal education and social class were important determinants of children's developmental outcomes (37). Thus, proper model specification regarding the inclusion of relevant confounders is critical for assessing associations between ART and children's intellectual development. Another systematic review analyzed 59 studies including 23 registry-based and 14 controlled studies and concluded that children born following IVF or ICSI were not at increased risk of severe cognitive impairment in comparison to naturally conceived children (5).

Sensory Impairments – Hearing and Vision

To date, there have not been many studies focusing specifically on sensory impairments or auditory and visual acuity despite their extreme relevancy for development. Ludwig and colleagues prospectively followed 276 term singleton ICSI children and 273 children who were spontaneously conceived and assessed hearing and vision at 5.5 years and reported no differences across groups of children (38). An important finding of this study is the low percentage of parents that were aware of children's hearing abnormalities as detected as part of this study, suggesting that parental reporting may not be a valid method for ascertaining children's sensory deficits.

An observational cohort of IVF children born from 1982-2007 was assessed for eye malformation (n=32,091) and the cohort born from 1985-2005 for severe visual impairment (n=24,628) using all births and the Swedish health registers, and the IVF cohorts were compared with all children born during the time periods involved. Only 36 cases of ocular malformation were identified, and this did not represent an increased risk after adjusting for potential confounders (AOR, 1.05; CI: 0.75, 1.47). The 25 IVF cases of severe visual impairment identified did represent a significant increase (AOR, 1.55; CI: 1.04, 2.32) compared with all children (39).

Activity Limitations

Children's development can be affected without altering structure or function or the so-called neurodevelopmental impairments. Rather, developmental deficits may become apparent particularly when assessed at developmentally appropriate ages (e.g., preschool or school-aged). Borrowing from the literature for high-risk infants such as those born early, of diminished birth size or as multiples, it is important that standardized assessment of ART-conceived children continue to identify deficits that may arise later in childhood or adulthood. We briefly review neurodevelopmental outcomes including attention deficit and hyperactivity below.

In the largest study conducted to date and known to us, 28,158 children born after IVF were compared with 2,417,886 children from the Swedish population, 1982-2005. Using prescription drug registries as the proxy for diagnosis, children with attention deficit/hyperactivity were compared to the children in the general population. An elevated risk for ADHD was observed for IVF children in comparison to population children after adjusting for potential confounders (1.18; CI: 1.03, 1.36). The association was stronger for girls (OR: 1.40, CI: 1.07, 1.83) than for boys (OR: 1.11, CI: 0.95, 1.31). However, the association was no longer significant after adjusting for length of involuntary childlessness, which the authors interpreted as offering weak evidence for an association between IVF and ADHD (40).

Regarding mental and psychomotor neurodevelopment in early childhood, there have been numerous studies examining this area with conflicting findings, again primarily relating to the percentage of children in the study who were twins or born preterm. Most studies have reported no significant differences in cognition, mental, or psychomotor development between ICSI and/or IVF children as compared to spontaneously conceived children (30, 41-49), but still some earlier studies did report a developmental deficit in ART-conceived children (50, 51). These studies were all prospective in design, with the exception of two retrospective studies (45, 50), and assessed developmental status through a variety of methods, complicating comparison. Most studies on follow-up utilized standardized examinations such as the Bayley Scales of Infant Development (BSID) (42, 44), the Griffith Scale (47-49), or the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) (43, 46), while others used a non-standardized neurologic examination (41), nation-wide registry data (30), or a list of developmental milestones collected through interview (44). Furthermore, there are other limitations to the existing studies that hamper the generalizability and interpretation of findings. As indicated earlier, criticisms of existing studies include not accounting for plurality and chorionicity if twins are included, restriction to singletons, small sample sizes, clinic-based populations, and failure to account for gestational age and other factors known to influence development.

Two recent studies, one with follow-up to 18 months (52) and the other to 3 years (53), have tried to address some of the concerns and are notable. Zhu and colleagues (52) followed up to 18 months of age, 37,897 singleton infants from fertile couples, 4,351 infants from

subfertile couples (TTP > 12 mo), and 3,909 infants born after infertility treatment (IVF, ICSI, intrauterine insemination, hormonal treatment) in the Danish National Cohort and evaluated them for gross and fine motor development (milestones), cognitive, and language skills. They found no effect of fertility or treatment on motor or attention skills, but they did find, comparing the infertility treatment with the subfertile group, that the infertility-treated group overall had a slight delay (OR: 1.24, CI: 1.01, 1.53) in achieving cognitive and language milestones (52). While not reflected in the global score (delay in meeting at least 3 milestones), the children conceived with ICSI, compared with those born from subfertile couples, did appear to be particularly prone to delays in gross motor development (e.g., sitting without support at 9 months, AOR: 1.33, CI: 0.84, 2.09; walking without support at 16 months, AOR: 1.40, CI: 0.96, 2.04).

However, in a more comprehensive study from the Millennium Cohort Study, 2000-2002, in England and Wales, Carson and colleagues (53) followed up infants to three years of age and found no differences in cognitive development after ART. These authors used the British Ability Scales II Naming Vocabulary (BAS-NV) test and compared the 99 children from ART singleton pregnancies with four groups from the cohort: a sample of 198 singleton children matched for gender, mother's age and socioeconomic status; 402 singleton children from planned pregnancies with a TTP greater than 12 months; 5,556 singleton children from planned pregnancies with a TTP less than 12 months; and 10,574 singleton children spontaneously conceived (53). For each comparison, the ART children outperformed the comparison group in ability, although no comparison was significant. The ability difference in the favor of the ART children was +1.10 (CI: -2.47, 4.68) with the matched group, +1.44 (CI: -1.74, 4.63) with a TTP greater than 12 months, +1.66 (CI: -1.34, 4.66) with a TTP less than 12 months, and +1.84 (CI: -1.07, 4.74) for any spontaneous conception. This cohort was also assessed at five years of age, again, with no evidence that ART adversely affected children's cognitive development after adjusting for sociodemographic factors (54).

Summary

The most cited population-based study that addressed neurodevelopmental outcomes among children conceived from infertility treatment raised tremendous concerns, finding that suspected developmental delay was increased nearly fourfold in children born after IVF (30). However, this study made it quite clear that the increased risk was primarily attributable to the complications of twins and to preterm delivery. Subsequently, while the picture has been less clear, the evidence that has been accumulated has been generally reassuring. Singleton children born at term or near term with normal birth weights, irrespective of conception mode (i.e., IVF, ICSI, ovulation stimulation, spontaneous after a prolonged TTP), appear to be developing normally. On the other hand, it will also be important to continue to evaluate other aspects of children's development with regard to generalized health status and hospitalization. Previous reports have noted significantly more childhood illnesses, surgeries, medical therapies, and hospital admissions for ART children in comparison with children conceived without such treatment (55, 56), although some of the increase in use of medical services has been attributed to multiple or preterm birth (26).

In sum, the available literature while initially suspect now suggests that ART-conceived children do not have a uniformly higher risk of NDDs than children conceived without such treatment. As such, the weight of evidence is reassuring, particularly when accounting for multiple births and other relevant factors such as parental sociodemographic characteristics. The absence of increased risks for impairments and, to a lesser extent, limitations in activity should not be interpreted to mean that follow up is no longer warranted. As noted by many authors, continued monitoring and follow-up of ART children is warranted in light of

methodologic gaps impacting the full interpretation of findings and an increasing percentage of children born following treatment which was estimated to be 5 million worldwide in 2011 (57). However, future research needs to move beyond select clinical or registry-based research to ensure treatment and other relevant exposures/confounders are ascertained in a valid and reliable manner and that outcomes are assessed relative to the whole child and not just one aspect of development. We suggest a strategy for moving forward and filling lingering data gaps.

Advancing Knowledge –Overcoming Methodologic Challenges

Using the many important findings from past research, our future research strategy should address four overarching methodologic limitations if we are to overcome lingering data gaps regarding the long-term developmental status of ART children. First, sampling frameworks need to be inclusive and not restricted to particular ART clinics to ensure external validity (i.e., generalizability) of results. This strategy includes country-specific follow-up to address varying clinical practices, especially single embryo transfer, *in vitro* maturation, natural cycle IVF. Also with regard to sampling, it is important to sample on families not just children to obtain the involvement of the couple along with the child to better measure fecundity and related impairments or treatments in addition to ART. This step is important when considering a possible shared etiology between fecundity in one generation and neurodevelopmental status in the offspring, and in delineating the causal model for fecundity, ART and NDDs.

Second, because they are at higher risk for adverse outcomes, such as intrauterine growth restriction, that may affect later child development, fetuses conceived with ART and by ovulation stimulation should be followed longitudinally through gestation to determine the nature of the growth restriction, if any, and minimize the risk of adverse outcomes. This is especially important for twins, where it has been shown that the smaller twin of a discordant pair will perform less well on intelligence tests at age three, while achieving a physical size comparable to the larger twin of the pair (58). The timing of intrauterine growth restriction associated with ART or ovulation stimulation is unknown, so that cases with growth restriction that is brain-sparing are not distinguished from those who are not.

The third consideration is the need for postnatal longitudinal follow up consistent with the ever changing nature of children's development including its transient unevenness. This design will position researchers to assess the potential shared etiology of impaired parental fecundity, ART, epigenetic changes and suboptimal fetal, infant and child development.

Lastly, choice of comparison group is most important given that some comparison children are conceived by couples with impaired fecundity or following other infertility treatments. Ascertaining pregnancy intention or time required for conception among planners may help provide insight regarding the underlying fecundity status of couples. Many registry-based studies involving large cohorts do not specifically address this issue despite its relevancy for interpreting findings.

We are unaware of any research that has prospectively followed ART-conceived and comparison infants from conception onwards in the context of other environmental influences, such as diet, household quality, and chemical exposures, to assess fetal growth and to assess growth and development continuing through infancy and childhood. Such strategies may help identify high-risk patterns and trajectories for ART and non-ART pregnancies along with the implications for infant and child health. Similarly, longitudinal studies of ART births through key developmental milestones that are the hallmark of childhood and adolescence are noticeably absent. The Upstate KIDS Study is one such attempt to longitudinally follow a population-based cohort of children irrespective of their

mode of conception across sensitive windows of infant and child growth and development (www.albany.edu/upstatekids).

There are many population level changes affecting childbearing in the United States and in other countries including a later age at first birth and smaller completed family size. These factors have implications for both couple fecundity (59) and fetal/infant growth and development. As such, there is a continual need to establish prospective cohorts for monitoring and assessment as we strive to understand how couple fecundity or evolving ART treatment may or may not imprint the next generation.

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