

# Outcomes from infancy to adulthood after assisted reproductive technology

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The outcomes of assisted reproductive technology (ART) should be not only the evaluation of successful initiation of pregnancy but also the birth of healthy infants and the evaluation of long-term outcomes of the offspring of the couple undergoing therapy. Maternal and neonatal outcomes are reported in another article in this series. This article will review the infant, childhood, adolescent, and young adult outcomes published after ART. The recent literature will be reviewed. (*Fertil Steril*® 2014;101:1217–21. ©2014 by American Society for Reproductive Medicine.)

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The outcomes of children conceived after assisted reproductive technology (ART) include data from national registries with large numbers and other studies with small sample sizes. The studies differ in the methods of evaluation, and many lack information on long-term follow-up of the offspring of couples undergoing ART. It is imperative that prospective longitudinal studies be conducted as ART involves ovulation induction and handling of the gametes and early embryos during a vulnerable period of development. Outcomes may be different based on the method of ART, and the underlying cause of infertility may also influence outcome. The number of offspring of couples undergoing ART continues to increase and was reported in 2012 to have exceeded 5 million (1). The outcome of children and young adults after conception by ART has been reviewed by other investigators (2–5); in this article, selected studies will be

reviewed in detail. The outcome from infancy to adulthood will focus on congenital anomalies; physical growth and health; neurological, cognitive, behavioral, and mental health; and metabolic disease and risk for cancer.

## CONGENITAL ANOMALIES

The rates of congenital anomalies after ART need to be assessed based on consistent definitions of major or minor anomalies, comparisons with a matched group of infants born without ART, and clarification of inclusion of stillbirths and abortions in the cohorts evaluated. Hansen et al. performed a systematic review of publications before 2003 that had examined the rate of congenital anomalies after ART; only seven of 25 studies met the criteria for inclusion in the meta-analysis (6). Major defects were increased in this meta-analysis (odds ratio [OR], 2.01; 95% confidence interval [CI], 1.49, 2.69). Some of the

selected studies did evaluate confounders such as the duration of infertility, which in itself is associated with risk for anomalies. Recent reports have examined the rate of anomalies after accounting for maternal age at therapy (which may serve as a surrogate for infertility). Al-Fifi et al. retrospectively evaluated 327 children delivered at a single center in Saudi Arabia over a 4-year period (2002–2007) after ART with a matched group of 354 children born after spontaneous conception over the same time period (7). Matching was based on maternal age with 253 women in the ART group and 349 in the control group; the average maternal age was 29 years in both groups. The rate of hypertension and diabetes was similar between groups. Multiple gestations were higher in the ART group, and the gestational age and birth weight were significantly lower compared with the control group. Absence of any anomalies was noted among 97% and 94% infants in the ART and control groups, respectively, with multiple anomalies seen in only two and four infants in the two groups, respectively. In a study from Leiden University, Knoester et al. prospectively evaluated anomalies at 5–8 years of age focusing only on singletons born between 1996 and 1999

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by method of ART, either intracytoplasmic sperm injection (ICSI) or in vitro fertilization (IVF), and natural conception, with approximately 85 children in each of the three cohorts. Evaluating the presence of anomalies in childhood is preferable as some anomalies are detected only after the neonatal period. There was no difference in the rate of congenital anomalies within the three groups (8).

## PHYSICAL GROWTH AND HEALTH OUTCOMES

Ceelen et al. recently reviewed the literature examining the height, weight, and health conditions of children after ART (3). There are no deficits in growth noted among children and adolescents conceived by ART. There was some evidence that children who were conceived by ART have more frequent diagnoses of illness and hospitalizations than children conceived naturally, however, it is unclear whether this is due to the ART itself or due to parents of children conceived by ART being more concerned and thus seeking medical help more frequently.

## NEUROLOGICAL SEQUELAE

In the systematic review of child neurodevelopmental outcomes after ART, Bay et al. has noted that there appears to be no significant differences between children conceived by ART or spontaneous conception when studies reporting outcomes among preschool, middle childhood, and teenage children are examined (5). However, the number of studies with consistent long-term follow-up is small. One of the studies with a large sample size, a population-based study, was the one reported by Stromberg et al. in 2002 (9), reflecting births between 1982 (when the first IVF infant was born in Sweden) and 1995. The 5,680 children born after IVF varied in age from 18 months to 14 years and were matched by gender, birth year, and hospital of birth with 11,360 children conceived naturally. The risk of neurological disability requiring rehabilitation was increased in the ART group (OR, 1.7; [95% CI, 1.3–2.2]); however, this difference was not significant when the analysis was adjusted for confounders that are known to be associated with an increased rate of neurological sequelae such as multiple births, birth weight, and gender, while maternal age did not impact risk.

In 2006, Ludwig reviewed neurological sequelae after ART as part of a systematic review of controlled studies (2). Most studies had a limited duration of follow-up; the only study that evaluated children at 5 years of age compared 300 children conceived by ICSI in three centers in Belgium, Sweden, and the United States with 266 spontaneously conceived children. The variables used for matching of the ART and control group varied by center. Fine and gross motor abnormalities were assessed by the Peabody Developmental Motor Scales, and data from two centers were included. The ICSI children scored lower than the control group, however, the frequency of children scoring lower than 1 SD below the mean was similar among both groups (10). Knoester et al. investigated the impact of ICSI on neuromotor development in 5- to 8-year-old singletons and compared detailed neurological outcomes of 81 children conceived by ICSI with 81

IVF and 85 normally conceived children (11). The frequency of minor neurological dysfunction was similar in the ICSI (66.3%) and IVF groups (61.3%) but was higher among ICSI compared with normally conceived children (50.6%). These differences were not significant when adjusted for maternal age and parity. When the analysis was limited to only the children born at term, the prevalence of the minor abnormalities was increased among ICSI compared with normally conceived children. It should be noted that the long-term implications of subtle neurological signs on adult neurological or mental health are unknown.

Kallen et al. recently reviewed cerebral palsy (CP) rates in Sweden (where the rate of ART is relatively high) among all children conceived by ART between 1982 and 2007 (12). The risk of CP was increased when the entire period of the study was considered. The OR, 95% CI of CP for children after ART was 1.81, 1.52–2.13, respectively, but when only singleton births were included in the analysis, the increased risk was not apparent. The rate of multiple gestations decreased over the later years of the study to <10% of births in the ART cohort. When the CP rates were adjusted for year of birth, maternal age, parity, and exposure to smoking, the rate of CP was not significantly increased for children conceived by ART from 2004 to 2007 (OR, 0.97; 95% CI, 0.57–1.66).

## PUBERTAL DEVELOPMENT

Data on pubertal development were obtained through a self-administered questionnaire administered to the first cohort of young adults aged 18–25 years conceived by IVF from 1981 to 1990 in the United States. Only 173 (30.9%) of the 560 eligible adults responded, and analysis was completed on 166 responses. The results revealed no delay in the onset of puberty among the IVF respondents; the age of onset was higher in males compared with in females (13). Bias due to the fact that only motivated individuals responded to the survey cannot be excluded.

## COGNITIVE OUTCOMES

Data on cognitive outcomes in long-term follow-up studies after ART are scarce. In the same cohort among whom congenital malformations was assessed (11), Knoester and coworkers compared cognitive outcomes in childhood among 83 singleton children in the ICSI group, 83 children born by IVF, and 85 normally conceived children (14). Cognitive outcome was assessed by the Revised Amsterdam Child Intelligence Test (normal  $\pm$  1 SD, 100  $\pm$  15) with examiners masked to the method of conception. The children in the ICSI group had an average IQ that was 5–7 points lower than children conceived normally and 3.6 points lower than those conceived by IVF. The clinical impact of IQ differences that are less than 1 SD from the normal may not be large; when the IQ ranges were categorized as less than 2 SD from normal, normal, and >1 SD above normal, these differences did not persist. The sample size of the study is small, and the investigators acknowledge that duration of infertility was not evaluated in the study. Higher cognitive function (information processing, attention, and visual-motor function using the computer-based Amsterdam Neuropsychological

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