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-Fi 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.
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 ± 1 SD, 100 ± 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
Tasks) has been assessed among adolescents conceived by ART and compared with that of those spontaneously conceived in a study by Wagenaar et al. in 2009 [15]. The 139 ART adolescents were comparable to the 146 control group adolescents in the neuropsychological tests.

BEHAVIOR

Data on child behavior after ART overall are reported to be reassuring when examining behavior among infants and young children [5]. Wagenaar et al. compared a cohort of children and adolescents aged 9–18 years from the VU University Medical Center Amsterdam who were born after IVF (n = 139) with those born spontaneously from parents with former fertility problems (n = 143) [16]. The parents responded to the Child Behavior Checklist (CBCL), while teachers responded to the Teacher Report Form (TRF); in both questionnaires, higher scores reflect more problem behavior. The mean CBCL and TRF scores were comparable between groups. On the CBCL, externalizing behavior as well as thought problems, attention problems, and aggressive behavior scores were lower in the IVF versus the control group. In 2011, the same investigators reported on the self-reported functioning of adolescents in the same cohorts [17]. The 11–to-18-year-old participants (86 IVF, 97 controls) responded to the Youth Self-Report (YSR) questionnaire. The YSR scores were all within the normal range, and no differences were found between the IVF and control groups. Golombok et al. has reported on the parent-child relationships and the psychological well-being of the first cohort of IVF children in the United Kingdom who reached adolescence. Thirty-four children born by IVF, 49 children from adoptive parents, and 38 naturally conceived children were interviewed at 12 years of age using the Child and Adolescent Functioning and Environmental Schedule, the Expression of Affection Inventory, and the Conflict Tactics Scale. No differences in all categories of behavior were noted [18]. In a more recent evaluation of the adolescents themselves at 18 years of age, no increase in anxiety or depression was noted among 26 participants born by IVF, 27 adopted in infancy, and 56 conceived spontaneously [19].

AUTISM SPECTRUM DISORDER AND OTHER DISORDERS

The risk of autism spectrum and other disorders has been assessed in large registries. Pinborg reports no increase in any mental health disorders among IVF and ICSI preadolescents at 13 years of age [20]. Zachor and Itzchak included a case-control study with 507 children diagnosed with autism spectrum disorder (ASD) and 108 with a diagnosis other than ASD, including developmental delay, attention deficit hyperactivity disorder (ADHD), behavior problems, and mental retardation [21]. The rate of ART in the ASD group was found to be significantly higher (10.7%) than in a large Israeli population registry (3.06%). Parental age distribution was similar in the ART and non–ART ASD groups, although maternal age was increased in the ASD group as compared with the case-control population data. There may be unknown biases in this case-control study.

The risk of ADHD after ART between 1982 and 2005 was assessed in a national cohort from Sweden by Kallen et al. [22]. In this population-based study, 28,158 children born after ART were compared with 2,417,886 children in the national population registry. After adjustment for many confounders including year of birth, maternal age and parity, maternal smoking, body mass index (BMI), and educational level, the OR of 1.18 (1.03–1.36) was noted. However, when length of childlessness was entered into the model, the risk decreased and was no longer statistically significant. Bay et al. in 2013 reported on the data from the Danish registry; all ART children (n = 33,139) born from 1995 to 2003 with follow-up assessments in 2012 at the age of 8–17 were compared with 555,828 children born after spontaneous conception [23]. The risks for mental disorders among the IVF/ICSI children were not higher than in those born after spontaneous conception except for a minimally increased risk of tic disorders only. Children born after ovulation induction/with or without intrauterine insemination did have a small increase in the incidence of any mental disorder, ASD, ADHD, conduct, and emotional or social disorder (hazard ratio approximately 1.20 in each condition and hazard ratio of 1.5 for tic disorders).

IMPRINTING-RELATED DISORDERS

The imprinting related disorders are rare, and large sample sizes are needed to accurately assess risk. There have been reports that ART may be associated with increased risk in the studies reported after ART was first practiced, but these studies did not control for confounders such as prematurity, multiple gestations, or advanced maternal or paternal age. It is unclear whether infertility itself may be associated with increased risk. The risk of imprinting–related diseases (Angelman syndrome, Russel–Silver syndrome, Beckwith–Weideman syndrome, Prader–Willi syndrome) or cancer (retinoblastoma, Wilms’ tumor, osteosarcoma, hepatoblastoma) has been examined in the Danish National Cohort study in 2010 [20]. The study registry data included 957 singletons conceived after cryopreservation and two control groups; the first control group was 10,329 fresh IVF/ICSI during the same period (1995–2007), and the second control group was a random sample of 4,800 non-ART singletons. No increase in imprinting related disorders or cancer was reported between those conceived after cryopreservation and the two control groups.

CANCER

The risk of cancer can only be assessed in large population-based registries owing to the low frequency of this condition. Participants in a study in the Netherlands of women with subfertility problems were queried regarding reproductive therapies and cancer diagnosis in the offspring [24]. There was a 66.9% response rate, providing data on 9,484 children conceived after ART and 7,532 children born to women with fertility problems who conceived naturally. There were 16 cancers noted in the entire study group after a 6-year follow-up, and the anticipated rate was 15.5 cases. There was thus no increase risk among children conceived by ART.
when compared with the general population or with children born spontaneously.

Kallen et al. in 2010 reported on a population-based Swedish Cancer Register comparing rate of cancer among children born by IVF (26,692 children during 1982–2005) with that of children not conceived by IVF (25). There were 53 cases of cancer in the IVF group among 38 anticipated cases, with a total cancer risk of 1.42 (1.09–1.87). Maternal age, parity, subfertility, BMI, and multiple births did not impact risk, while higher birth weight, premature delivery, respiratory distress, and low Apgar score among infants were related to cancer risk. The most recent publication is from Williams et al. who linked data on all children born in the United Kingdom between 1992 and 2008 after ART (24). As noted under perinatal development (13), only 173 individuals completed the questionnaire (31% of eligible adults); among these respondents, 35% were noted to be overweight and 10% were obese. Approximately 65% had a chronic condition, 50% were smokers, 62% did binge drink in previous year, and >90% were physically active in the preceding month. The participants were similar to a subsample of the respondents to the 1999–2004 National Health and Nutrition Examination Survey (30). Finally, a review of 25 years of population-based data from Sweden notes a minimally increased risk for impaired visual acuity and for asthma (31).

### CONCLUSION

In summary, when evaluating longer term outcomes among the offspring of parents who received ART compared with offspring conceived naturally, there does not appear to be an increase in congenital anomalies, and physical growth is similar between groups. The rates of cerebral palsy are not increased; however, soft neurological signs may be increased, but the significance of this finding is not known as yet. There appears to be no delay in pubertal development, although the data are sparse. Cognitive and behavioral outcomes are similar between adolescents and young adults conceived by ART or spontaneous conception. There is no increase in cancer risk among children born after ART compared with national normative data. Finally, the finding of elevated BP and thus risk for adult cardiovascular disease needs close follow-up.

### REFERENCES


