Long-term outcomes for children conceived by assisted reproductive technology

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Worldwide, more than 10 million children have been born after assisted reproduction technology (ART), comprising up to 7.9% of children born in Europe and up to 5.1 % of children born in the US in 2018. The short-term outcome for children born after ART is well-known from numerous publications, with higher rates of preterm birth and low birth weight in children born after fresh embryo transfer and higher rates of large for gestational age and high birth weight in children born after frozen embryo transfer compared with children born after spontaneous conception. Higher rates of birth defects in children born after ART have also been shown consistently over time. Studies on long-term health outcomes after ART are scarcer but suggest an increased risk of altered blood pressure and cardiovascular function in children born after ART. In this review, we summarize long-term health outcomes in children born after ART and discuss whether the increased health risks are associated with intrinsic maternal or paternal factors related to subfertility or ART treatments per se. Finally, we speculate where the future will bring us regarding ART treatment strategies and the safety of the mother and child. (Fertil Steril® 2023;120:449–56. ©2023 by American Society for Reproductive Medicine.)

Key Words: ART, long-term health, cardiometabolic disease, cancer, frozen embryo transfer

INTRODUCTION

Today the number of children born after assisted reproduction technology (ART) has exceeded 10 million worldwide, and delivery rates steadily rise and comprise up to 7.9% of the birth cohorts in Europe and up to 5.1% of children born in the US (1, 2). In recent years the best practice has gone from multiple embryo transfer to single embryo transfer to avoid multiple births, which has significantly lowered the risk of preterm birth after ART and improved the overall health of the ART progeny (3). Depending on the ART method, even singletons born after ART have higher obstetric and perinatal risks than their spontaneously conceived (SC) peers. Singletons from both fresh and frozen embryo transfer (FET) are more likely to be small for gestational age children (SGA) (4, 5), have low birth weight, and be born preterm, whereas singletons from FET are more likely to be large for gestational age (LGA) (6, 4). Further pregnancies after FET are at increased risk of postpartum hemorrhage and hypertensive disorder of pregnancy, including preeclampsia (4, 7). ART is associated with a higher risk of birth defects which seems to be steady over time (8, 9); intracytoplasmic sperm injection (ICSI) is associated with the transfer of poor semen quality to the male progeny (10, 11), and oocyte donation is associated with an increased risk of SGA and preeclampsia (12, 13). The current evidence on long-term health risks in children born after ART is still scarce but suggests an increased risk of altered blood pressure and cardiovascular function. In this review, we summarize long-term health outcomes in singletons born after ART and discuss whether the increased health risks are associated with intrinsic maternal or paternal factors related to subfertility or ART treatments per se. Finally, we outline the research gaps and the future perspectives on how to lower the health risk in ART progeny.

LONG-TERM DATA AVAILABLE

Some large national registers have been established to investigate the short- and long-term health of ART treatment in children and their mothers (14–20). The Committee of Nordic ART and Safety (CoNARTaS) is a Nordic research collaboration between

Received February 16, 2023; revised April 7, 2023; accepted April 13, 2023; published online April 20, 2023.

A.P. reports consulting fees from Preglem, Novo Nordisk, Ferring, Gedeon Richter, Cryos, Merck A/S; honoraria from Gedeon Richter, Ferring Pharmaceuticals, Merck A/S, Theramex, Organon; travel support from Gedeon Richter; on the advisory board for Preglem; and nonfinancial support from Gedeon Richter outside the submitted work. All other authors have nothing to disclose.

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Fertility and Sterility® Vol. 120, No. 3, Pt. 1, September 2023 0015-0282

https://doi.org/10.1016/j.fertnstert.2023.04.022

Denmark, Finland, Norway, and Sweden initiated in 2008 (21, 22). Data from several national health databases, quality registers, and population-based registers are cross-linked and pooled into one common database comprising more than 170,000 children born after ART from 1985 to 2015. The personal identification number, which is a unique code given to all Nordic residents at birth, makes this data linkage possible. With the inclusion of children born after ART from the mid-1980s until today, such data enable long-term follow-up of the children and their mothers to investigate the risk of, e.g., cardiovascular diseases, mental disorders, and malignancies, and for the children and young adults also pubertal disorders, reproductive health issues, and other rarer diseases. Currently, the CoNARTaS database includes approximately 8 million deliveries from the years 1985 through 2015.

The HFEA-ONS cohort is a national population-based cohort of children born after assisted conception in the UK (14). It consists of children recorded on the Human Fertilization and Embryology Authority (HFEA) register as being born after ART between 1992 and 2009, their SC siblings, and matched SC population controls linked to the Office for National Statistics birth registration dataset (14). This cohort has further been linked to the UK Hospital Episode Statistics database to allow monitoring of the child's long-term health outcomes up to 2015 (the HFEA-ONS-HES subcohort). Currently, the HFEA-ONS-HES cohort comprises approximately 200,000 individuals.

In the US, the Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART) is a unique data system comprised of cycle-based ART data linked to birth certificates, fetal death certificates, hospital utilization, and other health datasets in Massachusetts (15). ART treatment is identified through The Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS). Information on delivery outcomes and hospitalizations after delivery experienced by women and their children are obtained from the Massachusetts Pregnancy to Early Life Longitudinal data system. More recently, MOSART was further linked to the Massachusetts Cancer Registry. One strength of MOSART is the inclusion of a subfertile population as a control group. Currently, the MOSART database includes just over 1 million deliveries and covers the years 2004 through 2017 (15). Another US database links SART CORS data with cancer registries for 14 states (16).

In France, data from the French National Health System database has been used for the follow-up to early childhood in children born after ART (up to 2.5 years of age) (17) and for analysis of hospitalizations in women undergoing ART (18).

The OMEGA women's cohort was initiated in the Netherlands in 1995 to examine cancer risk among women who received ovarian stimulation for ART in 1983–2000 (19). The OMEGA offspring cohort consisted of their offspring and was constructed in 2013. The OMEGA offspring cohort comprises 47,690 children, including 24,269 ART conceived, 13,761 naturally conceived, and 9660 naturally conceived in women with subfertility. The cohort is unique as it includes women and children conceived by subfertile women who did not conceive by ART. However, the OMEGA cohort is not national and includes a subset of ART women and offspring in the Netherlands (19).

Examples of other data sets (11, 20, 23–26), although not national cohorts, established for long-term follow-up of health in general in ART children are the Growing up Healthy Study cohort in Perth, Australia (20) and Anhui Maternal-Child Health Study in China (23). Canadian projects have focused on neurodevelopmental (24), and Swiss projects on cardiovascular function (25). There are also ongoing projects on the health and reproductive outcomes of men and women conceived after ICSI in Brussels, Belgium (10, 11) and on men conceived after ICSI in Victoria, Australia (26).

In conclusion, several large databases constitute unique resources for assessing future health in ART-conceived children and their parents.

LONG-TERM MORBIDITY

Cardiometabolic disease

Cardiometabolic risks identified in children born after ART include altered glucose metabolism (27, 28), elevated blood pressure (27–31), and suboptimal cardiac diastolic function (32, 33). Furthermore, a few studies have found altered body fat composition in children born after ART (34, 35). Most of these studies, summarized in systematic reviews (36, 37), are based on small cohorts with low participation rates, resulting in a high risk of selection bias. Subsequent cohort studies, including small study populations, have not demonstrated any differences in cardiovascular profiles between ART and SC adolescents (38–40).

A few large studies have been published based on cardiovascular diseases. In a population-based cohort study of individuals born in Denmark, Finland, Norway, and Sweden between 1984 and 2015, data were obtained from national ART and medical birth registers and cross-linked with data from national patient registers and other population-based registers (41). In total, 122,429 children born after ART and 7,574,685 children born after SC were included. In all 135 (0.11%), 645 (0.65%), and 18 (0.01%) children born after ART were diagnosed with any cardiovascular disease (ischemic heart disease, cardiomyopathy, heart failure, or cerebrovascular disease), obesity, or type 2 diabetes, respectively. After adjustment, similar risks were observed for children born after ART and SC for any cardiovascular disease (adjusted hazard ratio [aHR] 1.02; 95% CI: 0.86–1.22) or type 2 diabetes (aHR 1.31; 95% CI: 0.82–2.09). For obesity, a small but significant increased risk was found among children born after ART (aHR 1.14; 95% CI 1.06–1.23). If true, this risk increase may be explained by the Barker hypothesis (42). According to the developmental origins of adult health and disease hypothesis, an abnormal intrauterine environment might be associated with adverse cardiometabolic outcomes in adult life, such as obesity and metabolic syndrome (42). Important limitations of the study were the relatively short follow-up time for children born after ART and SC of 8.6 and 14.0 years, respectively, and, for some outcomes, a few events. It was concluded that although the results were mainly reassuring, the short follow-up time makes further monitoring and surveillance of these diseases important.

Type 1 diabetes is another critical disease that until now has been explored only in one large cohort study based on register data from Sweden (43), including 47,038 children born after ART and 3,090,602 children born after SC. This study yielded 202 ART and 71,916 SC children with type 1 diabetes, respectively, corresponding to an incidence rate (IR) of 43.4 and 35.5 per 100,000 person-years in ART vs. SC, respectively. Overall, no increased risk of diabetes type 1 in children born after ART vs. SC was found (aHR 1.07; 95% CI: 0.95–1.23), whereas a higher rate was observed for children born after FET (FET vs. fresh embryo transfer: aHR 1.52 [95% CI: 1.08–2.14] and FET vs. SC: aHR 1.41 [95% CI: 1.05–1.89]) (43). A possible mechanism for the higher rate of type 1 diabetes in children born after FET might be the higher rate of high birth weight, and LGA found in these children associated with type 1 diabetes (44). The results raised some concerns, given the dramatically increased use of FET worldwide.

In conclusion, although limited data suggested a potential increase in elevated blood pressure and deteriorated metabolic profiles, large register-based studies cannot confirm any increased risks so far in cardiovascular disease. For type 1 diabetes, some concerns may be raised for children born after FET.

Malignancies

Childhood cancer is a severe condition for both the child and the family. Conflicting results have been presented concerning the risk of childhood cancer after using ART. Most large observational studies indicate similar overall cancer risk in children born after ART, and in children in the general population (45–48) but higher risk for both any cancer (16, 48, 49) and specific malignancies (16, 45, 46, 49, 50) have also been reported. In a Danish population-based register study, a higher risk of any childhood cancer was found in children born after FET compared with SC, but the finding was based on a few cases (47). A recent large Nordic register-based cohort study including 171,774 children born after ART and 7,772,474 children born after SC did not find any overall higher risk of childhood cancer in children born after ART (51). However, a higher risk was found for children born after FET (48 cases; IR 30.1/100,000 person-years) than both fresh embryo transfer (IR 18.8/100,000 person-years, aHR 1.59; 95% CI: 1.15–2.20) and SC (aHR 1.65; 95% CI: 1.24–2.19) (50). The most prevalent cancer type was leukemia, which was significantly increased both in FET vs. fresh embryo transfer and FET vs. SC. The mechanism behind a possible increased risk in children born after FET is not clear, but it is known that singletons born after FET are at increased risk of macrosomia that per se has been associated with a higher risk of childhood cancer (44).

In conclusion, the findings in most studies are reassuring, showing no elevated risk of overall cancer among children born after ART, however a higher risk was found among children born after FET. Although the absolute number of childhood cancer cases was low, the study raised concerns about the vast increase in FET, particularly freeze-all strategies without clear medical indications.

Neurodevelopmental and behavioral disease

Cerebral palsy. Based on the CoNARTaS data, the risk of cerebral palsy (CP) diminished over time among ART children due to the lowering of multiple birth rates (52). In 1990–1993, the adjusted odds ratio (aOR) of CP was significantly higher in ART children (aOR 2.76; 95% CI: 2.03–3.67) compared with SC children, whereas in 2011–2014, the risk was only moderately higher (aOR 1.39; 95% CI: 1.01–1.87). For singletons, the risk was no longer increased (aOR 1.11; 95% CI 0.98–1.24) in 2011–2014.

Attention deficit hyperactivity disorder and autism spectrum disease. A recent nationwide study from Ontario, Canada, including 925,488 children born from 2006 to 2014, found that infertility itself may be associated with attention deficit hyperactivity disorder (ADHD) in the offspring, but this was not amplified by the use of fertility treatment (53). The IR (per 1000 person-years) of ADHD was 12.0 among children in the SC group, 12.8 in the infertility without fertility treatment group, 12.9 in the ovulation induction/intrauterine insemination (IUI) group, and 12.2 in the IVF/ICSI group. Relative to the SC conception group, the aHR for ADHD was 1.19 (95% CI: 1.16–1.22) in the infertility without fertility treatment group, 1.09 (95% CI: 1.01–1.17) in the ovulation induction/IUI group, and 1.12 (95% CI: 1.04–1.20) in the IVF/ICSI group. This is in accordance with an earlier Swedish study of 28,158 children born after IVF, where ADHD was weakly associated with IVF, but after adjustment for length of involuntary childlessness, or when only singletons were analyzed, the significance disappeared (54). In addition, a previous Danish study showed that children (n = 124,269) born to women with fertility problems reported a higher risk of ADHD (HR 1.36; 95% CI: 1.29–1.45) than children born to women without fertility problems but no adjustment was made for multiple births in that study (55). Similarly, a Swedish study including 30,959 ART children found a similar risk of ASD as in children born after SC (56). Lastly, a meta-analysis by Liu et al. (32) concluded that ART was associated with a greater risk of ASD in an overall offspring group compared with SC children (relative risk [RR] 1.35; 95% CI: 1.09–1.68); however, this was not observed in singletons.

In conclusion, assisted conception methods per se do not increase the risk of ADHD and ASD, but the modestly increased risk is related to parental factors and multiple births.

Cognitive development. Two large population-based cohort studies from Denmark (n = 2836 singletons and n = 1930 twins) and Sweden (n = 8323 ART singletons) on academic performance in 15 to 17-year-old school children found higher crude mean test scores in ART singletons (7.16 $\pm$ 2.41 [mean $\pm$ SD]) than in SC controls (6.74 $\pm$ 2.46 [mean $\pm$ SD]) (57, 58). However, after adjustment for maternal educational level, the adjusted mean test score was slightly lower in ART than in SC singletons, with an adjusted mean difference of -0.15 (95% CI: -0.29 to -0.02) (57, 58). No difference was found in the adjusted analysis comparing ART with SC twins (57). A later population-based study reported academic performance in singletons from FET vs. fresh ET, which found similar test scores in the two groups (59). However, it was found that fewer twins than singletons attend the national test in the 9th grade indicating that twins were less likely to graduate the ground school (57).

Three systematic reviews on language development, behavior, and social functioning found no differences between children conceived by ART and SC (60–62). In the most recent systematic review focusing on cognitive development, Rumbold et al. (63) concluded that most studies on the subject had methodological limitations making it difficult to draw reliable conclusions, but that conflicting findings among studies of children conceived with ICSI required clarification in light of the increasing use of this technique for reasons other than male-factor infertility. However, in a large nationwide Swedish study, singletons from ICSI (n = 6953) had similar school performance as singletons from IVF (n = 11,713) and SC (n = 2,022,995) (43).

In conclusion, overall data on CP and cognitive development in ART children are reassuring if multiple birth rates are kept low.

Reproductive function

Two studies from Brussels have looked at the reproductive health of young adults born after ICSI (10, 11). The first showed that young males born after ICSI had a lower median sperm concentration and a lower total sperm count in comparison to their SC peers, and they were nearly three times more likely to have sperm concentrations below the World Health Organization reference value of 15 million/mL and four times more likely to have total sperm counts below 39 million (10). Furthermore, a weak negative correlation between total sperm count in fathers and their sons was found (10). The second study demonstrated that low inhibin B (<10th percentile) and high FSH (>90th percentile) levels were more often observed in men conceived after ICSI (11).

Based on a cohort in Victoria, Australia, Catford et al. (64) found no difference in the prevalence of severe oligozoospermia between 120 men conceived with IVF/ICSI and 356 men conceived without ART (9% vs. 5.3%). Further sperm concentration, total sperm count, and total motile count were similar in men conceived after IVF/ICSI than controls, but in this study, there was no distinction between men conceived either after IVF or ICSI neither in men of fathers with low sperm count (26, 64).

Based on 122,321 singletons conceived after ART and more than 6 million singletons from the background population, 37,869 children with diagnoses related to puberty disorders were identified in total, and 603 of them were born after ART. Children conceived after ART had a higher risk for early-onset puberty (aHR 1.45; 95% CI: 1.29–1.64) and late-onset puberty (aHR 1.47; 95% CI: 1.21–1.77). Girls had higher diagnoses related to early puberty (aHR 1.46; 95% CI: 1.29–1.66), and boys with late puberty (aHR 1.55; 95% CI: 1.24–1.95) (65).

Health of children born after preimplantation diagnostic testing

Although extensively used in many countries, only a few controlled studies have examined the health of children born after preimplantation diagnostic testing (PGT). A recent Swedish register-based study included all singletons born after PGT (n = 390) and IVF/ICSI singletons (n = 42,034) in Sweden from 1996 to 2019, with a mean follow-up time of 4.6 years for children born after PGT and 9.0 years for children born after IVF/ICSI (66). Perinatal outcomes and birth defects were similar for the two groups. Following the Cox proportional hazards models, no significant differences were found for asthma and allergic disorders. Sepsis, hypothyroidism, ADHD, autism spectrum disorders, mental retardation, CP, and epilepsy were diagnosed in a maximum of three PGT children (66). Although PGT does not seem to harm the offspring, PGT should only be used for parents carrying genetic disorders to limit the risk of their child inheriting this disorder and may be in subgroups of patients with a high risk of aneuploid embryos. Screening has not proven efficient as a general use for aneuploidy (67–70).

LONG-TERM HEALTH OF THIRD-PARTY REPRODUCTION

Third-party reproduction refers to the use of eggs, sperm, and embryos that have been donated by a third person (donor) to enable an individual or a couple to become parents (71).

Sperm donation

Two recent systematic reviews showed that in IUI pregnancies conceived with donor sperm vs. partner sperm, the pooled adjusted relative risk of hypertensive disorders of pregnancy was RR 1.44; 95% CI: 1.17–1.78, and aOR 1.55; 95% CI: 1.20–2.00 in the UK and Nordic analysis, respectively (72, 73). The corresponding risks for preeclampsia were also increased (adjusted reletive risk [aRR] 1.49; 95% CI: 1.0–2.09 and aOR 1.77; 95% CI: 1.26–2.48) (72, 73). Furthermore, an increased risk for SGA was observed in the UK meta-analysis (aRR 1.42; 95% CI: 1.17–1.79), whereas none of the other obstetric outcomes were increased in donor sperm IUI pregnancies (72). In the Nordic systematic review, no increased risk was observed for low birth weight or preterm birth after the use of donor sperm in IUI compared with the use of partner sperm in IUI (73). Subgroup analysis for singletons only did not change these results. The meta-analysis on low birth weight showed a lower risk after IVF with donor sperm than IVF with partner sperm (pooled aOR 0.89; 95% CI: 0.83–0.94) may be due to a healthy mother effect in IVF pregnancies with donor sperm as the women who had IVF with their partner sperm will be more likely to have a reproductive disease and thereby the higher risk of adverse obstetric outcomes than the women having IUI with homologous sperm. Hence, the IVF donor group is compared with a higher risk control population than the IUI donor group, which may explain why the risk of preeclampsia is not increased in women who conceived with an IVF donor. For hypertensive disorders of pregnancy, preeclampsia (PE), and preterm birth, no difference was found between IVF with donor sperm vs. partner sperm (73).

Egg donation

A recent Dutch meta-analysis found that the overall prevalence of PE after oocyte donation (OD) was 4–5 times higher than after SC and 2–3 times higher than after IVF with autologous oocytes (74). The pooled adjusted OR for PE was 2.67 (95% CI: 2.28–3.13) for OD vs. IVF. The pooled prevalence of PE in singleton pregnancies after OD was 10.7% (95% CI: 6.6–15.5) compared with 2.0% (95% CI: 1.0–3.1) after SC and 4.1% (95% CI: 2.7–5.6) after IVF. The prevalence of PE in multiple births was 27.8% (95% CI: 23.6–32.2) after OD, 7.5% (95% CI: 7.2–7.8) after SC, and 9.7% (95% CI: 6.2–13.9) after IVF (74). This finding confirms previous studies showing that OD carries the risk of adverse obstetric and perinatal outcomes, i.e., first-trimester bleeding, gestational diabetes, low birth weight, preterm birth, intrauterine growth restriction, and hypertensive disorders, such as gestational hypertension, PE, severe PE and early-onset PE (12, 75, 76). The causes for this higher PE risk may be multifactorial as both an impaired cardiovascular system at increasing maternal age, and the immune system in adapting to a completely allogeneic fetus and the lack of a corpus luteum in many OD pregnancies may mutually reinforce the susceptibility to the lack of vasoactive corpus luteum factors (77). A significant proportion of oocyte recipients are still able to ovulate and produce a corpus luteum; this is certainly the case for shared motherhood lesbian couples. It may be assumed that most OD recipients in the previous meta-analyses are scheduled for "HRT" FET, so-called "programmed" or artificial cycle FET where ovulation does not exist or is suppressed by sex steroid administration and a corpus luteum is therefore absent in early pregnancy. In these women, the risk of PE may therefore be substantially lower if natural or stimulated FET was performed instead of programmed cycles (78).

Psychosocial well-being in third-party reproduction families

A recent Swedish study on disclosure of OD and semen donation confirmed previous research indicating that early disclosure of the donor conception to children is not associated with negative outcomes for parents or children (79). In families conceiving with an oocyte or sperm donation, both mothers and fathers were shown to be well adjusted, reporting anxiety, depression, and parental stress within-normal range levels and a high relationship quality. The children had low levels of emotional and behavioral problems and were psychologically well adjusted. Disclosure is not detrimental to the psychological adjustment of families with heterosexual couples using oocyte or sperm donation when the child is 7–8 years old (79). In another recent UK study on parent-child relationship quality and child psychological adjustment in families using OD with different-sex couple parents, children's scores at 5-years of age indicated good parent-child relationship quality and high levels of psychological well-being, rating their relationships with their mothers as higher in warmth/enjoyment than children in a comparison group of families created using IVF (80). Early disclosure has also been integrated into recent guidelines on the topic (81). Apart from studies on psychosocial well-being, the literature on the long-term health of children born after third-party reproduction is scarce. Monitoring of these children is mandatory to explore the long-term health risk of the children.

DISCUSSION AND PERSPECTIVES

With more than 10 million children born after ART worldwide, it is reassuring that the long-term health of children born after ART overall seems to be good (Table 1). The most important achievement for the safety of mother and child has been the single embryo transfer policy lowering the multiple birth rates that have diminished the preterm birth rates and the rates of neurological impairment such as CP (52, 82). This has been facilitated by the vitrification cryopreservation technique and extended embryo culture leading to improved embryo survival rates and significantly improved embryo selection criteria. Hence, a significant shift toward elective freezing and postponing embryo transfer has been observed. This has, for sure, lowered the risk of ovarian hyperstimulation syndrome in women but increased the proportion of children born after vitrified/warmed blastocysts than fresh embryo transfer. Another game changer has been the intensive use of OD; thus, in some countries, OD now accounts for more than half of the ART treatment. The great demand for OD is derived from the increased childbearing age for women at the birth of the first child, whereas for some European countries, the mean childbearing is beyond 31 years (83). Worldwide third-party reproduction is becoming more and more common, reflected in the enhanced use of donor gametes, not only donated eggs but also the use of donor sperm in single women and women having same-sex partners has been rising. Further surrogacy has also become a more common way to build families; however, legislation on third-party reproduction varies tremendously between countries (84).

TABLE 1

Summary of long-term health outcomes for singletons conceived by ART compared with singletons from SC.

1. ART increases the risk of preterm birth, low birth weight, and birth defects. These risks are particularly observed in multiple births; however, a certain risk increase remains also in singletons born after ART. Children from FET are more likely to be large for gestational age and have a high birth weight.
2. The risk of cerebral palsy has diminished significantly over time, mainly because of the single embryo transfer policy, and is now similar in singletons born after ART and SC.
3. Studies on cardiometabolic health in children born after ART are conflicting, and there may be an increased risk of high blood pressure, and early markers of later onset compromised cardiometabolic health may be present.
4. The risk of malignancies is not increased in children born after ART in general but slightly increased in children after FET.
5. Neurodevelopmental health and school performance are similar in singletons born after ART and SC.

ART = assisted reproduction technology; FET = frozen embryo transfer; SC = spontaneous conception.

Pinborg. Long-term health in children born after ART. Fertil Steril 2023.

One limitation of long-term follow-up studies is that ART treatments have changed dramatically over the years, including ovarian stimulation, oocyte retrieval, embryo culture and selection, laboratory procedures, and embryo transfer (one embryo). To include populations of children conceived after more homogeneous ART procedures would require a narrowing of the study periods (i.e., after the year 2000); however, it will shorten the follow-up time of the children. In light of the safety of mothers and children, lowering multiple births has been the most important safety progress so far in ART; however, there are still some reasons for concern, in particular in FET pregnancies where we need to focus on endometrial preparation methods that create a corpus luteum to have the most optimal utero-placental development (85). Thus, more research is needed in natural and stimulated endometrial preparation methods before FET, as these cycles can also be performed in more flexible manners for logistics and planning in the clinics. Another concern that goes hand in hand is the increasing use of OD and the performance of HRT-FET cycles in this group of women, where the risk of PE is high. Hence, we need to develop more elegant and flexible protocols for FET, avoiding HRT-FET to try to mimic the natural cycle whenever possible (86).

The risk of cancer was higher in children born after FET in Nordic countries, and this needs further exploration in longitudinal studies focusing on different endometrial preparation protocols. The cause for this higher risk of cancer after FET may be due to the higher birth weight and/or epigenetic alterations (44, 87, 88). Further recent studies have pointed toward changes in the epigenetic control in the offspring after various ART methods (89, 90). Another reason for caution is the higher risk of LGA and SGA in children born after ART and the possible added long-term risk of cardiometabolic disease. As with all other medical treatments, we should aim to be as close to nature as possible and to use the ART methods only if medically indicated to increase reproductive outcomes. This applies to ICSI, elective freezing, FET endometrial preparation protocols, and PGT-a. Because long-term outcomes today are scarcely explored for many assisted reproduction methods, we should continue the long-term monitoring of the children and develop ART databases that can be cross-linked with health care registries to survey the new ART populations, in particular with a focus on new methods. In light of the safety of future ART generations, one rule should apply to all ART: if a method is clinically unnecessary, then avoid it.

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