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Cardiometabolic health of children conceived by assisted reproductive technologies

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Abstract

The cardiometabolic health of children conceived by assisted reproductive technologies (ART) compared with children conceived without medical assistance is unclear. Although the majority of published studies evaluating height, weight, and body mass index have not found differences by method of conception, some studies have indicated differences in adiposity by more direct measures such as skinfolds and dual X-ray absorptiometry. Far fewer studies have investigated other cardiometabolic characteristics, such as blood pressure and measures of lipid and glucose metabolism. Of these studies, some indications of increased blood pressure and recent findings of vascular dysfunction among children conceived by ART compared with children conceived without ART warrant further investigation. Epigenetic differences may be the global mechanism at work, resulting from different aspects of ART treatment, such as ovarian stimulation, in vitro culture, and manipulation of sperm, among other considerations. Fetal growth and placental development may serve as mediators of these effects. Future studies should consider recruiting sufficient numbers of ART and non-ART conceived multiples and collect information on indicators of cardiometabolic health in the parents. Despite some advantages of sibling cohorts in developmental origins research, its feasibility and utility for investigating health of children conceived by ART remains debatable.

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Keywords

Cardiometabolic risk; assisted reproductive technology; in vitro fertilization; intracytoplasmic sperm injection; children; growth; adiposity; glucose; blood pressure

Assisted reproductive technologies (ART) have aided millions of couples worldwide to have children. In 2009, approximately 1.4% of births in the United States were conceived with ART, an increase from the 2006 estimate of 1.0% of all US births (1, 2). With continued ART success and utilization, any long-term health risks due to ART treatment have the potential to affect a substantial proportion of the population and increase the future health care burden.

Prospective epidemiologic studies have documented associations between birth outcomes and future cardiometabolic health in offspring (3). Such outcomes include low birth weight (<2,500 g) and preterm birth (<37 weeks' gestation), both of which are well documented to be increased in ART singletons and twins (4–6). According to the developmental origins of health and disease hypothesis, these birth outcomes are indicators of non-ideal in utero conditions leading to compensatory fetal development that later increases risk of a host of diseases, including type 2 diabetes mellitus and cardiovascular disease (CVD) (7–9). Therefore, the increased risk of poor birth outcomes among neonates conceived by ART compared with others could be an indicator of greater future cardiometabolic risk.

The goal of this review is to evaluate the evidence to date on the cardiometabolic health of children conceived by ART, to identify important gaps that remain for consideration in future studies. To do so, this review will summarize the evidence to date, discuss some possible biological mechanisms, and comment on the design of future studies. Articles for review were identified through searches conducted on MEDLINE, Scopus, and hand searches of previous reviews (10–13). Case series or other studies lacking an internal comparison group (14–18) or not published in English were excluded. Studies included in this review collected information on cardiometabolic outcomes of growth (height, weight), adiposity, metabolism (glucose, lipids, adipokines, cytokines), and cardiovascular risk (blood pressure, vascular function). Assisted reproductive technologies are defined here as all techniques whereby both eggs and sperm are handled, therefore excluding studies of children conceived solely by, for example, IUI and ovulation induction (OI). However, non-ART comparison groups could consist of children conceived by other treatment methods apart from ART (e.g., OI) or children conceived without any specified medical assistance.

POSTNATAL GROWTH AND ADIPOSITY OF CHILDREN CONCEIVED BY ART

Seventeen studies regarding the growth of children conceived by ART ranging in age from 1 to 18 years were identified, with the majority observing no significant differences in height, weight, or body mass index (BMI) (19–35). Despite a large number of studies, differences in study methodology should be considered for remaining data gaps. Supplemental Tables 1 and 2 (available online) provide information regarding study design, methods, and results of these studies. None of the previous studies were conducted in the United States, even though treatment techniques and population characteristics may differ from the countries captured (36). Ten publications reported observations of children made at age 5 years or younger, but less evidence has been gathered regarding later growth and particularly pubertal growth. Related to the age of the children, studies with information on older children followed those conceived in the 1980s. Metabolic differences observed in the older ART children examined thus far could be related to the technologies used during that period and may be no longer relevant for more recent cohorts.

Moreover, all but one study (31) of children older than 5 years restricted recruitment to singletons. Of the studies at younger age, the evidence for growth among ART twins/ multiples remains inconclusive. Saunders et al. (34) expressed difficulty in recruiting non-ART children, especially matching on multiples, such that they had to exclude triplets and the twin sample size ended up imbalanced (91 IVF vs. 34 non-IVF twins), affecting statistical efficiency to test for differences. Kai et al. (26) included twins, but by 36 months of follow-up only 46 intracytoplasmic sperm injection (ICSI), 30 IVF, and 36 non-ART twins remained. Last, analyses presented were not always clear as to how twins were being counted in the studies. Kai et al. (26) indicated the twins were counted as individuals, but the methods used (e.g., analysis of variance) do not appropriately account for the correlation expected between twin observations with appropriate statistical methods (37). The evidence remains unclear, therefore, whether ART multiples grow differently from non-ART multiples.

Most studies recruited children from a limited number of infertility clinics over a certain time period, along with a comparison group commonly matched on different sociodemographic factors (Supplemental Table 1). In terms of the ART conception group, all studies except for one (28) included children conceived by IVF with or without ICSI, rather than other less frequently used ART techniques (e.g., zygote intrafallopian transfer [ZIFT], gamete intrafallopian transfer [GIFT]). However, the exception, the Taiwan Birth Cohort Study, which included ZIFT/GIFT (28), also included OI in their definition of ART without indicating the number of children conceived by OI (of the 366 total), even though it could be more common than ART. Conversely, Brandes et al. (24) included children conceived by OI in the non-IVF comparison group (32 of 116 non-IVF children). Last, Ceelen et al. (25, 38) recruited a comparison group of only children conceived by subfertile women who experienced unsuccessful conception after 1 year of unprotected intercourse but ultimately conceived without assistance.

As previously discussed by Buck Louis et al. (39), the choice of comparison group affects the interpretation of findings. For Ceelen et al., their comparisons aim to test for an IVF effect on growth among infertile couples. Whether children conceived by subfertile couples are the best comparison group to tease apart the effects of underlying infertility (if such exists) from treatment effects is debatable because couples conceiving after resolved infertility likely do not share the same risk profiles as couples who conceive by ART (39). They are also different from those who choose to utilize other infertility treatments, including medications for OI with or without IUI. That there is a causal effect of underlying infertility on long-term growth and cardiometabolic risk of children remains unproven, but some evidence has arisen that children conceived by couples who are subfertile (with time to pregnancy >2 years) had similar risks of adverse birth outcomes compared with ART-conceived children (40). For the studies by Lee (28) and by Brandes (24), the effect being tested is unclear owing to inclusion of the OI group. For the rest of the studies that did not report information on fecundity, it is assumed that the comparisons made tested for the combined effects of infecundity and treatment (39). Therefore, studies should not restrict inclusion of only children conceived by IVF/ICSI but should more comprehensively recruit those conceived by any infertility treatment while collecting information on underlying infertility (i.e., time to pregnancy).

Moreover, rather than recruiting comparison groups of children conceived by subfertile couples who ultimately resolve their infertility, considerations should be made in collecting and controlling for specific upstream factors that are demonstrated to be causes of infertility and causes of the child health outcomes in question. For example, obesity is heritable (41), and both maternal and paternal obesity are positively associated with subfertility (42–44). Many studies lacked information on parental BMI or used *t* tests for mean comparisons, which does not allow for adjustment for parental characteristics (Supplemental Table 2). Of the studies that accounted for parental or at least maternal anthropometry (21, 22, 25, 30, 31), results were in conflict but the studies differed in many aspects, including the age of the children.

Because children conceived by ART are at increased risk of preterm birth and low birth weight, the trajectory of growth, especially early catch-up growth, may be a better marker of abnormal growth and marker of long-term cardiometabolic health (45, 46) than cross-sectional comparisons of weight and height. Although studies of ART children had prospective longitudinal measures, some reports were made only of cross-sectional differences at one time point or multiple cross-sectional comparisons at different time points, without further analyses in changes in anthropometry between time points or use of longitudinal methods accounting for correlated repeated data (20, 21, 27). Kai et al. (26) plotted growth charts by conception method, concluding no differences, but ultimately reported *P* values from statistical tests made by cross-sectional comparisons at different time points. Ceelen et al. (38) captured growth data from periodic health examinations reported via postnatal growth charts. Children conceived by IVF had an average of 16 measurements from 0 to 4 years, whereas non-ART children of subfertile couples averaged 14 measurements. Growth velocity, as assessed by gain in weight, height, and BMI during late infancy (i.e., 3 months to 1 year), was significantly higher for the IVF group compared with the non-IVF group, suggesting catch-up growth achieved at that time period. These findings suggest that IVF children follow a similar pattern of growth acceleration early in life as observed in other cohorts of growth-restricted children (38). Growth trajectory by weight or height also did not seem to differ between 1 and 3 years by conception method (38). Those findings are corroborated in another study finding no differences in trajectory by conception methods at older childhood age, capturing data from 0, 5, 7–9, and 10–12 years (19).

Despite no dramatic differences in height, weight, or BMI, some studies measuring body fat more directly have suggested that increases in adiposity cannot be ruled out. Ceelen et al. (25) observed increased peripheral body fat by skinfolds (21.9 vs. 19.7 cm) without differences in BMI among children conceived by IVF vs. children conceived without infertility treatment by parents with resolved infertility. Significantly increased peripheral fat (7.59 vs. 6.69 kg) by dual energy x-ray absorptiometry was also observed in a subgroup of 100 children, comparing the IVF and non-IVF children from the same study who had reached puberty according to Tanner staging (25). Another study that measured adiposity by skinfolds found that girls conceived by ICSI had increased peripheral adiposity (by skinfolds +2.8 mm) and central adiposity (by skinfolds +3.1 mm, waist circumference +2.1 cm, BMI 1.1 kg/m^2) compared with non-ART girls (21). For boys, adjusted differences were significant only at advanced pubertal stage (3 or 4 and not 1 or 2), with a 3.5-mm increase in sum of peripheral skinfolds among the IVF compared with the non-IVF group (21). On the other hand, Miles et al. (31) found no differences in percent body fat measured by dual energy x-ray absorptiometry, despite finding lower BMI among prepubertal term children conceived by IVF compared with non-IVF children. Because these studies differ in many aspects of design (Supplemental Table 1), evaluation of adiposity in ART children requires replication.

In summary, despite the large number of studies previously published on weight, height, and/or BMI of children conceived by IVF/ICSI, data remain scarce in some areas, including [1] among children conceived in countries not previously captured, [2] among twins/ multiples, [3] sufficient adjustment for shared upstream factors of infertility and childhood growth/adiposity, [4] longitudinal analyses capturing height and weight trajectories over time, and [5] direct measures of adiposity rather than BMI alone. Future studies capturing information in these areas could help to complete the picture regarding growth and adiposity of children conceived by ART.

METABOLISM

Table 1 captures the handful of studies that have measured some traditional cardiometabolic measures among children conceived by ART compared to non-ART children. Similar to the studies reviewed above, these studies have limitations and are not comparable in study design and methods. Glucose metabolism among children of ART has been of interest. Hyperglycemia, or elevated glucose levels, causes microvascular damage and other sequela. Fasting plasma glucose, insulin, and their derived levels of insulin resistance have been compared between children conceived by ART and other children (31, 48–50). Three of the four studies found no differences in glucose levels, whereas the study by Ceelen et al. (48) found significantly increased levels (+0.2 mmol/L) among pubertal children conceived by IVF compared with children of subfertile parents (Table 1). In addition to investigating older children and comparing children of subfertile couples, the study also had a long recruitment period (1980–1994), which could be a weakness because the older children in the cohort may have been conceived under different ART protocols than the younger children. It also may explain why the other more recent cohorts found no differences. None of the studies found differences in fasting insulin levels. Measures of insulin resistance derived using fasting glucose and insulin by the homeostasis model also did not significantly differ. Taken together, these findings do not provide strong evidence for dysregulation of glucose metabolism among children conceived by ART.

Findings for fasting lipid values were also conflicting among three studies, with children conceived by IVF being observed to have a better lipid profile in one study, contrary to findings of higher triglyceride levels in another study and a third study finding no differences (31, 49, 50) (Table 1). Again, these three studies included very different populations of IVF and non-IVF children. Sakka et al. (49) included multiples, whereas Miles et al. (31) and Scherrer et al. (50) limited findings to term singletons with normal birth weight for the most part. Miles et al. studied a prepubertal group of children, whereas both Sakka et al. and Scherrer et al. had a mix of children at different stages of puberty. Fasting lipid levels have been shown to decrease during puberty, such that the National Heart, Lung, and Blood Institute recommends screening only before and after puberty (51), which may explain the discrepancies in results. As such, the evidence remains equivocal regarding lipid metabolism among ART children.

As for other biomarkers of metabolism, Sakka et al. (49) measured the adipokines adiponectin and leptin and inflammatory markers such as C-reactive protein and interleukin-6, also finding no differences in measured values by infertility treatment exposure. Because of this scant epidemiologic evidence, it is unclear whether these metabolic pathways are indeed associated with ART treatment exposure.

CARDIOVASCULAR RISK

Childhood hypertension has become a critical health concern, with indications that general population mean childhood blood pressure levels have been on the rise, especially among children in the younger age range (8–12 years) (52). Blood pressure tracks from childhood to adulthood (53). The Bogalusa Heart Study (53) has shown that both systolic (SBP) and diastolic (DBP) blood pressure were already significantly elevated during childhood (4–11 years) among individuals who later developed hypertension in adulthood compared with those who did not (54). Long-term consequences of high blood pressure include accelerated atherosclerosis and end organ damage, including increased risk of myocardial infarction, stroke, renal failure, and retinal damage. Moreover, childhood hypertension has been found to be associated with increased risk of premature death (occurring before 55 years) from endogenous causes among 4,857 American Indian individuals free of diabetes (relative risk 1.57; 95% confidence interval 1.10–2.24) (55). On a population level, even small shifts (2–5 mm Hg) in the distribution of adult blood pressure for a large proportion of individuals can translate into significant mortality (56).

Some evidence has recently emerged calling into question the vascular health of children conceived by ART (57). In an animal study, Watkins et al. (58) found that mice conceived by in vitro culture as well as mice conceived by ovulation stimulation alone had increased SBP later in life compared with naturally conceived mice, even after accounting for litter size (58). Sexual dimorphic results were found in this study as well, with elevated serum angiotensin-converting enzyme demonstrated in female but not the male mice, despite similar blood pressure elevations (58).

Three epidemiologic studies (20, 48, 49) have provided suggestive evidence for increased blood pressure among children conceived by IVF/ICSI, whereas two have not shown a difference (50, 59) (Table 1). Of the two studies that did not find a difference, one was conducted among a similar cohort of children conceived by ICSI that had earlier found a difference at age 8 years (20) but not again at age 14 years (59). The investigators suspect that pubertal influences on blood pressure and the necessity in stratifying results by gender, as well as other differences in measurement methods, may have contributed to the difference in findings for the younger and older ages (59). However, this study was also limited in its cross-sectional design.

In contrast, the study by Scherrer et al. (50), which found no differences in resting SBP or DBP among a small group of children conceived by IVF/ICSI (Table 1), nevertheless found differences in vascular function through more involved testing. Investigators recruited 65 healthy Swiss children conceived by ART (21 IVF, 44 ICSI) and 57 non-ART children recruited by the families of the ART children (including five sibling pairs). All children conceived by ART were singletons born at term without perinatal complications. At assessment, mean age, gestational age, birth weight, BMI, and presence of maternal CVD risk factor did not differ between the two groups. Investigators found significantly faster carotid–femoral pulse-wave velocity (indicating increased arterial stiffness), smaller flow-mediated dilation (FMD) of the brachial artery, and increased carotid intima–media thickness. These measures of atherosclerosis have been shown to correspond to increased risks of heart attacks and strokes in adults (60–62). To account for inherited differences due to parental vascular dysfunction, Scherer et al. also measured FMD in a subgroup of the parents and found it to not differ by fertility status, although the number of participants was small ($n < 25$ each). The suggestive evidence from this recent study and previous studies of blood pressure elevations calls into question whether vascular differences of children conceived by ART may be of concern, but the evidence can be greatly strengthened by longer follow-up and larger sample sizes, including children of subfertile couples (57).

BIOLOGICAL RATIONALE

Epigenetics as the Global Mechanism

Epigenetic differences have been hypothesized to be the global mechanism behind the health differences found in children conceived by ART (57, 63). The most commonly studied epigenetic mechanism has been DNA methylation, which plays a role in regulating gene transcription through the attachment of a methyl group to cytosine of DNA. A higher number of children conceived by ART in case series studies of children with rare imprinting disorders (such as Angelman syndrome and Beckwith-Wiedemann syndrome) first alerted the scientific community as to the possibility of DNA methylation differences (64, 65). Imprinting refers to the turning on and off of one copy of inherited genetic material by DNA methylation of either the paternal or maternal gene. In humans, the timing of the establishment of these imprinting marks remains unclear, leaving the possibility that defects can occur at multiple stages of ART, including during times of imprinting establishment in gametes and imprinting maintenance in the embryo (65). The association between ART and imprinting disorders has not been replicated in larger cohorts, including a study capturing all singleton births in Denmark from 1995 to 2001, which observed no imprinting diseases among 6,052 children conceived by IVF according to registry data (66). However, syndromes like Beckwith-Wiedemann syndrome remain very rare (1 in 12,000) (67), which suggests that this previous study could be underpowered. Underreporting could have also played a role because no cases of Beckwith-Wiedemann syndrome were identified even among the >440,000 children conceived without ART, and Angelman Syndrome was not an available diagnosis code (66).

Several DNA methylation studies targeting imprinted genes (e.g., *H19/IGF2, SNPRN, KCNQ10T1*) using cord blood lymphocyte or placental tissue specimens have not confirmed any global imprinting differences among children conceived by IVF compared with non-ART children (68, 69). Some evidence has surfaced, however, regarding other epimutations that may be specifically altered. Investigators using a custom-designed Illumina array platform covering 1,536 CpG sites from 736 genes found increased hypomethylation in the placenta (63% of the 246 CpGs that differed) and greater methylation in cord blood (77% of the 358 CpGs that differed) (70). Of the specific genes affected, *CEBPA*, which affects adipogenesis and regulates glucose and lipid metabolism (71), was differentially methylated in both cord blood and placental tissue in the ART group (70).

Treatment Differences

Assisted reproductive technologies comprise multiple heterogeneous procedures, which may include ovarian stimulation for oocyte retrieval, sperm injection, in vitro culture, and cryopreservation, among others. The literature to date has rarely evaluated cardiometabolic health among children according to these finer treatment exposures. Therefore, it is unknown whether each of these processes is associated with long-term health outcomes in children conceived by ART, but the evidence thus far is briefly considered below.

The health of children conceived by ovarian stimulation apart from ART has only recently begun to be investigated (72–75), given the lack of registries or other sampling frameworks in which to identify couples and their children. Low birth weight (74, 76, 77), preterm birth (74, 76, 77), and small for gestational age (78) have been found to be increased among births conceived using clomiphene citrate or injectable gonadotropin compared with births conceived without assistance. A recent study found that 3–10-year-old boys (n = 39) conceived by ovulation stimulation (by different regimens of clomiphene, FSH, or both) were on average 3 cm shorter than children conceived without assistance (75). In the study reviewed above (Table 1), Scherrer et al. (50) measured FMD in children conceived after ovulation stimulation and found no significant differences in comparison with the non-ART group, although the sample sizes were small (n = 16 and 53, respectively).

The associations between different brands of culture media and birth outcomes have also recently been examined, with mixed findings (79–81). Two retrospective observational studies found no differences in birth weight or gestational age by the different brands of media examined, although their use corresponded to the time periods in which their clinics used a particular brand of culture (79, 81). A study randomly allocating two types of media found one (Cook media) to be associated with lower birth weight among singletons (–112 g,

P=.03) than another type (Vitrolife), without a difference in mean gestational age (80). No studies have investigated long-term cardiometabolic outcomes among ART children conceived by different culture media.

Intracytoplasmic sperm injection may also have differential affects than in vitro culture alone, including the human selection of sperm with chromosomal abnormalities, physical damage, and point mutations due to chemical or environmental exposure (82). The studies reviewed above (19, 22, 26) do not suggest, however, that children conceived by ICSI differ in anthropometry from children conceived by IVF alone. The largest of these studies combined five European cohorts to compare 540 ICSI- and 437 IVF-conceived children, finding the same mean height (111 cm) and similar weight (ICSI with –0.2 kg) and head circumference (ICSI with –0.2 cm) (22).

The effects of cryopreservation are also important to consider, with evidence that frozen embryo transfers resulting in live births fare better (i.e., higher birth weight, longer gestational age) (83, 84). This association may be due to survival bias, whereby less hardy embryos do not result in live birth, or to the fact that women with embryos available for cryopreservation have higher-quality embryos. To our knowledge only one study has investigated postnatal growth of 255 children born after cryopreservation, finding no differences in growth at up to 18 months of observation when compared with children conceived by fresh IVF transfers or spontaneously (35).

Fetal Growth

Impaired fetal growth has been found to be associated with markers of endothelial dysfunction in early childhood (85). In adults, FMD (a marker for endothelial dysfunction [86]) is associated with birth weight (87). Deficiencies in fetal growth could lead to impaired vascular (including endothelial function and vascular responsiveness) and kidney development (which could alter blood pressure regulation through the renin–angiotensin system). Reduction in nephron number of the kidney is associated with elevated blood pressure (88). Even though kidney development occurs late in gestation, low protein exposure during the period of oocyte maturation in one study led to reduced nephron numbers, which may be a compensatory response or downstream effect of adverse programming induced much earlier in development, possibly to protect fetal growth (89). Catch-up growth later in life serves as an indicator of fetal growth restriction. Ceelen et al. (38) showed that infant growth acceleration may be one putative cause of later CVD risk, with accelerated growth being associated with the increased blood pressure found in the ART children. Belva et al. (59) also explored whether rapid weight gain in early and late infancy was associated with blood pressure differences of ICSI-conceived adolescents at age 14 years but found no associations. No studies, however, have quantified the direct and indirect effect of fetal growth on associations, which may be better than restricting recruitment to only term children, matching on gestational age, or adding birth outcomes to statistical models because these methods can introduce bias by conditioning on a known intermediate (90).

Placental Development

The placenta acts as the crucial intersection connecting maternal nutrient supply to the fetus, playing a crucial role in cardiometabolic health (91). Placental dysfunction therefore could be an indicator of later CVD risk through leading to abnormal fetal growth, or through other pathways (92). In the non-ART population, placental weight alone has been inconsistently found to be associated with CVD and hypertension, perhaps owing to nonuniform measurement techniques (91). Recently, placental thinness independent of placental weight and birth weight was associated with later sudden cardiac death in the Helsinki study, suggesting a possible indicator of autonomic nervous system programming (92). Placenta to birth weight ratio has been found to be increased among ART births, similar to births affected by pre-eclampsia (93). Ovarian stimulation leading to decreased endometrial receptivity could cause the placenta to compensate with abnormal growth. However, the role of the placenta as a mediator remains a data gap because no studies have investigated placental characteristics in connection with long-term cardiometabolic health in the ART population.

FUTURE STUDIES

As highlighted above, data gaps remain for determining whether growth and cardiometabolic risk differs in children conceived by ART compared with non-ART children. To account for confounding by inherited factors, some investigators have suggested that a cohort of siblings will be the ideal comparison group (94). Recent studies investigating other developmental origins of health and disease hypotheses, including gestational weight gain and diabetes exposure in utero, on future risk of obesity in the offspring have performed such sibling comparisons through the use of registry data (95, 96). Similar ART and non-ART sibling comparisons may be possible using registry data but would ideally need to have data on ovulation stimulation exposure apart from ART. However, comparison of siblings is not without limitations, including the fact that discordant siblings could be indicators of a wide range of factors, including change in partner (non–genetically identical sibs) and older parental age. Sibling cohorts will also be unable to provide more information regarding twins because few parents would have two sets of twins/multiples conceived by different methods. A sibling cohort may require recruitment over longer spans of time, because it is unlikely that there will be enough siblings born in any close period of time to evaluate small effects.

Longer periods of recruitment can generate associations due to secular differences occurring during the period, as discussed above for the study by Ceelen et al., (25, 38, 47) which recruited children as early as 1980. Assisted reproductive techniques have evolved much, as demonstrated in climbing live birth rates, especially with frozen transfers (97). It may be that the differences in children's health found by Ceelen et al. may not occur in more recent cohorts. On the other hand, does this mean that a new IVF cohort is needed in every decade to be representative? Perhaps the answer depends on the technological advancements that remain to be made and the research question at hand, with continuous recruitment also being a possibility.

In conclusion, many studies in non-ART populations have shown that cardiometabolic risk can be "programmed" in utero, manifesting as later glucose intolerance or CVD. The high rates of low birth weight and preterm birth are indicators that the ART population may be especially vulnerable to this "programming" effect. Apart from fetal growth deficits, some evidence of independent associations of vascular function has serviced. The cardiometabolic health of children conceived by ART requires further study, not only to replicate previous findings in more recent cohorts but also to tease apart the mechanisms that may be at play.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

CVD risk factors among childern conceived by ART.

				IVF/ICSI vs. non-ART							
First author, year (reference)	**Population**	**N**	**Age(s)**	**BMI (kg/m²)**	**SBP (mm Hg)**	**DBP (mm Hg)**	**HDL (mmol/L)**	**LDL (mmol/L)**	**TC (mmol/L)**	**TG (mmol/L)**	**FPG (mmol/L)**
Ceelen, 2007 (48)	The Netherlands, from one site of the OMEGA study (1980–1994)	225 IVF and 225 non-ART singletons born from women with subfertility	8–18 y (mean 12 y)	19.1 vs. 18.7	109 vs. 105[a]	61 vs. 59[a]	n/a	n/a	n/a	n/a	5.0 vs. 4.8[a]
Belva, 2007 (20)	Belgium, fertility clinic and schools in the area	150 ICSI (≥32 wk), 147 non-ART singletons	8y	16.2 vs. 16.3	100 vs. 95[a]	60 vs. 50[a]	n/a	n/a	n/a	n/a	n/a
Belva, 2012 (59)[b]	Belgium, fertility clinic and schools in the area	217 ICSI (≥32 wk), 223 non-ART singletons	14y	B: 19.1 vs. 19.2 G: 19.7 vs. 19.3	B: 113 vs. 116 G: 109 vs. 111	B: 64 vs. 65 G: 64 vs. 66	n/a	n/a	n/a	n/a	n/a
Miles, 2007 (31)	New Zealand, IV and peers (or 6 siblings)	69 IVF (34 ICSI) and 71 non-ART term singletons	4–10 y (mean 6 y) non-ART older by 1 y	15.68 vs. 16.47[a]	n/a	n/a	1.67 vs. 1.53[a]	2.37 vs. 2.42	4.33 vs. 4.31	0.65 vs. 0.78[a]	4.7 vs. 4.8
Sakka, 2010 (49)	Athens, fertility department vs. general hospital	106 IVF and 68 age-matched non-treated	4–14 y	BMI *z* score: 0.1 vs. 0	SDS: 03 vs. –0.3	SDS: 0.7 vs. 0.2[a]	1.38 vs. 1.41	2.61 vs. 2.63	4.29 vs. 4.32	0.67 vs. 0.59[a]	4.64 vs. 4.64
Scherrer, 2012 (50)	Switzerland, IVF and peers (or 5 siblings)	65 IVF (44 ICSI) and 57 non-ART term singletons	Mean 11 y (non-ART older by 1 y)	17.9 vs. 18.8	113 (both)	71 (both)	1.55 vs. 1.48	2.73 vs. 2.90	4.57 vs. 4.62	0.73 vs. 0.75	4.54 vs. 4.73

Note: Non-ART = conception without use of infertility treatment of any kind; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglycerides; FPG = fasting plasma glucose; n/a = not applicable; SDS = standard deviation score derived by Sakka et al. according to a national reference (98).

Yeung. Cardiometabolic health of ART kids. Fertil Steril 2013.

[a]Significant at $P < .05$ comparing IVF vs. controls.

[b]Belva, 2012 stratified by gender (B = boys; G = girls).

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