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Cardiovascular and metabolic profiles of offspring conceived by assisted reproductive technologies: a systematic review and meta-analysis

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Objective: To evaluate cardiovascular and metabolic features of offspring conceived by in vitro fertilization/intracytoplasmic sperm injection (IVF-ICSI).
Design: Literature review and meta-analysis.
Setting: Not applicable.
Patient(s): Offspring from IVF-ICSI versus natural conception.
Intervention(s): None.
Main Outcome Measure(s): Systolic and diastolic blood pressure (SBP and DBP), cardiovascular function, body mass index (BMI), and lipid and glucose profiles.
Result(s): We included 19 studies that had recruited 2,112 IVF-ICSI and 4,096 naturally conceived offspring, ranging from childhood to early adulthood. The blood pressure levels of IVF-ICSI offspring were statistically significantly higher than those of naturally conceived offspring (weighted mean differences and confidence intervals: 1.88 mm Hg [95% CI, 0.27, 3.49] for SBP and 1.51 mm Hg [95% CI, 0.33, 2.70] for DBP). In addition, cardiac diastolic function was suboptimal and vessel thickness was higher among IVF-ICSI offspring. Compared with the metabolism of naturally conceived offspring, IVF-ICSI offspring displayed comparable BMI, lower low-density lipoprotein cholesterol levels, and higher fasting insulin levels.
Conclusion(s): Children conceived by IVF-ICSI manifested a minor yet statistically significant increase in blood pressure without the clustering of increased BMI or impaired lipid metabolism by early adulthood. Our findings indicate a risk of cardiovascular disease among IVF-ICSI offspring, which calls for longer-term follow-ups and further investigation. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: IVF, ICSI, blood pressure, BMI, metabolism

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More than 5 million babies worldwide are born by in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) (1). Thus, the potential health risks associated with these treatments are of great importance to public health. Inherent to IVF and ICSI treatments are numerous artificial procedures, including ovulation stimulation, manipulation of the oocyte and sperm, and embryo culture. These operations occur during gametogenesis and in early embryogenesis, a critical window for the establishment of genome methylation patterns (2, 3). According to the developmental origins of health and disease theory, the early epigenetic changes caused by assisted reproductive technology (ART) may lead to not only adverse perinatal outcomes (4–7) but also chronic cardiometabolic diseases in the latter stages of life (8–10).

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Long-term cardiovascular and metabolic risks in IVF-ICSI offspring have gained increased attention in both animal models and human studies. In mice bred by ART, the following symptoms were documented: endothelial dysfunction and increased stiffness of the vasculature (11, 12), elevated systolic blood pressure (13, 14), altered glucose parameters (15, 16), and impaired activities of fatty acid metabolism-related enzymes (17). Similar to the animal data, the data from human studies has also indicated that ART offspring are prone to elevated blood pressure and impaired vascular function (18, 19) compared with their naturally conceived (NC) counterparts. In addition, ART offspring exhibited abnormal retinal vessel morphology (20), congenital heart defect (21), and different protein expression profiles in their umbilical veins (22). Furthermore, ART pregnancies were linked to preterm birth and low birth weight (5, 7), which are risk factors for future metabolic syndromes (23–25). Given these discoveries and the popularity of ART, a more comprehensive investigation of the cardiometabolic risk of ART offspring is necessary.

Despite the accumulating epidemiologic data, the conclusions are still preliminary and sometimes inconsistent. Studies on the individual effect of IVF and ICSI have been few. We took a combined approach and assessed the effect of these two techniques together to determine the cardiometabolic outcomes of the offspring. We summarize here the available clinical evidence on cardiometabolic parameters of IVF-ICSI offspring, including systolic and diastolic blood pressure (SBP and DBP), other cardiovascular functions, body mass index (BMI), lipid profiles (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglyceride), and glucose homeostasis variables (fasting serum glucose, fasting insulin, and homeostasis model of assessment for insulin resistance [HOMA-IR]).

MATERIALS AND METHODS

Search Strategy

An extensive literature search in PubMed and Scopus was last performed on October 1, 2016. We followed the PRISMA flow diagram to identify the studies (Supplemental Fig. 1, available online) based on the combinations of key terms in the following three categories. The first category was composed of "IVF, ICSI, ART, in vitro fertilization, assisted reproduction, assisted reproductive technology/technique, fertility treatment, cryopreservation, PGD, and preimplantation genetic diagnosis/screening." The second category consisted of "health, growth, outcome, physical, medical, phenotypic, development, blood pressure, hypertension, cardiac, vascular, metabolic, lipid, cholesterol, adiposity, body fat, BMI, obesity, glucose, insulin, and diabetes." The third category consisted of "cohort, follow up, case-control, children/childhood, adolescent/adolescence, puberty/pubertal, offspring, singleton, twin, adult, and postnatal."

A total of 1,911 articles were returned. After excluding irrelevant studies according to titles and abstracts, 37 full-text English clinical articles addressing the cardiovascular and metabolic profiles of IVF and ICSI offspring were obtained. Cross references of the included studies were manually searched for additional resources.

Selection Criteria

The literature selection process is detailed in Supplemental Table 1 (available online). The exclusion criteria were as follows: [1] studies that evaluated obstetric or perinatal events; [2] studies that did not evaluate the effects of IVF-ICSI but evaluated the effects of ovulation induction (26, 27) or preimplantation genetic diagnosis (PGD) (28); [3] no naturally conceived offspring as a comparison group (29–32); [4] overlapping subject groups (33–40) (in such cases, only the primary publication that had the highest study quality and provided the most information was selected for inclusion to prevent giving unreasonably larger weight to any study population when summarizing the data); and [5] studies with insufficient data (41–43). Additionally, three studies were excluded from the BMI analyses because they either lacked the standard deviation (44) or matched BMI as baseline (45, 46). The three studies, however, were still included in other analyses. Finally, among the 37 studies, 19 were included, which reported data on 2,112 IVF-ICSI offspring and 4,096 NC offspring.

Data Extraction and Quality Assessment

Basic study characteristics and main results were extracted by two independent reviewers and are presented in Supplemental Table 2 (available online) (44–62). We adapted the Newcastle-Ottawa quality assessment scale (63) to assess study quality, and the results are listed in Supplemental Table 3 (available online). In cases of uncertainty, a third author was consulted to reach a consensus. Study quality was considered high at 6–8 points, medium at 3–5 points, and low at 0–2 points.

Data Analysis

Meta analyses were performed on blood pressure, BMI, and metabolic parameters. Weighted mean differences (WMD) and 95% confidence intervals (CI) were calculated with inverse variance weighting. A random-effects model was used unless heterogeneity was low. In the latter case, a fixed-effect model was used instead. Heterogeneity between the studies was examined by chi-square tests for statistical significance. $P<.1$ was considered statistically significant. Inconsistency among studies was quantified using I-square tests, where I^2 values of $<25\%$ were considered low, 25% to 75% were considered moderate and $>75\%$ were considered high (64).

Substantial heterogeneity between studies was expected because the included studies recruited diverse study populations. First, the age of the study populations ranged from 1 year to 22 years. Concurrently, blood pressure, BMI, and metabolic profiles change dramatically from childhood to puberty to adulthood (65, 66). Second, the IVF-ICSI protocols have undergone major changes over the past years (67, 68). Therefore, the year of birth might reflect the development status of the IVF-ICSI technique and be a source of heterogeneity. Moreover, the plurality and conception mode of subjects, the choice of comparison group, study size, study