Assisted Reproductive Technologies Are Associated With Cardiovascular Remodeling In Utero That Persists Postnatally

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Background—Assisted reproductive technologies (ARTs) have been shown to be associated with general vascular dysfunction in late childhood. However, it is unknown whether cardiac remodeling is also present and if these changes already manifest in prenatal life. Our aim was to assess fetal and infant (6 months of age) cardiovascular function in ART pregnancies.

Methods and Results—This prospective cohort study included 100 fetuses conceived by ART and 100 control pregnancies. ART fetuses showed signs of cardiovascular remodeling, including a more globular heart with thicker myocardial walls, decreased longitudinal function (tricuspid ring displacement in controls: median, 6.5 mm [interquartile range, 6.1–7.1 mm]; tricuspid ring displacement in ART: 5.5 mm [interquartile range, 5.1–6.1]; P<0.001), impaired relaxation, and dilated atria (atrial area in controls, 1.46 cm² [interquartile range, 1.2–1.5 cm²]; atrial area in ART, 1.6 cm² [interquartile range, 1.3–1.8 cm²]; P<0.001). Additionally, ART infants showed persistence of most cardiac changes and a significant increase in blood pressure and aortic intima-media thickness (systolic blood pressure in controls, 74 mm Hg [interquartile range, 67–83 mm Hg]; systolic blood pressure in ART, 83 mm Hg [interquartile range, 75–94 mm Hg]; P<0.001; aortic intima-media thickness in controls, 0.52 mm [interquartile range, 0.45–0.56 mm]; aortic intima-media thickness in ART, 0.64 mm [interquartile range, 0.62–0.67]; P<0.001). We could not demonstrate that our findings were directly caused by ART because of their association with various confounding factors, including intrauterine growth restriction or factors related to the cause of infertility.

Conclusions—Children conceived by ART manifest cardiac and vascular remodeling that is present in fetal life and persists in postnatal life, suggesting opportunities for early detection and potential intervention. The underlying mechanisms and the effect of potential confounders such as growth restriction or prematurity remain to be elucidated. (Circulation. 2013;128:1442-1450.)

Key Words: fertilization in vitro ■ pediatrics ■ pregnancy ■ reproductive techniques, assisted ■ ventricular remodeling

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Cardiovascular remodeling has previously been described to be associated with low birth weight (LBW), and it is regarded as a manifestation of fetal programming defined as the permanent alteration of tissue structures and functions as a result of fetal environment. It is unknown whether cardiovascular changes in ART children occur already in fetal life. In addition, fetal cardiovascular programming associated with LBW has been demonstrated to be accompanied by cardiac remodeling, which constitutes an additional risk factor in later life. However, the potential association of ART with cardiac structural and functional remodeling was not investigated in previous studies. This information is relevant to advance our understanding of the long-term impact of ART on cardiovascular function and on the design of preventive strategies.

In the present study, we evaluated the hypothesis that pregnancies conceived by ART are associated with both cardiac and vascular remodeling in the offspring and that changes can be detected already during fetal life. We designed a prospective cohort study including 100 ART and 100 spontaneously conceived fetuses to comprehensively assess cardiac and vascular changes in ART children occur already in fetal life. However, the potential association of ART with cardiac remodeling, which constitutes an additional risk factor in later life. It is unknown whether cardiac and right ventricular sphericity indexes were calculated as base-to-apex length divided by basal diameter. Then, left and right cardiac outputs were calculated as left or right stroke volume times heart rate. Mitral/tricuspid annular displacement was assessed by M mode from a transverse 4-chamber view.

Fetal Assessment

All pregnancies underwent ultrasonographic examination at 28 to 30 weeks of gestation using a Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA) with 6- to 4-MHz linear curved-array and 2- to 10-MHz phased-array probes, including the measurement of estimated fetal weight, fetoplacental Doppler, and fetal echocardiography.

Fetoplacental Doppler assessment included pulsatility index measurement of the umbilical artery and middle cerebral artery according to a previously published methodology. Fetal echocardiography included a comprehensive examination to assess structural heart integrity and morphometry, as well as systolic and diastolic function parameters. Cardiac dimensions were measured on 2-dimensional images from an apical 4-chamber view. Left and right atrial areas were taken at maximum point of atrial distension and ventricular base-to-apex lengths and basal diameters at end diastole. Left and right ventricular sphericity indexes were calculated as base-to-apex length divided by basal diameter.

Methods

Study Populations and Study Protocol

The study design was a prospective cohort study including 100 singleton pregnancies conceived by in vitro fertilization or intracytoplasmic sperm injection in infertile patients and 100 control pregnancies conceived naturally identified in fetal life and followed up to 6 months of age. The ART group was a consecutive sample of patients with a normal first-trimester scan who accepted participation in the study. Cases were considered noneligible if any of the following were present: preimplantation genetic diagnosis, oocyte donation, multiple pregnancies, or any maternal medical disease. Likewise, later diagnosis of fetal malformations or any pregnancy complications leading to delivery before 34 weeks of gestation were considered exclusion criteria. The control group was recruited at 28 to 30 weeks’ gestation among women with low-risk pregnancies attending our Maternal–Fetal Medicine Unit for normal pregnancy follow-up. Controls were matched for maternal age (±1 year) with cases. Eligibility and exclusion criteria for controls were the same as for cases, and controls underwent the same study protocol as cases. The study protocol was approved by the Institutional Review Board at Hospital Clinic, and written parental consent was obtained for all study participants. Figure 1 shows a flow diagram of the study population. Cardiovascular assessment included echocardiography in fetal life, vascular assessment in the neonatal period, and both echocardiography and vascular assessment at 6 months of age.

Parental baseline and ART characteristics were collected by parental interview and review of medical records at the time of prenatal evaluation. LBW was defined as birth weight below the 10th percentile.

![Figure 1. Flow diagram of the study populations.](http://circ.ahajournals.org/)

ART indicates pregnancies conceived by assisted reproductive technologies.
Neonatal Assessment
Neonatal vascular assessment was performed within the first month of life, including the measurements of blood pressure and vascular intima-media thickness (IMT). Blood pressure centiles were calculated according to standard normograms.14

Carotid and aorta ultrasound assessment was performed by skilled sonographers using a Siemens Sonoline Antares (Siemens Medical Systems). Longitudinal clips of the far walls of both carotid arteries and abdominal aorta were obtained with a linear-array transducer. Carotid and aorta IMT measurements were performed offline according to a standardized protocol based on a trace method with the assistance of a computerized program (Siemens Syngo Arterial Health Package). IMT results were normalized by neonatal weight.

Table 1. Baseline Characteristics of the Study Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (n=100)</th>
<th>ART (n=100)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>35 (32–37)</td>
<td>36 (35–38)</td>
<td>0.066</td>
</tr>
<tr>
<td>BMI, kg/m²†</td>
<td>22 (21–25)</td>
<td>23 (21–25)</td>
<td>0.161</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>White, %</td>
<td>84</td>
<td>90</td>
<td>0.293</td>
</tr>
<tr>
<td>Primiparity, %</td>
<td>40</td>
<td>43</td>
<td>0.774</td>
</tr>
<tr>
<td>Early cardiovascular history, %‡</td>
<td>2</td>
<td>2</td>
<td>0.614</td>
</tr>
<tr>
<td>Low socioeconomic level, %</td>
<td>15</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>University education, %</td>
<td>63</td>
<td>52</td>
<td>0.153</td>
</tr>
<tr>
<td><strong>Paternal characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>36 (33–39)</td>
<td>38 (36–40)</td>
<td>0.077</td>
</tr>
<tr>
<td>BMI, kg/m²†</td>
<td>25 (23–26)</td>
<td>25 (24–28)</td>
<td>0.442</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>12</td>
<td>17</td>
<td>0.422</td>
</tr>
<tr>
<td>White, %</td>
<td>84</td>
<td>92</td>
<td>0.128</td>
</tr>
<tr>
<td>Early cardiovascular history, %‡</td>
<td>4</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Low socioeconomic level, %</td>
<td>7</td>
<td>5</td>
<td>0.766</td>
</tr>
<tr>
<td>University education, %</td>
<td>30</td>
<td>35</td>
<td>0.546</td>
</tr>
<tr>
<td><strong>Fertility and ART characteristics, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infertility cause</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Unexplained</td>
<td>NA</td>
<td>32</td>
<td>NA</td>
</tr>
<tr>
<td>Female</td>
<td>NA</td>
<td>25</td>
<td>NA</td>
</tr>
<tr>
<td>Male</td>
<td>NA</td>
<td>34</td>
<td>NA</td>
</tr>
<tr>
<td>Female+male</td>
<td>NA</td>
<td>9</td>
<td>NA</td>
</tr>
<tr>
<td>ART technique</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard IVF</td>
<td>NA</td>
<td>9</td>
<td>NA</td>
</tr>
<tr>
<td>ICSI</td>
<td>NA</td>
<td>85</td>
<td>NA</td>
</tr>
<tr>
<td>IVF+ICSI</td>
<td>NA</td>
<td>7</td>
<td>NA</td>
</tr>
<tr>
<td>Transferred embryos, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>NA</td>
<td>12</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>NA</td>
<td>70</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>NA</td>
<td>18</td>
<td>NA</td>
</tr>
</tbody>
</table>

ART indicates pregnancy conceived by assisted reproductive technologies; BMI, body mass index; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; and NA, not applicable. Data are median (interquartile range) when appropriate.

*P value calculated by the Student t test or Pearson χ² test.

‡BMI was calculated as weight in kilograms divided by the square of height in meters.

Early cardiovascular disease was defined by the presence of congenital heart disease, coronary disease, hypertension, diabetes mellitus, or hypercholesterolemia in men <55 years of age and women <65 years of age.

Assessment at 6 Months of Age
Infants’ follow-up evaluation, including anthropometric data, echocardiography, and vascular assessment, was scheduled at 6 months of age. Anthropometric data included the infants’ height and weight measured at the time of the examination.

Echocardiography was performed following a standardized protocol15 using a Vivid q (General Electric Healthcare, Norway) with a 2- to 10-MHz phased-array transducer. Infants were studied when resting quietly or asleep. A complete echocardiography was performed initially to assess structural heart integrity. Left and right atrial planimetric areas were measured on a 2-dimensional image from an apical 4-chamber view at end systole (greatest dimension, just before mitral or tricuspid valve opening). Ventricular base-to-apex length and transverse diameter were measured on a 2-dimensional image from an apical 4-chamber view at end diastole. Left and right ventricular sphericity indexes were calculated as base-to-apex length divided by midtransverse diameter. Ventricular end-diastolic wall thicknesses were measured by M mode from a parasternal long-axis view.15,16

Left shortening fraction was calculated from internal ventricular diameters obtained from a parasternal long-axis view by M mode using the following equation: (end-diastolic dimension−end-systolic dimension)/end-diastolic dimension. Left and right stroke volumes were calculated as follows: π/4×(aortic or pulmonary valve

Table 2. Perinatal Characteristics of the Study Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (n=100)</th>
<th>ART (n=100)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregnancy complications, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vanishing twin</td>
<td>0</td>
<td>8</td>
<td>0.012</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>0</td>
<td>4</td>
<td>0.123</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>1</td>
<td>17</td>
<td>0.001</td>
</tr>
<tr>
<td>Spontaneous preterm delivery</td>
<td>2</td>
<td>5</td>
<td>0.442</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>4</td>
<td>6</td>
<td>0.746</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>0</td>
<td>3</td>
<td>0.245</td>
</tr>
<tr>
<td>Obstructive cholestasis</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Prenatal corticoid exposure</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Delivery data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age at delivery, wk</td>
<td>40 (39–40)</td>
<td>38 (37–39)</td>
<td>0.032</td>
</tr>
<tr>
<td>Maternal systolic blood pressure, mmHg</td>
<td>111 (110–115)</td>
<td>114 (111–116)</td>
<td>0.437</td>
</tr>
<tr>
<td>Maternal diastolic blood pressure, mmHg</td>
<td>70 (68–71)</td>
<td>71 (65–72)</td>
<td>0.891</td>
</tr>
<tr>
<td>Cesarean section, %</td>
<td>24</td>
<td>31</td>
<td>0.342</td>
</tr>
<tr>
<td>Male, %</td>
<td>49</td>
<td>51</td>
<td>0.888</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3355</td>
<td>2740</td>
<td>0.022</td>
</tr>
<tr>
<td>(3020–3550)</td>
<td>(2585–2920)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight percentile</td>
<td>49 (31–73)</td>
<td>26 (5–55)</td>
<td>0.033</td>
</tr>
<tr>
<td>5-min Apgar score</td>
<td>10 (9–10)</td>
<td>10 (9–10)</td>
<td>0.102</td>
</tr>
<tr>
<td>Umbilical artery pH</td>
<td>7.2 (7.1–7.2)</td>
<td>7.2 (7.2–7.3)</td>
<td>0.920</td>
</tr>
<tr>
<td><strong>Neonatal outcome, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission to neonatal intensive care unit</td>
<td>1</td>
<td>1</td>
<td>0.477</td>
</tr>
<tr>
<td>Major neonatal morbidity‡</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

ART indicates pregnancy conceived by assisted reproductive technologies. Data are median (interquartile range) when appropriate.

*P value calculated by the Student t test or Pearson χ² test.

‡Major neonatal morbidity defined by the presence of bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukomalacia, retinopathy, persistent ductus arteriosus, or sepsis.
diameter)² × (aortic or pulmonary artery systolic flow velocity-time integral). Left and right cardiac outputs were calculated as stroke volume times heart rate. Tricuspid annular displacement was measured in real time in an apical 4-chamber view by placing the M-mode cursor at the atrioventricular junction, marked by the tricuspid valve rings at the right free wall. Maximum amplitude of motion was taken as the extent of displacement between end systole and end diastole and measured in millimeters. Tissue Doppler was applied at mitral and tricuspid lateral annuli from an apical 4-chamber view to record S'. E/A ratios were calculated. E deceleration time was measured as the time from the maximum mitral/tricuspid velocity to baseline. Tissue Doppler was applied at mitral and tricuspid lateral annuli from an apical 4-chamber view to record E', which is annular peak velocity in early diastole. PI, pulsatility index; and S', systolic annular peak velocity. Data are median (interquartile range).

Table 3. Fetal Assessment in the Study Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (n=100)</th>
<th>ART (n=100)</th>
<th>Crude P Value</th>
<th>Adjusted P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at scan, wk</td>
<td>29 (28–29)</td>
<td>28 (28–29)</td>
<td>0.062</td>
<td>0.130</td>
</tr>
<tr>
<td>Fetalplacental data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated fetal weight at scan, g</td>
<td>1375 (1205–1508)</td>
<td>1300 (1173–1446)</td>
<td>0.061</td>
<td>0.078</td>
</tr>
<tr>
<td>Estimated fetal weight percentile at scan</td>
<td>53 (26–80)</td>
<td>54 (29–69)</td>
<td>0.710</td>
<td>0.656</td>
</tr>
<tr>
<td>Umbilical artery PI</td>
<td>1.10 (0.98–1.25)</td>
<td>1.09 (0.95–1.25)</td>
<td>0.979</td>
<td>0.706</td>
</tr>
<tr>
<td>Middle cerebral artery PI</td>
<td>2.18 (1.8–1.3)</td>
<td>2.0 (1.5–2.3)</td>
<td>0.961</td>
<td>0.806</td>
</tr>
<tr>
<td>Fetal echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac morphometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial area, cm²</td>
<td>1.35 (1.1–1.4)</td>
<td>1.48 (1.2–1.7)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right atrial area, cm²</td>
<td>1.46 (1.2–1.5)</td>
<td>1.60 (1.3–1.8)</td>
<td>0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left sphericity index</td>
<td>1.77 (1.61–1.92)</td>
<td>1.71 (1.54–1.78)</td>
<td>0.002</td>
<td>0.003</td>
</tr>
<tr>
<td>Right sphericity index</td>
<td>1.58 (1.4–1.72)</td>
<td>1.37 (1.25–1.5)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left free wall thickness, mm</td>
<td>2.7 (2.4–3)</td>
<td>2.9 (2.7–3.1)</td>
<td>0.001</td>
<td>0.068</td>
</tr>
<tr>
<td>Interventricular septum thickness, mm</td>
<td>2.4 (2.4–2.8)</td>
<td>2.7 (2.4–2.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right free wall thickness, mm</td>
<td>2.8 (2.6–3.2)</td>
<td>3.2 (2.9–3.3)</td>
<td>0.026</td>
<td>0.038</td>
</tr>
<tr>
<td>Systolic function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ejection fraction, %</td>
<td>69 (63–73)</td>
<td>63 (57–68)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right ejection fraction, %</td>
<td>68 (63–73)</td>
<td>67 (60–73)</td>
<td>0.657</td>
<td>0.659</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>140 (136–148)</td>
<td>143 (136–150)</td>
<td>0.836</td>
<td>0.749</td>
</tr>
<tr>
<td>Left cardiac output, mL/min</td>
<td>25.6 (20–30)</td>
<td>25.5 (21–30)</td>
<td>0.838</td>
<td>0.798</td>
</tr>
<tr>
<td>Right cardiac output, mL/min</td>
<td>31 (26–37)</td>
<td>33 (28–38)</td>
<td>0.385</td>
<td>0.727</td>
</tr>
<tr>
<td>Mitral ring displacement, mm</td>
<td>4.7 (4.2–5.3)</td>
<td>4.2 (3.7–4.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tricuspid ring displacement, mm</td>
<td>6.5 (6.1–7.1)</td>
<td>5.5 (5.1–6.1)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral S', cm/s</td>
<td>6.9 (6–7.4)</td>
<td>6 (6–7)</td>
<td>0.031</td>
<td>0.038</td>
</tr>
<tr>
<td>Tricuspid S', cm/s</td>
<td>7.9 (6.7–8.8)</td>
<td>7 (6–8)</td>
<td>0.148</td>
<td>0.179</td>
</tr>
<tr>
<td>Diastolic function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral E/A ratio</td>
<td>0.71 (0.66–0.76)</td>
<td>0.74 (0.67–0.78)</td>
<td>0.681</td>
<td>0.320</td>
</tr>
<tr>
<td>Tricuspid E/A ratio</td>
<td>0.80 (0.70–0.90)</td>
<td>0.80 (0.72–0.91)</td>
<td>0.806</td>
<td>0.810</td>
</tr>
<tr>
<td>Mitral E deceleration time, ms</td>
<td>73 (55–91)</td>
<td>63 (51–78)</td>
<td>0.003</td>
<td>0.002</td>
</tr>
<tr>
<td>Tricuspid E deceleration time, ms</td>
<td>64 (51–77)</td>
<td>51 (44–66)</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Mitral E', cm/s</td>
<td>7.6 (6.9–8)</td>
<td>7 (6–8)</td>
<td>0.061</td>
<td>0.049</td>
</tr>
<tr>
<td>Tricuspid E', cm/s</td>
<td>8.3 (7.9–9.1)</td>
<td>8 (7–9)</td>
<td>0.003</td>
<td>0.002</td>
</tr>
<tr>
<td>Left isovolumic relaxation time, ms</td>
<td>30 (42–52)</td>
<td>48 (41.5–54.5)</td>
<td>0.031</td>
<td>0.003</td>
</tr>
</tbody>
</table>

A indicates ventricular inflow during atrial contraction; ART, pregnancy conceived by assisted reproductive technologies; E, ventricular inflow in early diastole; E', annular peak velocity in early diastole; PI, pulsatility index; and S', systolic annular peak velocity. Data are median (interquartile range).

*P value calculated by linear regression adjusted for gestational age at delivery, birth weight percentile, and preeclampsia.

Vascular assessment included blood pressure and aortic wall thickness by ultrasound. Aortic IMT measurement involved obtaining longitudinal clips of the far wall of the proximal abdominal aorta in the upper abdomen with a 10-MHz linear probe. Aortic IMT measurements were performed offline according to a standardized protocol based on a trace method with the assistance of a computerized program (GE EchoPAC PC 108.1.x, General Electric Healthcare). IMT results were normalized by infant weight.

Statistical Analysis
SPSS Statistics 19 (IBM) was used for the statistical analysis. The study outcome was fetal and postnatal cardiovascular assessment. The independent variable of interest was the type of conception (natural or ART), and the covariates were birth weight percentile,
gestational age at delivery, and the presence of preeclampsia. Annular peak velocities by tissue Doppler were chosen to calculate sample size because of their high sensitivity for preclinical cardiac dysfunction in fetuses and children. On the basis of previous studies measuring fetal cardiac function, sample size was calculated to allow observation of a difference of 25% in tricuspid E’ values in ART fetuses. For a power of 80% and an α risk of 0.05, a minimum of 91 subjects per study group were required. We decided to include 100 fetuses in each study group. Data are presented as median (interquartile range) or percentage as appropriate. Statistics to include 100 fetuses in each study group. Data are presented as

Table 4. Neonatal Vascular Outcome of the Study Groups Within the First Month of Life

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (n=75)</th>
<th>ART (n=60)</th>
<th>Crude P Value</th>
<th>Adjusted P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>82 (75–90)</td>
<td>84 (78–91)</td>
<td>0.163</td>
<td>0.489</td>
</tr>
<tr>
<td>Systolic blood pressure percentile</td>
<td>47 (28–74)</td>
<td>54 (30–79)</td>
<td>0.892</td>
<td>0.614</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>47 (39–57)</td>
<td>53 (46–61)</td>
<td>0.548</td>
<td>0.256</td>
</tr>
<tr>
<td>Diastolic blood pressure percentile</td>
<td>55 (21–85)</td>
<td>71 (44–91)</td>
<td>0.004</td>
<td>0.042</td>
</tr>
<tr>
<td>Vascular wall thickness†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic mean IMT, mm</td>
<td>0.45 (0.36–0.51)</td>
<td>0.55 (0.53–0.61)</td>
<td>&lt;0.001</td>
<td>0.035</td>
</tr>
<tr>
<td>Aortic mean IMT/weight, mm/kg</td>
<td>0.12 (0.10–0.14)</td>
<td>0.16 (0.14–0.18)</td>
<td>&lt;0.001</td>
<td>0.011</td>
</tr>
<tr>
<td>Aortic maximum IMT, mm</td>
<td>0.57 (0.47–0.64)</td>
<td>0.65 (0.62–0.66)</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Aortic maximum IMT/weight, mm/kg</td>
<td>0.14 (0.13–0.17)</td>
<td>0.19 (0.16–0.22)</td>
<td>0.001</td>
<td>0.024</td>
</tr>
<tr>
<td>Carotid mean IMT, mm</td>
<td>0.24 (0.21–0.27)</td>
<td>0.28 (0.25–0.30)</td>
<td>&lt;0.001</td>
<td>0.091</td>
</tr>
<tr>
<td>Carotid mean IMT/weight, mm/kg</td>
<td>0.06 (0.05–0.07)</td>
<td>0.07 (0.07–0.08)</td>
<td>0.001</td>
<td>0.035</td>
</tr>
<tr>
<td>Carotid maximum IMT, mm</td>
<td>0.29 (0.20–0.33)</td>
<td>0.32 (0.31–0.33)</td>
<td>&lt;0.001</td>
<td>0.005</td>
</tr>
<tr>
<td>Carotid maximum IMT/weight, mm/kg</td>
<td>0.07 (0.05–0.08)</td>
<td>0.09 (0.07–0.09)</td>
<td>0.003</td>
<td>0.018</td>
</tr>
</tbody>
</table>

ART indicates pregnancy conceived by assisted reproductive technologies; and IMT, intima-media thickness. Data are median (interquartile range).

*P value calculated by linear regression adjusted for gestational age at delivery, birth weight percentile, and preeclampsia.
†Vascular IMT normalized by neonatal weight.

Results

Baseline and Perinatal Characteristics

Baseline and perinatal characteristics of the study population are shown in Tables 1 and 2. The study groups were similar in terms of maternal and paternal baseline characteristics compared with controls (Table 1). As expected, ART pregnancies had a higher occurrence of pregnancy complications, mainly a higher prevalence of LBW and a tendency to increased incidence of preeclampsia (Table 2). Delivery and perinatal characteristics were similar among the study groups except for an earlier gestational age at delivery and lower birth weight percentile in ART compared with controls. Maternal blood pressure values were similar among the study groups.

Fetal Assessment

Results are shown in Table 3. Gestational age at evaluation, estimated fetal weight, and fetoplacental Doppler were similar between groups. As illustrated in Figure 2, fetuses conceived by ART showed increased atrial size and myocardial wall thickness and lower ventricular sphericity indexes compared with controls. Although cardiac output was similar between groups, ART fetuses showed a significant decrease in left ejection fraction, ring displacement, tricuspid E’, E deceleration time, and isovolumic relaxation time compared with controls. Most cardiovascular changes in ART fetuses remained significant after adjustment for gestational age at delivery, birth weight percentile, and association with preeclampsia.

Neonatal Assessment

Results are displayed in Table 4 and Figure 3. Systolic blood pressure was similar among the study groups, whereas diastolic blood pressure percentile was significantly higher after ART pregnancy compared with controls. Aorta and carotid IMTs were significantly increased in ART children, even after normalizing.
for neonatal weight and adjusting for gestational age at delivery, birth weight percentile, and association with preeclampsia.

Assessment at 6 Months of Age

Follow-up characteristics and cardiovascular results are shown in Table 5. ART infants showed anthropometric results at the time of evaluation similar to those of controls. ART infants showed increased right atrial size, lower right sphericity index, and thicker right ventricular wall. Although cardiac output was similar among the study groups, ART infants showed a significantly decreased shortening fraction and increased heart rate. ART cases also showed signs of both systolic and diastolic dysfunction as measured by significant decreases in ring displacement, E deceleration time, and tissue Doppler velocities and a significant increase in isovolumic relaxation time. Most cardiac changes remained significant after adjustment for gestational age at delivery, birth weight percentile, and preeclampsia.

Blood pressure was significantly higher in the ART group compared with controls. Aortic IMT was also significantly increased, even after normalizing by infant weight and adjustment for gestational age at delivery, birth weight percentile, and preeclampsia.

Discussion

This study demonstrates the presence of cardiac and vascular remodeling in fetuses and infants of pregnancies obtained by ART. These findings are consistent with previous reports demonstrating signs of vascular dysfunction in children conceived by ART6,7 and provide evidence for the existence of fetal cardiovascular programming in these pregnancies. We could not determine that our findings were caused by ART itself, by intrauterine growth restriction or prematurity in ART pregnancies, or by other confounders related to the indications for ART.

Fetuses from pregnancies conceived by ART showed more globular hearts together with increased myocardial wall thickness, decreased right longitudinal function, impaired relaxation, and dilated atria. The differences persisted after birth and were more prominent in the right side of the heart compared with the left side. The cardiac findings are consistent with experimental data showing an increased heart weight in an in vitro fertilization bovine model.17 From a pathophysiological viewpoint, more globular and hypertrophic ventricles with decreased longitudinal function are the usual ventricular response to pressure overload. Therefore, fetal observations are in line with postnatal findings of elevated blood pressure and increased IMT. In addition, cardiac remodeling described in our ART population resembles other fetal conditions with known pressure overload such as twin-to-twin transfusion syndrome18 or ductus arteriosus restriction.19 These clinical entities and experimental models of systemic pressure loading20 have been reported to show more pronounced changes in the right side of the heart. This might reflect the dominance of the right side of the heart during fetal life and a higher susceptibility to pressure overload of the right compared with the left ventricle.21,22 The dilated atria and impaired relaxation (decrease in E′ and E deceleration time) could be explained by a decrease in ventricular compliance, leading to higher end-diastolic pressures and increased atrial pressures. Finally, the changes described in vascular function and structure in neonates and infants reproduce the findings of previous reports in late childhood 23,24 and support the development and presence of these differences from early life.

Fetal cardiovascular programming has previously been described in fetuses and children who suffered from LBW.8,9 LBW is associated with globular hearts and longitudinal dysfunction in utero,25 and these changes, accompanied by increased blood pressure and vascular wall thickness, have been described to persist into childhood in humans9 and to adulthood in animal models.26 Direct cardiac effects of fetal growth restriction have been proposed to provide a link to explain the long-described epidemiological association of this prenatal condition with increased cardiovascular mortality in adults.8 Because of the high and expected prevalence of LBW in ART cases, it has been suggested that fetal growth restriction could be a potential confounder for cardiovascular remodeling in ART offspring.24 However, we believe that the results of this study strongly support a direct effect of ART on fetal and infant cardiovascular changes. First, ART fetuses and infants presented changes that have not previously been reported in LBW such as myocardial hypertrophy and increased atrial size.8,9 Second, most cardiovascular changes in ART remained significant even after adjustment by birth weight percentile. Finally, the differences between ART pregnancies and control pregnancies remained virtually unchanged after the LBW pregnancies were excluded from the study group (online-only Data Supplement).

The mechanisms driving fetal and postnatal cardiovascular remodeling in ART pregnancies remain to be elucidated. Parental predisposing factors, epigenetic changes secondary to the early embryo manipulation, hormonal effects, and postnatal environmental factors have been postulated as potential factors.1,5 Changes in fetuses and infants in this study were similar to those described in late childhood. Consequently, the role of postnatal environment as a potential factor determining long-term vascular dysfunction in ART children is possibly negligible. Advanced maternal age in ART has been proposed as a major contributor of childbearing ability/difficulties.4 In this study, cases and controls were matched by maternal age; however, we acknowledge that other parental factors related to their subfertility could still play a role.

Concerning epigenetic mechanisms, there is clinical and mainly experimental evidence that the processes involved in
egg manipulation might be associated with epigenetic changes, mediated mainly by changes in the DNA methylation pattern. The majority of the changes described affect imprinted genes, which have been involved mainly with fetal and placental growth. However, it has been suggested that methylation might be relevant for other functions not yet characterized. The importance of DNA methylation in the regulation of vascular endothelial function is being increasingly demonstrated, including nitric oxide expression and synthesis and endothelial angiogenesis. As indirect evidence, experimental models suggest that fetal cardiovascular programming occurring in LBW is associated with specific epigenetic signatures involving abnormal growth.

### Table 5. Anthropometric Data and Cardiovascular Assessment at 6 Months of Age

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (n=50)</th>
<th>ART (n=50)</th>
<th>Crude (P) Value</th>
<th>Adjusted (P) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometric data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>68 (65–69)</td>
<td>66 (65–68)</td>
<td>0.302</td>
<td>0.794</td>
</tr>
<tr>
<td>Weight, g</td>
<td>7650 (7170–8000)</td>
<td>7600 (6995–8200)</td>
<td>0.772</td>
<td>0.806</td>
</tr>
<tr>
<td><strong>Infant echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac morphometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial area, cm²</td>
<td>2.71 (2.6–3)</td>
<td>2.75 (2.6–3.1)</td>
<td>0.782</td>
<td>0.574</td>
</tr>
<tr>
<td>Right atrial area, cm²</td>
<td>2.50 (2.2–2.9)</td>
<td>2.70 (2.5–3.2)</td>
<td>0.018</td>
<td>0.005</td>
</tr>
<tr>
<td>Left sphericity index</td>
<td>1.81 (1.7–1.8)</td>
<td>1.83 (1.7–1.9)</td>
<td>0.271</td>
<td>0.650</td>
</tr>
<tr>
<td>Right sphericity index</td>
<td>1.91 (1.8–2)</td>
<td>1.82 (1.5–2)</td>
<td>0.021</td>
<td>0.010</td>
</tr>
<tr>
<td>Left ventricular wall thickness, mm</td>
<td>4.80 (4.4–5.4)</td>
<td>4.58 (4–5.2)</td>
<td>0.880</td>
<td>0.908</td>
</tr>
<tr>
<td>Septum thickness, mm</td>
<td>4.15 (3.4–4.5)</td>
<td>3.60 (3.3–4.1)</td>
<td>0.555</td>
<td>0.605</td>
</tr>
<tr>
<td>Right free wall thickness, mm</td>
<td>2.59 (2.3–3.2)</td>
<td>3.21 (2.9–3.5)</td>
<td>0.009</td>
<td>0.019</td>
</tr>
<tr>
<td><strong>Systolic function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left shortening fraction, %</td>
<td>36 (32–40)</td>
<td>29 (26–35)</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>132 (124–144)</td>
<td>141 (131–148)</td>
<td>0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Left cardiac output, mL/min</td>
<td>25 (21.9–30)</td>
<td>25 (21–29.7)</td>
<td>0.744</td>
<td>0.204</td>
</tr>
<tr>
<td>Right cardiac output, mL/min</td>
<td>32 (25–38)</td>
<td>33 (28–38)</td>
<td>0.208</td>
<td>0.587</td>
</tr>
<tr>
<td>Mitral ring displacement, mm</td>
<td>10.8 (10.1–11.8)</td>
<td>9.4 (7.4–10.3)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tricuspid ring displacement, mm</td>
<td>16.3 (15.1–17.2)</td>
<td>13.1 (11.9–14.1)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral S', cm/s</td>
<td>7.7 (7–8.9)</td>
<td>6.9 (5.7–7.5)</td>
<td>0.062</td>
<td>0.339</td>
</tr>
<tr>
<td>Tricuspid S', cm/s</td>
<td>11.5 (10.9–13.2)</td>
<td>10.9 (9.7–13.3)</td>
<td>0.462</td>
<td>0.381</td>
</tr>
<tr>
<td><strong>Diastolic function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral E/A ratio</td>
<td>1.3 (1.2–1.4)</td>
<td>1.2 (1.1–1.3)</td>
<td>0.374</td>
<td>0.133</td>
</tr>
<tr>
<td>Tricuspid E/A ratio</td>
<td>1 (0.8–1.1)</td>
<td>1.1 (1–1.3)</td>
<td>0.014</td>
<td>0.132</td>
</tr>
<tr>
<td>Mitral E deceleration time, ms</td>
<td>66 (52–90)</td>
<td>63 (49–78)</td>
<td>0.068</td>
<td>0.014</td>
</tr>
<tr>
<td>Tricuspid E deceleration time, ms</td>
<td>62 (51–77)</td>
<td>52 (44–66)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral E', cm/s</td>
<td>13.7 (12–14)</td>
<td>12.2 (10–13)</td>
<td>0.016</td>
<td>0.207</td>
</tr>
<tr>
<td>Tricuspid E', cm/s</td>
<td>15 (14–17)</td>
<td>13 (11–16)</td>
<td>0.015</td>
<td>0.077</td>
</tr>
<tr>
<td>Left isovolumic relaxation time, ms</td>
<td>50 (41–59)</td>
<td>63 (55–67)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Vascular assessment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>74 (67–83)</td>
<td>83 (75–94)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>50 (49–59)</td>
<td>50.5 (50–62)</td>
<td>0.070</td>
<td>0.214</td>
</tr>
<tr>
<td><strong>Aortic wall thickness†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic mean IMT, mm</td>
<td>0.52 (0.45–0.56)</td>
<td>0.64 (0.62–0.67)</td>
<td>&lt;0.001</td>
<td>0.003</td>
</tr>
<tr>
<td>Aortic mean IMT/weight, mm/kg</td>
<td>1.4 (1.2–1.5)</td>
<td>1.8 (1.60–1.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic maximum IMT, mm</td>
<td>0.60 (0.52–0.64)</td>
<td>0.72 (0.68–0.75)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic maximum IMT/weight, mm/kg</td>
<td>1.6 (1.4–1.8)</td>
<td>2.0 (1.9–2.1)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

A indicates ventricular inflow during atrial contraction; ART, pregnancy conceived by assisted reproductive technologies; E, ventricular inflow in early diastole; E', annular peak velocity in early diastole; IMT, intima-media thickness; and S', systolic annular peak velocity. Data are median (interquartile range).

*\(P\) value calculated by linear regression adjusted for gestational age at delivery, birth weight percentile, and preeclampsia.

†Aortic wall thickness normalized by infant weight.
methylation. Therefore, molecular pathways involved in cardiovascular regulation deserve further research to ascertain their potential involvement in the vascular changes described in ART pregnancies. However, because of the variability in ART protocols and the rarity of imprinting disorders, it can be challenging to determine reliably the causative relationship between and increased risk for imprinting disorders and ART exposure.

Concerning hormonal factors, the effect of supraphysiologic- cal estradiol levels on the outcome of in vitro fertilization–embryo transfer and subsequent pregnancies is a matter of controversy in the literature. Estradiol concentrations are not correlated with oocyte yield and quality, embryological outcome, implantation and pregnancy rates, abortion rate, congenital malformations, and birth weight. However, associations with pregnancy complications related to abnormal placenta-tion such as LBW, preeclampsia, and abnormal implantation of the placenta have been reported. The relationship between estradiol levels in ART and long-term cardiovascular function is unknown. As indirect evidence, a recent study reported no association between ovari an hyperstimulation, a condition associated with a dramatic increase in estrogen levels, with neuromotor development at 3 months of age, but again, a potential independent effect of a history of subfertility was suggested. Progesterone, another important hormone in human reproduction, has not been shown to have effects on fetal placental circulation or any association with the presence of LBW.

There are several limitations and considerations with regard to the present study. The changes reported here are subclinical, with most cardiovascular indexes lying within normal ranges. Although these differences are recognized as potential cardiovas cular risk factors, their long-term persistence and association with adult cardiovascular function and disease remain to be proven. Therefore, longer follow-up of these ART pregnancies to ascertain whether ART pregnancy remains a risk factor in later life is crucial. We acknowledge that several potential confound-ers could have interfered with our results. However, cases and controls were matched by maternal age, and twin pregnancies and mothers with medical diseases were excluded. The analysis was adjusted for other potential influences, including prematurity, birth weight percentile, and preeclampsia. Additionally, other potential confounders such as sex, race, cardiovascular history, socioeconomic status, parity, and parental smoking were similar among study groups. However, we acknowledge that analysis correcting for birth weight percentile may inadequately control for the differences in causality because children conceived by ART may be more likely to have in utero growth restriction from placental failure. In addition, there is increasing evidence that current definitions of fetal growth restriction most likely do not detect all instances of true restric-tion. Consequently, one could argue that by the same token, we cannot exclude that the whole distribution of fetal weights in our population was shifted to the left, reflecting a more general effect on fetal growth in ART fetuses. If this were the case, there would be forms of true fetal growth restriction that have been missed because of the lack of sensitivity of currently used definitions; therefore, the impact of fetal growth restriction on our results would be greater than is now apparent because hidden forms of growth restriction not detected by conventional criteria might have affected the cardiac outcome of the ART pregnancies. We fully acknowledge that prematurity and fetal growth restriction may have significantly contributed to the cardiac findings rather than ART via a mechanism of altered fetal programming. This concept deserves further clarification in future studies. Finally, we acknowledge that future studies might unveil nonobvious confounders not considered in the design of this study that might have affected the present results.

Conclusions

This study provides evidence that the use of ART in infertile couples is associated with fetal and postnatal cardiovascular remodeling, suggesting prenatal exposure to pressure overload. From a clinical perspective and regardless of the need to clarify the specific mechanisms, the existence of fetal programming in these infants presents important opportunities to improve cardiovas-cular health in a relevant proportion of the population. Nowadays, 1% to 4% of all newborns in developed countries are conceived by ART; therefore, the findings of this study involve thousands of children yearly. The importance of early identification of and the impact of interventions in pediatric risk factors for cardiovascular disease are now well recognized. Moreover, ART in infertile patients should be regarded as a potential cardiovascular risk factor, and strategies to detect and improve cardiovascular remodeling could be explored in children conceived with ART. The underlying mechanisms and the effect of the potential confounders in the primary observation reported here remain to be elucidated in future research.

Acknowledgments

We thank the study participants for their personal time and commit-ment to this project.

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Disclosures

None.

References


The findings of this study involve thousands of children yearly. The importance of early identification and the impact of interventions on pediatric risk factors for cardiovascular disease are now well recognized. Moreover, assisted reproductive technologies in infertile couples is associated with fetal and postnatal cardiovascular remodeling. Although the underlying mechanism remains to be elucidated, these data are of clinical importance.

This study provides evidence that the use of assisted reproductive technologies in infertile couples is associated with fetal and postnatal cardiovascular remodeling. Although the underlying mechanism remains to be elucidated, these data are of clinical importance.

Recent studies have shown that assisted reproductive technologies are associated with fetal and postnatal cardiovascular remodeling. Although the underlying mechanism remains to be elucidated, these data are of clinical importance.

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