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Cardiac Remodelling in ART-Conceived Singletons: A Prospective Cohort Study Comparing Biopsied and Non-Biopsied Embryos with Spontaneously Conceived Embryos

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Abstract

Objective: To compare cardiac remodelling in intracytoplasmic sperm injection (ICSI)-conceived singleton pregnancies (either biopsied or non-biopsied embryos) compared to spontaneously conceived (SC).

Methods: This prospective cohort study comprised 113 pregnant women with biopsied ICSI (n=37), non-biopsied ICSI (n=37), and SC embryos (n=39). Women were recruited from Wael ElBanna Clinic and the National Research Center in Cairo, Egypt, between November 2021 and September 2023. Included women were: (1) adults, (2) pregnant with a singleton fetus, and (3) agreed to attend consecutive ultrasonographic investigations during their pregnancy period and agreed to sign an informed consent. The fetal ultrasonography evaluation involved estimating the fetal weight and conducting fetoplacental Doppler and fetal echocardiography. Mean and standard deviation (SD) were utilized to present numerical data, and the One-Way ANOVA test and post hoc test were used for analysis. Frequency (n) and percentage (%) were employed to present categorical data, which were analyzed using the Chi-square test. Multiple linear regression was performed on fetal echocardiographic data with adjustments for some variables (parity and birthweight centile) to compare pregnancy methods.

Results: The cardiothoracic ratio and left ventricular free wall thickness were significantly higher in the biopsied ICSI group ($p< 0.001$). The right ventricular sphericity index was significantly lower in both ICSI groups, $p< 0.001$. After adjustment, the left ventricular sphericity index was higher in the non-biopsied ICSI group. In both ICSI groups, the septal wall thickness, right ventricular free wall thickness, Myocardial Performance Index, and the right atrial/heart ratio were significantly higher ($p< 0.001$, $p< 0.05$, respectively). The right ejection fraction and mitral E/A ratio were significantly lower in the non-biopsied ICSI

group (p=0.032, 0.022, respectively). After adjustment, the same result was observed for the ejection fraction but not for the mitral E/A ratio.
Conclusion: Cardiac remodelling was prominent among ICSI-conceived embryos compared to SC. However, these changes were subclinical, indicating the need for further investigation.

Keywords: Assisted reproductive technology, Cardiac remodelling, Singleton pregnancy, Intracytoplasmic sperm injection

Introduction

Assisted reproductive technology (ART) is a common and safe method for the treatment of infertility worldwide, contributing to 1.6% of all births (Thoma et al., 2014). It involves different reproductive techniques such as in-vitro fertilization (IVF), intrauterine insemination (IUI), ovulation induction (OI), and intracytoplasmic sperm injection (ICSI) (Zargar et al., 2022).

ART is linked with favourable pregnancy outcomes, though recent studies showed a heightened risk of congenital anomalies, principally cardiac anomalies (Hansen et al., 2013; Zargar et al., 2022). The odds of mild heart defects were 1.37 times greater among fetuses of pregnancies induced by ART compared with those of spontaneous pregnancies (Zargar et al., 2022).

Moreover, a link has been shown between adverse perinatal outcomes and both singleton and twin fetuses conceived by ART. These outcomes include a higher risk of pre-eclampsia, placenta previa, preterm birth, low birthweight, Cesarean section, and perinatal mortality compared to those conceived spontaneously (Elster et al., 2000; Helmerhorst et al., 2004; Sutcliffe and Ludwig, 2007; van Wely et al., 2006). Long-term adverse cardiovascular outcomes were also reported, including fetal cardiac remodeling and pulmonary and systemic vascular impairment (Ceelen et al., 2009; Scherrer et al., 2015, 2012a; Valenzuela-Alcaraz et al., 2018, 2013; Zhou et al., 2014).

The pattern of cardiac remodeling is affected by the type and duration of exposure to an insult. It may manifest as shape change, myocardial hypertrophy, cavity dilation, or hypoplasia. In most cases, subclinical cardiac remodeling is observed. But, in cases with severe or persistent insult, it can lead to impaired cardiac pumping and relaxation, resulting in heart failure, manifesting as fetal hydrops in utero (Crispi et al., 2020).

Furthermore, fetal cardiac remodeling is more prominent on the right side, which likely indicates that the right side was dominant before. In utero, the right ventricle functions as the "systemic" ventricle, supplying blood to the fetal organs and placenta; therefore, it is more vulnerable to pressure overload than the left ventricle (Crispi et al., 2020).

The exact cause of these cardiac remodeling patterns is unknown. However, it is suggested that cardiac remodeling could be associated with parental factors linked to infertility, gametes and embryo handling, cultural parameters, or the increased likelihood of fetal outcomes compared to pregnancies that occur naturally (Scherrer et al., 2015).

Scherrer et al. have previously observed signs of generalized vascular dysfunction among ART-conceived children and adolescents that might be associated with the ART process itself rather than parental factors (Scherrer et al., 2012b). Zhou et al. suggested that ovarian stimulation, embryo stage, and transfer count during the ART procedure are considered inde-

Table 1. Maternal and perinatal characteristics of the studied groups

	SC (n=39)	Non-biopsied ICSI (n=37)	Biopsied ICSI (n=37)	P value
Age (years)	31.36 ± 6.15	30.22 ± 5.13	32.24 ± 4.89	0.278
BMI (kg/m^2)	28.43 ± 5.32	28.71 ± 3.21	29.17 ± 3.32	0.731
Parity				
Zero	14 (35.9%) [a]	28 (75.7%) [b]	14 (37.8%) [a]	<0.001
Primipara	8 (20.5%)	8 (21.6%)	15 (40.5%)	
Multipara	17 (43.6%)	1 (2.7%)	8 (21.6%)	
	SC (n=39)	**Non-biopsied ICSI (n=37)**	**Biopsied ICSI (n=37)**	**P value**
Delivery data				
Gestational age (weeks)	37.46 ± 1.57	37.92 ± 0.8	37.21 ± 1.6	0.088
Preterm	6 (21.4%)	3 (8.1%)	9 (27.3%)	0.104
Cesarian section	26 (92.9%)	37 (100%)	33 (100%)	0.08
Gender				
Male	14 (50%)	15 (40.5%)	17 (51.5%)	0.609
Female	14 (50%)	22 (59.5%)	16 (48.5%)	
Birthweight (g)	2896.79 ± 578.79 [a]	3029.46 ± 305.41 [a]	3439.7 ± 576.73 [b]	<0.001
Birthweight centile	44.22 ± 33.8 [a]	42.62 ± 27.76 [a]	79.45 ± 22.97 [b]	<0.001
SGA	5 (17.9%) [a]	5 (13.5%) [a]	0 (0%) [b]	0.047
Neonatal outcome				
NICU admission	4 (14.3%) [ab]	1 (2.7%) [b]	8 (24.2%) [a]	0.026
Cause				
RDS	3 (10.7%)	1 (2.7%)	7 (21.2%)	0.641
Pulmonary HTN	1 (3.6%)	0 (0%)	1 (3%)	
Low birthweight	1 (3.6%)	0 (0%)	0 (0%)	
Major comorbidity				
RDS	1 (3.6%)	0 (0%)	0 (0%)	>0.999
Pulmonary HTN	1 (3.6%)	0 (0%)	1 (3%)	

Numerical data are presented as mean ± SD and categorical data are presented as frequency (%), Statistical significance at P value<0.05, Different lower-case letters indicate significant difference in pairwise comparison, BMI: Body mass index SGA: Small for gestational age, RDS: Respiratory distress syndrome.

pendent predictors for cardiac geometric morphology and diastolic dysfunction (Zhou et al., 2014).

Therefore, our study evaluated fetal cardiac remodeling and dysfunction in ICSI-conceived singleton pregnancies (Biopsied and Non-Biopsied ICSI) compared with spontaneously conceived (SC) ones. Since the direct biological effects on cardiac remodeling are not well understood, we compared the patterns of cardiac remodeling between biopsied and non-biopsied embryos. This comparison aims to evaluate the safety of biopsy procedures in ICSI.

Methods

Cohort Selection

This prospective cohort study included 113 adult women pregnant with a singleton fetus. Women were recruited from Wael ElBanna Clinic and the National Research Center in Cairo, Egypt, between November 2021 and September 2023. Included women were:

Table 2. Standard fetoplacental data of the studied groups

	SC (n=39)	Non-biopsied ICSI (n=37)	Biopsied ICSI (n=37)	P-value
Gestational age at time of ultrasound examination (weeks)	29.15 ± 0.9	29.03 ± 0.69	28.92 ± 0.86	0.464
Estimated fetal weight (g)	1483.59 ± 215.56 [a]	1375.68 ± 91.69 [b]	1376.76 ± 236.24 [b]	0.022
Estimated fetal weight (centile)	66.77 ± 30.92	57.47 ± 25.48	53.53 ± 26.96	0.109
Uterine artery mean PI	0.9 ± 0.38	0.82 ± 0.1	0.78 ± 0.12	0.073
Umbilical artery PI	1.04 ± 0.17	1.06 ± 0.18	0.98 ± 0.15	0.117
Middle cerebral artery PI	1.95 ± 0.52 [ab]	1.81 ± 0.23 [b]	2.06 ± 0.33 [a]	0.023
Cerebroplacental ratio	1.89 ± 0.49 [a]	1.7 ± 0.27 [a]	2.14 ± 0.47 [b]	<0.001
Ductus venosus PI	0.69 ± 0.3	0.74 ± 0.1	0.71 ± 0.14	0.617
Aortic isthmus PI	2.41 ± 0.27	2.4 ± 0.3	2.46 ± 0.23	0.624

Numerical data are presented as mean ± SD, Statistical significance at P value<0.05, Different lower-case letters indicate significant difference in pairwise comparison. PI: Pulsatility index

(1) adults, (2) pregnant with a singleton fetus, and (3) agreed to attend consecutive ultrasonographic investigations during their pregnancy period and agreed to sign an informed consent. However, women pregnant with multiple fetuses, those with any medical conditions, smokers, or addicts were excluded. Moreover, a woman with a fetus that was diagnosed with fetal malformations or Small-for-Gestational-Age (SGA), intrauterine Growth Restriction (IUGR) as determined through an ultrasound, was also excluded.

The included women were divided into 3 study groups: (1) Biopsied ICSI (embryos that underwent trophectoderm biopsy at the blastocyst stage, on day 5 post-fertilization, for preimplantation genetic screening (PGS) for aneuploidy (PGT-A) or other genetic conditions); (2) Non-Biopsied ICSI (embryos that did not undergo any biopsy for PGS); and (3) spontaneous pregnancies.

Exposure

Data was collected at 29 weeks ±1-week gestation, upon delivery, and 48 hours after delivery using the GE Voluson S10 Ultrasound Machine. The fetal ultrasonography evaluation involved estimating the fetal weight and conducting fetoplacental Doppler and fetal echocardiography.

The estimated weight of the fetus and the fetal and birthweight centiles were determined using the methods described by Hadlock et al. (Hadlock et al., 1985) and the fetal medicine Barcelona calculator (Calculadoras | Fetal Medicine Barcelona, n.d.), respectively. Doppler measurements of fetoplacental blood flow involved assessing the Pulsatility Index in the uterine arteries, umbilical artery, fetal middle cerebral artery, ductus venosus, and aortic isthmus (Arduini and Rizzo, 1990; Gómez et al., 2008; Hecher et al., 1994; Del Río et al., 2006). Furthermore, the cerebroplacental ratio was assessed by dividing the Pulsatility indices of the middle cerebral and umbilical arteries. (Baschat and Gembruch, 2003).

The structure and function of the heart were evaluated by echocardiography. The cardiothoracic ratio was calculated by the heart area/ the thoracic area (Paladini et al., 1990). The measurements of the left and right atrial areas were done at maximum distention, and the ratios of the atrial areas to the heart areas were calculated. Additionally, the sphericity indices of the left and right ventricles were determined by measuring the base-to-apex length and the basal ventricular diameters at end-diastole (Lowes et al., 1999; Schneider et al., 2005).

From a transverse four-chamber view, we as-

Table 3. Fetal cardiac assessment of the studied groups

	SC (n=39)	Non-biopsied ICSI (n=37)	Biopsied ICSI (n=37)	Unadjusted P value	Adjusted P1	Adjusted P2	Adjusted P3
Cardiac morphometric data							
Cardiothoracic ratio	0.27 ± 0.03 [a]	0.29 ± 0.03 [a]	0.31 ± 0.04 [b]	<0.001	0.358	<0.001	<0.001
Left atrial/heart ratio (mm^2)	13.31 ± 2.73	12.89 ± 2.38	13.35 ± 2.03	0.661	0.325	0.794	0.196
Right atrial/heart ratio	14.72 ± 1.5 [a]	17.78 ± 2.06 [b]	18.73 ± 1.79 [b]	<0.001	<0.001	<0.001	0.011
Left ventricular sphericity index	1.74 ± 0.25	1.84 ± 0.18	1.80 ± 0.22	0.142	0.028	0.267	0.298
Right ventricular sphericity index	1.57 ± 0.16 [a]	1.40 ± 0.11 [b]	1.43 ± 0.09 [b]	<0.001	<0.001	<0.001	0.470
Left ventricular free wall thickness (mm)	3.04 ± 0.19 [a]	3.17 ± 0.28 [a]	3.50 ± 0.32 [b]	<0.001	0.016	<0.001	0.002
Septal wall thickness (mm)	3.09 ± 0.21 [a]	3.44 ± 0.34 [b]	3.47 ± 0.34 [b]	<0.001	<0.001	<0.001	0.977
Right ventricular free wall thickness (mm)	3.03 ± 0.18 [a]	3.18 ± 0.23 [b]	3.18 ± 0.29 [b]	0.005	<0.001	<0.001	0.833
Myocardial Performance Index	0.49 ± 0.04 [a]	0.59 ± 0.05 [b]	0.6 ± 0.04 [b]	<0.001	<0.001	<0.001	0.587
Systolic function data							
Left ejection fraction (%)	85.62 ± 7.67	87.86 ± 3.15	87.16 ± 3.3	0.16	0.103	0.10	0.873
Right ejection fraction (%)	65.6 ± 7.27 [a]	61.46 ± 6.97 [b]	63.22 ± 6.04 [ab]	0.032	0.009	0.288	0.127
MAPSE (mm)	4.85 ± 0.8	4.95 ± 0.51	4.86 ± 0.59	0.774	0.785	0.532	0.331
TAPSE (mm)	5.95 ± 0.4	5.99 ± 0.33	5.92 ± 0.35	0.725	0.948	0.983	0.966
Diastolic function data							
Mitral E/A ratio	0.68 ± 0.07 [a]	0.64 ± 0.08 [b]	0.66 ± 0.06 [ab]	0.022	0.200	0.896	0.147
Tricuspid E/A ratio	0.73 ± 0.06	0.74 ± 0.08	0.71 ± 0.05	0.345	0.388	0.643	0.164
Left isovolumic relaxation time (ms)	54.44 ± 6.72	55.08 ± 4.4	55.14 ± 2.97	0.792	0.083	0.325	0.491

Numerical data are presented as mean ± SD, Statistical significance at P value<0.05, Different lower-case letters indicate significant difference in pairwise comparison. Comparisons were adjusted by parity and birthweight centile, Adjusted P1: Comparison between Non-biopsied ICSI and SC groups, Adjusted P2: Comparison between Biopsied ICSI and SC groups. Adjusted P3: Comparison between Non-biopsied ICSI and Biopsied ICSI, MAPSE: Mitral annular plane systolic excursion, TAPSE: Tricuspid annular plane systolic excursion

sessed the ventricular end-diastolic septal and free wall thicknesses using M-mode (Gardiner et al., 2006; Rychik et al., 2004). From an apical or basal four-chamber view, mitral and tricuspid annular plane systolic excursions (MAPSE/TAPSE) were measured using M-mode. The maximum displacement amplitude in millimeters was measured by placing the cursor at a right angle to the atrioventricular junction.(Gardiner et al., 2006).

A basal or apical four-chamber view was used to capture atrioventricular flows by placing the pulsed Doppler sample volume at the tip of the atrioventricular valve leaflets. The ultrasound beam was angled at an angle of less than 30 degrees to the orientation of the ventricular wall or the interventricular septum without any angle correction.

The early ventricular filling (E-wave) is compared to the late ventricular filling (A-wave) to calculate the right and left E/A ratios (DeVore, 2005). The duration of left ventricular isovolumic relaxation was determined from a four-chamber view by positioning the Doppler sample volume between the aortic and mitral valves. Valvular clicks in the Doppler waveform were utilized as reference points to calculate the timing between the closure of the aortic valve and the opening of the mitral valve (Cruz-Martínez et al., 2012).

The data collected also included the gestational age and the standard fetoplacental data. In Addition,

the collected maternal characteristics involved age, body mass index (BMI), and parity. The main recorded pregnancy-related complications and neonatal outcomes were pre-eclampsia, gestational diabetes, admission to the neonatal intensive care unit (NICU), and major neonatal morbidity. Also, delivery-related data such as the gestational age at delivery, the gender of the neonate, the mode of delivery, and the incidence of SGA were collected.

Statistical Analysis

IBM SPSS for Windows version 28 (IBM Co., Armonk, NY, USA) was utilized. Mean and standard deviation (SD) were used to present numerical data, and the One-Way ANOVA and post hoc tests (Tukey) were used for analysis. Frequency (n) and percentage (%) were employed to present categorical data, which were analyzed using the Chi-square test. Multiple linear regression was performed on fetal echocardiographic data with adjustments for some variables (parity and birthweight centile) to compare pregnancy methods. A p-value of less than 0.05 indicated statistical significance.

Ethics Approval

This clinical study was conducted according to the Declaration of Helsinki, and the Medical Research Ethics Committee of the National Research Centre approved the study (study number: 18092021). A written informed consent was obtained from all participants.

Results

Clinical Characteristics of the Study Population

This prospective cohort study was conducted on 113 singleton pregnant women, divided according to the method of pregnancy into three groups: SC group (n=39), non-biopsied ICSI (n=37), and biopsied ICSI (n=37) groups.

Regarding the maternal characteristics, there was a significant difference regarding parity (p<0.001), with a significantly higher percentage of nulliparity in the non-biopsied ICSI group than in the biopsied one and the control SC (75.7% vs 37.8% and 35.9%, respectively). Notably, the studied women had similar ages and BMIs. [Table 1]

Delivery and Neonatal Outcomes

Regarding delivery data, there was a significant difference in birthweight among groups (p<0.001), significantly higher among biopsied ICSI babies than the non-biopsied ones and the SC controls. The percentage of SGA was 17.9% of SC babies, and 13.5% of the non-biopsied ICSI ones evidenced SGA, with no incidence in the biopsied group (p=0.047).

In terms of neonatal outcome, the NICU admission rate was 14.3% in the SC group (10.7% for RDS, 3.6% for pulmonary HTN, and another 3.6% for low birthweight), 2.7% in the non-biopsied ICSI group (for RDS) and 24.2% in the biopsied group (21.2% for RDS and 3% for pulmonary HTN), and that difference in rates was statistically significant (p=0.026) being significantly higher in the biopsied ICSI group than the non-biopsied one. They were safely discharged from the NICU.

Fetoplacental Outcomes

Given standard fetoplacental data, the estimated fetal weight was significantly lower in both ICSI groups than in the control group (p=0.022). Also, middle cerebral artery PI significantly differed (p=0.023), significantly higher in the biopsied ICSI group than the non-biopsied one. Furthermore, there was a significant difference regarding cerebroplacental ratio (p<0.001) as it was significantly higher in the biopsied ICSI group than in both non-biopsied and SC groups. [Table 2]

Cardiac Changes in the Study Groups

Our analysis revealed that cardiothoracic ratio and

left ventricular free wall thickness were significantly higher in the biopsied ICSI group than in the non-biopsied and SC groups ($p<0.001$). We then adjusted factors that significantly differed between the groups and could influence outcomes, such as parity and birthweight centile, revealing the same results.

Also, the right atrial/heart ratio's value was higher in both ICSI groups (biopsied and non-biopsied) than that of the SC group, $p<0.001$. However, statistical significance was detected between all groups after adjustment.

The right ventricular sphericity index was significantly lower in both ICSI groups than the SC group, $p<0.001$, and the same result was observed after adjustment. On the other hand, after adjustment, the left ventricular sphericity index was higher in the non-biopsied ICSI group than in the SC group.

The left ventricular free wall thickness was significantly higher in the biopsied ICSI group than in the non-biopsied and SC groups ($p<0.001$). However, statistical significance was detected between all groups after adjustment.

For the Septal wall thickness, right ventricular free wall thickness, and Myocardial Performance Index, they were higher in both ICSI groups (biopsied and non-biopsied) than in the SC group ($p<0.05$). The same result was observed after adjustment for parity and birthweight centile.

Moreover, right ejection fraction and mitral E/A ratio significantly differed among groups ($p=0.032$, 0.022, respectively), with significantly lower values in the non-biopsied ICSI group than in the SC. After adjustment by parity and birthweight centile, the same result was observed for ejection fraction, but no difference was detected for the mitral E/A ratio between groups. [Table 3]

Discussion

This study reveals the development of fetal cardiac remodeling in singleton embryos conceived via ICSI, regardless of being biopsied or not, compared with embryos conceived spontaneously. Besides, cardiac remodeling patterns were more prominent among biopsied embryos. However, the cardiac function was preserved, and these changes were subclinical.

Our findings align with previous observational studies showing cardiac remodeling patterns in singleton and twin fetuses conceived by ICSI. Our findings present more evidence for fetal cardiac remodeling compared with fetuses conceived via SC, which could persist in infants, adolescents, and adults (Von Arx et al., 2015; Cui et al., 2021; Scherrer et al., 2012b; Valenzuela-Alcaraz et al., 2018, 2013).

We observed that fetuses conceived by ICSI showed a higher cardiothoracic ratio, MPI, and a lower right ventricular sphericity index and ejection fraction. Moreover, they exhibited right atrial dilatation and thicker left and right ventricular and septal walls compared to those conceived by SC.

Consistent with our findings, Valenzuela-Alcaraz et al. have previously shown that fetuses conceived via ART have more globular hearts with thicker myocardial walls. Additionally, they exhibited impaired relaxation and decreased longitudinal systolic excursion (Valenzuela-Alcaraz et al., 2013). Moreover, the children continued to exhibit these cardiac remodeling patterns and dysfunction until up to 3 years of age (Valenzuela-Alcaraz et al., 2019).

Among ART-conceived twins, the authors described larger atria, a pattern of right ventricular concentric remodeling, and signs of systolic and diastolic dysfunction compared to twins conceived naturally (Valenzuela-Alcaraz et al., 2018). These patterns were possibly more prominent on the right side of the heart due to pressure overload.

It was found that children conceived via ART aged 6 to 10 years exhibited increased blood pressure and a high prevalence of left ventricular hypertrophy, high relative wall thickness, and left ventricular geo-

metric remodeling patterns (Cui et al., 2021).

Likewise, a meta-analysis has demonstrated that fetuses conceived via IVF-ICSI manifested a statistically significant elevation in arterial blood pressure, suboptimal cardiac diastolic function, and higher vessel thickness compared with those conceived naturally (Guo et al., 2017).

Bi et al. have observed subclinical cardiac changes among infants conceived via ART who were followed up to 6 months of age, including a globular enlarged left ventricle, a larger right ventricle, and systolic dysfunction. These changes were comparable between IVF and ICSI groups and fresh ET and FET groups. However, these changes did not persist in the early infancy (Bi et al., 2022).

Therefore, the persistence of these subclinical cardiac changes and their progress to clinical manifestations later in life is more likely influenced by the presence of other conditions such as obesity, metabolic syndrome, and unhealthy lifestyle.

The exact mechanism of cardiac remodeling among ART-conceived fetuses is still poorly understood. It is hypothesized that fetal programming of cardiovascular disease and the condition of the fetal environment strongly influence the child's health and cardiac remodeling (Barker, 1990; Crispi et al., 2010).

Therefore, suboptimal maternal nutrition, stress factors, increased oxidative stress, and levels of corresponding hormones may significantly impact the development of the child and potentially influence his cardiovascular health (Sitzberger et al., 2021; Yang et al., 2020).

Other factors that could influence fetal cardiac remodeling include the coexistence of pregnancy complications, the parental causes of infertility, prematurity, and fetal growth restriction (Boutet et al., 2021; Henningsen et al., 2011; Zhou et al., 2014).

During ART procedures, manipulating the embryo may disrupt epigenetic processes and DNA methylation patterns, leading to changes in gene expression. Factors such as ovarian stimulation and Inadequate culture media have been identified to affect the embryo, impacting epigenetic imprinting and perinatal outcomes. Moreover, ovarian stimulation has been associated with increased estrogen, total cholesterol, and LDL-C (Sitzberger et al., 2021).

Concerning cardiac function in our cohort, the right ejection fraction and mitral E/A ratio were decreased in the ICSI groups; however, only the ejection fraction remained significantly different between the study groups after adjustment for parity and birth weight. In addition, the remaining systolic and diastolic functional parameters were comparable between groups.

This observation suggests mild signs of cardiac systolic dysfunction among ART-conceived fetuses with no significant impact on diastolic function.

This contrasts with Zhou et al., who showed an elevation in mitral E/A and mitral E/E′ ratios with no changes in the systolic function (Zhou et al., 2014). Valenzuela-Alcaraz and his colleagues reported both systolic and diastolic dysfunction in the presence of cardiac remodeling among ART-conceived children (Valenzuela-Alcaraz et al., 2013).

Though Liu et al. described significant cardiac systolic and diastolic dysfunction without significant changes in cardiac morphometry among ART-conceived children aged 5 (Liu et al., 2015). Von Arx et al. showed that preadolescents born at term with a normal birth weight exhibited right ventricular dysfunction when exposed to high-altitude stress (Von Arx et al., 2015).

Moreover, left ventricular dysfunction was detected among children who were conceived by ART compared to those conceived spontaneously. However, no significant difference was found after adjusting for birth weight percentiles and gestational age, M-mode-assessed left ventricular ejection fraction, and fractional shortening (Sciuk et al., 2023).

Similar findings regarding diastolic dysfunction were also reported among both groups, and no differences were observed after adjusting for age, birth weight percentile, and gestational age (Sciuk et al., 2022). This emphasizes the role of perinatal risk factors in cardiac dysfunction.

The impact of embryo biopsy on cardiac remodeling has not been adequately examined before, and there are conflicting findings in the literature concerning the effect of embryo biopsy on pregnancy and neonatal outcomes.

Here, we observed that biopsied embryos exhibit more significant structural and functional alterations. In contrast, Sites et al. have recently reported that embryo biopsy for preimplantation genetic testing with ART did not appear to elevate adverse maternal or neonatal outcomes (Sites et al., 2021).

Jing et al. also confirmed that blastocyst-stage biopsy with a frozen embryo transfer strategy had better neonatal outcomes than cleavage-stage biopsy and fresh embryo transfer or frozen blastocyst transfer after IVF/ICSI (He et al., 2019; Jing et al., 2016).

Strengths and Limitations of the Study

Strengths of the current study include: (1) the prospective collection of data, ruling out the recall bias; (2) the detailed assessment of cardiac parameters which allow in-depth analysis of the structural and functional changes; and (3) examining the impact of biopsy on the cardiac function among ICSI-conceived embryos which have not explored before.

The limitations of the study are as follows: (1) the small sample size; (2) the observational study design; (3) the difficulty of controlling the confounders, which might limit our conclusion; and (4) the absolute values of the altered parameters among the ICSI-conceived embryos remained within the reference range, potentially diminishing the clinical significance of our results despite the significant differences between groups. Therefore, the generalizability of our findings should be done with caution.

Conclusion

In summary, our study highlights the development of fetal cardiac remodeling in singleton embryos conceived via ICSI more prominently in biopsied embryos, compared with embryos conceived spontaneously. However, the changes in the cardiac functions were subclinical. Hence, the clinical significance of these findings remains to be established.

Therefore, long-term studies with larger cohorts are warranted to follow up on these cardiac changes and to examine the potential biological mechanism of this association and its impact on cardiovascular health in adolescence and adulthood to permit the reversal of these unfavourable cardiac structure and function alterations.

Credit authorship contribution statement

Wael Saad Elbanna: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis and Interpretation of the Results, Validation, Resources, Writing—Original Draft, Writing—Review and Editing, Acquisition, Supervision. *Osama Azmy:* Methodology, Investigation, Formal Analysis and Interpretation of the Results, Writing—Original Draft. *Manal Ahmed Elhinnawi:* Investigation, Data Curation, Writing—Review and Editing. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics Approval

This clinical study was conducted according to the Declaration of Helsinki, and the Medical Research Ethics Committee of the National Research Centre approved the study (study number: 18092021).

Consent to participate and Consent to publish

Written informed consent was obtained from the participant to be included in the study. The authors affirm that human research participants provided informed consent for publication.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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