Original Article

Vascular function in a cohort of children, adolescents and young adults conceived through assisted reproductive technologies—results from the Munich heARTerY-study

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Background: Over 8 million individuals worldwide have been conceived through assisted reproductive technologies (ART). There is conflicting evidence on the cardiovascular health of ART offspring. This study aimed to investigate vascular function in a cohort of children, adolescents and young adults conceived through ART compared to spontaneously conceived peers.

Methods: Anthropometric variables, diet quality, level of physical activity and sedentary behavior were assessed. An extensive evaluation of vascular function was conducted. Blood pressure as well as endothelial function were evaluated. Carotid intima-media thickness was recorded sonographically. Blood draws were taken to determine blood lipids as well as HbA1c.

Results: In total, 66 ART subjects conceived through in vitro fertilization (IVF) or intracytoplasmic sperm injection and 86 spontaneously conceived peers were included in this observational cohort study. Both groups were similar in age [11.31 (8.10–18.00) *vs.* 11.85 (8.72–18.27) years, P=0.373]. ART subjects displayed a significantly higher body fat percentage [19.30% (15.80–26.02%) *vs.* 15.91% (13.21–21.00%), P=0.007]. Both groups did not differ significantly in diet quality, physical activity, sedentary behavior, and vascular function. Blood lipids and HbA1c were comparable between both groups. ART subjects showed significantly lower levels of triglycerides compared to spontaneously conceived peers. The prevalence of lipoprotein (a) [Lp(a)] ≥50 mg/dL tended to be higher within the ART cohort. Vascular function did not deteriorate more profoundly with age in ART subjects than in spontaneously conceived peers.

Conclusions: The results of the current study do not indicate a significantly lower vascular function in a cohort of children, adolescents and young adults conceived through ART compared to spontaneously conceived peers. Future studies should address the prevalence of elevated Lp(a) levels in infertile individuals who sought ART treatment. In addition, more studies evaluating body fat percentage as well as cardiovascular morbidity in adult ART subjects are required. For a more precise cardiovascular risk stratification, multi-center studies with larger ART sample sizes, preferably at adult age, are required in the future.

Keywords: Assisted reproductive technologies (ART); vascular function; children; adolescents; adults

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Introduction

Infertility affects millions of couples worldwide (1). On July 25th 1978, Louise Brown was the first child conceived with the help of in vitro fertilization (IVF) (2). Since then, assisted reproductive technologies (ART) have been widely used to treat infertility (3). It is assumed that over 8 million individuals have been conceived through ART worldwide (4). Today, more than 2% of all European infants are conceived through ART (3). With 6.2%, Denmark holds the highest proportion of ART infants per national birth within Europe (3).

In the past, several studies suggested distinct vascular alterations, such as increased blood pressure, pulse wave velocity and carotid intima-media thickness (cIMT) as well as lower endothelial function, in ART children and adolescents (5-8). In the literature, multiple causes are proposed to be involved in the vascular pathophysiology of ART offspring being the ART procedure itself, the intrauterine environment, parental risk factors and lifestyle habits (9). In contrast to these results, a recent study by Halliday *et al.* did not detect significant vascular differences in 193 ART adults compared to spontaneously conceived controls (10). These results may indicate that vascular changes in the ART offspring are only transiently present during childhood and "vanish" later in life (10).

Highlight box

Key findings

- The results of the current study do not indicate a significantly lower vascular function in a cohort of children, adolescents and young adults conceived through assisted reproductive technologies (ART).

What is known and what is new?

- There is conflicting evidence on the cardiovascular health of ART offspring.
- An extensive vascular evaluation in a cohort of children, adolescents and young adults conceived through ART was conducted in this study.

What is the implication and what should change now?

- For a more precise cardiovascular risk stratification, multi-center studies with larger ART sample sizes, preferably at adult age, are required in the future.

As a rising number of children are conceived through ART, the potentially increased vascular morbidity remains of great concern for families and society. Regarding the currently ambiguous data situation, further studies are required to investigate the potential impact of ART on the offspring's cardiovascular health.

The aim of this study was to assess whether ART subjects develop vascular alterations compared to spontaneously conceived peers over their lifespan. We therefore conducted a single center observational cohort study, which included an ART cohort composed of children, adolescents, and young adults. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-67/rc).

Methods

Ethical approval

This study received ethical approval (No. 20-0844) on the 27th of December 2020 by the Ethics Committee of the Medical Faculty of LMU Munich (Munich, Germany). The study was conducted in accordance with the ethical standard of the Declaration of Helsinki (as revised in 2013). Prior written consent was obtained from all study participants. In minor study participants, prior written consent was additionally received from parents or legal guardians.

Study design and study population

The Munich heARTerY-study (Assisted Reproductive Technologies and their effects on heart and arterial function in Youth) was a single center observational cohort study. Between May 2021 and March 2022, individuals conceived through ART were enrolled in collaboration with the Division of Gynecological Endocrinology and Reproductive Medicine, Department of Obstetrics and Gynecology, University Hospital, LMU Munich (Munich, Germany). For this study, ART subjects conceived solely through IVF or intracytoplasmic sperm injection (ICSI) were included. In contrast to previous publications of our departments, subjects conceived through gamete intrafallopian transfer (GIFT) were excluded. While GIFT can be considered a conventional ART procedure, it does not include *in vitro* cultivation as fertilization happens in the natural environment of the fallopian tubes (11). Healthy spontaneously conceived peers matched in age and gender without known cardiovascular diseases were enrolled through public calls within the greater Munich area. To evaluate the influence of age on vascular function, subjects of different developmental stages (children, adolescents, adults) were included. All study participants were examined at the Division of Pediatric Cardiology and Intensive Care, University Hospital, LMU Munich (Munich, Germany).

Assessment of anthropometric variables

Bodyweight (kg) and height (cm) were determined. In addition, body mass index (BMI, kg/m^2) was measured. The following weight classification was defined for adult study participants: underweight if BMI <18.5 kg/m^2, normal weight if BMI ≥18.5 but <25 kg/m^2, overweight if BMI ≥25 but <30 kg/m^2 and obese if BMI ≥30 kg/m^2. In minor study participants, weight classification was determined in accordance with BMI percentiles (P.) provided by Kromeyer-Hauschild *et al.*: underweight if BMI <10 P., normal weight if BMI ≥10 P. but <90 P., overweight if BMI ≥90 P. but <97 P. and obese if BMI ≥97 P. (12). A skinfold caliper was utilized to measure skinfold thickness in study participants (Harpenden Skinfold Caliper, Baty International, UK). In all subjects, the skinfold thickness was measured three consecutive times and an average was calculated. For adult subjects, the gender-dependent, three-site skinfold protocol of Jackson *et al.* was utilized to assess body fat percentage (BFP, %) (13,14). In minors, the right triceps skinfold thickness and the right subscapular skinfold thickness were measured according to Neuhauser *et al.* (15). BFP was estimated in minor subjects using formulas established by Slaughter *et al.* (16).

Medical history, course of pregnancy and birth, maternal level of education, clinical examination

The assessment of medical history, smoking status and regular use of medication was performed. The following data regarding the course of pregnancy and birth was assessed by evaluating clinical records and by interviewing parents: birth weight (g), gestational age (week), maternal age at birth (years), case of multiple pregnancy, maternal BMI at conception (kg/m^2), presence of gestational diabetes, maternal blood pressure during pregnancy ≥140/90 mmHg. Maternal level of education was defined based on the German education system: no school leaving qualification [0], lower secondary school leaving certificate [1], intermediate secondary school leaving certificate [2], general qualification for university entrance [3], completed apprenticeship [4], completed university degree [5]. Additionally, all study participants underwent a physical examination.

Adherence to Mediterranean diet

High adherence to the Mediterranean diet was shown to positively influence cardiovascular health (17-19). To evaluate adherence to the Mediterranean diet in adult study participants, the validated 14-item Mediterranean diet assessment tool established by Martínez-González *et al.* was translated into German and applied (17). For minors, the validated KIDMED test established by Serra-Majem *et al.* was translated into German and utilized (20). For both questionnaires a score ≥8 was defined as high adherence to the Mediterranean diet (17,20).

Level of physical activity and sedentary behavior

The German version of the Global Physical Activity Questionnaire (GPAQ) provided by the World Health Organization (WHO) was utilized to assess the level of physical activity in study participants ≥18 years of age (21). Picture cards were shown for each activity type (21). Total and recreational Metabolic-Equivalent-(MET)-minutes per week were calculated according to GPAQ recommendations (21). Further, adult study participants were asked how many times muscle strengthening activities are performed per week. Adult subjects met WHO recommendation if ≥600 total MET-minutes per week were accomplished (21).

To assess the level of physical activity in study participants <18 years of age, subjects were asked how much time is spent per day on moderate and/or vigorous physical activities. Moreover, minor subjects were asked how many times vigorous, muscle strengthening and/or bone strengthening activities are performed per week. For each activity type, picture cards were shown. Pediatric subjects met WHO recommendations if (I) an average of ≥60 minutes per day was achieved for moderate and/or vigorous activities and (II) vigorous, muscle strengthening and/or bone strengthening activities were performed ≥3 times per week (22).

Sedentary behavior was defined as time spent sitting (22). Picture cards visualizing different examples of sedentary behavior (e.g., sitting on the train, driving the car, sitting while working or doing homework, watching TV) were presented to all study participants. Study participants were then asked how much time (min) is spent per day with such sedentary activities.

Vascular function

Pulse wave analysis

An oscillometric blood pressure device (Mobil-O-Graph®, IEM GmbH, Germany) was utilized to measure brachial systolic blood pressure (SBP, mmHg), brachial diastolic blood pressure (DBP, mmHg), mean arterial pressure (MAP, mmHg), heart rate (HR, bpm), central SBP (cSBP, mmHg), central DBP (cDBP, mmHg) and augmentation index averaged to a heart rate of 75 bpm (AIx@75, %). Cuff sizes were selected to match the right upper arm circumference. Study participants were asked to remain in a supine and calm position ≥5 minutes before and during the measurements. To enhance data validity, three consecutive measurements were executed and averaged as recommended by the European Society of Cardiology/European Society of Hypertension (23). In subjects ≥16 years of age, SBP was elevated if ≥130 mmHg and DBP if ≥85 mmHg (23). In subjects <16 years of age, elevated SBP and/or DBP was present if ≥90 P. of a reference population in Germany (15).

Endothelial function

The reactive hyperemia index (RHI), a marker of endothelial function (24), was measured using the EndoPAT™2000 device (Itamar Medical, Israel) and its corresponding software [version 3.7.2.(2.0)]. A fasting period ≥4 hours and an alcohol abstinence ≥24 hours prior to study participation was required. The examination was performed in a quiet and temperature-controlled room. Study participants were asked to remain in a supine and calm position for ≥15 minutes prior to as well as during the entire examination. The measurement consisted of a 5-minute baseline recording period, a 5-minute occlusion period and a 5-minute post occlusion period. A cuff was positioned on the right upper arm during occlusion period. The cuff was inflated between 200–300 mmHg in adult subjects and ≥60 mmHg above SBP in pediatric subjects for complete blood flow cessation.

Intima-media-thickness of the common carotid artery (CCA)

A Philips iE33 xMatrix or a Philips Epiq 7G ultrasound device (Philips Healthcare, The Netherlands) with a 3–12 MHz linear array transducer was used to image both CCAs in long axis view at bifurcation level. During sonography, subjects were asked to remain in a supine position while extending their neck up to a 45° angle and turning it to the contralateral side of examination (25). Under constant three-lead ECG tracking, three consecutive loops were recorded. The loops were then transferred to a separate workstation (QLAB cardiovascular ultrasound quantification software, version 11.1, Philips Healthcare, The Netherlands) for further analysis. At end-diastole (R wave in ECG), the carotid intima-media thickness (cIMT, mm) was evaluated semiautomatically for both sides individually. Proximal to the carotid bifurcation, the 10 mm long region of interest was set. An average of three measurements was calculated for both cIMT individually. CCA sonography and offline analysis was conducted by one investigator.

Cardiometabolic risk profile

To evaluate the cardiometabolic risk profile, total cholesterol (TC, mg/dL), low-density lipoprotein cholesterol (LDL-C, mg/dL), high density lipoprotein cholesterol (HDL-C, mg/dL), non-high density lipoprotein cholesterol (non-HDL, mg/dL), triglycerides (mg/dL), apolipoprotein A1 (Apo A1, mg/dL), apolipoprotein B (Apo B, mg/dL), lipoprotein (a) [Lp(a), mg/dL], HbA1c (%) and plasma homocysteine level (µmol/L) was measured. Prior to blood drawing, a fasting period of ≥4 hours was requested. The presence of elevated blood lipids was defined according to adult and pediatric recommendations (26-30). An HbA1c ≥5.7% and a plasma homocysteine level >12 µmol/L was considered to be increased in all study participants, independent of age (31,32).

Primary and secondary outcome variables

For this study, data on vascular function and cardiometabolic risk profile were considered as primary outcome variables. Data on anthropometric variables, medical history, course of pregnancy and birth, maternal level of education, diet quality, level of physical activity and sedentary behavior were defined as secondary outcome variables.

Statistical analysis

For data analysis, SPSS 28 (Release Date 2021, IBM SPSS Statistics for Windows, version 28.0, IBM Corp., Armonk, NY, USA) was used. The chi-square test was applied to compare nominal data. Continuous parameters were tested for normality using the Kolmogorov-Smirnov test and the Shapiro-Wilk test. In case of normal distribution, the unpaired t-test was used. For non-normally distributed continuous variables the Mann-Whitney-U test was utilized. For correlation analysis of normally distributed variables, the Pearson's correlation coefficient was applied. For correlation analysis of non-normally distributed variables, the Spearman's correlation was used. By using the Cocor software, z-scores were generated enabling the statistical comparison of correlations (33). A range between −1.96 and 1.96 at a 95% confidence level was defined as a normal Z-score level. Normally distributed data is presented as mean ± standard deviation (SD) and non-normally distributed data as median [interquartile range (IQR)]. A P<0.05 was regarded as statistically significant.

Results

Patient's characteristics

In total, 70 ART subjects and 86 spontaneously conceived peers were recruited for this study. Within the ART group, one patient was excluded due to history of T-cell lymphoma, one due to history of heart surgery, one due to GIFT and one due to the incomplete data assessment. The final analysis included 66 ART subjects (50 ICSI, 16 IVF) and 86 spontaneously conceived peers.

Within the ART group, one subject presented with long QT syndrome, one with bicuspid aortic valve, one with questionable history of myocarditis, one with history of hypercholesterolemia and one with hypothyroidism. Three ART subjects used oral contraceptives, one L-thyroxine and one methylphenidate. Six control subjects were on oral contraceptives, one on bisoprolol due to chronic migraine and one on methylphenidate. Three ART subjects and 2 controls were smoking (P=0.653).

There were no significant differences in age [11.31 (8.10–18.00) *vs.* 11.85 (8.72–18.27) years, P=0.373] and sex (females 57.58% *vs.* 51.16%, P=0.432) between the ART and the control group. The mean age was 12.61 years (absolute range: 4.41–24.38 years) within the ART group and 13.43 years (absolute range: 4.34–26.05 years) within the control group. Twenty-nine ART subjects and 31 controls were <10 years of age. Twenty-one ART subjects and 33 controls were between ≥10 and <18 years of age. Sixteen ART subjects and 22 controls were ≥18 years of age.

Anthropometric variables, including bodyweight, body height, BMI and weight classification, did not display significant differences between both groups. ART subjects showed, compared to spontaneously conceived peers, a significantly higher BFP.

Regarding the course of pregnancy and birth, ART subjects demonstrated a significantly lower birth weight as well as gestational age. Maternal age at birth and the prevalence of multiple pregnancy were significantly higher in the ART group. The remaining variables, including maternal BMI at conception, prevalence of gestational diabetes, prevalence of maternal blood pressure during pregnancy ≥140/90 mmHg as well as maternal educational level, were not significantly different between both groups.

Detailed information on patient's characteristics is given in *Table 1*.

Adherence to Mediterranean diet, level of physical activity and sedentary behavior

ART subjects and spontaneously conceived peers did not differ significantly in adherence to Mediterranean diet, level of physical activity and sedentary behavior. This was the case for adult as well as for pediatric subjects. *Table 2* summarizes data on adherence to Mediterranean diet, level of physical activity and sedentary behavior for adult as well as for pediatric subjects.

Vascular function

No significant differences in vascular function were demonstrated between ART subjects and spontaneously conceived peers. AIx@75 tended to be higher within the ART group, however, did not reach statistical significance. *Table 3* visualizes data on vascular function for both groups.

Cardiometabolic risk profile

Blood draws were taken in 65 ART subjects and 83 spontaneously conceived peers for the assessment of cardiometabolic risk profile. ART subjects displayed significantly lower levels of triglycerides compared to spontaneously conceived peers. The remaining blood lipids, HbA1c and homocysteine did not demonstrate significant differences between both groups. Interestingly, the prevalence of Lp(a) ≥30 and ≥50 mg/dL tended to be higher within the ART group, however, did not reach statistical significance. *Table 4* summarizes data on cardiometabolic

Table 1 Patients' characteristics

Variable	ART (n=66)	Control (n=86)	P value
Age (years)	11.31 [8.10–18.00]	11.85 [8.72–18.27]	0.373
Female	38 (57.58)	44 (51.16)	0.432
Body weight (kg)	36.95 [23.30–58.60]	42.70 [29.05–59.25]	0.213
Body height (cm)	145.00 [124.50–166.25]	157.00 [133.38–170.25]	0.085
BMI (kg/m^2)	16.77 [15.04–20.86]	17.66 [15.43–21.05]	0.459
Underweight	4 (6.06)	6 (6.98)	1.00
Normal weight	57 (86.36)	74 (86.04)	
Overweight	5 (7.58)	6 (6.98)	
Obese	–	–	
Body fat percentage (%)[1]	19.30 [15.80–26.02]	15.91 [13.21–21.00]	0.007**
Course of pregnancy and birth			
Birth weight (g)[2]	2,985.00 [2,362.50–3,240.00]	3,440.00 [3,210.00–3,670.00]	<0.001***
Gestational age (weeks)[3]	38.00 [36.00–39.50]	39.00 [38.00–40.00]	<0.001***
Maternal age at birth (years)[4]	35.41±3.74	33.07±4.10	<0.001***
Multiple pregnancy	21 (31.82)	2 (2.32)	<0.001***
Maternal BMI at conception (kg/m^2)[5]	22.49 [20.39–24.81]	21.38 [20.24–22.72]	0.100
Gestational diabetes[6]	3 (5.36)	3 (4.23)	1
Maternal blood pressure during pregnancy ≥140/90 mmHg[7]	0 (0)	3 (6.38)	0.289
Maternal educational level[8]	4 [3–5]	5 [4–5]	0.241

Data is presented as mean ± SD for normally distributed parameters and as median [IQR] for non-normally distributed parameters. Nominal data is presented as n (%). **, P≤0.01; ***, P≤0.001. [1], 85 control subjects were included in the analysis. [2], 64 ART subjects and 79 control subjects were included in the analysis. [3], 61 ART subjects and 77 control subjects were included in the analysis. [4], 65 ART subjects were included in the analysis. [5], 46 ART subjects and 61 control subjects were included in the analysis. [6], 56 ART subjects and 71 control subjects were included in the analysis. [7], 28 ART subjects and 47 control subjects were included in the analysis. [8], 44 ART subjects and 52 control subjects were included in the analysis. Maternal educational level was assessed according to the German educational system: no school leaving qualification [0], lower secondary school leaving certificate [1], intermediate secondary school leaving certificate [2], general qualification for university entrance [3], completed apprenticeship [4], completed university degree [5]. ART, assisted reproductive technologies; BMI, body mass index; SD, standard deviation; IQR, interquartile range.

risk profile in detail for both groups.

Correlation analysis

By conducting a correlation analysis, the effect of age on vascular function was investigated within the ART and the control group. Observed Z-scores (Z_{obs}) ranged between 0.40 and 1.54, indicating no significant differences between the correlations of both groups (*Table 5*).

Discussion

The present study included 66 ART subjects and 86 spontaneously conceived peers. Special care was taken to match both groups by age and gender as well as lifestyle factors (e.g., diet quality, level of physical activity, sedentary behavior). In contrast to previous studies (5,6,9), we were not able to display significant differences in vascular function between ART subjects and spontaneously conceived peers. To investigate the influence of age on

Table 2 Adherence to Mediterranean diet, level of physical activity and sedentary behavior

Variable	ART (n=66)	Control (n=86)	P value
Adult study participants	n=16	n=22	
MEDAS	6.06±2.49	7.27±1.67	0.081
Total MET (min/week)[1]	5,574.67±4,244.85	4,439.64±2,411.40	0.360
Recreational MET (min/week)[2]	1,920.00 (675.00–5,160.00)	1,600.00 (720.00–2,790.00)	0.570
Muscle strengthening activities (times/week)[1]	1.00 (0.00–2.00)	2.00 (0.00–3.00)	0.433
Sedentary behavior (min/day)	440.63±159.02	409.09±139.35	0.520
Minor study participants	n=50	n=64	
KIDMED	6.24±2.33	6.92±2.11	0.105
Moderate and/or vigorous physical activities (min/day)[3]	90.00 (60.00–127.50)	90.00 (60.00–120.00)	0.258
Vigorous, muscle strengthening and/or bone strengthening activities (times/week)	3.00 (2.00–5.00)	3.00 (2.00–4.00)	0.986
Sedentary behavior (min/day)[4]	360.00 (270.00–420.00)	420.00 (300.00–480.00)	0.134

Data is presented as mean ± SD for normally distributed parameters and as median (IQR) for non-normally distributed parameters. [1], 15 ART subjects were included in the analysis. [2], 14 ART subjects were included in the analysis. [3], 49 ART subjects and 63 control subjects were included in the analysis. [4], 49 ART subjects were included in the analysis. ART, assisted reproductive technologies; MEDAS, Mediterranean diet adherence score; MET, metabolic-equivalent; KIDMED, Mediterranean diet quality index for children and adolescents; BMI, body mass index.

Table 3 Vascular function

Variable	ART (n=66)	Control (n=86)	P value
SBP (mmHg)	113.74±12.10	113.22±8.96	0.768
Elevated SBP	17 (25.76)	14 (16.27)	0.151
DPB (mmHg)	64.33 (59.00–72.00)	63.50 (59.00–71.25)	0.873
Elevated DBP	6 (9.09)	6 (6.98)	0.632
MAP (mmHg)	87.00 (80.75–94.00)	86.00 (81.00–93.00)	0.929
cSBP (mmHg)[1]	99.50±12.69	98.45±10.45	0.588
cDBP (mmHg)[1]	66.00 (61.00–73.17)	65.50 (61.00–73.00)	0.936
Heart rate (bpm)	74.17±13.17	72.74±13.39	0.513
AIx@75 (%)[1]	19.18±11.80	15.54±11.09	0.054
Endothelial function			
RHI[2]	1.48 (1.21–1.92)	1.47 (1.21–1.97)	0.818
Intima-media thickness of the common carotid artery			
cIMT (mm)[3]	0.44±0.03	0.44±0.03	0.965

Data is presented as mean ± SD for normally distributed parameters and as median (IQR) for non-normally distributed parameters. [1], 65 ART subjects were included in the analysis. [2], 58 ART subjects and 81 control subjects were included in the analysis. [3], 62 ART subjects and 83 control subjects were included in the analysis. ART, assisted reproductive technologies; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; cSBP, central systolic blood pressure; cDBP, central diastolic blood pressure; AIx@75, augmentation index averaged to a heart rate of 75 bpm; RHI, reactive hyperemia index; cIMT, intima-media thickness of the common carotid artery; SD, standard deviation; IQR, interquartile range.

Table 4 Cardiometabolic risk profile

Variable	ART (n=65)	Control (n=83)	P value
TC (mg/dL)	169.89±29.06	167.51±26.63	0.604
Increased TC	10 (15.38)	11 (13.25)	0.712
LDL-C (mg/dL)	92.38±24.04	94.92±22.79	0.514
Increased LDL-C	8 (12.31)	10 (12.05)	0.962
HDL-C (mg/dL)	68.00 (54.00–78.00)	62.00 (55.00–74.00)	0.166
Decreased HDL-C	4 (6.15)	3 (3.61)	0.700
Non-HDL-C (mg/dL)	100.43±25.87	103.24±25.30	0.508
Increased non-HDL-C	7 (10.77)	4 (4.82)	0.213
Triglycerides (mg/dL)	60.00 (43.00–85.50)	73.00 (53.00–103.00)	0.036*
Increased triglycerides	4 (6.15)	13 (15.66)	0.072
Apo A1 (mg/dL)	157.00 (140.50–171.50)	148.00 (137.00–172.00)	0.287
Decreased Apo A1	0 (0)	0 (0)	–
Apo B (mg/dL)	77.58±17.61	78.43±18.15	0.775
Increased Apo B	3 (4.62)	6 (7.22)	0.732
Lp(a) (mg/dL)	6.00 (5.00–33.00)	6.00 (5.00–13.00)	0.377
≥30	16 (24.62)	11 (13.25)	0.076
≥50	13 (20.00)	8 (9.64)	0.073
HbA1c (%)[1]	5.18±0.37	5.27±0.28	0.088
≥5.7%[1]	9 (13.85)	6 (7.32)	0.194
Homocysteine (μmol/L)[2]	9.17±2.35	9.03±3.06	0.777
Homocysteine >12 μmol/L[2]	8 (16.33)	12 (17.39)	0.879

Data is presented as mean ± SD for normally distributed parameters and as median (IQR) for non-normally distributed parameters. Nominal data is presented as n (%). *, P<0.05. [1], 82 control subjects were included in the analysis. [2], 49 ART subjects and 69 control subjects were included in the analysis. ART, assisted reproductive technologies; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; non-HDL-C, non-HDL cholesterol; Apo A1, apolipoprotein A1; Apo B, apolipoprotein B; Lp(a), lipoprotein (a); SD, standard deviation; IQR, interquartile range.

vascular function, subjects at different developmental stages (children, adolescents, adults) were included to conduct a correlation analysis. The results of the current study do not indicate that the vascular system of ART individuals ages more profoundly compared to the one of spontaneously conceived controls.

Cardiovascular function in the ART offspring

Comparison to previous findings

Despite ART being used to treat infertility for over 40 years, there is still limited data on the health outcome of its offspring. To date, data on the long-term cardiovascular outcome of ART individuals is relatively sparse and rather inconsistent. A well-known Swiss study of Scherrer *et al.* described distinct vascular alterations visualised by a generalized endothelial dysfunction, an increased blood pressure and arterial stiffness as well as an elevated cIMT in ART children (6). A follow-up study of the authors confirmed the persistence of these vascular alterations in adolescent ART individuals (5). Moreover, the findings of systemic and pulmonary vascular dysfunction in a cohort of 65 ART singletons (mean age: 11.10±2.40 years) reinforces the conjecture of an elevated cardiovascular risk within this cohort (7). The assessment of cardiovascular health in a cohort study including 382 children who were conceived

Table 5 Correlation analysis between age and vascular function

Variable	ART (n=66)		Control (n=86)		Z_{obs}
	r	P value	r	P value	
SBP	0.706	<0.001***	0.634	<0.001***	0.78
DPB	0.644	<0.001***	0.509	<0.001***	1.22
MAP	0.712	<0.001***	0.632	<0.001***	0.88
cSBP[1]	0.774	<0.001***	0.715	<0.001***	0.79
cDBP[1]	0.644	<0.001***	0.467	<0.001***	1.54
Heart rate	−0.422	<0.001***	−0.495	<0.001***	0.55
AIx@75[1]	−0.387	0.001***	−0.443	<0.001***	0.40
Endothelial function					
RHI[2]	0.703	<0.001***	0.627	<0.001***	0.78
Intima-media thickness of the common carotid artery					
cIMT[3]	0.282	0.027*	0.191	0.083	0.56

[1], 65 ART subjects were included in the analysis. [2], 58 ART subjects and 81 control subjects were included in the analysis. [3], 62 ART subjects and 83 control subjects were included in the analysis. *, P<0.05; ***, P≤0.001. ART, assisted reproductive technologies; Z_{obs}, observed Z-score; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; cSBP, central systolic blood pressure; cDBP, central diastolic blood pressure; AIx@75, augmentation index averaged to a heart rate of 75 bpm; RHI, reactive hyperemia index; cIMT, intima-media thickness of the common carotid artery.

through ART and 382 control subjects (mean age: 7.20±1.21 *vs.* 7.20±1.21 years) supports the perception of abnormal vascular health in ART individuals (34). The examined ART subjects displayed elevated blood pressure as well as distinct changes in their left ventricular structure compared to spontaneously conceived controls (34). In a review and meta-analysis by Guo *et al.* the cardiovascular health of 2,112 IVF/ICSI subjects and 4,096 spontaneously conceived peers was investigated (9). A significantly higher blood pressure, an increased vessel wall thickness as well as a decreased cardiac diastolic function was detected within the IVF/ICSI cohort (9).

In contrast, a study conducted by Halliday *et al.* could not confirm the above-mentioned findings in a large cohort of young ART adults (10). Compared to spontaneously conceived peers, the authors could not find significant differences in vascular function measured by blood pressure, pulse wave velocity and cIMT. Metabolic markers, such as conventional blood lipids, fasting blood glucose and fasting insulin, were not significantly altered between both groups (10). A population-based cohort study, including 122,429 ART subjects and 7,574,685 spontaneously conceived peers from Norway, Sweden, Finland, and Denmark, reinforces these findings (35). No significant differences in the risk for cardiovascular disease (e.g., ischemic heart disease, cardiomyopathy, heart failure, cerebrovascular disease) were demonstrated between both groups (35). Another study by Shiloh *et al.* compared the number of hospitalizations due to cardiovascular disease (e.g., valvular disorders, arterial hypertension, cardiac arrhythmias, ischemic heart disease) between a pediatric IVF group (n=2,603), a pediatric ovulation induction group (n=1,721) and a pediatric control group (n=237,863) (36). Between groups, no significant differences in hospitalizations due cardiovascular disease were found (36). The cohort study of Wijs *et al.* including 163 ART subjects and 1,457 controls (age range: 13–21 years) did also not confirm the hypothesis of an impaired cardiometabolic health in ART offspring (37). Blood lipids, glucose, insulin, arterial stiffness and blood pressure were evaluated and mostly did not show any statistical differences (37). In some parameters, such as BMI, waist circumference and arterial stiffness, the ART group displayed an even more favourable profile (37). In accordance with the above-mentioned findings as well as with previous publications of our departments, the results of the current study do not indicate significant impairments of cardiovascular function in a cohort of children, adolescents and young adults conceived after using ART compared to spontaneously conceived peers (11,38).

Pathophysiological considerations

Increased oxidative stress levels

The health of the ART offspring has been an omnipresent discussion since its introduction in 1978 (39). It is assumed that some undesired health consequences are linked with the ART procedure itself as increased oxidative stress levels were demonstrated (40). The elevated oxidative levels may be driven by various factors during the ART procedure (e.g., cryopreservation, pH fluctuations, temperature fluctuations, culture media) as well as a lack of natural antioxidant mechanisms (40). In addition, women who suffer from infertility as well as mothers of an advanced age tend to have higher oxidative stress levels (40,41). In accordance with literature (42), ART mothers of the current study were significantly older when giving birth. Moreover, pregnancy complications as well as perinatal risk factors associated with ART (e.g., hypertensive disorders, gestational diabetes, prematurity) are linked with increased oxidative stress levels and are more frequently linked with ART pregnancies (40,43). As the cardiovascular system is one of the first to mature during fetal development, it is particularly sensitive to altered environmental stimuli (40). Epigenetic modifications due to elevated oxidate stress levels can result in vascular dysfunction at adult age (40). Within the last years, updated ART protocols (e.g., improved handling of oocytes, reduced exposure to atmospheric oxygen concentrations, modified culture media) have led to a better management of oxidative stress levels (41). Potentially, this might partially explain the discrepancies found in literature regarding the cardiovascular morbidity of the ART offspring.

Pregnancy complications and perinatal risk factors

The fetal origins hypothesis suggests that the intrauterine environment plays a crucial role during fetal development (44,45). If the fetus is exposed to an adverse intrauterine environment (e.g., maternal hypertensive disorder, gestational diabetes, maternal excess weight, prematurity, multiple pregnancy), an increased morbidity might be present in later life (44,45). Interestingly, a higher prevalence of pregnancy complications and perinatal risk factors can be observed after the use of ART. A meta-analysis of Qin *et al.* reported higher incidences of maternal hypertension [relative risk (RR): 1.30], gestational diabetes (RR: 1.31), preterm birth (RR: 1.71), very preterm birth (RR: 2.12) and small for gestational age (RR: 1.35) within ART cohorts compared to spontaneously conceived peers (43). Preeclampsia belongs to the group of maternal hypertensive disorders and is numerously described in pregnancies following ART (46). Women who underwent ART have a 1.71-fold higher risk of preeclampsia than those who conceived spontaneously (46). Individuals who were exposed to preeclampsia in-utero show higher SBP and DBP compared to peers (47). In the current study, no significant differences in maternal BMI at conception, prevalence of gestational diabetes, or maternal blood pressure during pregnancy ≥140/90 mmHg were displayed between both groups. Multiple pregnancy occurs in one of five IVF cycles and was also more present in the examined ART cohort (42,48). In accordance with literature (43,49), ART subjects displayed a significantly lower gestational age and birth weight in comparison to spontaneously conceived peers in this study. This needs to be addressed as prematurely born children show an elevated risk for arterial hypertension, excess weight as well as glucose and lipid metabolism disorders (50,51).

Parental cardiovascular morbidity

The literature suggests that individuals who suffer from infertility present an increased cardiovascular morbidity. Murugappan *et al.* revealed that postmenopausal women with a history of infertility show a moderately higher risk for atherosclerotic cardiovascular disease compared to peers (52). A cross-sectional analysis among 744 women in the United States evaluated the association between self-reported infertility and cardiovascular events (53). Interestingly, the authors found that women with a history of infertility exhibit 1.83 higher odds of having experienced a cardiovascular event (53). Men with infertility or with semen abnormalities also display a higher risk for cardiovascular disease including arterial hypertension, peripheral vascular disease and ischemic heart disease (54,55). A Danish study demonstrated a strong association between sperm concentration and subsequent hospitalization for cardiovascular disease in a cohort of 4,712 men seen for infertility (56). Potentially, couples who suffer from infertility and thus seek ART treatment pass down certain cardiovascular risk factors to their offspring.

Elevated Lp(a) levels are suggested to be a risk factor for atherosclerotic cardiovascular disease (27). Around 90% of an individual's Lp(a) level is inherited (27). A study by Krause *et al.* identified elevated Lp(a) levels as a risk factor for unexplained recurrent miscarriage in Caucasian women (57). In the current study, the presence of Lp(a) ≥50 mg/dL tended to be higher within the examined ART cohort.

Moreover, Vlachopoulos *et al.* demonstrated that children conceived through IVF display significantly higher Lp(a) levels compared to children conceived through ICSI and spontaneously conceived peers (58). To the best of our knowledge, limited data on the prevalence of elevated Lp(a) levels in infertile individuals who sought ART treatment exist. A general Lp(a) screening of such individuals could potentially help identifying families at increased cardiovascular risk. Hence, further research on this matter is required.

Lifestyle factors

Unfavourable lifestyle habits such as poor dietary habits, a low level of physical activity and increased sedentary behavior can contribute to an elevated cardiovascular risk profile (18,21). In this study, diet quality, level of physical activity and sedentary behavior did not differ significantly between both groups. In addition, conventional blood lipids and HbA1c, which can be negatively influenced by poor diet habits, did not show significant differences between ART subjects and controls. Triglycerides were significantly lower in ART study participants which could be due to a potentially lower adherence to the required fasting period ≥4 hours within the control group. While BMI was comparable between both groups, ART subjects displayed a significantly higher BFP compared to spontaneously conceived peers. These findings are in line with results of Ceelen *et al.* who described a disturbed body fat composition in IVF children (59). A population-based cohort study including 122,429 children born after ART and 7,574,685 spontaneously conceived children detected a slightly increased risk of obesity within the ART cohort (35) A recent study by Elhakeem *et al.* suggests that ART individuals demonstrate lower central and total adiposity in childhood but potentially higher levels in adulthood (60). Excess weight and BFP count as important cardiovascular risk factors (61). Moreover, increased BFP is highly associated with arterial hypertension, even if a normal BMI is present (62). Therefore, more studies evaluating BFP as well as cardiovascular morbidity in adult ART subjects are required.

Strengths and limitations

This study was designed as a single center study within Germany and included 66 ART and 86 spontaneously conceived peers. While special emphasis was put on precise age- and gender matching, a generalization of the demonstrated results does not apply. The sample size of the current study can be regarded as adequate. However, ART subjects can display various comorbidities and risk factors (e.g., prematurity, low birth weight) that could potentially impact cardiovascular function. Therefore, larger ART follow-up studies are required in the future. To investigate the influence of age on vascular function, subjects at different developmental stages (children, adolescents, adults) were included to conduct a correlation analysis. Consequently, a large age range was present in both groups. Intentionally, ART subjects with adverse perinatal conditions were included in this study to preserve the “true” cardiovascular risk profile of this cohort. The exclusion of these participants would have substantially reduced the sample size. However, it should be noted that the large age range as well as the inclusion of subjects with adverse perinatal conditions may have influenced the results of the current study.

Data on the course of pregnancy and birth was evaluated retrospectively by screening medical records and interviewing both parents. For some study participants a loss of information was unavoidable as medical records were missing or not fully completed by previous medical professionals. As the present study was not blinded, a potential participation bias cannot be fully ruled out. Nonetheless, parameters of pulse wave analysis and endothelial function were recorded automatically by devices.

For this study, three consecutive office blood pressure measurements were executed and averaged to enhance data validity. However, 24-hour ambulatory blood pressure monitoring is considered the gold standard for the assessment of arterial hypertension and its data should be included in future research. The Mobil-O-Graph® complies to the criteria of the European Society of Hypertension and is therefore recommended as blood pressure device for clinical practice (63). Compared to other devices, it is suggested that the Mobil-O-Graph® underestimates markers of pulse wave analysis (64).

To minimize operator-dependent assessment of endothelial function, the EndoPAT™2000 device was utilized enabling RHI calculation through peripheral artery tonometry (65). However, a study by Allan *et al.* indicates that flow-mediated dilatation might be a more sensitive measure of endothelial function in patients with peripheral arterial disease (66).

A fasting period ≥4 hours and an alcohol abstinence ≥24 hours prior to study participation was required. However, future studies should apply a stricter standardization of diet as well as physical activity ≥12 hours prior to vascular evaluation. Post-exercise hypotension, defined as a decline of SBP and DBP after exercise, can last between 2 and 13 hours after exercise (67). Therefore, an adjustment for this potential cofounder should be applied in future studies.

Modern developments of ART methods and their impact on the offspring's cardiovascular risk profile should be closely observed in the future. For a more precise cardiovascular risk stratification of the ART cohort, larger sample sizes, preferably at adult age, will be required in the future. Therefore, multi-center studies with a longitudinal study design should be established.

Conclusions

The results of the current study do not indicate a significantly lower vascular function in a cohort of children, adolescents and young adults conceived through ART compared to spontaneously conceived peers. Future studies should address the prevalence of elevated Lp(a) levels in infertile individuals who sought ART treatment. In addition, more studies evaluating BFP as well as cardiovascular morbidity in adult ART subjects are required. Ultimately, for a more precise cardiovascular risk stratification, multi-center studies with larger ART sample sizes, preferably at adult age, are required in the future.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Medical Faculty of LMU Munich (Munich, Germany; No. 20-0844) on the 27th of December 2020. Informed consent for this study and publication was obtained from all study participants and in minor study participants additionally from parents or legal guardians.

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