Increased blood pressure and impaired endothelial function after accelerated growth in IVF/ICSI children

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STUDY QUESTION: What is the effect of growth velocity (height and weight) in early infancy on metabolic end-points and endothelial function in children born after ART?

SUMMARY ANSWER: Neonatal, infant and childhood growth is positively related to blood pressure in 9-year-old IVF/ICSI offspring, while growth in childhood was negatively associated with endothelial function.

WHAT IS KNOWN ALREADY: Offspring of pregnancies conceived after ART are at risk for later cardiometabolic risk factors. It is well established that early growth is related to numerous later cardiometabolic risk factors such as high blood pressure. This concept is known as the Developmental Origin of Health and Disease theory.

STUDY DESIGN, SIZE, DURATION: The relation between early growth and later cardiometabolic risk profile was studied in the MEDIUM-KIDS study, a prospective observational cohort study in children born after an IVF/ICSI treatment. In 131 children (48.1% males) at the average age of 9.4 years, cardiometabolic outcomes were assessed and growth data from birth until age 9 years were collected from child welfare centers.

PARTICIPANTS/MATERIALS, SETTINGS, METHODS: The following cardiometabolic outcomes were assessed: blood pressure, skinfolds, lipid spectrum, hair cortisone and glucose and insulin levels. Data on maximum skin perfusion after transdermal delivery of acetylcholine as a measure of endothelial function were collected.

Growth charts were obtained electronically from child welfare centers, which offer free consultations and vaccinations to all Dutch children. At these centers, height and weight are recorded at predefined ages. Growth was defined as z-score difference in weight between two time points. Multivariable linear regression analysis was used to model the relation between growth and cardiometabolic outcomes. The following growth windows were studied simultaneously in each model: 0–1 month, 1–3 months, 3–6 months, 6–11 months, 11–24 months and 2–6 years. The model was adjusted for height growth in all intervals except for 0–1 month.

MAIN RESULTS AND THE ROLE OF CHANCE: In multivariable linear regression analyses, multiple growth windows were positively associated with blood pressure, for example growth from 2–6 years was significantly related to systolic blood pressure: $B = 4.13, P = 0.005$. Maximum skin perfusion after acetylcholine was negatively associated with height-adjusted weight gain from 2 to 6 years: $B = -0.09$ (log scale), $P = 0.03$. Several growth windows (weight 1–3 months, 3–6 months, 6–11 months, 11–24 months, 2–6 years) were positively linked with total adiposity. Lipids, glucose tolerance indices and cortisone were not related to growth.

LIMITATIONS, REASONS FOR CAUTION: This study is of modest size and of observational nature, and we did not include a control group. Therefore, we cannot assess whether the observed associations are causal. It is also not possible to analyze if our observations are specific for, or exacerbated in, the ART population. Ideally, a control group of naturally conceived siblings of IVF/ICSI children should simultaneously be studied to address this limitation and to assess the impact of the ART procedure without the influence of parental (subfertility) characteristics.

WIDER IMPLICATIONS OF THE FINDINGS: The results of this study contribute to our understanding of the reported increased risk for hypertension in ART offspring. We speculate that early, accelerated growth may be involved in the reported increased risk for hypertension...
in ART offspring, with endothelial dysfunction as a possible underlying mechanism. However, additional research into the mechanisms involved is required.

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**TRIAL REGISTRATION NUMBER:** NTR4220

**Key words:** IVF/ICSI outcome / cardiovascular / endothelium / infant growth / blood pressure

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**WHAT DOES THIS MEAN FOR PATIENTS?**

This study looked at how the speed with which children grow in early childhood is related to the health of these children at later age. We looked at health measures such as blood pressure and how the blood vessels function at 9 years of age.

Other research had shown that children who were very small at birth and grow fast at a young age have an increased risk for all sorts of diseases related to their heart and blood vessels at a later age.

Children born after an IVF or ICSI treatment are smaller when they are born than children born after natural conception. This means that these children might also be at risk for fast growth at a young age.

In this study, we measured whether the speed that children born after IVF and ICSI grow when they are very young is related to their blood pressure at 9 years of age. We looked at blood pressure and at the quality of the blood vessels and found that children who grew faster in their first month of life showed a higher blood pressure and a reduced quality of their blood vessels when they were 9 years old.

This study shows that fast growth at a young age might be involved in the reported increased risk for high blood pressure in children born after an IVF or ICSI treatment. Further research should be done to find out what the causes of these differences are.

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**Introduction**

Offspring of ART-conceived pregnancies have an increased risk for several cardiometabolic risk factors. These associations probably originate through epigenetic mechanisms in the early embryonic stage (Vroooman and Bartolomei, 2017; Fleming et al., 2018). This fits into the developmental origins of health and disease (DOHaD) concept, which states that early life aspects have lifelong health implications. In IVF or ICSI treatments, the fertilization of the oocyte and early embryo development occur outside the human body and therefore under non-natural circumstances. These processes coincide with epigenetic reprogramming events within the gametes and embryo. During the IVF/ICSI procedure, several environmental variables, such as embryo culture medium, may impact epigenetic reprogramming.

From a vascular perspective, children born after ART display endothelial dysfunction and vascular stiffness compared to controls of similar (and normal) gestational age and birthweight (Scherrer et al., 2012). Furthermore, persistent early cardiac remodeling (Valenzuela-Alcaraz et al., 2013) and increased blood pressure were identified (Ceelen et al., 2008a; Sakka et al., 2010; Valenzuela-Alcaraz et al., 2013). Metabolic changes have also been found in ART children. Compared to naturally conceived controls, fasting glucose levels were higher (Ceelen et al., 2008a), as well as triglycerides (Sakka et al., 2010). A recent meta-analysis showed increased blood pressure and higher fasting insulin levels but a slightly more favorable lipid profile in ART offspring (Guo et al., 2017).

From a growth perspective, ART newborns have an increased risk for premature birth and for low birthweight (Pandey et al., 2012). One would expect that relatively low birthweight would be followed by relatively fast infant growth (regression to the mean), as was shown in a study by Ceelen et al. (2009), at least in late infancy. On the contrary, in another study no rapid weight gain was seen in ART singletons in the first year and no differences were seen in any growth parameter in the first 3 years (Yeung et al., 2016). Also, normal growth in IVF and ICSI children up to 12 years of age was reported in a paper by Basatemur and colleagues (Basatemur et al., 2010). Altogether, it remains unclear whether ART (the procedure itself, parental subfertility characteristics or an indirect effect of the ART procedure on birthweight) predisposes to altered growth in infancy and childhood.

It is well established that early growth is related to numerous later cardiometabolic risk factors (DOHaD concept), for example high blood pressure (Kagura et al., 2016; Taine et al., 2016). There is an ongoing debate about the exact timing of these effects, but early postnatal growth (<3 months) has consistently been linked to later cardiometabolic risk factors (Leunissen et al., 2009a, 2009b; Fabricius-Bjerre et al., 2011; Khuc et al., 2012). Ceelen et al. (2009) analyzed the effects of postnatal growth in IVF children. They found early childhood growth, but not infant growth, to be positively related to later blood pressure (only in IVF) and skinfold thicknesses (both IVF and controls).

In the present study, we aimed to analyze neonatal, infant and childhood growth simultaneously, to study metabolic end-points and to examine endothelial function. We hypothesized a harmful effect of accelerated growth on our cardiometabolic outcome parameters. For reasons of generalizability, we only included healthy children, born at term.

**Materials and Methods**

**Participants**

Parents of all singletons born after an IVF treatment with fresh embryo transfer at Maastricht University Medical Centre between July 2003 and December 2006 were approached to participate in the MEDIUM-KIDS study. In this prospective observational cohort study, 9-year-old children were investigated with regard to cardiometabolic risk profile
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in relation to IVF culture medium (Cook and Vitrolife) (Dumoulin et al., 2010). In total, 47.7% of the potential participants gave informed consent (n = 136). The baseline characteristics at the time of birth of the participating children were comparable to those of the children not participating in the study (Zandstra et al., 2018). Pregnancy and neonatal characteristics were retrieved from the hospital charts. Gestational age was determined by the following formula: (date of birth – oocyte retrieval date) + 14 days. Prematurely born children (<37 weeks gestational age) were excluded from the analysis (n = 5). Two mothers had diabetes of pregnancy. Eight mothers had a hypertensive disorder during pregnancy (one HELLP i.e. hemolysis, elevated liver enzymes, low platelet count, one pre-eclampsia and six gestational hypertension, defined as clinical diagnosis in the hospital charts). These mothers were not excluded from the study. There were no relevant birth defects or later diagnosed illnesses.

Details of the IVF procedures were published previously, as the MEDIUM-KIDS study was part of an earlier study (Dumoulin et al., 2010). Only singletons born after transfer of fresh embryos were included.

Setting

Between March 2014 and December 2016, the participants were invited for a 2.5-h visit to our hospital. Two experienced researchers performed the tests. Information on possible confounders was recorded using a questionnaire completed by the parents during the visit.

Collection of independent variables

Growth data were received electronically from child welfare centers, which offer free consultations and vaccinations to all Dutch children. At these centers, height and weight are recorded. In the present study, we analyzed the data obtained at the approximate ages of 1, 3, 6, 11, 24 and 72 months. The obtained values were converted into sex- and age-specific z-scores by an online calculator (https://groeiweb.pgdata.nl/calculator.asp), by use of data from the Dutch 3rd national growth study (weight) and the Dutch 5th national growth study (height) (Schönbeck et al., 2011; Schönbeck et al., 2013). Birth length was missing in 50.4% of the cases and was therefore not analyzed. Birthweight was collected from the hospital charts and converted into z-scores by use of sex- and parity-specific reference data accurate to a gestational age of 1 day (Visser et al., 2009). Growth was defined as difference in weight z-scores. The following growth windows were studied: 0–1 month, 1–3 months, 3–6 months, 6–11 months, 11–24 months and 2–6 years.

Maternal pre-pregnancy weight and height were retrieved from hospital charts, and pre-pregnancy BMI was calculated. The highest completed maternal education level was dichotomized, high education level being defined as the completion of higher professional education or university. Breastfeeding was reported by the parents and dichotomized (yes/no). Maternal smoking during pregnancy was self-reported and dichotomized (yes/no).

Measurement of dependent variables

Children were measured lightly clothed; height (to the nearest 0.1 cm) and body weight (to the nearest 0.1 kg) were measured using a stadiometer (DGI 250D, The Netherlands) and scale (Seca 704, Germany). Skinfold thicknesses (triceps, biceps, subscapular and suprailiac) were measured in triplicate on the non-dominant side of the body using a Harpenden skinfold caliper (Baty International, UK). Total adiposity was calculated as the sum of the four averaged skinfold thicknesses. The sum of triceps and biceps skinfolds represented peripheral adiposity, and the sum of subscapular and suprailiac skinfolds represented truncal adiposity.

Systolic and diastolic blood pressures were measured in triplicate on the non-dominant arm while the child was sitting after a minimum of 30 min of rest in supine position on a bed. It was measured using a calibrated automatic device (Accutorr Plus, Datascope Inc., Montvale, NJ, USA) and averaged for analysis. All but 26 children gave permission for a venipuncture. Participants who did not fast overnight were excluded from the analyses of blood samples (n = 6). Five participants had incomplete results because not enough blood could be drawn. Fasting plasma glucose was measured using an enzymatic colorimetric assay (Cobas 8000 instrument, Roche Diagnostics, Mannheim, Germany). Fasting insulin was measured in serum using an immunometric assay (XP instrument, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by the following formula: ((insulin (pmol/l)/6.94)·glucose (mmol/l))/22.5. Total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were determined using an enzymatic colorimetric assay (Cobas 8000 instrument, Roche Diagnostics, Mannheim, Germany). Low-density lipoprotein (LDL) was calculated by the Friedewald formula (Rifai et al., 2006).

Hair samples were collected when the child had hair >3 cm and when parents consented. The hair strands (~3 mm in diameter) were collected from the posterior vertex region, as close to the scalp as possible. Cortisone was measured by use of chromatography of the 3-cm hair segment closest to the scalp. This measurement was performed in 116 out of the 131 children.

Laser doppler flowmetry of the forearm was performed to assess vascular function (PeriFlux 5000 system, Perimed A.B., Sweden). Using iontophoresis, acetylcholine and nitroprusside were administered transdermally (Periiont system; Perimed A.B., Sweden) and vasodilatation curves were constructed, as described previously (Touwslager et al., 2012a). Acetylcholine induces endothelium-dependent vasodilation via stimulation of the endothelium, while nitroprusside induces endothelium-independent vasodilatation as a direct nitric oxide donor. Maximum perfusion was recorded in perfusion units. The recordings were analyzed by H.Z. and R. T, who were blinded to the growth patterns and reached consensus about quality criteria, such as movement artifacts.

Ethical approval

The study was registered in the Dutch Trial register (trial number NTR4220), and the local ethics committee approved the study. Both parents of all children gave written informed consent.

Statistical analysis

Insulin values below the detection limit of 12 pmol/l were analyzed as 12 pmol/l. Hair cortisone values below the detection limit of 0.68 pmol/mg hair were similarly analyzed as 0.68 pmol/mg hair. In
Results

The baseline characteristics of the study sample are shown in Table I. We used national reference values based on large cohort studies to compare our population with a general population (Schönbeck et al., 2013). Gestational age and birthweight were normal compared to the general population.

Growth from 0 to 1 month, 3 to 6 months and 2 to 6 years was positively associated with systolic blood pressure at 9 years in the final height-adjusted models, for example growth from 2 to 6 years: $B = 4.13$, $P = 0.005$ (Table II), indicating a 4.13-mmHg rise in blood pressure per 1-unit increase in weight $z$-score between 2 and 6 years. Growth in the first month was also positively related to diastolic blood pressure: $B = 4.26$, $P = 0.004$.

In a paired samples Student’s $t$ test, there was no difference between baseline perfusion in the acetylcholine and nitroprusside protocols ($P = 0.96$). The correlation between baseline perfusion in the acetylcholine and nitroprusside protocols was 0.71 ($P < 0.001$). Maximum perfusion in response to acetylcholine was negatively related to growth from 2 to 6 years: $B = -0.09$ (log scale), $P = 0.03$. This effect size corresponds to a 19.5% decrease in maximum perfusion per one-unit increase in weight $z$-score. There were no significant associations between growth and maximum perfusion after nitroprusside, e.g. Model 3, growth from 2 to 6 years: $B = -0.03$ (log scale), $P = 0.38$.

Total adiposity was positively related to growth in all age windows, except 0–1 month, for example growth from 11 to 24 months: $B = 0.13$ (log scale), $P < 0.001$. This effect size corresponds to a 40.3% increase in total adiposity per one-unit increase in weight $z$-score. In Model 1, truncal: peripheral adiposity ratio was positively related to growth from 11 to 24 months: $B = 0.05$ (log scale), $P = 0.04$; this association was no longer significant in Models 2 and 3 (data not shown).

No significant relationships were identified between growth and cortisol, HOMA-IR, insulin, glucose, triglycerides, total cholesterol: HDL ratio or LDL (data not shown).

Discussion

In this study, we showed that in 9-year-old children born after IVF/ICSI, weight gain from 0 to 1 month was positively related to both systolic and diastolic blood pressure. Moreover, height-adjusted weight gain from 3 to 6 months and 2 to 6 years were positively related to systolic blood pressure. We report clinically relevant effect sizes of 4–5.5 mmHg per one-unit increase in weight $z$-score. The association between growth in early childhood and systolic blood pressure is in line with a previous study in IVF children (Ceelen et al., 2009), although we now add the fact that also infant growth, particularly growth from 0 to 1 month, is an influential growth window. Therefore, we cannot support the notion of a healthy infant growth trajectory in IVF/ICSI children, as postulated by Ceelen et al. (2009). However, it should be noted that our population had somewhat higher (and normal) birthweight than the population analyzed by Ceelen et al. and that our population was born at term (Ceelen et al., 2009).

To our knowledge, we are the first to describe an inverse association between growth in childhood and maximum perfusion in response to acetylcholine in ART offspring. No relationships were shown between growth and maximum perfusion in response to nitroprusside. Therefore, it can be concluded that our results reflect endothelial dysfunction. Endothelial dysfunction precedes atherosclerosis and can be tested by acetylcholine-induced vasodilatation (Puissant et al., 2013).

The identification of a relationship between growth and endothelial function is consistent with a study in non-ART individuals, although this study analyzed growth in the first 2 weeks (Singhal et al., 2004). The relationship is also consistent with a previous study in our hospital in non-ART children up to 2 years of age, although based on this study we expected early infant growth to be of importance (Touwslage et al., 2015). Perfusion measurement by laser doppler was used because of the suitability to use this technique in children. This can however be challenging in children because of movement artifacts and the high variability (Puissant et al., 2013) in these measurements. We have shown previously a good interobserver variability of the obtained signal (Touwslage et al., 2012b), and the high correlation and equality between baseline perfusion in both arms was reassuring. The exact clinical importance of maximum skin perfusion after acetylcholine at 9 years of age is not known, but a 19.5% decrease per one-unit increase in $z$-score appears to be a reasonably large effect size.

ART-conceived offspring are at increased risk for high blood pressure (Guo et al., 2017), possibly through endothelial nitric oxide synthase methylation changes (Rimoldi et al., 2014). ART offspring also display endothelial dysfunction (Scherrer et al., 2012). In turn, endothelial dysfunction plays a role in the development of hypertension (Brandes, 2014). Previously, it was shown that accelerated growth in early childhood in IVF children was associated with an increase in blood pressure, but this was not the case in spontaneously conceived controls (Ceelen et al., 2009). Combining these previous findings with our results, we speculate that early accelerated growth may be involved in the reported increased risk for hypertension in ART offspring, with endothelial dysfunction as a possible underlying mechanism. Accelerated growth could be a ‘second’ hit on an already increased risk for hypertension and endothelial dysfunction in ART offspring. Importantly, most of the studies identifying increased blood pressure in ART offspring did not control for growth, so growth could also be the ‘only’ hit. Alternatively, ART offspring may be extra susceptible to
### Table I  Baseline characteristics of the study population.

|                          | n   | Mean (SD) | Median (IQR) | %   |
|--------------------------|-----|-----------|--------------|-----|
| **General**              |     |           |              |     |
| Males                    | 131 | 48.1      |              |     |
| High maternal education  | 131 | 38.2      |              |     |
| Maternal pre-pregnancy BMI (kg/m²) | 131 | 24.47 (3.15) |          |     |
| **Obstetric**            |     |           |              |     |
| Gestational age (weeks)  | 131 | 39.83 (1.20) |             |     |
| Birthweight (SD)         | 131 | 3422.21 (461.60) |          |     |
| Received breastfeeding    | 131 | 55.7      |              |     |
| Gestational hypertension | 131 | 6.1       |              |     |
| Smoking during pregnancy | 131 | 5.3       |              |     |
| **ART**                  |     |           |              |     |
| Cook medium              | 131 | 45.0      |              |     |
| Maternal age (years)     | 131 | 64.9      |              |     |
| ICSI                     | 131 |           |              |     |
| **Growth**               |     |           |              |     |
| Age at measurement ‘1 month’ (days) | 123 | 29.46 (5.67) |      |     |
| Age at measurement ‘3 months’ (days) | 123 | 93.19 (10.77) |       |     |
| Age at measurement ‘6 months’ (days) | 122 | 181.02 (12.76) |     |     |
| Age at measurement ‘11 months’ (days) | 127 | 345.11 (18.28) |     |     |
| Age at measurement ‘24 months’ (years) | 123 | 2.09 (0.11) |         |     |
| Age at measurement ‘6 years’ (years) | 121 | 5.88 (0.52) |     |     |
| 0–1 month (Δ weight z-score) | 123 | 0.05 (0.81) |     |     |
| 1–3 months (Δ weight z-score) | 123 | 0.37 (0.75) |     |     |
| 3–6 months (Δ weight z-score) | 122 | −0.08 (0.63) |     |     |
| 6–11 months (Δ weight z-score) | 122 | −0.18 (0.61) |     |     |
| 11–24 months (Δ weight z-score) | 122 | −0.28 (0.66) |     |     |
| 2–6 years (Δ weight z-score) | 110 | 0.20 (0.76) |     |     |
| 1–3 months (Δ length z-score) | 110 | 0.44 (0.56) |     |     |
| 3–6 months (Δ length z-score) | 112 | −0.03 (0.50) |     |     |
| 6–11 months (Δ length z-score) | 117 | 0.02 (0.51) |     |     |
| 11–24 months (Δ length z-score) | 119 | −0.07 (0.68) |     |     |
| 2–6 years (Δ length z-score) | 113 | −0.24 (0.54) |     |     |
| **Cardiometabolic**      |     |           |              |     |
| Age on measurement day (years) | 131 | 9.43 (0.33) |     |     |
| BMI on measurement day (kg/m²) | 131 | 17.14 (2.45) |     |     |
| Baseline perfusion acetylcholine protocol (PU) | 121 | 3.73 (8.60) |     |     |
| Maximum perfusion acetylcholine protocol (PU) | 121 | 80.36 (60.69) |     |     |
| Baseline perfusion nitroprusside protocol (PU) | 115 | 3.65 (8.22) |     |     |
| Maximum perfusion nitroprusside protocol (PU) | 115 | 101.51 (69.04) |     |     |
| Systolic blood pressure (mmHg) | 131 | 100.38 (7.43) |     |     |
| Diastolic blood pressure (mmHg) | 131 | 60.05 (6.70) |     |     |
| Sum of skinfolds (mm)     | 131 | 33.66 (26.53) |     |     |
| Total:truncal adiposity ratio | 131 | 0.60 (0.22) |     |     |
| Insulin (pmol/l)          | 96  | 30.65 (28.70) |     |     |
| Glucose (mmol/l)          | 93  | 4.71 (0.34) |     |     |
| HOMA-IR                   | 91  | 0.94 (0.94) |     |     |
| Total:HDL cholesterol ratio | 97  | 2.47 (0.86) |     |     |
| Triglycerides (mmol/l)    | 97  | 0.63 (0.41) |     |     |
| LDL (mmol/l)              | 97  | 2.31 (0.56) |     |     |
| Cortisone (pg/mg hair)    | 116 | 12.68 (7.23) |     |     |

IQR = interquartile range. Δ = delta. PU = perfusion units. HOMA-IR = homeostatic model assessment insulin resistance. HDL = high-density lipoprotein. LDL = low density lipoprotein.
the deleterious effects of accelerated growth. Based on our study and the existing literature, we recommend cardiometabolic follow-up for fast-growing individuals after ART-conceived pregnancies: both for reasons of prevention and for possible pharmacological interventions (for example antioxidants) in the future (Rimoldi et al., 2015).

Growth in all windows except 0–1 month was positively related to total sum of skinfolds. This was not surprising since we defined growth as difference in weight z-score and adjusted the analyses for difference in height z-score. Our results were in agreement with a previous study in IVF children (Ceelen et al., 2009). Extensive evidence links early growth to later obesity in non-ART individuals (Baidal et al., 2016). We did not identify a relationship between growth and an unfavorable ratio of truncal to peripheral adiposity.

Importantly, the identified associations were shown in a term, healthy, normal birthweight group, which was prospectively collected. Cardiometabolic effects of prematurity, a complication of ART, could therefore be excluded. We did not perform an analysis to assess individual accelerated growth, but from the average differences in z-score in each growth window, it can be expected that growth was likely normal compared to the Dutch population. This is in line with...
the study by Yeung et al. (2016) which did not observe any risk for accelerated growth in the first year in ART children, rapid weight gain being defined as >0.50 SD. This apparently normal growth is important for reasons of generalizability (both towards the majority of ART conceived offspring and to the general population), which we consider to be good in our study. Given our simultaneous analyses of all infant growth windows and concurrent analysis of height gain in Model 3, our growth measures can be interpreted independently of each other, and as weight gain in excess of what can be expected based on height gain. Optimal growth trajectories remains to be elucidated (Singhal, 2017), especially for ART offspring. Promising interventions for prevention of fast infant growth include breastfeeding (Carling et al., 2015), the modification of protein content in formula (Patrò–Golab et al., 2016) and responsive parenting intervention programs (Savage et al., 2016).

This study is of modest size and of an observational nature, and we did not include a control group. Therefore we cannot assess whether the observed associations are causal. It is also not possible to analyze if our observations are specific for, or exacerbated in, the ART population. We are unable to report whether ART children have altered growth patterns. Furthermore, a possible increased risk for cardiovascular risk factors in ART offspring, regardless of growth, cannot be concluded. Ideally, a control group of naturally conceived siblings of IVF/ICSI children should simultaneously be studied to address this and to assess the impact of the ART procedure without the influence of parental (subfertility) characteristics. Data on birth length was poor, and to assess the impact of the ART procedure without the influence of IVF/ICSI children should simultaneously be studied to address this.

In conclusion, our study showed that neonatal, infant and childhood growth was positively related to blood pressure in IVF/ICSI offspring. Growth in childhood was negatively associated with endothelial function. This is an important step in understanding the increased risk for hypertension in ART offspring.

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Authors’ roles

All authors fulfilled the criteria for authorship. A.v.M. and H.Z. initiated the study; H.Z. collected the data; R.T, H.Z. and A.v.M. analyzed the data; A.v.M, H.Z., J.D., L.Z. and R.T interpreted the data. All authors commented on the draft and have seen and approved the final version.

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Conflict of interest

The authors have no conflict of interest to declare.

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