Cardiometabolic Differences in Children Born After *in Vitro* Fertilization: Follow-Up Study

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Context: Increasing evidence suggests that adverse conditions during early prenatal life are associated with cardiometabolic dysfunction in postnatal life. *In vitro* fertilization (IVF) conception may be an early prenatal life event with long-term health consequences.

Objective: Our objective was to investigate several cardiometabolic measures in 8- to 18-yr-old IVF singletons and spontaneously conceived controls born from subfertile parents.

Design and Setting: This follow-up study was conducted at the VU University medical center, Amsterdam, The Netherlands.

Participants: Blood pressure was examined in 225 IVF-conceived children and 225 age- and gender-matched spontaneously conceived control children. Several indicators of insulin resistance were studied in a pubertal subpopulation (131 IVF children and 131 controls).

Main Outcome Measures: Blood pressure, fasting glucose, and fasting insulin were determined.

Results: Systolic and diastolic blood pressure levels were higher in IVF children than controls (109 $\pm$ 11 *vs.* 105 $\pm$ 10 mm Hg, $P < 0.001$; and 61 $\pm$ 7 *vs.* 59 $\pm$ 7 mm Hg, $P < 0.001$, respectively). Children born after IVF were also more likely to be in the highest systolic and diastolic blood pressure quartiles (odds ratio = 2.1, 95% confidence interval 1.4, 3.3; odds ratio = 1.9, 95% confidence interval 1.2, 3.0, respectively). Furthermore, higher fasting glucose levels were observed in pubertal IVF children (5.0 $\pm$ 0.4 *vs.* 4.8 $\pm$ 0.4 mmol/liter in controls; $P = 0.005$). Blood pressure and fasting glucose differences could not be explained by current body size, birth weight, and other early life factors or by parental characteristics, including subfertility cause.

Conclusions: These findings highlight the importance of continued cardiometabolic monitoring of IVF-conceived children and might contribute to current knowledge about periconceptional influences and their consequences in later life. **(*J Clin Endocrinol Metab* 93: 1682–1688, 2008)**

According to the "developmental origins of adult disease" hypothesis, adaptive responses to environmental stimuli during critical or sensitive periods in early life may have long-lasting consequences due to permanent reprogramming of physiological, metabolic, and endocrine key systems (1, 2). Specific critical windows in prenatal development for long-term programming of cardiovascular and metabolic dysfunction have been identified. In rats and sheep, maternal undernourishment solely during either the periconceptional or preimplantation period induced irreversible programming of hypertension and cardiovascular dysfunction among offspring (3–5). Maternal undernutrition during the periconceptional period has also been associated with altered fetal metabolism in sheep (6). Furthermore, animal studies have shown that conditions during assisted

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Abbreviations: BMI, Body mass index; CI, confidence interval; HOMA, homeostasis assessment model; HPA, hypothalamo-pituitary-adrenal; IVF, *in vitro* fertilization; SDS, SD score; VUmc, VU University medical center.

reproductive technologies may interfere with normal programming of early development with subsequent postnatal developmental consequences (7), including aberrant cardiovascular physiology (8).

In humans, little is known about the effects of poor periconceptional and/or preimplantation environment on postnatal cardiovascular and metabolic functioning. Concerns have recently been raised about the children born after subfertility treatment (9). Accumulating evidence suggests that *in vitro* fertilization (IVF) singletons are at increased risk for adverse perinatal outcome (10, 11). It is still unclear whether the IVF process in humans could affect the vulnerable processes occurring during early embryonic development with long-term health consequences. Therefore, we studied postnatal growth and development in 8- to 18-yr-old children born from subfertile parents who were either successfully treated with IVF or conceived spontaneously. The main objective of the present study was to investigate blood pressure and indicators of insulin resistance in IVF and control children.

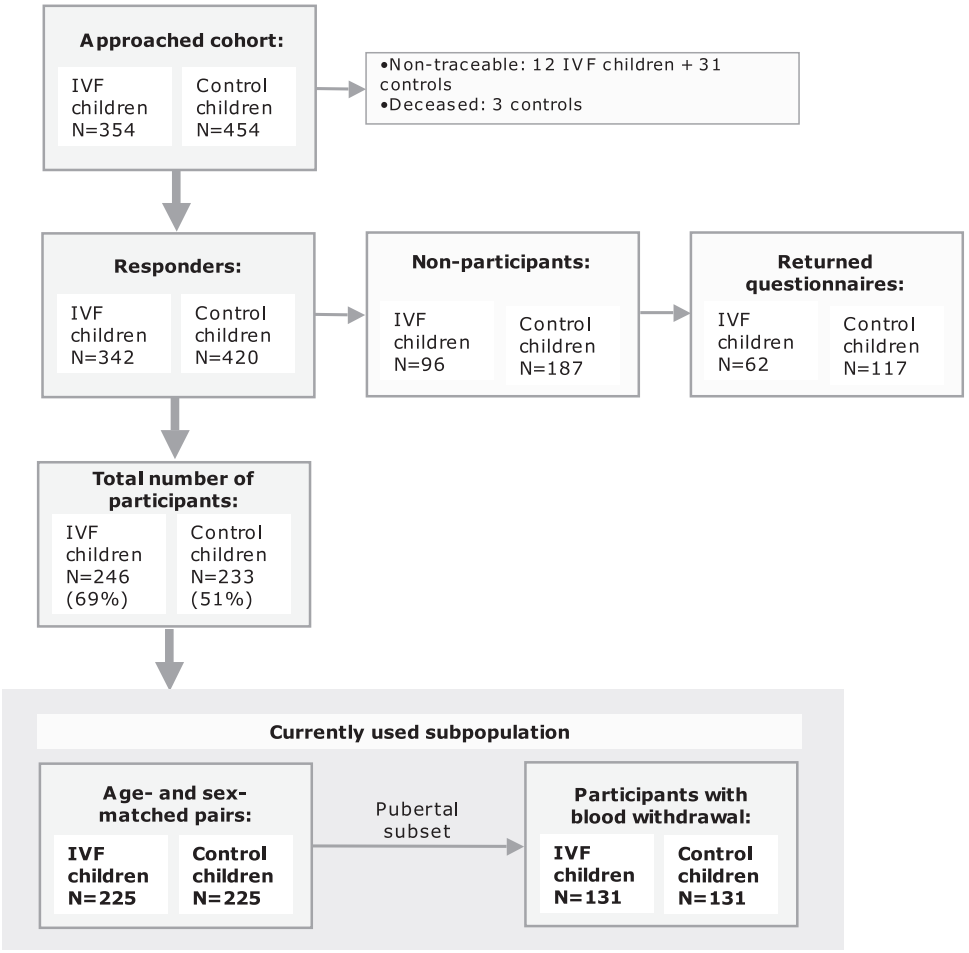

FIG. 1. Overview of the inclusion process.

Subjects and Methods

Study population

The OMEGA study is a Dutch retrospective cohort study aimed to examine long-term health effects of hormone stimulation. The cohort consists of 26,428 women diagnosed with subfertility problems in one of the 12 IVF clinics between 1980 and 1995; 19,840 women received IVF treatment, and 6,588 women did not (12–14). Eligible women had not achieved conception after at least 1-yr frequent unprotected intercourse at their first visit to the fertility clinic. Risk factor questionnaires to the women and detailed data collection from the medical records provided information on the children born from the OMEGA participants up to 1996–1997. The questionnaire response rate was 73% among subfertile women with children. The present study was restricted to IVF and spontaneously conceived children born from OMEGA participants who were treated for subfertility in the VU University medical center (VUmc). IVF children born from women treated in the VUmc who did not participate in the OMEGA study were also eligible for recruitment.

Approach of study subjects

From the 553 eligible singletons born after standard IVF treatment, we invited 95% of IVF children born between 1986 and 1991, 74% of IVF children born between 1992 and 1993, and 41% of IVF children born between 1994 and 1995 to achieve equal representation of all 1-yr age categories. For each participating IVF child, we searched one control child of the same gender and similar age (≤3-month age difference) born after spontaneous conception from subfertile parents. In case an approached control child did not want to participate, the control recruitment process was repeated until an appropriate control child was found that did agree to participate. Between 2003 and 2006, 354 IVF and 454 control children and their parents were informed by letter about our study on growth and development of IVF children (Fig. 1). Finally, 69% of the approached IVF children and 51% of the approached controls agreed to participate, resulting in 233 matched pairs. Subsequently, pubertal children were recruited for additional research, including the collection of a fasting blood sample [female criteria of puberty: ≥ stage 2 breast development; male criteria: ≥ stage 2 genital development and/or testis volume ≥ 4 ml (15)]. Additional research was restricted to pubertal children only to avoid low participation rates, especially among the youngest children, due to the invasive character of these tests. In total, 80% of the pubertal children underwent a blood withdrawal. All children and their parents gave written informed consent to participate in the study.

Families who refused to participate in the study received a single questionnaire regarding health, education, and other characteristics of the respective child (n = 283). A total of 179 families (63%) returned the questionnaire. Nonparticipation analysis yielded no significant differences between participants and nonparticipants regarding children's current height, weight, and body mass index (BMI). Nonparticipating children were older (12.9 ± 2.6 *vs.* 12.0 ± 2.6 yr; $P = 0.002$), and their mothers were less often highly educated (26 *vs.* 37%; $P = 0.015$), but these findings were observed in both the IVF and control population.

The study protocol was approved by the ethics committee of the VUmc and the National Medical Ethics Committee known as the "Cen-

trale Commissie Mensgebonden Onderzoek" located in The Hague, The Netherlands.

Data collection

Systolic and diastolic blood pressure was measured twice at the nondominant arm in the sitting position using an automatic device with appropriate cuff size (Dinamap PRO 100; Criticon, Munich, Germany). The first measurement was performed after a 30- to 45-min interview and the second measurement within a few minutes after the first one. The mean of these two readings was used in analyses. Body weight and height were assessed to the nearest 0.1 kg and 0.1 cm using an electronic scale (SECA, Hanover, MD) and a stadiometer (Holtain Ltd., Crymych, Dyfed, UK), respectively. Skinfold thickness measurements (triceps, biceps, subscapular, and suprailiac) were collected by a Harpenden caliper (Harpenden, West Sussex, UK). Other body fat measures have been reported elsewhere.

Blood samples were drawn between 0900 and 1000 h after an overnight fast. Fasting glucose and insulin were determined using the Glucoquant Glucose/HK, Roche assay kit (Roche Diagnostics GmbH, Mannheim, Germany) and Bayer/ACS Centaur immunoassay (Bayer Diagnostics, Mijdrecht, The Netherlands), respectively. The glucose to insulin ratio and the homeostasis assessment model (HOMA) were chosen as measures of insulin sensitivity. HOMA insulin resistance and β-cell function were calculated according the original formula (16). Laboratory measurements were performed at the Department of Clinical Chemistry of the VUmc.

Before the follow-up visit in the VUmc, a questionnaire was sent to the parents to gather information on various demographical, lifestyle, and medical factors, including the cause of subfertility, parental education level, maternal smoking during pregnancy, and birth weight and gestational age of the respective child. Maternal BMI and highest level of education completed by either parent were used as indicators of socioeconomic conditions (17). Information about drug use of the child and family history of disease in terms of diabetes type 2, cardiovascular disease, and hypertension among parents and grandparents was obtained by an interview. None of the children used medication that could have affected blood pressure. Birth weight, either extracted from VUmc birth certificates (49%) or outpatient clinic reports (38%), or self-reported by the parents (13%), was expressed as the SD score (SDS) to correct for gestational age and gender (18).

Statistical analysis

After exclusion of eight matched pairs due to missing blood pressure measurements, data of 225 IVF-control pairs and data of the subsequent pubertal subset consisting of 131 unmatched IVF children and 131 controls were analyzed (Fig. 1). Differences between IVF-control pairs were tested using the paired *t* test for continuous variables and McNemar's test for dichotomous variables. Metabolic data of pubertal IVF and control children were compared after correction for age and gender. Logistic regression analyses were performed to estimate crude odds ratios for being in the highest quartile of several outcome parameters associated with IVF conception. Furthermore, potential confounders of the association between blood pressure and indicators of insulin sensitivity on the one hand and IVF conception on the other hand were examined separately by regression analysis (*e.g.* gender, current weight, birth weight, gestational age, parity, maternal smoking during pregnancy, parental education, parental age, maternal BMI, subfertility cause, and family history of disease). Factors that changed the crude difference in outcome between IVF and control children with more than 10% were considered as confounders and included in the final regression model. Reported *P* values were based on two-sided tests of significance.

Results

Perinatal and follow-up characteristics of the study population are shown in Table 1. Birth weight, birth weight SDS, and gestational age were significantly lower in children conceived by IVF compared with controls. Age at follow-up of IVF and control children was 12.3 ± 2.6 yr. Both systolic and diastolic blood pressures were higher in IVF children (109 ± 11 *vs.* 105 ± 10 mm Hg in controls, $P < 0.001$; and 61 ± 7 *vs.* 59 ± 7 mm Hg in controls, $P < 0.001$, respectively). Furthermore, IVF children were 2.1 times more likely to be in the highest systolic blood pressure quartile (≥114.5 mm Hg) and 1.9 times more likely to be in the highest diastolic blood pressure quartile (≥65.5 mm Hg) than controls [highest quartile *vs.* lowest three quartiles: 95% confidence interval (CI) 1.4, 3.3; 95% CI 1.2, 3.0, respectively]. IVF children had a significantly higher sum of skinfolds compared with controls (40.5 ± 20.4 *vs.* 36.9 ± 17.5 mm; $P = 0.04$). In addition, higher fasting glucose levels were observed in IVF children (5.0 ± 0.4 *vs.* 4.8 ± 0.4 mmol/liter in controls; $P = 0.005$). IVF-conceived children were 2.5 times more likely to be in the highest fasting glucose quartile (≥5.2 mmol/liter) than controls (highest quartile *vs.* lowest quartile: 95% CI 1.2, 5.2). No significant differences in fasting insulin concentrations, insulin resistance measures, height, weight, and BMI were found between both study groups.

Influences of potentially confounding factors on the difference in blood pressure and fasting glucose levels between IVF children and controls are shown in Table 2. The systolic blood pressure difference was predominantly affected by birth weight, gestational age, and sum of skinfolds, whereas the diastolic blood pressure difference was also influenced by parity. By contrast, subfertility cause was the main factor that substantially changed the fasting glucose difference between IVF and control children. Multivariate regression analysis demonstrated that blood pressure and fasting glucose levels in IVF children remained significantly increased after controlling for the relevant confounding factors simultaneously (Table 3).

Discussion

This is the first follow-up study investigating blood pressure levels and several indicators of insulin resistance in 8- to 18-yr-old IVF and control children born from subfertile parents. Significant differences in both systolic and diastolic blood pressure, as well as in fasting glucose levels were found among IVF children compared with controls. These differences could neither be explained by current risk indicators, early life factors, nor by parental characteristics, including subfertility cause.

In clinical practice, the 3- to 4-mm Hg higher systolic blood pressure and the 1- to 2-mm Hg higher diastolic blood pressure in IVF children may seem like small increases, but at a population level, these differences might have a major impact on public health. A slight increase in blood pressure is associated with a remarkably increased risk of developing cardiovascular disease. For instance, lowering mean systolic blood pressure in adults by 2 mm Hg corresponds to an 8% reduction in the risk of stroke (19). Furthermore, it cannot be excluded that increased blood pressure after IVF may be amplified throughout life because blood pressure is known to track from childhood into adult life (20).

TABLE 1. Perinatal and follow-up characteristics of the study population

	IVF children	Controls	*P* value
Perinatal characteristics			
No. of subjects	225	225	
Birth weight (kg)	3.22 ± 0.63	3.44 ± 0.54	<0.001
Birth weight SDS[a]	−0.16 ± 1.00	0.09 ± 1.07	0.02
Gestational age (wk)	38.9 ± 2.5	39.6 ± 1.8	0.002
No. of preterm infants (%)[b]	29 (13)	13 (6)	0.01
Anthropometry and blood pressure			
No. of subjects	225	225	
Age (yr)	12.3 ± 2.6	12.3 ± 2.6	0.35
Gender (% male)	49	49	1.00
Height (cm)	156.4 ± 15.0	155.8 ± 15.7	0.39
Body weight (kg)	47.8 ± 16.0	46.7 ± 14.8	0.19
BMI (kg/m^2)[c]	19.1 ± 3.6	18.7 ± 3.2	0.25
Sum of skinfolds (mm)	40.5 ± 20.4	36.9 ± 17.5	0.04
Systolic blood pressure (mm Hg)	109 ± 11	105 ± 10	<0.001
Systolic blood pressure: quartiles			
≤99.5 mm Hg	44 (20%)	72 (32%)	0.001
100.0–106.0 mm Hg	50 (22%)	59 (26%)	
106.5–114.0 mm Hg	59 (26%)	53 (24%)	
≥114.5 mm Hg	72 (32%)	41 (18%)	
Diastolic blood pressure (mm Hg)	61 ± 7	59 ± 7	<0.001
Diastolic blood pressure: quartiles			
≤54.5 mm Hg	42 (19%)	63 (28%)	0.01
55.0–59.5 mm Hg	58 (26%)	65 (29%)	
60.0–65.0 mm Hg	56 (25%)	55 (24%)	
≥65.5 mm Hg	69 (31%)	42 (19%)	
Heart rate (beats per min)	74 ± 11	72 ± 11	0.02
Fasting glucose and insulin			
No. of subjects[d]	131	131	
Fasting glucose (mmol/liter)	5.0 ± 0.4	4.8 ± 0.4	0.005
Fasting glucose: quartiles			
≤4.6 mmol/liter	21 (16%)	39 (30%)	0.05
4.7–4.9 mmol/liter	43 (33%)	36 (28%)	
5.0–5.1 mmol/liter	25 (19%)	26 (20%)	
≥5.2 mmol/liter	41 (32%)	30 (23%)	
Fasting insulin (pmol/liter)[a]	47.5 (33.0–69.2)	47.2 (34.2–63.6)	0.58
Glucose to insulin ratio[a]	0.10 (0.07–0.15)	0.11 (0.08–0.14)	0.88
HOMA-insulin resistance[a]	1.8 (1.2–2.6)	1.8 (1.2–2.3)	0.35
HOMA β-cell function[a]	110.4 (77.6–151.4)	117.3 (81.7–164.2)	0.24

Data represent mean ± SD, percentages, or median (25th-75th percentile).

[a] Birth weight SDS is a measure of birth weight corrected for gestational age and gender using a reference population (18).

[b] Premature birth was defined as birth occurring before 37-wk gestation.

[c] BMI was defined as weight divided by height squared.

[d] Metabolic data were only available for children who participated in the pubertal substudy; these unmatched data were corrected for age and gender.

Over the past years, cardiovascular developmental consequences and potentially underlying mechanisms after environmental manipulation during early prenatal development have been documented in both human and animal studies (3, 5, 21, 22). The Dutch famine study demonstrated that exposure to malnutrition during early pregnancy is associated with an increased risk of coronary heart disease in adult life (22). Periconceptional undernutrition has been associated with the precocious activation of the hypothalamo-pituitary-adrenal (HPA) axis (23–26). Gardner *et al.* (27) recently reported minor influences on HPA axis function in young adult sheep after periconceptional undernutrition. It has been suggested that the early activation of the HPA axis may not only lead to inappropriate elevation of prostaglandin levels and early birth but may also be associated with further programming effects due to inappropriate exposure of the fetus to glucocorticoids (28). Other targets, like the renin-angiotensin system and the sympathoadrenal axis, have also been associated with developmental origins of nutritional or other influences on cardiovascular function (29). Due to the complexity of the cardiovascular system, it is unlikely that the relation between periconceptional insults and postnatal cardiovascular dysfunction originates from one single cause. Early prenatal developmental plasticity in relation to environmental stimuli has been reported to lead to changes in fetal development through changes in imprinted gene expression, nutrient and stress-related signaling pathways, or cell cycle and apoptotic rates (9). Further research is necessary to investigate the role of these pathways in the development of cardiovascular dysfunction after periconceptional insults. In addition, in view of the present study, it remains to be elucidated whether increased

TABLE 2. Differences in blood pressure (mm Hg) and fasting glucose (mmol/liter) between IVF children and control children after adjustment for current risk indicators, early life factors, and parental characteristics

Model adjustment for the following potential confounders	Systolic blood pressure			Diastolic blood pressure			Fasting glucose		
	Difference (mm Hg)	95% CI	*P* value	Difference (mm Hg)	95% CI	*P* value	Difference (mmol/liter)	95% CI	*P* value
Unadjusted	4.2	2.2–6.2	<0.001	2.3	1.1–3.6	<0.001	0.13	0.04–0.22	0.005
Gender	4.2	2.2–6.2	<0.001	2.3	1.1–3.6	<0.001	0.13	0.04–0.22	0.005
Current risk indicators									
Current weight (kg)	3.9	2.0–5.7	<0.001	2.3	1.0–3.6	0.001	0.13	0.04–0.22	0.006
Current height (cm)	4.2	2.3–6.0	<0.001	2.3	1.1–3.6	<0.001	0.13	0.04–0.22	0.005
BMI (kg/m^2)	4.0	2.1–5.9	<0.001	2.3	1.0–3.6	0.001	0.13	0.04–0.22	0.007
Sum of skinfolds (mm)	3.7	1.8–5.7	<0.001	2.1	0.8–3.4	0.001	0.13	0.04–0.22	0.007
Early life factors									
Birth weight (kg)	3.5	1.5–5.5	0.001	2.1	0.8–3.4	0.002	0.13	0.03–0.22	0.007
Gestational age (wk)	3.6	1.6–5.6	<0.001	2.1	0.8–3.4	0.002	0.13	0.04–0.22	0.007
Primiparity (Y/N)	3.8	1.7–5.9	0.001	1.8	0.5–3.2	0.009	0.13	0.03–0.23	0.010
Maternal smoking during pregnancy (Y/N)	3.8	1.8–5.8	<0.001	2.2	0.9–3.5	0.001	0.13	0.04–0.22	0.006
Parental characteristics									
Subfertility cause[a]	3.9	1.8–6.0	<0.001	2.2	0.9–3.6	0.001	0.11	0.02–0.21	0.022
Parental educational level[b]	4.1	2.1–6.1	<0.001	2.3	1.0–3.6	<0.001	0.13	0.03–0.22	0.008
Maternal age at follow-up (yr)	4.1	2.2–6.1	<0.001	2.3	1.1–3.6	<0.001	0.13	0.04–0.23	0.005
Paternal age at follow-up (yr)	4.2	2.2–6.2	<0.001	2.3	1.0–3.6	<0.001	0.13	0.04–0.22	0.005
Maternal BMI at follow-up (kg/m^2)	4.0	2.0–6.0	<0.001	2.2	0.9–3.5	0.001	0.13	0.04–0.22	0.006
Family history of diabetes type 2 (Y/N)[c]	4.3	2.3–6.3	<0.001	2.3	1.0–3.6	0.001	0.13	0.04–0.22	0.006
Family history of hypertension (Y/N)[c]	4.4	2.4–6.5	<0.001	2.4	1.0–3.7	<0.001	0.13	0.04–0.23	0.004
Family history of cardiovascular disease (Y/N)[c]	4.3	2.3–6.4	<0.001	2.3	1.0–3.6	0.001	0.13	0.04–0.23	0.005

Each row represents a separate regression analysis. N, No; Y, yes.

[a] Subfertility was categorized as female subfertility (tubal factors, endometriosis, ovarian disorders, cervical factors, and uterine abnormalities), male subfertility, subfertility caused by both parents, or unexplained subfertility. In 14 cases the cause of subfertility was missing.

[b] Highest level of education completed by either parent was categorized as low (primary school, low occupational training), medium (high school, medium occupational training), and high (high occupational training, university).

[c] Family history of diabetes type 2, hypertension, and cardiovascular disease was considered positive if any of the parents or grandparents was reported to suffer from this type of disease. Data on the family history of disease of 14 children were missing.

blood pressure among IVF children originates from early prenatal life adaptations mediated through neuroendocrinal pathways related to the HPA axis and/or through one of the unidentified mechanisms. However, increased blood pressure levels in IVF children were to a large extent independent of birth weight, suggesting that the underlying mechanisms can modify the cardiovascular system even without affecting size at birth. This is in line with previous studies examining associations between early life factors and blood pressure among offspring (22, 30). It is important to realize that birth weight is just a proxy for fetal growth. Prenatal environmental insults that may affect embryonic and/or fetal growth trajectories can result in altered postnatal physiology without an effect on birth weight (31). Similarly, exposure to early prenatal life effects may even induce developmental adaptations in organ development and function that are not accompanied by changes in fetal growth characteristics.

Although exposure to adverse prenatal conditions, especially during late gestation, has been linked to decreased glucose tolerance in adults (32), it is unclear whether early prenatal insults in humans can influence postnatal glucose metabolism. Fasting glucose levels studied in the present study are within the normal range, and the difference in fasting glucose levels between pubertal IVF children and controls is small, not accompanied by differences in fasting insulin levels and other related measures. However, in view of the observed differences in blood pressure and body fat composition between IVF children and controls, considerable research is necessary to investigate the hypothesis

TABLE 3. Differences in blood pressure (mm Hg) and fasting glucose (mmol/liter) between IVF children and control children after adjustment for confounders: multivariate analysis

Multivariate models	Unstandardized regression coefficient	95% CI	*P* value
SBP difference (mm Hg) after adjustment for birth weight, gestational age, and sum of skinfolds	3.0	1.1–5.0	0.003
DBP difference (mm Hg) after adjustment for birth weight, gestational age, parity, and sum of skinfolds	1.4	0.03–2.8	0.046
Glucose difference (mmol/liter) after adjustment for subfertility cause	0.11	0.02–0.21	0.02

DBP, Diastolic blood pressure; SBP, systolic blood pressure.

that further changes in glucose metabolism might manifest in later life. Gold standard assessments, *i.e.* euglycemic hyperinsulinemic clamp tests and hyperglycemic clamp tests, will be useful to additionally investigate insulin sensitivity and β-cell capacity in IVF-conceived offspring.

When interpreting our results, the strengths and limitations of our study need to be considered. The strengths of our study include the relatively large study size and the comparison group consisting of spontaneously conceived children born from subfertile parents. Furthermore, we collected various variables related to blood pressure and metabolism that provided the opportunity to examine blood pressure and fasting glucose differences between IVF children and controls while adjusting for these potentially confounding factors. It is possible that we have underestimated the true association between IVF and outcome parameters by adjusting for intermediate factors (*e.g.* sum of skinfolds in case of evaluated blood pressure). In addition, the slight attenuation of the blood pressure differences by adjusting for birth weight and gestational age was to be expected. IVF is known to be associated with lower birth weight and shorter gestational age (11, 33), whereas these factors themselves have been found to increase blood pressure. Another limitation is potential selection bias because our study was based on 56% (n = 450) of the total number of subjects approached (n = 808). However, nonparticipation analysis yielded no significant differences between participants and nonparticipants in anthropometric measures. The main reason for nonparticipation was unwillingness of the child to participate. In addition, it cannot be excluded that the degree of subfertility in those who conceived after IVF was more severe compared with those who conceived spontaneously and that this difference in subfertility contributed to the physiological abnormalities observed in IVF offspring. Nevertheless, most control mothers who participated in the present study were diagnosed with subfertility in an era (1982–1990) when IVF was not a routine procedure and was not ethically acceptable to many women. Moreover, estimated differences in blood pressure between IVF and control children were hardly affected by adjustment for parental subfertility causes, rendering residual confounding very unlikely. Similarly, the fasting glucose difference between IVF and control children remained statistically significant after adjustment for subfertility cause.

In conclusion, increased blood pressure and fasting glucose levels among IVF children could not be explained by current risk indicators, early life factors, and parental characteristics. Although underlying mechanisms are largely elusive, the periconceptional period of IVF-conceived children might be a critical time window during which cardiometabolic function can be perturbed. Before definitive conclusions can be drawn, our results need to be reproduced by other prospective follow-up studies. Nevertheless, our findings underscore the importance of the continuing worldwide monitoring of postnatal development of IVF children and contribute to the current understanding of periconceptional exposure effects with regard to the development of both short- and long-term consequences in humans.

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