Parental subfertility is associated with higher blood pressure in offspring

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BRIEF REPORT

Parental subfertility is associated with higher blood pressure in offspring

Increased childhood blood pressure (BP) can lead to increased BP later in life and even small increases have been associated with a higher risk of adult cardiovascular disease. In contrast, lower childhood BP has been associated with more favourable health outcomes. One study found that a 2 mmHg reduction in childhood diastolic BP was associated with a 17% decrease in the prevalence of adult hypertension (1).

Multiple studies reported that children born after *in vitro* fertilisation (IVF) have a higher BP in childhood (2). Using data from the Groningen assisted reproductive technology (ART) cohort study, we found no association between IVF, or more specific, of ovarian hyperstimulation or the *in vitro* procedure, on BP in 9-year-old offspring (3). Parental subfertility, *per se* may thus be the decisive factor explaining the elevated BP levels of IVF offspring. Therefore, we compared the BP of 149 9-year-old children who were born to subfertile couples from the Groningen ART study (assessed in 2014–2016) with that of 277 9-year-olds born at term to fertile couples from the LCPUFA study (assessed in 2006–2008). Subfertility was defined as the failure to achieve a successful pregnancy within 12 months of unprotected intercourse. In the subfertile group, 61 children had been naturally conceived and 88 had been conceived by IVF with or without ovarian hyperstimulation (3). No association between the *in vitro* procedure or ovarian hyperstimulation was found on cardiometabolic health at 9 years of age.

The children of the fertile group participated in a randomised controlled trial focusing on the effect of the addition of LCPUFA to infant formula during the first two months after term birth on cardiometabolic health. No association between the nutritional formula on cardiometabolic health in 9-year-olds was found: type of infant feeding did not affect BP (4). Both studies were carried out, after being approved by the ethics committee, by the Institute of Developmental Neurology of the University Medical Center Groningen using similar methods and having the same supervisor (MH-A).

The children's BP (mmHg) was measured 4–6 times on one day using an automated Datascope Accutorr plus BP monitor (Mindray North America, Mahwah, NJ, USA). Overall means were used to calculate BP percentiles based on standards of the US National High BP Education Program. The BP percentiles were based on the BP of a representative sample of

Table 1 Background characteristics and cardiovascular outcomes

	Subfertile group n = 149	Fertile group n = 277
Child characteristics		
Male sex, n (%)	74 (50)	148 (53)
Age at examination in years, median (range)	**9.2 (9.0–11.0)**	**9.0 (8.5–9.6)**
Fertility parameters		
TTP in years, median (range)*	3.1 (0.1–13.3)	n.a.
IVF/ICSI, n (%)	88 (59)	n.a.
Maternal subfertility, n (%)	47 (31)	n.a.
Paternal subfertility, n (%)	68 (46)	n.a.
Unknown cause for subfertility, n (%)	34 (23)	n.a.
Gestational characteristics		
Smoking during pregnancy, n (%)	**14 (9)**	**78 (28)**
Gestational diabetes, n (%)	3 (2)	5 (2)
Pregnancy–induced hypertension, n (%)	19 (13)	22 (8)
Birth characteristics		
Gestational age in weeks, median (range)	40.0 (37.0–42.6)	40.0 (37.0–42.0)
Birthweight in grams, mean (σ)	3603 (431)	3570 (450)
Neonatal characteristics		
NICU admission, n (%)	2 (1)	0 (0)
Breastfed for >6 weeks, n (%)†	**70 (48)**	**78 (29)**
Parental characteristics		
Maternal age at conception, median (range)	**32.9 (23.1–40.9)**	**29.8 (20.0–44.0)**
Education level mother high, n (%)†,‡	**65 (44)**	**36 (14)**
Maternal BMI before pregnancy, median (range)†	23.4 (16.8–46.7)	23.4 (17.2–40.9)
Parental diabetes/heart/vascular disease, n (%)	**4 (3)**	**45 (16)**
Cardiovascular outcomes		
SBP in mmHg, mean (σ)†	**106.2 (5.9)**	**104.4 (8.1)**
DBP in mmHg, mean (σ)†	**65.4 (6.1)**	**63.2 (8.2)**
SBP percentile, mean (σ)†	**60.6 (19.2)**	**56.0 (24.5)**
DBP percentile, mean (σ)†	**62.5 (18.6)**	**56.1 (23.3)**
Heart rate in beat/min, mean (σ)†	**81.4 (9.7)**	**77.0 (9.7)**
Weight in kg, median (range)†	32.9 (20.0–56.0)	32.0 (23.0–56.9)
Height in cm, mean (σ)†	**141.3 (6.5)**	**139.6 (5.7)**
BMI (weight/height^2), median (range)†	16.3 (12.7–24.7)	16.5 (12.3–26.1)

Mann–Whitney *U*-tests, Student's *t*-tests and Fisher's exact tests were used where appropriate to estimate group differences for background characteristics and outcome measurements. Statistically significant values ($p < 0.05$) are displayed in bold. Values are number (percentage), mean (standard deviation) or median (range). BMI = Body mass index; DBP = Diastolic blood pressure; ICSI = Intracytoplasmic sperm injection; n.a. = Not available; NICU = Neonatal intensive care unit; SBP = Systolic blood pressure; TTP = Time to pregnancy.

*In case of miscarriage TTP can be <1 year, as TTP has a new onset.

†Missing data in the subfertile group: breastfed for >6 weeks n = 2; maternal BMI n = 1. Missing data in the fertile group: BMI n = 16, breastfed for >6 weeks n = 6; DBP in mmHg n = 10; DBP percentile n = 12, education level mother high n = 12, Heart rate n = 15, Height n = 2, SBP in mmHg n = 10; SBP percentile n = 12, Weight n = 15.

‡Higher vocational education or University education.

63 227 healthy children and took sex, age in months and height in centimetres into account (5).

To estimate differences in background and outcome characteristics, univariable and multivariable statistics were used. The multivariable linear regression analyses we adjusted for the following confounders: breastfeeding for more than six weeks, high maternal education, maternal age, parental diabetes/hypertension/heart disease, method of conception, pregnancy-induced hypertension, smoking during pregnancy, child's age and sex. Results are expressed as regression coefficients (B) with 95% confidence intervals (95% CI). Probability values of <0.05 were considered statistically significant. Analyses were performed in SPSS Statistics 20.0 (IBM Corp, Armonk, NY, USA).

At the time of assessment, the children in the subfertile group were slightly older (9.2 vs 9.0 years), mothers smoked less often during pregnancy (9% vs 28%), were older (32.9 vs 29.8 years), were more often highly educated (44% vs 14%), and breastfed more often greater than six weeks (48% vs 29%) compared to the fertile group (Table 1). The children in the subfertile group had higher systolic BP percentiles (60.6 vs 56.0) and diastolic BP percentiles (62.5 vs 56.1) than the fertile group. Adjusted analyses showed that differences remained significantly different, regression coefficient B [95% confidence interval (CI)]: SBP percentile (B 8.10, 95% CI: 2.10–14.20); DBP percentile (B 7.31, 95% CI: 1.56–13.07). Comparing only the subgroup of naturally conceived children of subfertile couples with the fertile group yielded similar results.

Blood pressure percentiles of 9-year-old offspring of subfertile couples were higher than those of peers born to fertile couples. Our findings are in line with other reports that children born to couples with a history of subfertility have a less optimal health, such as adverse perinatal outcomes and birth defects, compared to naturally conceived children of fertile couples (5). These suboptimal outcomes, including a higher BP, in the offspring of subfertile couples may be attributed to the multifactorial inherent risk associated with subfertility and presumably not with the IVF procedure itself.

A major strength of the study was the use of BP percentiles, which take age in month, length in centimetres and sex into account. Based on the National High BP Education Program, the BP percentiles provide valid reference values for the general population. As the BP percentiles of the subfertile group are above the 60th percentile this supports the hypothesis that parental subfertility is linked to higher BP levels in the offspring.

The group selection was a limitation. The fertile group was a slightly disadvantaged group, with more smokers during pregnancy, lower educational level of parents, and greater percentages of parental diabetes, heart disease or vascular disease compared to the subfertile group. Thus the difference in BP between the groups may have been underestimated (4). The fertile group took part in a study on infant formula and were not randomly selected from the general fertile population. However, formula has been associated with less optimal health outcomes than breastfeeding. Nevertheless, this group had better BP values at nine years.

Our results suggest that parental subfertility was associated with a higher BP in school-aged offspring. Additional studies are needed to study the effect of parental subfertility on the BP of their offspring.

CONFLICT OF INTEREST

None.

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