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ARTICLE

Childhood growth of term singletons born after frozen compared with fresh embryo transfer

BIOGRAPHY

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KEY MESSAGE

Similar growth was found in term singletons born after frozen compared with fresh embryo transfer and natural conception up to 5 years of age. This offers reassurance about the safety and feasibility of the steadily increasing use of embryo cryopreservation in assisted reproduction.

ABSTRACT

Research question: Is the growth of term singletons born after frozen embryo transfer (FET) comparable to those born after fresh embryo transfer and natural conception up to 5 years of age?

Design: Observational cohort study in an academic medical centre and municipal child health clinics with repeated measurements carried out by medical professionals. Term singletons born after FET (n = 110) and fresh embryo transfer (n = 181) and their matched natural conception controls (n = 543) born in Oulu, Northern Finland, were included. Mean weights, lengths, heights and head circumferences at the ages of 4, 8 and 18 months and 3 and 5 years were compared. At 3 and 5 years, body mass indices were compared.

Results: Childhood growth did not differ between term singletons born after FET, fresh embryo transfer and natural conception, correcting for exact age at measurement and adjusting for maternal body mass index and paternal height.

Conclusions: Similar growth between children born after FET, fresh embryo transfer and natural conception offers reassurance of the safety and feasibility of the steadily increasing use of embryo cryopreservation in assisted reproduction.

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KEYWORDS
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INTRODUCTION

The health of children born after assisted reproductive technology (ART) has improved over the past few years, mainly because of a reduction in multiple gestations (*Henningsen et al., 2015*). In Finland, a policy of elective single embryo transfer (SET) was implemented in the late 1990s (*Martikainen et al., 2004*; *Tiitinen et al., 2004*), which was possible only when combined with extensive use of frozen embryo transfer (FET). Nowadays in Finland, more children are born after FET than after fresh embryo transfer (*THL, 2019a*) and, in Europe, the number of FET treatments has exceeded that of conventional IVF (*Wyns et al., 2020*). In the USA, FET was used in 32.7% of ART treatment cycles in *CDC 2016*.

Knowledge of the early growth and development of children born after FET is still limited. In a register-based cohort study of the morbidity of children born after FET, no difference was found in the somatic health between children born after FET compared with those born after fresh embryo transfer up to the age of 3 years (*Pelkonen et al 2015*). Some differences, however, were observed in pregnancy-related complications and adverse perinatal outcomes of pregnancies conceived after FET compared with fresh embryo transfer (*Maheshwari et al., 2018*; *Sha et al., 2018*). Furthermore, singletons born after FET have higher mean birth weight and a higher risk of being large-for-gestational-age (LGA) than fresh embryo transfer singletons (*Pelkonen et al., 2010*; *Sazonova et al., 2012*; *Wennerholm et al., 2013*; *Pinborg et al., 2014*; *Maheshwari et al., 2018*; *Sha et al., 2018*; *Terho et al., 2021*). The clinical significance of this intrauterine growth difference remains unclear. A few studies have described the growth of children born after FET, fresh embryo transfer and natural conception, and the evidence has been mostly reassuring. Some contradictory findings, however, with unclear clinical significance, have been reported (*Wennerholm et al., 1998*; *Green et al., 2013*; *Hann et al., 2018*; *Ainsworth et al., 2019*; *Turner et al., 2020*; *Magnus et al. 2021*).

In Finland, 98% of all children attend scheduled, standardized check-ups in municipal child health clinics, which are free of charge for the purpose of screening for growth and developmental abnormalities (*THL, 2019b*). This makes meticulous, prospectively collected child growth data available. The main goal of an ART treatment is a healthy child. Therefore, reliable data on the growth patterns of children born after ART are needed to provide patients with exact and up-to-date information on their treatment choices. The aim of the present study was to investigate the childhood growth of children born after FET compared with fresh embryo transfer and natural conception derived from high-coverage municipal follow-up data from child health clinics in Finland.

MATERIALS AND METHODS

Study population

This study is an observational cohort of all term (gestational weeks 37–42) singletons born after FET and fresh embryo transfer in Oulu University Hospital between 2006 and 2011 and residing in the Oulu city area in Northern Finland. For each child in the study, two controls who had a natural conception from the same geographical area were obtained from the Finnish Medical Birth Register. The controls were matched for sex, birth year, maternal age (+/– 1 year) and parity. All data were prospectively collected by the infertility clinics, Oulu University Hospital and the municipal child health clinics, and then retrospectively linked by the study group.

The data on the fertility treatments were obtained from the two infertility clinics operating in the area: Oulu University Hospital Infertility Clinic and Family Federation of Finland, Oulu. Fresh and frozen embryo transfers were carried out on day 2–3, and, at the time, in all FET treatments, slow freezing was used. Of the FET treatments, 90.8% were carried out in a natural cycle, and luteal (progesterone) support was routinely used. The mothers' unique personal identifier codes were used to link the data to the pregnancy, delivery and perinatal health information from the medical records at the Oulu University Hospital. These records consist of the clinical notes made by the treating physicians and midwives, and they are recorded in a structured manner. For controls who had a natural conception, pregnancy and perinatal health data were obtained from the Finnish Medical Birth Register, which includes nationwide data on all births of fetuses with a birth weight of at least 500 g or with a gestational age of at least 22 weeks, as well as data on their mothers based on medical records from primary care and birth hospital (*THL, 2021*). Child growth data were then obtained from municipal child health clinics using the children's unique personal identifier codes. The study population is presented in FIGURE 1.

Study approval

Study permission was granted on 6 October 2017 by the Finnish Institute for Health and Welfare, THL (THL/540/5.05.00/2017). In Finland, separate ethical approval is not required in scientific projects based on data from registers and medical records, as no registered person is contacted.

Outcomes and statistical analyses

Mean weights, lengths, heights and head circumferences were compared between the groups at birth, at 4, 8 and 18 months and at 3 and 5 years of age. At 3 and 5 years of age, the mean body mass indices were also compared. All analyses were carried out for the entire population and further stratified by the sex of the child. Some measurement values were missing because not all children attended every scheduled child health clinic appointment. Over 80% of the included children for each study group, however, were measured at each point. At the age of 5 years, data on weight were available for 96 children (87.3%) in the FET, 165 children (91.2%) in the fresh embryo transfer and 531 children (97.8%) in the natural conception group.

Chi-squared test was used to compare categorical variables and, where significant differences were found, standard normal deviation test was used to compare percentages between any two groups. One-way analysis of variance was used to compare continuous variables with post-hoc Tukey's honest significance test correction for multiple comparisons. Growth measurement values were compared using linear mixed model corrected for exact age at measurement and adjusted for maternal body mass index (BMI) and paternal height. For all statistical analyses, IBM SPSS Statistical Software (IBM Statistics for Windows, Version 25, IBM Corp, Armonk, NY, USA) was used. For figures, draw.io and GraphPad Prism 8.0.1 softwares were used.

RESULTS

Background characteristics

A description of the study population is presented in TABLE 1. Fewer SET took

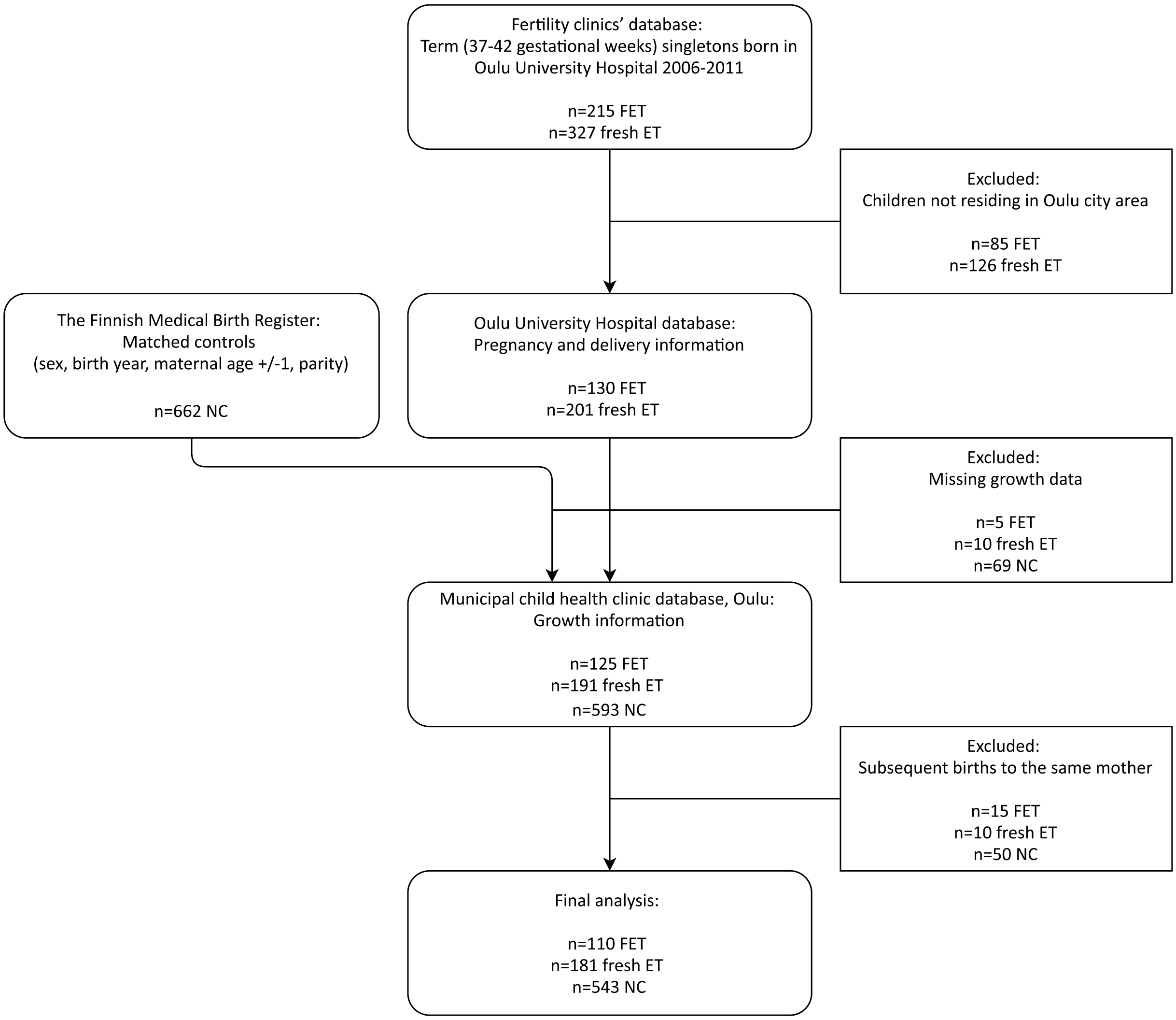

FIGURE 1 The study population. ET, embryo transfer; FET, frozen embryo transfer; NC, natural conception.

place in the FET group compared with fresh embryo transfer group (52.7% versus 64.6%; *P* = 0.038). No other significant differences between FET and fresh embryo transfer were found. Compared with natural conception, gestational age at birth was shorter (277 versus 280 days; *P* = 0.001) and the incidence of blood pressure disorders was higher (13.6 versus 6.3%; *P* = 0.010) in the FET group. For fresh embryo transfer, the incidence of blood pressure disorders (13.3 versus 6.3%; *P* = 0.003) and gestational diabetes (13.3. versus 7.7%; *P* = 0.026) was higher compared with natural conception. In the natural conception group, data on gestational diabetes were missing in 46.4% of cases.

Growth measurements

Stratified by sex of the child, the mean weight, length/height of boys did not differ between the FET, fresh embryo transfer and natural conception groups in crude measurements (corrected for exact age) nor when adjusted for maternal BMI and paternal height, up to 3 years of age. At the age of 5 years, the adjusted mean weight of FET, fresh embryo transfer and boys who were conceived naturally was 19,742, 19,607 and 20,218 g, respectively, which were not significantly different (*P* = 0.653 for FET versus natural conception and *P* = 0.261 for fresh embryo transfer versus natural conception) (TABLE 2 and FIGURE 2).

The mean weight, length/height of girls, crude and adjusted, did not differ between the FET, fresh embryo transfer and natural conception groups at 4, 8 and 18 months or at 3 and 5 years of age (TABLE 3 and FIGURE 2).

Considering head circumference measurements and BMI, at the age of 5 years (FIGURE 2), no significant differences were found between the study groups, nor at any of the earlier measurement points (data not shown). For the entire study population, no statistically significant differences were found between children born after FET, fresh embryo transfer and natural conception at any of the measurement points (data not shown).

DISCUSSION

In this regional cohort, growth did not differ between term singletons born after FET, fresh embryo transfer and their natural conception controls matched for sex, birth year, maternal age and parity at several measurement points up to the age of 5 years.

Previously, it was shown in a large Finnish register-based cohort study that children

TABLE 1 BACKGROUND CHARACTERISTICS OF PREGNANCIES ORIGINATED AFTER FROZEN EMBRYO TRANSFER, FRESH EMBRYO TRANSFER AND NATURAL CONCEPTION

	Frozen embryo transfer (*n* = 110)	Fresh embryo transfer (*n* = 181)	Natural conception (*n* = 543)	*P*-value
Maternal age, years, mean (SD)	32.4 (4.0)	32.0 (4.0)	32.3 (4.1)	0.708[a]
Missing, *n* (%)	–	–	–	
Maternal BMI, kg/m^2, mean (SD)	23.6 (3.8)	24.2 (4.5)	24.3 (4.5)	0.315[a]
Missing, *n* (%)	–	–	5 (0.9)	
Maternal smoking, *n* (%)	9 (8.2)	23 (12.8)	52 (9.7)	0.370[a]
Missing, *n* (%)	–	2 (1.1)	9 (1.7)	
Maternal SES, upper or lower white-collar worker, *n* (%)	89 (80.9)	148 (81.8)	407 (75.0)	0.065[a]
Missing, *n* (%)	–	–	13 (2.4)	
Primiparous, *n* (%)	71 (64.5)	132 (72.9)	382 (70.3)	0.318[a]
Missing, *n* (%)	–	–	–	
Paternal height cm, mean (SD)	179 (5.6)	179 (6.1)	179.1 (6.2)	0.986[a]
Missing, *n* (%)	1 (0.9)	1 (0.6)	3 (0.6)	
ICSI, *n* (%)	47 (42.7)	85 (47.0)	NA	0.347[b]
Missing, *n* (%)	–	–	NA	
SET, *n* (%)	58 (52.7)	117 (64.6)	NA	0.038[*,b]
Missing, *n* (%)	–	–	NA	
Gestational diabetes, *n* (%)	14 (12.7)	24 (13.3)	42 (7.7)	0.045[*,a] (0.999; 0.068; 0.026*)[b]
Missing, *n* (%)	–	–	252 (46.4)	
Blood pressure disorders,[c] *n* (%)	15 (13.6)	24 (13.3)	34 (6.3)	0.002[*,a] (0.999; 0.010;* 0.003*)[b]
Missing, *n* (%)	–	–	-	
Caesarean delivery, *n* (%)	28 (25.5)	49 (27.1)	125 (23.0)	0.517[a]
Missing, *n* (%)	–	–	-	
Gestational age at birth, days, mean (SD)	277 (8.1)	279 (8.7)	280 (8.6)	0.001[*,a] (0.120; 0.001;* 0.190)[b]
Missing, *n* (%)	–	–	1 (0.2)	
Newborn umbilical artery pH, mean (SD)	7.2 (0.1)	7.2 (0.1)	7.2 (0.1)	0.538[a]
Missing, *n* (%)	9 (8.2)	14 (7.7)	32 (5.9)	
Sex of child (male), *n* (%)	55 (50)	88 (48.6)	266 (49.0)	0.978[a]
Missing, *n* (%)	–	–	–	

[a] Chi-squared test for categorical variables and one-way analysis of variance with post-hoc Tukey's honest significant difference correction for multiple comparisons for continuous variables.

[b] Standard normal deviation test was used where Chi-square test was statistically significant to compare percentages between any two groups (FET versus fresh embryo transfer; FET versus natural conception; fresh embryo transfer versus natural conception).$P < 0.05$ was considered to be significant.

[c] Chronic hypertension and hypertensive disorder of pregnancy.

BMI, body mass index; FET, frozen embryo transfer; ICSI, intracytoplasmic sperm injection; SD, standard deviation; SES, socioeconomic status; SET, single embryo transfer; SND, standard normal deviation; *, indicates significance; –, indicates no cases missing.

born after FET have higher mean birth weight and a higher risk of being LGA than children born after fresh embryo transfer (Pelkonen et al. 2010). This has been confirmed in studies from other countries (Sazonova et al., 2012; Wennerholm et al., 2013; Pinborg et al., 2014; Maheshwari et al., 2018; Sha et al., 2018; Terho et al., 2021). In the present study, surprisingly, the adjusted birth weight of children born after FET did not significantly differ from that of children born after fresh embryo transfer and natural conception. In the previous Finnish study (Pelkonen et al., 2010), the incidence of LGA (birth weight >2 SD) was 2.1–3.6%, whereas, in the present study, only one case of LGA (0.9%) was found among the FET group and eight cases of LGA (4.4%) among the fresh embryo transfer group. This difference is likely due to chance, considering the smaller sample size.

Previous studies on the long-term growth of children born after FET present variable settings and results. The growth data are often based on a scarce number of measurements or may be self-reported. Even in the larger studies, the number of children born after FET is often limited. In a Swedish study, the growth of children (singletons and multiples) born after FET (*n* = 255) did not differ from the growth of children born after fresh embryo transfer or natural conception up to 18 months' of age. The groups were matched for maternal age, parity, singleton or twin status and date of delivery (Wennerholm et al., 1998). A study from New Zealand compared the prepubertal growth of term singletons born after FET (*n* = 43)

TABLE 2 CRUDE AND ADJUSTED MEAN WEIGHT AND HEIGHT OF BOYS BORN AFTER FROZEN EMBRYO TRANSFER, FRESH EMBRYO TRANSFER AND NATURAL CONCEPTION

	Weight, g, mean (95% CI)				Height, cm, mean (95% CI)			
Boys crude[a]								
Age	**Frozen embryo transfer (*n* = 55)**	**Fresh embryo transfer (*n* = 88)**	**Natural conception (*n* = 266)**	***P*-value**	**Frozen embryo transfer (*n* = 55)**	**Fresh embryo transfer (*n* = 88)**	**Natural conception (*n* = 266)**	***P*-value**
Birth	3616 (3493–3739)	3557 (3459–3654)	3610 (3554–3666)	0.623	50.7 (50.1–51.2)	50.7 (50.3–51.1)	50.7 (50.4–50.9)	0.997
4 months	7441 (7216–7665)	7518 (7340–7695)	7512 (7410–7614)	0.838	65.6 (65.0–66.2)	65.7 (65.2–66.1)	65.7 (65.5–66.0)	0.909
8 months	9263 (8971–9555)	9257 (9025–9489)	9267 (9136–9398)	0.997	72.4 (71.8–73.0)	72.6 (72.1–73.1)	72.5 (72.2–72.7)	0.869
18 months	11,786 (11,420–12,152)	11,649 (11,362–11,935)	11,878 (11,714–12,042)	0.388	83.8 (83.0–84.5)	83.6 (83.0–84.2)	84.0 (83.6–84.3)	0.590
3 years	15,285 (14,730–15,840)	15,075 (14,671–15,479)	15,398 (15,171–15,624)	0.389	97.3 (96.2–98.4)	96.7 (95.9–97.5)	97.0 (96.6–97.5)	0.674
5 years	19,569 (18,706–20,433)	19,558 (18,895–20,221)	20,244 (19,880–20,609)	0.113	111.9 (110.6–113.2)	111.5 (110.5–112.5)	111.9 (111.4–112.4)	0.755
Boys adjusted[b]								
Birth	3624 (3504–3744)	3561 (3467–3656)	3611 (3556–3666)	0.624	50.7 (50.2–51.2)	50.7 (50.3–51.1)	50.7 (50.5–50.9)	0.994
4 months	7448 (7233–7663)	7528 (7359–7698)	7520 (7422–7618)	0.819	65.5 (65.0–66.1)	65.7 (65.3–66.1)	65.8 (65.5–66.0)	0.734
8 months	9294 (9016–9573)	9278 (9057–9498)	9273 (9147–9398)	0.990	72.4 (71.9–73.0)	72.6 (72.2–73.1)	72.5 (72.2–72.7)	0.785
18 months	11,806 (11,460–12,153)	11,674 (11,404–11,944)	11,889 (11,733–12,045)	0.397	83.8 (83.1–84.4)	83.7 (83.1–84.2)	84.0 (83.7–84.3)	0.584
3 years	15,318 (14,797–15,839)	15,125 (14,746–15,504)	15,402 (15,189–15,615)	0.455	97.3 (96.3–98.3)	96.8 (96.1–97.6)	97.0 (96.6–97.4)	0.757
5 years	19,742 (18,917–20,567)	19,607 (18,976–20,238)	20,218 (19,870–20,566)	0.190	112.0 (110.8–113.2)	111.6 (110.7–112.5)	111.9 (111.4–112.4)	0.844

[a] Corrected for exact age at measurement, gestational age at birth.

[b] Adjusted for maternal body mass index and paternal height.Linear mixed model. $P < 0.05$ was considered to be significant.

Over 80% of included children were measured at each measurement point.

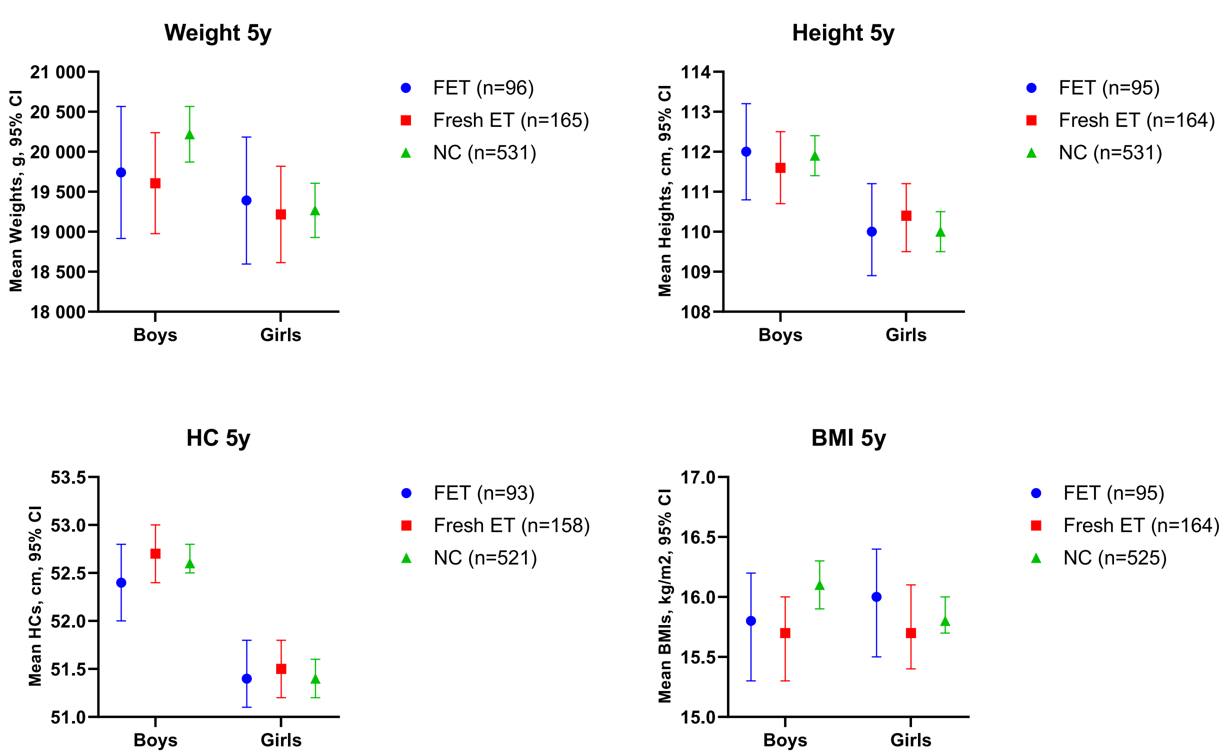

FIGURE 2 Mean weights, heights, head circumferences and body mass indices of children born after frozen embryo transfer (FET), fresh embryo transfer (ET) and natural conception (NC) at the age of years, corrected for exact age at measurement and adjusted for maternal body mass index (BMI) and paternal height. NA, not applicable.

TABLE 3 CRUDE AND ADJUSTED MEAN WEIGHT AND HEIGHT OF GIRLS BORN AFTER FROZEN EMBRYO TRANSFER, FRESH EMBRYO TRANSFER AND NATURAL CONCEPTION

	Weight, g, mean (95% CI)				Height, cm, mean (95% CI)			
Girls crude[a]								
Age	**Frozen embryo transfer (*n* = 55)**	**Fresh embryo transfer (*n* = 93)**	**Natural conception (*n* = 277)**	***P*-value**	**Frozen embryo transfer (*n* = 55)**	**Fresh embryo transfer (*n* = 93)**	**Natural conception (*n* = 277)**	***P*-value**
Birth	3364 (3236–3493)	3462 (3364–3561)	3457 (3400–3 514)	0.406	49.4 (48.9–49.9)	49.8 (49.4–50.2)	49.7 (49.4–49.9)	0.544
4 months	6772 (6559–6985)	6826 (6663–6990)	6905 (6812–6998)	0.438	63.9 (63.3–64.4)	64.0 (63.6–64.5)	64.0 (63.7–64.2)	0.886
8 months	8453 (8171–8734)	8546 (8325–8766)	8 591 (8466–8715)	0.665	70.5 (70.0–71.1)	70.8 (70.3–71.3)	70.6 (70.4–70.9)	0.758
18 months	10,834 (10,481–11,187)	10,969 (10,701–11,237)	11,063 (10,910–11,216)	0.471	81.8 (81.0–82.6)	82.0 (81.4–82.6)	82.3 (81.9–82.6)	0.475
3 years	14,256 (13,754–14,759)	14,753 (14,372–15,135)	14,498 (14,284–14,712)	0.280	94.5 (93.5–95.5)	95.9 (95.1–96.7)	95.3 (94.9–95.7)	0.096
5 years	19,200 (18,379–20,021)	19,286 (18,660–19,912)	19,232 (18,881–19,584)	0.984	109.7 (108.4–110.9)	110.6 (109.6–111.5)	110.0 (109.5–110.5)	0.458
Girls adjusted[b]								
Birth	3385 (3259–3512)	3468 (3371–3564)	3459 (3403–3516)	0.539	49.5 (49.0–50.0)	49.8 (49.4–50.2)	49.7 (49.4–49.9)	0.635
4 months	6794 (6580–7008)	6824 (6661–6987)	6912 (6818–7005)	0.464	63.9 (63.4–64.5)	64.0 (63.6–64.4)	64.0 (63.8–64.2)	0.973
8 months	8479 (8197–8761)	8545 (8326–8763)	8608 (8483–8733)	0.671	70.6 (70.0–71.2)	70.8 (70.3–71.2)	70.7 (70.4–70.9)	0.883
18 months	10,881 (10,532–11,230)	10,960 (10,698–11,222)	11,088 (10,937–11,239)	0.463	81.9 (81.2–82.7)	82.0 (81.4–82.6)	82.3 (82.0–82.6)	0.526
3 years	14,366 (13,881–14,851)	14,739 (14,372–15,105)	14,527 (14,321–14,732)	0.443	94.8 (93.9–95.7)	95.8 (95.1–96.5)	95.3 (94.9–95.7)	0.181
5 years	19,390 (18,596–20,184)	19,215 (18,613–19,818)	19,268 (18,929–19,607)	0.942	110.0 (108.9–111.2)	110.4 (109.5–111.2)	110.0 (109.5–110.5)	0.776

[a] Corrected for exact age at measurement, gestational age at birth.

[b] Adjusted for maternal body mass index and paternal height

Linear mixed model. $P < 0.05$ was considered to be significant.

Over 80% of included children were measured at each measurement point.

and fresh embryo transfer (*n* = 72) with a natural conception control group. Girls born after fresh embryo transfer were taller compared with natural conception and FET at a single measurement, which was taken between 3.5 and 11.0 years, corrected for parental height and BMI. No other statistically significant differences were found (*Green et al., 2013*). In a recently published retrospective cohort from the USA (*Ainsworth et al., 2019*), the growth of children born after FET (*n* = 49) and fresh embryo transfer (*n* = 87) was similar up to the age of 5 years, but loss to follow-up was significant, with only six children in the FET group and 18 children in the fresh embryo transfer group measured at 5 years.

In a UK cohort study, preterm and term singletons born after FET (*n* = 1091) and fresh embryo transfer (*n* = 4127) were compared with matched natural conception controls. The measurements were made at birth, at 6–8 weeks and at 4–7 years, when growth information was available for 48–51% of the children. Primary covariates in the analyses were deprivation, maternal smoking, age, year, month of delivery and gender. By 4–7 years of age, no significant differences were identified in weight between the groups. Compared with natural conception, however, children born after FET were slightly taller and children born after fresh embryo transfer had a slightly lower BMI. Probabilistic matching of different health records based on names and dates of birth was used, as no unique identifiers were available, and no parental anthropometric data were available for adjustments (*Hann et al., 2018*). Another recently published UK study found no difference in growth at the age of 5 years between children born after FET (*n* = 179), fresh embryo transfer (*n* = 576) and natural conception, adjusting for maternal age, parity, smoking, weight, height, socioeconomic status and offspring sex (*Turner et al.. 2020*). In a recent Norwegian study, preterm and term children born after FET (*n* = 179) were longer and heavier for the first 2 years compared with fresh embryo transfer (*n* = 1073). At the age of 17 years, no significant differences were found. Adjustments were made for maternal age, parity, educational level, smoking, parental BMI, height and gestational age at birth. The growth data were self-reported (*Magnus et al. 2021*).

The present study is in line with previous studies (*Wennerholm et al., 1998*; *Green et al., 2013*; *Hann et al., 2018*; *Ainsworth et al., 2019*; *Turner et al., 2020*) in finding similar childhood weights between the groups. Regarding height, this study somewhat contradicts *Green et al. (2013)*, *Hann et al. (2018)* and *Magnus et al. (2021)*, as no significant difference in height between the groups for boys, girls or the entire population was found. Also, in contrast to the results of *Hann et al. (2018)* and *Magnus et al. (2021)*, the childhood BMIs did not differ significantly between the groups in the present study. Different adjustments and the inclusion of only term-born children in the present study might explain these differences.

In recent years, accumulating evidence has shown that FET in a hormonally programmed cycle, in which there is no functioning corpus luteum, increases the risk of adverse perinatal outcomes, such as hypertensive disorders in pregnancy, preterm birth and fetal macrosomia (*Ginström Ernstad et al., 2019*; *Asserhøj et al., 2021*; *Hu et al., 2021*). In the present study population, most (over 90%) of the FETs were carried out in a natural cycle, which may offer additional explanation to the similar growth between the study groups. No data on the mode of FET cycles have been presented in the previous child growth studies (*Wennerholm et al., 1998*; *Hann et al.,* 2018; Ainsworth et al., 2019; Turner et al., 2020; Magnus et al., 2021), except for the study by Green et al. (2013), in which 81% of FETs were carried out in a natural cycle.

Child growth is complexly regulated, with genetic, epigenetic and environmental components having an effect. Increasing maternal and paternal height, weight and BMI are positively correlated with child growth, with especially maternal obesity associating strongly with childhood obesity of the offspring (Addo et al., 2013; Sørensen et al., 2016; Ohlendorf et al., 2019). Furthermore, excessive maternal gestational weight gain and gestational diabetes increase the risk of childhood obesity (Josey et al. 2019; Ohlendorf et al., 2019). First-borns tend to be smaller than their later-born peers, and it has been suggested that postnatal catch-up growth may increase their metabolic risks (Wells et al., 2011; Kwok et al., 2016). Low parental educational level has also been shown to be associated with elevated risk of child obesity (Bramsved et al., 2018). Breastfeeding is protective of childhood obesity (Yan et al., 2014; Pattison et al., 2019). In the present study, only pre-pregnancy maternal BMI was available with no data on gestational weight gain. Also, no data on breastfeeding were available. Information on a large number of other confounding factors, however, was available, and adjustments were made for exact age at measurement, maternal BMI and paternal height. Considering the study size, we were not able to adjust for the number of embryos transferred.

One major strength of the present study is the reliability of the child growth data derived from high-coverage municipal child health clinic follow-up appointments in Finland (THL, 2019b). Growth data collection in the child health clinics is prospective, based on standardized methods used in the regular scheduled visits to see either a public health nurse or a physician (THL, 2017). Therefore, loss to follow-up was minimal in this study, with growth data covering over 80% of all the children included in the study at each measurement point throughout the 5 years. This made accurate information provided by medical professionals available for both FET and fresh embryo transfer groups, as well as children born after natural conception, adding to the plausibility of these results. Only term-born singleton children were included to minimize confounders associated with multiple gestations, preterm birth, or both. Furthermore, siblings, i.e. subsequent births to the same mother, were excluded to ensure the groups were totally independent for statistical analyses. Another strength is the ability to link information reliably based on the unique personal identifier codes given to every Finnish citizen and permanent resident at birth or immigration.

The main weakness of this study is the relatively small sample size, which was limited by the two-centre setting and the exclusion of preterm children and all multiple births. Also, within this study period, the effects of prolonged embryo culture times or vitrification could not be investigated. It should also be considered that these results represent a geographically restricted area in a high-income country with inhabitants whose ethnic background is mainly white.

Although causality can seldom be shown in an observational epidemiological study, the similarities in childhood growth seem to imply that the mode of conception is not the only contributing factor in the growth pattern of the term-born singleton child. It has been suggested that the intrauterine growth differences shown in a number of previous studies might be explained by the underlying cause of infertility or subfertility, laboratory procedures, placentation or epigenetic changes of the offspring, or a combination of all these factors (Berntsen et al., 2019). Whatever the cause, it does not seem to have a clinically significant effect on long-term growth after birth.

In conclusion, the rate of embryo cryopreservation is steadily increasing worldwide, as more SETs, donor treatments, fertility-sparing treatments and even freeze-all policies in routine treatments are advocated. This study provides important further evidence that FET does not cause long-term harm for the offspring.

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