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Growth in children conceived by ART

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STUDY QUESTION: Is the growth pattern of children conceived by ART different compared to naturally conceived children.

SUMMARY ANSWER: Both ART and underlying parental subfertility may contribute to differences in early childhood growth between children conceived with and without the use of ART.

WHAT IS KNOWN ALREADY: Children conceived by ART weigh less and are shorter at the time of delivery. The extent to which differences in growth according to mode of conception persist during childhood, and the role of underlying parental subfertility, remains unclear.

STUDY DESIGN, SIZE, DURATION: We conducted a prospective study population-based study. We studied 81 461 children participating in the Norwegian Mother, Father and Child Cohort Study (MoBa) and 544 113 adolescents screened for military conscription.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Conception by ART as registered in the Medical Birth Registry. We compared maternally reported length/height and weight among children in MoBa from mid-pregnancy to age 7 according to mode of conception using mixed-effects linear regression. Differences in self-reported height and weight at 17 years of age at screening for military conscription were assessed with linear regression.

MAIN RESULTS AND THE ROLE OF CHANCE: At birth, children conceived by ART were shorter (boys −0.3 cm; 95% CI, −0.5 to −0.1), girls −0.4 cm; 95% CI, −0.5 to −0.3) and lighter (boys −113 grams; 95% CI, −201 to −25, girls −107 grams; 95% CI, −197 to −17). After birth, children conceived by ART grew more rapidly, achieving both greater height and weight at age 3. Children conceived by ART had a greater height up to age 7, but did not have a greater height or weight by age 17. Naturally conceived children of parents taking longer time to conceive had growth patterns similar to ART children. Children born after frozen embryo transfer had larger ultrasound measures and were longer and heavier the first 2 years than those born after fresh embryo transfer.

LIMITATIONS, REASONS FOR CAUTIONS: Selection bias could have been introduced due to the modest participation rate in the MoBa cohort. Our reliance on self-reported measures of length/height and weight could have introduced measurement error.

WIDER IMPLICATIONS OF THE FINDINGS: : Our findings provide reassurance that offspring conceived by ART are not different in height, weight or BMI from naturally conceived once they reach adolescence.

STUDY FUNDING/COMPETING INTEREST(S): Research Council of Norway; Medical Research Council; National Institute of Environmental Health Sciences. The authors have no competing interest.

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Key words: ART / BMI / growth / height / weight

Introduction

ART is associated with lower birthweight (Dhalwani *et al.*, 2016; Qin *et al.*, 2016; Romundstad *et al.*, 2008). The extent to which differences in growth persist during childhood is not clear (Bay, 2014). The assessment of effects of ART on childhood and adolescent growth should take into account the role of underlying parental subfertility (Ceelen *et al.*, 2008), parental height and weight (Bonduelle *et al.*, 2005) and possible sex-specific differences (Bay, 2014). There might also be differences according to the type of ART on childhood growth (Ceelen *et al.*, 2008; Bay *et al.*, 2019). These aspects have not been adequately addressed in existing studies. Children conceived by ART may have increased risk of chronic diseases (Vrooman and Bartolomei, 2017), and it is important to understand whether this might be reflected in an altered growth pattern. A plausible mechanism underlying a relationship between ART and offspring health and development includes epigenetic changes (Mani *et al.*, 2020).

The objective of the current study was to compare growth patterns of children conceived by ART to naturally conceived children. We assessed growth from foetal life to age 7 in 81 461 children participating in the Norwegian Mother, Father and Child Cohort Study (MoBa). We also examined growth among naturally conceived children of parents using longer time to conceive. We adjusted for parental anthropometric measurements and explored possible sex differences. Differences in body size at age 17 were explored using data for 544 113 adolescents mandatorily screened for military service.

Materials and methods

This study was approved by the Regional Committee for Medical and Health Research Ethics for South/East Norway.

The Norwegian Mother, Father and Child Cohort Study

The MoBa recruited pregnant women across Norway between 1999 and 2008 at the time of the routine ultrasound screening around gestational Week 18, and includes more than 114 500 children (Magnus *et al.*, 2006, 2016). The data collection in MoBa is approved by the Norwegian Data Inspectorate. All participants provided a written informed consent. Ultrasound measurements and maternal-completed questionnaires from pregnancy up to age 7 were linked to data from the Medical Birth Registry of Norway (MBRN) (Irgens, 1998). Children in MoBa were eligible for the current study if they were singletons and had at least two measurements of length/height and weight. Flow chart and inclusion criteria are shown in Supplementary Fig. SI. The proportion of missing data for the various covariates is shown in Supplementary Table SI. We included 81 461 singletons with at least two measurements of weight and length/height between birth and 7 years of age and complete covariate information in our analyses.

The Armed Forces Health Registry

We included all men and women who were mandatorily screened for military service through an online questionnaire and registered in the Armed Forces Health Registry. To participate in the military screening is a citizen duty, but those who are seriously ill or impaired are exempted, another small portion do not participate due to their citizenship, foreign residence or civil disobedience. The use of the national health registries for research purposes, including the Armed Forces Health Registry, does not require consent according to Norwegian legislation. We linked self-reported height and weight at 17 years of age to birth records on all singletons born between 1992 and 2001 (n = 544 113), comprising 94% of all singletons registered in the MBRN who were alive at the time of linkage. Thus only 6% of all children born during this period in Norway had not undergone the mandatory screening, and the proportion of ART children was similar among those screened and those not screened (~0.8%).

A description of the data sources and linkage procedures are provided in the Supplementary methods. The childhood growth among participants in MoBa and differences in height and weight at 17 years of age in the Armed Forces Registry were therefore evaluated separately.

ART and parental subfertility

Use of ART was registered in the MBRN with the following subtypes: IVF, ICSI or ‘other/unknown’ fertilization methods. The registry also provided information on whether the transferred embryo was fresh or had been frozen. Children conceived by intrauterine insemination (54 children in MoBa; 12 in the Armed Forces Health Registry) were included in the naturally conceived. The MBRN was used to defined conception by ART both for MoBa and individuals registered in the Armed Forces Health Registry. Through the questionnaires administered in MoBa at 18 gestational weeks, women reported how long the couple had actively been trying to conceive. We categorized time to pregnancy as ‘within 3 months’, ‘between 4 and 12 months’ and ‘more than 12 months’. Subfertility was defined as having tried to conceive for more than 12 months.

Anthropometric measurements

Prenatal care of pregnant women in Norway is part of the universal health care system. All pregnant women undergo an ultrasound examination at ~18 gestational weeks. Ultrasound data from this routine screening were available for 82% of children in MoBa, with information on date of examination, femur length (mm), middle abdominal diameter (mm) and biparietal diameter (mm). The MBRN provided length and weight at birth. In MoBa, mothers reported through questionnaires their child’s length/height and weight as measured by public health nurses according to guidelines from the Norwegian Directorate of Health and registered on their child’s health report cards, at ages 6 weeks, 3, 6, 8, 12, 15, 18, 24 and 36 months, and at 5 and 7 years. Men and women self-reported height and weight at age 17 as part of screening for fitness for military services.

We calculated BMI as weight in kg/height in m^2.

Covariates

We examined characteristics that could influence the associations between parental subfertility (time to pregnancy >12 months) or use of ART and offspring growth, including maternal age (continuous), parity (0, 1, 2, 3 or higher), the child’s sex (boy or girl) and gestational age at delivery (estimated from ultrasound measurements) or at time of ultrasound examination (estimated from the embryo transfer date). See

Supplementary methods for details. Self-reported information on maternal educational level (less than high school, high school, up to 4 years of college, more than 4 years of college), smoking during pregnancy (never, former, quit before 12 gestational weeks, continued smoking after 12 gestational weeks), and maternal and paternal height and weight at the beginning of pregnancy was available through MoBa questionnaires. In 87% of the adolescents screened for military service, their fathers' measures of height and weight from age 17–19 (the time of the fathers' military screening) was registered in the Armed Forces Health Registry.

A priori, we decided not to exclude children likely to have poor intrauterine growth (such as preterm, small-for-gestational age or children with congenital malformations) or children of mothers with pregnancy complications known to influence intrauterine growth (gestational diabetes or pre-eclampsia). These factors are likely to be on the causal pathway of differences in growth seen between children conceived by ART and naturally. We also did not exclude children with chronic conditions or children who required medications, because underlying health problems could influence growth patterns and therefore be part of the explanatory mechanism for differences in growth according to conception by ART.

Measurements of gestational age in the birth registry

For the analysis of growth from birth to 7 years of age, we used the estimated gestational age in weeks based on ultrasound measures as recorded in the birth registry. The gestational age at the time of the routine foetal ultrasound measurements was estimated among children conceived by ART as the date of the ultrasound measurement minus the date of the embryo transfer plus 2 days to account for the time of culture duration. We did not have the exact number of culture days, but this was routinely either 2 or 3 days during the time when the MoBa children were born (between 1999 and 2009). As we did not compare this estimate of the gestational age among children conceived by ART to the gestational age estimated based on the last menstrual period among naturally conceived children, we did not add an additional 14 days to the estimated gestational age. Adding a constant of 14 days to the estimated gestational age of the children conceived by ART would not have changed our results when comparing different subgroups of children conceived by ART.

Statistical analyses

All analyses were conducted in STATA version 15 (Statacorp, TX, USA).

Women using ART to conceive do not have a comparable last menstrual period to other women due to controlled ovarian stimulation. It is therefore difficult to define gestational age at routine ultrasound in the same way for ART and naturally conceived foetuses. This complicates the comparison of foetal size based on ultrasound measurements between ART and naturally conceived children. We therefore decided to compare foetal growth in second trimester only between children conceived by fresh and frozen embryo transfer, since we could use the embryo transfer date to estimate the gestational age. We adjusted for maternal age, education, parity, smoking during pregnancy, parental height, parental BMI and estimated gestational age at the time of ultrasound examination based on embryo transfer date. We accounted for dependency between siblings by using robust cluster variance estimation. We also conducted a sensitivity analysis including stillbirths and live born children without postnatal anthropometric measurements.

Differences in length/height, weight and BMI from birth until 7 years were modelled with mixed-effects linear regression with a random intercept and slope (Rabe-Hesketh, 2012). This approach accounts for missing data in the outcome of interest at the individual measurement points. We restricted the analysis to those with complete information on all potential confounders. We chose not to use multiple imputation to account for missing information on potential confounders due to the collinearity in the repeated outcome measures, making it difficult to include all outcome measurement points in an imputation model simultaneously. Furthermore, only 9% of children were excluded due to missing information on potential confounders (Supplementary Fig. S1). We first compared children conceived by any type of ART to all naturally conceived children, before estimating differences according to ART subtypes and cryopreservation. We explored the effect of underlying subfertility by comparing naturally conceived children of parents who conceived within 3 months (reference group) to children of parents who tried to conceive for 4–12 months, for more than 12 months, and also to children conceived by ART. We used linear splines to model change in weight, length/height and BMI over time. Knot points were chosen at 3, 18, 36 months and 5 years by examining models with a decreasing number of restricted cubic splines and comparing the likelihood ratio tests. All estimates were adjusted for maternal age, education, parity, smoking during pregnancy, parental height, parental BMI and length of gestation. After fitting the mixed-effects models, we predicted the marginal mean differences at the designated time points at the means for continuous covariates, and the largest/most common category for categorical covariates. Results are presented as differences in z-scores, which were internally standardized by age and sex based on the distribution of the MoBa cohort. We also present the absolute differences stratified by sex. As a sensitivity analysis, we included maternal identity as an extra level in the mixed-effects model, in addition to the child's identity, to account for the presence of siblings in the cohort.

Using linear regression, we estimated differences in height, weight and BMI at age 17 according to mode of conception among individuals with information from the Armed Forces Health Registry. Among those conceived by ART, we compared those born after frozen and fresh embryo transfer. We accounted for dependency between siblings by using robust cluster variance estimation. The multivariable analysis for estimates at age 17 adjusted for maternal age, parity, year of birth, sex and age (in years) at the time of screening. The proportion of individuals excluded due to missing covariate information from the analysis of differences in height and weight at age 17 in the Armed Forces Health Registry was <3%.

Results

Singletons in MoBa included and excluded from the analyses due to missing covariate information were similar with regard to maternal age at delivery, parity and sex. A total of 79 740 children included in the analysis were conceived naturally and 1721 children were conceived by ART. None of the children died during the first 7 years of life. Among the naturally conceived, 5279 children were born to subfertile parents (more than 12 months to conception). Children conceived through ART or by subfertile parents had older mothers who were more likely to be nulliparous have a higher educational attainment and less likely to smoke (Table I). Parents of children conceived by ART tended to have a higher BMI and be slightly taller than parents of naturally conceived children (Table I).

Differences in foetal life

Among children in MoBa conceived by ART, a total of 1252 children was registered with either frozen or fresh embryo transfer and had ultrasound measurements from around 18 gestational weeks (mean 17 weeks and 2 days, SD 6 days). All foetal dimensions tended to be larger in those conceived after frozen embryo transfer than those conceived after fresh embryo transfer (Table II). The sensitivity analysis including stillbirths and children without any postnatal anthropometric measurements did not notably change the results.

Differences from birth to age 7

An average of seven measurements per child was available during this period (minimum 2, maximum 12). Children born after ART had a mean birthweight of 3495 g (SD, 536) and a mean length of 50.2 cm (SD, 2.1), compared to 3608 g (SD, 500) and 50.5 cm (SD, 1.9) in

Table I Characteristics of children born after ART and after natural conceptions.

Background characteristics	Naturally conceived children (n = 79 740)		Children conceived by ART (n = 1721)
	Children of fertile parents (n = 74 461)	Children of subfertile parents (n = 5279)	
Maternal age, mean (SD)	30 (5)	32 (5)	33 (4)
Maternal parity, N (%)			
0	36 068 (45)	2949 (56)	1197 (67)
1	28 438 (39)	1602 (30)	424 (25)
2	12 004 (15)	570 (11)	75 (4)
3 or higher	3230 (4)	158 (3)	25 (2)
Maternal education, N (%)			
Less than high school	5355 (7)	402 (8)	95 (6)
High school	22 921 (29)	1690 (32)	447 (26)
Up to 4 years of college	33 007 (41)	2092 (40)	728 (42)
More than 4 years of college	18 457 (23)	1096 (21)	451 (26)
Maternal BMI,[a] mean (SD)	24 (4)	25 (5)	24 (4)
Paternal BMI,[a] mean (SD)	26 (3)	26 (3)	26 (4)
Maternal height, mean (SD)	168 (6)	168 (6)	169 (6)
Paternal height, mean (SD)	182 (6)	182 (6)	182 (7)
Maternal smoking in pregnancy, N (%)			
No	41 309 (52)	2615 (50)	929 (54)
Former	20 369 (26)	1272 (24)	594 (35)
Quit before 12 gestational weeks	10 583 (13)	801 (15)	100 (6)
Continued after 12 gestational weeks	7479 (9)	591 (11)	98 (6)
Ovarian stimulation			
No	73 733 (99.0)	4207 (79.7)	NA
Yes	728 (1.0)	1072 (20.3)	NA
Offspring sex, N (%)			
Male	40 904 (51)	2747 (52)	871 (51)
Female	38 836 (49)	2532 (48)	850 (49)
Offspring gestational age, mean (SD)	40 (2)	39 (2)	39 (2)
Small-for-gestational age[b]			
No	67 002 (91.2)	4589 (88.4)	1470 (87.1)
Yes	6506 (8.9)	600 (11.6)	218 (12.9)

Fertile parents were those using up to 12 months to conceive, subfertile parents were those using more than 12 months to conceive.
[a]The BMI is the weight in kilograms divided by the square of the height in metres.
[b]Defined as a birthweight below the 10th percentile for sex and gestational age.

Table II Mean and adjusted a differences (in mm) in ultrasound measures of foetal size around 18 gestational weeks after frozen as compared to fresh embryo transfer.

Embryo transfer		Femur length in mm		Biparietal diameter in mm		Middle abdominal diameter in mm	
	No. of children	Mean (SD)	Difference (95% CI)[a]	Mean (SD)	Difference (95% CI)[a]	Mean (SD)	Difference (95% CI)[a]
Fresh	1073	28.1 (2.5)	Reference	45.3 (2.7)	Reference	42.4 (3.08)	Reference
Frozen	179	28.5 (2.4)	0.3 (0.1 to 0.6)	45.7 (2.5)	0.3 (0.0 to 0.5)	42.6 (2.86)	0.1 (−0.3 to 0.5)

[a]Adjusted for maternal age, education, parity, smoking during pregnancy, parental height, parental BMI (weight in kilograms divided by the square of the height in meters), sex and gestational age at the time of the routine ultrasound screening.

naturally conceived children (Supplementary Table SII). The means and SD of the measurements from birth to age 7 by sex are shown in Supplementary Table SIII, while the absolute differences at each time point are shown in Supplementary Table SIV. Children conceived by ART experienced a more rapid growth during the first 18 months of life (Fig. 1 and Supplementary Table SIV). After around 1 year of age, children born after ART were slightly longer and heavier until age 7 (Fig. 1). The results were similar for boys and girls (Supplementary Fig. S2). Findings were also similar in first born (primiparous mothers) and later born (multiparous mothers) children (Supplementary Fig. S3). Children born to subfertile parents were also smaller at birth, although not as small as children born after ART, and showed a similar rapid growth during the first years of life as children conceived by ART (Fig. 2). There was an apparent dose–response relationship between how long the couple had tried to conceive and differences in offspring growth, as indicated by greater differences with increasing time to pregnancy reported by the parents (Fig. 2). A total of 28% of the children had at least one participating sibling in the cohort. Adding maternal identification number as an extra random effects level in the mixed-effects model, to account for the presence of siblings, did not change the results.

Differences up to age 7 by ART methods

At birth, children conceived by fresh embryo transfer were smaller than naturally conceived children, while those born after frozen embryo transfer were more similar to naturally conceived children (Fig. 3 and Supplementary Table SII). Frozen embryo transfer children remained heavier than fresh embryo transfer children up to age 6 (Supplementary Fig. S4). Children in all ART groups experienced a rapid postnatal growth (Fig. 3). When comparing four mutually exclusive ART groups (fresh embryo IVF, fresh embryo ICSI, frozen embryo IVF and frozen embryo ICSI) to naturally conceived children, there were little differences in growth according to IVF versus ICSI, but differences appeared to be between fresh versus frozen embryo transfer children (Supplementary Fig. S5).

Differences at age 17

At age 17, men were on average 180.4 cm tall (SD, 6.8) and women were 167.3 cm (SD, 6.1). Mean weight was 74.5 kg (SD, 13.6) for men and 63.0 kg (SD, 11.4) for women. Differences between individuals

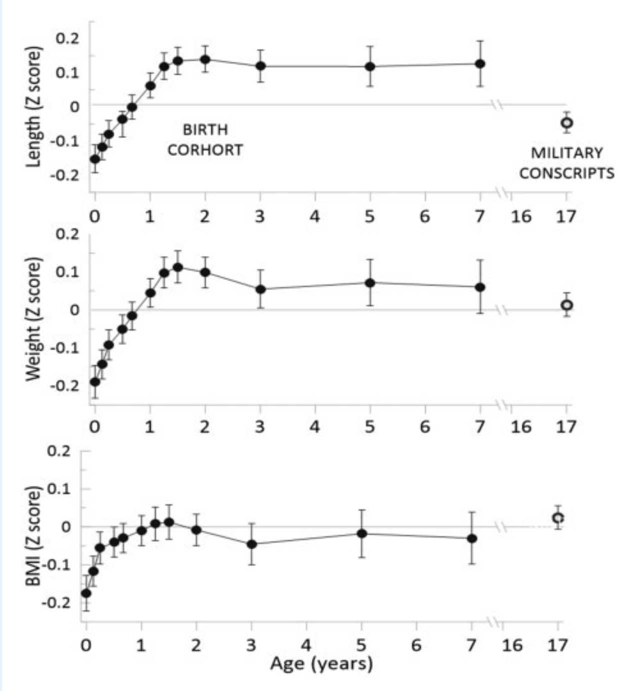

Figure 1. Adjusted[a] mean (±95% CI) differences in length/height, weight and BMI[b] between children born after use of ART and naturally conceived children (reference group). The open circle indicates the one measure at 17 years of age available from the online screening of eligibility for military service, while the closed circles reflect the postnatal measurements available for children participating in the Norwegian Mother and Child Cohort Study. [a]Adjusted for maternal age, maternal parity, maternal educational level, maternal smoking during pregnancy, parental BMI, parental height and gestational age at birth. To obtain the marginal estimate of adjusted means, we predicted the adjusted mean differences at the means of continuous covariates and at the largest category for categorical covariates. We therefore predicted the adjusted mean differences for children with a mother who was age 30 years at delivery, primiparous, had up to 4 years of higher education, was 168 cm tall, had a BMI of 24 and had never smoked, having a father who was181 cm tall and had a BMI of 25 and who was born at 40 gestational weeks. [b]The BMI is the weight in kilograms divided by the square of the height in metres.

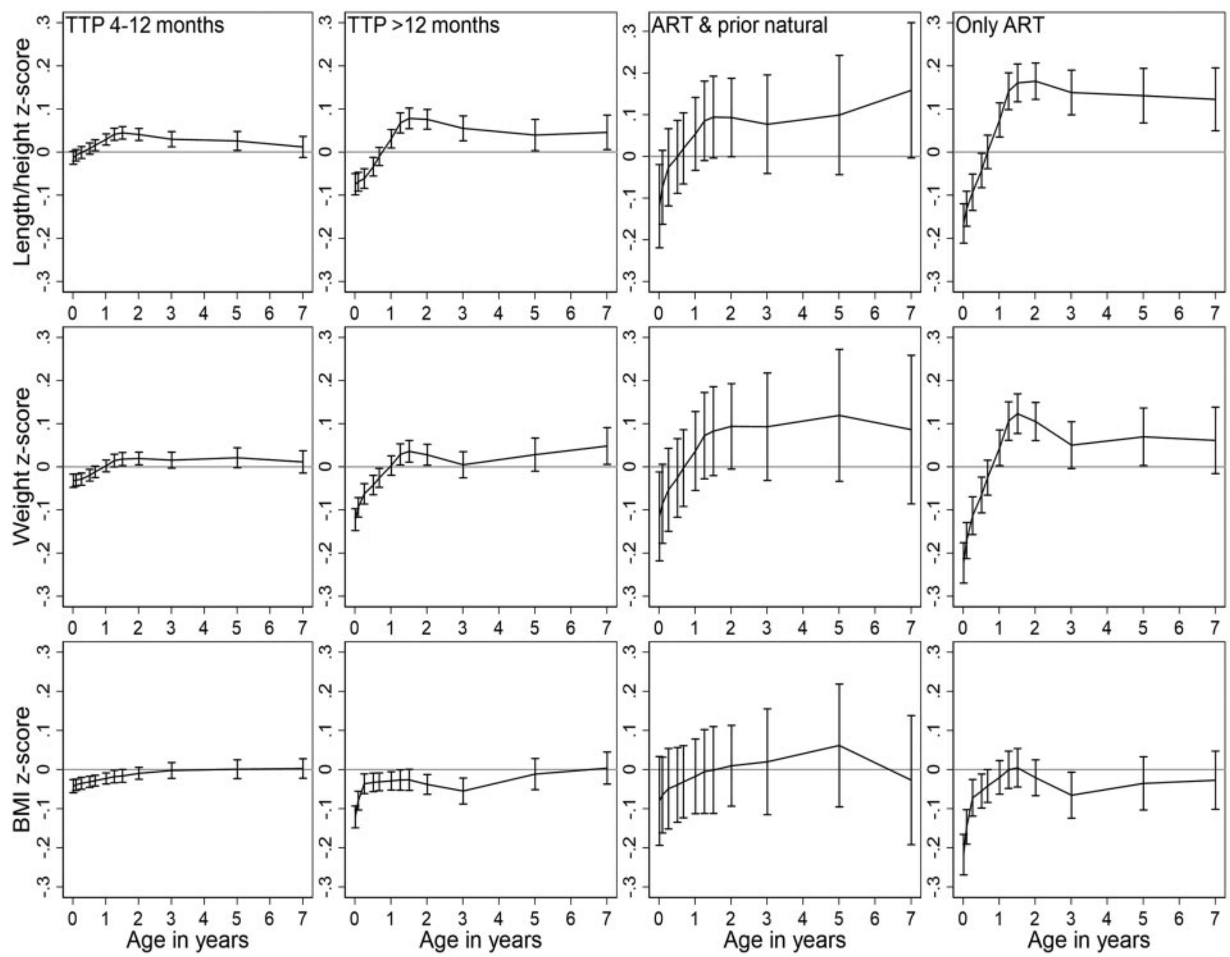

Figure 2. Adjusted[a] mean (±95% CI) differences in z-scores of length/height, weight and BMI[b] in children born after a time to pregnancy (TTP) of either 4–12 months or more than 12 months, or born after ART by mothers who had a previous naturally conceived child (ART and prior natural), or had no previous naturally conceived child (only ART). Children of parents who became pregnant within 3 months were the reference group. [a]Adjusted for maternal age, maternal parity, maternal educational level, maternal smoking during pregnancy, parental BMI, parental height and gestational age at birth. To obtain the marginal estimate of adjusted means, we predicted the adjusted mean differences at the means of continuous covariates and at the largest category for categorical covariates. We therefore predicted the adjusted mean differences for children with a mother who was age 30 years at delivery, primiparous, had up to 4 years of higher education, was 168 cm tall, had a BMI of 24 and had never smoked, having a father who was181 cm tall and had a BMI of 25 and who was born at 40 gestational weeks. [b]The BMI is the weight in kilograms divided by the square of the height in metres.

conceived naturally or by ART were very small (Fig. 1 and Supplementary Table SV). When comparing those conceived by frozen embryo transfer to those conceived by fresh embryo transfer, there was no clear evidence of differences in anthropometric measurements (Supplementary Table SV). The results were similar after additional adjustment for paternal height and BMI in the subpopulation with this information (Supplementary Table SV).

Discussion

Using two large-scale population-based data sources, we found differences in body size between children conceived by ART and naturally up until around age 3, while at age 17 ART adolescents were overall similar to naturally conceived adolescents. Children conceived by frozen embryo transfer tended to be larger from foetal life up to age six, than children born after fresh embryo transfer. Children born to subfertile parents had similar growth as children born after ART, suggesting that at least part of the difference in growth pattern among children conceived by ART may be due to factors underlying parental fertility problems, rather than the ART procedure itself.

Our results show that children conceived by ART are smaller at the time of delivery, experience a rapid catch-up growth, but are largely similar in length/height and weight to naturally conceived children at school age. A recent meta-analysis of postnatal growth among ART children pooled findings from 13 studies (in total 3972 ART conceived children and 11 012 naturally conceived children) (Bay *et al.*, 2019), and found no strong evidence of a difference in weight up to the age

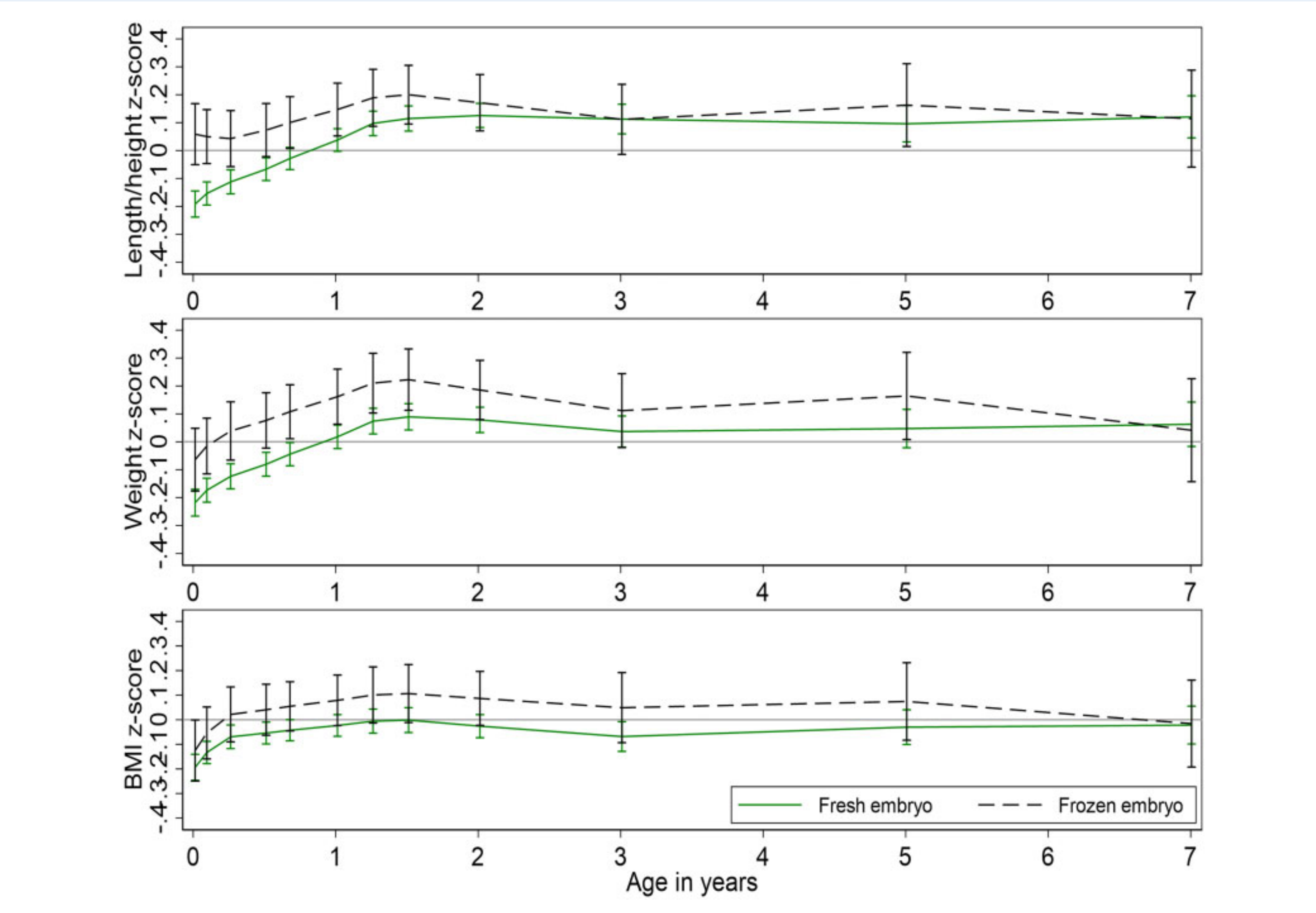

Figure 3. Adjusted[a] mean (±95% CI) differences in z-scores of length/height, weight and BMI[b] between children conceived by frozen or fresh embryo transfer compared to naturally conceived children (reference group). [a]Adjusted for maternal age, maternal parity, maternal educational level, maternal smoking during pregnancy, parental BMI, parental height and gestational age at birth. To obtain the marginal estimate of adjusted means, we predicted the adjusted mean differences at the means of continuous covariates and at the largest category for categorical covariates. We therefore predicted the adjusted mean differences for children with a mother who was age 30 years at delivery, primiparous, had up to 4 years of higher education, was 168 cm tall, had a BMI of 24 and had never smoked, having a father who was 181 cm tall and had a BMI of 25 and who was born at 40 gestational weeks. [b]The BMI is the weight in kilograms divided by the square of the height in metres.

22 according to mode of conception. However, when they stratified by age groups, 0–4 and 5 years and older, they found some evidence of a lower weight among ART conceived children 0–4 years. This is in line with our observations. They did not find differences in length, in contrast to our study. Notably, the studies included in the meta-analysis are heterogeneous and varied greatly in their multivariable adjustment strategy. They were European, Australian or North American and included measurements up until between 2 and 12 years of age. Several of these studies chose to match cases and control on a few specific characteristics instead of multivariable adjustment. Also, a lot of them only accounted for a limited number of covariates due to modest sample size.

Based on our observations in the MoBa cohort, the differences in growth according to mode of conception were more pronounced for children conceived by fresh embryo transfer, while children conceived by frozen embryo transfer were more similar to naturally conceived children. A meta-analysis of 31 studies compared pregnancy complications between children conceived by fresh versus frozen embryo transfer and found that children conceived by frozen embryo transfer had a lower risk of being small-for-gestational age and a greater risk of being large-for-gestational age (Sha et al., 2018). A Scottish study comparing 5200 ART to 20 800 naturally conceived children found that children born after fresh embryo transfer grew faster from birth but remained lighter at 6–8 weeks than naturally conceived children (Hann et al., 2018). This study also reported that children born after frozen embryo transfer grew similarly to naturally conceived children. A smaller study including 87 fresh embryo transfers and 49 frozen embryo transfers found no difference in growth up until 5 years of age between these two groups (Ainsworth et al., 2019). Our study is the first to show difference in growth between fresh and frozen embryo transfer children up until school age.

Various explanations have been proposed for why children conceived by ART are smaller at birth, including influences by maternal hormone treatment used to stimulate ovulation and the growth medium (Pinborg *et al.*, 2013). Another explanation may be that ART induces epigenetic alterations, as the early embryonic development occurring during ART procedures is vulnerable to epigenetic dysregulation (Novakovic *et al.*, 2019). Evidence from animal studies support differences in DNA methylation according to preimplantation embryo culture procedures (Young et al., 2001; Mann *et al.*, 2004; Fauque *et al.*, 2010; Pinborg *et al.*, 2016), although evidence from human studies is scarce. A potential explanation for the differences observed between fresh and frozen embryo transfer is that the intrauterine environment may be more favourable with frozen embryo transfer since these transfers are less influenced by hormone treatments (Kolibianakis *et al.*, 2002; Ng *et al.*, 2004).

While ART is associated with differences in growth *in utero* and after birth, the clinical significance of these observations is not well understood. The rapid growth of ART babies after birth is sometimes described as 'catch-up growth', but this term can be misleading. It has been proposed that a rapid growth rate during infancy is detrimental for later cardiometabolic health. One study of rapid weight gain in children born after IVF indicated a higher blood pressure at 8–18 years of age (Ceelen *et al.*, 2008). A recent large registry-based study from Sweden suggests that ART children also have a higher risk of type 1 diabetes (Norrman *et al.*, 2020). More information is needed on long-term cardiometabolic health in children born after ART.

Strengths of the current study include the use of large health registries including the Armed Forces Health Registry of 17-year olds, and the detailed information on potential confounders. These large sample sizes made it possible to stratify by sex and compare fresh and frozen embryo transfer. An important strength of the MoBa cohort was the opportunity to compare children born after ART to naturally conceived children of subfertile parents. We adjusted for parental body size as important markers of the underlying genetic growth potential, which most previous studies have not adjusted for (Bonduelle *et al.*, 2004).

MoBa studies are limited by possible selective enrolment (Nilsen *et al.*, 2009). However, the proportion of singleton ART children in MoBa (2.8%) was similar to the proportion of singleton children conceived by ART registered in the MBRN during the MoBa recruitment period (2.6%), indicating that selection into the MoBa cohort was not strongly related to use of ART. ART practices and methods are rapidly evolving. It is possible that the relationships we observed with childhood growth do not represent current ART practices. We excluded stillbirths and children without two postnatal anthropometric measurements from the main analysis of the ultrasound measurements. Including these children did not change the associations observed.

We were able to include the gross majority of children born in Norway between 1992 and 2001, alive and still living in Norway at age 17 and eligible for the universal screening for military service. However, in the registry-based analyses of military recruits, we had limited ability to adjust for potential confounders. The screening provided self-reported height and weight through online screening questionnaires which could have resulted in a degree of measurement error. To examine the validity of these self-reported measurements, we assessed the correlation between self-reported and measured height and weight among individuals who were selected for further evaluation by a military doctor in preparation for conscription (n = 155 335). The correlation was 0.91 for weight and 0.97 for height, indicating an overall high validity of the self-reported measurements.

Conclusions

Children conceived by ART grow differently in early life than naturally conceived children. Part of this difference is likely to be due to the ART procedures, but the difference in growth also reflects underlying factors influencing parental fertility problems. ART-related differences in weight and height decreased with age, and had waned by age 17.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article are available by application to the Norwegian Mother and Child Cohort Study (mobaadm@fhi.no). An ethical approval is required.

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Authors' roles

M.C.M., A.J.W. and S.E.H. contributed substantially to conception and design of the study. M.C.M conducted the statistical analysis and wrote the first draft of the manuscript. All authors contributed to the interpretation of results and critically revised the article for publication. All authors approved the final manuscript.

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Conflict of interest

All authors declare no conflict of interest.

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