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Infertility treatment and children's longitudinal growth between birth and 3 years of age

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STUDY QUESTION: Does early childhood growth from birth through to 3 years of age differ by mode of conception?

SUMMARY ANSWER: Findings suggest early childhood growth was comparable for children irrespective of infertility treatment, but twins conceived with ovulation induction with or without intrauterine insemination (OI/IUI) were slightly smaller than twins conceived without treatment.

WHAT IS KNOWN ALREADY: Although studies have found that babies conceived with infertility treatment are born lighter and earlier than infants conceived without treatment, little research especially for non-assisted reproductive technology (ART) treatments has focused on their continued growth during early childhood.

STUDY DESIGN, SIZE, DURATION: Upstate KIDS recruited infants born (2008–2010) to resident upstate New York mothers. Infants were sampled based on birth certificate indication of infertility treatment; specifically, for every singleton conceived by infertility treatment, three singletons without infertility treatment were recruited and matched on region of birth. All multiple births irrespective of treatment were also recruited. Children were prospectively followed, returning questionnaires every 4–6 months until 3 years of age. In total, 3905 singletons, 1129 sets of multiples (96% of whom were twins) enrolled into the study. Analyses included 3440 (88%) singletons (969 conceived with treatment; specifically, 433 with ART and 535 with OI/IUI) and 991 (88%) sets of multiples (439 conceived with treatment; specifically 233 with ART and 206 with OI/IUI) with growth data available.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Mothers reported infertility treatment use at baseline and children's height and weight from pediatric visits. Self-reported use of ART was previously verified by linkage with the US Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) database. Mixed linear models with cubic splines accounting for age and age–gender interactions were used to estimate mean differences in growth from birth to 3 years by infertility treatment status and adjusting for maternal age, race, education, private insurance, smoking status during pregnancy, maternal pre-pregnancy and paternal body mass indices (BMI).

MAIN RESULTS AND THE ROLE OF CHANCE: Compared with singletons conceived without treatment ($n = 2471$), singletons conceived by infertility treatment (433 by assisted reproductive technologies (ART), 535 by OI/IUI and 1 unknown specific type) did not differ in growth. Compared with twins not conceived with treatment ($n = 1076$), twins conceived with OI/IUI ($n = 368$) weighed slightly less over follow-up (122 g). They were also proportionally smaller for their length (−0.17 weight-for-length *z*-score units). No differences in mean size over the 3 years were observed for twins conceived by ART, though some evidence of rapid weight gain from birth to 4 months (adjusted OR 1.08; 95% CI: 1.00–1.16) suggestive of catch up growth was observed.

LIMITATIONS, REASONS FOR CAUTION: Participants from upstate New York may not be representative of US infants. Although accounted for in statistical analysis, attrition during follow-up may have limited power to detect small differences.

WIDER IMPLICATIONS OF THE FINDINGS: This study is the first to prospectively track the growth of children conceived with and without infertility treatment in the USA, including a substantial number of twins. Our findings are similar to what was previously observed in the ART literature outside of the states.

STUDY FUNDING/COMPETING INTEREST(S): Supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD; contracts #HHSN275201200005C, #HHSN267200700019C). Authors have no competing interests to declare.

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Key words: assisted reproductive technologies / infertility treatment / growth / infant weight gain / ovulation induction

Introduction

With the rising global use of infertility treatments (Kupka *et al.*, 2014; Sunderam *et al.*, 2014), many children are now conceived with assisted reproductive technologies (ART) or fertility enhancing drugs such as clomiphene citrate (Schieve *et al.*, 2009). Arising from the concerns observed in animal models of overgrowth syndromes (Feuer *et al.*, 2013) and the higher risk of low birthweight and preterm delivery found in quantitative meta-analyses (McDonald *et al.*, 2009, 2010), the growth of children conceived with infertility treatment remains controversial in light of its implications for children's health (Yeung and Druschel, 2013). Particularly, impaired fetal growth can precede rapid catch-up growth with potential long-term cardiovascular risk later in childhood (Kelishadi *et al.*, 2015). Most recently, evidence has surfaced that catch-up may increase risk of atherosclerosis and fat deposition even at 3–6 years of age. It is hypothesized therefore that children conceived by infertility treatment may grow differently early in life (i.e. continue to be smaller and experience catch-up in growth) compared with children not conceived by treatment. Although unproven, possible underlying mechanisms include type of hormonal treatment, media culture (Kleijkers *et al.*, 2014) or other aspects of treatment such as ICSI that may induce epigenetic changes during sensitive windows of embryonic development.

Although studies from outside of the U.S. have generally found no difference in growth by infertility treatment exposure (Yeung and Druschel, 2013), crucial data gaps remain. To date, most studies have only included singleton and not multiple-birth infants. Moreover, much of the research has only followed children conceived by *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) with little to no attention to the children conceived with infertility treatments not requiring ART. In addition, despite the genetic contribution of body mass index (BMI) and its association with risk of infertility, parental BMIs are inconsistently adjusted for in analyses investigating childhood growth. Lastly, risk of rapid weight gain during infancy or childhood has also been rarely examined.

Collectively, these findings and data gaps provided the impetus for us to design and implement the Upstate KIDS Study. Specifically using a population-based US sampling framework, we sought to delineate the relation between conception mode (use or not of infertility treatment) and children's growth from birth through to 3 years of age.

Materials and Methods

Study design and population

The Upstate KIDS Study is an ongoing birth cohort, which recruited 5034 women who delivered in New York State (excluding the 5 boroughs of New York City) between 2008 and 2010 (Buck Louis *et al.*, 2014). Parents of all infants conceived by infertility treatment as indicated on birth certificates were invited to participate at approximately 4 months of age. Singleton infants not conceived with infertility treatment were recruited and frequency matched on region of birth to singleton infants whose conceptions were aided by treatment at a 3:1 ratio (Buck Louis *et al.*, 2014). Response rates were slightly higher among infants conceived with infertility treatment (32%) than not (27%) but were otherwise similar by plurality (Buck Louis *et al.*, 2014). Birthweight and gestational age of participants were also similar to non-participants after accounting for plurality and exposure status by birth certificate indication suggesting no bias in participation by these perinatal factors (data not shown). All multiples were also invited to participate. In total, 3905 singletons, 2132 twins and 145 higher-order multiples enrolled. The primary cohort comprised all singletons and one randomly selected multiple of each set.

Ethical approval

The New York State Department of Health (NYSDOH) and the University at Albany (State University of New York) Institutional Review Boards approved the Study and entered into a Reliance Agreement with the National Institutes of Health. All parents provided written informed consent prior to data collection.

Infertility treatment exposure

Using a standardized questionnaire, mothers were queried about specific infertility treatment at 4 months post-partum (Buck Louis *et al.*, 2014). ART included any combination of IVF, ICSI, assisted hatching, frozen embryo transfer, zygote intrafallopian transfer (ZIFT), gamete intrafallopian transfer (GIFT) and/or donor eggs or embryos. Ovulation induction included any combination of oral or injectable medications with or without intrauterine insemination (OI/IUI). We previously compared maternal report of ART use against the US clinical gold standard by linking our cohort with the Society for Assisted Reproductive Technology—Clinical Outcome Reporting System (SART-CORS), and found sensitivity (93%) and specificity (99%) to be excellent (Buck Louis *et al.*, 2015). For this analysis, ART was defined by maternal report, as no registry exists for non-ART infertility treatments. Where maternal self-report was missing (3%), birth certificate information was used to complete exposure status. Hence, no child in the cohort was missing infertility treatment exposure information.

Growth measures

In their invitation packets, mothers received child health journals that were designed to record children's health through to 3 years of age. Mothers were encouraged to take journals to children's regular medical visits for the recording of height and weight performed by healthcare providers. Standardized questionnaires were mailed to mothers every 4–6 months to capture growth information. In each questionnaire, mothers were given a grid to complete with multiple entries corresponding to each time that their children were measured. For example, a mother completing the 4-month questionnaire could report on weight and length at 6 weeks, 2 months etc. up to 4 entries. Mothers indicated the age and date of visit. Weight was elicited in grams/pounds and height in inches/centimeters and converted into SI units.

Birthweight was from birth certificates whereas birth length was from maternal report (Yeung *et al.*, 2015). Observations two interquartile ranges (IQR) below the 25th percentile or 2 IQR above the 75th percentile (Tukey, 1977) for grouped age categories were removed as necessary (<1%). Observations of a child's length decreasing by 1 cm or more were also removed (<1%). To better standardize the responses and to evaluate weight relative to length, *z*-scores were calculated using the World Health Organization Child Growth Standards (de Onis *et al.*, 2006).

In addition to analyses of growth trajectories, rapid infant weight gain was examined among singletons and twins. Infants were classified as having experienced rapid weight gain (yes/no) at 4, 9 and 12 months, respectively. Infant weight gain since birth was calculated at three different time points by taking the differences between weights predicted at 4, 9 and 12 months from our statistical models and birthweight. Predicted weights were used because children did not always visit the pediatrician at those exact time points. Weights before and after those time points (e.g. 3 and 5 months to predict 4 months) then informed the predictive models for estimating weight at those time points. We then calculated standard deviation scores (SDS) for each child at each time point by taking the difference between the child's weight gain and average weight gain among singletons in our sample, divided by their standard deviation (Breij *et al.*, 2014). A child was classified as having experienced rapid weight gain if his/her SDS was above 0.5 for 4 or 9 months or above 0.67 for 12 months (Breij *et al.*, 2014).

Statistical analysis

Twelve percent ($n = 751$) of children were missing information on weight after birth and were excluded from analyses. An additional 344 (5.5%) children were excluded due to missing data for length analyses. Missing data were more likely in the unexposed group than the exposed group with no material differences by plurality (Supplementary data, Fig. S1). Comparisons were made in baseline characteristics by exclusion and infertility status using χ^2 or *t*-test of difference for categorical and continuous data, respectively. Baseline comparisons by infertility treatment exposure were made using similar statistical tests.

Mixed linear models with random coefficient cubic splines for age and age–gender interactions were used to estimate mean differences in growth from birth through to 3 years by infertility treatment exposure status. Furthermore, models included maternal-level random effects and nested infant-level random effects to account for the correlation between repeated measures and between siblings (i.e. for multiples) (Molenberghs, 2006). Analyses which included singletons and one child per family (i.e. the primary cohort) included an infant-level random effect. Longitudinal analyses were first limited to observations before 2 years of age, as pediatricians would begin measuring standing height rather than supine length, *per se*. However, the full longitudinal association with growth to 3 years was then repeated to evaluate whether observations changed. Logistic regression was used to estimate odds ratios (95% CI) for rapid infant weight gain and for risk of childhood overweight/obesity at 36 months. To account for the correlation within families, generalized estimating equations were used for the analysis of multiples.

All analyses were adjusted for maternal age (years), race (white versus non-white), education (college education or not), married or living as such (yes/no), private health insurance (yes/no), smoking during pregnancy (yes/no), maternal pre-pregnancy BMI (kg/m^2) and paternal BMI (kg/m^2). Both maternal and paternal BMI were retained in statistical models as they were not highly correlated (Pearson's correlation = 0.34) but both were significantly positively associated with growth, as measured by weight and length/height. Analyses were repeated stratifying on plurality. Sampling weights were derived based on vital records data on the births occurring during the recruitment period for infertility treatment, plurality and region of birth. They were applied to all analyses to account for the oversampling of infertility treatment and twins by design. Missing covariate data were imputed using the most common response for those with few missing ($n < 10$) and with multiple imputations for all others (i.e. 3.5% missing marital status, 6.7% missing paternal BMI). All analyses were conducted in SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Exclusions based on missing growth data were associated with several baseline characteristics. Mothers of children included in the analysis (88%) were more likely to have higher socioeconomic status (i.e. college or more education, private insurance, married/cohabitating), were non-Hispanic White, of older age, less likely to smoke and were nulliparous compared with mothers of children without sufficient weight information (12%) (data not shown). After accounting for these sociodemographic differences, exclusions for missing data were not significantly associated with infertility treatment status ($P = 0.30$).

Infertility treatment was associated with multiple birth, non-Hispanic white race and higher socioeconomic status (Table I). Maternal pre-pregnancy BMI and paternal BMI were higher among those who underwent infertility treatment, particularly for parents who used OI/IUI. The average age at last reported weight and height was 3–4 months older for the infertility treatment group than the group not conceived by treatment. Birthweight and gestational age did not differ by treatment exposure groups after stratifying by plurality (data not shown).

Among all children (including twins and higher-order multiples), infertility treatment was significantly associated with smaller size from birth through to 3 years irrespective of growth measure (Table II). However, these differences were largely due to the greater percentage of multiples (31 versus 18%) among children conceived by infertility treatment. In fact, no differences were observed among singletons for any treatment or for the two specific types of treatment (OI/IUI or ART). Twins conceived by infertility treatment were on average smaller than twins not conceived with treatment, with most of the difference observed for twins conceived with OI/IUI rather than with ART. Twins conceived with OI/IUI weighed on average 122 g less, had lower weight for age (−0.18 *z*-score units; 95% CI: −0.33, −0.03), weight for length (−0.17 *z*-score units; 95% CI: −0.33, −0.01), BMI (−0.28 kg/m^2; 95% CI: −0.50, −0.05) and BMI *z*-score (−0.19 units; 95% CI: −0.35, −0.03) than twins not conceived by any infertility treatment throughout early childhood up to 3 years of age. No differences in growth measures were observed for twins conceived by ART compared with twins that were not conceived with any treatment.

With regard to rapid infant weight gain at 4, 9 and 12 months of age, approximately 19% of children at 4 months of age, 25% at 9 months and 22% at 12 months were estimated to have been affected. The odds of rapid weight gain was 2–3 times greater among infants conceived with than without infertility treatment, but only earlier during childhood (i.e. 4 and 9 months) (Table III). Twins conceived by infertility treatment, and particularly by ART, had slightly greater odds of rapid infant weight gain by 4 months (adjusted OR 1.08; 95% CI: 1.00–1.16). No significant differences were observed for singletons.

Discussion

To our knowledge, Upstate KIDS is the first US study to longitudinally track the growth of children specifically by mode of conception. We

Table I Baseline characteristics of the primary cohort by infertility treatment status, Upstate KIDS.

Characteristic	No treatment (*n* = 3023)		Infertility treatment (*n* = 1408)		OI/IUI (*n* = 741)		ART (*n* = 666)	
	n	%	*n*	%	*n*	%	*n*	%
Singleton[†a,b]	2471	82	969	69	535	72	433	65
White[a,b]	2402	80	1333	95	667	90	566	85
College or more[a,b]	1358	44	1040	74	516	70	523	79
Private insurance[a,b]	2213	70	1336	95	693	94	643	97
Nulliparous[a]	1238	41	836	60	442	60	394	60
Pregnancy smoker[a]	504	17	52	4	32	4	20	3
Married[a]	2545	87	1295	95	682	95	613	96
Maternal obesity[b]	767	25	389	28	251	34	138	21
Gestational Hypertension[b]	309	10	178	13	90	12	88	13
Gestational Diabetes[b]	255	8	177	13	94	13	83	12
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Maternal age (years)[a,b]	29.3	5.73	34.0	5.1	32.5	4.6	35.8	5.1
Pre-pregnancy BMI (kg/m^2)[a,b]	26.9	6.8	27.3	6.9	28.3	7.5	26.3	6.0
Paternal BMI (kg/m^2)[a,b]	28.0	5.4	28.9	5.4	29.4	5.8	28.5	5.0
Birthweight (g)[a,b]	3236	662	3049	755	3088	768	3006	739
Gestational age (weeks)[a,b]	38.3	2.3	37.6	2.9	37.7	2.9	37.4	2.8
Age at last weight (months)[a]	19.4	12.5	23.4	12.3	23.4	12.5	23.6	12.1
Age at last length (months)[a]	18.0	12.4	21.5	12.3	21.3	12.2	21.3	12.2

[†]Among multiples, there were 3 sets of higher-order multiples (i.e. triplets and quadruplets) conceived without treatment and 34 sets with treatment.
Missing data: 281 (6.3%) length, 295 (6.7%) paternal BMI, 156 (3.5%) marital status, 1 missing specific treatment exposure (OI/IUI vs. ART).
[a]$P < 0.05$ in comparison between infertility treatment and no treatment.
[b]$P < 0.05$ in comparison between ART and OI/IUI.

observed that children were smaller through to 3 years of age primarily due to the greater frequency of twins and high order multiples. These differences may not be a direct function of having been conceived with infertility treatment as singletons' growth during early childhood did not differ by treatment status. Contrarily, twins conceived with OI/IUI relative to twins conceived without any treatment were smaller, though the absolute differences were small (e.g. ~122 g in weight). However, no significant differences in growth through to 3 years of age were observed among twins born by ART compared with twins not conceived with treatment. Rapid infant weight gain was evident among twins conceived by ART only at 4-months and the risk was small.

Our study builds upon previous research while being more inclusive in important regards. To our knowledge, this is the first population-based cohort of US children prospectively followed through to 3 years of age (Yeung and Druschel, 2013). Similar to many previous studies (Brandes et al., 1992; Ron-El et al., 1994; Saunders et al., 1996; Bowen et al., 1998; Wennerholm et al., 1998; Koivurova et al., 2003; Place and Englert, 2003; Kai et al., 2006; Ludwig et al., 2009; Lee et al., 2010; Woldringh et al., 2011) on ART and childhood growth, we evaluated growth early in childhood (≤6 years old), though several other studies have included older children (Belva et al., 2007; Miles et al., 2007; Makhoul et al., 2009) or adolescents (Ceelen et al., 2007; Belva et al., 2012). To date, much of the available data is cross-sectional in nature, with growth measured at one time point rather than evaluating longitudinal trajectories, as we have done (Yeung and Druschel, 2013). Our cohort also includes multiples that have typically been excluded from previous analyses. Some studies also excluded singletons not meeting a gestational age threshold (e.g. ≥32 weeks gestation). We included a substantially larger number of children conceived by ART than almost all studies with the exception of one combining children from four European countries (Bonduelle et al., 2005). Our findings suggest that they are indeed smaller over the first 3 years of life compared with those not conceived by treatment. However, as growth of twins and higher-order multiples differ so greatly, we also stratified results by plurality. Despite the myriad of differences in study design, population and statistical methods, overall we find no evidence suggesting altered growth in early childhood for children conceived with ART, and no evidence of either over- or under-growth after accounting for plurality.

Compared with the few studies (Makhoul et al., 2009; Savage et al., 2012) that tracked growth of children conceived by non-ART treatments, our study found that twins conceived by OI/IUI were significantly smaller from birth through to age 3 years than twins not conceived by infertility treatment. Although not completely comparable, Savage et al. (2012) also found that pre-pubertal children (3–11 years old) conceived by ovarian stimulation were more likely to be of shorter stature than children who were not conceived by treatment. Their study was restricted to singletons born appropriate for gestational age (Savage et al., 2012). We did not limit our sample by birth size because we wanted to evaluate the total effect of infertility treatment, which may be in part due to mediating effects on size for gestational age (Schisterman et al., 2009). We

Table II **Adjusted mean differences in growth from birth through 3 years of age by infertility treatment exposure, Upstate KIDS Study.**

All children							
Mean difference (95% CI)	**n^a**	**Any infertility treatment**	***P*-value**	**OI/IUI**	***P*-value**	**ART**	***P*-value**
Weight (g)	5420	−151 (−217, −84)	<0.0001	−180 (−262, −97)	<0.0001	−116 (−204, −27)	0.01
Weight for age (*z*-score)	5420	−0.25 (−0.32, −0.18)	<0.0001	−0.27 (−0.36, −0.18)	<0.0001	−0.23 (−0.33, −0.14)	<0.0001
Length (cm)	5076	−0.61 (−0.83, −0.40)	<0.0001	−0.61 (−0.88, −0.34)	<0.0001	−0.63 (−0.91, −0.34)	0.0001
Length for age (*z*-score)	5076	−0.29 (−0.39, −0.20)	<0.0001	−0.29 (−0.40, −0.17)	<0.0001	−0.30 (−0.43, −0.18)	<0.0001
Weight for length (*z*-score)	4986	−0.11 (−0.20, −0.02)	0.02	−0.14 (−0.26, −0.03)	0.02	−0.08 (−0.20, 0.04)	0.20
BMI (kg/m^2)	5042	−0.29 (−0.43, −0.17)	<0.0001	−0.33 (−0.49, −0.17)	0.0003	−0.26 (−0.44, −0.09)	0.005
BMI (*z*-score)	5042	−0.21 (−0.30, −0.13)	<0.0001	−0.23 (−0.34, −0.12)	0.0002	−0.19 (−0.30, −0.07)	0.003
Singletons							
Mean difference (95% CI)	*n*	Any infertility treatment	*P*-value	OI/IUI	*P*-value	ART	*P*-value
Weight (g)	3440	−8.81 (−40.90, 58.52)	0.72	15.74 (−44.54, 76.03)	0.60	−4.12 (−85.72, 77.48)	0.92
Weight for age (*z*-score)	3440	−0.002 (−0.05, 0.06)	0.94	−0.0005 (−0.06, 0.07)	0.99	0.04 (−0.09, 0.10)	0.88
Length (cm)	3223	−0.16 (−0.34, 0.02)	0.08	−0.13 (−0.35, 0.09)	0.25	−0.22 (−0.52, 0.07)	0.13
Length for age (*z*-score)	3223	−0.08 (−0.16, −0.001)	0.05	−0.07 (−0.17, 0.03)	0.14	−0.10 (−0.23, 0.003)	0.14
Weight for length (*z*-score)	3182	0.06 (−0.02, 0.14)	0.15	0.06 (−0.04, 0.16)	0.22	0.05 (−0.08, 0.18)	0.42
BMI (kg/m^2)	3196	−0.01 (−0.10, 0.13)	0.83	−0.03 (−0.11, 0.16)	0.71	−0.01 (−0.20, 0.17)	0.89
BMI (*z*-score)	3196	−0.02 (−0.06, 0.09)	0.61	−0.02 (−0.07, 0.11)	0.61	0.01 (−0.11, 0.13)	0.85
Twins							
Mean difference (95% CI)	n^b	Any infertility Treatment	*P*-value	OI/IUI	*P*-value	ART	*P*-value
Weight (g)	1872	−81 (−185, 24)	0.12	−122 (−251, 7)	0.06	−42 (−168, 5)	0.50
Weight for age (*z*-score)	1872	−0.12 (−0.24, 0.0003)	0.05	−0.18 (−0.33, −0.03)	0.02	−0.06 (−0.20, 0.08)	0.40
Length (cm)	1747	−0.13 (−0.47, 0.22)	0.45	−0.26 (−0.69, 0.16)	0.22	−0.004 (−0.42, 0.41)	0.98
Length for age (*z*-score)	1747	−0.03 (−0.18, 0.12)	0.68	−0.10 (−0.28, 0.08)	0.26	0.04 (−0.14, 0.22)	0.67
Weight for length (*z*-score)	1708	−0.14 (−0.28, −0.01)	0.03	−0.17 (−0.33, −0.01)	0.03	−0.12 (−0.27, 0.03)	0.12
BMI (kg/m^2)	1742	−0.22 (−0.40, −0.03)	0.02	−0.28 (−0.50, −0.05)	0.02	−0.16 (−0.38, 0.06)	0.15
BMI (*z*-score)	1742	−0.14 (−0.27, −0.01)	0.04	−0.19 (−0.35, −0.03)	0.02	−0.09 (−0.25, 0.07)	0.24

Model adjusted for infant age, gender and their interactions, maternal age (years), maternal race (White, Black, Asian, Hispanic, other), education (less than HS, HS, some college, college, advanced), pregnancy smoking (yes/no), private insurance (yes/no), maternal pre-pregnancy BMI (kg/m^2) and paternal BMI (kg/m^2).

[a]All children including 108 higher-order multiples.

[b]All twins counting each sibling separately. There were 954, 902, 888 and 900 twins, respectively, from the primary cohort.

Table III Odds ratios (95% CI) for risk of rapid infant weight gain by infertility treatment status in the primary cohort of Upstate KIDS.

Age at measurement	Primary cohort[a]				Singletons		Twins	
	n	Unadjusted	Model I	Model I + plurality	n	Model I	n	Model I
4-Months								
Any treatment	1408	2.00 (1.41, 2.84)	2.59 (1.80, 3.72)	1.17 (0.76, 1.81)	969	1.24 (0.72, 2.15)	784	1.06 (1.00, 1.13)
OI/IUI	741	1.73 (1.04, 2.87)	2.24 (1.33, 3.76)	1.08 (0.59, 1.96)	535	1.21 (0.57, 2.58)	361	1.05 (0.98, 1.12)
ART	666	**2.30 (1.43, 3.70)**	2.98 (1.83, 4.86)	1.27 (0.71, 2.26)	433	1.28 (0.59, 2.80)	423	**1.08 (1.00, 1.16)**
9-Months								
Any treatment	1408	1.19 (0.83, 1.70)	**1.53 (1.06, 2.22)**	1.02 (0.66, 1.54)	969	0.98 (0.55, 1.72)	784	1.02 (0.97, 1.08)
OI/IUI	741	1.02 (0.60, 1.73)	1.26 (0.74, 2.17)	0.88 (0.50, 1.56)	535	0.85 (0.38, 1.88)	361	1.01 (0.94, 1.08)
ART	666	1.36 (0.84, 2.23)	**1.83 (1.11, 3.02)**	1.18 (0.69, 2.03)	433	1.13 (0.52, 2.49)	423	1.04 (0.97, 1.11)
12-Months								
Any treatment	1408	0.87 (0.58, 1.32)	1.17 (0.77, 1.78)	0.91 (0.58, 1.43)	969	0.78 (0.41, 1.48)	784	1.01 (0.96, 1.07)
OI/IUI	741	0.78 (0.42, 1.42)	0.99 (0.53, 1.82)	0.79 (0.42, 1.49)	535	0.66 (0.26, 1.67)	361	0.99 (0.93, 1.05)
ART	666	0.98 (0.56, 1.70)	1.37 (0.78, 2.41)	1.04 (0.57, 1.90)	433	0.92 (0.38, 2.23)	423	1.03 (0.96, 1.10)

[a]Primary cohort includes singletons and one randomly selected multiple of a set.
Model I adjusted for infant age, gender and their interactions, maternal age (years), maternal race (White, Black, Asian, Hispanic, other), education (less than HS, HS, some college, college, advanced), pregnancy smoking (yes/no), private insurance (yes/no), maternal pre-pregnancy BMI (kg/m^2) and paternal BMI (kg/m^2). Bold value indicates significance at $P < 0.05$.

were also careful to account for parental BMI in our analyses, as some evidence has shown maternal and paternal obesity to be associated with infertility treatment (Campbell et al., 2015) and may confound findings. Savage's study adjusted for variation in mid-parental height as a measure of genetic growth potential (Savage et al., 2012), though it is unclear whether height is a true confounder given the lack of data supporting an association with infertility or its treatment. To address this consideration, we adjusted for both parents' BMI that were positively associated with children's weight and height.

The focus of research on mode of conception and childhood health has traditionally been on ART procedures, where use of *in vitro* culture with or without ICSI may have implications for children's growth. We were unable to account for the type of culture media in our analysis, given that we did not have this data available. When available in previous research, the findings relative to fetal growth have been inconsistent (Nelissen et al., 2013; Lemmen et al., 2014; Wunder et al., 2014). One study on post-natal growth comparing Vitrolife and Cook culture media used in IVF found that singletons conceived differed in growth persisting to 2 years (Kleijkers et al., 2014). Specifically, Cook media was associated with a lower trajectory of weight and height among singletons than Vitrolife without any differences in growth velocity (Kleijkers et al., 2014). Hence, culture data may be necessary to examine the potential for differences in growth.

The rationale for why children conceived by ovulation induction or ovarian stimulation may be smaller than children conceived without this treatment remains unclear (Savage et al., 2012). Although our findings remain to be confirmed in both singletons and twins conceived by OI/IUI, some potential mechanisms for why hormonal medications may lead to differences in growth have been hypothesized (Wennerholm et al., 1998). Our OI/IUI group included women who used oral (e.g. Clomid©) as well as injectable medications (e.g. Ovidrel©, Profasi©). One hypothesis is that stimulation leads to ovulation of abnormal oocytes by developing them too rapidly or developing oocytes that would have otherwise perished (Sato et al., 2007; Fortier et al., 2008). Alternatively, stimulation may impact the endometrium by exposure to supra-physiological levels of estradiol, progesterone and other hormones (Weinerman and Mainigi, 2014). Estradiol, for example, is increased after application of gonadotrophins due to the higher number of follicles, as compared with only a dominant follicle, being present. Estradiol levels have also been found to be elevated after clomiphene citrate (Maxson et al., 1984). Elevations of estradiol and other hormones can then impact endometrial receptivity (as demonstrated in histological studies) and potential adaptations made to accommodate for successful placentation and survival have been hypothesized to play a role in fetal growth (Weinerman and Mainigi, 2014) and, therefore, potentially influence later growth. Some evidence from epidemiological studies showing better birth outcomes after cryopreservation has supported this latter hypothesis (Weinerman and Mainigi, 2014). However, due to the few number of our participants reporting frozen embryo transfer in the cycle of the index birth ($n = 124$) (Stern et al., 2016), we were unable to disentangle this aspect of treatment. That only twins were found to differ requires replication for a more complete understanding of these associations.

Rapid infant weight gain has been linked with adverse long-term health outcomes including higher risks of childhood obesity and metabolic dysfunction (Breij et al., 2014). Hence, we evaluated rapid infant weight gain as a way to better understand whether the velocity of growth differs by infertility treatment status, especially given indications that children may have lower birthweight. Our observation that twins conceived with ART experience a slightly higher odds of rapid infant weight gain suggest that treatment may not be a strong risk factor. Other literature for infant weight gain remains equivocal. A recent study using data from the Danish National Birth Cohort included children conceived by OI/IUI in their fertility treatment group along with ART and showed no differences in clinically measured anthropometry at 5 years of age despite smaller birth size, suggestive of catch up growth (Bay et al., 2014).

Greater change in weight at 3 months and 1 year was also observed in one study of IVF children compared with spontaneously conceived children (Ceelen *et al.*, 2009). However, another study in Europe did not observe the same (Basatemur *et al.*, 2010). Our study differs from previous work by defining rapid catch-up growth at multiple time points defined by cut-points previously found to be associated with higher risks of childhood fatty liver (Breij *et al.*, 2014) rather than purely change in weight at different time points. We used such cut-points to evaluate rapid growth that may be of concern to future health.

The strengths of our study include having maternal reported ART exposure validated against SART-CORS data (Buck Louis *et al.*, 2015), a substantially large number of children conceived by infertility treatment compared with previous studies, and longitudinal data on growth from birth through to 3 years of age. However, we relied on maternal report of pediatrician-measured values and we were not able to validate those measures. We recognize there may be error in the measurement of length; however, we are unaware of any empirical data suggesting that it systematically varies by mode of conception that would bias findings. Nevertheless, as there is concern that clinically measured length may be reduced compared with research measured values, we also implemented an adjustment previously published (Rifas-Shiman *et al.*, 2005) for clinically measured lengths (up until 18 months) and observed no difference in our findings (data not shown). Also, we re-ran our analyses restricting to measurements up to the first 18 months of age to distinguish length from height measures and observed similar findings (data not shown). Although we were also limited by loss to follow-up in the study, we used generalized linear mixed effects modeling with the modeling assumption of missing at random (Molenberghs, 2006). The extent to which this assumption is true remains unknown. We cannot entirely eliminate residual confounding in light of the study's observational design. The small differences identified may not be clinically meaningful, but we here rule out large differences that may be more relevant.

In conclusion, we found that children grew similarly irrespective of mode of conception from birth through to 3 years of age. While twins conceived by OI/IUI were slightly smaller than twins conceived without such treatment, the differences were minor (absolute difference in weight of 121 g and in length of 0.26 cm). These findings offer reassurance for couples using infertility treatment to aid conception, and provide evidence that children conceived by infertility treatment are not stunted or over-grown in early childhood.

Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

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Authors' roles

E.H.Y., R.S. and Y.X. had full access to the study data and takes responsibility for the integrity of its analysis and statistical analysis; G.M.B.L.: study concept and design; E.M.B., C.D., C.K.: oversight for implementation of the protocol and linkage with New York State registries; E.M.B., G.M.B.L., C.K., E.H.Y.: data interpretation; E.H.Y.: drafting the manuscript; E.M.B., G.M.B.L., C.K., Y.X., E.H.Y.: critical revision; G.M.B.L.: Obtained funding; E.H.Y., C.D., E.M.B.: study supervision.

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Conflict of interest

None declared.

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