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ARTICLE

Growth of children conceived by IVF and ICSI up to 12 years of age

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Abstract Recent studies have given conflicting results regarding growth in children born following assisted reproductive treatments up to the age of 18 years. It has been suggested that children conceived via IVF may be taller than naturally conceived children and that this may due to subtle epigenetic alteration of imprinted genes as a result of the IVF process. A prospective match-controlled study was performed to investigate the growth of children born in the UK following standard IVF and intracytoplasmic sperm injection (ICSI) up to the age of 12 years. The study assessed 143 IVF and 166 ICSI children with 173 matched naturally conceived controls. Primary end-points were height and weight at various time points: birth, 5 years, 7–9 years and 10–12 years. In addition, head circumference was assessed at birth. No significant differences were observed regarding head circumference, height and weight between the three groups at any of the time points. In conclusion, this preliminary study provides reassuring information regarding the growth of IVF and ICSI children up to 12 years. Further studies must continue to investigate the growth and other outcomes in assisted-conception children as they develop through puberty into early adulthood. RBMOnline

KEYWORDS: children, growth, ICSI, in-vitro fertilisation, intracytoplasmic sperm injection, IVF

Introduction

Assisted reproduction treatments, namely in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), have become widely used in the treatment of human infertility. At present, 1–3% of children born in developed countries are conceived via assisted reproduction treatments (Andersen et al., 2008; Wright et al., 2008). It is well established that assisted reproduction is associated with adverse perinatal outcomes, including increased risks of preterm delivery, low birthweight and neonatal mortality (Helmerhorst et al., 2004; Jackson et al., 2004; McDonald et al., 2005).

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In recent years there has been considerable work investigating health outcomes in IVF and ICSI children beyond the neonatal period (Basatemur and Sutcliffe, 2008; Sutcliffe and Ludwig, 2007).

A number of well-designed case control studies have investigated the growth of assisted-conception children up to the age of 18 years. The majority of these have not found any differences between children conceived via assisted reproduction treatments and naturally conceived children. The height, weight and head circumference of IVF and ICSI children at the ages of 6–12 months (Wennerholm et al., 1998), 1–3 years (Brandes et al., 1992), 5 years (Bonduelle et al., 2005; Ludwig et al., 2008) and 8 years (Belva et al., 2007; Knoester et al., 2008) have been reported to be the same as naturally conceived controls. Recently, a Dutch group reported no difference in growth between IVF children and naturally conceived controls aged between 8 and 18 years (Ceelen et al., 2008). Similar findings have recently been reported in children aged from 3 months to 4 years conceived after preimplantation genetic diagnosis (Banerjee et al., 2008).

In contrast to these reassuring findings, two studies have reported differences in growth between assisted-conception children and naturally conceived controls (Koivurova et al., 2003; Miles et al., 2007). A study in Finland (Koivurova et al., 2003) reported that their cohort of 299 IVF children were significantly lighter in weight than 558 naturally conceived controls up to the age of 3, although at the age of 3 no significant difference in weight remained. Recently, a New Zealand study (Miles et al., 2007) found that a cohort of 69 IVF and ICSI children aged between 4 and 10 years (mean age of 5.9 years) were significantly taller than 71 naturally conceived controls, after adjustment for age and parental height. They also reported higher serum concentrations of insulin-like growth factors I and II in the assisted-conception children and concluded that the observed differences in stature and growth factors may be due to subtle epigenetic alteration of imprinted genes as a result of the IVF process.

In response to the conflicting outcomes of previous studies, a prospective cohort study was designed to compare the growth of IVF and ICSI children up to the age of 12 years with naturally conceived controls. As far as is known, this is the first match controlled cohort study to investigate the growth of ICSI children above the age of 10 years.

Materials and methods

Subjects

Children were recruited from an established cohort in the UK as part of a longitudinal study into outcomes in assisted-conception children (Bonduelle et al., 2005; Fisher-Jeffes et al., 2006; Ponjaert-Kristoffersen et al., 2005; Sutcliffe et al., 2001, 2003). Twins and higher order births were excluded from the study, and all children were born at 32 weeks of gestation or later. ICSI children were originally recruited from 22 participating fertility clinics in the UK, whilst children conceived following conventional IVF were recruited from five clinics in the UK. Local schools and nurseries were used to recruit a matched comparison group of naturally conceived children. Children in the control group were matched for age, sex, maternal education and parental socio-economic status. Maternal education was assessed using a five-category system (1 higher degree, 2 degree, 3 university entry, 4 school matriculation full pass, 5 school matriculation part pass) and paternal socio-economic status using a six-category system (I professional, II intermediate, III N skilled non-manual, III M skilled manual, IV semi-skilled manual, V unskilled manual). These were subsequently recoded to reflect low levels of education (school matriculation or less) and low social class (social class VI or lower) to reflect these variables as risk factors and also to make the statistical analysis manageable. Growth data had been collected for these children at birth and at the age of 5 years as part of previous studies (Bonduelle et al., 2005; Sutcliffe et al., 2001). The primary outcome measures were weight, height and head circumference. In total, data was available for 299 assisted-conception children (IVF and ICSI) and 159 naturally conceived children, although data was not available for all of the children for all measures at both time points.

In this study, information was obtained regarding the growth of these children at two further time points, when the children were aged 7–9 years and 10–12 years. At each of these time points, the parents of the children were contacted by post with a short questionnaire requesting their participation. The parents who did not respond to the first letter were sent a reminder. A small number of additional children (10 assisted-conception children and 13 control children) were recruited at this point from major fertility clinics and local schools, for whom growth data was only available for the ages of 7–12 years. In total, data was available for 186 assisted-conception children (83 IVF and 103 ICSI) and 76 natural conception children at one or both of these time points. Data was not available at both time points for all of the children.

Responses to questionnaires were received from 186 out of a total of 309 parents of assisted-conception children at one or both of the time points (response rate of 60%), in comparison to 76 out of 173 parents of control children (response rate of 44%). These response rates are as expected for this type of postal-based study (Boreham et al., 2003; Cummings et al., 2001). Ethical approval for the study was obtained from the North London Multicentre Research Ethics Committee (MREC).

Information regarding the children at birth was obtained from fertility clinic records and from the parent-held personal child-health record (the red book). This information included mode of conception, sex, gestational age at birth, birthweight, length and head circumference. Information regarding growth at the age of 4–5 years was obtained by physical examination of the children by two consecutive paediatricians (Bonduelle et al., 2005). Height and weight were measured using standard equipment.

Growth data at the ages of 7–9 years and 10–12 years was obtained via a postal questionnaire. Parents of the children were sent a short questionnaire requesting them to measure their child's height and weight and return this information along with the date of examination and child's date of birth in a prepaid addressed envelope.

Statistical analysis

Parental characteristics across the three conception groups were analysed using one-way analysis of variance (ANOVA) (age, alcohol units) and χ^2-tests (social class, education, smoking status). Differences between the three conception groups at birth were assessed using one-way ANOVA. The independent variable was conception group and the dependent variables were gestational age, weight, length and head circumference at birth. To assess longitudinal changes a two-way mixed analysis of covariance (group × time) was carried out separately for both weight and height. The group factor represented conception status (IVF, ICSI and natural) and the time factor represented the four measurements of height and weight. Mother's age was included in the analysis as a covariate.

Results

In total, 482 children were enrolled in the study. The participants were from three conception groups: IVF, ICSI and natural. The study groups consisted of 143 singleton children conceived after conventional IVF (69 male and 74 female) and 166 singleton children conceived after ICSI (92 male and 74 female). The control group consisted of 173 naturally conceived singletons (94 male and 79 female).

Details of parental characteristics across the three conception groups are presented in Table 1. There were significant differences between the three groups in terms of mother's age [$F(2.439) = 29.13$, $P = 0.00$] although the effect size was small ($\eta^2 = 0.11$). Post hoc Bonferroni comparisons showed that the mean age of the mothers in the natural group was significantly lower than for the IVF and ICSI groups ($P < 0.05$). There was no significant difference between the IVF and ICSI groups. The groups also differed in terms of education, with a larger percentage of IVF and ICSI groups reporting school matriculation or less as their highest level of educational attainment. There were significant differences between the three groups in terms of father's age [$F(2.439) = 29.13$, $P < 0.001$] although the effect size was small ($\eta^2 = 0.08$). Post hoc Bonferroni comparisons showed that the mean age of the fathers in the natural group was significantly lower than for the IVF and ICSI groups ($P < 0.05$). There was no significant difference in age between the IVF and ICSI groups. The fathers in the IVF and ICSI groups were of higher social class, had poorer education levels and smoked less compared with the natural conception group.

Details of gestational age, weight, length and head circumference at birth are presented in Table 2. The groups did not differ significantly at birth in terms of weight [$F(2.435) = 1.91$], length [$F(2.263) = 0.59$] or head circumference [$F(2.342) = 1.13$]. There were significant differences between the groups in terms of gestational age at birth [$F(2.253) = 5.71$, $P < 0.01$], and post hoc Bonferroni comparisons showed that the ICSI group had a lower mean (270.58 days) than either the IVF (275.78 days) or the natural conception (276.27 days) group.

Three subsequent measures of height and weight were recorded at average ages of 59.61 (SD = 3.60), 106.86 (SD = 8.73) and 131.86 (SD = 8.28) months. The descriptive statistics are reported in Tables 3 and 4. For height measurements there was a significant main effect for the time factor [$F(3.44) = 44.80$, $P < 0.01$] but no significant effect for the group factor [$F(2.46) = 0.21$], and the time by group interaction was not significant [$F(6.138) = 0.25$]. These results indicated that there were significant increases in height for all participants and that there were no differences between the three groups.

For weight measurements, there was a significant main effect for the time factor [$F(3.79) = 13.81$, $P < 0.01$] but no significant effect for the group factor [$F(2.81) = 1.56$], and the time by group interaction was not significant [$F(6.160) = 1.39$]. These results indicate that there were significant increases in weight for all participants and that there were no differences between the three groups.

Discussion

The majority of previous well designed cohort studies investigating the growth of children born following assisted

Table 1 Parental characteristics for the three conception groups.

	IVF (n = 143)	*ICSI* (n = 166)	*Normal* (n = 173)	*P-value*
Mother				
Age (years)	35.03 ± 3.65	34.46 ± 3.56	31.56 ± 4.99	< 0.001
Social class VI or lower	14 (9.8)	6 (3.6)	14 (8.1)	NS
School matriculation or less	87 (60.8)	89 (53.6)	61 (35.2)	0.016
Non-smokers	121 (84.6)	136 (81.9)	113 (65.3)	NS
Alcohol units/week	4.94 ± 5.47	4.67 ± 5.58	4.03 ± 4.69	NS
Father				
Age (years)	36.04 ± 4.60	35.22 ± 5.17	32.51 ± 5.28	< 0.001
Social class VI or lower	0 (0.0)	4 (2.4)	17 (9.8)	< 0.001
School matriculation or less	82 (57.3)	88 (53.0)	55 (31.8)	0.016
Non-smokers	122 (85.3)	133 (80.1)	97 (56.1)	0.008
Alcohol units/week	9.95 ± 10.20	8.35 ± 9.75	7.46 ± 10.90	NS

Values are mean ± SD or *n* (%).
ICSI = intracytoplasmic sperm injection; NS = not statistically significant.

Table 2 Details of gestational age, weight, length and head circumference at birth.

Parameter	*Group*	n	*Mean*	*SD*
Gestation (days)	IVF	138	275.78	13.51
	ICSI	160	270.58	18.57
	Normal	158	276.27	16.68
	Total	456	274.13	16.68
Birth weight (g)	IVF	131	3264.15	479.84
	ICSI	161	3171.14	696.83
	Normal	146	3305.98	637.37
	Total	438	3243.90	620.03
Birth length (cm)	IVF	84	51.71	3.02
	ICSI	91	51.20	4.20
	Normal	91	50.92	6.51
	Total	266	51.27	4.83
Head circumference (cm)	IVF	111	34.25	1.44
	ICSI	125	34.17	1.92
	Normal	109	34.51	1.86
	Total	345	34.30	1.76

ICSI = intracytoplasmic sperm injection.

Table 3 Descriptive statistics for height measurements.

Time of measurement	*Number*			*Mean height ± SD (cm)*		
	IVF	*ICSI*	*Normal*	*IVF*	*ICSI*	*Normal*
Time 1 (birth)	84	91	91	51.58 ± 2.90	50.91 ± 3.79	51.57 ± 2.88
Time 2 (59.61 months)	138	161	157	110.10 ± 3.36	110.40 ± 5.30	110.10 ± 5.42
Time 3 (106.86 months)	44	48	44	133.71 ± 5.69	136.90 ± 6.40	134.68 ± 5.22
Time 4 (131.86 months)	64	92	67	146.25 ± 5.90	148.76 ± 7.72	145.89 ± 6.81

ICSI = intracytoplasmic sperm injection.

Table 4 Descriptive statistics for weight measurements.

Time of measurement	*Number*			*Mean weight ± SD (kg)*		
	IVF	*ICSI*	*Normal*	*IVF*	*ICSI*	*Normal*
Time 1 (Birth)	131	161	146	3.32 ± 0.50	3.03 ± 0.82	3.44 ± 0.57
Time 2 (59.61 months)	138	157	158	19.21 ± 2.30	20.30 ± 4.52	20.01 ± 2.89
Time 3 (106.86 months)	43	48	44	29.56 ± 5.17	33.23 ± 9.08	31.67 ± 6.09
Time 4 (131.86 months)	66	92	67	39.33 ± 10.75	42.64 ± 9.64	40.51 ± 11.95

ICSI = intracytoplasmic sperm injection.

reproductive techniques have not found any differences in the growth of IVF and ICSI children when compared with naturally conceived controls (Belva et al., 2007; Bonduelle et al., 2005; Brandes et al., 1992; Ceelen et al., 2008; Knoester et al., 2008; Ludwig et al., 2008; Wennerholm et al., 1998). However, the study by Ceelen et al. (2008) suggested that IVF children may exhibit higher blood pressure and fasting glucose concentrations than spontaneously conceived controls

A recent case—control study from New Zealand compared the growth of 4—10 year old IVF and ICSI singletons born at term with naturally conceived controls (Miles et al., 2007). It was found that the IVF children were significantly taller than naturally conceived controls (by a mean of approximately 3 cm) after adjustment for age and parental height. They also reported significantly higher serum concentrations of insulin-like growth factor II and a serum fasting lipid profile consisting of higher high-density lipoprotein and lower triglycerides in the assisted reproduction group. The authors suggest that their findings may represent epigenetic alteration of imprinted or non-imprinted genes as a result of the IVF process. Concerns have been raised regarding an increased risk of imprinting disorders such as Beckwith–Wiedemann syndrome and Angelman syndrome in IVF children (Gicquel et al., 2003; Maher et al., 2003; Orstavik et al., 2003; Sutcliffe et al., 2006), although these have not been replicated in other studies (Bowdin et al., 2007; Doornbos et al., 2007; Lidegaard et al., 2005). Mild phenotypic features such as taller stature have been reported in relatives of children with Beckwith–Wiedemann syndrome and the authors of the New Zealand study postulated that their findings in assisted-conception children might represent subtle alterations in DNA methylation patterns in imprinted genes that are more markedly deranged in Beckwith–Wiedemann syndrome and associated with growth.

A prospective match-controlled cohort study was conducted to investigate the growth of IVF and ICSI children up to the age of 10–12 years. The aim was to identify whether term assisted-conception children exhibit differences in growth compared with naturally conceived controls to further investigate the hypothesis that the IVF process may influence growth through subtle epigenetic alteration of imprinted genes (Miles et al., 2007). Children born before 32 weeks of gestation were excluded due to the confounding effect of preterm birth on subsequent growth. This report investigates the growth of ICSI children beyond the age limit of previous studies.

No significant difference was found between the three groups regarding weight, length and head circumference at birth. Gestational age at birth was significantly lower in the ICSI group (by a mean of 5 days) compared with the IVF and control groups. There was no significant difference in gestational age between the IVF and control groups. The similarity in growth parameters at birth is likely to be due to the exclusion of twins and higher order pregnancies and children born before 32 weeks of gestation from the study. Various meta-analyses have demonstrated that singleton children born after assisted reproductive treatments are at increased risk of adverse perinatal outcomes including preterm delivery and low birthweight when compared with naturally conceived controls (Helmerhorst et al., 2004; Jackson et al., 2004; McDonald et al., 2005). These meta-analyses have included studies with cohorts of over 3000 children and, thus, have considerably greater power than this study.

Regarding growth at later age points, while controlling for mother's age, no significant difference in height and weight was found between the three groups at the ages of 5 years, 7–9 years and 10–12 years. These results are consistent with the majority of previous studies that have investigated the growth of assisted-conception children up to the age of 8 years and suggest that IVF and ICSI children continue to exhibit similar growth to natural controls into early teenage years. They do not support the recent observation in New Zealand by Miles et al. (2007) that IVF children may be taller than naturally conceived controls between the ages of 4 and 10 years. A major strength of the present study is the cohort size: 83 IVF, 103 ICSI and 76 naturally conceived children aged between 7 and 12 years were investigated, and the New Zealand study had cohorts of 35 IVF, 34 ICSI and 71 controls aged between 4 and 10 years. However, unlike the study by Miles et al. (2007), the present study was not able to control for parental height. Selection criteria represent another important difference in study design. This study included children born at 32 weeks of gestation or later, in comparison to the New Zealand study which only included children born at term ($>$ 36 weeks). Given the well-established associations between preterm birth and low birthweight and subsequent effects upon post-natal growth, it is conceivable that differences in selection criteria may have contributed to the differences in childhood growth observed in the studies.

This study involved cumulative data collection but the final two growth measurements were by postal survey. Like most postal studies, this was limited by low response rates, which might be a source of bias. Parents who do not wish to disclose information about their children, for whatever reason, might be less likely to respond. The difference in response rates between the assisted reproduction treatments group (60%) and the control group (44%) also represents a potential source of bias. Also, there were some significant differences between the parental characteristics of the three conception groups. As expected, the mother's age was significantly higher for the IVF and ICSI groups, but the effect of this was statistically controlled for in the analysis. Another limitation of this study is that parents were requested to measure their children's weight and height themselves at the latter two time points (7–9 years and 10–12 years). Thus, there was no control over the equipment used or the accuracy of measurement at these time points. However, for the purposes of identifying clinically significant differences in height and weight between the groups, a high level of discriminatory accuracy is unlikely to be necessary. Measurements to the nearest centimetre and nearest tenth of a kilogram are probably sufficient for this purpose and, on the whole, parents did provide measurements to this degree of discrimination. This preliminary study used a relatively small sample size and therefore caution must be used in the interpretation of the negative inferences, i.e., that IVF and ICSI do not influence growth. However, a further major follow-up study of outcomes in the UK cohort of assisted-conception children is being planned, in which the children will be individually examined by trained paediatricians.

Overall, this study provides reassuring information regarding the growth of IVF and ICSI children up to 12 years of age. No significant differences in the weight and height of assisted-conception children up to the age of 10–12 years were identified when compared with naturally conceived controls. Further studies must continue to investigate the growth and other outcomes in assisted-conception children as they develop through puberty into early adulthood.

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