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## ARTICLE

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


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Dr Alastair Sutcliffe is a paediatrician who has conducted a series of studies from 1993 looking at the health of children born after interventions in early life. These include the first on embryo cryopreservation outcome and twin–twin transfusion syndrome. He has collaborated with researchers in Belgium, Denmark, Sweden, Greece, Australia and Germany on ICSI outcome studies and is currently working on a study of oocyte cryopreservation outcome with Italian collaborators. He is author of over 40 papers and two books. His work has resulted in the ESHRE-established clinician award (1999) and the Donald Patterson prize (2003) from the Royal College of Paediatrics.

**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. 

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**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).

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.

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