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Original Article

Physical and mental development of children after *in vitro* fertilization and embryo transfer

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Objective: To evaluate the physical and mental development of children after *in vitro* fertilization (IVF) and frozen embryo transfer (FET).

Methods: Between July 1995 and November 2003, 506 patients delivered 658 babies after IVF and ET treatment at our clinic (intracytoplasmic sperm injection (ICSI), 418; conventional IVF, (C-IVF) 125; FET, 115). A survey of the physical and mental developmental of the children was conducted by mailing questionnaires to parents. Comparisons were made between three treatment procedures, and development of singleton, twin and triplet delivery.

Results: The response rate was 73.4% (483/658) for 324 children born after ICSI, 78 born after C-IVF, and 81 born after FET. The height and weight of assisted reproductive technology (ART) children at birth were significantly lower than that of naturally conceived babies (ART children: natural delivery; 46.8 cm, 49.0 cm and 2524 g, 3040 g, respectively). However, there was no significant difference between the singletons alone and naturally conceived children irrespective of the ART method. In addition, mental development was the same between singletons and naturally conceived children. The ART group tended to delay body development such as 'holding their head up', 'sitting up', 'crawl' to moving growth in multiple births.

Conclusion: The physical and mental development of twins or triplets was significantly more delayed than that of naturally conceived babies, but had improved to a similar extent of the singletons after the age of 6 months. (Reprod Med Biol 2004; **3**: 63–67)

Key words: assisted reproductive technology, congenital aberration, malformation, physical and mental development.

INTRODUCTION

TODAY MANY INFERTILE couples are able to benefit from assisted reproductive technology (ART). At present, approximately 1.0% of all babies in Japan are born as a result of conventional *in vitro* fertilization (C-IVF) treatment and intracytoplasmic sperm injection (ICSI). Assisted reproductive technology was established for infertility treatment and in particular, ICSI has contributed to the treatment of severe male infertility. However, infertile women are frequently of advanced age at the time of conception and can have a variety of underlying causes of infertility. Furthermore, during the IVF process, the embryo is exposed to mechanical, thermal and chemical alterations. It is unclear whether these factors can increase chromosomal abnormalities, risk of congenital malformations, and so on. In addition, many studies have concluded that IVF pregnancies carry an increased risk for multiplicity, perinatal mortality, preterm birth and low birthweight in comparison with spontaneous pregnancies.[1–3] However, to date, published reports discussing such aspects is sparse and controversial. It is therefore very important to evaluate whether infants born as a result of ART experience increased rates of developmental complications when compared to those delivered after natural pregnancies.

In the present study, data from physical and mental examinations of ART children at their follow-up visit at the age of certain years was compared with that from controls.

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MATERIALS AND METHODS

THE STUDY INCLUDED 506 couples that underwent C-IVF (n = 93) or ICSI (n = 316), frozen embryo transfer (FET) (n = 97). Conventional IVF resulted in 65 singletons, 24 sets of twins (n = 48) and four sets of

Table 1 Medical record when babies delivered at clinic

Congenital malformation	Yes ( )	No ( )
Duration of pregnant	( ) weeks	( ) days
Apgar score	( )	
Weight	( ) g	
Height	( ) cm	
Chest measurement	( ) cm	
Head measurement	( ) cm	

Table 2 Mental and physical records of 1-year-old children

Weight ( ) g		
Height ( ) cm		
1. Weaning period completed	Yes ( )	No ( )
2. Walks with helping hand	Yes ( )	No ( )
3. Express self using gestures	Yes ( )	No ( )
4. Moves to music	Yes ( )	No ( )
5. Response to person's gesture	Yes ( )	No ( )
6. Shows happiness when receiving care	Yes ( )	No ( )
7. Eats three meals a day	Yes ( )	No ( )

triplets (n = 12) and ICSI resulted in 222 singletons, 86 twins (n = 172) and eight triplets (n = 24) after fresh embryo transfer. In addition, 80 singletons, 16 sets of twins (n = 32) and one set of triplets (n = 3) were delivered between July 1995 and November 2003 after FET. Twenty-four of 506 couples underwent ART treatments twice; 15 of 24 patients delivered a singleton after both treatments, eight of 24 patients delivered a singleton on the first occasion, and twins on the second, whereas one delivered a singleton on the first occasion, and triplets on the second, and all resulted in physically and mentally healthy babies.

We sent written questionnaires to the parents of 658 children in order to assess development until the age of 3 months. Thereafter, 242, 220, 215, 204, 149, and 128 children were assessed at the age of 3 months, 6 months, 9 months, 1 year, 1.5 years and 2 years, respectively. Questionnaire responses were statistically analyzed. Examples of questionnaire content are shown in Table 1 (record of delivery) and Table 2 (growth at 1 year). Other questionnaires (physical and mental development) were administered at growth phases from 3 to 4 months, from 6 to 7 months, from 9 to 10 months, at 1.5 years, and at 2 years after delivery.

We examined physical growth and mental development in comparison with recommended standards of the Japanese Ministry of Health and Welfare. In addition, we evaluated data concerning whether maternal or paternal causes of infertility might have influenced development.

RESULTS

WE RECEIVED COMPLETED questionnaires from the parents of 483 children (response rate: 483/658, 73.4%); 248 for children born by ICSI treatment, 78 for those born following C-IVF and 81 for those born following FET. The male: female ratio was approximately 1:1 for the child population in the current study.

Similar to C-IVF and FET, ICSI singleton children from fathers with low sperm quality had a similar developmental outcome to that of children from fathers with normal sperm parameters.

In singleton children, the mean (± SD) height and weight were as follows: ICSI, 48.5 ± 2.4 cm and 2905 ± 486 g; C-IVF, 48.5 ± 3.8 cm and 2862 ± 632 g; FET, 48.5 ± 3.8 cm and 3063 ± 636 g; naturally conceived children 49.0 cm and 3040 g. In twins and triplet children, the corresponding values were: ICSI, 44.9 ± 3.8 cm and 2227 ± 459 g; 37.1 ± 3.2 cm and 1304 ± 281 g; C-IVF 43.5 ± 4.6 cm and 2055 ± 519 g; 44.3 ± 2.0 cm and 1788 ± 282 g; FET, 44.5 ± 4.0 cm and 2196 ± 477 g; 44.3 ± 0.5 cm and 2077 ± 110 g (Table 3).

We obtained similar results for height and weight development for singletons, twins and triplets, and there was no significant difference in growth patterns between the ages of 3 months to 2 years for the ICSI and C-IVF or FET children (Figs 1, 2).

The physical growth rate showed corresponding growth to 50th percentile curve from birth until 2 years

Table 3 Physical growth of assisted reproductive technology children at delivery time

	Singleton			Twin			Triplet		
	ICSI	C-IVF	FET	ICSI	C-IVF	FET	ICSI	C-IVF	FET
n (babies)	217	64	74	165	44	28	24	12	3
Weight (g)	2905 ± 486	2834 ± 632	3023 ± 636	2227 ± 459	2055 ± 515	2196 ± 477	1304 ± 281	1788 ± 282	2077 ± 110
Height (cm)	48.5 ± 2.4	48.4 ± 3.8	48.5 ± 3.8	44.9 ± 3.8	43.5 ± 4.6	44.5 ± 4.0	37.1 ± 3.2	41.5 ± 2.0	44.3 ± 0.5

C-IVF, conventional IVF; FET, frozen embryo transfer; ICSI, intracytoplasmic sperm injection.

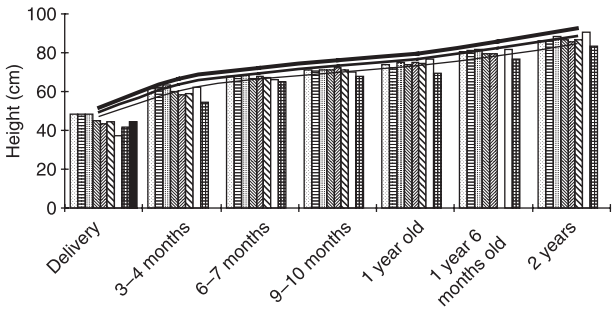

Figure 1 Growth curve of height at developmental stages in assisted reproductive technology children. ⬚, single ICSI; ▤, single C-IVF; ▥, single FET; ▧, twin ICSI; ▨, twin C-IVF; ▧, twin FET; □, triplet ICSI; ▦, triplet C-IVF; ■, triplet FET; ⎯, 10th percentile; ⎯, 50th percentile; ▬, 90th percentile.

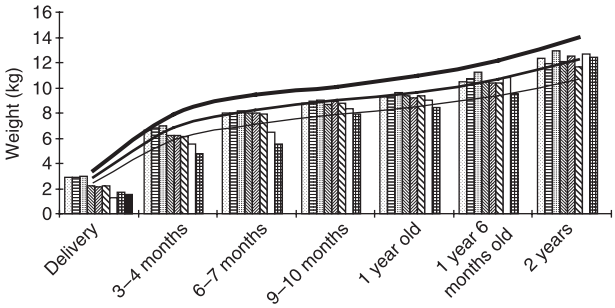

Figure 2 Growth curve of weight at developmental stages in assisted reproductive technology children. ⬚, single ICSI; ▤, single C-IVF; ▥, single FET; ▧, twin ICSI; ▨, twin C-IVF; ▧, twin FET; □, triplet ICSI; ▦, triplet C-IVF; ■, triplet FET; ⎯, 10th percentile; ⎯, 50th percentile; ▬, 90th percentile.

of age in singletons. At birth, the weight ratio was low in singletons and high in multiple births (singleton 2.5%, twins 9.2%, and triplets 48.7%). Twins and triplets had a delay of 6 months more than singleton groups, however, twins was able to catch up the 50th percentile curve at approximately 6 months after birth. Moreover, triplets catch up to the 50th percentile curve at 1 year after birth (Figs 1, 2).

Table 4 showed the physical and mental development of ART children from 3 months to 2 years. Three groups (singleton, twin, triplet) in the ART group were compared. The ART group tended to delay body

Table 4 Achievement rate of mental and physiological development at several growth stages

Developmental stage	*n*	Developmental milestone	Singleton (%)	Twin (%)	Triplet (%)
3–4 months	238	Hold their head up	82.8	71.4	30.8
	(singleton, 134)	Laughed when played with	96.3	95.6	75.0
	(twin, 91)	Voice reaction	91.7	94.5	58.3
	(triplet, 13)	Can eat soup	74.1	80.2	40.0
6–7 months	220	Turns over in bed	86.8	72.0	80.0
	(singleton, 130)	Sits up	87.6	54.6	41.7
	(twin, 75)	Extends hand to toy	97.7	96.0	100.0
	(triplet, 15)	Vocal expression	99.2	97.3	100.0
		Reacts to television	98.5	98.7	100.0
9–10 months	215	Crawl	84.8	72.0	66.7
	(singleton, 125)	Hangs on and can stand up	88.0	66.7	42.9
	(twin, 75)	Develop grip	96.8	93.3	66.7
	(triplet, 15)	It play alone	96.8	97.3	80.0
		It turns around when whispering	100.0	100.0	80.0
1 year	204	Walks with support	91.1	86.2	93.3
	(singleton, 124)	Mimics gestures	92.7	89.2	100.0
	(twin, 65)	Moves baby to music	96.8	83.1	100.0
	(triplet, 15)	Adult words are understood	100.0	100.0	100.0
		Pleased when meeting others	94.3	95.4	100.0
1 year and 6 months	149	Child walks alone	98.9	100.0	83.3
	(singleton, 89)	Child speaks	97.7	100.0	83.3
	(twin, 48)	Uses glass to drink	93.3	87.5	77.8
	(triplet, 12)	The nursing bottle is used	23.6	47.9	75.0
		Response to name	97.7	100.0	100.0
2 years	128	Can run	98.7	100.0	100.0
	(singleton, 76)	Use a spoon	98.7	100.0	100.0
	(twin, 43)	Child scribbles with crayon	100.0	93.0	100.0
	(triplet, 9)	Mimic gestures	100.0	97.7	100.0
		Uses more than one word	93.4	90.7	77.8

Table 5 Incidence of congenital malformation and chromosome abnormality at birth in assisted reproductive technology children

Malformation mild atrial septal defect	3
Multiple fingers	2
Hydrocephalus	1
Esophageal atresia	1
Groin herniation	3
Jejunal stenosis	1
Palatal abscess	1
Intestinal stenosis	1
Hemangioma	1
Talipes equino varus	1
Chromosomal abnormality	
Trisomy 21 (Down's syndrome)	1
Trisomy 18	1

Incidence of malformation: 4.8% (17/354).

development such as 'holding their head up', 'sitting up', and 'hangs on and can stand up' to moving growth in multiple births. However, a significant difference was not discovered regarding movement, reaction, and understanding such as 'extends hand to toy', 'reacts to television', and 'baby plays alone' between three groups (singleton, twin, triplet). About each item, the significant differences were not found among the three groups after 1 year old.

Congenital malformations were observed in 17 of the 354 children (4.8%). A complete list of all specific congenital malformations and chromosomal abnormalities is given in Table 5.

DISCUSSION

FEW REPORTS TO DATE have investigated in detail whether the postnatal development of children born following ART is comparable to that of naturally conceived children. There are especially few papers in Japan.[4–6]

Compared to a natural conception, there is a slight increase in prevalence of congenital malformations in infants born after IVF,[1–3,7] but there is no significant increase in the prevalence of malformations.[8–10] Recently, in Katayama and Iida's study of the growth and development of IVF babies in their postnatal follow-up study, IVF babies showed no remarkable disparity from naturally conceived babies, with the exception of developmental delay in the early infantile period due to multiple or premature deliveries.[4] Bonduelle *et al*. reported no indication that ICSI children have a lower psychomotor development than IVF children.[11] In addition, paternal risk factors associated with male-factor infertility were found to play no role in developmental outcome,[10,12] which is supported by our findings in that there was no significant difference in developmental outcome despite different quality sperm used for IVF treatment. Moreover, Sutcliffe *et al*. concluded that children conceived after ICSI did not differ from their naturally conceived peers in physical health or development at ages up to 15 months.[8]

Our findings are in agreement with the above-mentioned studies.[8–10] Although the height of the twins and triplets was less than the 10th percentile before the age of 3 months, twins were able to catch up to the 50th percentile curve at approximately 6 months of age. Even triplets, who showed developmental delay of 6 months more than the singletons and twins, caught up to the 50th percentile curve at 6 months or 1 year of age. These findings, plus that of males and females showing a similar growth curve, indicate that ART babies without congenital malformation develop similar to naturally conceived babies (data no shown).

In terms of weight development, twins caught up to the 50th percentile curve at 6 months, while triplets caught up to the 50th percentile curve at between 6 months and 1 year of age. This finding strongly suggests that development is severely delayed only until 1 year of age regardless of the method of ART. Furthermore, babies born following ICSI or C-IVF showed similar findings. While the development of triplets in the present study was most delayed, they went through the same developmental stages as the singletons and twins, except for the milestones of movement, reaction and the understanding such as 'extends hand to toy', 'reacts to television', and 'plays alone'.

These findings suggest that ART treatment should avoid multiple pregnancies whenever possible. We had a comparatively high rate of multiple pregnancies because we included data from the establishment of our clinic, at which time we made every effort to achieve pregnancy. The incidence of congenital malformation among our ART children was not significantly higher than the normal incidence rate of 5–6%. However, one case of jejunal stenosis and one of intestinal stenosis did result from multiple pregnancies, and thus physicians should be cognizant of these risks of multiple pregnancies associated with ART treatment. Today's efforts to avoid multiple pregnancies should reduce these risks and make ART a safer treatment.

In the present study, the physical development of ART children was significantly more delayed than that of naturally conceived children. In ART children, while

physical development was delayed until the age of 3–4 months, growth was not significantly different from that of naturally conceived babies after 6 months of age. Almost all singletons, irrespective of the ART procedure, showed similar physical and mental growth curves. Hypothetically then, if the number of embryos to be fertilized could be controlled freely, and singletons obtained, we could use different procedures without worrying about problems related to infant growth (ICSI, C-IVF or FET). This in turn suggests that ART treatment especially singletons does not have a negative effect on the physical and mental development of children when compared with natural pregnancy and delivery as most children will reach average development rates by the age of 2. However, we recognize that our data was drawn from only a small number of babies born following ART treatment at a private clinic. Therefore, to further advance the safety and efficiency of ART treatment, it is necessary to extend the study of children conceived by ART to larger populations and to include such factors as investigation of antenatal development and a more thorough pediatric examination generally in early infancy or childhood.

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