Weight of in vitro fertilization and intracytoplasmic sperm injection singletons in early childhood

Birth weight and longitudinal growth in the first 4 years of life of term singletons conceived with the use of IVF and intracytoplasmic sperm injection (ICSI) were compared with those of naturally conceived singletons. Although IVF and ICSI singletons had a statistically significantly lower birth weight than naturally conceived singletons, the average individual weight curves showed that this difference was lost before the age of 4 years in all subgroups: IVF, ICSI, boys, and girls. (Fertil Steril® 2011;95:2775–7. ©2011 by American Society for Reproductive Medicine.)

Key Words: IVF, ICSI, singleton, birth weight

Singletons conceived through IVF and intracytoplasmic sperm injection (ICSI) have a lower birth weight than children conceived spontaneously, even after correction for gestational age, sex, and maternal factors (1). Whether the effect is limited to birth weight or reflects a general delay in growth is not yet known. Reduced birth weight and delayed growth are not without health consequences (2). Epidemiologic studies have established associations between intrauterine and extrauterine growth restriction and the risk of development of health problems in later life, for example, cardiovascular disease (3). Only a few studies have investigated postnatal growth of IVF children and ICSI children as well (4, 5), but a longitudinal growth pattern with at least four measurements of the children has never been published before.

The objective of our study was to compare birth weight and longitudinal growth in the first 4 years of life of IVF and ICSI term singletons with those of term singletons of a national reference group. In addition we investigated whether there are differences within these groups for treatment (IVF, ICSI) and sex (male, female).

The study included 347 IVF and 330 ICSI (with ejaculated sperm) term singletons (gestational age of $\geq$37 weeks) conceived at the Radboud University Nijmegen Medical Center and born between June 1995 and December 2003. Information on fertility treatment and pregnancy outcome was retrieved from medical records. In addition, questionnaires were sent to the parents of all children at the first and fourth birthday to obtain data on parental, pregnancy, and child factors. These questionnaires included questions about weight at 1, 3, 4, 12, and 18 months and 2, 3, and 4 years of age. These points of measurement are part of the protocol of the regular periodic health examinations by general practitioners at municipal infant welfare centers in the Netherlands. The weight data are documented on a card that the parents take home. The parents were asked to use these weight data to fill in the questionnaire.

The reference group included a total of 5,059 term singletons, from a large population-based cross-sectional growth study in the Netherlands of children between 0 and 5 years measured in 1996 and 1997 (6). Measurements of weight after birth were performed by a general practitioner during the regular periodic health examinations at the municipal infant welfare centers, at the same intervals as in our study population. Statistically significant differences ($P<0.01$ using the Fisher's exact test) between the IVF and ICSI groups and references were seen in smoking behavior during pregnancy and in birth order. More IVF and ICSI mothers did not smoke during pregnancy (IVF 89.3%, ICSI 88.2%, and the references 76.7%). Moreover, there were more firstborns in the IVF and ICSI groups (respectively 67% and 77.0%) compared with the reference group (45.1%).

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TABLE 1

Weight, ratio to reference group, and time of intersection with 95% confidence interval at birth and at 4 years by gestational age, sex, and type of conception.

Sex	Type of conception	No.	Birth weight				Weight at 4 y				Time of intersection[a]	
			Mean (g)	95% CI (g)	Ratio	95% CI	Mean (g)	95% CI (g)	Ratio	95% CI	Year	95% CI (y)
Boys	IVF	169	3,407	3,332–3,483	0.97	0.95–1.00	16,875	16,576–17,179	1.00	0.98–1.02	3.5	0.1–84.9
	ICSI	150	3,404	3,323–3,487	0.97	0.95–1.00	16,524	16,184–16,870	0.98	0.96–1.00	>4	
	IVF-ICSI	319	3,406	3,351–3,461	0.97	0.96–0.99	16,711	16,486–16,939	0.99	0.98–1.01	>4	
	Natural	2,519	3,500	3,480–3,520	1.00	Ref	16,863	16,743–16,984	1.00	Ref	NA	
Girls	IVF	178	3,301	3,234–3,369	0.98	0.96–1.01	15,964	15,644–16,291	0.99	0.97–1.01	>4	
	ICSI	180	3,264	3,181–3,350	0.97	0.95–0.99	15,950	15,614–16,292	0.99	0.97–1.01	>4	
	IVF-ICSI	358	3,282	3,229–3,337	0.98	0.96–0.99	15,962	15,730–16,197	0.99	0.97–1.00	>4	
	Natural	2,521	3,356	3,337–3,374	1.00	Ref	16,184	16,065–16,304	1.00	Ref	NA	

Note: CI = confidence interval; NA = not applicable; Ref = reference group.
[a] Point of crossing of the weight curves of IVF and/or ICSI group and the associated reference group.

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A linear regression model was developed to estimate the average weight curves in the two sex categories of the reference group, separately. The dependent variable was the logarithmic transformed weight. The independent continuous variable was the logarithmic transformed age (days after birth).

The mean birth weights were calculated from the observed data, and the weights from 1 month to 4 years were calculated by using the linear mixed model. We found that the differences between the IVF and ICSI group were never statistically significant, and therefore the results of the IVF and ICSI combined groups also are presented.

Table 1 shows the mean birth weights and ratios of the different subgroups and their associated references. We found that there was a statistically significant difference (the value 1 is not included into the 95% CI of the mean ratios) between the study groups and their associated reference groups at birth but no longer at the age of 4 years. We also calculated the intersection of the growth curves of the study groups and their associated reference group. Specifically the point of intersection of the study group of IVF boys and the associated reference group occurred before 4 years.

Our study showed that term IVF and ICSI singletons had a significantly lower birth weight than children from a national reference group. This difference in birth weight between IVF and ICSI singletons and reference singletons is in accordance with findings of others (7). The mechanism behind this difference in birth weight is unknown, but several explanations have been given, such as a late effect of the hormonal ovary stimulation, the IVF-ICSI procedure itself (oocyte retrieval, culture medium, ET), the preexisting condition of the mother, factors related to subfertility, or double ET (8, 9). It was not possible in our study to verify all these explanations. For instance, information on the preexisting condition of the mother or the number of early vanishing twins was lacking. However, because there were no differences between the IVF and ICSI groups, it is not plausible that the factors related to subfertility or the ICSI procedure itself are of a great influence. In most cases the indication for ICSI was a male factor and the women had no other fertility problems themselves. Other influences on the birth weight that may play a role are maternal age, parity, and smoking behavior during pregnancy (10, 11). The first two factors could have contributed to the lower birth weight in our study group. Parity was significantly lower in the study group. The age of the mothers of the reference group at time of birth was not available. However, the mean age at delivery in the Netherlands in 1990 was 29.2 years and in 2004 was 31.0 years (http://www.cbs.nl). This is substantially lower than in the study group and is in agreement with previous data (12). Because significantly more IVF and ICSI mothers did not smoke during pregnancy, the weight difference between IVF and ICSI children and the reference group could have been more pronounced if the smoking behavior had been equal in both groups (13).

Previous studies reported on postnatal growth of IVF children (14, 15) and other studies about ICSI children as well (4, 5). Although almost all studies are reassuring, they have some limitations such as having not differentiated for gestational age, having performed only one single weight measurement at 5 years of age, or having included only IVF children. However, our study differentiated for gestational age, had at least four measurements, and included IVF and ICSI children. Our study

shows that the weight difference at birth is lost in both IVF and ICSI children before the age of 4 years.

Ludwig et al. (16) reported in a review an increase in childhood illnesses, in chronic diseases, and in the use of health care in IVF children, which may be related to the lower birth weight and higher frequency of preterm birth. Children with a low birth weight have a risk for development of health problems in later life, for example, cardiovascular disease (3). For these reasons it is important to know the weight curves of the IVF and ICSI children with a gestational age of <37 weeks as well. In our study, because these groups were too small to describe for a reliable conclusion, we recommend future studies for preterm IVF and ICSI infants with a long follow-up time.

Children with diagnosed growth disorders and those receiving medication known to interfere with growth were excluded from the reference group, but these children were not identified in the study group. It was not possible to exclude the IVF and ICSI children from the reference group, because the type of conception was not known. However, the proportion of IVF children in this reference group will be very low. In 1996, one out of 77 Dutch children was born after an IVF or ICSI treatment (17). Close to 25% of these children are from a twin pregnancy and 5.8% to 15% of the singletons were born before 37 weeks of gestational age (18); therefore, the number of IVF and ICSI term singletons in the reference group is <1%.

We compared longitudinal data of IVF and ICSI children with cross-sectional data of a reference group. This approach has disadvantages although it gave us the opportunity to have a large population-based control group. In future studies control groups with longitudinal data are to be preferred, with all confounding factors taken into account. The large sample size (especially the reference group), high response rate, and relatively long follow-up with at least four measurements are the strengths of our study. The scheme with frequent measurements of weight made it possible to assess a detailed longitudinal pattern of growth in both IVF and ICSI children.

We conclude that IVF and ICSI singletons with a gestational age of ≥37 weeks have a significantly lower birth weight than natural conceived singletons. It is reassuring that the longitudinal growth of the IVF and ICSI children is comparable with the growth of natural conceived children and that the difference of birth weight is lost before the age of 4 years.

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