Incidence of Handicaps in Multiple Births and Associated Factors

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Abstract. This study investigated the degree of risk of handicap in twins, triplets, quadruplets and quintuplets and associated factors, and examined the clustering tendency of handicaps. The sample was recruited from the Kinki University Twin and Higher Order Multiple Birth Registry. This panel consisted of 705 pairs of twins (1410 twins), 96 sets of triplets (287 triplets excluding 1 infant death), 7 sets of quadruplets (27 quadruplets excluding 1 infant death), and 2 sets of quintuplets (10 quintuplets), all of whom were born after 1977. The incidence of handicap was 3.7% in twins, 8.7% in triplets, 11.1% in quadruplets, and 10.0% in quintuplets. The risk of prodicing at least 1 handicapped child was approximately 1 in 13 pairs of twins (7.4%), 1 in 4 or 5 sets of triplets (21.6%), and 1 in 2 sets of quadruplet and quintuplets (50%). There was a significantly higher clustering tendency of handicaps in twins and triplets compared with the expected frequency calculated from the incidence rate of handicap. Four significant risk factors for subsequent handicap were found by logistic regression: gestation number, shortening of gestational age, premature rupture of the membrane, and toxemia during pregnancy.

Key words: **Multiple birth, Handicap, Clustering tendency, Gestational age, Premature rupture of the membrane, Toxemia during pregnancy**

INTRODUCTION

In Japan, as in the United Kingdom [3, 19] and the United States [17], multiple births have increased in recent decades as a result of infertility treatment. The twinning rate per 1000 births was 6.4 in 1951 and by 1991 had increased to 7.2. Furthermore, triplet, quadruplet and quintuplet births have increased remarkably: the triplet rate per million births was 58 in 1951 and 176 by 1991, a more than threeford increase over the period,

while the quadruplet rate rose even more dramatically over the same period, from 0 per million births in 1951 to 15.7 by 1991; the quintuplet rate per million births was 0 in 1951, and 1.04 by 1991 [9-12, 16].

It has been reported that twin or triplet pregnancy places greater physical strains on the mother than singleton pregnancy [4, 5, 21] and that the mortality rates for twin and higher-order birth infants are higher than that for singleton infants [13-15]. Moreover, twins and triplets are at higher risk of developing cerebral palsy [26, 27]. It has recently been estimated that 15% of all cerebral palsy in Japan occurrs in multiples [28], an extremely high proportion, given that the multiple gestation rate per total live births in Japan has been put at only 1.4% [16]. This study investigated the degree of risk of handicap in twins and higher-order multiple births, including triplet, quadruplet and quintuplet births, and examined the clustering tendency and frequency of handicaps in twins and triplets. The study also identified factors associated with the increased risk of handicaps.

MATERIALS AND METHODS

Sample

Sets of twins, triplets, quadruplets, and quintuplets were recruited from Kinki University Twin and Higher Order Multiples Registry [28-32]. This panel consisted of 705 pairs of twins (1410 twins), 96 sets of triplets (287 triplets excluding 1 infant death), 7 sets of quadruplets (27 quadruplets excluding 1 infant death), and 2 sets of quintuplets (10 quintuplets), all of whom were born after 1977. The twins triplets, quadruplets, and quintuplets in this panel had been found in several ways, such as by newspaper advertisement, and through the Twin and Supertwin Mothers Club (the Japanese Mothers' Organization for Twin and Higher Order Multiple Births), as well as referrals from midwives.

Data gathering

Data on handicaps, year of delivery, gestational age, mode of delivery, intrapartum complications and maternal information on twins and higher-order multiples were obtained from hospital birth records or interviews with the parent(s).

Data analysis

Chi-square analysis was performed to examine ratios. Logistic regression analysis was used to examine associations between handicaps and each of the following independent variables: gestation number, maternal age at delivery, toxemia during pregnancy, gestational age, mode of delivery, premature rupture of the membrane, and intrapartum asphyxia. The data were analyzed by the SPSSX statistical package, and the clustering-tendency of handicaps in twins and triplets was analysed using the following formulae:

p = prevalence rate of handicap
q = 1−p = prevalence rate of absence of handicap
n = number of pairs/sets of twins and triplets

(1) *Twins*

Expected frequency of pairs in which neither twin was handicapped:
$$q^2n = (1-p)^2n$$

Expected frequency of pairs in which one of the twins was handicapped:
$$2qpn = 2(1-p)pn$$

Expected frequency of pairs in which both of the twins were handicapped:
$$p^2n$$

(2) *Triplets*

Expected frequency of sets in which none of the triplets were handicapped:
$$q^3n = (1-p)^3n$$

Expected frequency of sets in which one of the triplets was handicapped:
$$3q^2pn = 3(1-p)^2pn$$

Expected frequency of sets in which two of the triplets were handicapped:
$$3qp^2n = 3(1-p)p^2n$$

Expected frequency of sets in which all three of the triplets were handicapped:
$$p^3n$$

The clustering tendency of the handicaps was tested by Chi-square analysis with Yates' correction.

RESULTS

Table 1 summarizes the characteristics of multiples in the sample and their mothers. The mean maternal age at birth of twins, triplets, quadruplets and quintuplets respectively was 28.8 ± 3.34 (mean $\pm$ standard deviation, range 21 to 42), 29.5 ± 2.88 (range 24 to 38), 31.4 ± 1.79 (range 28 to 34), and 29.0 ± 0.00 years of age (both mothers were 29). Toxemia during pregnancy occurred in 198 mothers of twins (28.1%), 23 mothers of triplets (24.0%), 2 mothers of quadruplets (28.6%) and 1 mother of quintuplets (50.0%). Mean gestational age at birth was 36.8 ± 2.47 for twins (range 25 to 42 weeks): 5.2% of infants were born before 31 weeks, 14.5% from 32 to 35 weeks, 79.9% after 36 weeks and the gestational age of 0.4% were unknown. Mean gestational age at birth was 34.2 ± 2.70 for triplets, (range 27 to 39 weeks): 15.3% of infants were born before 31 weeks, 48.1% from 32 to 35 weeks, and 36.6% after 36 weeks. In quadruplets, mean gestational age at birth was 31.2 ± 2.79 (range 28 to 35 weeks): 55.6% of infants were born before 31 weeks and 44.4% from 32 to 35 weeks. The mean gestational age at birth was 27.5 ± 1.58 in quintuplets, (range 26 to 29 weeks): all the infants were born before 31 weeks.

291 pairs (41.3%) of twins were delivered by cesarean section, 396 pairs (56.2%)

Table 1 - Major characteristics of multiples in the sample and their mothers

	Twins	Triplets	Quadruplets	Quintuplets
Maternal age at delivery				
Mean $\pm$ SD	28.8 $\pm$ 3.34	29.5 $\pm$ 2.88	31.4 $\pm$ 1.79	29.0 $\pm$ 0.00
Range	21 – 42	24 – 38	28 – 34	29
Toxemia during pregnancy[1]	198 (28.1)[3]	23 (24.0)	2 (28.6)	1 (50.0)
Gestational age[2]				
< 32	74 (5.2)	44 (15.3)	15 (55.6)	10 (100.0)
32 – 35	204 (14.5)	138 (48.1)	12 (44.4)	0 (0.0)
36 and over	1126 (79.9)	105 (36.6)	0 (0.0)	0 (0.0)
Unknown	6 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Mean $\pm$ SD	36.8 $\pm$ 2.47	34.2 $\pm$ 2.70	31.2 $\pm$ 2.79	27.5 $\pm$ 1.58
Range	25 – 42	27 – 39	28 35	26 – 29
Mode of delivery[1]				
Cesarean section	291 (41.3)	82 (85.4)	7 (100.0)	2 (100.0)
Vaginal delivery	396 (56.2)	14 (14.6)	0 (0.0)	0 (0.0)
Cesarean section after vaginal delivery	11 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	7 (1.0)	—	—	—
Premature rupture of membrane[2]	176 (12.5)	17 (5.9)	4 (14.8)	0 (0.0)
Intrapartum asphyxia[2]	103 (7.3)	8 (2.8)	1 (3.7)	1 (10.0)

[1] Numbers of mothers
[2] Numbers of sets of multiples
[3] Bracketed figures expressed in percentages

were delivered vaginally and in 11 pairs (1.6%), the second infant was delivered by cesarean section after vaginal delivery of the first twin. Of the vaginal deliveries, 128 infants were delivered by vacuum extraction and 18 were delivered by forceps. 82 sets of triplets (85.4%) were delivered by cesarean section and 14 sets (14.6%) by vaginal delivery. Of the vaginal deliveries, 2 infants were delivered by vacuum extraction. All 7 sets of quadruplets (100.0%) were delivered by cesarean section. Both sets of quintuplets (100.0%) were also delivered by cesarean section.

Premature rupture of the membrane occurred in 176 twins infants (12.5%), in 17 triplet infants (5.9%), in 4 quadruplets (14.8%) and in none of the quintuplets in the sample. Intrapartum asphyxia occurred in 103 twin infants (7.3%), in 8 triplet infants (2.8%), in 1 quadruplet (3.7%) and in 1 quintuplet (10%).

As shown in Table 2, 1272 of 1410 twins (90.2%) were not handicapped, but 52 twins (3.7%) were; the parents of 86 twins (6.1%) did not provide information concerning handicap in interview. Of the 52 handicapped twins, 12 (0.8%) had cerebral palsy, 2 (0.1%) had impaired hearing, 8 (0.6%) impaired sight, and 17 (1.2%) internal anomalies (of these, 10 had congenital heart disease, 2, anomalies of the respiratory system, 1, esophageal atresia, and 1, anomalies of the renal system).

Mental retardation occurred in 2 twin infants, (0.1%) and other handicaps in 11 (0.8%). Of 287 triplets, 244 (85.0%) were not handicapped, but 25 (8.7%) were and the parents of 18 triplets (6.3%) did not provide information concerning handicap at interview. Of the 25 handicapped triplets, 9 (3.1%) had cerebral palsy, 3 (1.1%) had internal anomalies (congenital heart disease and others), and 5 (1.7%) had other handicaps (among these infants, 3 had crippled limbs due to anomaly, and 2, delayed development). Of 27 quadruplets, 24 (88.9%) were not handicapped, but 3 (11.1%) were. All 3 handicapped quadruplets were affected by cerebral palsy. Of the 10 quintuplets, 9 (90.0%) were not handicapped, but 1 (10.0%) was. This quintuplet had an internal anomaly (congenital heart disease). One twin and two triplets had anomalies of the ear, although we did not classify them as handicapped.

As can be seen from Table 3, among the twin pregnancies, there were 49 pairs (7.4%)

Table 2 - Distribution of various types of handicaps in multiples in the sample

	Twins No. (%)		Triplets No. (%)		Quadruplets No. (%)		Quintuplets No. (%)	
No. of subjects	1410	(100.0)	287	(100.0)	27	(100.0)	10	(100.0)
Not handicapped	1272	(90.2)	244	(85.0)	24	(88.9)	9	(90.0)
Handicapped	52	(3.7)	25	(8.7)	3	(11.1)	1	(10.0)
Cerebral palsy	12	(0.8)	9	(3.1)	3	(11.1)	0	(0.0)
Impaired hearing	2	(0.1)	3	(1.1)	0	(0.0)	0	(0.0)
Impaired sight	8	(0.6)	5	(1.7)	0	(0.0)	0	(0.0)
Internal anomalies (disease)	17	(1.2)	3	(1.1)	0	(0.0)	1	(10.0)
Mental retardation	2	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Other handicaps	11	(0.8)	5	(1.7)	0	(0.0)	0	(0.0)
No information concerning handicap available	86	(6.1)	18	(6.3)	0	(0.0)	0	(0.0)

Table 3 - Prevalence of handicaps per set of multiples

	Twins No. (%)		Triplets No. (%)		Quadruplets No. (%)		Quintuplets No. (%)	
At least one handicapped child in the set	49	(7.4)	19	(21.6)	3	(42.9)	1	(50.0) *
No handicapped children in the set	610	(92.6)	69	(78.4)	4	(57.1)	1	(50.0)
Total	659	(100.0)	88	(100.0)	7	(100.0)	2	(100.0)

Note: Sets in which handicap status was unknown were excluded.
* $p < 0.001$

in which at least one child was handicapped, and 610 pairs (92.6%) in which neither twin was handicapped. Among the triplet pregnancies, there were 19 sets (21.6%) in which at least one child was handicapped and 69 (78.4%) in which none of the triplets was handicapped. There were 3 quadruplet pregnancies (42.9%) in which at least 1 child was handicapped and 4 (57.1%) in which none of the quadruplets was handicapped. Among the quintuplet pregnancies, handicap occurred in at least 1 child in 1 of the 2 sets (50%). The risk of handicap increased with the number of children in the multiple pregnancy.

Table 4 shows the clustering tendency of handicaps among twins. Of 659 pairs, there were 7 in which both twins were handicapped and 42 in which 1 of the twins was handicapped. As the incidence of handicap was 3.7% in twins, the expected frequency of pairs in which both twins were handicapped was 0.9, and the expected frequency of pairs in which 1 of the twins was handicapped was 46.9. The clustering tendency of handicaps among twins was significantly higher than the expected frequency of pairs in which both twins were handicapped ($p < 0.001$).

Table 5 indicates the clustering tendency of handicaps among triplets. Of 88 sets, there were 2 in which all 3 triplets were handicapped, 3 sets in which 2 were handicapped, and 14 sets in which 1 triplet was handicapped. Since the incidence of handicap was 8.7% among triplets, the expected frequency of sets in which all 3 triplets were handicapped was 0.06, the expected frequency of sets in which 2 triplets were handicapped was 1.82,

Table 4 - Clustering tendency of handicaps among twins

Number of handicapped children in the pair		Twins	
		Observed frequency	Expected frequency
0	q^2	610	611.2
1	2pq	42	46.9
2	p^2	7	0.9
Total		659	659.0

Note: $\chi^2 = 35.3$, d.f. $= 2$, $p < 0.001$.

Table 5 - Clustering tendency of handicaps among triplets

Number of handicapped children in the set		Triplets	
		Observed frequency	Expected frequency
0	q^3	69	66.96
1	$3q^2p$	14	19.16
2	$3qp^2$	3	1.82
3	p^3	2	0.06
Total		88	88.00

Note: $\chi^2 = 36.2$, d.f. $= 3$, $p < 0.001$.

and the expected frequency of sets in which 1 triplet was handicapped was 19.16. The clustering tendency of handicaps was significantly higher among triplets (p < 0.001) than the expected frequency of sets in which all 3, or 2 triplets were handicapped. There were few sets of quadruplets and quintuplets in this sample, and there was none in which more than 2 children were handicapped.

Table 6 shows the results of logistic regression on handicaps in infants in the sample. In this analysis, four factors showed significant associations with subsequent handicaps: triplet and higher-order multiple birth (odds ratio (OR) = 2.42, 95% confidence interval (CI):1:31 – 4.48); toxemia during pregnancy (OR = 2.49, 95% CI:1.53 – 4.05); premature rupture of the membrane (OR = 2.55, 95% CI:1.42 – 4.59), and shortening of gestational age (< 32 weeks). In particular, children whose gestational age was less than 32 weeks were at greatest risk for subsequent handicaps: the odds ratio indicated that such children were 4.84 times more likely to develop these than children whose gestational age was more than 36 weeks.

Table 6 - Results of logistic regression on handicaps

Independent variable	Odds ratio (OR)	95% Confidence interval (CI)
Gestation number		
Twin	1.00	
Triplet and higher-order multiple birth	2.42 *	1.31 – 4.48
Maternal age of delivery		
< 35	1.00	
35 and over	1.99	0.85 – 4.65
Toxemia during pregnancy		
No	1.00	
Yes	2.49 **	1.53 – 4.05
Gestational age		
< 32	4.84 **	2.39 – 9.82
32 – 35	1.63	0.87 – 3.06
36 and over	1.00	
Mode of delivery		
Cesarean section	1.00	
Vaginal delivery	1.54	0.89 – 2.68
Cesarean section after vaginal delivery	1.05	0.13 < 8.79
Premature rupture of membrane		
No	1.00	
Yes	2.55 *	1.42 – 4.59
Intrapartum asphyxia		
No	1.00	
Yes	1.95	0.91 – 4.15

* p < 0.01
**p < 0.001

DISCUSSION

The incidence of multiple births, especially of triplets and higher order births has risen dramatically during the past decade, although the overall birthrate in Japan has decreased. The mortality rate among multiples is higher than that among singletons, and the vast majority of multiple births involve low or very low birthweight infants [6, 23, 30]. It has also been reported that multiples are at greater risk of developing cerebral palsy [2, 8, 22, 24, 25]. However, among multiple gestations, the incidence of post-neonatal handicap and factors associated with its increased risk are unknown, and few comparable figures are available for quadruplets and quintuplets.

There may be some sampling bias in this study, because the data are not based on total ascertainment of Japanese multiple births. Due to Japanese law protecting individual privacy and the rights of the handicapped, it was difficult to obtain information on handicapped patients from Japan's birth registries. Moreover, there have been few previous studies on handicaps in multiple births. As described above, our sample was obtained from responses to advertisements in newspapers and journals and multiple birth clubs, and the impression gained from these responses is that many mothers experienced problems in their multiple pregnancies. It should, however, be borne in mind that public services providing support to multiples and their families are virtually non-existent in Japan, and the great majority of Japanese mothers of multiples are concerned about childcare issues, whether or not their children are handicapped. This fact may reduce the potential bias of our sample, which has not been verified as large in comparison to the population data. However, as reported above, this study observed the incidence of handicaps as 3.7% in twins, 8.7% in triplets, 11.1% in quadruplets and 10.0% in quintuplets. Of these handicaps, internal anomaly was the most frequent in twins, where the rate was 1.2%. In triplets, while the rate of internal anomaly was similar to that in twins, cerebral palsy was the most frequent handicap (occurring in 3.1% of infants). The incidence of cerebral palsy increased with the order of multiple birth, with the exception of quintuplets (of which there were only 2 sets in the sample).

As the risk of producing at least 1 handicapped child was 7.4% in twin pregnancy, in approximately 1 in 13 pairs of twins, at least 1 child was handicapped. Moreover, the risk of handicap is considered to be higher in triplets and higher-order births than in twins, since the incidence of handicaps and the number of children per set is higher. In this study, the risk of producing at least 1 handicapped child was 21.6% in triplet pregnancies: approximately 1 in 4 or 5 sets of triplets had at least 1 handicapped child. Furthermore, the risk of producing at least one handicapped child was 42.9% in quadruplet and 50.0% in quintuplet pregnancies: 1 in 2 sets in both cases.

There was also a significantly higher clustering tendency for handicaps in twins and triplets. The expected frequency of pairs in which both twins were handicapped, calculated from the incidence of handicaps among twins, was 0.9, whereas the observed frequency of pairs in which both twins were handicapped was 7. Among triplets, the expected frequency of sets in which either all 3, or 2 of 3 children were handicapped, was 0.06 and 1.82 respectively, whereas the observed frequency was 2 and 3 sets respectively. The results indicated that the risk of producing multiply handicapped children in a pair/set was high in twins and triplets. Since there were few quadruplet and quintuplet

sets in the present study, the clustering tendency of handicaps in quadruplets and quintuplets could not be examined. This should be investigated in a future study.

In Japan, 28 sets of quintuplets were delivered between 1975 and 1991. Of these sets, 4 were all live births, 8 were all stillbirths, and 16 contained both live- and stillborn infants. It was therefore rare for all five infants of a set to be liveborn.

As has been stated, the proportion of multiple births has been increased considerably by the use of fertility drugs and in vitro fertilization techniques. It is a serious issue for mothers and families that 1 in 13 pairs of twins, 1 in 4 or 5 sets of triplets, and 1 in 2 sets of quadruplets or quintuplets contained handicapped children, and the risk of producing multiply handicapped infants was high. When a multiple gestation seems likely, prospective parents may need special counselling that includes information on the higher risk of producing handicapped and multiply handicapped children.

To summarise, four significant risk factors for subsequent handicaps were identified by this study. One of those factors was gestation number (number of infants per multiple birth): triplets and higher-order multiple births had a higher risk for subsequent handicaps than twins. In a study of twins and triplets carried out in the United States, the relative risk of handicap for post-neonatal surviving infants was 1.4 and 2.0 respectively compared with singletons [20]. These results confirm the finding of our study that triplets were at greater risk for subsequent handicaps than twins.

However, it was the shortening of gestational age that was the highest risk factor for subsequent handicaps in multiples. It has been reported that the prevalence of cerebral palsy is associated with shortening of gestational age and has also been indicated that shortening of gestational age increased not only the risk of cerebral palsy but also the overall risk of handicap [24, 28]. In particular, the odds ratio (OR) indicated that the risk of handicap in children whose gestational age was less than 32 weeks was considerably higher than that in children whose gestational age was more than 36 weeks.

Premature rupture of the membrane was also associated with an increased risk of handicap. Rupture of the membranes often precedes premature rapid labour and lower gestational age at birth. One study reported a significant association between premature rupture of the membranes – more than 24 hours before labour – and subsequent handicaps (cerebral palsy, mental retardation, epilepsy, and severe defects of vision and hearing) among singleton children [7]. Moreover, toxemia during pregnancy is also associated with the risk of handicaps. It was reported that the condition significantly increased perinatal mortality [1] and was one of the risk factors for growth retardation in the fetus [18]. Deterioration of uterine conditions due to toxemia were thought to cause subsequent handicaps.

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