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Infant Mortality Attributable to Birth Defects in Singletons and Twins in Japan, 1995-2008

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Abstract

Objective: To evaluate the Infant Mortality Rate (IMR) associated with birth defects in singletons and twins and to identify risk factors for IMR.

Study design: IMR was estimated using Japanese vital statistics from 1995 to 2008.

Results: All IMRs associated with birth defects significantly decreased from 1995 to 2008 for both singletons and twins. IMR was approximately 3-fold higher in the latter than in the former during the period 1995–2008. In contrast, IMR with chromosomal abnormalities was the same in singletons and twins. The proportion of infant deaths associated with all birth defects among the total number of infant deaths was nearly constant (40%) during the examination period in singletons. In contrast, the value in twins was 20% in 1995 and increased to 25% in 2008. During the period, IMR significantly decreased in six categories of birth defects in singletons and two categories in twins. The Relative Risk (RR) in twins vs. singletons was 52-fold for anencephaly and 14-fold for patent ductus arteriosus. RR in twins vs. singletons was 2.9-fold for IMR and 3.8-fold for the neonatal mortality rate. With regard to the circulatory system (Q20-Q28), RR of IMR in twins vs. singletons decreased with maternal age (MA) (from 7.6-fold to 2-fold). For chromosomal abnormalities (Q90-Q99), IMR in singletons was 15-fold higher for the oldest MA group than in the youngest group. With regard to the Gestational Age (GA) and birth weight, IMR associated with all birth defects decreased with an increase in GA from the shortest week of GA to the longest and from the lowest birth weight to the highest.

Conclusion: IMR associated with all birth defects decreased significantly from 1995 to 2008 for both singletons and twins. RR in twins vs. singletons was approximately 3-fold during the period 1995-2008. IMR for Q90-Q99 was similar in singletons and twins. IMR of anencephaly in twins increased following in vitro fertilization and stimulation of ovulation. To reduce different IMRs between twins and singletons, it is important to provide intensive care for twin babies during the neonatal period.

Keywords: Infant mortality; Neonatal mortality; Birth defects; Twins; Singletons; Risk factors

Introduction

According to Little and Bryan [1], Congenital Malformations (CMs) occurred more frequently in twins than in singletons in most studies. In Japan, the prevalence of CMs was higher in twins (1.2%) than in singletons (1.07%) [2]. Several studies have reported that the prevalence of birth defects in multiple births increased following Assisted Reproductive Technology (ART) [3-6]. In Japan, the twinning rate has increased since 1987 and is attributed to ovulation stimulation treatments and ART [7]. It is of interest to know the yearly change in the Infant Mortality Rate (IMR) associated with birth defects for both singletons and twins.

According to Broussard et al. [8], birth defects were a major contributor to Infant Mortality (IM) in the US. In Japan, the proportion of CMs among all infant deaths was 1.9% in 1947 and increased to 10.7% in 1965 and 26.9% in 1981 [9] and to 35.3% in 1995 [10].

The purpose of this study was to compare all-cause IMRs associated with birth defects in singletons and twins during the period 1995-2008 and to identify risk factors for IMR associated with birth defects.

Materials and Methods

Data on Live Births (LBs) and infant deaths were obtained from the vital statistics of Japan for the years 1995-2008 (Health and Welfare Statistics and Information Department, Ministry of Health, Labour and Welfare, Japan). These data cover the entire population of Japan. Death certificates provide information regarding nationality, sex, dates, Birth Weight (BW), Gestational Age (GA), parental age, single or multiple births, birth order of multiple births, cause of death, and other details. LB certificate records contain the same information, except for data related to cause of death. In Japan, Neonatal Mortality (NM) refers to the death of a live-born infant occurring within 28 days from the time of birth. The NM Rate (NMR) is defined as the number of NM cases per 10000 LBs. IM refers to the death of a live-born infant occurring within 1 year from the time of birth. IMR is defined as the number of IMs per 10000 LBs.

All birth defects were classified into 11 categories according to the ICD 10th revision [11]: Q00-Q07 (CMs of the nervous system), Q10-Q18 (CMs of the eye, ear, face, and neck), Q20-Q28 (CMs of the circulatory system), Q30-Q34 (CMs of the respiratory system), Q35-Q37 (the cleft lip and cleft palate), Q38-Q45 (other CMs of the digestive system), Q50-Q56 (CMs of genital organs), Q60-Q64 (CMs of the urinary system), Q65-Q79 (CMs and deformations of the musculoskeletal system), Q80-Q89 (other CMs), and Q90-Q99 (chromosomal abnormalities, not elsewhere classified). Of the 19 specific causes of deaths in Table 1, 18 causes of deaths were chosen in accordance with the large number of infant deaths resulting from each cause of deaths in singletons and twins as well as conjoined twins. In Table 2, the linear regression coefficients of IMR on the year was

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Cause of death (ICD-10th code)	Number of deathsIMR[1]		Odds ratio		[95% CI]
	Singletons	Twins	Singletons	Twins	
Q00-Q07 CMs of the nervous system	714 (4.1%)	151 (15.1%)	0.45	4.82	10.63 [8.92-12.67]*
Q00.0 Anencephaly	109	112	0.07	3.58	51.64 [39.67-67.22]*
Q04.2Holoprosencephaly	200	18	0.13	0.57	4.52 [2.79-7.32]*
Q10-Q18 CMs of eye, ear, face and neck	3	1	0	0.03	-
Q20-Q28 CMs of the circulatory system	8289 (47.6%)	451 (45.1%)	5.27	14.41	2.74 [2.49-3.01]*
Q20.1Double outlet right ventricle	401	12	0.26	0.38	1.5 [0.85-2.67]
Q20.3 Discordantventriculoarterial connection	523	23	0.73	0.33	2.21 [1.46-3.34]*
Q20.4 Double inlet ventricle	435	11	0.28	0.35	1.27 [0.70- 2.31]
Q21.0 Ventricularseptal defect	662	25	0.42	0.8	1.90 [1.27-2.83]*
Q21.2 Atrioventricularseptal defect	636	11	0.4	0.35	0.87 [0.48 1.58]
Q23.4 Hypoplastic left heart syndrome	1086	29	0.69	0.93	1.34 [0.93-1.94]
Q24.9 CM of heart, unspecified	599	23	0.38	0.73	1.93 [1.27-2.93]*
Q25.0 Patentductusarteriosus	542	147	0.34	4.7	13.68 [11.36-16.36]*
Q25.1 Coarctation of aorta	469	23	0.3	0.73	2.46 [1.62-3.74]*
Q25.5 Atresia of pulmonary artery	309	28	0.2	0.89	4.55 [3.09-6.73]*
Q26.2 Total anomalous pulmonary venous connection	576	10	0.37	0.32	0.87 [0.47-4.24]
Q30-Q34 CMs of the respiratory system	1947	129	1.24	4.12	3.33 [2.79- 3.98]*
Q33.6 Hypoplasia and dysplasia of lung	1567	109	1	3.48	3.50 [2.88-4.24]*
Q35-Q37 Cleft lip and cleft palate	15	2	0.01	0.06	-
Q38-Q45 Other CMs of the digestive system	526	39	0.33	1.25	3.73 [2.69-5.16]*
Q50-Q56 CMs of genital organs	3	2	0	0.06	-
Q60-Q64 CMs of the urinary system	574	45	0.36	1.44	3.94 [2.91- 5.34]*
Q60.6 Potter's syndrome	431	23	0.27	0.73	2.68 [1.76-4.08]*
Q65-Q79 CMs anddeformations of themusculoskeletal system	1150	45	0.73	1.44	1.97 [1.46 -2.65]*
Q79.0 Congenital diaphragmatic hernia	644	16	0.41	0.51	1.25 [0.76-2.05]
Q80-Q89 Other CMs	969	80	0.62	2.56	4.15 [3.30-5.21]*
Q89.4 Conjoined twins	-	20	-	0.64	-
Q90-Q99 Chromosomal abnormalities, not elsewhere classified	3241 (18.6%)	56 (5.6%)	2.06	1.79	0.87 [0.67-1.13]
Q91.3Edwards syndrome, unspecified	2076	29	1.32	0.93	0.70 [0.49 1.01]
Q91.7Patau syndrome	455	11	0.29	0.35	1.21 [0.67-2.21]
Q00-Q99CMs, deformations and chromosomal abnormalities	17431 (70.2%)	1001 (65.7%)	11.08	31.98	2.89 [2.71-3.08]*

Note: [1] per 10000 live births (n=313,045 for twins and n=15,727,022 for singleton); CI: Confidence interval; *Significant at the 5% level; , CMs: Congenital malformations

Table 1: Number of Infant Deaths due to 11 Categories of All CMs and 19Specific Cause of Deaths and Infant MortalityRatein Singletons and Twins, 1995-2008.

used to test the change in IMR from 1995-1996 to 2007-2008. The odds ratio (OR) and 95% Confidence Intervals (CIs) were used to test IMRs between the two categories. The correlation coefficient was also used to test the relationship between IMR and MA in Table 3. The average of MA in each group was computed in each CM category for both singletons and twins. The following numbers of infant deaths did not differ between singletons and multiple births: 366 (7.2%) in 1995, 313 (6.9%) in 1996, 337 (7.7%) in 1997, 330 (7.5%) in 1998, 271 (6.8%) in 1999, 268 (7.0%) in 2000, 259 (7.2%) in 2001, 220 (6.3%) in 2002, 206 (6.1%) in 2003, 199 (6.4%) in 2004, 209 (7.1%) in 2005, 185 (6.5%) in 2006, 169 (6.0%) in 2007, and 192 (6.9%) in 2008.

Results

Yearly change in IMRs associated with birth defects

Table 2 shows IMRs in singletons and twins according to 11 categories of birth defects from 1995-1996 to 2007-2008. The percentage of infant deaths associated with birth defects among the total infant deaths was nearly constant (39%-42%) in singletons during the period, whereas it was 21% in 1995-1996 and gradually increased to 27% in 2007–2008 in twins. Excluding the small number of infant deaths in three CM categories (Q10-Q18, Q35-Q37, and Q50-Q56) among 11 categories, IMR decreased significantly for Q00-Q07, Q20-Q28, Q30-Q34, Q38-Q34, Q65-Q79, and Q80-Q89 in singletons from 1995-1996 to 2007-2008 and decreased significantly for Q20-Q28 and Q30-Q34 in twins. For Q00-Q07 in twins, IMR increased during the period; however, the increase was not statistically significant. IMR associated with all birth defects decreased significantly in both singletons and twins. The Relative Risk (RR) in twins vs. singletons was nearly constant between 1995-1996 and 2007-2008 (2.7-3.4-fold) for all birth defects. In contrast, the ratio for Q00-Q07 was 5.5-fold in 1997-1998, increased to 19-fold in 2005-2006, and decreased to 13.2-fold in 2007–2008. Table 2 also shows IMR associated with all birth defects in both sexes. With one exception, IMRs between males and females were similar in each period in both singletons and twins. The exception was IMR for the period 2005–2006 in twins where the rate was significantly higher in males than in females.

Table 2 also shows the proportion of neonatal deaths among infant deaths in each CM category. Excluding the small number of infant deaths in three categories of CMs, the proportions ranged between 36% and 92% in singletons and 37% and 100% in twins. For all birth defects, these values were 57% in singletons and 75% in twins. The highest difference between percentages of singletons and twins was 29% (Q00-Q07), followed by 18% (Q20-Q28 and the total birth defects). NMR for all birth defects was significantly higher in twins (23.80 per 10000 LBs) than in singletons (6.26) (OR, 3.81; 95% CI, 3.54-4.11).

Comparison of IM between singletons and twins

Table 1 shows IMRs for 11 CM categories and 19 specific causes

ICDICDICD-10th	Number of infant deaths							Infant mortality rate (IMR) per 10000 live births							1995-2008 NMR1) (%)	Regretion coefficient
	1995	1997	1999	2001	2003	2005	2007	1995	1997	1999	2001	2003	2005	2007		
Singletons																
Q00-Q07	146	133	104	98	79	68	82	0.62	0.57	0.45	0.43	0.36	0.32	0.38	0.27(61)	-0.02*
Q10-Q18	2	0	0	1	0	0	0	0.01	0	0	0	0	0	0	0	-
Q20-Q28	1614	1419	1265	1204	1082	845	838	6.86	6.04	5.45	5.29	4.95	4.01	3.93	2.49(47)	-0.24*
Q30-Q34	394	322	299	268	254	246	156	1.68	1.37	1.29	1.18	1.16	1.17	0.73	1.04(84)	-0.06*
Q35-Q37	0	4	3	2	3	2	1	0	0.02	0.01	0.01	0.01	0.01	0	0.01	-
Q38-Q45	128	91	72	62	66	46	60	0.54	0.39	0.31	0.27	0.3	0.22	0.28	0.12(36)	-0.02*
Q50-Q56	0	1	0	0	0	1	1	0	0	0	0	0	0	0	0	
Q60-Q64	91	80	86	87	93	64	71	0.39	0.34	0.37	0.38	0.43	0.3	0.33	0.33(92)	-0.003
Q65-Q79	212	206	169	157	155	119	129	0.9	0.88	0.73	0.69	0.71	0.56	0.6	0.60(82)	-0.03*
Q80-Q89	162	179	165	155	111	107	90	0.69	0.76	0.71	0.68	0.51	0.51	0.42	0.38(61)	-0.03*
Q90-Q99	488	494	439	508	413	396	501	2.08	2.1	1.89	2.23	1.89	1.88	2.35	1.01(49)	0.01
Total	3237	2929	2602	2542	2256	1894	1929	13.76	12.46	11.21	11.17	10.33	8.99	9.04	6.26(57)	-0.39*
Males	1697	1489	1354	1298	1172	995	967	14.06	12.34	11.34	11.1	10.46	9.21	8.82	6.56(59)	
Females	1540	1440	1248	1244	1084	899	962	13.46	12.58	11.06	11.24	10.19	8.77	9.26	5.93(54)	
% of infant deaths due to CM among total infant deaths								39.8	39.6	39.6	42.1	41.3	38.6	39.9		
Twins																
Q00-Q07	15	13	20	20	30	29	23	3.74	3.11	4.52	4.34	6.21	6.13	5.08	4.31(90)	0.21
Q10-Q18	1	0	0	0	0	0	0	0.25	0	0	0	0	0	0	0.03	-
Q20-Q28	78	77	74	68	61	43	50	19.47	18.43	16.73	14.77	12.63	9.09	11.04	9.39(65)	-0.86*
Q30-Q34	26	25	24	15	18	16	5	6.49	5.98	5.43	3.26	3.73	3.38	1.1	3.77(92)	-0.41*
Q35-Q37	1	0	1	0	0	0	0	0.25	0	0.23	0	0	0	0	0.1	-
Q38-Q45	5	5	10	5	4	5	5	1.25	1.2	2.26	1.09	0.83	1.06	1.1	0.45(37)	-0.04
Q50-Q56	0	0	0	0	0	2	0	0	0	0	0	0	0.42	0	0.06	-
Q60-Q64	6	7	6	7	6	7	6	1.5	1.68	1.36	1.52	1.24	1.48	1.32	1.44 (100)	-0.02
Q65-Q79	5	6	4	10	6	7	7	1.25	1.44	0.9	2.17	1.24	1.48	1.55	1.31 (91)	0.03
Q80-Q89	10	10	21	16	8	8	7	2.5	2.39	4.75	3.47	1.66	1.69	1.55	1.95(76)	-0.130
Q90-Q99	4	5	10	5	15	10	6	1	1.2	2.26	1.09	3.11	2.11	1.32	0.99(56)	0.07
Total	151	148	170	146	148	127	109	37.7	35.41	38.43	31.7	30.65	26.84	24.06	23.80(75)	-1.18*
Males	75	79	78	74	70	79	55	37.39	37.34	34.95	31.89	28.63	32.98*	24.26	24.21(75)	
Females	76	69	92	72	78	48	54	38.01	33.44	41.98	31.51	32.73	20.54	23.86	23.38(74)	
% of infant deaths due to CM among total infant deaths								21.2	22.7	25.7	26.6	25.9	26.3	26.8		
Ratio of twins to singletons (Q00-Q07)								6	5.5	10.1	10.1	17.2	19	13.2	16	
		(Q00-Q99)						2.7	2.8	3.4	2.8	3	3	2.7	3.8	
		(Q10-Q99)2.6							2.7	3.2	2.5	2.5	2.4	2.2	3.3	

1): Neonatal mortality rate per 10000 live births; *: Significant at the 5% level between IMRs for males and females

Table 2: Number of Congenital Malformations, Deformations and Chromosomal Abnormalities (CM) of Infant Deaths and Death Rates in Singleton and Twins, 1995-2008.

of deaths during the period 1995-2008. Excluding the small number of deaths in three categories (Q10-Q18, Q35-Q37, and Q50-Q56), IMRs were significantly higher in twins than in singletons for seven CM categories, where the highest RR in twins vs. singletons was 10.6-fold for Q00-Q07 and the lowest was 2-fold for Q65-Q79. In contrast, RR in twins vs. singletons was 0.87-fold for Q90–Q99. Of IMRs for 18 specific causes of deaths, IMRs for 10 specific causes of deaths were higher in twins than in singletons. In singletons, the highest IMR was 1.32 for Edward's syndrome, unspecified (Q91.3), followed by 1.00 for hypoplasia and dysplasia of the lung (Q33.6) and 0.69 for hypoplastic left heart syndrome (Q23.4). In twins, the highest IMR was 4.70 for patent ducts arteriosus (Q25.0), followed by 3.58 for anencephaly (Q00.0) and 3.48 for Q33.6. RR in twins vs. singletons was 51.6-fold for Q00.0, followed by 13.7-fold for Q25.0. IMR in conjoined twins (Q89.4) was 0.64; in this case, the cause of death is peculiar to twins.

IMRs by maternal age (MA)

Table 3 shows IMRs for Q00-Q07, Q20-Q28, Q90-Q99, and the total birth defects according to MA during 1999-2008. IMRs for Q00-Q07 in singletons were 0.3-0.4 for MA <25 to 35-39 groups and 1.0 for the oldest MA group, where the differences between the lowest IMR and those for the oldest MA group were statistically significant at the 5% level. In contrast, IMRs in twins were also similar (4.5-5.6) for MA <25 to 35-39 years and the lowest (1.8) for MA ≥ 40 years, where the number of infant deaths was only one. IMRs in twins were independent of MA. Excluding the small number of infant deaths, RRs in twins vs. singletons were between 11- and 17-fold. For Q20–Q28, IMR in singletons was 4.2 for MA <25 years to 25-29 years and increased thereafter (11.1) up to MA ≥ 40 years. IMR was significantly lower for MA <25 years than for MA 35-39 years and ≥ 40 years. In contrast, IMR in twins decreased from 17.4 for MA <25 years to 11 at 30–34 years and increased thereafter to 22 up to MA ≥ 40 years. IMR for MA 30–34 years was significantly lower than that for MA <25 years or ≥ 40 years. IMR was significantly higher in twins than in singletons for each MA group. RR in twins vs. singletons was the highest for the youngest MA group (4.1-fold) and decreased (2-fold) for MA ≥ 40 years. For Q90–Q99, IMR in singletons was the lowest (1.1) for MA <25 years and increased (13.5) with an increase in MA up to ≥ 40 years. IMR was significantly lower for MA <25 years than for MA of 30-34, 35-39, and ≥ 40 years. In contrast, IMR in twins was 0.5 for MA <25 years and increased to 9.2 with an increase in MA up to ≥ 40 years. IMR for MA 25-29 years was significantly lower than those for

Maternal age	Singletons	Twins	Odds ratio [95%CI]		Odds ratio [95%CI] Twins vs. singletons	Odds ratio [95%CI] Singletons	Twins
	Number	IMR[1)]	Number	IMR[1)]			
Q00-Q07		-0.73		(-0.60)			
<25	64	0.4	9	4.5	11.09 [5.52-22.28]*	1.25 [0.92-1.69]	1.00 Reference
25-29	124	0.3	38	5.6	17.38 [12.08-24.99]*	1.00 Reference	1.26 [0.61-2.60]
30-34	149	0.4	51	5.4	14.28 [10.39-19.63]*	1.17 [0.92-1.48]	1.20 [0.59-2.44]
35-39	63	0.4	23	5.2	12.03 [7.46-19.39]*	1.34 [0.99-1.81]	1.16 [0.54-2.51]
≥ 40	18	1	1	1.8	-	2.95 [1.80-4.83]*	-
Q20-Q28		-0.8		-0.31			
<25	670	4.2	35	17.4	4.12 [2.93-5.79]*	1.00 Reference	1.59 [1.08-2.33]*
25-29	1623	4.2	88	13	3.08 [2.48-3.81]*	1.00 [0.92-1.10]	1.19 [0.89-1.58]
30-34	1765	4.5	104	11	2.46 [2.02-3.00]*	1.06 [0.99-1.15]	1.00 Reference
35-39	795	5.5	55	12.4	2.28 [1.73-3.00]*	1.29 [1.17-1.43]*	1.13 [0.82-1.57]
≥ 40	209	11.1	12	22.2	2.00 [1.12-3.59]*	2.62 [2.24-3.06]*	2.02 [1.11-3.68]*
Q90-Q99		(0.84)		-0.82			
<25	180	1.1	1	0.5	-	1.00 Reference	
25-29	453	1.2	6	0.9	0.75 [0.34-1.68]	1.04 [0.88-1.24]	1.00 Reference
30-34	686	1.7	14	1.5	0.85 [0.50-1.44]	1.53 [1.30-1.80]*	1.66 [0.64-4.33]
35-39	634	4.4	20	4.5	1.04 [0.67-1.62]	3.84 [3.25-4.53]*	5.10 [2.05-12.71]*
≥ 40	254	13.5	5	9.2	0.69 [0.28-1.66]	11.87 [9.80-14.37]*	10.43 [3.18-34.17]*
Q00-Q99		-0.81		-0.67			
<25	1405	8.9	66	32.8	3.71 [2.90-4.75]*	1.04 [0.98-1.11]	1.16 [0.88-1.54]
25-29	3264	8.5	191	28.2	3.32 [2.87-3.85]*	1.00 Reference	1.00 Reference
30-34	3699	9.3	270	28.5	3.05 [2.69-3.45]*	1.10 [1.04-1.15]*	1.01 [0.84-1.21]
35-39	1975	13.6	146	33	2.44 [2.06-2.89]*	1.59 [1.51-1.69]*	1.17 [0.94-1.45]
≥ 40	cde581	30.8	25	46.2	1.50 [1.01-2.24]*	3.62 [3.32-4.00]*	1.64 [1.08-2.49]*

[1)] IMR per 10000 live births; CI: Confidence interval; *Significant at the 5% level. Figures in parentheses indicate correlation coefficients between IMR and MA.

Table 3: Infant Mortality Rate (IMR) according to Maternal Age (MA), and Correlation Coefficients between IMR and MA, 1999-2008.

Gestational age (weeks)	Singletons Twins		Odds ratio[95%CI]		Odds ratio[95%CI] Twins vs. singletons	Odds ratio[95%CI] Singletons	Twins
	Number	IMR[1)]	Number	IMR[1)]			
Q00-Q07							
<31	41	8.5	15	12.6	1.48 [0.82-2.68]	58.95 [41.12-84.51]*	4.74 [2.51-8.95]*
31-32	32	9.8	10	11	1.12 [0.55-2.28]	68.15 [45.91-101.16]*	4.14 [2.00-8.59]*
33-34	46	6.4	26	12.8	2.00 [1.24-3.24]*	44.27 [31.33-62.55]*	4.82 [2.80-8.30]*
35-36	78	2.3	39	4.9	2.14 [1.46-3.14]*	15.84 [11.83-21.21]*	1.84 [1.12-3.02]*
37-38	108	0.3	26	2.77	65 [4.99-11.74]*	2.41 [1.84-3.14]*	1.00 Reference
≥ 39	107	0.1	6	5	34.52 [15.17-78.57]*	1.00 Reference	1.87 [0.77-4.56
Q20-Q28							
<31	433	89.8	118	99	1.10 [0.90-1.35]	31.32 [28.23-34.74]*	17.20 [8.02-36.88]*
31-32	158	48.5	31	34.1	0.70 [0.48-1.03]	16.85 [14.33-19.82]*	5.88 [2.59-13.36]*
33-34	243	33.7	29	14.3	0.42 [0.29-0.62]*	11.70 [10.2413.36]*	2.46 [1.08-5.61]*
35-36	529	15.5	47	5.9	0.38 [0.51-0.58]*	5.37 [4.88-5.90]*	1.01 [0.46-2.24]
37-38	1589	5.1	64	6.5	1.28 [0.997-1.64]	1.77 [1.66-1.89]*	1.13 [0.52-2.46]
≥ 39	2144	2.9	7	5.8	2.01 [0.96-4.22]	1.00 Reference	1.00 Reference
Q90-Q99							
<31	125	25.9	11	9.2	0.36 [0.19-0.66]*	33.56 [27.65-40.73]*	11.13 [1.44-86.20]*
31-32	155	47.6	2	2.2	0.05 [0.01-0.19]*	61.76 [51.70-73.77]*	2.65 [0.24-29.22]
33-34	221	30.7	11	5.4	0.18 [0.10-0.32]*	39.74 [34.02-46.42]*	6.52 [0.84-50.52]
35-36	431	12.6	10	1.3	0.10 [0.05-0.19]*	16.33 [14.41-18.50]*	1.51 [0.19-11.79]
37-38	708	2.3	11	1.1	0.49 [0.27-0.90]*	2.94 [2.64-3.28]*	1.35 [0.17-10.49]
≥ 39	574	0.8	1	0.8	1.07 [0.15-7.62]	1.00 Reference	1.00 Reference
Q00-Q99							
<31	996	206.5	222	186.2	0.90 [0.78-1.04]	45.23 [42.12-48.56]*	14.27 [8.59-23.72]*
31-32	596	183	66	72.5	0.39[0.30-0.51]*	39.98 [36.63-43.64]*	5.50 [3.18-9.49]*
33-34	922	128	96	47.2	0.37 [0.30-0.45]*	27.81 [25.85-29.91]*	3.57 [2.10-6.06]*
35-36	1667	48.8	153	19.2	0.39 [0.33-0.46]*	10.53 [9.93-11.16]*	1.44 [0.86-2.42]
37-38	3327	10.7	147	15	1.40 [1.20-1.66]*	2.30 [2.19-2.41]*	1.13 [0.68-1.90]
≥ 39	3455	4.7	16	13.3	2.85 [1.74- 4.66]*	1.00 Reference	1.00 Reference

[1)]IMR per 10000 live births; CI: Confidence Interval; *Significant at the 5% level

Table 4: Infant Mortality Rate according to Gestational Age, 1999-200.

Birth weight	Singletons Twins		Odds ratio[95%CI]		Odds ratio[95%CI] Twins vs. singletons	Odds ratio[95%CI] Singletons	Twins
	Number	IMR1)	Number	IMR1)			
Q00-Q07							
<1000	46	13.9	23	28.3	2.04 [1.24-3.37]*	145.15 [101.30-207.97]*	48.88 [18.58-128.60]*
1000-1499	75	14.9	41	27.3	1.84 [1.25-2.69]*	155.49 [113.87-212.32]*	47.10 [18.61-119.22]*
1500-1999	132	10.3	58	11.6	1.13 [0.83-1.54]	107.05 [81.42-140.74]*	19.98 [8.02-49.83]*
2000-2499	194	2	23	1.6	0.80 [0.52-1.24]	21.00 [16.25-27.12]*	2.78 [1.06-7.33]*
2500-2999	163	0.3	5	0.6	2.06 [0.85-5.02]	2.94 [2.26-3.82]*	1.00 Reference
≥ 3000	84	0.1	0	0	-	1.00 Reference	-
Q20-Q28							
<1000	469	141.7	153	188.4	1.34[1.11-1.61]*	149.89 [133.81-167.91]*	100.89 [25.00-407.19]*
1000-1499	455	90.3	76	50.6	0.56 [0.44-0.71]*	95.04 [84.76-106.56]*	26.72 [6.56-108.82]*
1500-1999	802	62.3	92	18.4	0.29 [0.24-0.36]*	65.38 [59.34-72.03]*	9.68 [2.39-39.31]*
2000-2499	1575	16.3	100	7	0.43 [0.35-0.53]*	17.07 [15.70-18.56]*	3.70 [0.91-15.01]*
2500-2999	2724	4.7	28	3.3	0.69 [0.48-1.003]	4.91 [4.54-5.30]*	1.71 [0.41-7.18]
≥ 3000	840	1	2	1.9	1.98 [0.50-8.0]	1.00 Reference	1.00 Reference
Q90-99							
<1000	200	60.4	14	17.2	0.28 [0.17-0.49]*	719.70 [551.10-939.87]*	81.75 [23.49-284.54]*
1000-1499	691	137.2	26	17.3	0.12 [0.08-0.18]*	1646.35 [1295.20-2092.70]*	82.09 [24.84-271.24]*
1500-1999	1175	91.3	12	2.4	0.03 [0.01-0.05]*	1090.53 [862.16-1379.38]*	11.36[3.21-40.27]*
2000-2499	797	8.3	3	0.2	0.03 [0.01-0.08]*	97.97 [77.21-124.32]*	1.00 Reference
2500-2999	242	0.4	0	0	-	4.95 [3.81-6.42]*	-
≥ 3000	74	0.1	0	0	-	1.00 Reference	-
Q00-Q99							
<1000	1094	330.6	268	329.9	0.998 [0.87-1.14]	104.20 [97.11-111.81]*	54.35 [40.53-72.87]
1000-1499	1803	357.9	228	151.8	0.42 [0.36-0.48]*	113.14 [106.60-120.08]*	24.55 [18.24-33.04]*
1500-1999	3109	241.5	254	50.8	0.21 [0.18-0.23]*	75.44 [71.69-79.39]*	8.13 [6.06-10.91]*
2000-2499	3785	39.3	182	12.8	0.33 [0.28-0.38]*	12.02 [11.45-12.62]*	2.04 [1.51-2.77]*
2500-2999	4317	7.5	54	6.3	0.84 [0.64-1.10]	2.28 [2.17-2.38]*	1.00 Reference
≥ 3000	2873	3.3	13	12.4	3.77 [2.19-6.51]*	1.00 Reference	1.97 [1.08-3.61]*

1) IMR per 10000 live births; CI: Confidence interval; *Significant at the 5% level

Table 5: Infant Mortality Rate (IMR) due to Congenital Malformations according to Birth Weight, 1995-2008.

MA of 35-39 years and ≥ 40 years. IMR was similar in both singletons and twins in each MA group. With regard to the birth defects, IMR in singletons was the lowest (8.5) for MA of 25-29 years, which was significantly lower than those for MA of 30-34 (9.3), 35-39 (13.6), and ≥ 40 years (30.8). Similarly, IMR in twins was the lowest (28) for MA 25-29 years, whereas IMRs in the oldest MA groups were the highest (46). The former IMR was significantly lower than the latter. IMR was significantly higher in twins than in singletons for each MA group. RR in twins vs. singletons was the highest in the youngest MA group (3.7-fold) and decreased (1.5-fold) with MA up to ≥ 40 years.

Correlation coefficients between MA groups and IMRs are shown in Table 3 for Q00-Q07, Q20-Q28, Q90-Q99, and the total birth defects. For singletons, correlation coefficients indicated higher values (0.73-0.84); however, these were not significant at the 5% level. In contrast, these coefficients in twins were −0.60 for Q00-Q07, 0.31 for Q20-Q28, 0.82 for Q90-Q99, and 0.67 for the total birth defects, which were not significant at the 5% level.

IMRs by GA

Table 4 shows IMR for three categories of CMs and the total birth defects according to GA in singletons and twins during the period 1999-2008. With one exception, IMRs in singletons and twins decreased with an increase in GA from the shortest GA to the longest for three CM categories and the total birth defects, with the exception of Q00-Q07 at GA of 37-38 weeks in twins. IMR for Q00-Q07 was significantly higher in twins than in singletons for four GA groups ≥ 33-34 weeks. In contrast, IMRs for Q20-Q28 (33-34 and 35-36 weeks), Q90-Q99 (five GA groups <39 weeks), and the total birth defects (three GA groups ranging between 31-32 and 35-36 weeks) were significantly higher in singletons than in twins. IMRs for the total birth defects at GA of 37-38 and ≥ 39 weeks were significantly higher in twins than in singletons, where the corresponding RRs in twins vs. singletons were 1.4-fold and 2.9-fold, respectively.

IMRs by BW

Table 5 shows IMR for the three categories of CMs and the total birth defects according to BW in singletons and twins during 1995-2008. With two exceptions, BW-specific IMRs in singletons and twins decreased with an increase in BW from the lightest to the heaviest weight in both singletons and twins. The exceptions were for the total birth defects at BW 1000-1499 g in singletons and ≥ 3000 g in twins. For Q00-Q07, IMRs were significantly higher in twins than in singletons for BW <1000g and 1000–1499 g. For Q20-Q28, IMR was significantly higher in twins than in singletons for BW <1000 g and ≥ 3000 g. In contrast, IMRs were higher in singletons than in twins from 1000-1499 g to 2000-2499 g. For Q90-Q99, IMRs were significantly higher in singletons than in twins from BW <1000 g to 2000-2499 g. With regard to the total birth defects, IMR was significantly higher in singletons than in twins from BW 1000-1499 g to 2000-2499 g, whereas the opposite result was obtained at the heaviest weight.

IMRs according to birth order of twins

Table 6 shows IMR for categories of CMs according to the birth order of twins during 1995-2008. With respect to the total birth defects, IMR in the second birth order of twins was significantly higher than that in the first order of twins (1.3-fold). A similar tendency was

	First-born Second-born		Odds ratio		
	No. of deaths	IMR	No. of deaths	IMR	[95% CI]
Q00-Q07	60	3.8	90	5.8	1.52 [1.09-2.10]*
Q20-Q28	220	14	31	14.8	1.06 [0.88-1.28]
Q30-Q 34	55	3.5	74	4.8	1.36 [0.96-1.93]
Q38-Q45	12	0.8	26	1.7	2.19 [1.10-4.34]*
Q60-Q64	21	1.3	24	1.5	1.15 [0.64-2.07]
Q65-Q79	15	1	29	1.9	1.95 [1.05-3.64]*
Q80-Q89	31	2	49	3.1	1.60 [1.02-2.50]*
Q90-Q99	26	1.7	29	1.9	1.13 [0.66-1.91]
Q00-Q99	443	28.2	555	35.6	1.27 [1.12-1.44]*

Table 6: Infant Mortality Rate (IMR) due to Congenital Malformations according to Birth Order of Twins, 1995-2008.

observed for Q00-Q07 (1.5-fold), Q38-Q45 (2.2-fold), Q65-Q79 (2.0-fold), and Q80-Q89 (1.6-fold).

Discussion

In the present study, IMRs for CMs of the nervous system in twins increased from 1995–1996 to 2005–2006. In contrast, the rate in singletons decreased during this period. The corresponding RRs in twins vs. singletons were 6-fold and 19-fold, respectively. Similarly, RR in twins vs. singletons was 51.6-fold for anencephaly during 1995-2008. Lancaster [3] reported that the prevalence of neural tube defects increased following in vitro fertilization and stimulation of ovulation. A significant correlation was observed only between anencephaly and twin births [12]. In Japan, the twinning rate was 8.9 per 1000 births in 1995-1998 and increased to 10.2 in 1999-2003 and 11.1 in 2004-2008 [13]. According to Hansen et al. [4], children born following ART were at a high risk of birth defects. Ooki [5] reported that the early NMR was slightly higher in the ART group (5.09 per 10000 LBs) than in the general population (3.86) in Japan during the period 2004-2008. In Japan, the higher RR of anencephaly is related to the effect of in vitro fertilization and stimulation of ovulation.

RR in twins vs. singletons was 2.9-fold for IMR and 3.8-fold for NMR during the period 1995-2008. Therefore, intensive care of twins in the neonatal period is important to reduce the difference in IMRs between singletons and twins. IMR for patent ductus arteriosus (PDA; Q25.0) was 13.6-fold higher in twins than in singletons. Layde et al. [14] reported that incidence rates of PDA were 17.43 per 10000 LBs in white singletons and 86.07 in white twins in the US during 1969-1976, where RR in twins vs. singletons was 4.9-fold. The corresponding values in the black population were 24.38-, 184.44-, and 7.6-fold, respectively. They also reported that a high concordance rate was observed in same-sex twin pairs, which suggested a strong genetic component to the etiology of PDA. In the present study, excluding infant deaths due to anencephaly, PDA, and conjoined twins from the total infant deaths associated with birth defects, IMR was recomputed using Table 1 and IMR of 10.67 was obtained in singletons and 23.06 in twins. RR in twins vs. singletons was 2.2-fold. The difference between IMRs in twins and singletons can be reduced by 25% compared with IMRs associated with all birth defects. It should be possible to reduce IMR associated with birth defects in twins through management for the reduction of premature and low BW and care for the second order of twins.

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