

## The End of a Triplet Epidemic and Infant Mortality in Japan, 1999-2008

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### Abstract

**Objective:** To estimate triplet rates for like-sexed and unlike-sexed sets, and infant mortality rate (IMR), and also to find risk factors for IMR in triplets.

**Study design:** These rates were estimated using Japanese Vital Statistics from 1999 to 2008.

**Results:** Like-sexed and unlike-sexed triplet rates decreased significantly from 1999 to 2008. In 1999, the rate was 2.0-fold higher in unlike-sexed triplets than in like-sexed ones, but the difference decreased to 1.6 fold in 2008. The overall triplet rate was 284 per million deliveries in 1999 and decreased to 163 in 2008. The proportion of neonatal deaths among total infant deaths was 79%. Intensive care of triplets during the neonatal period is very important to decrease IMR. IMR was 36 per 1000 live births in 1999-2000 and decreased to 21 in 2007-2008. The relative risk for younger mothers (<25 years) vs. mothers aged 35-39 years was 2.0-fold and that of mothers aged  $\geq 40$  years vs. age 35-39 years was 3.0-fold. IMR decreased as gestational age increased, and the lowest IMR was 4.9 for  $\geq 34$  weeks. IMR decreased as birth weight (BW) increased and the lowest IMR was 4.5 for BW  $\geq 1500$  g.

**Conclusion:** Triplet rates for unlike-sexed sets decreased by 50% during the period. The changes in the rate of triplets may signal the end of a triplet epidemic. IMR for extremely low BW infants was independent of maternal age but not of gestational age. The lowest IMR was for second-order triplets.

**Keywords:** Triplet rate; Infant mortality; Risk factors; Gestational age; Birth weight; Maternal age; Birth order

### Introduction

The total triplet rate per million pregnancies in Norway increased from 100 during 1967-1971 to 350 during 1987-1992, followed by a decline to 270 during 2002-2006 [1]. The triplet rate in Japan was 58.1 per million births in 1951, which was maintained up to 1968, then it increased gradually from 1974 (58.3) to 1987 (109.2), and rapidly increased to 274.5 in 1998 [2-4]. Increased triplet rates have been attributed to ovulation stimulation treatments and assisted reproductive technology [5,6]. The prevalence of cerebral palsy in triplets is higher than that in twins [7]. The Infant Mortality Rate (IMR) for triplets in Japan was 95.7 per 1000 Live Births (LBs) in 1974 [8] and decreased to 25.4 in 1998 [9]. The triplet IMR decreased with Gestational Age (GA) up to 32-35 weeks and increased thereafter [8]. IMR in triplets decreased as Birth Weight (BW) increased until 1700-1799 g and increased thereafter [9]. The present study considered the triplet rate and IMR during 1999-2008 using vital statistics data. We also aimed to identify risk factors for IMR in triplets. Risk factors were sex, Maternal Age (MA), GA, BW, and the sex combination of triplets.

### Materials and Methods

Data on LBs, Fetal Deaths (FDs) and infant deaths were obtained from the vital statistics of Japan for the years 1999-2008 (Health and Welfare Statistics and Information Department, Ministry of Health, Labour, and Welfare, Japan). These data cover the entire population of Japan. FD was defined as that occurring after the beginning of gestational week 12. Fetal and infant death certificates provide information concerning nationality, sex, dates, BW, GA, parental age, single or multiple births, birth order of multiple births, cause of death, and other details. LB certificate records contain this same information, except for data related to cause of death. In Japan, Early Neonatal Mortality (ENM) refers to death of a live-born infant occurring <7 completed days from the time of birth, whereas Late Neonatal Mortality (LNM) refers to death of a live-born infant occurring after seven completed days of age but before 28 completed days. The sum of these two represents Neonatal Mortality (NM). The ENM Rate (ENMR) and the NM Rate (NMR) are defined as the number of ENM or NM per

1000 LBs, respectively. In contrast, the LNM Rate (LNMR) defines the number of LNM per 1000 survivors. Odds Ratio (OR) is used to test IMRs between twins and singletons or between two categories of risk factors (e.g. maternal ages).

Triplet sets consist of monozygotic, dizygotic and trizygotic triplet sets. To estimate numbers of like-sexed and unlike-sexed triplet sets, we used tapes for LB and FD certificate records during 1999-2008. The former consists of three types of triplet sets, but the later consists of two types excluded from monozygotic triplet sets. After introduction of fertility treatments, frequencies of like-sexed triplet sets were not increased in comparison with unlike-sexed triplet sets. In the present analysis, when a set of triplets was male, female, and unknown sex (FD), the set of triplets was determined to be unlike-sexed triplets.

The following numbers of infant deaths did not distinguish between singletons and multiple births. These data were 271 (6.8% of the total number of infant deaths) 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 triplet rate

Table 1 shows the like-sexed and unlike-sexed triplet rates during 1999-2008. Like-sexed and unlike-sexed and overall triplet rates

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Received November 29, 2012; Accepted January 09, 2013; Published January 16, 2013

Citation: Imaizumi Y, Hayakawa K (2013) The End of a Triplet Epidemic and Infant Mortality in Japan, 1999-2008. *Gynecol Obstet* 3:139. doi:[10.4172/2161-0932.1000139](https://doi.org/10.4172/2161-0932.1000139)

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Year	Number of triplet sets					Triplet rate <sup>1)</sup>			
	MMM	MMF	MFF	FFF	UK	Total sexed	Like sexed	Unlike	Total
1999	56	112	107	56	10	341	93.2	182.3	283.8
2000	61	106	106	48	7	328	89.6	174.3	269.7
2001	63	83	90	46	11	293	91.2	144.7	245.1
2002	50	109	104	42	14	319	78.1	180.9	270.9
2003	61	82	68	51	24	286	97.8	130.9	249.7
2004	57	99	86	52	13	307	96.3	163.5	271.3
2005	43	63	80	40	20	246	76.8	132.2	227.5
2006	46	63	73	48	16	246	84.7	122.2	221.5
2007	35	61	65	48	10	219	75.0	113.9	198.0
2008	25	57	46	41	12	181	59.6	93.0	163.4

1) per million deliveries

**Table 1:** Triplet Rate according to Like- and Unlike-sexed Triplets, 1999-2008.

Maternal age	Number of triplet sets					Triplet rate per million deliveries			
	MMM	MMF	MFF	FFF	UK	Total	Like sexed	Unlike-sexed	Total <sup>1)</sup>
< 25	29	37	29	30	11	136	34.3	38.3	78.9
25-29	143	244	212	141	37	777	71.2	114.4	194.9
30-34	210	358	409	186	54	1217	95.8	185.5	294.3
35-39	102	187	164	107	28	588	134.9	226.6	379.6
≥ 40	13	10	10	8	7	48	99.7	94.9	227.8
Total	497	836	824	472	137	2766	83.5	143.1	238.4

1) Including unknown sexes

**Table 2:** Triplet Rate according to Maternal Age during the Period, 1999-2008.

Year	Number of infant deaths			Infant death rate per 1000 live births			Odds ratio [95%CI]
	Males	Females	Total	Males	Females	Total	
1999-2000	39	28	67	41.3	30.7	36.1	1.36 [0.83-2.23]
2001-2002	15	14	29	17.2	17.1	17.2	1.01 [0.48-2.10]
2003-2004	18	30	48	21.7	38.9	30.0	0.55 [0.30-0.99]
2005-2006	17	17	34	26.9	24.8	25.8	1.09 [0.55-2.15]
2007-2008	13	10	23	25.6	17.0	21.0	1.09 [0.55-2.15]
Total	102	99	201	27.0	26.2	26.6	1.52 [0.66-3.51]
1 <sup>st</sup> day		38 (19%)			5.0		1.03 [0.79-1.36]
Early neonatal death		99 (49%)			13.1		
Neonatal death		159 (79%)			21.0		

**Table 3:** Yearly Change of Infant Mortality Rate of Triplets according to Sex, 1999-2008.

decreased from 1999 to 2008. The linear regression coefficients of triplet rates on the year were  $-2.68 \pm 1.0$  for like-sexed triplets and  $-8.81 \pm 1.74$  for unlike-sexed triplets. These values are significant at the 5% level. In 1999, the rate was 2.0-fold higher in unlike-sexed triplets than in like-sexed ones, but the difference decreased to 1.6-fold in 2008. The overall triplet rate was 284 per million deliveries in 1999 and decreased to 163 in 2008.

### Triplet rate by maternal age

Table 2 shows like-sexed and unlike-sexed triplet rates according to MA during 1999-2008. The two types of triplet rates were similar for MA <25 years of age (34-38 per million deliveries) and for those aged ≥ 40 years (95-100). For MA groups 25-29, 30-34, and 35-39 years, the rate was higher in unlike-sexed triplets than in like-sexed ones, and the corresponding ratios of the former to the latter were 1.6-fold, 1.9-fold, and 1.7-fold, respectively.

### Infant mortality and risk factors

Table 3 shows IMR of triplets according to sex from 1999-2000 to 2007-2008. IMR was 36 per 1000 LBs in 1999-2000 and decreased to 21 in 2007-2008, and IMR was significantly higher during 1999-2000 than

during 2007-2008 (OR, 1.75; 95% CI, 1.08-2.82). The overall IMR was 27 for males and 26 for females, but the difference between IMRs for both sexes was not significant.

Table 3 also shows first-day death rates, ENMR, and NMR in triplets during 1999-2008. The corresponding rates were 5.0, 13.1, and 21.0, respectively. The corresponding proportions among total infant deaths were 19%, 49%, and 79%, respectively.

Table 4 shows IMR according to survival states in like-sexed and unlike-sexed triplets during 1999-2008. IMR was 21.5 in like-sexed, 23.2 in unlike-sexed triplets, and 23.4 in overall triplets for three LB triplet sets at birth. IMR was 160.7 for like-sexed and 86.2 for unlike-sexed triplet sets for two LB and one FD triplet sets at birth. The corresponding rates were 111.1 and 90.9, respectively, for one LB and two FD triplet sets at birth. The overall IMR was 88.0 for two LB and one FD triplet sets at birth and 85.7 for one LB and two FD triplet sets at birth. IMR was significantly lower for three LB triplet sets than for the other two survival categories. The overall IMRs for both like-sexed (24.7) and unlike-sexed (26.1) triplets was not significant at the 5% level.

Table 5 shows IMR of triplets according to sex and MA group. IMR

Sex combination	3LB at birth					IMR	2LB and 1FD					IMR	1LB and 2FD			IMR
	3LB	2LB	1LB	3D	Total		2LB	1LB	1D	2D	Total		1LB	1D	Total	
Like-sexed	824	38	6	2	870	21.5	22	3		3	28	160.7	8	1	9	111.1
Unlike-sexed	1485	57	17	8	1567	23.2	52	2		4	58	86.2	10	1	11	90.9
UK	0	0	0	0	0	-	22	0		0	22	-	14	1	15	-
Total	2309	95	23	10	2437	23.4	96	5		7	108	88.0	32	3	35	85.7
Odds ratio [95% CI]	2LB & 1FD vs. 3LB 4.0 [2.5-6.6]					1LB & 2FD vs. 3LB 3.9 [1.2-12.9]										

LB: Live Birth; D: Infant death; FD:Fetal Death; CI: Confidence Interval

**Table 4:** Infant Mortality Rate (IMR) of Triplets according to Survival States in Like- and Unlike-sexed Triplets, 1999-2008.

	Number of infant deaths			Infant mortality rate			Odds ratio [95%CI]	Odds ratio [95%CI]
	Males	Females	Total	Males	Females	Total		
<b>Maternal age (MA), yr.</b>								
<25	5	9	14	28.7	52.6	40.6	0.53 [0.17-1.62]	1.96 [1.04-3.69]*
25-29	33	32	65	32.0	30.4	31.2	1.05 [0.64-1.73]	1.49 [0.98-2.27]
30-34	42	38	80	24.6	22.3	23.5	1.11 [0.71-1.72]	1.11 [0.74-1.67]
35-39	17	17	34	21.0	21.3	21.1	0.99 [0.50-1.95]	1.00 Reference
≥ 40	4	3	7	65.6	56.6	61.4	1.17 [0.25-5.48]	3.03 [1.31-6.99]*
<b>Gestation, weeks</b>								
<24	20	29	49	689.7	743.6	720.6	0.77 [0.26-2.22]	521.46 [250.43-1085.83]*
24-25	22	21	43	386.0	308.8	344.0	1.41 [0.67-2.95]	106.03 [56.62 -198.56]*
26-27	25	6	31	136.6	38.0	90.9	4.01 [1.60-10.04]*	20.22 [10.80-37.87]*
28-29	14	16	30	49.8	61.3	55.4	0.80 [0.38-1.68]	11.85 [6.33-22.18]*
30-31	8	6	14	14.0	11.1	12.6	1.26 [0.43-3.66]	2.58 [1.24-5.35]*
32-33	5	14	19	4.3	12.2	8.2	0.35 [0.12-0.96]*	1.67 [0.84-3.29]
≥ 34	8	7	15	5.4	4.5	4.9	1.21 [0.44-3.33]	1.00 Reference
<b>Birth order</b>								
1 <sup>st</sup> -born	39	29	68	30.4	23.0	26.7	1.69 [1.002-2.84]*	1.24 [0.87-1.78]
2 <sup>nd</sup> -born	26	29	55	19.5	24.0	21.6	0.84 [0.49-1.44]	1.00 Reference
3 <sup>rd</sup> -born	37	41	78	31.8	31.3	31.5	1.02 [0.65-1.60]	1.47 [1.04-2.09]*

CI: Confidence Interval; \*significant at the 5% level

**Table 5:** Infant Mortality Rate according to Maternal Age and Sex, 1999-2008.

between males and females in each MA group was not significant. The highest IMR was 61.4 for mothers aged ≥ 40 years followed by 40.6 for those aged <25 years, whereas the lowest rate was 21.1 for mothers aged 35-39 years. The relative risk of the youngest mothers vs. mothers aged 35-39 was 2.0-fold and that of the oldest mothers vs. those aged 35-39 years was 3.0-fold, and IMRs for the youngest or the oldest mothers were significantly higher than those for mothers aged 35-39 years.

Table 5 also shows sex-specific and GA-specific IMR of triplets during 1999-2008. The GA categories were as follows: <24, 24-25, 26-27, 28-29, 30-31, 32-33, and ≥ 34 weeks. IMR decreased with increase in GA from the shortest week of gestation (720.6) to the longest GA (4.9). The IMRs for GAs <32weeks were significantly higher than those for GAs ≥34 weeks. IMR was significantly higher among male infants than female infants at a GA of 26-27 weeks, but the opposite result was obtained at a GA of 32-33 weeks.

Table 5 also shows IMR according to birth order of triplets during 1999-2008. The IMR was significantly lower in second-order triplets (21.6) than in third-order ones (31.5).

Table 6 shows BW-specific IMRs in triplets during 1999-2008. The BW categories were as follows: <500, 500-599, 600-699, 700-799, 800-899, 900-999, 1000-1499, and ≥ 1500 g. IMR was 600 for infants <500 g, decreased drastically to 50 for those 900-999 g, and gradually decreased to 4.5 for those ≥ 1500 g. Odds ratios between IMRs for

eight categories of BWs were computed for 28 combinations: (64-8)/2. Among these combinations, 26 differences between IMRs were statistically significant. The two exceptions were <500 g vs. 500-599 g and 700-799 g vs. 800-899 g. IMR in triplets was closely related to BW.

### GA and BW

Table 7 shows IMR between BW and MA or GA in triplets during 1999-2008. IMR was not related to the MA groups for the BW category <1000 g. In contrast, IMR was significantly lower for MA of 35-39 years than for MAs of 25-29, 30-34, and ≥ 28 years. The lowest IMR for 26-27 weeks (85) was significantly lower than that for other GA categories (<24, 24-25, and ≥ 28 weeks) for the BW category <1000 g. IMR was significantly higher for 26-27 weeks than for ≥ 28 weeks for the BW category ≥ 1000 g. The lowest IMR of triplets was 8.0 for the category ≥ 1000 g and GA ≥ 28 weeks.

### Discussion

Rates of triplet and higher-order multiples in the US increased rapidly from 1991 to 1998, remained stable between 1998 and 2003, and then decreased until 2007 [10]. According to Blickstein and Keith [11], the decrease in triplet birth rates in the US was attributed to the 1999 guidelines issued by the American College of Obstetricians and Gynecologists and the American Society of Reproductive Medicine, which lowered the number of transferred embryos. The triplet rate

Birth Weight (g)	Infant deaths		Odds ratio [95%CI]	Odds ratio [95%CI]	Odds ratio [95%CI]	Odds ratio [95%CI]
	Death	IMR				
<500	30	600.0	334.9 [164.7-681.1]*	76.2 [40.0-145.2]*	28.6 [12.5-65.6]*	11.8 [5.7-24.5]*
500-599	35	479.5	205.7 [109.7-385.4]*	46.8 [26.9-81.4]*	17.6 [8.2-37.6]*	7.2 [3.8-13.9]*
600-699	25	290.7	91.5 [48.6-172.3]*	20.8 [11.9-36.4]*	7.8 [3.6-16.8]*	3.2 [1.7-6.2]*
700-799	18	148.8	39.0 [20.2-75.4]*	8.9 [4.9, 16.0]*	3.3 [1.5-7.3]*	1.4 [0.7-2.7]
800-899	20	113.0	28.4 [15.1-53.6]*	6.5 [3.7-11.3]*	2.4 [1.15-2]*	1.00 Reference
900-999	11	49.8	11.7 [5.6-24.6]*	2.7 [1.4-5.3]*	1.00 Reference	
1000-1499	41	19.3	4.4 [2.6-7.5]*	1.00 Reference		
≥ 1500	21	4.5	1.00 Reference			
<500			8.6 [4.0-18.3]*	3.7 [1.8-7.6]*	1.6 [0.8-3.4]	
500-599			5.2 [2.7-10.4]*	2.3 [1.2-4.3]*	1.00 Reference	
600-699			2.4 [1.2-4.7]*	1.00 Reference		
700-799			1.00 Reference			

IMR: Infant Mortality Rate per 1000 live births; CI: Confidence Interval

**Table 6:** Infant Mortality Rate according to Birthweight, 1999-2008.

BW	Infant deaths		Infant mortality rate		Odds ratio [95% CI]	
	<1000	≥ 1000	<1000	≥ 1000	<1000	≥ 1000
Maternal age						
<25	13	1	216.7	3.5	1.32 [0.66-2.63]	0.85 [0.10-7.12]
25-29	45	20	209.3	10.7	1.26 [0.81-1.98]	2.62 [1.05-6.54]*
30-34	49	31	173.1	9.9	1.00 Reference	2.43 [1.01-5.83]*
35-39	28	6	189.2	4.1	1.11 [0.67-1.86]	1.00 Reference
≥ 40	4	3	181.8	32.6	1.06 [0.34-3.27]	8.17 [2.01-33.20]*
Gestational age						
<24	49	0	720.6	-	27.81 [14.08-54.92]*	-
24-25	43	0	344.0	-	5.65 [3.22-9.94]*	-
26-27	23	8	84.9	114.3	1.00 Reference	16.0 [7.3-35.1]*
≥ 28	24	54	90.9	8.0	1.08 [0.59-21.96]	1.00 Reference

CI: Confidence Interval; \*significant at the 5% level

**Table 7:** Infant Mortality Rates between Birth Weight (BW) and Maternal Age or Gestational Age in Triplets, 1999-2008.

in Japan increased gradually from 1974 to 1986, increased rapidly from 1987 to 1994, and remained stable between 1995 and 1998 [4]. However, the following year, the rate reached a maximum (284) and decreased until 2008 (163 per million deliveries) where the unlike-sexed triplet rate (182) decreased by half (93). According to Imaizumi and Inouye [2], natural like-sexed, unlike-sexed and overall triplet rates were 43.0, 12.1, and 55.1 during the period 1955-1967 which rates were recomputed from table 1 [2]. After introduction of infertility treatment, the declining rate of triplets occurred because of the following reasons. In February 1996, the Japan Society of Obstetrics and Gynecology recommended that only three and never more than four eggs or embryos should be transferred per treatment cycle. In May 2008, the Japan Society of Obstetrics and Gynecology decided that a single embryo should be transferred per treatment cycle as a general rule. According to vital statistics, the triplet rate was 145 in 2009, 149 in 2010, and 142 in 2011. Thus, the triplet rate will be decreased to near natural fertility level in the future.

The IMR for triplets in the US was 34.3 in 2001-2002 [12]. The IMR during the same period in Japan was 17.2, which rate was half of that in the US. According to Imaizumi and Hayakawa [13], IMR of singletons decreased from 1999-2000 (2.8) to 2007-2008 (2.3). The corresponding rates in twins were 15.0 and 9.0, respectively. The relative risks for IMRs of triplets to singletons decreased 12.9-fold from 1999-2000 to 9.1-fold in 2007-2008. The corresponding risks for triplets to twins were 2.4-fold and 2.3-fold, respectively. Then IMRs in twins and triplets decreased more rapidly compared with singletons. According to Imaizumi and Hayakawa [13], proportions of first-day

deaths and neonatal deaths among the total number of infant deaths was 18% and 54% for singletons and 22% and 74% for twins. The corresponding values for triplets were 19% and 79%, respectively. Thus, intensive care is very important during the neonatal period to decrease IMR for twins and triplets. According to Alexander et al. [14], NMR and IMR of triplets were significantly higher for teenage mothers than for mothers aged 20-29 years during 1995-1998 in the US. In our study, no triplets were born to teen-age mothers. IMR was significantly lower for mothers aged 35-39 years than for younger mothers (<25 years) and the oldest mothers (≥ 40 years). In the US [12], IMRs were 49.0 for mothers aged <30 years and 28.0 for those aged ≥ 30 years during 2001-2002. Similarly, from recomputed table 5 in this study, the corresponding rates were 32.5 and 23.6, respectively during 1999-2008 in Japan where the former was significantly higher than the latter (OR, 1.39; 95% CI, 1.04-1.86).

Approximately 95% of all triplets were delivered by cesarean in the US during 1995-1998 [15]. This mode of delivery for all three fetuses is associated with the lowest NMR and IMR rates. The rate of cesarean delivery in Norway was 92% during 1988-2006 [1]. However, this rate is unknown in Japan, but it seems to be at a similar level with Norway and the US. From table 5, the IMR was the lowest in second-born triplet individuals which was significantly lower than those in third-born. This result might be true in the above two countries.

#### Acknowledgments

We are grateful to the staff of the Statistics and Information Department, Ministry of Health, Labour and Welfare, Japan.

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