



## Rising Trizygotic Triplet Rates in Japan, 1975-1994

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**Abstract.** Zygosity of triplet births in Japan was estimated by Allen's equation with the assumption that the rate of dizygotic (DZ) triplets reflects that of twins. Whereas the DZ triplet rate increased during the period from 1975 to 1994, reflecting the increase in the DZ twinning rate in the period, monozygotic (MZ) triplet rates remained constant from 1975 (28 per million births) to 1994 (23). The trizygotic (TZ) triplet rate gradually increased from 1975 (18) up to 1985 (29), and rapidly increased thereafter to 1994 (202). The higher TZ triplet rate since 1986 is most likely attributed to the higher proportion of mothers treated with ovulation-inducing hormones and partially to *in-vitro* fertilization in Japan. As for maternal age, MZ triplet rates remained nearly constant for all the maternal age groups except the youngest and the oldest ones. On the other hand, TZ triplet rates increased up to the age group of 30-34 years and decreased thereafter in almost every year. The TZ rate in the age group of 30-34 years slowly increased from 1975 to 1988 (63 per million births) and rapidly increased thereafter (314 in 1994). The TZ rate was statistically significantly higher in the period 1986-1994 than in the period 1975-1985 in each of the nine districts in Japan. Geographical variations in the TZ rates in the latest period have drastically changed from those during the period from 1955-1959 and in 1974.

**Key words:** Triplet rate, Zygosity, Maternal age, Geographical variations

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### INTRODUCTION

It is well-known that the use of ovulation-inducing hormones brings a high rate of multiple births. In Japan ovulation-inducing hormones have been used since 1966 [13], and since January 1975 the use of HMG (human menopausal gonadotropin) has been covered by the health insurance system. Bromocriptine has been commercially available since

1979. In a nation-wide survey in Japan, Kurachi et al. [9] examined the effect on the multiple birth rate of the ovulation-inducing hormones (combined use of HMG and human chorionic gonadotropin) during the period from 1975 to 1979. The multiple birth rate following treatment with HMG-HCG therapy was 20.5% where the rates were 13% for twins, 4.4% for triplets, 1.76% for quadruplets, 1.10% for quintuplets, and 0.22% for sextuplets.

In Japan, the first *in-vitro* fertilized baby was born in 1983. A survey of *in vitro* fertilization (IVF) was conducted on december 31, 1986 through questionnaires [11] and it found that among the 142 *in-vitro* fertilized pregnancies, 11 (8%) were multiple pregnancies. According to another survey on IVF in 1991 [12], 290 (21%) of the 1,349 *in-vitro* fertilized pregnancies were multiple pregnancies.

In Japan, multiple birth rates have been increasing since 1975 in triplets [3], since 1974 in quadruplets [3, 5], and the overall and the dizygotic twinning rate has been increasing since 1987 [4, 5, 7]. Imaizumi [5] mentioned that the higher rate of multiple births since 1987 was attributed to the higher proportion of mothers treated with ovulation-inducing hormones and partially to *in-vitro* fertilization in Japan.

The present study focuses attention on recent trends in triplet rates by zygosity and geographical variations of triplet rates by zygosity in Japan. It also deals with the effects of maternal age on zygotic triplet rates.

## MATERIALS AND METHODS

Vital statistics data on triplet births in Japan have been available in computer files since 1968, and in this study the computerized data between 1975 and 1994 were analyzed. The vital statistics include information on parental ages, place of residence, sex of triplet births, date of birth or fetal death, period of gestation, occupation of the head of household, and others.

Registration of births (live births and stillbirths) has been made on an individual basis, giving three separate records for each triplet maternity. In order to identify each set of triplet we used the information on date of birth, place of residence (codes for prefecture and city or town within the prefecture), and ages of both parents. There were a total of 10,392 triplet births (8,383 live births and 2,009 stillbirths) during the 20-year periods. First we sorted out all of the records using the above key fields, then checked adjacent records for their identity. If three adjacent records were exactly identical for every field, they were judged as the co-triplets form a set. With this criterion we identified 3,275 sets (9,825 births, or 94.5% of the total triplet births) with 567 births unmatched. In order to obtain more sets allowing possible difference in birth dates and parental ages, we repeated the above matching procedure for the remaining unmatched cases. At the second cycle, we allowed maximum 20 days' difference between birth dates of co-triplets and one year difference in paternal and maternal ages for adjacent three birth records. We could further identify 103 sets, and thus a total of 3,378 sets of triplets (97.5% of all the triplet births). Analysis was made in this study for the matched 3,275 sets of triplets.

**RESULTS**

**Secular changes in zygotic triplet rates**

Triplet rates by zygosity were estimated using Allen's method [1]. In applying this method, triplet sets with unknown sex in one or more children were excluded. Table 1 and Figure 1 show the secular changes in the rates of triplets by zygosity during the period from 1975 to 1994. The monozygotic (MZ) triplet rate remained nearly constant during that period, whereas the trizygotic (TZ) triplet rate gradually increased from 1976 up to 1988 and rapidly increased thereafter. As for dizygotic (DZ) triplets, the rate increased two times during the period from 1975 to 1994, reflecting the corresponding increase in the DZ twinning rate during that period.

**Effect of maternal age on zygotic triplet rates**

Table 2 shows the number of like-sexed and unlike-sexed triplet sets according to maternal age group during the period from 1975 to 1994. Table 3 and Figure 2 show secular changes in the MZ, DZ, and TZ triplet rates by maternal age during that period. In all

**Table 1 - Secular change of triplet deliveries and triplet rates by zygosity, 1975-1994**

Year	Triplet deliveries					Triplet rate per million births		
	Total*	MMM	MMF	MFF	FFF	Monozygotic Triplets	Dizygotic Triplets	Trizygotic Triplets
1975	123	37	16	25	43	28	14	18
1976	119	33	17	17	46	30	14	14
1977	127	42	17	24	39	31	16	19
1978	122	36	16	26	42	30	16	21
1979	123	32	24	25	39	26	17	26
1980	123	40	19	25	35	31	18	24
1981	149	39	34	18	53	40	18	31
1982	161	44	40	33	38	30	18	49
1983	137	39	24	22	42	35	18	27
1984	135	41	28	22	40	35	18	31
1985	129	34	19	27	41	34	18	29
1986	126	36	30	24	33	29	18	38
1987	151	40	32	31	43	38	19	47
1988	149	35	29	38	39	31	20	52
1989	157	36	45	41	27	19	21	74
1990	211	42	53	59	45	32	22	102
1991	224	42	61	73	38	20	24	125
1992	285	57	99	58	51	36	26	149
1993	281	57	97	80	36	18	29	172
1994	346	62	98	117	53	23	33	202

\* Including unknown sexes.

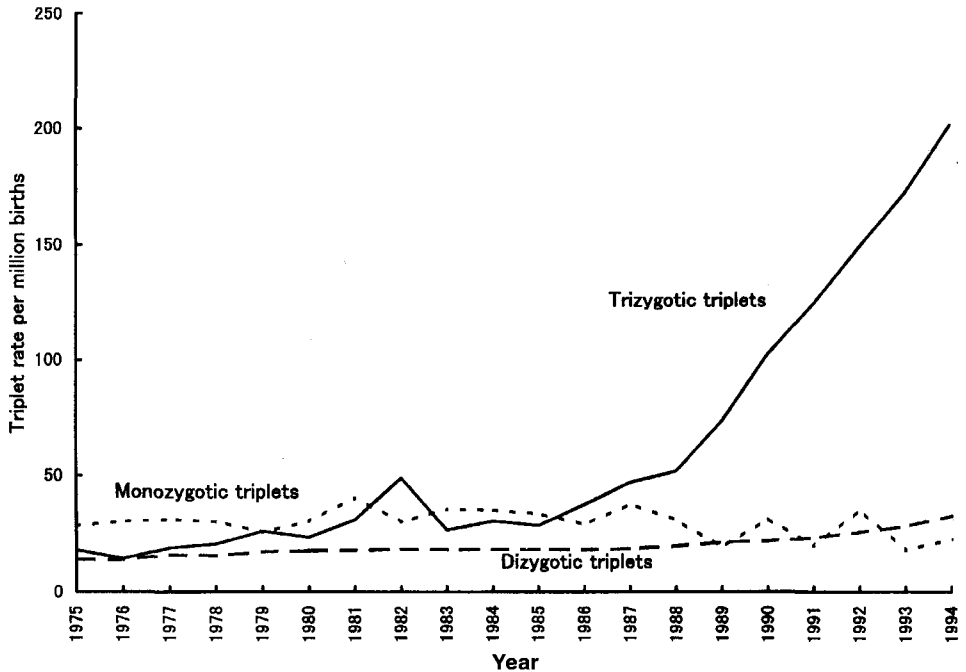


Fig. 1 - Secular changes in the rates of triplets by zygosity during the period from 1975 to 1994.

maternal age groups, MZ triplet rates remained nearly constant through the observed years except for the recent years. On the other hand, DZ triplet rates significantly increased with the year in all maternal age groups. The TZ rate in the youngest maternal age group (< 25 years) remained constant from the 1975-1976 to the 1983-1984, and increased thereafter. The TZ rate for the age group 30-34 years slowly increased from the 1975-1976 to 1988 (63 per million births) and rapidly increased thereafter (314 in 1994). Similarly, the TZ rate in the age group of 35 years and over slowly increased from 1981-1982 to 1989 and rapidly increased thereafter. For the age group of 25-29 years, the TZ rate slowly increased from 1975-1976 to 1991 and rapidly increased thereafter.

Figure 3 shows zygotic triplet rates by maternal ages in the years 1975-1985, 1986-1990, and 1991-1994. The MZ triplet rate remained constant with maternal age group in the oldest period and similar trends were also seen under 35 years of age for the other periods. On the other hand, the DZ triplet rate increased with the maternal age group up to 35-39 years of age and decreased thereafter. As for the TZ triplets, the rate increased with the maternal age group up to 30-34 years of age and decreased thereafter.

### Geographical variation in triplet rates

Table 4 shows sex-concordance in triplet sets and the total triplet rate in each prefecture for two period 1975-1985 and 1986-1994. In the former period, the triplet rate ranged from 31.3 in Wakayama Prefecture to 117.6 in Nara Prefecture, and in the latter period, the rate

Table 2 - Sex composition of Japanese triplets by maternal age, 1975-1994

Year	Maternal age									
	- 24		25-29		30-34		35-39		40+	
	Like*	Unlike#	Like*	Unlike#	Like*	Unlike#	Like*	Unlike#	Like*	Unlike#
1975	20	7	37	26	18	6	5	2	0	0
1976	16	9	46	17	15	8	2	0	0	0
1977	13	3	47	24	17	12	3	2	1	0
1978	10	8	45	23	21	10	2	1	0	0
1979	9	9	41	23	15	14	5	3	1	0
1980	12	4	39	25	18	15	6	0	0	0
1981	22	5	43	33	25	13	2	1	0	0
1982	17	6	33	33	23	30	6	4	3	0
1983	10	5	39	21	26	16	6	3	0	1
1984	13	1	42	28	23	15	3	4	0	2
1985	16	5	31	22	25	16	3	3	0	0
1986	6	7	32	28	23	16	8	3	0	0
1987	11	7	45	35	19	15	8	6	0	0
1988	10	5	38	37	21	22	5	3	0	0
1989	7	7	30	39	21	36	4	4	1	0
1990	14	12	37	39	26	50	10	10	0	1
1991	8	9	36	40	28	71	7	14	1	0
1992	9	8	49	58	40	64	10	25	0	2
1993	10	10	45	74	35	74	2	17	1	2
1994	8	17	56	78	42	99	6	20	3	1

Like\*: Like-sexed; Unlike#: Unlike-sexed.

ranged 97.7 in Saga Prefecture to 291.1 in Kagawa Prefecture. The ratio of the maximum to the minimal rate of triplets among the 47 prefectures was 3.8 for the former and 3.0 for the latter period. The ratio of the total triplet rate of the latter to the former period in each prefecture ranged 0.96 in Kochi Prefecture to 4.06 in Yamanashi Prefecture.

Table 5 shows triplet rates by zygosity for nine districts with some prefectures combined. As for the period 1975-1985, with two exceptions, the MZ triplet rate was the highest in each district. The exceptions were Chubu and Chugoku districts where the TZ rate was the highest. With two exceptions, the DZ rate was the lowest. The exceptions were Tohoku and Kyushu districts. On the other hand, for the period 1986-1994, the TZ triplet rate was the highest in each district. With two exceptions, the DZ triplet rate was the lowest in each district. The exceptions were Chubu and Shikoku districts. The ratio of the TZ rate in the latter period to the rate in the former period ranged from 2.5 (Hokkaido) to 7.1 (Tohoku), whereas the corresponding ratio of the MZ ranged from 0.39 (Shikoku) to 1.83 (Chugoku). Similarly, the corresponding ratio of the DZ ranged from 1.28 (Tohoku) to 1.49 (Chugoku). The TZ triplet rate was significantly higher in the latter period than the former period in each district.

Table 3 - Zygotic triplet rate per million births according to maternal age, 1975-1994

Year	Maternal age											
	-24			25-29			30-34			35+		
	MZ*	DZ#	TZ†	MZ*	DZ#	TZ†	MZ*	DZ#	TZ†	MZ*	DZ#	TZ†
1975-76	27.1	10.7	14.2	27.5	14.35	17.4	38.5	16.81	17.9	32.8	16.2	5.3
1977-78	20.2	11.8	10.5	32.8	16.10	20.6	38.7	18.72	30.5	24.1	20.1	11.3
1979-80	19.4	14.0	15.7	31.1	17.45	25.3	22.6	20.35	35.0	62.8	21.6	11.1
1981-82	50.6	13.3	14.0	28.6	18.21	44.3	33.0	20.88	54.1	51.2	22.1	27.1
1983-84	29.1	13.2	4.0	37.6	18.16	32.0	39.7	21.26	35.8	20.1	22.1	49.9
1985-86	24.3	13.2	16.7	25.2	18.16	32.9	38.1	21.26	37.4	36.2	22.1	24.0
1987	21.3	13.9	25.9	44.7	19.37	58.7	30.3	20.50	39.3	45.0	22.2	55.6
1988	28.4	13.2	17.4	34.3	19.87	65.5	28.7	23.13	62.7	26.7	22.6	19.2
1989	14.9	13.4	29.8	22.3	21.16	75.6	15.9	25.94	113.5	23.3	26.5	29.1
1990	46.4	12.5	61.0	35.3	21.80	77.7	16.6	26.89	164.3	55.3	27.3	109.9
1991	16.5	13.0	41.2	33.1	23.80	80.6	2.3	28.55	238.9	19.7	29.4	145.6
1992	21.3	14.7	34.3	46.8	25.69	127.1	40.0	32.77	210.7	-1.5	31.0	298.3
1993	23.8	14.5	47.6	29.8	27.46	170.7	16.1	36.47	245.3	-42.2	37.2	201.3
1994	3.9	17.8	83.5	45.6	30.90	173.1	9.6	41.25	314.5	0.9	47.0	201.0

MZ\*: Monozygotic; DZ#: Dizygotic; TZ†: Trizygotic.

## DISCUSSION

Imaizumi and Inouye [6] reported secular trends of the triplet rate according to zygosity during the period from 1955 to 1967 and in 1974 in Japan. The rates of MZ triplets had slightly decreased with the year, but the DZ triplet rate as estimated from the MZ and the DZ twinning rate had decreased with the year. The TZ rate had remained constant from 1955 to 1967 and increased double in 1974. In the present study, the TZ triplet rate gradually increased from 1976 up to 1988 and rapidly increased thereafter. Therefore, the higher TZ triplet rate since 1976 is most likely attributed to the higher proportion of mothers treated with ovulation-inducing hormones, and since 1988 partially to *in-vitro* fertilization in Japan.

It seems that the proportion of mothers treated with ovulation-inducing hormones or *in-vitro* fertilization were the highest for the maternal age group of 30-34 years, followed by the maternal age group of 35-39 years (Table 3). From the present study, it seems that the mothers at the age group of 25-29 years and 40 years or over have been also treated with ovulation-inducing hormones or *in-vitro* fertilization in the recent years.

Figure 4 shows triplet rates by zygosity in each district for three periods: 1955-1959 and 1974 [6], 1975-1985 and 1986-1994. There were no tendencies for geographical variations in the MZ triplet rate among the three periods. As for TZ triplets, the TZ rates in the latest period were especially higher than those in the other periods in each district. In the latest period, the TZ rate in Hokkaido is especially lower compared with those in the other districts. According to Imaizumi and Nonaka [7], the overall DZ twinning rate

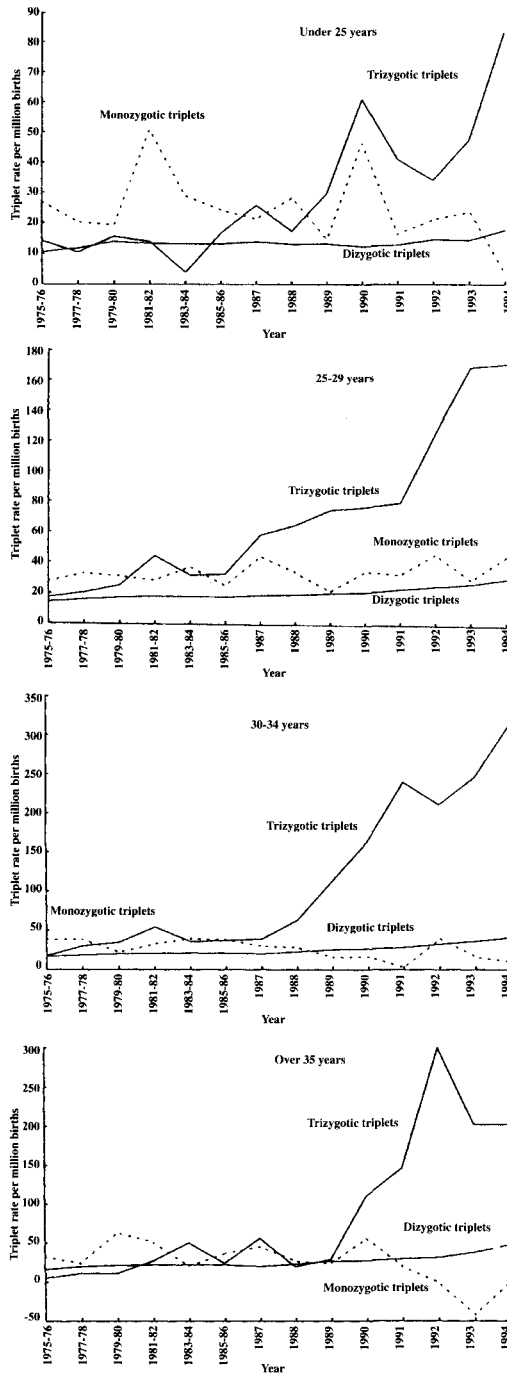


Fig. 2 - Secular changes in the MZ, DZ, and TZ triplet rates by maternal age during the period from 1975 to 1994.

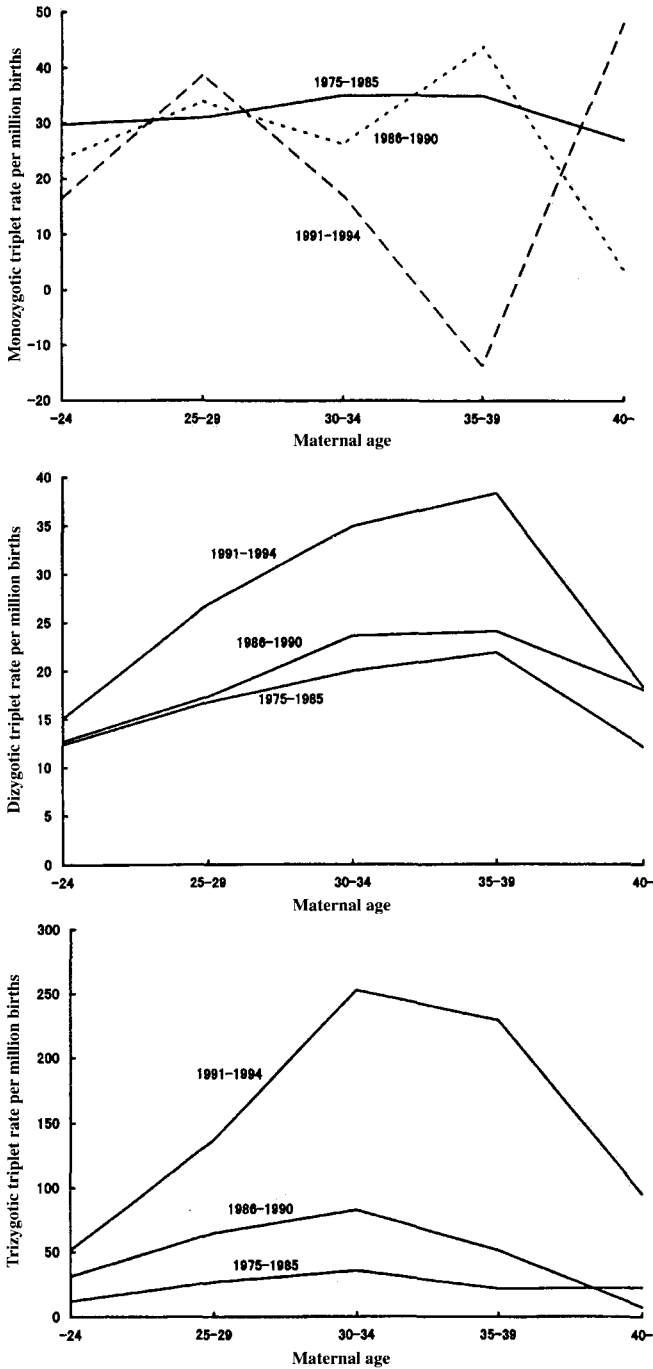


Fig. 3 - MZ, DZ, and TZ rates by maternal ages in the periods 1975-1985, 1986-1990, and 1991-1994.



**Table 4 - Number of like-sexed and unlike-sexed triplets sets and triplet rates in each prefecture, 1975-1985 and 1986-1994.**

Prefecture and pref. no.	Number of triplets						Triplet rate per million births	
	1975-1985			1986-1994			1975-85	1986-94
	Like*	Unlike#	Total †	Like*	Unlike#	Total †		
1. Hokkaido	46	26	74	28	33	68	80.8	127.0
2. Aomori	12	3	16	13	7	21	63.6	142.7
3. Iwate	12	11	23	9	18	28	100.7	202.7
4. Miyagi	10	8	18	9	10	23	50.0	100.9
5. Akita	15	3	19	7	12	20	102.1	185.1
6. Yamagata	10	5	15	7	14	21	78.2	172.4
7. Fukushima	20	1	21	15	23	40	61.3	180.6
8. Ibaraki	19	22	42	15	18	36	99.3	128.9
9. Tochigi	12	15	28	12	33	45	92.2	232.9
10. Gunma	19	12	32	12	26	41	107.9	216.6
11. Saitama	40	21	66	43	47	94	73.0	154.4
12. Chiba	36	14	57	35	32	69	72.5	134.1
13. Tokyo	63	48	118	61	71	140	69.0	138.6
14. Kanagawa	50	28	81	46	61	112	71.6	147.5
15. Niigata	10	7	18	13	28	43	47.2	184.0
16. Toyama	6	7	14	5	13	20	86.1	205.6
17. Ishikawa	7	7	15	6	10	18	83.5	162.7
18. Fukui	7	3	10	2	15	18	79.8	216.6
19. Yamanashi	4	2	6	4	12	17	49.7	201.9
20. Nagano	12	12	24	8	35	45	76.1	219.6
21. Gifu	9	11	20	10	20	32	65.3	163.9
22. Shizuoka	29	21	52	33	48	81	91.3	225.3
23. Aichi	53	39	92	41	59	105	87.3	153.2
24. Mie	9	7	16	10	17	28	62.8	164.0
25. Shiga	9	6	15	15	7	26	81.1	203.3
26. Kyoto	16	4	20	16	27	45	51.8	192.2
27. Osaka	69	32	103	61	70	134	74.8	158.5
28. Hyogo	44	24	72	33	36	70	87.3	136.2
29. Nara	18	4	22	8	8	18	117.6	141.5
30. Wakayama	5	0	5	4	7	12	31.3	122.1
31. Tottori	8	8	17	5	6	13	178.1	214.5
32. Shimane	6	6	13	5	9	14	113.5	194.6
33. Okayama	13	8	24	25	16	42	82.4	227.4
34. Hiroshima	16	13	30	24	33	59	67.4	213.1
35. Yamaguchi	11	8	19	11	15	27	80.7	197.1

(continued)

Prefecture and pref. no.	Number of triplets						Triplet rate per million births	
	1975-1985			1986-1994			1975-85	1986-94
	Like*	Unlike#	Total †	Like*	Unlike#	Total †		
36. Tokushima	5	2	7	4	6	11	56.8	145.4
37. Kagawa	13	5	18	11	16	27	118.7	291.1
38. Ehime	8	7	16	6	15	21	68.5	147.2
39. Kochi	11	8	19	3	7	11	157.3	150.5
40. Fukuoka	33	17	53	24	32	62	69.6	130.1
41. Saga	6	1	7	4	5	9	48.5	97.7
42. Nagasaki	9	7	17	10	13	24	63.2	146.1
43. Kumamoto	16	8	25	15	20	35	87.2	186.3
44. Oita	8	2	11	9	8	19	57.0	162.8
45. Miyazaki	9	3	13	6	1	18	64.8	146.8
46. Kagoshima	21	6	28	13	19	35	97.7	189.6
47. Okinawa	11	6	17	16	17	33	72.6	195.1

\* Like-sexed; # Unlike-sexed; † Including cases with unknown sex of the one or more of the co-triplets.

**Table 5 - Triplet rates by zygoty in each district for two periods, 1975-1985 and 1986-1994**

District †	1975-1985				1986-1994				Ratio#
	MZ	DZ	TZ	Total*	MZ	DZ	TZ	Total*	
Hokkaido	34.9	17.5	26.2	80.8	24.0	23.4	66.6	127.0	1.6
Tohoku	38.0	18.4	14.2	71.8	25.3	23.6	100.4	158.6	2.2
Kanto	27.9	16.6	27.3	76.3	28.4	22.8	92.8	151.1	2.0
Chubu	25.5	17.3	33.7	78.1	12.2	24.6	139.4	184.5	2.4
Kinki	37.8	14.8	20.6	75.0	35.2	21.4	94.1	157.3	2.1
Chugoku	28.3	15.9	37.9	87.1	51.8	23.7	128.3	212.0	2.4
Shikoku	41.7	16.3	35.8	95.4	16.4	23.6	137.0	182.2	1.9
Kyushu	35.3	16.3	16.5	71.9	25.8	22.9	91.8	150.2	2.1
Okinawa	32.2	18.6	21.7	72.6	52.7	25.2	117.2	195.1	2.7

\* Including cases with unknown sex of the one or more of the co-triplets.

# Ratio of total triplet rate in the period 1986-1994 to that in 1975-1985.

† Each district corresponding to the following prefectures (see Table 4 for the prefecture numbers): Hokkaido (1), Tohoku (2-7), Kanto (8-14), Chubu (15-24), Kinki (25-28), Chugoku (29-35), Shikoku (36-39), Kyushu (40-46), and Okinawa (47).

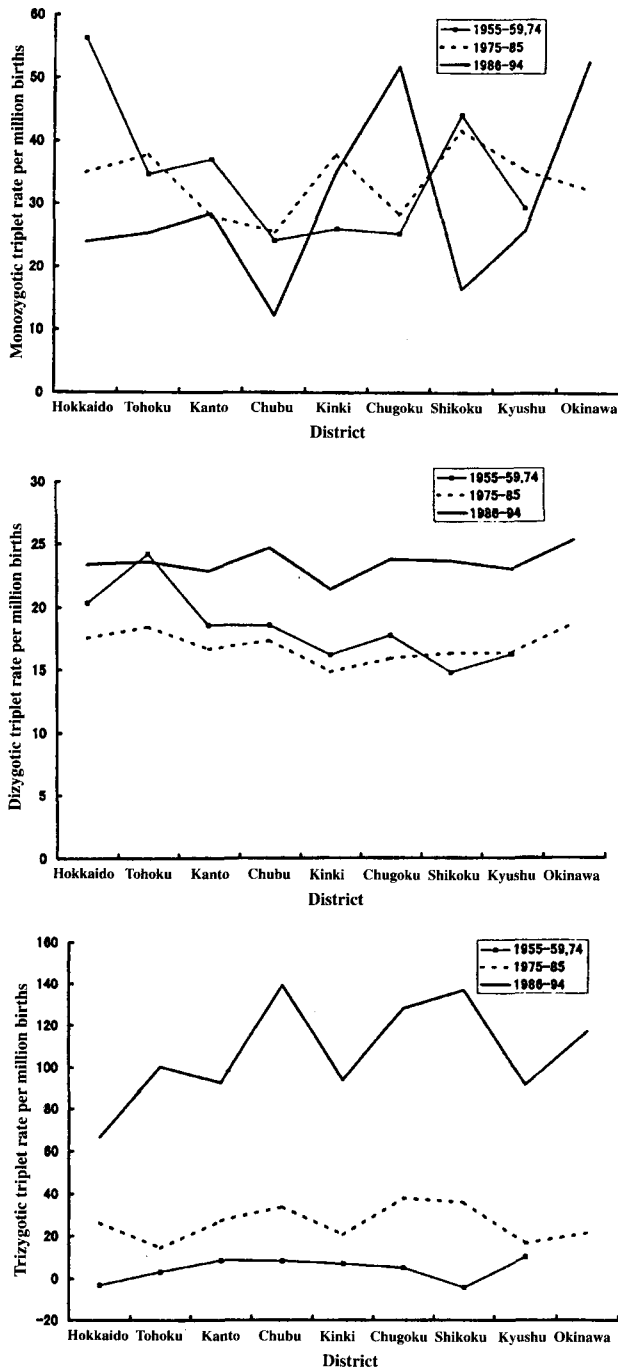


Fig. 4 - Triplet rates by zygoty in nine districts in the periods 1955-1959 and 1974, 1975-1985, and 1986-1994.

remained constant from 1975 to 1986, and increased thereafter. However, in Hokkaido, the DZ twinning rate remained constant from 1986 to 1991, and increased thereafter, where the regression coefficient of the DZ twinning rate on the year was the lowest among the 47 prefectures during the period from 1986 to 1994. Therefore, in Hokkaido, the proportion of mothers treated with ovulation-inducing hormones and *in-vitro* fertilization might be the lowest in Japan. Accordingly, the TZ triplet rate in Hokkaido was the lowest during that period. On the other hand, the DZ triplet rate reflects the zygotic twinning rates in each district and each period because of the assumptions in Allen's method to estimate the DZ triplet rate. Before 1974, the DZ twinning rate increased from a low level in the Southwest of Japan to a high level in the Northeast [4,8]. As seen from Figure 4, the DZ triplet rate was higher in the Northeast than the Southwest of Japan during the period 1955-1959 and 1974. The DZ twinning rate remained constant before 1986 so that the DZ triplet rates were also similar to the former two periods.

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