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Annual Trend in Zygotic Twinning Rates and their Association with Maternal Age in Japan, 1999-2008

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Abstract

Objective: We aimed to determine the recent trend in monozygotic (MZ) and dizygotic (DZ) twinning rates and their association with maternal age (MA).

Study design: The MZ and DZ twinning rates were estimated using Japanese vital statistics from 1999 to 2008.

Results: The DZ twinning rate per 1000 deliveries increased from 5.10 in 1999 to 7.66 in 2005 and decreased thereafter (5.98 in 2008). The MZ twinning rate increased significantly with an increase in MA in 2002, 2003, 2006, and 2008. Both the DZ and overall twinning rates increased significantly with an increase in MA in each year. From 1960-1967 to 1999-2008, the DZ twinning rates increased 280% for MA 30-34 years, 290% for MA 35-39, and 370% for MA 40 and over. On the contrary, the MZ twinning rates remained nearly constant with MA for both periods.

Conclusion: The DZ twinning rate increased till 2005 and decreased thereafter. The rate in 2005 (7.66) was 339% higher than that between 1955 and 1967 (2.26) whereas the MZ twinning rate remained constant before and after the introduction of reproductive technology.

Keywords: Trend; Monozygotic; Dizygotic; Twinning rates; Maternal age

Introduction

In Japan hormonal stimulation of ovulation has been used since 1966 [1]. In July 1975, the "Survey on Socio-Economic Aspects of Vital Events–Plural Births in 1975" was conducted by the Health and Welfare Statistics and Information Department, Ministry of Health and Welfare [2]. Questionnaires were distributed directly to all mothers with multiple births through January 1 to June 30, 1974. This Survey examined the proportion of mothers treated with hormonal stimulation. Based on the data from this survey, Imaizumi and Inouye determined that the proportion of mothers treated with hormonal stimulation, was 4.5% (158/3485) for like-sexed pairs and 9.2% (72/786) for unlike-sexed pairs [3]. In February 1996, the Japan Society of Obstetrics and Gynecology recommended that only 3-4 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.

Dizygotic (DZ) twinning rate has increased since the introduction of reproductive technology in many countries [4-9]. Japan witnessed an increase in the DZ twinning rate from 1987 to 1998 [6,10]. According to vital statistics in Japan, the overall twinning rates increased till 2005 and decreased thereafter (http://www.e–stat.go.jp/SG1/estat). In the US, the rate has stabilized in 2006 [11]. On the contrary, the monozygotic (MZ) twinning rate increased following the introduction of ovulation induction and assisted reproductive technology (ART) and increased the risk of monochorionic twinning associated with the ART [12-14]. However, the recent trend in the MZ twinning rates in Japan is unknown. The summary incidence (27 studies) of monozygotic twins after the ART was 0.9% (0.8–0.9%) [15]. In Japan, the estimated MZ twinning rate after single embryo transfer was around 2% from 2007 to 2009 [16].

This study therefore aimed to estimate the MZ and DZ twinning rates during the period 1999-2008. It also deals with comparison of the MZ and DZ twinning rates before and after the introduction of reproductive treatments.

Materials and Methods

Data on live births (LBs) and fetal deaths (FDs) were obtained from vital statistic records maintained by the Health and Welfare Statistics and Information Department, Ministry of Health, Labour and Welfare (Tokyo, Japan) for the years 1999-2008. These data cover the entire population of Japan. LB certificates contain information concerning the decedents' nationality, sex, dates of birth, birth weight, gestational age, parental dates of birth and age, single or multiple births, birth order in multiple births, and other details. FD certificates contain the same information, including the date and cause of FD, but not the parental dates of birth.

Twin pairs were estimated using three record pairings: LB-LB (2LB), FD-FD (2FD), and LB-FD. 2LB and 2FD cases were obtained from the LB and FD certification records, respectively. The LB-FD cases were obtained from LB and FD certification records that excluded 2LB and 2FD twin pairs. We identified 122,758 pairs of twins (99.9% of the total twin births).

The numbers of MZ and DZ twins were estimated by Weinberg's method [17]. The maternal age (MA) of twin is not always the same because twin pairs could be born on different dates. Then numbers of like- or unlike-sexed twin pairs were comprised of even numbers of twin pairs according to MA and odds numbers of twin pairs.

The parameters of the linear regression model ($y=\alpha x+\beta$) were estimated by the least squares method. The linear regression coefficient

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(α) of the twinning rate (y) on the year (x) was used to determine the trend from 1999 to 2008. The linear regression coefficient for MA (x) was also assessed (19, 22.5, 27.5, 32.5, 37.5, 42.5, and, 47.5 years). The rates are described as per 1000 births.

In addition, we compared the MZ and DZ twinning rates before (1955-1967) and after (1975-1998) the introduction of reproductive treatments [3,7,10]. To enable comparison of the twinning rates, the rates determined in the present study were combined with the results of Imaizumi and Inouye and recomputed using the total number of births as denominators (Table 3 in their report) [3].

Results

Annual change in the twinning rate by zygosity

Table 1 shows the annual change in MZ, DZ, and overall twinning rates from 1999 to 2008. The MZ twinning rates remained fairly constant (3.60-4.34) over this period, while the DZ twinning rate increased from 5.10 in 1999 to 7.66 in 2005, before decreasing to 5.98 in 2008. The overall twinning rates in 1999, 2005, and 2008 were 9.65, 11.51, and 10.37, respectively. Linear regression coefficients (p-values) of the twinning rates on the year were -0.015 (0.544) for MZ twins, 0.165 (0.046) for DZ twins, and 0.151 (0.037) for overall twins. The latter two coefficients were significant at the 5% level (Table 1).

Zygotic and overall twinning rates by MA

Table 2 shows the MZ, DZ, and overall twinning rates according to MA from 1999 to 2008. In general, the twinning rates slightly increased in each MA group (DZ and overall twins), but did not reach significance at the 5% level. The DZ twinning rate for MA 20-24 years and overall rate for MA ≥ 40 years between 1999 and 2008 were exceptions. Figure 1 shows the annual change in the MZ twinning rate according to MA. In the youngest MA group (<20 years), the MZ twinning rate was approximately 4 throughout the period. The rate for MA ≥ 40 years increased from 3.64 in 1999 to 5.40 in 2008, with a twinning rate linear regression coefficient (p–value) of 0.099 (0.189); this was not statistically significant at the 5% level. The MZ twinning rate significantly increased according to MA in 2002 (α=0.042, p=0.012), 2003 (0.032, 0.047), 2006 (0.072, 0.004), and 2008 (0.073, 0.003). The DZ and overall twinning rates significantly increased according to MA annually (Table 2 and Figure 1).

Comparison of twinning rates before and after introduction of reproductive technology

Figure 2 shows the annual change in the MZ and DZ twinning rates during 1955-1967 and 1974-2008. The MZ twinning rates remained approximately constant (3.56-4.43) for the overall period, whereas the DZ twinning rates were consistent from 1955 to 1987 (1.86-2.47) and gradually increasing up to 2005 (7.57) and finally decreasing slightly in 2008 (5.92). The DZ twinning rate was 2.02-fold higher in 1997 (4.56) than that for the period 1955-1967 (2.26). In 1997 the twinning rate was similar for both MZ (4.40) and DZ twins. The DZ rate was 3.35-fold higher in 2005 than that during 1955-1967 (Figure 2).

Figure 3 shows comparison of the MZ and DZ twinning rates according to MA for the period 1999-2008 vs. 1960-1967. The MZ and DZ twinning rates in Figure 3 are a composite of those obtained from Table 3 of the report by Imaizumi and Inouye and from the present study (Table 2) [3]. The MZ twinning rate was constant with MA between the two periods: 0.9-fold for MA <20 years; and 1.0-fold for MA 20-24 years to ≥ 40 years. Conversely, the DZ twinning rate increased with MA between the two periods: 1.2-fold for MA <20 years, gradually increasing to 3.7-fold for MA ≥ 40 years (Figure 3).

Discussion

The MZ twinning rate remained fairly constant from 1999 to 2008. The rate for MA ≥ 40 years slightly increased during the period where the regression coefficient was 0.099 (p=0.19). The fact may have reflected the increase in the number of older mothers (≥ 35 years) undergoing fertility treatment in recent years. The DZ twinning rate increased from 1999 to 2005 and decreased thereafter. The number of twin cases delivered by ART in Japan was 1975 cases in 1999, which increased to 3559 cases in 2005 and decreasing to 2099 cases in 2008 [18]. Saito reported that restriction of the number of embryos transferred certainly takes effect. This reflected on the decline in the DZ twinning rate after 2005 in the present study [19]. Thus, the DZ twinning rate in Japan may be slowly decreasing to near the levels achieved with natural fertility.

Data on multiple pregnancies from vital statistics are very useful information which covers the entire population of Japan. However, there was no information of pregnancies achieved by ART and pregnancy outcomes.

It is very important to reduce twinning rates regarding to stillbirth and infant mortality rates. In Japan, stillbirth rates were more than two times higher in MZ twins than in singletons and in DZ twins during

Year		Monozygotic twin deliveries					Dizygotic twin deliveries					Overall twin deliveries[4]					Total number
	2LB[1]	LB-FD	2FD[2]	Total	TR[3]	2LB	LB-FD	2FD	Total	TR[3]	2LB	LB-FD	2FD	Total	TR[3]	of deliveries
1999	4723	136	341	5200	4.33	5914	88	128	6130	5.10	10637	273	679	11589	9.65	1201381
2000	4683	100	334	5117	4.21	6528	102	90	6720	5.53	11211	263	618	12092	9.94	1216168
2001	4536	98	323	4957	4.15	6518	82	96	6696	5.60	11054	233	622	11909	9.96	1195616
2002	4628	130	290	5048	4.29	7082	80	142	7304	6.20	11710	287	624	12621	10.72	1177562
2003	4550	121	273	4944	4.32	7306	80	128	7514	6.56	11856	278	595	12729	11.11	1145592
2004	4359	93	273	4725	4.18	7650	98	122	7870	6.95	12009	274	598	12881	11.38	1131567
2005	3514	91	288	3893	3.60	8100	72	108	8280	7.66	11614	237	592	12443	11.51	1081393
2006	4267	100	285	4652	4.19	7528	78	84	7690	6.93	11795	264	564	12623	11.37	1110448
2007	4395	103	259	4757	4.30	7196	66	92	7354	6.65	11591	270	525	12386	11.20	1106288
2008	4322	89	236	4647	4.20	6492	62	68	6622	5.98	10814	219	452	11485	10.37	1107467
Linear regression coefficient (p–value) of twinning rate on the year																
	MZ twins: –0.015 (0.544)					DZ twins: 0.165 (0.046)					Overall twins: 0.151 (0.037)					

Note: [1]LB: Live Births; [2]FD: Fetal Death; [3]TR: Twinning Rate per 1000 total deliveries; [4]Overall twin deliveries are including unknown sex pairs such as Male-UK, Female-UK and UK-UK

Table 1: Monozygotic (MZ) and dizygotic (DZ) twin deliveries according to survival states of twins and twinning rates for zygotic and overall twins, 1999-2008.

MA	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	RC1 (p-value)
MZ twins											
<20	85	98	117	95	91	84	61	61	67	67	
20–24	769	669	650	655	635.5	596	447	506	515	473	
25–29	1956	2090	1945	1778	1622.5	1549	1238	1448	1408	1263	
30–34	1793	1663.5	1659	1840	1842	1778	1448.5	1712	1784	1736	
35–39	533	529.5	523	595	666	615	624	804	878	947	
≥ 40	63	67	63	85	87	103	74.5	121	105	161	
DZ twins											
<20	34	30	32	26	28	32	51	28	22	26	
20–24	372	418	406	380	364	364	423	388	320	367	
25–29	2124	2128	2012	2116	1998	1842	1955	1584	1557	1458	
30–34	2540	2850	2880	3148	3262	3540	3711	3540	3208	2791	
35–39	962	1170	1238	1490	1678	1876	1850	1958	1986	1744	
≥ 40	98	124	128	144	184	216	290	192	261	236	
Overall twin pairs											
<20	129	142	163	134	129	125	119	98	93	101	
20–24	1168	1113	1085	1069	1037.5	987	899	932	868	862	
25–29	4178	4314	4034	3980	3705.5	3468	3257	3102	3038	2769	
30–34	4423	4593.5	4620	5075	5195	5424	5268.5	5335	5082	4601.5	
35–39	1522	1732.5	1808	2127	2383	2550	2522	2831	2930	2744.5	
≥ 40	168	197	199	236	279	327	377.5	325	375	406	
MZ twinning rate per 1000 births											
<20	3.55	3.80	4.32	3.47	3.66	3.63	3.00	3.14	3.66	3.64	–0.046 (0.274)
20–24	4.41	3.95	3.95	4.09	4.26	4.15	3.32	3.71	3.91	3.64	–0.065 (0.057)
25–29	4.02	4.35	4.23	4.09	4.01	4.10	3.57	4.23	4.26	3.90	–0.019 (0.462)
30–34	4.54	4.11	4.06	4.43	4.42	4.19	3.51	4.02	4.25	4.22	–0.032 (0.351)
35–39	4.42	4.05	3.97	4.39	4.62	3.97	3.95	4.57	4.58	4.61	0.039 (0.246)
≥ 40	3.99	3.95	3.69	4.67	4.46	4.92	3.40	5.11	3.93	5.40	0.099 (0.189)
DZ twinning rate per 1000 births											
<20	1.42	1.16	1.18	0.95	1.13	1.38	2.50	1.44	1.20	1.41	0.039 (0.439)
20–24	2.13	2.47	2.46	2.37	2.44	2.54	3.14	2.84	2.43	2.82	0.062* (0.041)
25–29	4.37	4.43	4.38	4.87	4.94	4.87	5.64	4.62	4.71	4.50	0.041 (0.368)
30–34	6.43	7.04	7.06	7.59	7.82	8.34	8.99	8.31	7.63	6.78	0.111 (0.224)
35–39	7.97	8.94	9.40	11.00	11.64	12.10	11.70	11.14	10.36	8.49	0.157 (0.365)
≥ 40	6.21	7.31	7.50	7.91	9.43	10.31	13.22	8.11	9.77	7.91	0.318 (0.158)
Overall twinning rate per 1000 births											
<20	5.39	5.50	6.02	4.89	5.19	5.39	5.84	5.05	5.09	5.48	–0.023 (0.577)
20–24	6.69	6.56	6.59	6.68	6.95	6.88	6.68	6.83	6.60	6.63	0.005 (0.752)
25–29	8.59	8.97	8.78	9.15	9.17	9.18	9.40	9.06	9.19	8.55	0.020 (0.548)
30–34	11.20	11.34	11.32	12.23	12.46	12.78	12.76	12.53	12.09	11.17	0.078 (0.309)
35–39	12.61	13.24	13.73	15.70	16.54	16.45	15.95	16.11	15.28	13.36	0.203 (0.238)
≥40	10.64	11.61	11.65	12.96	14.29	15.61	17.20	13.72	14.03	13.61	0.413* (0.047)
Linear regression coefficient (p–value) of twinning rate on the MA											
Year		1999		2000	2001	2002	2003	2004		2005	
MZ twins	0.015		0.004	–0.019	0.042*	0.032*	0.035		0.022		0.072**
	(0.488)	(0.698)	(0.078)	(0.012)	(0.047)	(0.089)	(0.182)	(0.004)	(0.288)	(0.003)	
DZ twins	0.258*	0.313**	0.327**	0.376*	0.429**	0.458**		0.495**	0.495**	0.415**	0.308**
	(0.016)	(0.009)	(0.009)	(0.016)	(0.006)	(0.004)		(<0.001)	(<0.001)	(0.001)	(0.002)
Overall twins	0.276*		0.314**	0.311*	0.418*	0.462**	0.498**		0.527**	0.444**	0.439**
	(0.019)	(0.009)	(0.012)	(0.010)	(0.005)	(0.001)		(<0.001)	(0.007)	(0.002)	(<0.001)

*RC1: Regression coefficient of twinning rate on the year, *Significant at the 5% level, **Significant at the 1% level.

Table 2: Number of twin pairs and twinning rates by zygosity and overall twins by maternal age (MA), 1999-2008

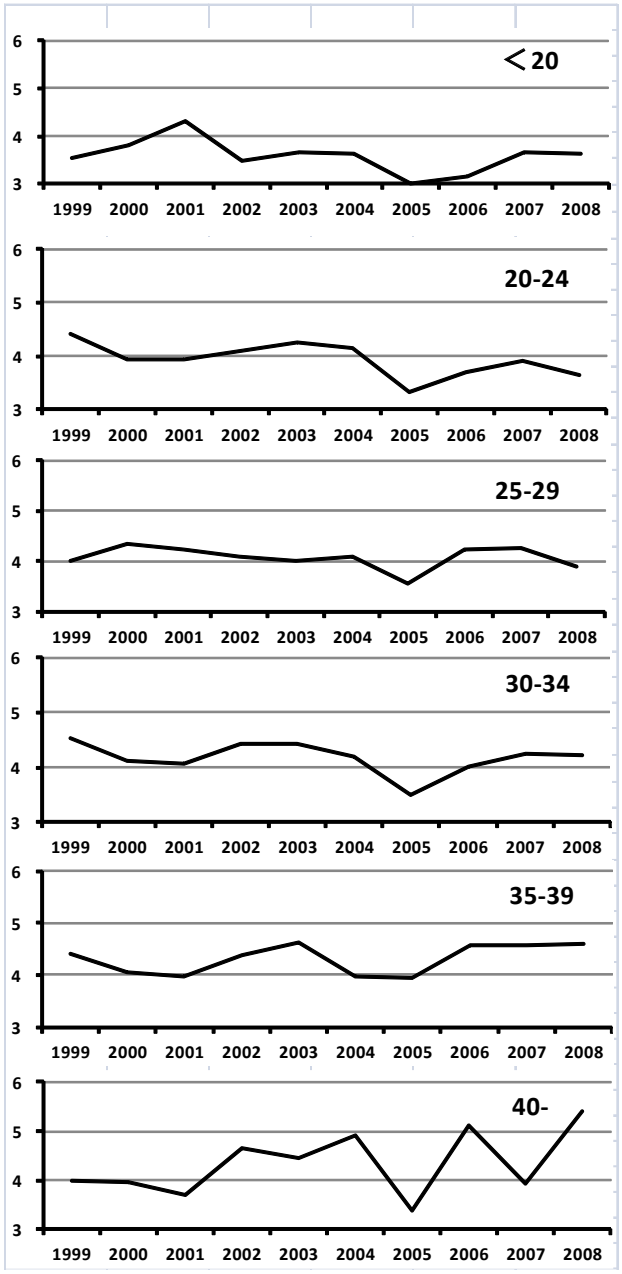

Figure 1: Yearly change of MZ twinning rate per 1000 births by maternal age, 1999-2008.

1986-1994 [20]. The infant mortality rate was also 4.6 times higher in twins than in singletons during 1999-2008 [21]. Then It is very good policy that a single embryo should be transferred per treatment cycle as a general rule by the Japan Society of Obstetrics and Gynecology.

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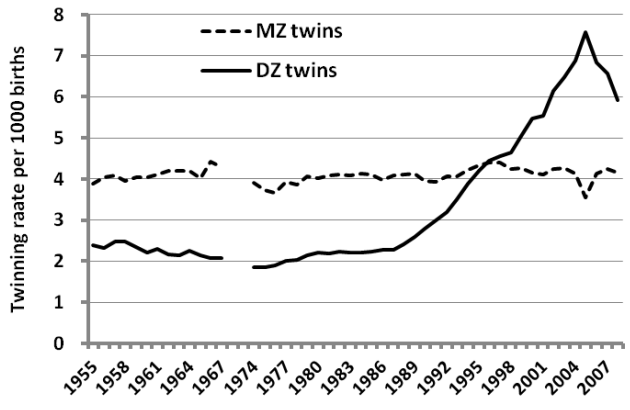

Source: 1955-1974 (Imaizumi and Inouye, 1979); 1975-1994 (Imaizumi and Nonaka, 1997); 1995-1998 (Imaizumi, 2003), and 1999-2008 (present study)

Figure 2: Yearly change of MZ and DZ twinning rates, 1955-1967and 1974-2008.

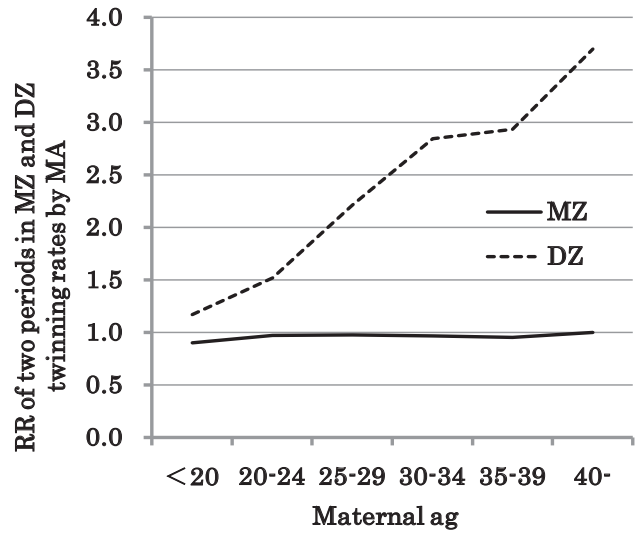

Figure 3: Comparison of MZ and DZ twinning rates according to maternal age (MA) for the period 1999-2008 vs. 1960-1967. RR: Comparison of twinning rates for the period 1999-2008 vs. 1960-1967.

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