Perinatal Mortality Rates and Risk Factors for Mortality among Zygotic Twins and Singletons in Japan, 1995-2008

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Abstract

Objective: We aimed to determine the perinatal mortality rates (PMRs) for monozygotic (MZ) twins, dizygotic (DZ) twins, and singletons, together with the associated risk factors for these PMRs.

Study design: PMRs of zygotic twins and singletons were estimated using Japanese vital statistics from 1995 to 2008.

Results: Declines were seen in fetal death rates [FDRs; defined as deaths after a gestational age of (GA) 22 weeks], early neonatal death rates (ENDRs), and PMRs from 1995 to 2008 to approximately 1/4–1/3 for DZ twins and to 1/2 for both MZ twins and singletons. ENDRs and PMRs were the lowest at maternal ages (MAs) of 30–34 years for MZ and DZ twins and at 25–29 years for singletons. Each mortality rate in singletons was significantly lower at 25–29 years compared with those at other MAs. PMRs were significantly higher for MZ and DZ twins than for singletons in each MA group, except when MA was ≥40 years for DZ twins. PMR was the lowest at GA of 37 weeks for both MZ (6.6) and DZ (3.0) twins but was the lowest at GA of ≥40 weeks in singletons (1.1). PMRs were higher for both MZ and DZ twins than for singletons, except for GA of <36 weeks. PMR was significantly higher for MZ twins than for DZ twins for all GAs, except when GA was ≥39 weeks. The recent increase in preterm birth (i.e., GA of <37 weeks, excluding fetuses delivered at GA of <22 weeks) was associated with a reduction in PMRs for both MZ and DZ twins.

Conclusion: In this Japanese population, PMRs decreased for zygotic twins and singletons between 1995 and 2008. The most marked decline was for DZ twins.

Keywords: Perinatal mortality rate; Zygotic twins; Singletons; Maternal age; Gestational age; Preterm birth

Introduction

Research has shown that perinatal mortality rates (PMRs) have decreased for both singletons and twins [1–4]. Moreover, studies have demonstrated that maternal age (MA) [3], gestational age (GA) [2–5], birth weight (BW) [2–3], BW discordance (BWD) [6–8], zygosity [9], and chorionicity [5, 10–13] are important risk factors that affect PMR.

In Japan, the fetal death rate (FDR; defined as death after GA of ≥22 weeks) decreased significantly between 1980/81 and 1998 [3]. During this period, FDRs for monozygotic (MZ) and dizygotic (DZ) twins decreased from 73 to 32 per 1000 twin deliveries and from 33 to 10 per 1000 twin deliveries, respectively [3]. However, there is no information on early neonatal deaths (ENDs) and PMRs for zygotic twins and singletons in Japan.

This study aimed to estimate PMRs for MZ twins, DZ twins, and singletons between 1995 and 2008 and to identify risk factors associated with perinatal mortality.

Materials and Methods

Data sources

Data on live births (LBs), fetal deaths (FDs), and ENDS for twins were obtained from statistical records between 1995 and 2008. We used the records maintained by the Statistics and Information Department, Ministry of Health, Labour and Welfare (Tokyo, Japan) that covered the entire Japanese population. LB certificates included details about the nationality, sex, date of birth, BW, and GA, as well as the ages and dates of birth of parents and dates of birth, whether the birth was single or multiple, and the birth order in multiple births. FD certificates were provided for deaths occurring at ≥12 completed gestational weeks and mostly contained the same information, including the date, but excluding the dates of parents' births. ENDS refer to deaths of live-born babies before the first week of life. Infant death certificates contained the same information as the LB and FD certificates; however, they excluded paternal age. PMR included all FDRs from 22 completed weeks of gestation and over (i.e., FDR for GA of ≥22 weeks) and all ENDS. Data for singleton births (males and females) were obtained using the vital statistics records [14].

Describing twin data

Twin pairs at delivery were described as LB–LB (2LB), FD–FD (2FD), and LB–FD. The 2LB and 2FD cases were obtained from the LB and FD records, respectively, while the LB–FD cases were obtained from the LB and FD records that excluded 2LB and 2FD twin pairs. We identified 99.99% of the 166,690 twin pairs (including unknown sexes) during the study period.

Data for ENDS were obtained from twin pairs of 2LBs (2LB–2END or 2LB–END) and LB–FD (LB–END). The number of MZ and DZ twins was estimated using the Weinberg method [15]. MA and GA were not always the same between twin pairs because each twin could be born on different dates; thus, the number of like- or unlike-sexed twin pairs included odd numbers of twins in some cases. All rates are presented

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as those per 1000 deliveries or LBs, as appropriate. Statistical analyses were performed with SPSS software (Version 22; SPSS, Chicago, IL).

**Results**

**Yearly changes in PMRs for zygotic twins and singletons**

Table 1 shows the yearly change in FDR, ENDR, and PMR for MZ and DZ twins between 1995 and 2008. For MZ and DZ twins, each death rate significantly decreased every year during the study period. By 2008, each mortality rate declined to approximately half of the 1995 value for MZ twins, but this decrease was to a third or a quarter of the initial value for DZ twins. FDRs and PMRs were also significantly higher for MZ twins than DZ twins in each year. However, ENDRs were only significantly higher for MZ twins than for DZ twins in eight years (1995, 1996, 1999, 2000, 2003, 2005, 2007, and 2008).

Table 2 shows the yearly changes in FDR, ENDR, and PMR for singletons during the study period. Each mortality rate significantly decreased every year during this period. By 2008, each mortality rate declined to approximately half of the 1995 value. Each, the mortality rates were significantly higher for MZ twins and DZ twins than for singletons, and all mortality rates decreased every year.

**PMRs in zygotic twins and singletons by MA**

Table 3 shows FDRs, ENDRs, and PMRs for zygotic twins by MA group during the study period. FDR for MZ twins was the highest for MA of ≥ 40 years, followed by MA of <20 years and was lowest for MA of 35–39 years where the rate was significantly lower than MA of 20–24 years. The highest FDR for DZ twins was at MA of >40 years and the lowest was at MA 30–34 years where the rate was significantly lower than the rates for MAs of 20–24 years, 25–29 years, and 35–39 years. FDR was significantly higher for MZ twins than for DZ twins in each MA group, except when MA was <20 years. As for ENDRs, the highest rates were the youngest MA groups for both zygotic twins. The lowest rates occurred at MA of 30–34 years for MZ twins and the oldest MA groups for DZ twins. ENDR was significantly higher for MZ twins than for DZ twins in each MA group except MA of <20 years and MA of ≥ 40 years.

**Table 1**: Perinatal Mortality Rates and Risk Factors for Mortality among Zygotic Twins and Singletons in Japan, 1995-2008.

| Year | Twin pairs of FDs | FDR | Twin pairs of ENDs | ENDR | Twin pairs of LBs | PMR | Odds ratio [95% CI] : MZ vs. DZ twins |
|------|------------------|-----|-------------------|------|------------------|-----|----------------------------------|
|      |                  |     |                   |      |                  |     | FDR | ENDR | PMR                              |
|      |                  |     |                   |      |                  |     |      |      |                                  |
| 1995 | 167.5            | 33.5| 60.5              | 12.5 | 228.0            | 45.6| 4831.5 | 4990.0 | 2.13 [1.63-2.79] | 1.50 [1.01-2.22] | 1.92 [1.53-2.40] |
| 1996 | 161.8            | 31.6| 58.5              | 11.8 | 220.3            | 43.0| 4958.5 | 5120.3 | 2.47 [1.86-3.28] | 1.96 [1.27-3.03] | 2.32 [1.83-2.94] |
| 1997 | 152.5            | 29.8| 41.5              | 8.4  | 194.0            | 37.9| 4963.5 | 5116.0 | 3.21 [2.33-4.41] | 1.25 [0.80-1.96] | 2.40 [1.86-3.10] |
| 1998 | 161.8            | 32.2| 45.5              | 9.3  | 207.3            | 41.2| 4866.5 | 5026.3 | 3.12 [2.32-4.21] | 1.43 [0.92-2.21] | 2.48 [1.94-3.17] |
| 1999 | 136.5            | 27.7| 49.5              | 10.3 | 186.0            | 37.7| 4791.0 | 4927.5 | 2.25 [1.69-2.99] | 2.48 [1.53-4.01] | 2.32 [1.81-2.96] |
| 2000 | 105.3            | 21.8| 49.0              | 10.4 | 154.3            | 31.9| 4733.0 | 4838.3 | 1.89 [1.40-2.54] | 2.54 [1.84-3.07] | 2.06 [1.61-2.65] |
| 2001 | 110.5            | 23.5| 30.0              | 6.5  | 140.5            | 29.9| 4585.0 | 4695.5 | 2.75 [1.99-3.79] | 1.48 [0.89-2.47] | 2.33 [1.76-3.05] |
| 2002 | 118.0            | 24.5| 34.0              | 7.2  | 152.0            | 31.6| 4695.0 | 4813.0 | 3.34 [2.42-4.63] | 1.23 [0.78-1.94] | 2.42 [1.87-3.13] |
| 2003 | 107.5            | 22.8| 37.5              | 8.1  | 145.0            | 30.7| 4610.5 | 4716.0 | 3.06 [2.21-4.23] | 2.00 [1.24-3.24] | 2.70 [2.06-3.53] |
| 2004 | 86.8             | 19.3| 27.0              | 6.1  | 113.8            | 25.3| 4405.5 | 4492.3 | 2.45 [1.76-3.39] | 1.35 [0.82-2.23] | 2.05 [1.56-2.70] |
| 2005 | 92.3             | 20.4| 42.5              | 9.6  | 134.8            | 29.9| 4420.0 | 4512.3 | 3.49 [2.43-5.02] | 3.52 [2.07-6.00] | 3.52 [2.60-4.75] |
| 2006 | 93.8             | 21.3| 42.5              | 9.6  | 134.8            | 29.9| 4420.0 | 4512.3 | 3.49 [2.43-5.02] | 3.52 [2.07-6.00] | 3.52 [2.60-4.75] |
| 2007 | 95.8             | 21.1| 27.5              | 6.2  | 123.3            | 27.1| 4446.5 | 4542.3 | 4.04 [2.78-5.89] | 1.72 [1.01-2.95] | 3.11 [2.30-4.22] |
| 2008 | 82.5             | 18.5| 22.0              | 5.0  | 104.5            | 23.5| 4366.5 | 4449.0 | 3.52 [2.37-5.24] | 2.20 [1.14-4.24] | 3.13 [2.23-4.40] |

**Table 2**: Fetal deaths rate (≥ 22 weeks of gestation and over), early neonatal death rate, and perinatal mortality rate in zygotic twins, 1995-2008.

**Linear regression coefficient (p-value) of FDR, ENDR, and PMR on the year:**

|       | FDR   | ENDR  | PMR   |
|-------|-------|-------|-------|
| MZ twins | -1.11 (<0.001) | -0.49 (<0.001) | -1.58 (P<0.001) |
| DZ twins | -0.72 (<0.001) | -0.36 (P<0.001) | -1.04 (P<0.001) |

FD: Fetal deaths (22 weeks of gestation and over); FDR: Fetal death rate per 1000 births; ENDR: Early neonatal death rate per 1000 live births (LBs); PMR: Perinatal mortality rate (PMR) per 1000 births
Table 3: Fetal death rate (≥22 weeks of gestation), early neonatal death rate, and perinatal mortality rate in singletons, 1995-2008

Table 4 shows FDRs, ENDRs, and PMRs for singletons according to maternal age, 1995-2008.

Table 5 shows FDRs, ENDRs, and PMRs for zygotic twins by maternal age, 1995-2008.

Table 6 shows the odds ratios for singletons compared to both MZ and DZ twins by maternal age.

Table 7 shows the odds ratios for MZ twins vs. DZ twins for singletons by maternal age.

Table 8 shows the linear regression coefficients for FDR, ENDR, and PMR on the year.

Figure 1 shows PMR by MA for MZ twins, DZ twins, and singletons during the study period. With one exception, PMR was significantly higher for MZ than for singletons in each MA group. At MA of ≥ 40 years in the DZ twin cohort, PMRs were similar between DZ twins and singletons, except for the MA group of <20 years.

Figure 2 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 3 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 4 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 5 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 6 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 7 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 8 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 9 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 10 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 11 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 12 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 13 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 14 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 15 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 16 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 17 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 18 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 19 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 20 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 21 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 22 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 23 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 24 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 25 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 26 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 27 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 28 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 29 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 30 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 31 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 32 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 33 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 34 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 35 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 36 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 37 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 38 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 39 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.

Figure 40 shows the odds ratios for MZ vs. DZ twins by maternal age, 1995-2008.
PMRs for zygotic twins and singletons by GA

Table 5 shows FDRs, ENDRs, and PMRs for zygotic twins by GA during the study period. FDR for MZ twins was 665 per 1000 twin deliveries at GA of <24 weeks but decreased with increasing GA to 37 weeks (5.7). However, FDR at 37 weeks’ GA was significantly lower than that at <36 weeks and ≥ 40 weeks. FDR for DZ twins was 419 at GA of <24 weeks and decreased with increasing GA to 37 weeks (1.7), when FDR was significantly lower than that for other GA groups. ENDR for MZ twins was 581 for GA of <24 weeks and decreased with increasing GA to 37 weeks (0.8) and was significantly lower at 37 weeks than at either <36 weeks or at 38–39 weeks. In DZ twins, ENDR was 333 at GA of <24 weeks and decreased with increasing GA up to 39 weeks (0.7) before increasing by ≥ 40 weeks (4.3). ENDR at 39 weeks’ GA was significantly lower than at either <36 weeks or ≥ 40 weeks. PMR for MZ twins was 859 at GA of <24 weeks and decreased with increasing GA to 37 weeks (6.6). The rate for DZ twins was 612 for GA of <24 weeks and decreased with increasing GA to 37 weeks (3.0). PMR for DZ twins was significantly lower at GA of 37 weeks than in the other GA groups but was significantly higher for MZ twins than for DZ twins per GA group, except for GA of ≥ 39 weeks.

Table 4 also shows FDRs, ENDRs, and PMRs for singletons according to maternal age (MA) and gestational age (GA), 1995-2008 period.

Singletons (males and females); FDs: Fetal deaths (22 weeks of gestation and over); FDR: Fetal death rate per 1000 births; ENDR: Early neonatal death rate per 1000 live births (LBs); PMR: Perinatal mortality (PM) rate per 1000 births

Table 4: Fetal death rate (≥22 weeks of gestation), early neonatal death rate, and perinatal mortality rate in singletons according to maternal age (MA) and gestational age (GA), 1995-2008 period.

Discussion

PMR was 6-fold higher for twins than for singletons in Japan between 1980 and 1991 [16]. In the present study, we showed that the relative risk of PMR for MZ twins versus singletons was 7-fold (45.6/6.46) higher than that of singletons in 1995 and that this risk decreased to 5.9-fold (23.5/4.01) in 2008; these relative risks were 3.8-fold (24.7/6.46) and 1.9-fold (7.6/4.01) for DZ twins versus singletons in 1995 and 2008, respectively. The relative risk of PMR increased 2- to 3-fold between MZ and DZ twins during the study period. PMR was markedly improved for DZ twins than for MZ twins and singletons. As for FDRs, declines to approximately 1/4–1/3 for DZ twins and to 1/2 for both MZ twins and singletons were seen during the study period. Imaiizuomi [3] estimated FDRs for zygotic twins from 1980–1981 to 1998. However, ENDRs and PMRs for zygotic twins were estimated for the first time in the present study.
Loos et al. [10] reported that the stillbirth rate was significantly higher for MZ monochorionic (MC) twins than for DZ twins in Belgium. Unfortunately, the data available did not include all of the risks for twin chronicity, which precludes direct comparison. Gianinaia et al. [13] also reported that MC twins have higher stillbirth rates compared with MZ dichorionic (DC) twins in England for the period between 1998 and 2007.

The increased risk of stillbirth in MC twins than DC twins has been primarily attributed to twin-twin transfusion syndrome (TTTS) [11-13, 17,18]. In addition, Morikawa et al. [19] reported that Japanese women with MC, diamniotic twins were 2.2-fold more likely to experience stillbirth than those who had DC, diamniotic twins between 2005 and 2008. Imaizumi and Hayakawa [20] also reported that 14% of stillbirths in MZ twins were attributed to TTTS and that 4% of stillbirths were due to birth defects, whereas the corresponding values in DZ twins were 0% and 3%, respectively, between 1995 and 2008. In the present study, PMRs for MZ and DZ twins significantly decreased between 1995 and 2008, and the rate was significantly higher for MZ twins than for DZ twins every year. The higher PMR for MZ twins than DZ twins could be attributed to the higher rates of TTTS and birth defects.

In a comprehensive literature review, Mercuro et al. [21] reported that preterm birth and low BW contributed to an increase in cardiovascular risk in later life. Although preterm birth rates increased by 18% for MZ twins and by 16% for DZ twins from 1995 to 2008, PMR decreased for both MZ and DZ twins. As for singletons, preterm birth rates increased by 16% for both MZ and DZ twins from 1998 and 2007, and the rate was significantly higher for MZ twins than for DZ twins every year. The higher PMR for MZ twins than DZ twins could be attributed to the higher rates of TTTS and birth defects.
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Table 6. Rates of preterm birth in zygotic twins and singletons, 1995–2008.

| Year | Twin pairs or singletons of LBs and FDs (<37 weeks) | Rates of preterm birth (%) |
|------|---------------------------------------------------|-----------------------------|
|      | MZ twins DZ twins Singletons MZ twins DZ twins Singletons |
| 1995 | 2210.0 1914.5 – 44.2 38.6 – |
| 1996 | 2339.3 2241.0 – 45.7 41.8 – |
| 1997 | 2431.0 2303.5 – 47.5 42.5 – |
| 1998 | 2453.5 2522.0 – 48.8 44.3 – |
| 1999 | 2611.0 2680.5 53653 53.0 44.4 4.6 |
| 2000 | 2528.8 3132.5 55955 52.3 47.1 4.8 |
| 2001 | 2581.0 3192.5 53897 55.0 48.3 4.7 |
| 2002 | 2571.0 3497.5 53081 53.5 49.8 4.7 |
| 2003 | 2702.5 3658.0 52166 57.3 49.4 4.7 |
| 2004 | 2634.3 3973.0 52210 58.7 51.2 4.8 |
| 2005 | 2768.3 3714.5 49842 61.3 50.8 4.8 |
| 2006 | 2612.8 4020.0 51443 59.2 52.8 4.8 |
| 2007 | 2841.8 3705.0 52169 62.6 52.0 4.9 |
| 2008 | 2762.5 3581.0 52499 62.1 54.6 4.9 |

Linear regression coefficients (p-value) of preterm birth rates for MZ twins, DZ twins and singletons per year:

- MZ twins: 1.43 (<0.001)
- DZ twins: 0.49 (<0.001)
- Singletons: 0.026 (0.006)

LBs: Live births, FDs: Fetal deaths (>22 weeks of gestation), Rates of preterm birth (<37 weeks): Nos. of preterm births divided by nos. of LBs and FDs.