Gynecology & Obstetrics
ISSN: 2161-0932

Imaizumi and Hayakawa, Gynecol Obstetric 2012, 2:1
DOI: 10.4172/2161-0932.1000116

Research Article Open Access

Deaths from Twin-Twin Transfusion Syndrome in Japan, 1995 – 2008

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Abstract

Objective: To estimate rates of fetal death, perinatal mortality, and infant mortality as well as the prevalence, concordance rates, and birth weight discordance attributed to twin-twin transfusion syndrome (TTTS).

Study design: These rates were estimated using Japanese Vital Statistics from 1995 to 2008. The total number of one or both members of a twin pair with TTTS was 1102.

Results: During 1999 and 2000, fetal death and perinatal and infant mortality rates related to TTTS decreased (48 per 10,000 births, 44 per 10,000 live births and fetal deaths after 22 weeks of gestation, and 16 per 10,000 live births, respectively) compared with those during 2007 and 2008 (31, 21 and 7, respectively). The fetal death rate was higher in male than in female fetuses. Furthermore, fetal death and infant mortality rates were the highest during gestational weeks 22–25; these rates decreased with gestational age and reached their lowest values at ≥38 weeks. Frequency of birth weight discordance ≥15% was 82% among all subjects. The concordance rate was 44% (484/1102 pairs of twins), whereas the overall prevalence was 1.1 per 100 monozygotic twin pairs from 1995 through 2008.

Conclusion: Fetal death and infant mortality rates decreased with maternal age. The declining rates of fetal death and perinatal and infant mortality related to TTTS may be related to recent improvements in medical treatments for TTTS in Japan.

Keywords: Twin-twin transfusion syndrome; Concordance rate; Prevalence; Infant mortality; Birth weight discordance

Introduction

In Japan, twin fetal death [1] and infant mortality rates [2-3] have been decreasing since 1974, while perinatal deaths [4] have decreased since 1980. Sebire et al. [5] reported that twin-twin transfusion syndrome (TTTS) accounted for 17% perinatal mortality and nearly 12% neonatal and 8.4% infant deaths among twins. Fisk and Taylor [6] reported that TTTS occurs in 10%–15% monochorionic (MC) twins and in approximately 1 out of 3200 pregnancies or 1 out of 1600 fetuses. In Japan, TTTS occurred in 11.9% (12/101) monochorionic-diamniotic twins during the years 1997 to 2004 [7].

The present study aimed to estimate fetal death and perinatal and infant mortality rates as well as concordance rates, prevalence, and birth weight (BW) discordance attributed to TTTS, using Japanese Vital Statistics for 1995 through 2008. It also deals with the risk factors for TTTS.

Materials and Methods

Data on live births, fetal, and infant deaths were obtained from the Vital Statistics of Japan for the years 1995 through 2008 (Health and Welfare Statistics and Information Department, Ministry of Health, Labour and Welfare, Japan); these data cover the entire population of Japan. Fetal death was defined as that which occurred after the beginning of gestational week 12. Fetal and infant death certificates provide information concerning 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. Deaths attributed to TTTS were assigned the code P50.3 in the ICD 10th revision [8]. Live birth certificate records contain this same information, except for data related to death. In Japan, fetal death rate (FDR) refers to the number of fetal deaths at the beginning of or after gestational week 12 per 1000 live births and fetal deaths. Perinatal mortality rate (PMR) refers to the number of fetal deaths at or after gestational week 22 and deaths in the first week of life (early neonatal deaths) per 1000 live births and fetal deaths. Infant mortality rate (IMR) refers to the number of infant deaths (upto one year of age) per 1000 live births. BW discordance was computed by subtracting the BW of the smaller twin from that of the larger, and dividing the difference by the heavier BW, and multiplying by 100 [9]. Blickstein and Kalish [10] reported that the frequency of BW discordance was concordant (<15%), mildly discordant (>15% to <25%), and severely discordant (≥25%).

The monozygotic (MZ) twinning rate (per 1000 births) during the years 1995 through 2008 was presumed on the basis of the following considerations (rates are per 1000 births). The MZ twinning rate remained nearly constant (3.9–4.4) from 1955 to 1998 [11-13]. However, the overall Japanese twinning rate increased from 1987 (6.6) through 2005 (11.4) and decreased thereafter (10.3 in 2008). In the present study, the MZ twinning rate was assumed to be 4.35 per 1000 births (average for 1995 through 1998) for 1999 through 2008. To estimate the number of MZ twin pairs from 1999 through 2008, the total twin pairs in each year and the estimated MZ twinning rate were used to generate the data, which is shown in Table 5. We determined the odds ratio to test the difference between FDRs, PMRs, and IMRs for males and females and between maternal age (MA) groups.

Results

Fetal death rates

Table 1 shows the number of fetal deaths attributed to TTTS and FDR according to sex from 1995 through 2008. FDR was 31.0 (all values stated are per 10,000 twin live births and fetal deaths) during 1995-1996, increased to 47.5 during 1999–2000, and then decreased to

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Received February 24, 2012; **Accepted** March 15, 2012; **Published** March 20, 2012

Citation: Imaizumi Y, Hayakawa K (2012) Deaths from Twin-Twin Transfusion Syndrome in Japan, 1995–2008. Gynecol Obstetric 2:116. doi:10.4172/2161-0932.1000116

31.4 during 2007–2008. The overall rate for the entire period was 35.5 for males and 31.4 for females, the difference being significant at the 5% level. Among 20, 515 fetal deaths, the proportion of TTTS cases was 6.0%.The proportion of TTTS was higher for the 2nd-born twin (56% of 1234 cases) than for the 1st-born (44%).

Table 2 shows the FDR from TTTS according to GA and MA from 1999 through 2008. The overall FDR was 385 per 10,000 births before gestational week 22; this increased to 604 during gestational weeks 22–25 and then decreased rapidly after gestational weeks 30–33. The lowest FDR was 4.6 after gestational week 38. In contrast, the overall

Year	Number of fetal deaths			Number of perinatal deaths			Number of infant deaths			Number of twin live births	Total number of twin fetal deaths
	Males	Females	Total	Males	Females	Total	Males	Females	Total		
1995-1996	71	50	134	67	59	132	29	25	54	40057	3162
1997-1998	79	76	171	73	69	145	27	22	49	41791	2908
1999-2000	104	103	225	80	112	197	27	45	72	44236	3157
2001-2002	95	71	188	74	65	142	26	22	48	46053	3029
2003-2004	99	86	197	76	81	160	28	30	58	48283	2970
2005-2006	80	61	169	51	50	115	19	22	41	47324	2829
2007-2008	68	59	150	46	40	97	16	14	30	45301	2460
Total	596	506	1234	467	476	988	172	180	352	313045	20515
	Fetal death rate[1]			Perinatal mortality rate[2]			Infant mortality rate[3]			Number of twin fetal deaths after 22 weeks of gestation	
	Males	Females	Total	Males	Females	Total	Males	Females	Total		
1995-1996	32.8	24.0	31.0	32.6	28.9	32.1	14.5	12.5	13.5	1055	
1997-1998	35.1	35.4	38.3	33.8	32.8	33.9	12.8	10.7	11.7	944	
1999-2000	43.3	44.8	47.5	35.2	50.2*	43.6	12.1	20.5*	16.3	903	
2001-2002	38.6	30.1	38.3	31.4	28.1	30.3	11.2	9.6	10.4	778	
2003-2004	38.4	35.0	38.4	30.7	33.6	32.6	14.6	12.6	12.0	731	
2005-2006	31.3	25.0	33.7	21.0	21.2	24.0	7.9	9.4	8.7	673	
2007-2008	28.6	25.4	31.4	20.0	17.5	21.1	7.1	6.2	6.6	623	
Total	35.5	31.4*	37.0	29.1	30.2	31.0	10.9	11.6	11.2	5707	

Note: [1]Per 10000 total births, [2]Per 10000 live births and fetal deaths after 22 weeks of gestation, [3]Per 10000 live births, *comparison of males vs. females (P<0.05)

Table 1: Number of fetal, perinatal and infant deaths attributed to TTTS and fetal death rate, perinatal and infant mortality rates by sex, and the number of twin births, 1995-2008.

Gestational age (Weeks)	Maternal age (MA)				Maternal age (MA)			
	<25	25-34	≥35	Total	<25	25-34	≥35	Total
	Fetal deaths from TTTS				Infant deaths from TTTS			
12-21	64	303	47	414	0	0	0	0
22-25	38	137	36	211	17	65	9	91
26-29	22	80	18	120	18	91	6	116[1]
30-33	12	58	16	86	3	20	2	25
34-37	9	55	17	81	1	14	1	16
≥38	4	11	2	17	0	1	0	1
Total	149	644	136	929	39	191	18	249
	Fetal death rate per 10000 births				Infant mortality rate per 10000 live births			
12-21	318.7	454.0	227.9	385.3	-	0	0	0
22-25	790.0	578.3	557.3	603.5	607.1	413.0	213.8	400.0
26-29	239.7	154.5	124.8	159.2	219.0	191.5	44.6	167.7
30-33	56.8	43.0	37.5	43.3	14.5	15.3	4.8	13.0
34-37	6.6	4.7	4.6	4.9	0.7	1.2	0.3	1.0
≥38	11.6	4.1	2.9	4.6	0	0.4	0	0.3
Total	66.2	37.5	26.1	37.7	19.5	11.8	3.7	10.8
OR [95% confidence interval]								
12-21 weeks	MA 25-34 vs. MA ≥35	2.0 [1.5, 2.8]						
22-25 weeks	MA <25 vs. MA ≥35	3.0 [1.3, 6.7]						
26-29 weeks	MA <25 vs. MA ≥35	1.94 [1.04, 3.64]	5.0 [2.0, 12.6]					
	MA 25-34 vs. MA ≥35	4.4 [1.9, 10.0]						
Total								
	MA <25 vs. MA ≥35	2.6 [2.0, 3.2]	5.3 [3.1, 9.3]					
	MA 25-34 vs. MA ≥35	1.4 [1.2, 1.7]	3.2 [2.0, 5.2]					

Note: [1]Including unknown maternal age

Table 2: Fetal death and infant mortality rates due to TTTS according to gestational age and maternal age, 1999-2008.

FDR was the highest for an MA of <25 years (66 per 10,000 births); this decreased to 38 for an MA of 25–34 years, and further decreased to 26 for an MA of ≥35 years. The difference between overall FDR for an MA of <25 years and that for an MA of ≥35 years was significant at the 5% level, as was the difference between FDR for an MA of 25–34 years and that for an MA of ≥35 years. With regard to GA, the difference between FDR for an MA of <25 years and for an MA of ≥35 years was significant at the 5% level during gestational weeks 26–29, as was the difference between FDR for an MA of 25–34 years and that for an MA of ≥35 years during gestational weeks 12–21.

Perinatal mortality

Table 1 shows the number of perinatal deaths and the PMR for both sexes during the period 1995–1996 to 2007–2008. The PMR was 32.1 (per 10,000 live births and fetal deaths at or after gestational week 22) during 1995–1996 and increased to 43.6 during 1999–2000, decreasing thereafter to 21.1 during 2007–2008. Overall PMR was similar for both sexes, except that it was significantly higher in females than in males during 1999–2000. Among the total number of perinatal deaths, the proportion of TTTS cases was 12.5% (988/7876).

Infant mortality rate

Table 1 also shows the number of infant deaths resulting from TTTS and the IMR according to sex during the period 1995–1996 to 2007–2008. For the entire period, the highest cause of infant deaths was TTTS (8.7% or 352/4035). The overall IMR was 13.5 per 10,000 live births during 1995–1996, which decreased to 6.6 during 2007–2008. The annual decrease was significant at the 5% level. The overall rate for the entire period was 10.9 in males and 11.6 in females, but this difference was not statistically significant.

Table 2 also shows the IMRs from TTTS according to GA and MA from 1999 through 2008. The overall IMR was 400 per 10,000 live births during gestational weeks 22–25, and it decreased with GA. The lowest IMR was 0.3 after gestational week 38. In contrast, the overall IMR was the highest for an MA of <25 years (20 per 10,000 live births), and this value decreased for an MA of 25–34 years (12) and for an MA of ≥35 years (4). The difference between the IMR for an MA of <25 years and that for an MA of ≥35 years was significant at the 5% level, as was the difference between the IMR for an MA of 25–34 years and that for an MA of ≥35 years. With regard to GA, the difference between the IMR for an MA of <25 years or of 25–34 years and that for an MA of ≥35 years was significant at the 5% level during gestational weeks 26–29, as was the difference between the IMR for an MA of 25–34 years and that for an MA of ≥35 years during gestational weeks 22–25.

BW discordance

Table 3 shows the distribution of BW discordance for fetal and infant deaths from TTTS. The frequency of BW discordance <15% was 19% (80/415) in fetal death-fetal death (FD-FD) twin pairs, 8% (4/34) in FD-infant death twin pairs (FD-Inf), and 11% (4/36) in Inf-Inf death twin pairs. The frequency of BW discordance <15% was 18% with respect to overall twin pairs. The frequency of BW discordance ≥15% to <25% was 18%, and that of BW discordance ≥25% was 63%. As for sex, the frequency of BW discordance >15% was 81% for MM twin pairs and 84% for FF twin pairs.

Concordance rate

Table 4 shows the number of TTTS cases among the total number of fetal and infant deaths according to concordance and discordance for TTTS. The total number of one or both members of a twin pair with TTTS was 1102. Among the cases of fetal death from TTTS, the concordance rate was 58% and 51% for male and female fetuses, respectively. Of the 1102 pairs of twins, 484 (44%) were concordant for TTTS; this rate was 46% for male twin pairs and 41% for female twin pairs. The overall concordance rate decreased from 46% from 1999 through 2003 to 40% from 2004 through 2008.

Prevalence

Table 5 shows the number of estimated MZ twin pairs, number of death from TTTS, and the prevalence of TTTS during each of the three time intervals and during the entire study period. The prevalence (per 10,000 MZ twin pairs) was 94.8, 128.8, and 103.7 from 1995 through 1998, 1999 through 2003, and 2004 through 2008, respectively. The overall prevalence was 110.1.

Discussion

According to Fraser et al. [14], BW discordances are caused by TTTS or abnormal functioning of the twins' placenta. Blickstein and

Birth weight discordance (%)	FD-FD[1]				FD[2]-Inf[3]			Inf-Inf			Total			Percentage		
	MM	FF	Total[4]	(%)	MM	FF	Total	MM	FF	Total	MM	FF	Total[4]	MM	FF	Total[4]
<15	41	29	80	(19)	3	1	4	2	2	4	46	32	88	19	16	18
15-25	40	35	78	(19)	1	4	5	1	4	5	42	43	88	18	22	18
25-35	54	42	105	(25)	3	3	6	5	4	9	62	49	120	26	25	25
35-45	39	35	81	(20)	3	3	6	3	4	7	45	42	94	19	21	19
45≥	33	18	69	(17)	5	8	13	5	6	11	43	32	93	18	16	19
Total	207	159	414	(100)	15	19	34	16	20	36	238	198	484	100	100	100

Note: [1]Fetal death, [2]Number of heavier birth weight are 16 in FD and 18 in Inf., [3]Infant death, [4]Including unknown sex pairs

Table 3: Distribution of birth weight discordance for fetal and infant deaths from TTTS, 1995-2008.

Years	Concordant								Discordant						Concordance rate		
	FD-FD			FD-Inf		Inf-Inf		Total	FD(TTTS)			Inf(TTTS)		Total	Total		
	MM	FF	UU	MM	FF	MM	FF		MM*	FF*	UU*	MM*	FF*		MM	FF	Total
1995-1998	51	44	10	9	6	4	3	127	40	34	6	39	35	154	0.45	0.43	0.45
1999-2003	95	70	17	3	10	7	10	212	61	78	8	47	55	249	0.49	0.40	0.46
2004-2008	66	49	12	3	3	5	7	145	60	52	33	39	31	215	0.43	0.42	0.40
Total	212	163	39	15	19	16	20	484	161	164	47	125	121	618	0.46	0.41	0.44

Note: FD=fetal death, Inf=infant death, M*=unaffected male, F*=unaffected female, U*=unaffected unknown sex

Table 4: Concordance rate of TTTS according to survival states and sex, 1995-2008.

Year	Twinning rate[1]			No. of twin pairs	No. of MZ twin pairs	No. of deaths from TTTS[2]	Prevalence per 10000 MZ twin pairs
	MZ	DZ	Total				
1995-1998	4.35	4.54	8.89	43989	21524.4	204	94.8
1999-2003	4.35	5.81	10.16	61008	26120.6	336.5	128.8
2004-2008	4.35	6.70	11.05	61876	24358.4	252.5	103.7
Total	4.35	5.73	10.08	166873	71994	793	110.1

Note: [1]Per 1000 births, [2]Number of concordant for TTTS plus half number of discordant for TTTS

Table 5: Twinning rate, number of monozygotic (MZ) twin pairs, number of deaths due to TTTS and prevalence of TTTS, 1995-2008.

Kalish [10] reported that approximately 75% twins exhibit concordant, 20% exhibit mild discordant, and about 5% exhibit severely discordant. For TTTS, the concordant was 18% and 82% cases were mildly or severely discordant.

To estimate the number of MC twin pairs, we assumed that they represented 70% of the estimated number of MZ twin pairs [15]. The estimated prevalence of MC twin pairs was 135.5, 184.1, and 148 per 10,000 MC twin pairs from 1995 through 1998, 1999 through 2003, and 2004 through 2008, whereas that during the entire study period was 157.4. Deaths from TTTS occurred in atleast 1 of 97 MZ twin pairs (103.6 per 10,000 MZ twin pairs) in the period 2004 through 2008, and prevalence decreased from 1999 through 2003 to 2004 through 2008. According to Murakoshi et al. [7], TTTS in Japan occurred in 11.9% (12/101) of monochorionic-diamniotic twins from 1997 through 2004 in Japan. Using the prevalence of TTTS (11.9%), the death rate of TTTS could be estimated as 13.4% (1.6%/11.9%) during 1995 through 2008. Our present results agree with those reported by Sebire et al. [5]. Thus, TTTS accounted for 12.5% perinatal mortality and 8.7% infant deaths in twins.

According to Sago [16], the total number of TTTS cases treated with fetoscopic laser photocoagulation during April 2008 was over 300 in Japan. After laser surgery for TTTS, the fetal survival rate was 81.5% (295/362), the neonatal survival rate was 76.8% (278/362), and the infant survival rate at 6 months after birth was 73.8% (267/362). Sago [16] also reported that survival rates improved after fetoscopic laser photocoagulation. Taken together with our analyses, the declining rates of FDR, PMR, and IMR related to TTTS may be attributed to improved medical treatments for TTTS now available in Japan.

Acknowledgments

We are grateful to the staff of the Statistics and Information Department, Ministry of Health, Labour and Welfare in Japan. We are indebted to Professor L. Keith for his helpful comments on the first draft.

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