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Prospective Risk of Intrauterine Fetal Death in Monoamniotic Twin Pregnancies

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This study was conducted to review the overall short-term outcome of monoamniotic twins in Japan and to determine the prospective risk of fetal death so as to adequately counsel parents with monoamniotic twins. Study subjects were 101 women with monoamniotic twins who were registered with the Japan Society of Obstetrics and Gynecology Successive Pregnancy Birth Registry System and who had given birth at ≥22 weeks of gestation during 2002–2009. The gestational week at delivery (mean ± *SD*) was 31.8 ± 3.7. Fourteen women experienced intrauterine fetal death (IUFD). Short-term outcomes of co-twins born to the 14 women included 8 IUFDs, one early neonatal death within 7 days of life (END), and 5 survivors. Four other women experienced 5 ENDs. Thus, 13.9% (28/202) of infants died perinatally (22 IUFDs and 6 ENDs), 13.9% (14/101) of women experienced IUFD, and 82.2% (83/101) of women experienced neither IUFD nor END. Structural anomalies and twin-to-twin transfusion syndrome explained 17.9% (five infants) and 10.7% (three infants) of the 28 perinatal deaths, respectively. The prospective risk of IUFD was 13.9% (14/101) for women who reached gestational week $22^{-0/7}$, gradually decreasing thereafter but remaining at between 4.5% and 8.0% between gestational week $30^{-0/7}$ and $36^{-0/7}$.

■ **Keywords:** monoamnionicity, preterm birth, prospective risk, twin

Monoamniotic twins occur in approximately 1% of monozygotic twin pregnancies. Monoamniotic twins are at increased risk of preterm delivery and fetal/neonatal death. The causes of these deaths include cord accidents, cord entanglement, and structural anomalies of the infants (Lewi, 2010). A perinatal mortality of 30–70% has been reported (Beasley et al., 1999). However, improvement of ultrasonographic resolution has enabled the detection of monoamniotic twinning during an early stage of pregnancy, and intensified monitoring of such twins may have reduced the overall perinatal mortality (Hack et al., 2009; Heyborne et al., 2005). However, the prospective risk of intrauterine fetal death (IUFD) according to gestational week has not been extensively studied.

This retrospective study was conducted to review the overall short-term outcome of monoamniotic twins in Japan and to determine the prospective risk of IUFD so as to adequately counsel parents with monoamniotic twins.

Materials and Methods

This study was approved by the Ethics Committee of Hokkaido University Hospital. A total of 101 women with monoamniotic twin pregnancies were studied. Data on these 101 women were abstracted from the Japan Society of Obstetrics and Gynecology Successive Pregnancy Birth Registry System (JSOG-SPBRS), in which approximately 120 secondary and tertiary hospitals participated and provided information on successive deliveries that occurred at ≥22 weeks of gestation in these hospitals. Approximately 60,000 women were registered annually. The available information from this system included maternal age, parity, gestational week at delivery, chorionicity of the placenta, sex of the infants, birthweight, live-born/stillborn, early neonatal death within 7 days after birth, delivery mode, use of assisted reproductive techniques, maternal complications such as preterm premature rupture of membranes (PPROM), pregnancy-induced hypertension (PIH) including gestational hypertension and pre-eclampsia, placental abruption, placenta previa, twin-to-twin transfusion

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syndrome (TTTS), hyperglycemia, and structural abnormalities of the infants. A possible cause of death was sometimes described as a special reference for infants with perinatal mortality. These 101 women all had monoamniotic twin pregnancies (maternities) that were registered in this system during an 8-year period between January 2002 and December 2009, corresponding to approximately 0.5% of approximately 20,000 twin pregnancies that were registered during the study period.

Confirmation and/or diagnoses of various conditions such as placental amnionicity and TTTS depended on the institutions that participated in this registry system. However, we have guidelines for the management of twin pregnancies in Japan (JSOG and JAOG, 2011). According to the guidelines, it is recommended not to determine chorionicity until the end of 10 weeks of gestation, to count the numbers of chorions and amnions using ultrasonography, to diagnose as diamniotic in cases of monochorionic twins with a thin dividing membrane, to presume monoamniotic twins and repeat the ultrasonography examination in cases with an unrecognizable dividing membrane, to determine amnionicity (mono- or di-) before 14 weeks of gestation, to examine using ultrasonography at least once every 2 weeks in cases with monochorionic diamniotic twin pregnancy, paying attention to discordances in volumes of the amniotic fluid and/or fetal development, to presume TTTS and examine extensively in a case with a tendency toward polyhydramnios in one twin and oligohydramnios in the co-twin, and to diagnose as TTTS when one twin exhibited polyuric polyhydramnios, with the deepest vertical pool measuring at least 8 cm, and the co-twin exhibited oliguric oligohydramnios, with the deepest vertical pool measuring at most 2 cm.

We focused on the short-term outcomes of twins, including IUFD, early neonatal death within 7 days of life (END), and survivors until 7 days after birth (Alive). The prospective risk of at least a single IUFD at gestational week N can be obtained using the following equation: number of all women who experience a single IUFD and a double IUFD at $\geq$ gestational week N/number of all women who give birth at $\geq$ gestational week N (Minakami et al., 1993).

Statistical analyses were performed using the statistical software package StatView 5.0 for Macintosh (SAS Institute Inc. Cary, NC, USA). All the data were presented as the mean $\pm$ *SD*.

Results

The mean gestational week at delivery was 31.8 $\pm$ 3.7 (Table 1). Ninety (89.2%) women underwent a cesarean delivery. Sixty-four (63.4%) and 32 (31.7%) women gave birth to twins at <34 and <30 weeks of gestation, respectively. Female–female pairs accounted for 55.4% (56/101). Double IUFD and double END occurred in eight and one women, respectively. A total of 28 perinatal deaths (22 IUFDs and 6 ENDs) occurred in 18 women and 174 infants born to 91 women survived 7 days after birth (Tables 1 and 2). Thus, the uncorrected perinatal mortality rate was 13.9% (28/202).

TABLE 1
Demographic Characteristics of 101 Women

Age (years)	29.6 $\pm$ 4.8
≥35 years old	11 (10.9%)
Nullipara	66 (65.3%)
After ART	5 (5.0%)
Cesarean delivery	90 (89.2%)
Gestational week at delivery	31.8 $\pm$ 3.7
<37 weeks	92 (91.1%)
<34 weeks	64 (63.4%)
<30 weeks	32 (31.7%)
<27 weeks	6 (5.9%)
Sum of birth weights (g)	3,188 $\pm$ 1,051
<3,000 g	42 (41.6%)
<2,000 g	14 (13.9%)
<1,000 g	1 (1.0%)
Female–female pair	56 (55.4%)
Twin-to-twin transfusion syndrome	4 (4.0%)
Preterm premature rupture of the membranes	2 (2.0%)
Pregnancy-induced hypertension	2 (2.0%)
Short-term outcomes of twin pairs	
IUFD/IUFD	8 (7.9%)
IUFD/END	1 (1.0%)
IUFD/Alive	5 (5.0%)
END/END	1 (1.0%)
END/Alive	3 (3.0%)
Alive/Alive	83 (82.2%)
Perinatal mortality rate	28/202 (13.9%)
Birthweight discordance (%)*	10.4 $\pm$ 9.1
Malformed infants	13/202 (6.4%)

Note: ART, assisted reproductive technology; IUFD, intrauterine fetal death; END, early neonatal death within 7 days of life. *For 83 twin pairs in whom both twins survived.

A double demise including IUFD/IUFD, IUFD/END, and END/END was more likely to occur during the second trimester, while a single demise (IUFD/Alive or END/Alive) appeared likely to occur at any time during gestation (Figure 1). All 10 double demises occurred exclusively at $\leq$29 weeks of gestation.

A total of 13.9% of women (14/101) who reached gestational week (GW) $22^{-0/7}$ experienced at least a single IUFD (Table 2). The prospective risk of at least a single IUFD was 13.9% for women who reached gestational week (GW) $22^{-0/7}$, gradually decreasing thereafter but remaining at a relatively high level throughout the third trimester (Figure 2).

As the causes of IUFD and END were not specified for some infants, we focused on maternal complications including PPROM, TTTS, PIH, placental abruption, placenta previa, and structural anomalies of the infants. None of the 101 women developed placental abruption or placenta previa, four (4.0%) developed TTTS, two (2.0%) developed PPROM, and two (2.0%) developed PIH (Table 1). A total of 13 infants (6.4%) had structural anomalies explaining 17.9% (five infants; Cases 8, 10, and 16 in Table 2) of the 28 perinatal deaths. Other structural anomalies such as otocleisis, cleft lip and palate, cleft lip and upper mandible,

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TABLE 2

Specific Causes of 28 Infant Deaths

		Structural abnormalities		Outcome (cause)	
Case #	GW at delivery	1st Twin	2nd Twin	1st Twin	2nd Twin
1	22	–	–	IUFD	IUFD
2	23	–	–	IUFD (CE)	IUFD (CE)
3	23	–	–	END (Sepsis)	END (Sepsis)
4	26	–	–	IUFD	IUFD
5	26	–	–	END	Alive
6	27	–	–	IUFD (CE)	IUFD (CE)
7	27	–	–	IUFD	IUFD
8	27	Present #	Present #	IUFD	IUFD
9	27	–	–	Alive	END (TTTS, SH)
10	28	Conjoined twinning	Conjoined twinning	IUFD	IUFD
11	29	–	–	IUFD (CE)	IUFD (CE)
12	29	–	–	IUFD (TTTS)	END (TTTS)
13	29	–	–	IUFD	Alive
14	31	Cleft palate	Cleft palate	Alive	IUFD
15	32	–	–	IUFD	Alive
16	34	–	CDH	Alive	END (PH)
17	35	–	–	Alive	IUFD
18	37	–	–	Alive	IUFD (CE)

Note: GW, gestational week; –, absent; #, unknown details; CDH, congenial diaphragmatic hernia; IUFD, intrauterine fetal death; END, early neonatal death within 7 days of life. The cause of death (CE, cord entanglement; TTTS, twin-to-twin transfusion syndrome; SH, subarachnoid hemorrhage; and PH, pulmonary hypertension) were described as special references on the registered forms. Thus, no description of the cause of death does not imply that these events did not occur in other infants with a poor outcome.

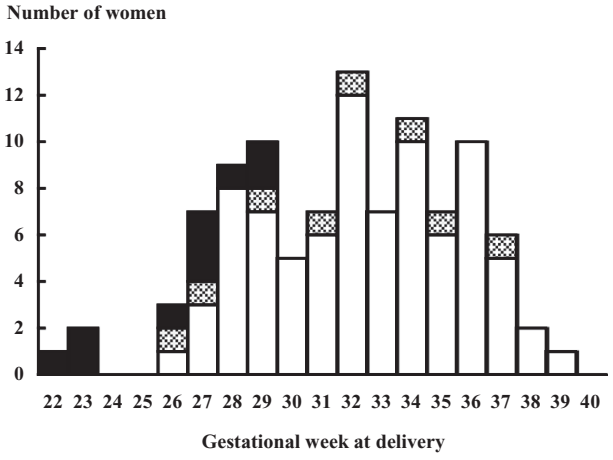

FIGURE 1

Distribution of gestational week at delivery and outcome of infant; ■ (black square), double demise including intrauterine death and early neonatal death within 7 days of life; ■ (gray square), single demise including intrauterine death or early neonatal death within 7 days of life; □ (white square), both twins alive at 7 days after birth.

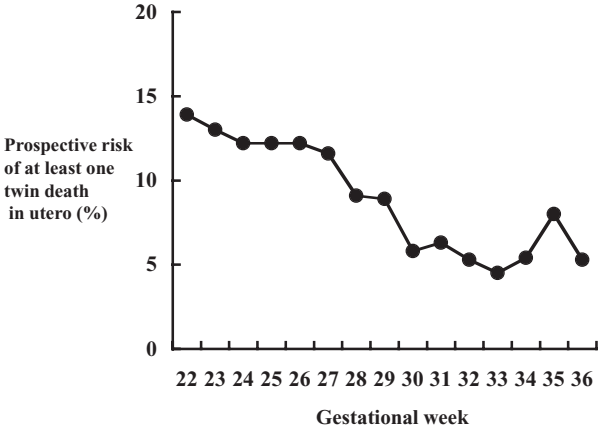

FIGURE 2

Prospective risk of at least a single intrauterine death according to gestational week.

and one lung agenesis not causing infant death were seen in eight infants. TTTS explained 10.7% (three infants; Cases 9 and 12 in Table 2) of the 28 perinatal deaths. Other causes of death were described in nine infants: seven from cord entanglement (Cases 2, 6, 11, 18 in Table 2) and two from sepsis (Case 3 in Table 2).

Discussion

Although the policies for managing monoamniotic twins may have varied between hospitals participating in the JSOG-SPBRS, the overall perinatal mortality rate was 13.9% (28/202). Malformation of infants explained 5 of the 28 perinatal mortalities in this study. The prospective risk of at least a single IUFD was 13.9% for women who reached 22 weeks of gestation, decreasing during the second trimester but remaining relatively high (around 6.0%) at between 30 and 36 weeks of gestation in this study.

Two reports similar to ours with respect to the maternity number of monoamniotic twins are available (Hack et al., 2009; Heyborne et al., 2005): one included 96 cases in which both twins were alive at 12 weeks of gestation and were delivered between January 1993 and December 2003 (Heyborne et al., 2005); and another included 98 women at ≥20

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TABLE 3

Comparison of Infant Outcome in Three Reports Regarding Monoamniotic Twins

	Heyborne et al. (2005)	Hack et al. (2009)	Present study
Study period (year)	1993–2003	2000–2007	2002–2009
No. of women at ≥22 weeks	91	92	101
No. of female pairs	60 (66.7%)	61 (66.3%)	56 (55.4%)
Perinatal mortality	28/182 (15.4%)§	27/184 (14.7%)§	28/202 (13.9%)
Fetal death	21	12	22
Neonatal death	7	15	6
Death at ≥30 weeks	5	11*	5
Double demise¶	10/91 (11.0%)	7/92 (7.6%)	10/101 (9.9%)
Single demise†	8/91 (8.8%)	13/92 (14.1%)	8/101 (7.9%)
Cause of death			
TTTS	2**/28 (7.1%)	1/27 (3.7%)	3/28 (10.7%)
Malformation	5/28 (17.9%)	7/27 (25.9%)	5/28 (17.9%)
Entanglement‡	Not specified	10/27 (37.0%)	7/28 (25.0%)

Note: §these two studies included neonatal deaths within 28 days of life, while the present study included early neonatal deaths within 7 days of life; *includes 5 infants with major anomalies and 1 therapeutic feticide; **attending perinatologist felt that these deaths were due to cord entanglement not TTTS; ¶includes double intrauterine deaths, single intrauterine deaths followed by neonatal co-twin death, and double neonatal deaths; †includes intrauterine death and neonatal death; ‡includes true knot.

weeks of gestation between January 2000 and December 2007 (Hack et al., 2009). For comparison purposes, only data for women with ≥22 weeks of gestation were abstracted from these two studies (Hack et al., 2009; Heyborne et al., 2005) (Table 3). Table 3 underscores the common features of the three studies. The perinatal mortality rates were very comparable among the three studies, as shown in Table 3. The crude perinatal mortality is around 15% for women with monoamniotic twins at ≥22 weeks of gestation, although several small studies have reported better outcomes (Baxi & Walsh, 2010; Cordero et al. 2006; DeFalco et al., 2006; Dias et al., 2010; Pasquini et al., 2006; Rodis et al., 1997).

As shown in the present study, the prospective risk of at least a single IUFD remained high (around 6.0%) at between 30 and 36 weeks of gestation. Although cord entanglement has been implicated as a cause of fetal/neonatal death, cord entanglement is observed frequently irrespective of the presence or absence of fetal/neonatal demise (Cordero et al. 2006; DeFalco et al., 2006; Dias et al., 2010; Pasquini et al., 2006; Rodis et al., 1997; Suzuki et al., 2001): among 11 monoamniotic twin pregnancies, cord entanglement was seen in two (67%) of three pregnancies with IUFD versus seven (88%) of eight pregnancies without IUFD (Suzuki et al., 2001); among 36 pregnancies, cord entanglement was seen in 15 (42%) (Cordero et al., 2006); among 20 pregnancies with two live structurally normal twins at 20 weeks of gestation, 19 (95%) already had cord entanglement at <20 weeks gestation and all 40 twins survived perinatally (Pasquini et al., 2006); among 23 pregnancies, cord entanglement was seen in 10 (47.6%) of 21 pregnancies with both-twin survival versus one (50.0%) of two with IUFD (DeFalco et al., 2006); and cord entanglement was noted in all 13 and 18 monoamniotic twin pregnancies in two reports (Dias et al., 2010; Rodis et al., 1997). Thus, the presence of cord entanglement itself appeared not to affect the outcome of infants with monoamniotic twins. However, monoamniotic twins were likely to exhibit fetal distress or non-reassuring fetal surveillance: 36 (45.6%) of 79 women and 10 (43.5%) of 23 women underwent a prompt delivery because of fetal distress or non-reassuring fetal surveillance in two reports (DeFalco et al., 2006; Heyborne et al., 2005). Therefore, although not yet verified, many investigators consider that inpatient management and the intensive monitoring of monoamniotic twins and early delivery at 32 to 34 weeks of gestation may improve outcome (Allen et al., 2001; DeFalco et al., 2006; Dias et al., 2010; Heyborne et al., 2005; Lewi, 2010; Pasquini et al., 2006; Rodis et al., 1997).

In the present study, structural anomalies — including one set of conjoined twins — explained a large fraction of the 17.9% perinatal mortality, consistent with previous studies (Table 3) (Allen et al., 2001; Cordero et al., 2006; Dias et al., 2010; Hack et al., 2009; Heyborne et al., 2005). Apparently, structural anomalies in monoamniotic twins explain a larger fraction of infant deaths than TTTS. TTTS occurs in 10% of cases and is the main cause of death in monochorionic diamniotic twins (Lewi et al., 2008; Morikawa et al., 2011). However, TTTS is less common in monoamniotic twins, with incidences of 3.1% (3/96) (Heyborne et al., 2005), 4.0% (4/101) in the present study, 6.1% (6/98) (Hack et al., 2009), 8.3% (3/36) (Cordero et al., 2006), and 9.1% (1/11) (Suzuki et al., 2001) reported to date.

In conclusion, the present study demonstrated that the prospective risk of IUFD was 13.9% for women who reached gestational week $22^{-0/7}$, gradually decreasing thereafter but remaining at between 4.5% and 8.0% between gestational week $30^{-0/7}$ and $36^{-0/7}$, implying that a considerable number of women experience IUFD at ≥30 weeks of gestation. Structural anomalies of infants explained 17.9% (5/28) of perinatal deaths, but no structural anomalies were seen in four IUFD infants born to four mothers at ≥30 weeks in the present study. Literature review suggested that the presence of cord entanglement is not a reliable risk factor for perinatal deaths. Inpatient management and the

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intensive monitoring of monoamniotic twins irrespective of the presence or absence of cord entanglement and early delivery at 32 to 34 weeks of gestation may improve outcome.

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