CLINICAL ARTICLE

Clinical features and short-term outcomes of triplet pregnancies in Japan

Mamoru Morikawa [a,*], Kazutoshi Cho [a], Takashi Yamada [a], Takahiro Yamada [a], Shoji Sato [b], Hisanori Minakami [a]

[a] Center for Perinatal Medicine, Hokkaido University Hospital, Sapporo, Japan

[b] Maternal and Perinatal Care Center, Oita Prefectural Hospital, Oita, Japan

***** Corresponding author: Mamoru Morikawa

Department of Obstetrics, Hokkaido University Hospital, Kita-ku N15 W7, Sapporo 060-8638, Japan. Tel.: +81 11 706 6051; fax: +81 11 706 6051.

E-mail address: mmamoru@med.hokudai.ac.jp

Keywords: Fetal death; Perinatal mortality; Preterm birth; Triplet

Synopsis: Among 320 triplet pregnancies in Japan, perinatal mortality decreased

with increasing number of chorionic membranes. **[Author: Yes, Ok]**

ABSTRACT

Objective: To review clinical features and short-term outcomes of triplet pregnancies among Japanese women.

Methods: A retrospective analysis was carried out among 320 Japanese women with triplet pregnancies (8 monochorionic, 75 dichorionic, and 150 trichorionic triplets; 87 with unknown placental chorionicity) who delivered at 22 gestational weeks or more between January 2005 and December 2008.

Results: Delivery was by cesarean for 315 (98%) women. Gestational age at delivery was 32.3 ± 2.8 weeks (mean ± SD) and 33.2 weeks (median), and 97%, 61%, and 14% of women delivered at less than 37, less than 34, and less than 30 gestational weeks, respectively. For live-born infants, mean birth weight was 1762 ± 437 g, 1608 ± 396 g, and 1406 ± 380 g for the heaviest, middle, and lightest triplet, respectively. Eighteen (5.6%) women experienced perinatal mortality (3 triplets for 1 woman, 2 triplets for 4 women, and 1 triplet for 13 women). Perinatal mortality was 25 deaths per 1000 deliveries, and decreased with increasing number of chorionic membranes (125, 44, and 20 per 1000 mono-, di-, and trichorionic triplet deliveries, respectively).

Conclusion: Short-term outcomes were good among triplet pregnancies in Japan.

The data may be useful for counseling Japanese women with triplet pregnancies.

1. Introduction

The general clinical features of triplet pregnancy, as assessed by studies of more than 100 pregnancies, have been reported from many countries [1–4] but not Japan. Since 1998, the incidence of triplet pregnancy has decreased in England and Wales [5], as well as in Japan: according to information released by the Japanese Ministry of Health, Labour and Welfare, the annual number of triplet pregnancies has been decreasing gradually from 337 pregnancies in 1995 to 246 in 2005, 246 in 2006, 219 in 2007, 181 in 2008, and 157 in 2009 [6]. **[Author: please provide reference (in numeric order) for these data, Yes we did]** Meanwhile, approximately 1100000–1200000 neonates are currently born annually in Japan [6]. **[Author: again, please provide reference (in numeric order) for these data Yes we did]** Thus, the number of triplets accounts for only 0.04%–0.08% of all neonates born in Japan.

The incidence of monozygotic twinning is relative constant throughout the world, varying between approximately 3 and 5 per 1000 pregnancies; by contrast, the rate of dizygotic twinning varied from 1.3 (Japan) to 49 (Nigeria) per 1000 pregnancies even before the era of clinically available assisted reproductive techniques [7]. Therefore,

the proportions of placental chorionicity in triplet pregnancies may differ between Japanese women and women from other countries.

As a result, the aim of the present retrospective study was to review the clinical features and outcomes of triplet pregnancy among Japanese women by using a relatively large cohort of women with triplet pregnancies who participated in the registry system established by the Japan Society of Obstetrics and Gynecology (JSOG).

2. Materials and methods

Data were analyzed from women with triplet pregnancies who gave birth between January 1, 2005, and December 31, 2008, at one of approximately 120 secondary and tertiary hospitals participating in the JSOG Successive Pregnancy Birth Registry System, which collected information on successive deliveries that occurred at a gestational age of 22 weeks or more in the participating hospitals. **[Author: Yes, Ok]**

The present study was conducted after being approved by the Ethics Committee of Hokkaido University Hospital.

The information available from this system includes maternal age; parity; gestational age at delivery; chorionicity of the placenta; sex of the infant; birth weight; live-born, stillborn, or early neonatal death (END) within 7 days of life; delivery mode; use of assisted reproductive techniques; and maternal complications such as premature membrane rupture, pregnancy-induced hypertension, placental abruption, placenta previa, feto-fetal transfusion syndrome, and hyperglycemia during pregnancy.

For each woman with triplets, the heaviest, middle, and lightest triplet was defined as that with the heaviest, middle, and lightest birth weight, respectively. To compare birth weight according to gestational age at delivery between triplets and singletons, we excluded stillborn triplets and used the normative birth weight of singletons according to gestational age at delivery, a benchmark that is widely used in Japan [8]. Because approximately 99.7% of all pregnant Japanese women receive regular prenatal care, including 2–3 prenatal visits during the first trimester [9], and obstetric ultrasonography is widely used in Japan, gestational age was expected to be accurate for most of the study participants. Perinatal mortality was defined as stillbirth

at a gestational age of 22 weeks or more, and END.

Statistical analyses were performed via the statistical software package StatView 5.0 (SAS Institute, Cary, NC, USA). All data are presented as the mean ± SD. The unpaired *t* test and Mann–Whitney *U* test were used to analyze the data. The Fisher exact test was used to compare the frequencies. In all analyses, a *P* value of less than 0.05 was taken to indicate statistical significance.

3. Results

A total of 320 triplet pregnancies were registered in the JSOG Successive Pregnancy Birth Registry System between January 1, 2005, and December 31, 2008, corresponding to 36% of all 892 women with triplet pregnancies occurring across Japan between these dates. Eight, 75, and 150 women were registered as having monochorionic (MC), dichorionic (DC), and trichorionic (TC) triplets, respectively; placental chorionicity was not specified for the remaining 87 women. **[Yes, OK]**

As expected, two-thirds of triplet pregnancies were established after treatment for

infertility (Table 1). After excluding 87 women with unknown placental chorionicity, the frequency of mono-, di-, and trichorionic triplets among the remaining 233 women was 3.4%, 32%, and 64%, respectively. However, this proportion varied in accordance with the mechanism leading to triplet pregnancies: the majority of triplets were mono- or dichorionic for women who conceived spontaneously, whereas most triplets were trichorionic for women who underwent ovulation induction alone (Figure 1). The fraction of women with spontaneously conceived triplets decreased with increasing number of chorionic membranes: such women accounted for 75% of monochorionic triplet pregnancies, but only 18% of trichorionic triplet pregnancies (Figure 1).

Among all 320 women, 315 (98%) underwent cesarean delivery (Table 1) and 5 women gave birth to triplets vaginally at a gestational age of 22 weeks (1 woman), 24 weeks (1 woman), 32 weeks (1 woman), and 34 weeks (2 women). The mean and median gestational age at delivery was 32.3 ± 2.8 weeks and 33.2 weeks, respectively. The duration of pregnancy increased with increasing number of chorionic membranes: that of trichorionic triplets was significantly longer than those of

other triplets (*P*= 0.030 vs monochorionic, *P*=0.001 vs dichorionic, and *P*<0.001 vs unknown chorionicity). **[Author: please state the *P* value, Yes we did]**

In total, 310 (97%) of the 320 pregnancies ended in preterm delivery before 37 weeks of gestation (Figure 2), and 927 (99%) of the 939 live-born triplets were born with a low birth weight of less than 2500 g (Table 1). The overall mean birth weight for live-born infants was 1762 ± 437 g, 1608 ± 396 g, and 1406 ± 380 g for the heaviest, middle, and lightest triplet, respectively. The corresponding birth weights were 1443 ± 496 g, 1320 ± 492 g, and 1085 ± 376 g for monochorionic triplets; 1709 ± 468 g, 1503 ± 428 g, and 1301 ± 379 g for dichorionic triplets; and 1870 ± 414 g, 1718 ± 379 g, and 1505 ± 373 g for trichorionic triplets. The mean birth weight of the heaviest triplet corresponded to the median value for singletons, that of the middle triplet fell between the median and 10th percentile values for singletons, and that of the lightest triplet was on the 10th percentile line for neonates born at earlier gestational ages and below this line for neonates born at later gestational ages (Figure 3).

Overall, perinatal mortality was 2.5% (24 deaths among 960 deliveries) and appeared to decrease with increasing number of chorionic membranes (Table 1): perinatal mortality was significantly higher among monochorionic triplets than among trichorionic triplets. Eighteen women experienced perinatal mortality: 3 triplet deaths for 1 woman, 2 triplet deaths for 4 women, and 1 triplet death for 13 women (Table 2). **[Author: there is no Table 2?, Please see the end of this text, We missed to send this Table at the revision. Please add this Table as Table 2]** After excluding 3 triplets stillborn at 22 gestational weeks, the birth weights of the remaining 12 stillborn triplets were markedly lower than those of their surviving co-triplets, suggesting that their deaths may have occurred long before the actual time of delivery. Cord entanglement and feto-fetal transfusion syndrome were recorded as causes of perinatal deaths for 2 women. **[Yes, Ok]**

4. Discussion

The overall perinatal mortality rate of 25 deaths per 1000 deliveries (including intrauterine death at and after 22 gestational weeks and END within 7 days of life) was lower in the present study than in studies from other countries, which have

reported rates ranging from 32 [10], 38 [11], 46 [12], and 80 [13] deaths per 1000 deliveries to 150 [3] and 152 [14] **[Author: reference cited out of order – please renumber to ensure that all references are cited and listed in numeric order, Yes, we did]** deaths per 1000 deliveries. However, other studies have adopted different definitions of perinatal mortality, including deaths occurring among triplets born at and after 20 [3,14], 21 [13], 22 [11], 24 [12], and 26 [10] gestational weeks, and neonatal deaths within 28 days of life [3,10–14]. It is possible that some triplets who survived for 7 days after birth in the present study may have died within 28 days of life, but were not counted as perinatal deaths. **[Yes, Ok]** In addition, the neonates in other studies were born at different periods: 1986–2000 [3,14], 1989–2001 [10], 1995–1997 [12], 1996–2002 [13], and 2001–2002 [11]. According to Getahun et al. [11], perinatal mortality decreased from 60 deaths per 1000 deliveries in 1990–1991 to 38 deaths in 2001–2002 in the United States. We speculate that the lower rate observed in the present study may be due partly to differences in the definition of perinatal mortality and partly to the more recent study period as compared with previous studies.

The mean and median pregnancy durations were 32.3 ± 2.8 and 33.2 weeks, respectively, consistent with most previous studies, which have reported mean or median durations of 32–33 weeks [3,10–15]. In addition, the distribution of gestational age at delivery in the present study (Figure 2) was very similar to that reported by Getahun et al. [11]—that is, the largest number of women gave birth at 34 gestational weeks in both studies.

The number of chorionic membranes, however, affects the duration of pregnancy. In the present study, pregnancy duration was significantly longer for trichorionic than for dichorionic or monochorionic triplet pregnancies. This is consistent with previous studies, in which durations (mean or median) of 31.8 [2], 33.3 [15], and 33 [3,14] gestational weeks have been recorded for trichorionic triplets, and 30.9 [2], 30.0 [3,14], and 32.0 gestational weeks have been recorded for mono- and dichorionic triplets. Thus, the duration of triplet pregnancies with a monochorionic element is often shorter than that of trichorionic triplet pregnancies, similar to twin pregnancies where the pregnancy duration of monochorionic twins has been found to be shorter than that of dichorionic twin pregnancies [16,17]. This may be due to early neonatal

delivery in both triplet and twin pregnancies with complications specific to monochorionic placentas, such as feto-fetal transfusion syndrome [18] and cord entanglement [19]. The higher rate of perinatal mortality for monochorionic and dichorionic triplets than for trichorionic triplets [2,3,14] may reflect the shorter durations of pregnancy induced by complications [18]. Similar neonatal outcomes of triplets, when compared with twins and singletons matched for gestational age, have been reported previously [20]. **[Yes, Ok]**

The results of the present study confirmed that the frequency of trichorionic triplets was less common among women who conceived spontaneously than among those who conceived after treatment for infertility (42% [27/64] vs 73% [123/169]; *P*<0.0001). The frequencies of trichorionic triplets in previous studies have been reported as 55% (16/29) [2] and 56% (49/88) [14] among women with spontaneous triplets; and 76% (106/140) [3] and 87% (128/147) [2] among women with iatrogenic triplets. Thus, the frequency of triplet pregnancies not containing monochorionic pairs is partly dependent on the frequency of iatrogenic triplet pregnancies, as found for twin pregnancies [21].

Although not examined in the present study, placental chorionicity is closely associated with zygosity of triplets [22]; among spontaneous triplet pregnancies, 30% and 70% were found to be mono- and dizygotic, respectively, for dichorionic triplet pregnancies, and 20% and 80% were di- and trizygotic, respectively, for trichorionic triplet pregnancies, resulting in a monozygotic twin pair incidence of 48%. Among triplet pregnancies conceived after ovulation induction only and in vitro fertilization, 100% were dizygotic for dichorionic triplet pregnancies, and 4% and 96% were di- and trizygotic, respectively, for trichorionic triplet pregnancies, resulting in a monozygotic twin pair incidence of 6.5% [22].

In the present study, fetal growth in triplet pregnancies was comparable to that in singleton pregnancies until 30 gestational weeks, and the number of triplets with a birth weight lower than the 10th percentile for singleton pregnancies increased with advancing gestation at and after 30 gestational weeks (Figure 3). These results are also consistent with previous studies [1,16], in which the average birth weight of 2155 triplets at each gestational week was reported to be similar to those of 36 931

singletons for all gestational ages until 29 gestational weeks [1], although the 10th, 50th, and 90th percentile birth weight values were found to be substantially lower for triplets than for singletons [16]. Although the association between maternal weight gain and fetal growth was not examined in the present study, inadequate weight gain or a slow change in body mass index during early triplet pregnancy may be risk factors for small-for-gestational-age triplets [23,24]. However, weight gain during early triplet pregnancy has been reported not to be associated with low birth weight or small-for-gestational-age triplets among women with a normal pre-pregnancy body mass index [25].

In the present study, 98% of the 320 women delivered by cesarean, compared with 29% [10], 81% [3], 83% [15], 89% [26], 93% [13], 95% [1,27], and 99% [20] of women in previous studies. Vintzileos et al. [27] **[Author: Yes OK]** have proposed that vaginal delivery among triplet pregnancies should be avoided on the basis of findings that cesarean delivery of all 3 triplet fetuses was associated with the lowest neonatal and infant mortality rate among 7067 triplet pregnancies. By contrast, Alran et al. [10] **[Author: Yes, Ok]** have suggested that offering vaginal delivery is an acceptable

management plan for triplets in a center with a sufficient number of triplet deliveries, on the basis of their experience in which 66 of 78 women who underwent a trial of labor had successful vaginal delivery of all 3 neonates among 93 consecutive triplet pregnancies.

In summary, data from 320 triplet pregnancies, accounting for approximately one-third of all triplet pregnancies occurring in Japan during the study period, were assessed to give an overview of Japanese triplet pregnancy. More than 95% of the women underwent cesarean delivery before 37 weeks of gestation. The distribution of gestational week at delivery, growth patterns, and short-term outcomes were similar or comparable to those reported in other countries. The proportions of mono-, di-, and trichorionic triplet pregnancies were partly dependent on the frequency of iatrogenic triplet pregnancies. These data may be useful for counseling Japanese women about the clinical features and outcomes of triplet pregnancy.

Conflict of interest

The authors have no conflicts of interest.

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Figure 1 Relationship between mechanisms leading to triplet pregnancies and placental chorionicity. A–C, Mechanisms leading to monochorionic (A), dichorionic (B), and trichorionic (C) triplet pregnancies. Sp, triplets conceived spontaneously; IVF, triplets conceived after in vitro fertilization; and IO, triplets conceived after ovulation induction alone. D–F, Chorionicity of triplet pregnancies conceived spontaneously (D), after in vitro fertilization (E), and after ovulation induction alone (F). MC, monochorionic; DC, dichorionic; and TC, trichorionic.

Figure 2 Distribution of gestational week at delivery among 320 triplet pregnancies.

[Author: in Figures 2 and 3, please reword the x-axis as "Gestational age at delivery, weeks", Yes, we did]

Figure 3 Birth weight according to gestational week among 320 triplet pregnancies. Dashed and dotted lines indicate the 10th and 90th percentile values and the median value for normal Japanese singletons, respectively [8]. Filled circles, triangles, and squares indicate the mean birth weight for the heaviest, middle, and lightest triplet, respectively.

Table 1 Demographic characteristics according to placental chorionicity

	Overall	MC	DC	TC	Unknown	*P* value
Mothers/infants	320/960	8/24	75/225	150/450	87/261	
Nullipara	225 (70.3)	5 (62.5)	48 (64.0)	108 (72.0)	64 (73.6)	0.481
Age, yr	31.7 ± 4.1	32.9 ± 4.4	31.6 ± 4.0	32.1 ± 4.1	31.1±4.1	0.263
Spontaneous	109 (34.1)	6 (75.0)	31 (41.3)	27 (18.0)	45 (51.7)	0.001 (MC vs TC) <0.001 (DC vs TC)
IVF	84 (26.3)	2 (25.0)	32 (42.7)	45 (30.0)	5 (5.7)	<0.001 (DC, TC vs unknown)
Induced ovulation [a]	127 (39.7)	0 (0.0)	12 (16.0)	78 (52.0)	37 (42.5)	0.006 (MC vs TC) 0.008 (MC vs unknown) <0.001 (DC vs TC, unknown)
PIH	11 (3.4)	0 (0.0)	3 (4.0)	5 (3.3)	3 (3.5)	0.999
Hyperglycemia	4 (1.3)	0 (0.0)	0 (0.0)	2 (1.3)	2 (2.3)	0.620
Placenta previa	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0.531
FFTS	2 (0.6)	1 (12.5)	1 (1.3)	0 (0.0)	0 (0.0)	0.051
Cesarean delivery	315 (98.4)	8 (100)	73 (97.3)	148 (98.7)	86 (98.9)	0.752
Pregnancy duration, wk	32.3 ± 2.8	30.3 ± 15.4	31.7 ± 8.3	33.1 ± 7.4	31.6 ± 5.5	0.030 (MC vs TC) 0.001 (DC vs TC) <0.001 (TC vs unknown)
<37 weeks	310 (96.9)	8 (100)	75 (100)	140 (93.3)	87 (100)	0.033 (DC vs TC) 0.015 (TC vs unknown)
<34 weeks	195 (60.9)	6 (75.0)	51 (68.0)	71 (47.3)	67 (77.0)	0.004 (DC vs TC) <0.001 (TC vs unknown)
<30 weeks	45 (14.1)	3 (37.5)	16 (21.3)	12 (8.0)	14 (16.1)	0.029 (MC vs TC) 0.009 (DC vs TC)
Birth weight [b], g	1592 ± 433 (n=939)	1300 ± 498 (n=21)	1520 ± 444 (n=216)	1798 ± 419 (n=442)	1494 ± 396 (n=260)	<0.001 (MC, DC, unknown vs TC)
<2500 g	927 (98.7)	21 (100)	210 (97.2)	437 (98.9)	259 (99.6)	0.120
<2000 g	778 (82.9)	19 (90.5)	186 (86.1)	338 (76.5)	235 (90.4)	0.004 (DC vs TC) <0.001 (TC vs unknown)
<1500 g	375 (39.9)	14 (66.7)	106 (49.1)	122 (27.6)	133 (51.2)	<0.001

						(MC, DC, unknown vs TC)
<1000 g	97 (10.3)	5 (23.8)	28 (13.0)	33 (7.5)	31 (11.9)	0.031 (MC vs TC) 0.022 (DC vs TC)
Female infant	501 (52.2)	10 (41.7)	131 (58.2)	218 (48.4)	142 (54.4)	(0.018) DC vs TC
Perinatal mortality	24 (2.5)	3 (12.5)	9 (4.0)	9 (2.0)	3 (1.1)	0.019 (MC vs TC) 0.009 (MC vs unknown)
Stillbirth	21 (2.2)	3 (12.5)	9 (4.0)	8 (1.8)	1 (0.4)	0.014 (MC vs TC) 0.002 (MC vs unknown) 0.007 (DC vs unknown)
END	3 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.8)	0.486

Abbreviations: MC, monochorionic; DC, dichorionic; TC, trichorionic; IVF, in vitro fertilization; PIH, pregnancy-induced hypertension (including gestational hypertension, pre-eclampsia, and eclampsia); END, early neonatal death within 7 days of life; FFTS, feto-fetal transfusion syndrome.

[a] ~~Comparison among frequencies of mono-, di-, and trichorionic pregnancies after excluding women with unknown chorionicity of the placentas.~~ **[Author: please check that this superscript has been applied to the correct data in the table Yes, we did]**

[a] Induced ovulation indicates pregnancy conceived after ovulation induction without the aid of IVF.

[b] Birth weight included only live-born infants.

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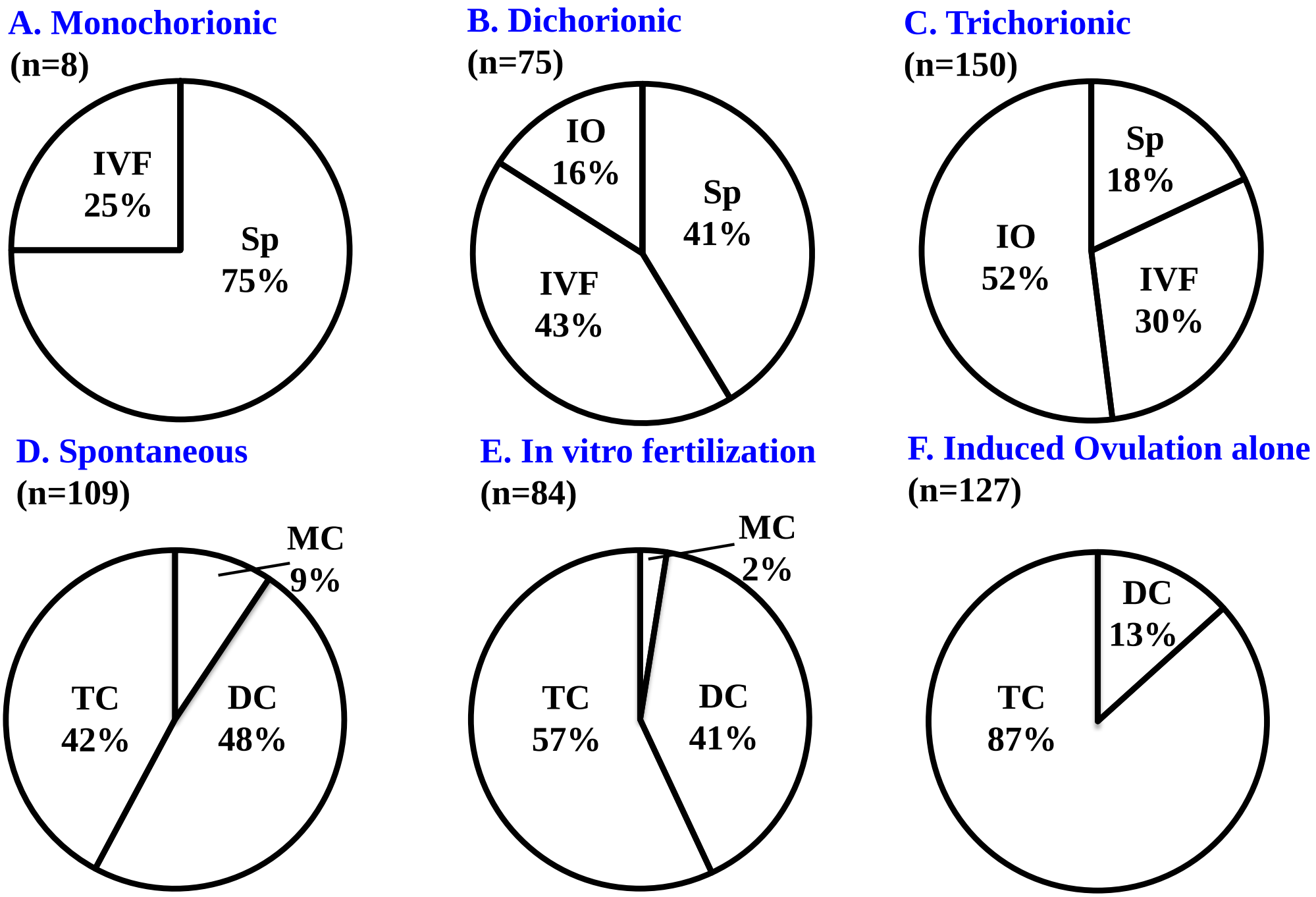
Please add following Table 2

Table 2. Eighteen women who had infants with stillbirth and/or early neonatal death

Case no.	GW	Chorionicity	Birth weight (g) and Outcome					
			Triplet A		Triplet B		Triplet C	
1 †, ‡	22	TC	494	SB	408	SB	460	SB
2 †, §	24	Unknown	398	END	492	SB	520	Survived
3	26	TC	170	SB	801	Survived	889	Survived
4 †	26	TC	780	END	892	Survived	812	Survived
5	26	TC	830	Survived	510	SB	880	Survived
6	27	DC	560	SB	850	Survived	659	Survived
7	27	Unknown	954	END	948	Survived	856	Survived
8	28	MC	136	SB¶	130	SB¶	1220	Survived
9	29	DC	1086	Survived	1390	SB	1350	Survived
10	31	TC	872	Survived	1608	Survived	125	SB
11	32	DC	540	SB*	534	SB*	1510	Survived
12	32	TC	1535	Survived	1640	Survived	1268	SB
13 †	34	TT	1817	Survived	1532	Survived	165	SB
14 †	35	DC	2090	Survived	2016	Survived	200	SB
15 †, §	35	DC	2260	Survived	130	SB	250	SB
16	35	MC	1880	Survived	1618	Survived	765	SB
17	36	DC	2716	Survived	2506	Survived	61	SB
18	36	DC	2450	Survived	1896	Survived	168	SB

GW, gestational week at delivery; TC, trichorionic, DT, dichorionic; MC, monochorionic; SB, stillbirth; END, early neonatal death within 7 days of life; *, Fetofetal transfusion syndrome; ¶, cord entanglement; §, abruption placentae; †, preterm rupture of fetal membranes; ‡, vaginal delivery.

Figure 1


A. Monochorionic
(n=8)
IVF
25%
Sp
75%
B. Dichorionic
(n=75)
IO
16%
Sp
41%
IVF
43%
C. Trichorionic
(n=150)
Sp
18%
IO
52%
IVF
30%
D. Spontaneous
(n=109)
MC
9%
TC
42%
DC
48%
E. In vitro fertilization
(n=84)
MC
2%
TC
57%
DC
41%
F. Induced Ovulation alone
(n=127)
DC
13%
TC
87%