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Perinatal Backgrounds and NICU Bed Occupancy of Multiple-Birth Infants in Japan

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Multiple pregnancies (twin, triplet, and higher-order pregnancy) are associated with an increased risk of resultant preterm and low birth weight infants. The increase of multiple pregnancies for several decades in Japan has been an important consideration in bed allocation planning for neonatal intensive care unit (NICU). The guideline of the Japan Society of Obstetrics and Gynecology (JSOG) in 2008 recommended that embryo transfer be limited to one. The epidemiological data of Japanese regional multiple pregnancies before the JSOG recommendation are valuable in assessing the perinatal effects after this recommendation. The aim of this study was to investigate regional backgrounds of multiple pregnancies and neonatal outcomes of multiple births including NICU admission before the JSOG recommendation. This is a retrospective population-based study for 20 months (January, 2007 through August, 2008) in Shiga Prefecture, Japan. Sending questionnaires to institutions treating multiple births in Shiga, we extracted relevant data from the responses of respective obstetricians and neonatologists. There were 245 multiple births including 241 twins and 4 triplets. We found more twin deliveries with higher risks such as monochorionic diamniotic twins or preterm twins less than 34 weeks in hospitals including perinatal centers than in primary obstetrics clinics. More than half of multiple-birth infants (57%) required NICU admission, and nearly 20% of NICU beds in Shiga are occupied with multiple-birth infants. Furthermore, half of multiple-birth infants were conceived with medical assistance. We conclude that multiple pregnancies resulting from medically assisted conception could have a significant impact upon the NICU bed occupancy in Japan.

Keywords: medically assisted conception; multiple pregnancies; neonatal intensive care unit; neonatal outcome; population-based study
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Introduction

The rate of multiple pregnancies (twin, triplet, and higher-order ones) has increased in developed countries, including Japan for several decades (Imaizumi 1998; Kurosawa et al. 2012), as a consequence of advanced maternal age and the development of fertility treatments (Adashi et al. 2003; Templeton et al. 2004). Twin pregnancies, constituting the vast majority of multiple ones, are subject to increased risks of having preterm and low birth weight infants compared with singleton pregnancies (Glinianaia et al. 1998; McDonald et al. 2005). As a result, quite a few multiple births infants need to be admitted to a neonatal intensive care unit (NICU). The increase of multiple pregnancies has been an important consideration in NICU bed allocation planning. Shiga has one of the highest crude birth rates (9.3 per 1,000 population in 2013) in Japan and also is one of the few prefectures with a growing population (Ministry of Health, Labor and Welfare 2013). The incidence of multiple pregnancies in Shiga is higher than the Japanese average, which is also higher than England or France, but lower than U.S.A. or Korea (Choi et al. 2010; Fell and Joseph 2012; Smith et al. 2014). There has been an average of 13,000 annual births in Shiga, two thirds of which in primary obstetric clinics and the remaining one third in general hospitals and perinatal centers. Despite this higher birth rate including multiple births, there are much fewer NICU beds per 1,000 deliveries in Shiga than in other prefectures, less than half of the Japanese average (Ministry of Health, Labor and Welfare 2008). Due to shortage of NICU beds, we often had to transport urgent maternal cases to other area out of Shiga in case of no available NICU beds in Shiga. Considering this relative shortage of NICU beds in Shiga, population-based studies of

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regional perinatal medical circumstances are indispensable (Koshida et al. 2015). Although there are some perinatal center-based studies related to multiple pregnancies in Japan (Murakami et al. 2011; Nakayama et al. 2012), there have been no population-based studies of multiple-birth infants associated with their occupation of regional NICU beds.

Importantly, the guideline of the Japan Society of Obstetrics and Gynecology (JSOG) recommended that embryo transfer was limited to one, in principle, in 2008 (Hayashi et al. 2015). After the recommendation of JSOG, the ratio of multiple birth deliveries to total ones both in the Japanese average and Shiga in 2013 decreased nearly 12% compared with that in 2007 (Ministry of Health, Labor and Welfare 2013). The epidemiological data of Japanese regional multiple pregnancies before the recommendation of JSOG are valuable in assessing the effect of perinatal backgrounds of multiple pregnancies or multiple-birth infant outcomes after this recommendation.

We, therefore, investigated regional multiple pregnancies delivered in primary obstetric clinics and general hospitals as well as in perinatal centers retrospectively before the JSOG recommendation. Firstly, we analyzed backgrounds of regional multiple pregnancies. Secondly, we classified neonatal outcome of multiple births and assessed their impact on NICU bed occupancy in Shiga.

Materials and Methods

There are approximately 13,000 deliveries annually, in 30 primary obstetrics clinics, 7 general hospitals, and 4 perinatal centers in Shiga. Initially, we sent questionnaires about the occurrence of multiple births to all institutions providing obstetrical care for 20 months between January 1, 2007 and August 31, 2008. Next, we sent questionnaires to institutions treating multiple births addressing backgrounds of multiple pregnancies including methods of conception, chorionicity and also neonatal outcome including gestational age, birth weight, and admission to NICU. We subsequently assessed the returned questionnaires filled out by obstetricians and neonatologists.

Primary obstetrics clinics ("clinics") were defined as institutions without any neonatal units for intermediate or intensive care. We defined general hospitals as institutions with neonatal intermediate care units for slightly or moderately ill infants and defined perinatal centers as ones with intensive care units for the most seriously ill infants. Further, general hospitals and perinatal centers were classified as "hospitals" in this study. Infants admitted to NICU were designated as neonates, either born in hospitals or transported from other clinics after delivery having spent time in NICU.

The methods of conception of multiple births were classified as such: natural, assisted reproductive technology (ART), ovulation induction, and artificial insemination of husband (AIH). ART includes in vitro fertilization-embryo transfer and intracytoplasmic sperm injection. Ovulation induction is the method of using injectable human menopausal gonadotropins to stimulate the ovaries to produce mature eggs. We classified twins according to their chorionicity into monochorionic diamniotic (MD), dichorionic diamniotic (DD), and monochorionic monoamniotic (MM), as perinatal outcome of twins depends on chorionicity rather than zygosity (Dube et al. 2002; Carroll et al. 2005).

The statistical significance of the differences was assessed with a chi-square test using IBM SPSS Statistics 22. A p value less than 0.05 was considered statistically significant.

This study was approved by the Institutional Review Board, Shiga University of Medical Science.

Results

The 247 multiple births occurred in 17 institutions including 6 clinics, 7 general hospitals and 4 perinatal centers during the study period. The institutional response rates of the distributed questionnaires were 95% in clinics and 100% in hospitals. We assessed 245 multiple births (241 twins and 4 triplets) after 22 gestational weeks excluding 2 co-abortion twin cases. The number of multiple births investigated in this study accounts for 86% of total in Shiga during study periods. Of these births, 33 (13%) occurred in clinics, 46 (19%) in general hospitals, and 166 (68%) in perinatal centers, (Fig. 1). The 133 (74%) of 166 multiple births in perinatal centers were delivered after maternal referral from clinics (n = 100), general hospitals (n = 23), or other perinatal centers (n = 10), while the 26 (57%) of 46 delivered in general hospitals were from clinics (n = 21) or other general hospitals (n = 5). The difference of the referral ratio between perinatal centers and general hospitals was significant ($p < 0.001$).

Methods of conception and chorionicity

We investigated the effect of the method of conception on the chorionicity of twins and triplet, because it is important to assess the impact of multiple pregnancies by medically assisted conception on limited NICU beds in our region. Natural conception constituted the most common method (44%) and ART the second most common (31%). We evaluated the relationship between conception and cho-

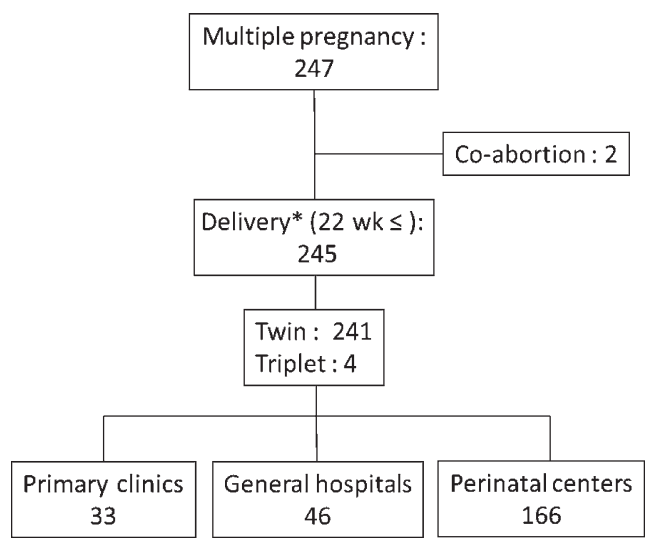

Fig. 1. Overview of this study.
*Including five deliveries with one interauterine fetal demise and another live birth.

rionicity of twins. The genesis by natural conception in MD twins (47/58, 81%) was significantly higher than that in DD twins (60/182, 33%) (Table 1). The occurrence of medically assisted conception (ART, ovulation induction, and AIH) in DD twins (118/182, 65%) was significantly higher than in MD twins (11/58, 19%). Classifying chorionicity of twins by delivery location, the ratio of MD/DD twins in clinics is significantly lower than in hospitals (MD/DD: 3/30, 10% in clinics, 55/152, 36% in hospitals; p = 0.0294, data not shown in Tables).

Infantile outcome

We counted the number of infants, but not that of multiple births, because some of the multiple-birth infants had different outcome such as birth weight and NICU admission. Most of the multiple births (50%) were delivered at 37 weeks of gestational age (GA), and the second most (22%) were at 36 weeks both in clinics and hospitals (Table 2). The incidence of preterm deliveries (< 37 weeks) was 47%. There were significantly more preterm deliveries (< 34 weeks of GA) in hospitals than in clinics, although there was little difference between them after 35 weeks of GA. Multiple-birth infants with birth weight 2,000-2,500 g were most frequent. Low birth weight infants (< 2,500 g) accounted for 71% of all multiple births. All of the very low birth weight infants (< 1,500 g) were delivered in hospitals. The incidence of normal weight infants (≥ 2,500 g) delivered in clinics was significantly higher than in hospitals. More than half of multiple-birth infants (57%) were admitted to NICU (Table 2). The infants born in clinics were noticeably fewer (23%) to be admitted than those born in hospitals. NICU admission rates by GA were as follows: 100% (≤ 34 weeks), 93% (35 weeks), 57% (36 weeks), 38% (37 weeks), and 47% (≥ 38 weeks).

Table 1. Classification of multiple pregnancies according to methods of conception.

	All n (%)	Twin			Triplet
		DD	MD	MM	
• Natural	108 (44)	60	47*	1	0
• Medically assisted	129 (53)	118*	7	0	4
ART	76 (31)	70	2	0	4
Ovulation induction	37 (15)	33	4	0	0
AIH	16 (6)	15	1	0	0
• Unknown	8 (3)	4	4	0	0
Total	245 (100)	182	58	1	4

Reclassification of twins on the basis of the chorionicity.
*p < 0.05.
DD, dichorionic diamniotic; MD, monochorionic diamniotic; MM, monochorionic monoamniotic.

Table 2. Neonatal outcome by locations.

	All (n = 489)	Clinics (n = 65)	Hospitals		p value*
			General (n = 93)	Perinatal centers (n = 331)	
Gestational age					
< 34 w	58 (12)	0 (0)	7 (8)	51 (15)	0.002
34 w	32 (7)	0 (0)	8 (9)	24 (7)	0.022
35 w	29 (6)	4 (6)	12 (13)	13 (4)	0.93
36 w	106 (22)	18 (28)	24 (26)	64 (18)	0.21
37 w	245 (50)	38 (58)	34 (37)	173 (52)	0.15
37 w <	19 (4)	5 (8)	8 (9)	6 (2)	0.09
Birth weight					
< 1500 g	36 (7)	0 (0)	5 (5)	31 (9)	0.015
1,500-2,000 g	80 (16)	8 (12)	12 (13)	60 (18)	0.342
2,000-2,500 g	237 (48)	26 (40)	54 (58)	157 (47)	0.142
> 2,500 g	136 (28)	31 (48)	22 (24)	83 (25)	< 0.001
Admission in NICU	278 (57)	14 (23)	60 (65)	204 (62)	< 0.001

Data: n (%).
*Infants born at clinics compared with those at hospitals.

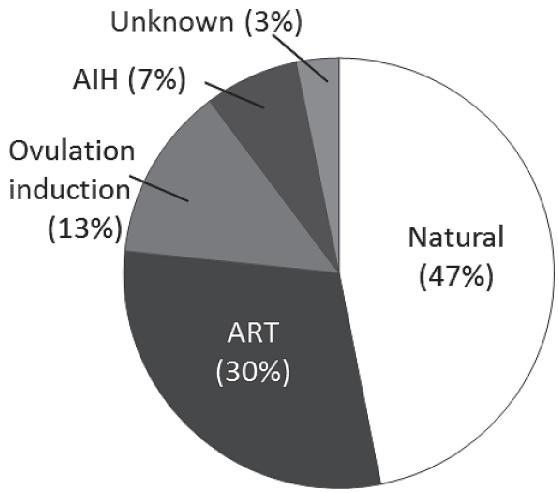

Fig. 2. Classification of NICU beds occupancy by the methods of conception.
ART, assisted reproductive technology; AIH, artificial insemination of husband.

NICU bed occupancy rate of multiple births

We have 64 NICU beds including 39 beds of two perinatal centers and 25 beds of two general hospitals in Shiga. The sum of NICU-stay days of admitted infants was 8,035 person-days during this study period. As there were 38,400 bed-days in Shiga for this study period (64 beds × 600 days), NICU bed occupancy of multiple-birth infants was estimated as 20.9% (8,035/38,400).

The sum of NICU-stay days, according to the method of conception, was classified into 3,769 days (47%) by natural conception, 2,389 days (30%) by ART, 1,053 days (13%) by ovulation induction, and 567 days (7%) by AIH (Fig. 2). Multiple-birth infants through medically assisted conception were estimated to occupy 10.5% of regional NICU beds.

Discussion

Reviewing 247 multiple pregnancies in a region of Japan for twenty months, we evaluated backgrounds of regional multiple pregnancies not only in perinatal centers but also in general hospitals and primary obstetrical clinics. In addition, we assessed neonatal outcome of subsequent multiple-births and evaluated their impact on regional NICU bed occupancy.

Evaluating backgrounds of regional multiple pregnancies, we found that a significant number of multiple births were delivered in clinics or general hospitals, rather than perinatal centers. Moreover, multiple-birth deliveries were much fewer than other deliveries, including singletons, in clinics in our region (of the two thirds of all births born in clinics, only 13% were multiple births). The difference between multiple-birth deliveries and all other deliveries, including singletons, in clinics indicates that the referrals system of high risked pregnancy such as multiple pregnancies from primary obstetrical clinics to perinatal centers or general hospitals works well in our region. This assertion is also supported by the fact that the majority of multiple births in hospitals (80% in perinatal centers and 57% in general hospitals, data not shown) were delivered after maternal referral.

In addition to backgrounds of regional multiple pregnancies, our study found that most of the MD twins were conceived through natural conception while there were very few MD twins through medically assisted conceptions, including ART, ovulation induction, and AIH. The difference of chorionicity by the method of conception was consistent with a previous study (Murakami et al. 2011). MD twins have a greater perinatal risk including twin-to-twin transfusion syndrome, growth discordance, and perinatal death (Dube et al. 2002; Hack et al. 2006; Skiadas et al. 2008). The lower percentage of MD twins born in clinics (10%) than in hospitals (36%) also suggests that the obstetricians in clinics, recognizing the high risk of such pregnancy in our region, tend to refer MD twin pregnancy to hospitals.

Next, we assessed neonatal outcome of multiple births, showing the relatively high incidence of preterm delivery and subsequent low birth weight infants of multiple births. Our result is consistent with previous studies indicating similar higher incidences of such births compared to total live births including singletons (Minakami and Sato 1996; Choi et al. 2010). We also found that the location of multiple birth deliveries was associated with GA and birth weight (BW): mature delivery (≥ 38 weeks of GA or ≥ 2,500 g of BW) in clinics and very premature delivery (≤ 34 weeks of GA or ≤ 1,500 g of BW) in hospitals. Among multiple-birth infants in term period (37 to 41 weeks of GA), 39% required NICU admission (Table 2). Term infants including singletons are generally considered low risk and the incidence of NICU admission is 5.3-8.8% (Sengupta et al. 2013). Our results suggest that multiple-birth infants even in term period had a higher risk of NICU admission. In addition to neonatal outcome of multiple births, 20.9% of NICU beds were occupied with multiple-birth infants, and half of those beds were occupied with infants through medically assisted conception. More NICU beds in our region might be needed if multiple-births increase along with the development of fertility treatments in the future.

We have several limitations in this study. There is no unified indication for NICU admission regarding GA and BW of infants in term or near term period in our region. Some of them might be admitted only for the purpose of observation for a few days because of their potentially high risk. Our results related to NICU admission were possibly affected by this ascertainment bias. Our study also had a limitation associated with gestational age of preterm delivery in which we were unable to analyze maternal condition and obstetrical indication. As a result, it was impossible to include these factors although they may impact on preterm delivery.

We concluded that delivery locations of twins depended on the factors of GA and chorionicity. It was preferred that

those with less than 34 weeks of GA or MD twins be delivered in hospitals rather than in clinics. In addition, nearly 20% of regional NICU beds were occupied with multiple-birth infants, and half of them consisted of infants through medically assisted conception. Our regional data regarding multiple births will assist in allocation planning of limited healthcare resources including NICU beds.

Conflict of Interest

The authors declare no conflict of interest.

References

Adashi, E.Y., Barri, P.N., Berkowitz, R., Braude, P., Bryan, E., Carr, J., Cohen, J., Collins, J., Devroey, P., Frydman, R., Gardner, D., Germond, M., Gerris, J., Gianaroli, L., Hamberger, L., et al. (2003) Infertility therapy-associated multiple pregnancies (births): an ongoing epidemic. *Reprod. Biomed. Online*, **7**, 515-542.

Carroll, S.G., Tyfield, L., Reeve, L., Porter, H., Soothill, P. & Kyle, P.M. (2005) Is zygosity or chorionicity the main determinant of fetal outcome in twin pregnancies? *Am. J. Obstet. Gynecol.*, **193**, 757-761.

Choi, S.H., Park, Y.S., Shim, K.S., Choi, Y.S., Chang, J.Y., Hahn, W.H. & Bae, C.W. (2010) Recent trends in the incidence of multiple births and its consequences on perinatal problems in Korea. *J. Korean Med. Sci.*, **25**, 1191-1196.

Dube, J., Dodds, L. & Armson, B.A. (2002) Does chorionicity or zygosity predict adverse perinatal outcomes in twins? *Am. J. Obstet. Gynecol.*, **186**, 579-583.

Fell, D.B. & Joseph, K. (2012) Temporal trends in the frequency of twins and higher-order multiple births in Canada and the United States. *BMC Pregnancy Childbirth*, **12**, 103.

Glinianaia, S.V., Rankin, J. & Renwick, M. (1998) Time trends in twin perinatal mortality in northern England, 1982-94. Northern Region Perinatal Mortality Survey Steering Group. *Twin Res.*, **1**, 189-195.

Hack, K.E., Derks, J.B., de Visser, V.L., Elias, S.G. & Visser, G.H. (2006) The natural course of monochorionic and dichorionic twin pregnancies: a historical cohort. *Twin Res. Hum. Genet.*, **9**, 450-455.

Hayashi, M., Satoh, S., Matsuda, Y. & Nakai, A. (2015) The effect of single embryo transfer on perinatal outcomes in Japan. *Int. J. Med. Sci.*, **12**, 57-62.

Imaizumi, Y. (1998) A comparative study of twinning and triplet rates in 17 countries, 1972-1996. *Acta Genet. Med. Gemellol.*, **47**, 101-114.

Koshida, S., Ono, T., Tsuji, S., Murakami, T. & Takahashi, K. (2015) Recommendations for preventing stillbirth: a regional population-based study in Japan during 2007-2011. *Tohoku J. Exp. Med.*, **235**, 145-149.

Kurosawa, K., Masuno, M. & Kuroki, Y. (2012) Trends in occurrence of twin births in Japan. *Am. J. Med. Genet. A*, **158A**, 75-77.

McDonald, S., Murphy, K., Beyene, J. & Ohlsson, A. (2005) Perinatal outcomes of in vitro fertilization twins: a systematic review and meta-analyses. *Am. J. Obstet. Gynecol.*, **193**, 141-152.

Minakami, H. & Sato, I. (1996) Reestimating date of delivery in multifetal pregnancies. *JAMA*, **275**, 1432-1434.

Ministry of Health, Labor and Welfare (2008) Number of NICU beds per 10,000 live births by prefecture, 2008. http://www.mhlw.go.jp/toukei/saikin/hw/hoken/national/dl/22-03.pdf [*Accessed*: May 13, 2012] (in Japanese).

Ministry of Health, Labor and Welfare (2013) *Japanese National Vital Statistics of Japan 2013*, Japan, Ministry of Health, Labor and Welfare Statics Association, Tokyo (in Japanese).

Murakami, M., Iwasa, T., Kiyokawa, M., Takahashi, Y. & Morine, M. (2011) Investigation of the factors affecting the perinatal outcome of monochorionic diamniotic twins. *Arch. Gynecol. Obstet.*, **283**, 1239-1243.

Nakayama, S., Ishii, K., Kawaguchi, H., Hayashi, S., Hidaka, N., Murakoshi, T. & Mitsuda, N. (2012) Perinatal outcome of monochorionic diamniotic twin pregnancies managed from early gestation at a single center. *J. Obstet. Gynaecol. Res.*, **38,** 692-697.

Sengupta, S., Carrion, V., Shelton, J., Wynn, R.J., Ryan, R.M., Singhal, K. & Lakshminrusimha, S. (2013) Adverse neonatal outcomes associated with early-term birth. *JAMA Pediatr.*, **167**, 1053-1059.

Skiadas, C.C., Missmer, S.A., Benson, C.B., Gee, R.E. & Racowsky, C. (2008) Risk factors associated with pregnancies containing a monochorionic pair following assisted reproductive technologies. *Hum. Reprod.*, **23**, 1366-1371.

Smith, L.K., Manktelow, B.N., Draper, E.S., Boyle, E.M., Johnson, S.J. & Field, D.J. (2014) Trends in the incidence and mortality of multiple births by socioeconomic deprivation and maternal age in England: population-based cohort study. *BMJ Open*, **4**, e004514.

Templeton, A. (2004) Joseph Price oration. The multiple gestation epidemic: the role of the assisted reproductive technologies. *Am. J. Obstet. Gynecol.*, **190**, 894-898.