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Impact of the recommendation for embryo transfer limitation on multiple pregnancy: A population-based study in Japan



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ABSTRACT

Objective: Limitations on the number of embryos transferred have been recommended worldwide to reduce the number of medically assisted multiple births. Our aim was to evaluate the impact of this recommendation for embryo transfer limitation on perinatal outcomes of multiple births.

Study design: A retrospective and population-based study compared all multiple births in Shiga prefecture of Japan in 2014–2015 (2015 group) with those in 2007–2008 (2008 group). The perinatal background and neonatal outcomes of multiple births were compared.

Results: The number of multiple pregnancies in the 2015 group (n = 251) was almost the same as in the 2008 group (n = 245). The proportion of multiple pregnancies conceived through assisted reproductive technology significantly decreased to 23% in the 2015 group compared to 31% in the 2008 group. In contrast, the rate of ovulation induction significantly increased to 24% in the 2015 group from 15% in the 2008 group. There was no significant difference in the outcome of multiple-birth infants between the two groups.

Conclusion: The method of conception in multiple pregnancies markedly shifted from in vitro fertilization to non-in vitro fertilization after the issuance of a recommendation for limits on embryo transfer. It should be necessary for the assessment of the impact of this recommendation to monitor closely multiple pregnancies via non-in vitro fertilization as well as via in vitro fertilization.

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Introduction

Fertility treatments, including in vitro fertilization (IVF) and non-IVF fertility treatments, have been major factors influencing the genesis of multiple births [1]. Multiple births carry greater risks of having preterm birth and low birth weight infants than singletons [2,3]. Consequently, many multiple-birth infants require medical care in neonatal intensive care unit (NICU). Trends in the occurrence of multiple births have a high impact on NICU bed allocation planning.

To reduce the number of medically assisted multiple births, limitations on the number of embryos transferred have been

recommended worldwide [4,5]. In Japan as well, the guidelines from the Japan Society of Obstetrics and Gynecology recommended that the number of embryo transfer be limited to one, in principle, in 2008 [6]. Population-based perinatal data on multiple births, comparing the numbers before and after the recommendation of embryo transfer limitation, is important for assessing the impact of this recommendation on perinatal healthcare resources [7]. However, few population-based studies on multiple births comparing numbers before and after this recommendation have been reported in Japan [8,9].

Therefore, we assessed the recent perinatal backgrounds and neonatal outcomes of multiple births among all of the clinics and hospitals in our region and compared the data with our previous data obtained in 2007 before the recommendation of embryo transfer limitation. We also assessed the association between the outcomes of multiple-birth infants and their methods of conception.

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Materials and methods

This was a retrospective population-based study conducted in Shiga prefecture of Japan. This study protocol was reviewed and approved by the Institutional Review Board of Shiga University of Medical Science.

Data collection

This is a retrospective population-based surveillance of multiple births in Shiga, where there are nearly 13,000 annual deliveries, two-thirds of them in 30 primary obstetric clinics and the remaining in 11 hospitals, including 4 tertiary centers. We sent all of the institutions in Shiga treating deliveries questionnaires about the backgrounds of multiple pregnancies, including the methods of conception, chorionicity, maternal age, and locations of delivery, and also inquired about the neonatal outcomes, including the gestational age, birth weight, and admission to the NICU, for 20 months between January 1, 2014, and August 31, 2015. We analyzed the returned questionnaires and compared the data with those obtained from the previous survey, which was conducted using the same method for 20 months between January 1, 2007, and August 31, 2008.

Definitions

The definitions of primary clinics, general hospitals, and perinatal centers were the same as in our previous publication [10]. In brief, primary clinics were the institutions without any intermediate or intensive-care units for neonates. General hospitals were the institutions with slight or moderate neonatal care units, and perinatal centers were the ones with intensive-care units. We classified the methods of the conception of multiple births as natural, assisted reproductive technology (ART), ovulation induction (OI), and intrauterine insemination (IUI). ART includes in vitro fertilization-embryo transfer and intracytoplasmic sperm injection. OI is the stimulation of the ovaries to produce mature eggs using injectable human menopausal gonadotropins. Twins were classified according to their chorionicity into mono-chorionic diamniotic (MD), dichorionic diamniotic (DD), and mono-chorionic monoamniotic (MM).

Statistical analyses

The data were shown as the means (standard deviation) or n (%). The statistical significance of the differences was analyzed by an unpaired *t*-test or chi-squared test as appropriate using the IBM SPSS Statistics 22 (IBM Japan, Tokyo, Japan). A *p* value of less than 0.05 was considered statistically significant.

Results

A reported 252 multiple births were delivered at 18 institutions, including 7 clinics, 7 general hospitals, and 4 perinatal centers, during the 20-month period from January 1, 2014, to August 31, 2015. Excluding 1 abortion case, we analyzed 251 multiple births, including 247 twins and 4 triplets, and compared them ("2015 group") with those born from January 2007 to August 2008 ("2008 group").

Perinatal backgrounds

The perinatal backgrounds of multiple pregnancies of the two groups are listed in Table 1. The number of multiple births in 2015 was almost the same as in 2008 (251 in 2015, 245 in 2008), and there was no marked difference in the proportion of twins or

Table 1

Perinatal backgrounds of multiple pregnancies before / after the recommendation.

	2008 (N = 245)	2015 (N = 251)	<i>p</i> value
Multiple birth			
Twins	241 (98)	246 (98)	0.97
Triplets	4 (2)	5 (2)	
Maternal age (years)	32 ± 0.3	33 ± 0.3	0.009
>35	179 (73)	165 (66)	0.054
≤35	63 (26)	85 (34)	
Methods of conception			
Natural	108 (44)	119 (47)	0.003
ART	76 (31)	58 (23)	
OI	37 (15)	59 (24)	
IUI	16 (7)	15 (6)	
Unknown	8 (3)	0 (0)	
Chorionicity of twins	n = 241	n = 246	
MD	58 (24)	66 (27)	0.741
DD	182 (76)	179 (72)	
MM	1 (0)	1 (0)	

Data are mean ± standard deviation or n (%). ART, assisted reproductive technology; IUI, intrauterine insemination; MD, mono-chorionic diamniotic; DD, dichorionic diamniotic; MM, mono-chorionic monoamniotic.

triplets between the two groups (twins/triplets: 246/5 in 2015, 241/4 in 2008). The average maternal age at birth in the 2015 group was 33 years old, which was higher than that in the 2008 group. There is no significant difference in the proportion of women with an advanced maternal age (≥35y) between the two groups.

Methods of conception and chorionicity

Natural conception of multiple births was the most common conception method (47%) in the 2015 group as well as in the 2008 group. OI constituted the second-most common method (24%), followed by ART (23%) in the 2015 group, while ART was the most common method (31%) followed by OI (15%) in the 2008 group. OI was more likely to be a common method (24% in 2015, 15% in 2008), whereas ART was less likely to be a common method (23% in 2015, 31% in 2008). The differences in the proportion of ART and OI between the 2008 and 2015 groups were significant. There were no marked differences in the chorionicity of twins between the two groups.

Neonatal outcomes

The neonatal outcomes of multiple-birth infants are summarized in Table 2. Births at 37–42 weeks of gestation were the most common time frame in both groups. Although the rate of preterm births infants (born earlier than 37 weeks of gestation) slightly increased in 2015 group, the differences in gestational age at birth between the two groups were not significant. There were no marked differences in the birth weight nor the number of infants admitted to NICU between the two groups. In addition,

Table 2

Neonatal outcome of multiple-birth infants before / after the recommendation.

	2008 (N = 489)	2015 (N = 490)	<i>p</i> value
Gestational age at births			
<34 weeks	58 (12)	71 (14)	0.18
34–36 weeks	167 (34)	197 (40)	
37–42 weeks	264 (54)	222 (45)	
Birth weight			
<1500 g	35 (7)	42 (9)	0.48
1500–2500 g	317 (65)	301 (62)	
≥2500 g	136 (28)	147 (30)	
Admission to the NICU	278 (57)	249 (51)	0.058

Data: n (%). NICU, neonatal intensive care unit.

Table 3
Neonatal outcome according to methods of conception in 2015 group.

	ART (N = 113)	OI (N = 118)	Natural (N = 228)	p value
Gestational age at birth				
<37 weeks	68 (60)	67 (57)	115 (50)	0.19
≥37 weeks	45 (40)	51 (43)	113 (50)	
Birth weight				
<2500 g	79 (70)	83 (70)	157 (69)	0.95
≥2500 g	34 (30)	35 (30)	71 (31)	
Admission to the NICU				
Yes	51 (45)	58 (49)	118 (52)	0.51
No	62 (55)	60 (51)	110 (48)	

ART, assisted reproductive technology; OI, Ovulation induction; IUI, intrauterine insemination; NICU, neonatal intensive care unit.

Data: n (%).

Table 3 shows the neonatal outcome according to the method of conception. There were not significant differences in the outcome of multiple-birth infants, including gestational age at birth, birth weight, and admission in NICU between the methods of conception.

Comment

On analyzing the perinatal backgrounds of multiple pregnancies in our region, we ascertained two important points. First, we found a significant shift in the frequency of conceiving via ART versus OI without a decrease in the total number of multiple births after the recommendation of embryo transfer limitation, and also found that this significant shift in conception method did not affect the subsequent neonatal outcomes. Second, we found that the neonatal outcomes, including gestational age at birth, birth weight, and rate of NICU admission, were independent of the conception method.

First, we found that there was a significant shift in the frequency of conceiving via ART versus OI without a decrease of multiple births after the recommendation of embryo transfer limitation in our region. This is a new finding regarding the shift of the method of conception on multiple pregnancies after this recommendation in Japan. Our finding is inconsistent with previous data stating that the incidence of multiple pregnancies significantly decreased after the issuance of the single embryo transfer recommendation in Japan [9]. A major potential explanation for this discrepancy in findings is that we surveyed multiple births for all methods of conception, including non-IVF treatment, such as OI and IUI but not ART, while Hayashi assessed multiple births conceived only via ART. Although multiple births conceived via ART have been closely monitored by the Japan Society of Obstetrics and Gynecology, data is not available for those conceived via non-IVF treatments, including OI in Japan [8]. Non-IVF fertility treatment such as OI has accounted for more multiple births than ART in the USA in recent years [1,11]. Our data also indicates that multiple births conceived via non-IVF treatments, including OI, have also become more common than those conceived via ART in Japan as well (Table 1).

Another possible explanation for the difference in the incidence of multiple births is that we surveyed those of all institutions, including primary obstetric clinics, general hospitals, and perinatal centers, in our region, while Hayashi conducted the assessment only at tertiary centers of the Perinatal Research Network in Japan. About 40% of deliveries in Japan were made in primary obstetric clinics, and the remaining were made in hospitals, such as general hospitals and tertiary perinatal centers [12]. Our previous study showed that about 30% of multiple births were delivered in non-tertiary perinatal centers, including primary obstetric clinics or general hospitals, in our region [7]. Our data may be more reliable

as a population-based study. This significant increase in the rate of conception through OI possibly resulted in a less-marked decline of the number of medically assisted multiple births after the recommendation of embryo transfer limitation. Thus, close monitoring of multiple births conceived via non-IVF treatments is necessary in order to assess the impact of this recommendation on the occurrence of multiple births.

Next, on evaluating the neonatal outcomes of multiple births, we found that the outcomes, including gestational age at birth, births weight, and rate of NICU admission, were independent of the conception method. We have detected a remarkable shift in the conception methods for multiple births from ART to OI without a notable effect of subsequent neonatal outcomes after the recommendation. We, therefore, evaluated the association between the neonatal outcomes and the methods of conception. No significant differences were noted in the outcome of multiple-birth infants between those conceived via ART, OI, and natural conception (Table 3). Our results are consistent with those of other studies suggesting that there are no significant differences among the outcomes of twin infants conceived via ART or OI compared with those conceived via natural conception [13–15].

It is reasonable that the shift in the method of conception after the recommendation of embryo transfer limitation did not reduce the incidence of multiple births in our region. The significant increase in the rate of multiple-birth infants conceived via OI in our region of Japan is also consistent with the findings of recent studies in the USA that non-IVF fertility treatment, including OI, accounts for more multiple births than IVF [1,11]. While the rate of multiple births conceived via ART was successfully reduced by limiting the number of embryos transferred [1], it is more difficult to reduce multiple births conceived via OI due to the unpredictability of dynamic follicular growth [16]. Women should be informed about the probability of multiple pregnancy by non-IVF fertility treatment as well as IVF.

Our data have several strengths, including the population-based samples and comparison data in the same region for the same period of 20 months before and after the recommendation of embryo transfer limitation. As few population-based studies have examined the data of multiple births according to the method of conception in Japan [8], our data are valuable not only for assessing the impact of the recommendation on the occurrence and outcomes of multiple births but also for assisting in the allocation planning of perinatal care resources, including NICU beds.

However, several limitations associated with the present study warrant mention. The data on conception methods, including fertility treatments, were self-reported by obstetricians. There were 14 monozygotic twins and 44 dizygotic ones among the 58 conceived by ART (data not shown). Although this result indicated that some dizygotic twins were conceived by more than 2 embryos transfer, we did not investigate the number of embryos transferred. Given the recommended limitations on single embryo transfer, the numbers of multiple births conceived via ART might be underreported. Another limitation is that there was no definitive indication of medical termination in cases of multiple pregnancies. Although it may affect the neonatal outcome, including admission to the NICU, it is difficult to analyze the maternal conditions and obstetrical indications associated with the termination of the pregnancies.

We concluded that the method of conception in multiple births significantly shifted from ART to OI after the recommendation of embryo transfer limitation. This recommendation did not influence the outcomes of multiple-birth infants, including NICU admission. It should be necessary for the assessment of the impact of the recommendation to monitor closely multiple pregnancies via non-IVF fertility treatment as well as via IVF. Our data may prove useful for developing more effective strategies to prevent unintended multiple-births conceived through medical assistance.

Conflict of interests

The authors declare that they have no other competing interests.

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Authors contribution

SK, TO, ST, TM, YS and KT conceived the idea for the study. SK, OT, ST, and YS performed the data collection for the original studies. HA performed statistical analyses. SK wrote the first draft. All authors revised the article, and approved the final version.

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