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Estimation of the Contribution of Assisted and Non-Assisted Reproductive Technology Fertility Treatments to Multiple Births During the Past 30 Years in Japan: 1979–2008

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The effect of assisted reproductive technology (ART) and non-ART ovulation stimulation fertility treatment on the number and rate of multiple live births from 1979–2008 in Japan was estimated using two independent data sources, ART statistics and vital statistics. Japanese ART statistics presented by the Japan Society of Obstetrics and Gynecology between 1989 and 2008 were gathered and reanalyzed. The number and rates of ART between 1984 and 1988 were interpolated using an approximation formula, using the values from 1983, when the first ART baby was born in Japan, and the 1989–1992 values. The number of ART multiples between 1979–1982 was set as equal to zero. The minimum (or maximum) number of non-ART iatrogenic multiple births was estimated by subtracting the maximum (or minimum) ART multiples from the total iatrogenic multiples, which was estimated by vital statistics assuming that spontaneous multiple-birth rates according to maternal age class would be constant. There was an overall increase in the non-ART multiple births during the 30-year period, whereas ART multiples tended to increase from 1983 to 2005, and then rapidly decreased thereafter. The number or percentage of ART multiples was almost consistently lower than that of non-ART multiples. The percentage of non-ART multiples (33%) among the total multiples was estimated to be about three times more than the ART multiples (11–12%) in 2008. Given the medical and social impact of multiple births, it is imperative to construct a hospital-based monitoring system for fertility treatments, specially non-ART fertility treatments and multiple births.

■ **Keywords:** multiple births rate, spontaneous multiple births, iatrogenic multiple births, assisted reproductive technology (ART), non-ART fertility treatment

Japan's striking increase in multiple births in the past decades is attributed primarily to fertility treatments that include ovulation stimulation medications (Imaizumi, 1997; Ooki, 2010). Such treatments are generally divided into assisted reproductive technology (ART) and non-ART treatments (Schieve et al., 2009). The high multiple-gestation and multiple-birth rates associated with both treatment types tend to induce adverse sequelae, including markedly higher risks of pregnancy complications, preterm delivery, infant death, and neurological impairments in survivors of multiple births compared to singletons (Boulet et al., 2008; MacDorman et al., 2005; Pharoah, 2002).

Many countries construct national ART surveillance systems (Tandberg et al., 2007; Wright et al., 2008), but most have no population-based official data on non-ART ovulation stimulation. Estimating the numbers or rates of non-ART singletons is very difficult since the total number of fertility treatments, including both ART and non-ART, is generally unknown (Schieve et al., 2009).

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TABLE 1

ART and Vital Statistics Data used for Present Estimation

Year	ART statistics									Vital statistics				
	Registered institutions	Responding institutions	Total pregnancies	Multiple pregnancies	Twin pregnancies	Triplet pregnancies	Live deliveries in ART (X)	Live births in ART (Y)	Live multiple births in ART	Stillbirth rates of live-stillbirth twin pairs (k)[a]	Live births (T)	Multiple live births (M)	Spontaneous multiple live births (S)[a]	Iatrogenic multiple live births (I) [a]
1989	125	87	587	93	No data	No data	350	449	No data	0.0564[b]	1246802	16893	13900	2993
1990	156	142	1195	219	No data	No data	784	1048	No data	0.0506[b]	1221585	16730	13633	3097
1991	189	161	2072	290	No data	No data	1349	1700	No data	0.0454[b]	1223245	17335	13640	3695
1992	237	199	2823	544	No data	No data	2070	2626	No data	0.0408[b]	1208989	18147	13481	4666
1993	270	234	3992	726	No data	No data	2934	3554	No data	0.0368[b]	1188282	18656	13262	5394
1994	303	269	5007	957	No data	No data	3577	4576	No data	0.0334[b]	1238328	20832	13835	6997
1995	348	305	6301	1248	No data	No data	4604	5687	No data	0.0305	1187064	20468	13280	7188
1996	388	350	8066	1523	No data	No data	5689	7410	No data	0.0285	1206555	21503	13509	7994
1997	394	360	10311	1738	1498	222	7305	9224	No data	0.0266	1191665	21625	13351	8274
1998	442	425	11955	2181	1964	206	9020	11119	No data	0.0255	1203147	22049	13501	8548
1999	471	469	13712	2196	1975	211	9614	11930	No data	0.0250	1177669	22538	13231	9307
2000	511	503	14228	2343	2096	238	10005	12274	No data	0.0229	1190547	23621	13394	10227
2001	552	545	15753	2705	2422	275	10942	13158	No data	0.0206	1170662	23166	13181	9985
2002	578	568	18636	2972	2698	259	12654	15228	No data	0.0239	1153855	24605	13010	11595
2003	590	584	22047	3526	3232	287	14697	17400	No data	0.0229	1123610	24810	12703	12107
2004	627	620	23916	3612	3392	217	15426	18168	No data	0.0223	1110721	25157	12587	12570
2005	641	626	26308	3784	3559	224	16275	19112	No data	0.0201	1062530	24130	12061	12069
2006	575	572	28211	3424	3250	169	17171	19587	No data	0.0219	1092674	24539	12421	12118
2007	606	603	29165	3221	3078	139	17620	19595	3914	0.0228	1089818	24081	12403	11678
2008	609	603	32511	2139	2099	38	20422	21704	2670	0.0198	1091156	22359	12421	9938

Note: a estimation using vital statistics (Ooki, 2011)
b approximation derived from the 1995–1999 values
Regarding the symbols 'X', 'Y', 'k', 'T', 'M', 'S', and 'I', see text.

Data source of ART (in Japanese):
http://www.jsog.or.jp/activity/pdf/Rinri_report6209.pdf
http://www.jsog.or.jp/activity/pdf/Rinri_report6109.pdf
http://www.jsog.or.jp/activity/pdf/Rinri_report6006.pdf
http://www.jsog.or.jp/activity/pdf/Rinri_report5909.pdf
http://www.jsog.or.jp/activity/pdf/Rinri_report5808.pdf
http://www.jsog.or.jp/activity/pdf/Rinri_report5710.pdf
http://www.jsog.or.jp/activity/pdf/Rinri_report5701.pdf
http://www.jsog.or.jp/activity/pdf/Rinri_report5510.pdf
http://www.jsog.or.jp/kaiin/html/Rinri/Rinri_report5308.html
http://www.jsog.or.jp/kaiin/html/Rinri/Rinri_report5207.html
http://www.jsog.or.jp/kaiin/html/Rinri/Rinri_report5106.html

However, it is possible to estimate the numbers or rates of non-ART multiples under several conditions, as will be discussed later.

Japan's rapid increase in the observed number of multiple births and the multiple-birth rate in the past 30 years is mainly due to iatrogenic, not spontaneous, multiple births of advanced-age mothers, especially in the 30- to 34-year-old group (Ooki, 2011). The purpose of the present study was to estimate the effect of ART and non-ART ovulation stimulation fertility treatment on the number and rate of multiple live births during this time period in Japan using two independent data sources, ART statistics and vital statistics, which cannot be directly linked.

Materials and Methods

OUTLINE OF JAPANESE ART DATA

Almost all medical institutions performing ART are registered with the Japan Society of Obstetrics and Gynecology (JSOG). The JSOG administers questionnaire surveys for these medical institutions. Some of the survey data are presented in annual reports (with no information available in English). All available ART statistics on multiple births were gathered, combined and reanalyzed.

The JSOG has gathered ART data from registered institutions since 1985. However, there is incomplete data on the total number of deliveries and live births from 1985-1988, and the author therefore used the 1989–2008 (the latest) data. The data items were not necessarily constant throughout the surveillance period, and data on multiple deliveries/births were not available until 2007. The total number of live deliveries (X), i.e. number of mothers and live births (Y), were the only available data throughout 1989-2008. There was no information on the combination of live births and stillbirths among multiples. The numbers of multiple live births according to subtype (e.g., twins, triplets) were presented only in the 2007 and 2008 surveys. Among multiple deliveries that contained stillbirths, definitions of 'live delivery' and 'live births' were as follows: For the multiple pregnancies, the mothers who had at least one live birth neonate were counted as a live delivery. For the multiple births, the births were counted as live only when all neonates in the pair were born alive. For example, if both members of certain twin pairs were alive, then they are counted as two live births (neonates). On the other hand, when one member of certain twin pairs are alive (the other a stillbirth), then they are counted as no live births (neonates), or as one live singleton. No data on maternal age were available. ART was divided into in vitro fertilization, intracytoplasmic sperm injection and other methods. All these methods were treated as ART in the present study.

Table 1 shows the raw data used in the present study, including both ART by JSOG and vital statistics by the Ministry of Health, Labor and Welfare. The response rate (= responding institutions/total institutions) for ART surveillance was not high during the early periods, as calculated using Table 1.

STATISTICAL ANALYSES

This study defined the rate of multiple births as the proportion of all live multiple births per 1,000 live births.

1. Estimation of Numbers and Rates of ART Multiples

It was impossible to calculate the number of ART multiple births directly due to insufficient data, as mentioned in the definitions of 'live births'. Since the following estimation contains many assumptions, the minimum and maximum possible values are provided for reference.

The total number of ART multiple live births was estimated by the following method under the assumption that the percentage of triplets/+ in the total ART births was sufficiently small. Only when the total number of mothers with a live delivery (X = a+b+c) and live neonate (Y = a+2b+3c), where all neonates of the pair are born alive in the case of multiple births, is known, where a, b and c denotes the number of mothers of singletons, twins, and triplets, respectively, can the total number of ART multiple births (2b+3c) be approximated as 2(Y-X) = 2b+4c. To adjust for the excess of 'c' (2b+4c = 2b+3c+c), X*t was subtracted, where 't' denotes the triplet/+ pregnancy rate in ART pregnancies, assuming that the triplet/+ pregnancy rate is equal to the triplet/+ live births rate. Thus, the minimum estimation formulae of 2(Y-X)-X*t was obtained.

In the present data, X includes mothers who had multiples, even if some were stillbirths. To exclude mothers of live-stillbirth pairs in multiples, the author used the general stillbirth rates of live-stillbirth twin pairs (k), including both spontaneous and iatrogenic stillbirths, from vital statistics. The number of twin mothers with live-stillbirth pairs (X') was thus estimated by multiplying the total number of multiple deliveries (b+c) and live-stillbirth rates in twin pairs (k). The total number of multiple deliveries in the total ART pregnancies was approximated as Y-X (=b+2c). Thus, X' is approximated as (Y-X)k. The approximation formula for the ART live multiples was 2(Y-(X-X')) = 2(Y-(X-(Y-X)k)) =2(Y-X)(1+k). Finally, the inverse of the number of response rates was multiplied, assuming that the mean number of ART multiples in responding and non-responding institutions is equal. The final approximation formula for the number of ART multiples was then 2(Y-X)(1+k)/(response rate), which gives a maximum estimation value. As the stillbirth rates of twin pairs were included in the vital statistics after 1995, the 1989–1994 values were extrapolated using approximation formula derived from the 1995-1999 values (quadratic function, $R^2 = .999$).

The validity of the estimation method mentioned above was determined using 2007 and 2008 data on the observed number of live multiple births with ART. As the estimated error was nearly 1–2% (observed number was 3,914 and estimated minimum was 3,854; the difference

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was 1.53% in 2007, the observed number was 2,670 and the estimated maximum was 2,641, while the difference was 1.09% in 2008) for both years, this estimation method was valid, at least for the most recent years.

Using the estimated number of ART multiples between 1989–1992, and the fact that the first ART baby was born in Japan in 1983, the number of ART multiple births between 1984–1988 was interpolated using an approximation formula derived from the 1983 and 1989–1992 values. The number of ART multiples between 1979–1982 was set as equal to zero.

2. Estimation of Numbers and Rates of Non-ART Multiples

Iatrogenic multiples could be estimated by subtracting spontaneous multiples from all multiple births, which are presented as vital statistics. Moreover, the number of maximum (or minimum) non-ART iatrogenic multiple births was estimated by subtracting the minimum (or maximum, corresponding non-ART) ART multiples from the total iatrogenic multiples.

The number of spontaneous and iatrogenic multiple births during 1977–2008 were estimated assuming that the spontaneous multiple-birth rates according to maternal age class would be constant and equal to those of the baseline values, the weighted means between 1974 and 1976, when the occurrence of multiple births by fertility treatment were negligible. The details and limitations of this method, a kind of age standardization, are described elsewhere (Ooki, 2011). The spontaneous multiple-birth rate according to maternal age is nearly constant irrespective of the birth year, at least in Japan (Imaizumi & Inouye, 1979). Using this fact, the number of spontaneous (S) and iatrogenic (I) multiple live births in a certain age class could be estimated as $S = T^*s$ and $I = M - T^*s$, respectively (T, total number of live births; M, total number of multiple live births; S, total number of spontaneous multiple live births; I, total number of iatrogenic multiple live births; s, the proportion of spontaneous multiple births of a certain age class, that is, the age class specific multiple-birth rate). By summing up the number of all age classes, the total number of multiple births according to the method of conception (iatrogenic or spontaneous) could be estimated and the multiple-birth rate then calculated.

Results

Figure 1 shows secular trends of the multiple pregnancy rate in the total ART pregnancies, calculated using the values in Table 1. The twinning rate gradually decreased to 14% in 2005, then decreased rapidly to 7% in 2008. The triplets/+ rate gradually linearly decreased from 2% in 1997 to almost 0% in 2008.

Figure 2 shows the percentage of twin pregnancies in the total ART multiple pregnancies, calculated using the values in Table 1. In recent years, the percentage has tended to increase linearly, reaching 98% in 2008.

Figure 3 shows the estimated minimum and maximum number and rates of ART and non-ART live multiples with the total iatrogenic and spontaneous multiple births. As mentioned in the METHODS section, the 1984–1988 values for ART were interpolated using approximation formula (cubic function, $R^2 = .998$). The percentage dif-

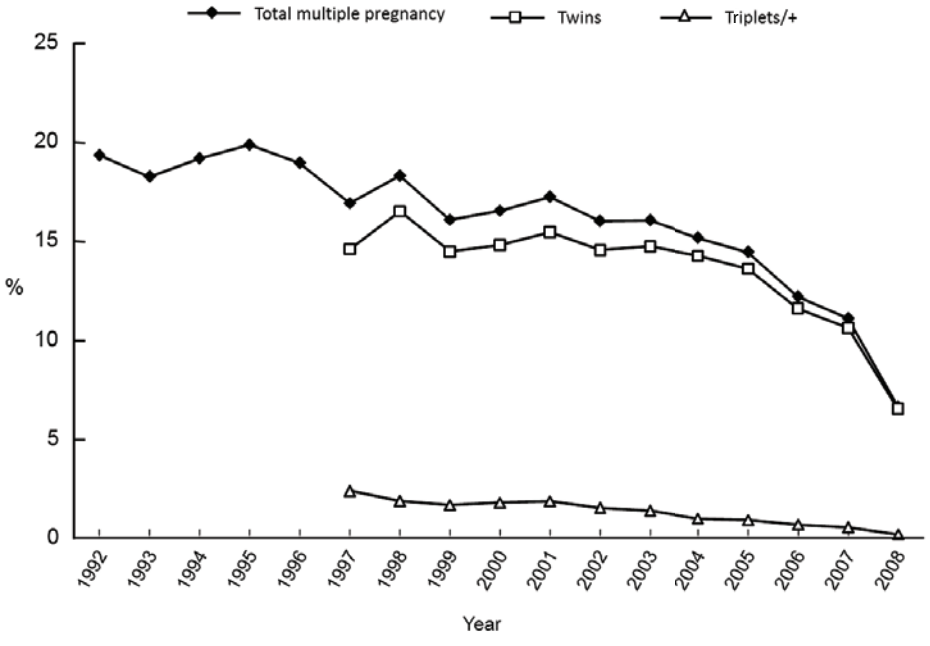

FIGURE 1
Percentage of multiple pregnancies in ART.

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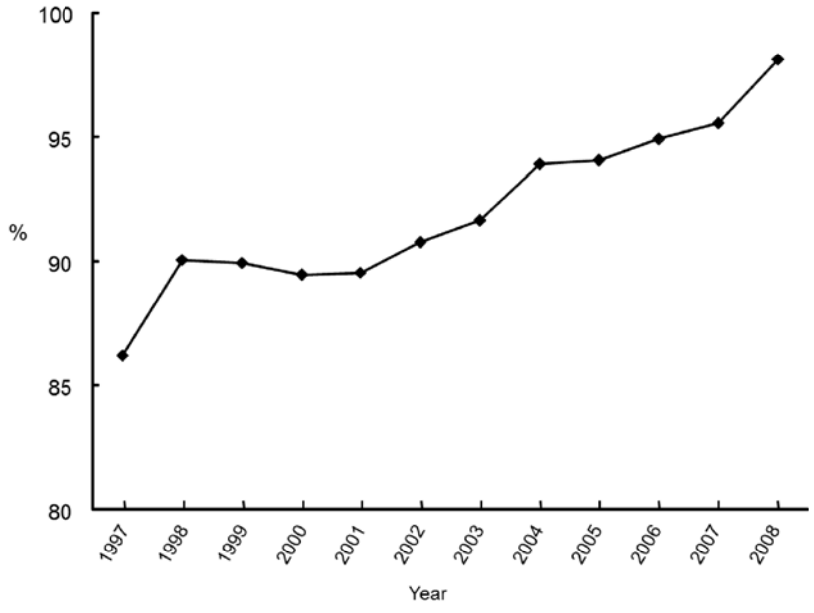

FIGURE 2

Percentage of twin pregnancies in ART multiple pregnancies.

ference between the maximum and minimum estimation in total iatrogenic multiples (= [maximum – minimum]/total*100) was small, within 4% after 1999, partly reflecting the more accurate observed number obtained in the ART survey, which had a very high response rate.

Non-ART multiples tended to gradually increase overall, whereas ART multiples increased from 1989 to 2005, then rapidly decreased. The percentage of non-ART multiple births in iatrogenic multiples tended to be higher than ART multiples. Almost all of the iatrogenic multiples occurred due to non-ART before 1988. The percentage of ART multiples in iatrogenic multiples was small in 1989 (6–10%), but gradually increased, peaking at around 50% between 1998–1999. The percentage rapidly decreased beginning in 2005, falling to 26–27% in 2008. The percentage of non-ART multiples (33%) in total multiples was estimated to be about three times more than ART multiples (11–12%) in 2008.

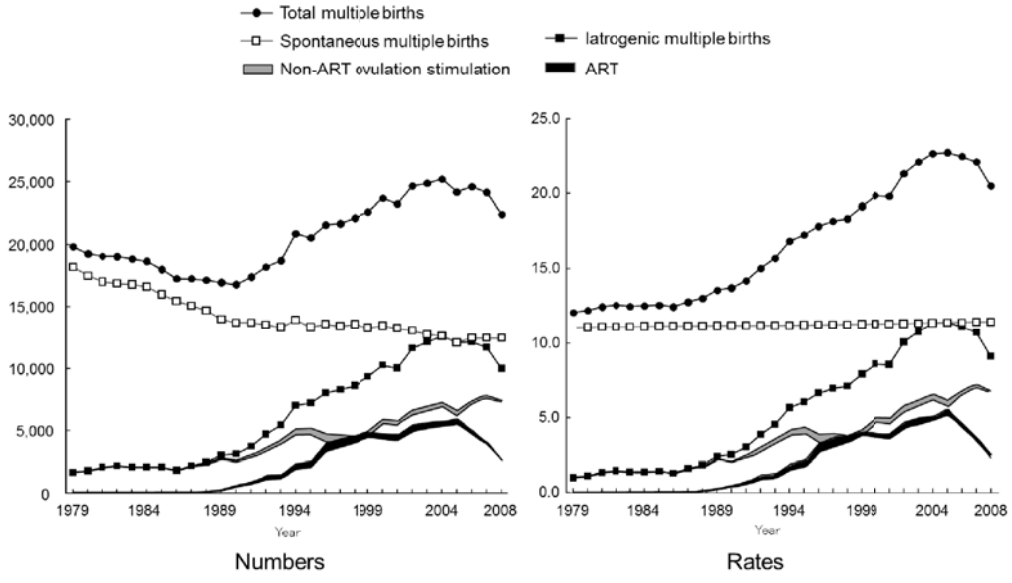

FIGURE 3

Estimated numbers and rates of multiple births according to the method of conception.

Note: The minimum and maximum possible values of ART and non-ART were provided. The number of maximum (or minimum) non-ART iatrogenic multiple births was estimated by subtracting the minimum (or maximum, corresponding non-ART) ART multiples from the total iatrogenic multiples.

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Discussion

The present study determined the number of ART and non-ART multiples in iatrogenic multiples during the past 30 years in Japan. Even though the author had to use several assumptions to make the present estimation, the estimation was made because the secular trend of non-ART multiples is unknown, in contrast to its importance. If precise data on iatrogenic or ART pregnancies/births were offered annually, there would be no need for this cumbersome estimation. Given the limitation of available data, the estimation method itself is not to be discussed in detail. However, the small estimated error in 2007 and 2008 (nearly 1–2%) showed that there were no serious mistakes in the present estimation, at least for the most recent years.

The 1996 JSOG guidelines for ART stated that embryo transfer should be limited to three, while the 2008 guidelines specified single embryo transfer (Gelbaya et al., 2010). The secular trends of ART multiples may reflect these policies. As shown in Figures 1 and 2, ART multiple pregnancies have rapidly decreased in recent years, especially that of triplets/+. On the other hand, as shown in Table 1, the total numbers of ART live deliveries (X) and births (Y) are still increasing, suggesting that the number of ART singletons have recently increased. As shown in Figure 3, the rapid increase of ART multiple births after the late 1980s slowed between 1994 and 2005, and then reversed, rapidly decreasing after 2005. These trends reflect the ART policy in Japan.

From 2005–2008, the percentage of ART multiples decreased linearly. If this trend continues, then in three years the effect of ART on multiple births will be undetectable in Japan. However, non-ART multiples will not necessarily decrease. In 2008, 33% of infants from multiple gestations born in Japan were conceived with a non-ART ovulation treatment, equating to over 7,000 live births.

Several hospital-based studies with relatively small sample sizes have reported the percentage of multiples with non-ART fertility treatments. According to Pinborg et al. (2003), 17% (n = 566) of non IVF/ICSI twins received ovulation stimulation in 1997.

In a New Zealand study with data for the period 1996-2001, Bolton et al. (2003) estimated that multiple births conceived by ovulation induction constituted 37% (n = 201) of the multiples from fertility treatment.

Jones (2007) used US vital statistics and CDC (Centers for Disease Control) ART data, and estimated the contribution of 2000–2003 non-ART (ovulation induction and enhancement) fertility treatment in multiple births. The method used in this study was very simple; the natural twin and triplet/+ birth rate of 1980 was constant and applied to the years 2000–2003. The results show that the percentage of non-ART multiples in the total multiple births increased slightly from 31 to 34%, and ART multiples in the total multiple births also increased from 7% to 9% (recalculation by present author using Table 1 and Table 2 in the article, which showed the total and non-ART twin and triplet/+ births, respectively).

In a recent study, Schieve et al. (2009) used US vital statistics and CDC's ART data to estimate the contribution of non-ART ovulation stimulation fertility treatment to multiple births in the United States. The percentage of iatrogenic multiple births due to fertility treatment in 2005 was 40.1% (17.3% for ART, 22.8% for non-ART). These values are about 10% lower than the present results in the same year (50.0% in total, 22.8–24.6% for ART, 25.5–27.2% for non-ART). Although secular trends in the United States are unclear, ART multiples still seemed higher in Japan during this period.

However, according to Park et al. (2010), the total ART multiple births was 14.7% of the entire multiple births in 2006 in Korea (19.2–20.2% in Japan).

Estimations of the percentage of ART and/or non-ART multiple births vary widely, according to the reports. These cross-sectional results should be interpreted carefully, since secular trends differ between countries due to the influence of ART policies. For example, the multiple birth rate was still increasing in Korea even in 2008, while it declined beginning in 2006 in Japan.

In estimating the influence of fertility treatment, non-ART should be considered. According to Tandberg et al. (2007), the twinning rate increased 50% in Norway during the years 1988–2004, even after excluding pregnancies from ART. These researchers concluded that neither pregnancies from ART, nor delayed child bearing, could explain the rise in the twinning rate. However, the effect of non-ART fertility treatment, which could be strongly confounded with maternal age, was not considered.

The author demonstrated that in Japan, non-ART ovulation induction is currently associated with a higher percentage of multiple births than ART; thus, non-ART treatments are very likely associated with an even higher proportion of multiple gestation pregnancies overall. To date, no accurate population-based tracking system exists for births resulting from non-ART treatment.

This study has the following limitations. First, in estimating ART multiples, the author assumed that the percentage of triplets/+ in total ART births was significantly lower than that of twins. This assumption may not be true in the earlier years of ART data collection, as shown in Figure 2. The percentage of triplets/+ pregnancies in total multiples was more than 10% before 2002, although the percentage of triplets/+ is likely to be lower in deliveries than in pregnancy, since abortion or stillbirths are more likely to occur in triplets/+ than in twins. Second, the author assumed that the general, including both spontaneous and iatrogenic, stillbirth rates of live-stillbirth twin pairs (k) per multiple delivery (maternity) was equal to that in ART multiple delivery. Since the general stillbirth rate includes artificial abortion, this

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value may be higher than that in ART. If this is the case, then estimation by the approximation formula of the present study slightly favors overestimation of ART multiple births. Third, the correction of the response rate of the ART survey had to have been inaccurate in earlier periods, since the response rates were low between 1989 and 1997. If institutions that did not perform ART did not respond, then the correction the author made for the response rate overestimates ART multiple births. Nevertheless, the present results offer an important overview of the secular trend of ART and non-ART iatrogenic multiples.

Mothers of multiple-birth children are clearly older than mothers of singletons in Japan according to an estimation using vital statistics (Ooki, 2011), and in recent years, about 40–50% of mothers of multiples have undergone fertility treatment. Their advanced age makes the physical, mental and social burden of rearing two babies at once even greater, which could increase the risk of maternal problems such as postpartum depression, child rearing difficulties, and in the worst case scenario, child abuse (Bryan et al., 1997; Denton, 2005; Thorpe et al., 1991)

Although the number of iatrogenic multiples has recently decreased due to the decrease of ART multiple births based on the single embryo transfer policy (Gelbaya et al., 2010), the relative contribution of non-ART multiple births are increasing. Considering the medical and social impact of all types of iatrogenic multiple births (Callahan & Greene, 1998; Hall & Callahan, 2005; Ooki, 2006; Scholz et al., 1999), there is an urgent need for a hospital-based monitoring system for fertility treatments, especially for non-ART and multiple births.

In conclusion, the present study demonstrated that in contrast to the recent rapid decrease of ART multiple births, the relative impact of non-ART multiples, especially twins, are increasing and should not be overlooked.

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