

Research Paper

The Effect of Single Embryo Transfer on Perinatal Outcomes in Japan

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Received: 2014.08.17; Accepted: 2014.11.04; Published: 2015.01.01

Abstract

Objective: In 2007 and 2008, the Japan Society for Reproductive Medicine and the Japan Society of Obstetrics and Gynecology issued a recommendation for single embryo transfer (SET). Thereafter, SET was implemented in 73% of *in vitro* fertilization (IVF) cases in Japan. The purpose of this study was to evaluate the effects of compliance with the SET recommendation on perinatal outcomes.

Methods: An electronic audit of the perinatal database of the Japanese Society of Obstetrics and Gynecology was conducted from 2001 through 2010. The database comprised data of 610,726 women. Totally, 20,923 women conceived through IVF. To compare perinatal outcomes, these women were categorized into two study groups depending on whether they conceived before (2004–2005, $n = 3,865$) or after (2009–2010, $n = 6,842$) the SET recommendation statement was issued.

Results: The proportion of women who conceived through IVF increased from 1.3% in 2001 to 4.8% in 2010. Compliance with the SET recommendation led to a decrease in the incidence of twin pregnancies (33.9% versus 13%, $p < 0.01$), incidence of preterm delivery (odds ratio [OR]: 0.54, 95% confidence interval [CI]: 0.50–0.59), low birth weight (OR: 0.42, 95% CI: 0.39–0.45), and neonatal intensive care unit admission (OR 0.70, 95% CI 0.65–0.76), but an increase in the incidence of monozygotic twins (1.6% versus 2.5%, $p < 0.01$).

Conclusion: Compliance with the SET recommendation improved perinatal outcomes by reducing the incidence of twin pregnancies.

Key words: *in vitro* fertilization, twin pregnancy, monozygotic twin, obstetric outcome, perinatal outcome.

Introduction

Since the birth of the first baby conceived through *in vitro* fertilization (IVF) in 1978, assisted reproductive technology (ART) has been a highly successful and widely employed modality for treating infertility. Initially, because inadequate embryo culture techniques resulted in a poor success rate following IVF, clinicians transferred multiple embryos to maximize the chances of conception. As advances in culture techniques improved the pregnancy rate of

IVF, multiple-gestation pregnancies increasingly became a problem (1, 2).

Recently, elective single embryo transfer (eSET) has been adopted by ART centers worldwide as a means to reduce the multiple pregnancy rates (3, 4). In European countries, national legislation restricts the number of embryos transferred (3, 5). In 1998, the American Society for Reproductive Medicine issued practice guidelines on the number of embryos to

transfer, and has periodically revised these guidelines, most recently in 2013 (4). These guidelines recommend consideration of eSET in women with a favorable prognosis aged under 35. Single-embryo transfer (SET) has been slowly adopted in many countries, and a few studies have assessed the contribution of the eSET strategy on perinatal outcomes (6-8).

In Japan, the Japan Society for Reproductive Medicine (JSRM), concerned about the number of multiple births resulting from ART, prepared concrete recommendation regarding the number of embryos transferred in 2006, and developed specific guidelines about the number of embryos to be transferred in March 2007(9, 10). In 2008, the Japan Society of Obstetrics and Gynecology (JSOG) issued a recommendation for SET for all cases except in cases of repeated IVF failure or in patients >35 years where two embryos could be transferred (11).

This study evaluates the effect of compliance with the SET recommendation on perinatal outcomes in pregnancies conceived through IVF using a large Japanese database.

Materials and Methods

The study protocol was reviewed and approved by the Institutional Review Board of Nippon Medical School, Tokyo, Japan. We selected a case-control design to evaluate the effect of the SET recommendation statement on the perinatal outcomes of pregnancies conceived through IVF.

Data in this study derived from the perinatal database of JSOG. This nationwide registry was established in 1974. Detailed descriptions of the database have been published previously (12, 13). In brief, the attending physicians at 139 tertiary centers of the Perinatal Research Network in Japan collected data annually on all pregnant women in an offline clinical database with a common format. The data were sent to the perinatal committee of JSOG, where quality control for the database was assessed.

We used data of 638,268 deliveries reported between 2001 and 2010. Gestational age was determined on the basis of menstrual history, prenatal examination, and ultrasound findings, such as gestational sac diameter, crown-rump length, and biparietal diameter. Linked data included information on maternal characteristics, such as maternal age, parity, cigarette smoking, and alcohol consumption during pregnancy, history of treatment for infertility (ovulation stimulation, intrauterine insemination, or IVF-embryo transfer), medical complications, and pregnancy complications. Fetal and infant outcomes were also

routinely recorded by attendants at delivery. These data conform to uniform coding specifications, have passed a rigorous quality check, and have been edited and reviewed. The current study limited the analysis to women who delivered a live birth or stillbirth at 22 weeks of gestation or more. After excluding missing data, 610,719 pregnancies were included in this study.

Two study groups were created according to whether they conceived before or after the SET recommendation statement was issued. We did not adopt the data from 2006 through 2008 to exclude influence of the shift period, because the guidelines on JSRM were announced for one year before 2007 by their journal and website, and JSOG issued a statement of recommendation for SET in 2008. The IVF group included both women who received eggs spontaneously fertilized by sperm *in vitro*, or eggs fertilized by intracytoplasmic sperm injection (ICSI), followed by transfer of the embryo back into the uterine cavity. However, further information on the use of ICSI was unavailable in our database.

Data were analyzed using SPSS Statistics version 17.0 (SPSS Inc., Chicago, IL, USA) and Excel (Microsoft, Redmond, WA, USA). Statistical analysis was performed using the Mann-Whitney U test for continuous variables, such as maternal age, body mass index (BMI), birth weight, and the chi-squared test for categorical variables. A p value of <0.05 was considered statistically significant. Logistic regression analysis was used to compare adjusted odds ratios (OR) and 95% confidence intervals (CI) for adverse obstetric and perinatal outcomes before and after the issue of the SET recommendation.

Results

In total, 20,923 (3.4%) women conceived through IVF during the study period. The proportion of women who conceived through IVF increased dramatically from 1.3% in 2001 to 4.8% in 2010 (Figure 1). From 2001-2006, the incidence of twin pregnancies conceived through IVF increased concurrently with the proportion of women who conceived through IVF. After the issue of the SET recommendation statement in 2007 and 2008, although a marked increase in the proportion of pregnancies conceived through IVF was evident, the incidence of twin pregnancies conceived through IVF significantly decreased (Figure 1). The incidence of twin pregnancies among the pregnancies conceived with IVF was significantly decreased from 33% to 13% due to a reduction of dichorionic twins. In contrast, the incidence of monochorionic twins conceived through IVF continuously increased between 2001 and 2010, from 1.1% to 2.6% (Figure 2).

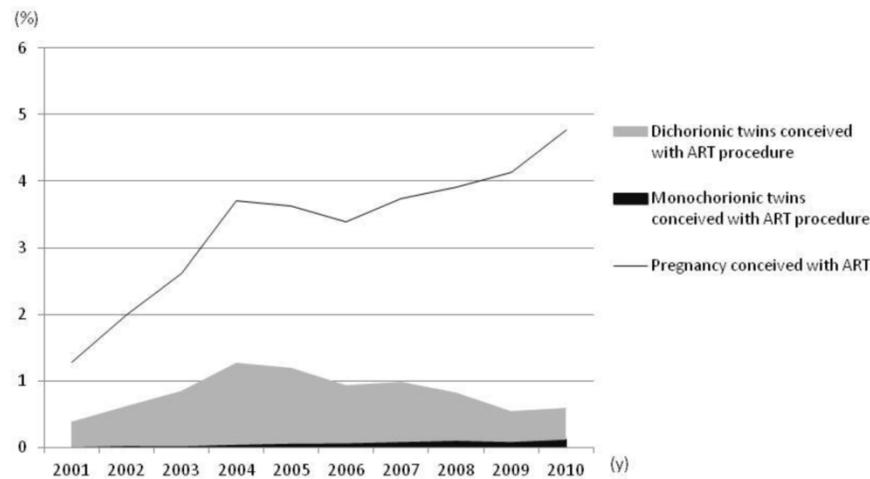


Figure 1. Changes in incidence of the pregnancies conceived with IVF and twin pregnancies after IVF treatment among the total pregnancy. Pregnancies from IVF increased dramatically from 1.3% in 2001 to 4.8% in 2010. Twin pregnancies conceived through IVF increased concurrently with the proportion of women who conceived through IVF, but after the SET recommendation statement was issued in 2007 and 2008, the incidence of twin pregnancies conceived through IVF significantly decreased.

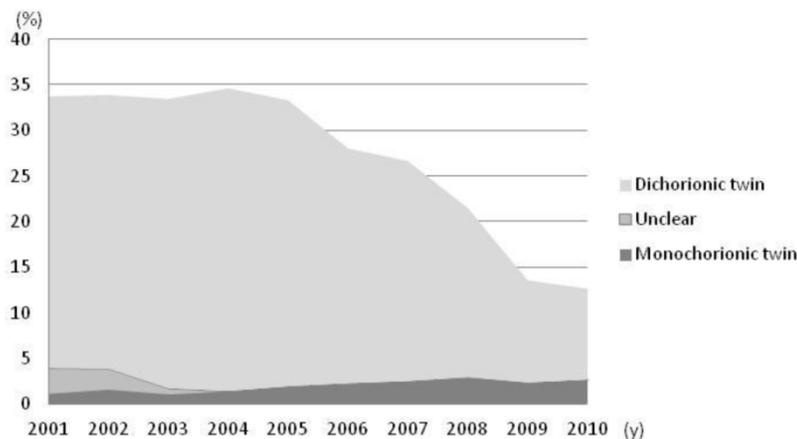


Figure 2. Changes in incidence of twin pregnancies conceived with IVF. The incidence of twin pregnancies among the pregnancies conceived with IVF was significantly decreased from 33% to 13% with the reduction of dichorionic twins. In contrast, the incidence of monozygotic twins conceived through IVF continuously increased between 2001 and 2010, from 1.1% to 2.6%.

To evaluate the effect of compliance with the SET recommendation on the perinatal outcomes of pregnancies conceived through IVF, women who conceived through IVF were categorized into two study groups depending on whether they conceived before (2004–2005, $n = 3,865$) or after (2009–2010, $n = 6,842$) the SET recommendation statement issued. The maternal characteristics of the two study groups are summarized in Table 1. Maternal age and the proportion of women with preexisting medical complications tended to be higher in 2009–2010 than in 2004–2005. The proportion of nulliparous women decreased in 2009–2010. No significant differences were observed in BMI and alcohol consumption between the two groups.

The overall incidences of obstetric and perinatal complications in the study population are shown in Table 2. The incidence of multiple pregnancies dras-

tically declined after the issue of the SET recommendation (twins: 33% versus 13%; triplets: 2.1% versus 0.3%; $p < 0.01$). However, the incidence of monozygotic twins was significantly higher in 2009–2010 (2.5%) than in 2004–2005 (1.6%; OR 1.54, 95% CI 1.15–2.07). The incidence of cesarean section decreased after the SET recommendation was issued (OR 0.71, 95% CI 0.66–0.77). Marked decreases in the incidences of threatened miscarriage (OR 0.52, 95% CI 0.44–0.62), preterm labor (OR 0.51, 95% CI 0.47–0.56), and preterm delivery at <37 weeks (OR 0.54, 95% CI 0.50–0.59) and at <34 weeks (OR 0.61, 95% CI 0.54–0.69) were also evident in 2009–2010.

Delivery of low-birth weight infants (<2,500 g) was common among women who conceived through IVF. In 2004–2005, over a half of newborns were low-birth weight infants. Compared with the 2004–2005 group, the incidences of low-, very low-,

and extremely low-birth weight infants significantly decreased in 2009–2010, at 52.3% versus 31.5%, 9.4% versus 6.5%, and 3.9% versus 2.9%, respectively. The incidence of small-for-gestational-age infants also decreased in 2009–2010 (OR 0.55, 95% CI 0.48–0.63). Compliance with the SET recommendation was associated with a decrease in adverse neonatal outcomes, such as neonatal intensive care unit (NICU) admission (OR 0.70, 95% CI 0.65–0.76), and infant death (OR 0.71, 95% CI 0.55–0.93).

Table 1. Maternal characteristics of the study population.

	2004 - 2005	2009 - 2010	P
	n = 3865	n = 6842	
Maternal age (y)*	35 (19 - 54)	37 (21 - 58)	< 0.01
-34	1743 (45.3)	2075 (30.3)	< 0.01
35 - 39	1566 (40.7)	3234 (47.3)	
40-	536 (13.9)	1531 (22.4)	
unclear / missed	20	2	
Parity			
Nulliparous	3201 (82.9)	5228 (76.5)	< 0.01
Multiparous	662 (17.1)	1607 (23.5)	
Unclear / missed	2	7	
Body mass index*	20.5 (14.6 - 40.7)	20.5 (11.9 - 50.2)	0.39
-18.4	228 (15.5)	933 (16.0)	0.88
18.5 - 24.9	1096 (74.5)	4273 (73.4)	
25.0 - 29.9	113 (7.7)	472 (8.1)	
30.0-	35 (2.4)	140 (2.4)	
unclear / missed	2393	1024	
Smoking in pregnancy			
Yes	79 (2.3)	64 (1.0)	< 0.01
No	3356 (97.7)	6515 (99.0)	
unclear/missed	430	263	
Alcohol consumption in pregnancy			
Yes	84 (2.5)	165 (2.5)	0.89
No	3293 (97.5)	6351 (97.5)	
unclear/missed	488	326	
Preexisting medical complications			
Yes	1209 (31.3)	2749 (40.2)	< 0.01
No	2656 (68.7)	4093 (59.8)	
Diabetes mellitus			
Yes	89 (2.3)	219 (3.2)	< 0.01
No	3775 (97.7)	6623 (96.8)	
Hypertension			
Yes	21 (0.5)	80 (1.2)	< 0.01
No	3844 (99.5)	6762 (98.8)	
Thyroid disease			
Yes	80 (2.1)	307 (4.5)	< 0.01
No	3785 (97.9)	6535 (95.5)	

Values are %. * median (range). NA: not applicable.

Discussion

Our data show that compliance with the SET recommendation successfully reduced multiple pregnancies conceived through IVF and dramatically reduced multiple pregnancy-related complications.

The proportion of pregnancies conceived through IVF has rapidly increased in Japan. Until 2007, the incidence of twin pregnancies conceived

through IVF increased *pari passu* with the rate of pregnancies conceived through IVF (Figure 1). Previous studies (14, 15) have suggested that multiple pregnancies are the most serious complication of IVF for both mother and child. The main risk factor of ART treatment for dizygotic twinning and high-order multiple pregnancies is the transfer of more than one embryo (16, 17). It is established that multiple gestations carry a high risk of perinatal morbidity and mortality and are associated with increased risk of miscarriage, preterm delivery, and cesarean section compared with singleton pregnancies (14, 18, 19).

SET has been gradually accepted worldwide as a means to reduce multiple pregnancy rates (5). Recently, several studies (6, 20–24) have reported the efficacy of SET, which yields an excellent pregnancy rate and drastically decreases twin pregnancies. Other retrospective studies (25, 26) have demonstrated that SET after transfer of thawed embryos results in similar pregnancy rates as double-embryo transfer and significantly decreased multiple pregnancy rates. However, the number of SETs performed remains modest in many countries. In the US, only 13.5% of ART cycles employed SET in 2009 (27) and even in Europe, only 22% of transfers were SET in 2008 (3). Conversely, in Japan, the proportion of SET among IVF cycles was high: 50% in 2007, 63.6% in 2008, 70.6% in 2009, and 73% in 2010(28) although there was no contract punitive clause for non-observance.

Our results indicate that the incidence of multiple pregnancies drastically declined after the SET recommendation statement was issued. Simultaneous to the reduction in multiple pregnancies, reductions in the incidences of neonatal resuscitation, neonatal NICU admission, preterm delivery, and cesarean section were evident. These results suggest that a higher ratio of SET among IVF cycles in other countries, as Japan, could have profound public health implications by reducing the occurrence of iatrogenic twin pregnancies.

On the other hand, despite the reduction in twin pregnancies, we found that the incidence of monozygotic twins conceived through IVF increased from 1.6% in 2004–2005 to 2.5% in 2009–2010. To date, several possible explanations have been proposed for this increase in monozygotic twinning. Several authors have speculated that extended culture and/or an increase in the use of ICSI to improve the pregnancy rate could contribute to the increased incidence of monozygotic twins (29–32). Some studies (29, 30) have concluded that the risk of monozygotic twinning is increased when culture is extended to the blastocyst stage. Another report (31) suggested that the risk of monozygotic twinning may relate to the composition of culture medium. A further report (32) found no

association between the type of culture medium and the risk of monozygotic twinning, although there was a 24-fold increased risk of monozygotic twinning in cycles involving both ICSI and extended culture. We acknowledge that our results cannot support any of these possibilities: the inability to identify fresh, frozen-thawed, cleavage-stage embryo transfer, blastocyst transfer, or ICSI cycles is a limitation of our database.

In conclusion, this study indicates that compliance with the SET recommendation improved peri-

natal outcomes through a reduction in multiple gestation rates. These results suggest that a higher proportion of SET among IVF cycles in other countries as in Japan, could have profound public health implications by reducing the occurrence of iatrogenic twin pregnancies.

Our results also demonstrate that the incidence of monochorionic twins increased with the increased compliance with the SET recommendation, which requires further study.

Table 2. Comparison of perinatal outcome before (2004-2005, n=3865) and after (2009-2010, n=6842) the SET recommendation statement issued.

Outcome	2004 - 2005 year		2009 - 2010 year		OR (95%CI)	
	Mother	n = 3865	n = 6842	Infant		n = 7780
Pregnancies						
Singleton		2472 (64.0)	5927 (86.6)		< 0.01	3.65 (3.32 - 4.02)
Twin		1311 (33.9)	892 (13.0)		< 0.01	0.29 (0.27 - 0.32)
Monochorionic twin		62 (1.6)	168 (2.5)		< 0.01	1.54 (1.15 - 2.07)
Dichorionic twin		1246 (32.2)	719 (10.5)		< 0.01	0.25 (0.22 - 0.27)
Unclear		3	5			
Triplet		82 (2.1)	23 (0.3)		< 0.01	0.16 (0.10 - 0.25)
Type of delivery						
Spontaneous cephalic		1338 (34.6)	2798 (40.9)		< 0.01	1.31 (1.20 - 1.42)
Instrumental		285 (7.4)	634 (9.3)		< 0.01	1.28 (1.11 - 1.48)
Cesarean		2220 (57.4)	3345 (48.9)		< 0.01	0.71 (0.66 - 0.77)
Others		22 (0.6)	65 (1.0)		0.04	1.68 (1.03 - 2.72)
Threatened miscarriage		281 (7.3)	269 (3.9)		< 0.01	0.52 (0.44 - 0.62)
Preterm labor		1269 (33.0)	1374 (20.1)		< 0.01	0.51 (0.47 - 0.56)
PIH		212 (5.5)	384 (5.6)		0.78	1.02 (0.86 - 1.22)
Placenta previa		119 (3.1)	243 (3.6)		0.2	1.16 (0.93 - 1.45)
Placenta accreta		29 (0.8)	95 (1.4)		< 0.01	1.86 (1.23 - 2.83)
Postpartum hemorrhage		207 (5.4)	443 (6.5)		0.02	1.22 (1.03 - 1.45)
Preterm delivery <37w		1271 (32.9)	1436 (21.0)		< 0.01	0.54 (0.50 - 0.59)
Preterm delivery <34w		483 (12.5)	547 (8.0)		< 0.01	0.61 (0.54 - 0.69)
blood loss during delivery (g*)		747 (2-5448)	716 (7 - 6000)		0.03	
Maternal death		0 (0.0)	2 (0.0)		0.54	NA
Infants						
Birthweight (g*)		2459 (252 - 4910)	2800 (50 - 4790)		<0.01	
< 2500g		2783 (52.3)	2440 (31.5)		<0.01	0.42 (0.39 - 0.45)
< 1500g		502 (9.4)	504 (6.5)		<0.01	0.67 (0.59 - 0.76)
< 1000g		205 (3.9)	221 (2.9)		<0.01	0.73 (0.60 - 0.89)
SGA		534 (10.0)	447 (5.7)		<0.01	0.55 (0.48 - 0.63)
UmApH <7.0		13 (0.5)	40 (0.7)		0.34	1.36 (0.72 - 2.54)
Apgar score (5min) <7		229 (4.3)	278 (3.6)		0.04	0.83 (0.69 - 0.99)
Neonatal resuscitation		2071 (39.3)	2205 (28.6)		<0.01	0.62 (0.58 - 0.67)
NICU admission		1460 (27.3)	1628 (20.9)		<0.01	0.70 (0.65 - 0.76)
Infant death		112 (2.1)	117 (1.5)		0.01	0.71 (0.55 - 0.93)

Values are n (%). * median (range). NA: not applicable.

Acknowledgments

We sincerely thank Mr. Norio Sugimoto for his help to our statistical analysis. We also thank Professor Yukihiro Terada for valuable advice with regard to interpretation of the results.

Contributions

1) Conception and design: M.H., A.N.,

2) Acquisition of data: S.S., Y.M.

3) Analysis and interpretation of data: M.H., A.N

4) Drafting article: M.H., A.N.

5) Final approval of the version to be submitted: M.H., S.S., Y.M., A.N

Conflicts of interest

There are no conflicts of interest.

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