ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Impact of single embryo transfer policy on perinatal outcomes in fresh and frozen cycles—analysis of the Japanese Assisted Reproduction Technology registry between 2007 and 2012

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Objective: To investigate whether the introduction of single embryo transfer (SET) policy in Japan has improved perinatal outcomes.
Design: A retrospective cohort study.
Setting: Not applicable.
Patient(s): A total of 140,718 live births and 510 stillbirths (after 22 weeks of gestation) conceived by assisted reproductive technology in Japan between 2007 and 2012 were reviewed.
Intervention(s): None.
Main Outcome Measure(s): Preterm birth (PTB), low birth weight (LBW), very low birth weight (VLBW), small for gestational age (SGA), large for gestational age (LGA), perinatal mortality, and other pregnancy complications.
Result(s): The rate of SET increased significantly from 52.2% in 2007 to 82.6% in 2012, while the rate of multiple pregnancy decreased significantly from 10.7% to 4.1% over the same period. The rates of PTB, LBW, and SGA decreased significantly, while that of LGA increased. Perinatal mortality decreased from 0.70% to 0.40% in fresh cycles, while that of frozen cycles did not change. Double ET or more was associated with a significantly increased risk for multiple pregnancy, placenta accreta, preterm premature rupture of membrane, cesarean section (CS), PTB, LBW, SGA, and early neonatal death compared with SET. Compared with before the SET policy was launched, the risks of multiple pregnancy, CS, early PTB before 32 weeks, LBW, VLBW, and SGA were significantly decreased after the policy was launched, with significant interactions of fresh/frozen status.
Conclusion(s): The results suggest that the SET policy improved perinatal outcomes in Japan. The impact of SET policy was different in fresh and frozen cycles for several perinatal outcomes. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Assisted reproductive technology, perinatal outcome, preterm delivery, low birth weight, single embryo transfer

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K.T. and S.C.J. should be considered similar in author order.
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Since the first IVF baby was born in 1978 (1), assisted reproductive technology (ART) has been widely performed globally. However, along with ART treatment, the rate of multiple pregnancy and poor perinatal outcome is on the rise. To that end, single embryo transfer (SET) has been introduced (2, 3) and advocated as a preventive measure in several countries (4).

In Japan, multiple pregnancy caused by ART has also been a concern. In 1996, the Japan Society of Obstetrics and Gynecology (JSOG) recommended that the number of transferred embryos should be confined to three or less. Although the rate of high-order multiple pregnancy (triplet or more) has decreased since then, the real number of twin pregnancies has increased (5, 6).

Subsequently, in 2008, the JSOG recommended that SET should normally be performed to prevent multiple pregnancy, while double embryo transfer (DET) is allowed in women who are over 35 years old and/or have experienced failure of implantation for more than two consecutive attempts. As a result, the rate of SET being performed between 2007 and 2010 surged from 49.9% to 73.0%, while the rate of multiple pregnancy decreased from 11.5 % to 4.8% (7). In view of these facts, it is worthwhile to investigate whether perinatal outcomes, including preterm delivery and low birth weight (LBW) rates, are affected by the introduction of the SET policy from 2008 onward.

In the present study, we analyzed the data of the national ART registry from 2007 to 2012 to evaluate whether the SET policy improved perinatal outcomes including perinatal mortality, multiple pregnancy, preterm birth (PTB), LBW, small for gestational age (SGA), large for gestational age (LGA), and other pregnancy complications. Since it was suggested that frozen-thawed embryo transfer (frozen ET) has better perinatal outcome than fresh embryo transfer (fresh ET) (8), we also investigated whether the impact of SET policy on perinatal outcomes is different in fresh and frozen cycles.

MATERIALS AND METHODS

Data Source

All data analyzed were obtained from the ART online registry provided by the JSOG. Since 2007, the JSOG has required all institutes that perform ART to register cycle-specific information including patient's age, number of ETs, and perinatal outcomes with an online system. Over 99% of registered facilities record their treatment data in the registry every year. The data were provided by the JSOG upon approval by the registration and research subcommittee of the JSOG ethics committee. Further, the Institutional Review Board at the National Center for Child Health and Development approved this study.

Patients

The number of registered institutions in the database each year between 2007 and 2012 was 606, 609, 625, 591, 586, and 589, respectively. Pregnancy rate stratified by age from the data announced officially by JSOG are shown as Supplemental Table 1 (available online) (9). The pregnancy rate decreased as age rose, and the trend was particularly prominent in patients over 40 years old. There was no trend in pregnancy rate from 2007 to 2012 in the groups under 40 years old. However, the pregnancy rate slightly increased by approximately 1% in these 6 years in the group over 40 years old.

Those with live birth at 22–41 of gestational weeks and stillbirth after 22 weeks of gestation were analyzed. There were 144,808 eligible cycles for live births with known gestational age at delivery and birth weight. Among them, treatment cycle of gamete intrafallopian transfer (n = 36), unknown fertilization method (n = 465), cancellation cycles for ET (n = 252), unknown number of ETs (n = 1), cycles using frozen oocytes (n = 57), and cases with missing or incomplete records (n = 3,279) were excluded. There were 510 eligible stillbirth cases after 22 weeks of gestation. Consequently, the total number of analyzed subjects was 141,228. Since donor gametes or embryos are not allowed to be used in ART in Japan, all of the embryos transferred were autologous.

Perinatal Outcomes

Our primary outcomes are gestational age and birth weight. Gestational age was divided into three groups: delivery at over 37 gestational weeks (term delivery), delivery before 37 weeks (PTB), and delivery before 32 weeks (early preterm birth [EPTB]). In terms of birth weight, we classified the newborns into three groups: newborns of over 2,500 g (normal birth weight), newborns of 1,500–2,499 g (LBW), and newborns of less than 1,500 g (very low birth weight [VLBW]). Further, according to the new standard of average size and weight of newborns of the Japan Pediatric Society, we also classified birth weight into SGA defined as below the 10th percentile of standard and LGA defined as above the 90th percentile (10). As secondary outcomes, stillbirth, early neonatal death within 7 days after birth, multiple pregnancy, cesarean section (CS), and other pregnancy complications including pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), placenta previa, placenta accreta, placenta abruption, and preterm premature rupture of membrane (pPROM) were included for the analysis. Perinatal mortality was calculated as incidence of stillbirth or early neonatal death among known cycles for each year. Multiple pregnancy was defined based on the number of live births.

Statistical Analyses

We evaluated whether there is a linear trend for each variable over the years 2007–2012 by calculating linear regression using each variable as a dependent variable and the calendar year as the independent and ordinal variable. If a variable was continuous or dichotomous, it was put into the regression model directly as a dependent variable. If a variable consisted of more than two categories, indicator variables were created and those indicator variables were separately put into the regression model. For perinatal outcomes, whether there is a linear trend from year 2007 to 2012 was separately evaluated according to fresh/frozen status. Further, we evaluated whether these trends were changed after restricting SET