ORIGINAL ARTICLE: ASSISTED REPRODUCTION

How compliant are in vitro fertilization member clinics in after embryo transfer guidelines? An analysis of 59,689 fresh first in vitro fertilization autologous cycles from 2011 to 2012

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Objective: To determine whether IVF clinics are compliant with American Society for Reproductive Medicine (ASRM) and Society for Assisted Reproductive Technology (SART) (ASRM/SART) guidelines and assess the multiple pregnancy outcomes according to the number of embryos transferred.
Design: Retrospective cohort study.
Setting: Not applicable.
Patient(s): Data from 59,689 fresh first autologous IVF cycles from the 2011–2012 SART registry.
Intervention(s): None.
Main Outcome Measure(s): Percentage of compliant cycles, multiple pregnancy rate (PR).
Result(s): Between 2011 and 2012, a total of 59,689 fresh first autologous cycles were analyzed. Among cleavage-stage ET cycles, the noncompliance rate ranged from 10%–27.4% depending on the age group. The multiple PR was significantly increased in noncompliant cycles involving patients <35 years (38.1% vs. 28.7%) and 35–37 years (35.4% vs. 24.5%) compared with compliant cycles. Among blastocyst-stage ET cycles, the highest rate of noncompliance was seen in patients <35 years old (71%), which resulted in a statistically higher multiple PR (48.3% vs. 2.8%) compared with compliant cycles. Far fewer cycles were noncompliant in patients 35–40 years of age. In a subanalysis of compliant cycles, transferring two blastocyst embryos in patients 35–37 years and 38–40 years resulted in a higher live birth rate compared with the transfer of one embryo (50.4% vs. 40.9% and 42.1% vs. 30.0%, respectively) but the multiple PR was also significantly higher (40.5% vs. 1.7% and 34.0% vs. 2.0%, respectively).
Conclusion(s): Most first fresh autologous IVF cycles performed from 2011–2012 were compliant with ASRM/SART guidelines, except those that involved a blastocyst ET in patients <35 years. Despite compliance, cycles that involved the transfer of >1 embryo resulted in a high multiple PR, whereas noncompliant cycles resulted in an even more remarkable multiple PR for both cleavage and blastocyst-stage embryos. Clinics need to be more compliant with ET limits and ASRM/SART need to consider revising their guidelines to limit the number of blastocyst transfer to one in patients ≤40 years of age undergoing their first IVF cycle. Furthermore, decreasing the number of cleavage-stage embryos transferred in patients ≤40 years of age should also be considered. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: In vitro fertilization, IVF, autologous, blastocysts, embryo transfer, multiple pregnancy

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Since the birth of Louise Brown in 1978, IVF has become an effective treatment for infertility and has resulted in millions of births worldwide. Despite being a relatively safe procedure, one of the most common complications of IVF is the increased risk of multiple gestation as a result of transferring multiple embryos (1–4). In 2013, nearly 41% of all IVF births were multiple-birth deliveries (5). Nationwide, IVF infants accounted for 18.5% of all twin and 25.2% of all triplets and higher order multiples born in 2013 (5). The risks of multiple gestation are well documented and include prematurity, low birth weight, disability, and death. Furthermore, the complications of multiple pregnancies typically worsen with increasing numbers of fetuses; twins and triplets have a fourfold and sixfold increase in mortality compared with singleton pregnancies, respectively (6). Multiple pregnancies also generate large healthcare expenditures. In 2012, costs associated with preterm births as a result of IVF resulted exceeded $1.3 billion (7).

To reduce the multiple pregnancy rate (PR), the American Society for Reproductive Medicine (ASRM) and Society for Assisted Reproductive Technology (SART) have been publishing guidelines since 1998 for the recommended number of embryos to be transferred in IVF cycles, with nearly every revision advocating a reduction in the recommended number of embryos to be transferred (8–14). The newest guidelines were updated in 2013 but were identical to those published in 2009. Although these guidelines are thought to have reduced the number of higher order pregnancies during the past 15 years, the rate of twin gestation has not declined substantially (5, 6).

Although guidelines regarding the number of embryos to be transferred have been issued and regularly updated, it is unclear whether IVF clinics in the United States are compliant with these guidelines. The objective of this study was to determine the proportion of cleavage-stage and blastocyst transfer cycles that did not comply with current ASRM/SART recommended transfer limits and to assess the multiple pregnancy outcomes according to the number of embryos transferred.

MATERIALS AND METHODS

The data used for this study were obtained from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART-CORS). It contains comprehensive data from >90% of all clinics performing assisted reproductive technology (ART) cycles in the United States.

The SART-CORS data are collected through voluntary submission and then reported to the Centers for Disease Control and Prevention in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493). Annual validation of this registry is performed by random selection of 7%–10% of the reporting clinics. This data validation involve randomly selecting a sample of ART data from a member clinic and comparing it with information recorded in the medical records. The discrepancy rates for the variables evaluated in this study are <5%.

To analyze compliance with ASRM/SART ET guidelines, we included all first fresh autologous IVF cycles performed between 2011 and 2012 for women ≤40 years of age. We excluded gamete intrafallopian transfer (GIFT) and ZIFT procedures as well as any IVF cycle that was undertaken for the purpose of egg donation, embryo banking, or preimplantation genetic diagnosis. We excluded all cycles that did not have an oocyte retrieval or ET performed. The cycles were first separated into those with a cleavage-stage (day 2 or 3) or blastocyst-stage (day 5 or 6) ET and were then stratified into cohorts based on ASRM-defined age bins. Within each age cohort, cycles were classified as compliant or noncompliant based on their adherence to published 2013 ASRM/SART Guidelines for Number of Embryos Transferred for the stage of ET (8). For cleavage-stage embryos, compliance was defined as transferring ≤2 embryos for patients <35 years, ≤2 embryos for patients 35–37 years, and ≤3 embryos for patients 38–40 years. For blastocyst-stage embryos, compliance was defined as transferring 1 embryo for patients <35 years, ≤2 embryos for patients 35–37 years, and ≤2 embryos for patients 38–40 years (Supplemental Table 1, available online).

We specifically used the criteria for favorable prognosis patients and defined these patients as those who underwent their first IVF cycle. According to the ASRM practice committee report in 2009 and updated in 2013, the following characteristics have been associated with a favorable prognosis: "[1] first cycle of IVF; [2] good-quality embryos as judged by morphologic criteria; and [3] excess embryos of sufficient quality to warrant cryopreservation. Patients who have had previous success with IVF also should be regarded as being in a more favorable prognostic category" (8).

The variables assessed in this study included number of oocytes retrieved, number of embryos transferred, number of embryos cryopreserved, and pregnancy outcomes. Cycles with missing data for any of these parameters were excluded from the analysis, as well as any cycle resulting in an ectopic pregnancy (EP). The main outcomes evaluated in this study were percentage of compliant and noncompliant cycles and the multiple PR. Secondary outcomes of interest were clinical PR, live birth rate (LBR), multiple LBR, and singleton pregnancy rate; these are all reported as percentages. Clinical pregnancy was defined as visualization of an intrauterine gestational sac by ultrasound regardless of whether a heartbeat or fetal pole was observed. Live birth was defined as delivery of a live-born infant at ≥24 weeks' gestation. Singleton pregnancy was defined as the presence of one fetal heartbeat on ultrasound and similarly, multiple pregnancy was defined as the presence of two or more fetal heartbeats on ultrasound per pregnancies with any number of fetal heartbeats.

The *P* values for our main analysis and subsequent subanalyses obtained from *t*-tests (after comparing means) and χ^2 tests (after comparing frequencies/proportions) were appropriately adjusted for multiple comparisons using Benjamini-Hochberg method (FDR correction). For our subanalyses, we Q1 compared reproductive outcomes for subgroups within compliant cycles for cleavage-stage and blastocyst-stage ETs. For cleavage-stage embryos, we compared transferring different numbers of embryos for every age group, whereas for blastocyst-stage ETs, we compared transferring different numbers of embryos only in women aged 35–40 years. Only