Guidance on the limits to the number of embryos to transfer: a committee opinion

Practice Committee of the American Society for Reproductive Medicine, and the Practice Committee of the Society for Assisted Reproductive Technology

American Society for Reproductive Medicine; and Society for Assisted Reproductive Technology, Birmingham, Alabama

Based on American Society for Reproductive Medicine (ASRM) and Society for Assisted Reproductive Technology data available through 2014, ASRM's guidelines for the limits on the number of embryos to be transferred in in vitro fertilization (IVF) cycles have been further refined in continuing efforts to promote singleton gestation and reduce the number of multiple pregnancies. This version replaces the document titled Criteria for number of embryos to transfer: a committee opinion that was published most recently in August of 2013 (Fertil Steril 2013;99:44–6). (Fertil Steril® 2017;107:901–3. ©2017 by American Society for Reproductive Medicine.)

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/14894-23732

BACKGROUND

Based on American Society for Reproductive Medicine (ASRM) and Society for Assisted Reproductive Technology (SART) data available through 2014, ASRM's guidance for the limits to the number of embryos to be transferred in in vitro fertilization (IVF) cycles has been revised in an effort to promote singleton gestation and reduce the number of multiple pregnancies.

High-order multiple pregnancy (three or more fetuses in one pregnancy) has diminished in frequency in recent years, but is still an outcome of assisted reproductive technology (ART) that is undesirable. Multiple gestations lead to an increased risk of complications in both the fetuses and the mothers (1–3). Even twin gestations have significant additional morbidity compared to singletons (3). Ideally, the goal of ART is to achieve a singleton gestation (4–6). Almost half of all multiple gestations resulting from ART in the United States occur in women who were younger than 35 years old when two fresh or frozen blastocysts were transferred (7). Among reported cycles to SART in 2014, 23% of the women under 38 years of age who had a successful IVF cycle had a twin gestation (8).

Respect for a patient's autonomy to choose placement of more than one embryo requires a full discussion of available, ethical, medically sound options, ensuring that a patient is able to make a fully informed, non-coerced decision from among those choices. Elective placement of multiple embryos is influenced by financial consideration. Studies have shown that insurance coverage for IVF is associated with the transfer of fewer embryos and with significantly lower rates of high-order multiple birth (9). Financial pressures may be a coercive tipping point in favor of multiple embryo transfer. In contrast, if patients are informed of risks inherent in twin or high-order pregnancy with these financial pressures removed or at least alleviated, most patients would opt to maximize their chance of a singleton, safe pregnancy, and birth (10).

Although multifetal pregnancy reduction can be performed to reduce fetal number, the procedure may result in the loss of all fetuses, does not completely eliminate the risks associated with multiple pregnancy, and may have adverse psychological consequences (11). Moreover, multifetal pregnancy reduction is not an acceptable option for many women.

RECOMMENDATIONS

In an effort to promote singleton gestations, reduce twin gestation, and eliminate high-order multiple gestations, ASRM and SART have developed the following guidelines to assist ART programs and patients in determining the appropriate limit to the number of cleavage-stage embryos or blastocysts to transfer. National data from 2013 demonstrate that clinics that perform higher rates of elective single-embryo transfer (eSET) in women aged <38 years have decreased rates of multiple gestation, with no significant impact on cumulative live-birth rates (12). Preimplantation genetic screening may also be a tool to reduce the rate of

Received January 13, 2017; accepted February 3, 2017; published online March 11, 2017.
Reprint requests: Practice Committee, American Society for Reproductive Medicine, 1209 Montgomery Hwy, Birmingham, Alabama 35216 (E-mail: ASRM@asrm.org).

Fertility and Sterility® Vol. 107, No. 4, April 2017 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2017.02.107

multiple gestations. In women 42 years or younger, transferring a single euploid blastocyst resulted in pregnancy rates similar to transferring two untested blastocysts while dramatically reducing the risk of twins (13). Strict limitations on the number of embryos transferred, as required by law in some countries, do not allow treatment plans to be individualized after careful consideration of each patient's own unique circumstances. Therefore, transferring a fewer or greater number of embryos than the limits recommended by these criteria within reason may be rarely justified, with documentation of justification for greater number of embryos recorded in the medical record according to individual clinical conditions, including patient age, parity, medical conditions, embryo quality, the opportunity for cryopreservation, and clinical experience with newer techniques.

Individual programs are encouraged to generate and use their own data regarding patient characteristics and the number of embryos to be transferred with the goal of maintaining pregnancy rates and minimizing multiple gestations. For example, if a program notes a particularly high implantation rate for cleavage-stage embryos among their patients aged 41–42, they should adjust their clinic-specific range downward for number of embryos to transfer. Accordingly, programs should monitor their results continually and consider decreasing the number of embryos transferred to minimize undesirable outcomes. Conversely, use of a clinic's own data cannot be used to routinely exceed the recommended limits. Programs that have a multiple pregnancy rate that is well above average for all SART-reporting clinics may be audited by SART, and persistent non-compliance may result in expulsion from SART.

Apart from young age, the following characteristics have been associated with a favorable prognosis: 1) expectation of one or more high-quality embryos available for cryopreservation; 2) euploid embryos; and 3) previous live birth after an IVF cycle. Additional favorable criteria for frozen embryo transfer (FET) cycles includes the availability of vitrified, high-quality, day-5, or day-6 blastocysts for transfer (14). The number of embryos transferred should be agreed upon by the physician and the treated patient(s), informed consent documents completed, and the information recorded in the clinical record. In the absence of data generated by the individual program, and based on data generated by all clinics providing ART services, the following guidelines are recommended for upper limits (Table 1):

A. Patients with a favorable prognosis:
   1. In patients of any age, transfer of a euploid embryo has the most favorable prognosis and should be limited to one.
   2. Patients under the age of 35 should be encouraged to receive a single-embryo transfer, regardless of the embryo stage.
   3. For patients between 35 and 37 years of age, strong consideration should be made for a single-embryo transfer.
   4. For patients between 38 and 40 years of age, no more than three cleavage-stage embryos or two blastocysts should be transferred. In cases where euploid embryos are available, a single-blastocyst embryo transfer should be the norm.
   5. Patients 41–42 years of age should plan to receive no more than four cleavage-stage embryos or three blastocysts. In cases where euploid embryos are available, a single-blastocyst transfer should be the norm.

B. Other scenarios:
   1. In each of the above age groups, patients who do not meet criteria for a favorable prognosis may have an additional embryo transferred according to individual circumstances (Table 1). The patient must be counseled regarding the additional risk of twin or higher-order multiple pregnancy.
   2. If otherwise favorable patients fail to conceive after multiple cycles with high-quality embryo(s) transferred, physicians and patients may consider proceeding with an additional embryo to be transferred.
   3. Patients with a co-existing medical condition for which a multiple pregnancy may increase the risk of significant morbidity should not have more than one embryo transferred.
   4. In the rare cases where the number of embryos or blastocysts transferred exceeds recommended limits, both the counseling and the justification must be documented in the patient's permanent medical record.
   5. In women ≥43 years of age, there are insufficient data to recommend a limit on the number of embryos to transfer when the patient uses her own oocytes. Caution should be exercised as the risk associated with multiple pregnancy increases dramatically with advancing maternal age.

C. In donor-oocyte cycles, the age of the donor should be used to determine the appropriate number of embryos to transfer. For example, when the donor is <35 years of age and other favorable criteria exist, single-embryo transfer should be planned.

D. In frozen-embryo transfer cycles, favorable characteristics should be based on the age of the woman when the

TABLE 1

Recommendations for the limit to the number of embryos to transfer.

Prognosis	Age (y) < 35	35–37	38–40	41–42
Cleavage-stage embryos[a]				
Euploid	1	1	1	1
Other favorable[b]	1	1	≤3	≤4
All others	≤2	≤3	≤4	≤5
Blastocysts[a]				
Euploid	1	1	1	1
Other favorable[b]	1	1	≤2	≤3
All others	≤2	≤2	≤3	≤3

[a] See text for more complete explanations.
[b] Other favorable = Any ONE of these criteria: *Fresh cycle*: expectation of 1 or more high-quality embryos available for cryopreservation, or previous live birth after an IVF cycle; *FET cycle*: availability of vitrified day-5 or day-6 blastocysts, euploid embryos, 1st FET cycle, or previous live birth after an IVF cycle.

Please note: Justification for transferring additional embryos beyond recommended limits should be clearly documented in the patient's medical record.

ASRM. Limits on number of embryos to transfer. Fertil Steril 2017.

embryos were frozen and include the presence of high-quality vitrified embryos, euploid embryos, first FET cycle, or previous live birth after an IVF cycle. Embryo transfer numbers should not exceed the recommended limit on the number of fresh embryos transferred for each age group.

Acknowledgments: This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine (ASRM) in collaboration with the Society for Assisted Reproductive Technology (SART) as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committees and the Board of Directors of ASRM and SART have approved this report.

This document was reviewed by ASRM members and their input was considered in the preparation of the final document. The Practice Committee acknowledges the special contribution of Barbara Luke, Sc.D., M.P.H. and Morton Brown, Ph.D. in the preparation of this document. The following members of the ASRM Practice Committee participated in the development of this document. All committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. Members of the committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of this document.

Alan Penzias, M.D.; Kristin Bendikson, M.D.; Samantha Butts, M.D., M.S.C.E.; Christos Coutifaris, M.D.; Gregory Fossum, M.D.; Tommaso Falcone, M.D.; Susan Gitlin, Ph.D.; Clarisa Gracia, M.D., M.S.C.E.; Karl Hansen, M.D., Ph.D.; Andrew La Barbera, Ph.D.; Jennifer Mersereau, M.D.; Randall Odem, M.D.; Richard Paulson, M.D.; Samantha Pfeifer, M.D.; Margareta Pisarska, M.D.; Robert Rebar, M.D.; Richard Reindollar, M.D.; Mitchell Rosen, M.D.; Jay Sandlow, M.D.; Michael Vernon, Ph.D.

REFERENCES

1. Rao A, Sairam S, Shehata H. Obstetric complications of twin pregnancies. Best Pract Res Clin Obstet Gynaecol 2004;18:557–76.
2. Multiple gestation pregnancy. The ESHRE Capri Workshop Group. Hum Reprod 2000;15:1856–64.
3. Twin Pregnancy and Severe Maternal Outcomes: The World Health Organization Multicountry Survey on Maternal and Newborn Health. Obstet Gynecol 2016;127:631–41.
4. Practice Committee of American Society for Reproductive Medicine. Multiple gestation associated with infertility therapy: an American Society for Reproductive Medicine Practice Committee opinion. Fertil Steril 2012;97:825–34.
5. Practice Committee of Society for Assisted Reproductive TechnologyPractice Committee of American Society for Reproductive Medicine. Elective single-embryo transfer. Fertil Steril 2012;97:835–42.
6. ESHRE Guideline Group on Good Practice in IVF Labs, De los Santos MJ, Apter S, Coticchio G, Debrock S, Lundin K, Plancha CE, et al. Revised guidelines for good practice in IVF laboratories (2015). Hum Reprod 2016;31:685–6.
7. Kissen DM, Kulkarni AD, Mneimneh A, Warner L, Boulet SL, Crawford S, et al. Embryo transfer practices and multiple births resulting from assisted reproductive technology: an opportunity for prevention. Fertil Steril 2015;103:954–61.
8. Society for Assisted Reproductive Technology (SART). National Summary Report. Available at: https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?ClinicPKID=0. Accessed January 12, 2017.
9. Jain T, Harlow BL, Hornstein MD. Insurance coverage and outcomes of in vitro fertilization. N Engl J Med 2002;347:661–6.
10. Johnston: Health Economics, Policy and Law (2015). 10, 243–250. London, England.
11. Stone J, Eddleman K, Lynch L, Berkowitz RL. A single center experience with 1000 consecutive cases of multifetal pregnancy reduction. Am J Obstet Gynecol 2002;187:1163–7.
12. Mancuso A, Boulet SL, Duran E, Munch E, Kissin DM, Van Voorhis BJ. Elective Single Embryo Transfer in Women Under Age 38 Reduces Multiple Birth Rates, but Not Live Birth Rates in United States Fertility Clinics. Fertil Steril 2016;106:1107–14.
13. Forman EJ, Hong KH, Ferry KM, Tao X, Taylor D, Levy B, et al. In vitro fertilization with single euploid blastocyst transfer: a randomized controlled trial. Fertil Steril 2013;100:100–7.
14. Richter KS, Ginsburg DK, Shipley SK, Lim J, Tucker MJ, Graham JR, et al. Factors associated with birth outcomes from cryopreserved blastocysts: experience from 4,597 autologous transfers of 7,597 cryopreserved blastocysts. Fertil Steril 2016;106:354–62.