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

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On the basis of American Society for Reproductive Medicine and Society for Assisted Reproductive Technology data, the American Society for Reproductive Medicine's guidelines for the limits on the number of embryos to be transferred during in vitro fertilization 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 2017 (Fertil Steril 2017;107:901–3). (Fertil Steril® 2021;116:651-54. ©2021 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: Assisted reproduction, transfer, blastocyst, euploid, IVF

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BACKGROUND

The American Society for Reproductive Medicine's (formerly The American Fertility Society) guidance for the limits to the number of embryos to be transferred during in vitro fertilization (IVF) cycles aims to promote singleton gestation and reduce the number of multiple pregnancies while maximizing the cumulative live birth rates.

Although the incidence of high-order multiple pregnancies (three or more fetuses in one pregnancy) have diminished in recent years, twin gestations are still a relatively common occurrence with assisted reproductive technology (ART). Multiple gestation leads to an increased risk of complications in both the woman carrying the pregnancy and the fetuses (1–3). Even twin gestations have significant additional morbidity compared with that of singletons (3). Ideally, the goal of ART is to achieve a healthy singleton gestation (4–6). Among cycles reported to the Society for Assisted Reproductive Technology (SART) in 2017, 12.4% of women <38 years of age who had a successful IVF cycle had a twin gestation (7), down from 23% in 2014 but still significantly more than baseline. Almost half of all ART multiple gestations in the United States occurred in women <35 years old when 2 fresh or frozen blastocysts were transferred (8).

Respect for a patient's autonomy to consider placement of more than one embryo requires a full discussion of the ethical and medical considerations, ensuring that a patient is able to make a fully informed decision. Elective placement of multiple embryos is often influenced by financial considerations. Studies showed that insurance coverage for IVF was associated with the transfer of fewer embryos and with significantly lower rates of high-order multiple births (9). Financial pressures may be a coercive tipping point in favor of multiple embryo transfer. In contrast, if patients are informed of the risks inherent in twin or high-order pregnancy and these financial pressures are 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 the fetal number, the procedure may result in the loss of all fetuses, it does not completely eliminate the risks associated with multiple pregnancies, and it 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 gestations, and eliminate high-order multiple gestations, the American Society for Reproductive Medicine and SART have developed the following guidance to assist ART programs and patients in determining the appropriate number of cleavage-stage embryos or blastocysts to transfer. National data from 2013 demonstrated that clinics that

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performed higher rates of elective single-embryo transfer in women aged <38 years had decreased rates of multiple gestations with no significant impact on clinic-level live birth rates (12). In addition, preimplantation genetic testing for aneuploidy maybe a tool to reduce the rate of multiple gestations, especially in women >37 years of age. In women ≤42 years, transferring a single euploid blastocyst resulted in pregnancy rates similar to those of transferring 2 untested blastocysts while dramatically reducing the risk of twins (13). Strict limitations on the number of embryos transferred, which may be 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, on rare occasions, transferring more or fewer embryos than recommended by this document may be justified; documentation of justification for transferring a greater number of embryos should be recorded in the medical record, noting the individual clinical conditions, including patient age, parity, medical conditions, embryo quality, the opportunity for cryopreservation, and the patient prognosis.

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 years, they should adjust their clinic-specific range for the number of embryos to transfer downward. 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 noncompliance may result in expulsion from SART.

Apart from young age, characteristics like the expectation of one or more high-quality embryos available for cryopreservation; euploid embryos; and previous live birth after an IVF cycle have been associated with a favorable prognosis for pregnancy. Additional favorable criteria for frozen embryo transfer (FET) cycles include the availability of vitrified, high-quality blastocysts for transfer (14). The number of embryos transferred should be determined by the physician and the patient(s), informed consents completed, and the information recorded in the clinical record. In the absence of data generated by the individual program, and on the basis of 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. Transfer of a euploid embryo should be limited to one, regardless of patient age.
   2. Patients <35 years of age should be strongly 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 3 untested cleavage-stage embryos or 2 blastocysts should be transferred.
   5. Patients 41–42 years of age should plan to receive no more than 4 untested cleavage-stage embryos or 3 blastocysts.

B. Other scenarios:
   1. In each of the preceding age groups, patients who do not meet the criteria for a favorable prognosis may have an additional embryo transferred according to their 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, the physicians and patients may consider proceeding with an additional embryo to be transferred.
   3. Patients with a coexisting 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 in which the number of embryos or blastocysts transferred exceeds the 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 <38 years of age and other favorable criteria exist, single-embryo transfer should be planned.

D. Single-embryo transfer should be strongly recommended in all gestational carrier (GC) cycles, given the health risks associated with multiple gestations for the GC. At a minimum, it is recommended to follow age-related limits on the number of embryos to transfer in GC cycles, on the basis of the age of the woman who produced the oocytes (either the intended parent or oocyte donor).

E. In FET cycles, favorable characteristics should be on the basis of the age of the woman when the embryos were cryopreserved and include the presence of high-quality vitrified embryos, euploid embryos, first FET cycle, or previous live birth after a prior transfer with sibling embryo(s). Embryo transfer numbers should not exceed the recommended limit on the number of fresh embryos transferred for each age group.

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TABLE 1

Recommendations for the limit to the number of embryos to transfer

	Age			
Prognosis	**< 35**	**35-37**	**38-40**	**41-42**
Cleavage stage embryos				
Euploid[a]	1	1	1	1
Other Favorable[b]	1	1	≤3	≤4
Embryos not Euplod[a] or Favorable[b]	≤2	≤3	≤4	≤5
Blastocysts				
Euploid[a]	1	1	1	1
Other Favorable[b]	1	1	≤2	≤3
Embryos not Euploid[a] or Favorable[b]	≤2	≤2	≤3	≤3

[a] Demonstrated euploid embryos, best prognosis
[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 a prior transfer with sibling embryo(s); *FET cycle*: availability of vitrified day-5 or day-6 blastocysts, euploid embryos, 1st FET cycle, or previous live birth after an IVF cycle.

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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 Boards of Directors of the ASRM and SART have approved this report.

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Orientación sobre los límites del número de embriones a transferir: la opinión del comité.
Teniendo como base los datos de la Sociedad Estadounidense de Medicina Reproductiva y la Sociedad de Tecnología de Reproducción Asistida, las recomendaciones de la Sociedad Estadounidense de Medicina Reproductiva sobre los límites en el número de embriones que se transferirán durante los ciclos de fecundación *in vitro* se han perfeccionado aún más con continuos esfuerzos para promover la gestación única y reducir el número de embarazos múltiples. Esta versión reemplaza el documento titulado "Criterios para el número de embriones a transferir: la opinión del comité" que se publicó recientemente en agosto de 2017.