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Embryo transfer practices and multiple births resulting from assisted reproductive technology: an opportunity for prevention

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Abstract

Objective—To evaluate assisted reproductive technology (ART) ET practices in the United States and assess the impact of these practices on multiple births, which pose health risks for both mothers and infants.

Design—Retrospective cohort analysis using the National ART Surveillance System data.

Setting—US fertility centers reporting to the National ART Surveillance System.

Patient(s)—Noncanceled ART cycles conducted in the United States in 2012.

Intervention(s)—None.

Main Outcome Measure(s)—Multiple birth (birth of two or more infants, at least one of whom was live-born).

Result(s)—Of 134,381 ART transfer cycles performed in 2012, 51,262 resulted in live births, of which 13,563 (26.5%) were multiple births: 13,123 twin and 440 triplet and higher order births. Almost half (46.1%) of these multiple births resulted from the following four cycle types: two fresh blastocyst transfers among favorable or average prognosis patients less than 35 years (1,931 and 1,341 multiple births, respectively), two fresh blastocyst transfers among donor-oocyte recipients (1,532 multiple births), and two frozen/thawed ETs among patients less than 35 years (1,452 multiple births). More than half of triplet or higher order births resulted from the transfer of two embryos (52.5% of births among fresh autologous transfers, 67.2% of births among donor-oocyte recipient transfers, and 42.9% among frozen/thawed autologous transfers).

Conclusion(s)—A substantial reduction of ART-related multiple (both twin and triplet or higher order) births in the United States could be achieved by single blastocyst transfers among favorable and average prognosis patients less than 35 years of age and donor-oocyte recipients.

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Keywords

Assisted reproductive technology (ART); in vitro fertilization (IVF); multiple birth; embryo transfer guidelines

Soon after the introduction of assisted reproductive technology (ART) and non-ART fertility treatments more than three decades ago, the previously stable rate of multiple births in the United States (2.0% of all births) started rapidly increasing in the early 1980s and remains at around 3.4% since early 2000s (1–3). Although the incidence of triplet and higher-order births has decreased in the United States during the past 15 years, a similar decrease in the rate of twin births has not been observed (1, 2). This increase in multiple births has contributed to an increased rate of preterm births in the United States, which at 12% ranks as one of the highest in the world (4). Multiple births carry the risk of increased morbidity and mortality for mother and infants (5). Although it is difficult to limit multiple births after non-ART fertility treatments, such as ovulation induction or ovarian stimulation, plurality resulting from the use of ART can be controlled by limiting the number of embryos transferred. The only contributing factor outside of providers' control is monozygotic twinning, embryo splitting during early development, which is 2–12 times more prevalent among ART conceived pregnancies than the rate of 0.4% in the general population (6–9).

In the United States, one of the most influential means by which the number of embryos transferred during ART procedures could be limited is the practice guidelines published by the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) (10). The guidelines provide recommendations on how many embryos to transfer given various patient and treatment characteristics to balance safety with the effectiveness of ART. The guidelines were first published in 1998 and subsequently reissued six times with the recommendations for number of embryos to transfer remaining unchanged from 2009 to 2013 (11–16). Although the optimal outcome of an ART cycle is the birth of a healthy singleton (17), one major challenge in reducing multiple births is the strong desire of couples experiencing infertility to maximize their chance for a successful treatment, particularly when facing limited insurance coverage and high out-of-pocket costs. Such costs, along with many couples' willingness to raise multiples, may result in the transfer of more embryos than are necessary to achieve an optimal treatment outcome, even among patients with the best prognosis.

In an effort to reduce multiple births and associated maternal and infant morbidity, it is important to identify current treatment practices that contribute to this outcome. The objectives of this study were to evaluate ET practices in the United States and to assess the influence of these practices on multiple births.

MATERIALS AND METHODS

We used the Centers for Disease Control and Prevention National ART Surveillance System (NASS), which collects data on all ART procedures performed in the United States, including characteristics of patients, ART treatments, and resultant outcomes (18). The NASS contains data on nearly all (98% in 2012) ART procedures performed in the United

States (19). The accuracy of reported data is validated by the clinics' medical director before submission. In addition, 7%–10% of reporting clinics are randomly selected each year for data validation, during which ART data reported by the clinics are compared with information recorded in medical records and discrepancy rates are calculated (20). For the current analysis, we used data on 157,662 nonresearch, nonembryo banking ART cycles performed in 2012 and reported to NASS by 456 clinics, including 356 (78.1%) SART member clinics and 74 (16.2%) non-SART member clinics (affiliation of the remaining 26 reporting clinics [5.7%] at the time of data submission was unknown). The ART cycles that progressed to the ET stage (134,381; 85.2% of all cycles) were included in the analysis.

Assisted reproductive technology is defined as a fertility treatment in which eggs and sperm are handled for the purpose of establishing a pregnancy. The ART cycles were classified as fresh (using newly fertilized embryos) or frozen/thawed (using previously fertilized and cryopreserved embryos that were thawed), and as autologous (woman's own oocytes) or donor (donor oocytes). Embryo stage was calculated by subtracting the oocyte retrieval date from the ET date, and classified as cleavage stage (days 2–3) or blastocyst stage (days 5–6). A multiple birth was defined as the birth of two or more infants, at least one of whom was live-born. Therefore, stillbirths, deliveries after completion of 20 weeks of gestation, or fetal weight >350 g when no fetus showed signs of life after the complete expulsion or extraction, were not classified as multiple births in the current study (79 twin stillbirths and 11 triplet and higher order stillbirths).

Patients were classified as having a favorable, average, or less favorable prognosis for a successful ET, similar to the classification used in the ASRM/SART Guidelines on Number of Embryos Transferred (12). Favorable prognosis patients were defined as those who underwent their first IVF cycle and had extra embryo(s) cryopreserved. Less favorable prognosis patients were defined as those who had previous IVF cycle(s), no previous live births, and no extra embryos cryopreserved. The remaining patients, classified as average prognosis patients, included those who: [1] underwent their first IVF cycle and had no extra embryos cryopreserved, [2] had previous IVF cycle(s), no previous live birth(s), but had extra embryo(s) cryopreserved, or [3] had previous IVF cycle(s) and previous live birth(s). Due to the limitations of data reported in NASS, this classification differs from that used in the ASRM/SART guidelines. The ASRM/SART definition of favorable prognosis includes two criteria that are not available in NASS: good-quality embryos as judged by morphologic criteria and previous success with IVF. The ASRM/SART definition of less favorable prognosis includes patients with two or more previous failed fresh IVF cycles. Although the ASRM/SART guidelines do not define average prognosis, this group is implied because of the large group of cycles that do not fall under the favorable or less favorable prognosis groups.

We calculated the number and percentage of multiple births among ET cycles performed overall, and in the following patient groups: fresh autologous, fresh donor, frozen/thawed autologous, and frozen/thawed donor. We then calculated the number and percentage of fresh ETs, by oocyte source, patient age, prognosis, and embryo stage. In addition, we calculated the proportion of ETs performed in accordance with the 2009 ASRM/SART Guidelines on Number of Embryos Transferred (12). A c2 test was used to compare the

proportion of ETs performed in accordance with ASRM/SART guidelines between SART member clinics and clinics that were not members of SART in 2012. Finally, we calculated the number and percentage of multiple births among ET cycles by oocyte source, patient age, prognosis, and embryo stage. The SAS statistical software 9.2 (SAS Institute) was used for analyses. The study was approved by the Centers for Disease Control and Prevention's Institutional Review Board.

RESULTS

Of the 134,381 ET cycles performed in 2012, 80,745 (60.1%) were fresh autologous cycles, 35,486 (26.4%) were frozen/thawed autologous cycles, 9,944 (7.4%) were fresh donor cycles, and 8,206 (6.1%) were frozen/thawed donor cycles. Of these ET cycles, 51,262 (38.1%) resulted in live births. Among live births, 37,699 (73.5%) were singleton live births and 13,563 (26.5%) were multiple live births, of which 13,123 (96.8%) were twin births and 440 (3.2%) were triplet and higher order births. Among multiple births, most (59.1%) resulted from fresh autologous cycles followed by frozen/thawed autologous cycles (21.7%), fresh donor cycles (14.1%), and frozen/thawed donor cycles (5.1%) (Fig. 1). A total of 65,153 infants were born as a result of ET cycles performed in 2012: 37,699 (57.9%) singletons and 27,454 (42.1%) multiples, of which 26,139 (95.2%) were twins and 1,315 (4.8%) were triplets and higher order multiple infants.

Among fresh ETs, 20.0% involved transferring one embryo, 58.6% involved transferring two embryos, and 15.8% involved transferring three embryos; the remaining 5.6% of transfers involved transferring four or more embryos (Table 1). Almost all ET cycles (94.5%) were performed in accordance with the 2009 ASRM/SART Guidelines on Number of Embryos Transferred, as indicated by superscript f in Table 1. The proportion of ETs performed in accordance with ASRM/SART guidelines was significantly higher among SART member clinics (94.7%), compared with non-SART member clinics (89.7%) ($P<.0001$). The proportion of births that were multiple births reported by SART member clinics (27.3%) was lower than that reported by non-SART member clinics (30.6%) ($P<.01$). Embryo transfers that were not in accordance with guidelines included transferring three cleavage stage embryos using autologous oocytes to favorable prognosis patients 35–37 years old (17.6% of transfers in that group) and to average prognosis patients less than 35 years old (14.7% of transfers in that group). Among favorable prognosis patients less than 35 years old with available blastocysts using autologous oocytes, for whom ASRM/SART guidelines recommend transferring a single embryo but allow for the transfer of two embryos, one embryo was transferred in 34.8% of cycles, and two embryos were transferred in 64.4% of cycles.

Most multiple births among patients using fresh embryos from autologous oocytes were among cycles involving the transfer of two embryos (6,362, 81.2%) and among patients less than 35 years of age (5,100, 65.1%) (Fig. 2). The largest number of multiple births in this group resulted from the transfer of two blastocysts to favorable prognosis patients less than 35 years of age (1,931, 24.7%) (Fig. 2A), followed by the transfer of two blastocysts to average prognosis patients less than 35 years of age (1,341, 17.1%) (Fig. 2C). Almost all multiple births (93.4%), those marked with an asterisk in Figure 2, resulted from ETs that

were performed in accordance with ASRM/SART guidelines: 94.1% of twin births and 72.1% of triplet and higher order births. More than half of all triplet and higher order births (52.5%) resulted from monozygotic twinning after transferring two embryos.

Most multiple births among patients using donor oocytes resulted from the transfer of two fresh blastocysts (1,532, 59.7%), followed by the transfer of two frozen/thawed embryos at an unknown stage (572, 22.3%) (Fig. 3A). Among fresh ETs using donor oocytes, almost all multiple births (94.9%) resulted from ETs that were performed in accordance with ASRM/SART guidelines: 95.2% of twin births and 78.9% of triplet and higher order births. More than half of all triplet and higher order births (41, 67.2%) resulted from the transfer of two embryos.

Among multiples that resulted from frozen/thawed autologous ETs, 1,700 (58.9%) were among patients less than 35 years of age, 687 (23.8%) were among patients 35–37 years, 403 (14.0%) were among patients 38–40 years, and 97 (3.4%) were among patients 41–42 years (Fig. 3B). Most multiple births (2,369, 82.1%) resulted from the transfer of two embryos. More than 40% of all triplet and higher order births (39, 42.9%) resulted from the transfer of two frozen/thawed embryos.

DISCUSSION

Findings from our population-based study of the National ART Surveillance System indicate that most ART-related multiple births in the United States during 2012 resulted from cycles practiced in accordance with ASRM/SART guidelines and involved the transfer of two embryos. Almost half of ART-related multiple births resulted from ETs in the following four groups: [1] transferring two fresh blastocysts to favorable prognosis patients younger than 35 years, [2] transferring two fresh blastocysts to average prognosis patients younger than 35 years, [3] transferring two fresh blastocysts to donor-oocyte recipients, and [4] transferring two frozen/thawed embryos to patients younger than 35 years. We also found that more than half of triplet and higher order multiples resulted from monozygotic twinning after transferring two embryos.

Previous research showed that there has been a notable decline in the transfer of three or more embryos in the United States since 1998 (when ASRM/SART guidelines were first published), with a corresponding decline in triplets and higher order births, and considerable, although less prominent, increase in single ETs, with a corresponding increase in singleton births (2, 21). However, there has been little overall progress decreasing double ETs and, consequently, twin births (1, 2). Because most multiple births are twin births, further improvements of ART outcomes are possible by reducing the number of embryos transferred from two to one among those patients who have a good chance of pregnancy and live birth with single ET. The largest contributors to ART-related multiple births are ART procedures among the four previously mentioned patient groups who are also the best candidates for single ET. Although the transfer of two embryos in these groups is consistent with current ASRM/SART guidelines, performing single ET could almost eliminate the risk of multiple births in these groups, but would not substantially reduce the live birth rate (22–24). A recent Cochrane review (23) found no statistically significant differences in

cumulative live birth rates but significant reductions in multiple pregnancy rates (PRs) when repeated single ETs were compared with double ET.

Implementation of the ASRM/SART guidelines on the number of embryos to transfer has played a major role in improving ET practices in the United States and has contributed to a significant decline in procedures that involved the transfer of three or more embryos and decreases in triplet and higher order births (25). However, in the groups that contribute almost half of ART-related multiple births, the transfer of two embryos is consistent with ASRM/SART guidelines (10). Therefore, the largest impact on further reducing ART-related multiple births in the United States could be achieved by single blastocyst transfers for favorable and average prognosis patients less than 35 years of age and donor-oocyte recipients.

Interestingly, our study showed that more than half of triplet and higher order births now result from double ET. In the past, the main contributor of triplet and higher order births was the transfer of three or more embryos. After considerable reductions in ART cycles involving three or more embryos, one of the main factors contributing to higher order births appears to be monozygotic twinning. The increased incidence of monozygotic twinning after ART, especially with the use of assisted hatching or blastocyst stage embryos, has been previously shown (6, 26, 27). Because our knowledge on the causes of monozygocity is limited, prevention of triplet and higher order births can be achieved by transferring a single embryo at a time. The estimated prevalence of monozygotic twinning after single ET has been shown to be 1.7% and 2.5% with cleavage and blastocyst ETs, respectively (27).

Our analysis is subject to several limitations. The NASS definitions of patient prognosis groups differed from those used in the ASRM/SART guidelines on the number of embryos transferred during ART. For example, because information on previous success with IVF is not currently available in NASS, we were not able to use this criterion to define the favorable prognosis group. This could result in the misclassification of favorable prognosis patients as patients with average prognosis, which may underestimate multiple births in the favorable prognosis group and overestimate this measure in the average prognosis group. In addition, we used the combination of “no previous live births” and “previous IVF cycles” to approximate the “two or more previously failed IVF cycles” measure that is used to define the less favorable prognosis group in the ASRM/SART guidelines. This approach could misclassify some average prognosis patients into the less favorable prognosis group, which may underestimate multiple births in average prognosis group and overestimate this measure in the less favorable prognosis group. Due to the limited information on frozen/thawed cycles in NASS, we were unable to classify them according to adherence to ASRM/SART guidelines. Although our definition of multiple birth did not include delivery of two or more stillborn infants, inclusion of stillbirths would not have changed the results of the study as they only represent 0.6% of all deliveries. Another important limitation of our analysis is the lack of data on embryo quality in NASS. However, we used the availability of supernumerary embryos, which has been shown to be a good predictor of embryo quality (28). In addition, limitations common to observational retrospective analyses apply to our study. For example, we were not aware of circumstances surrounding individual patients that were known to ART providers when decisions on the number of embryos to transfer

were made. Although we stratified the results by the most important patient and treatment factors available in NASS, we cannot exclude the possibility that other factors may modify the observed effects.

A healthy singleton birth is the optimal outcome of ART (17). This outcome is most achievable if no more than one embryo is transferred in the best circumstances, such as cycles in young favorable or average prognosis patients or donoroocyte recipients where blastocysts are available. One of the major barriers to widespread implementation of single ET is the high out-of-pocket cost of ART, often not covered by health insurance, which stimulates patients' demands to transfer more embryos, thereby maximizing the "success" of a single cycle (29). Although insurance coverage of ART may allow more patients with infertility to have access to treatment (30), it is not likely to succeed in significantly decreasing multiple births without being accompanied by restrictions on the number of embryos transferred during ART. Other countries, such as Australia, Sweden, Belgium, have been successful in achieving marked reductions in multiple births when they removed financial pressures for patients with infertility by covering ART in exchange for mandatory single ET in the best prognosis groups (31–34). Improving ART practices may require coordinated and multidisciplinary effort by health care professionals and professional societies, patients with infertility and organizations representing people coping with infertility, the scientific community, insurance providers, non-profit organizations, and governmental agencies, as outlined in the recently published "National Public Health Action Plan for the Detection, Prevention and Management of Infertility" (35).

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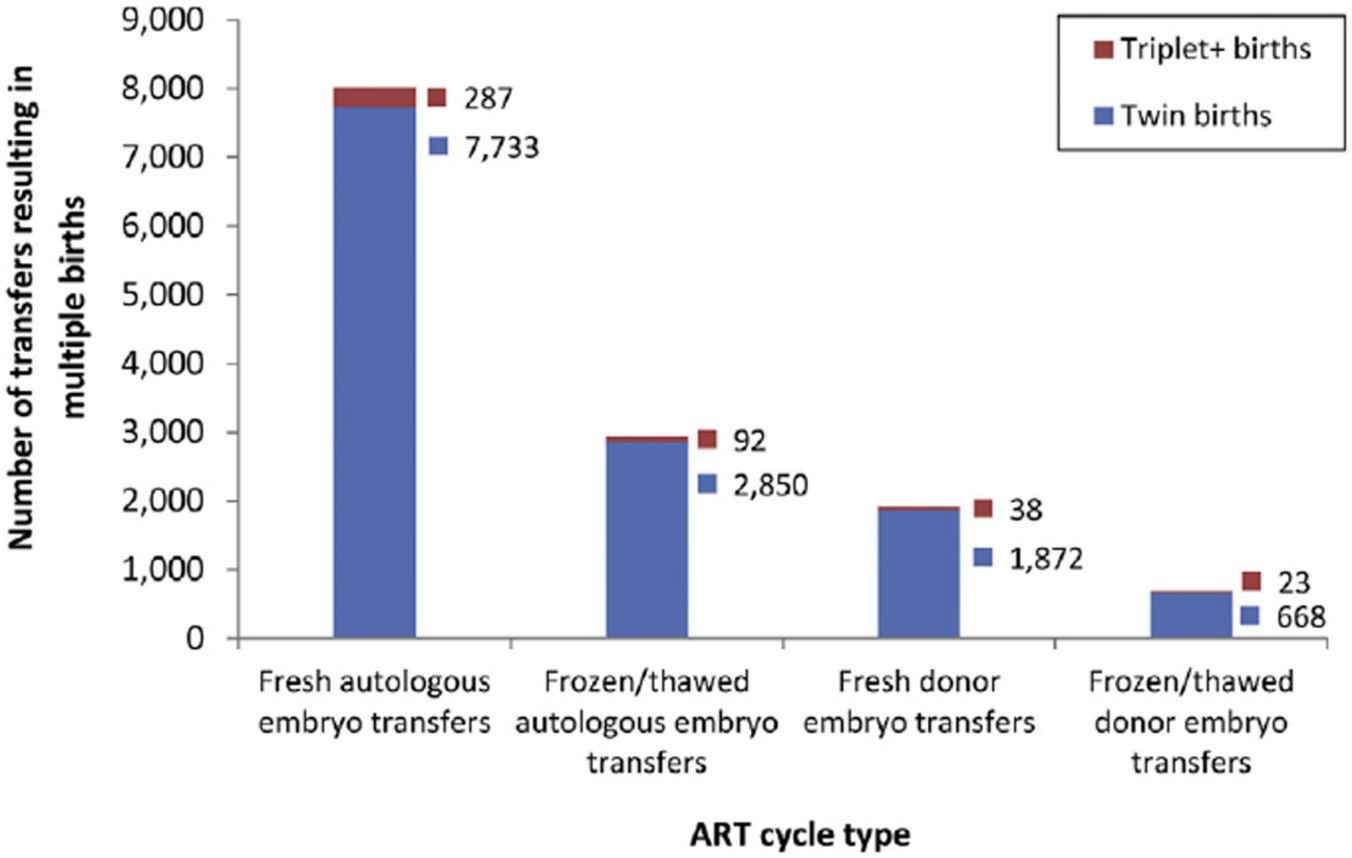

FIGURE 1.

Number of multiple births by type of assisted reproductive technology (ART) cycle and plurality, National ART Surveillance System (NASS), United States, 2012.

Kissin. Multiple births after ART. Fertil Steril 2015.

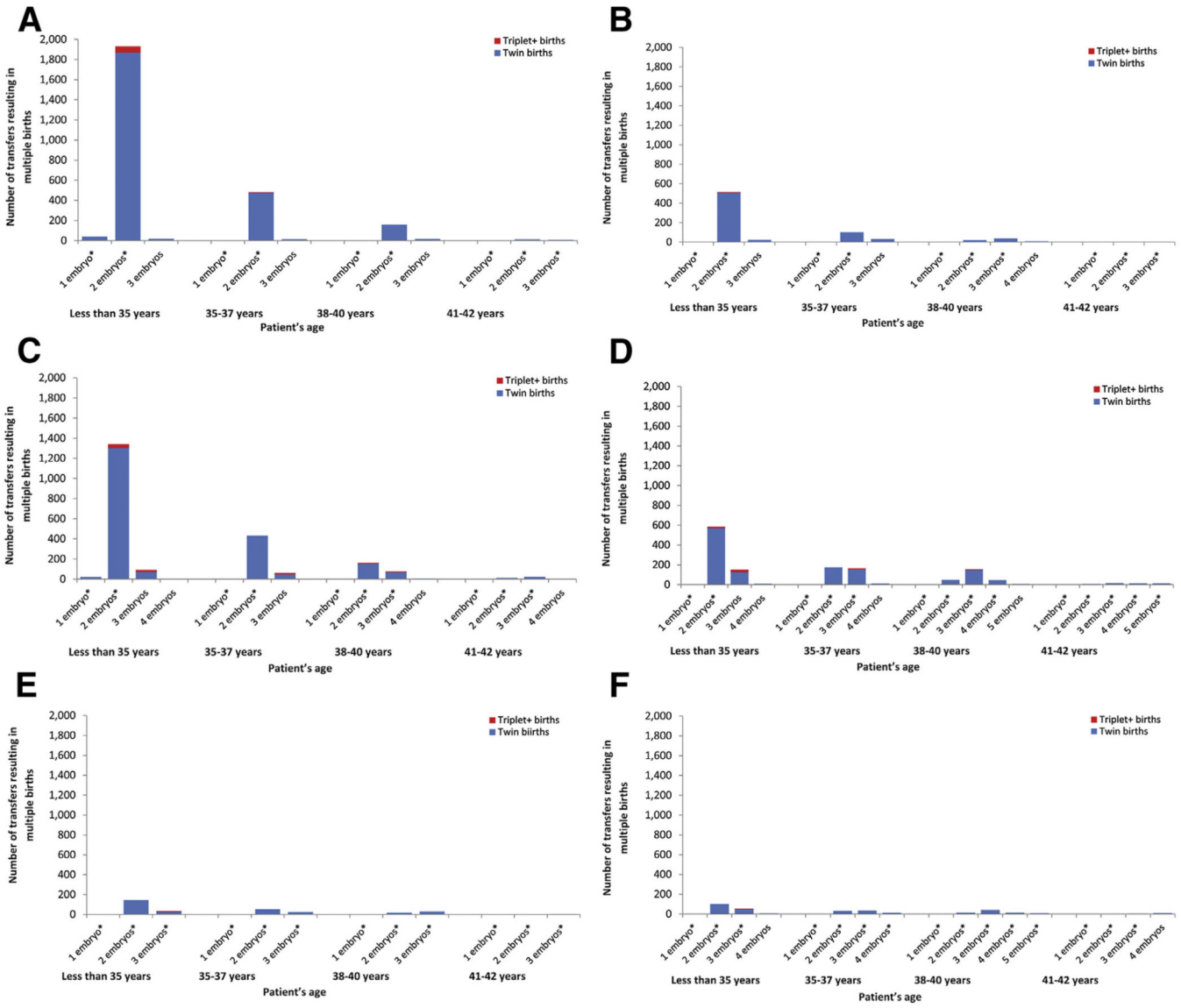

FIGURE 2.

Number of transfers resulting in multiple births by patient's age and number of embryos transferred among patients using fresh embryos from autologous oocytes, United States, 2012. (**A, B**) Favorable prognosis patients (first assisted reproductive technology [ART] cycle and extra embryo(s) cryopreserved) using (**A**) blastocyst stage (days 5–6) and (**B**) cleavage stage (days 2–3) embryos. (**C, D**) Average prognosis patients ([1] first ART cycle and no extra embryo(s) cryopreserved, [2] previous ART cycle(s), no previous live birth(s), but extra embryo(s) cryopreserved, or [3] previous ART cycle(s) and previous live birth(s)) using (**C**) blastocyst stage (days 5–6) and (**D**) cleavage stage (days 2–3) embryos. (**E, F**) Less favorable prognosis patients (previous ART cycle(s), no previous live birth(s), and no extra embryo(s) cryopreserved) using (**E**) blastocyst stage (days 5–6) and (**F**) cleavage stage (days 2–3) embryos. Numbers 1 through 4 are not shown due to confidentiality requirements to suppress small cell tabulations. *Indicates acceptable number of embryos to transfer

according to 2009 American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) Guidelines on Number of Embryos Transferred (12).

Kissin. Multiple births after ART. Fertil Steril 2015.

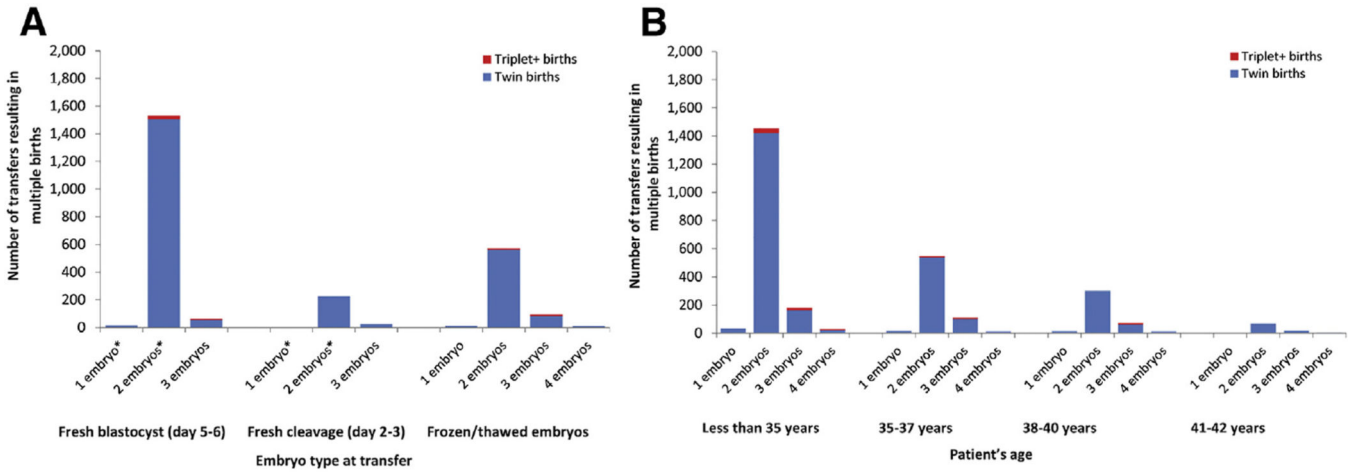

FIGURE 3.

Number of transfers resulting in multiple births among (**A**) patients using donor oocytes and (**B**) patients using frozen/thawed embryos from autologous oocytes by number of embryos transferred, embryo state (fresh and frozen/thawed), embryo stage at transfer (for fresh cycles only), and patient age (for nondonor cycles only), United States, 2012. Numbers 1 through 4 are not shown due to confidentiality requirements to suppress small cell tabulations. *Indicates acceptable number of embryos to transfer according to 2009 American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) Guidelines on Number of Embryos Transferred (for fresh cycles only) (12).

Kissin. Multiple births after ART. Fertil Steril 2015.

TABLE 1

Number and percentage of fresh ETs, by oocyte source, patient age, prognosis, and embryo stage.

			Number and percentage of ETs by number of embryos transferred[f]						
Patient group	**Prognosis**	**Embryo stage**	**1 embryo**	**2 embryos**	**3 embryos**	**4 embryos**	**5 embryos**	**6 embryos**	**7 + embryos**
Autologous oocyte, age <35 y	Favorable[a]	Cleavage[d]	372 (10.7%)[f]	2,941 (84.5%)[f]	165 (4.7%)	1–4[g]	0	0	0
		Blastocyst[e]	3,723 (34.8%)[f]	6,877 (64.4%)[f]	80 (0.7%)	1–4	0	0	0
	Average[b]	Cleavage	1,093 (13.9%)[f]	5,508 (69.8%)[f]	1,159 (14.7%)	104 (1.3%)	18 (0.2%)	1–4	1–4
		Blastocyst	1,920 (21.4%)[f]	6,504 (72.6%)[f]	493 (5.5%)	41 (0.5%)	1–4	1–4	1–4
	Less favorable[c]	Cleavage	371 (14.2%)[f]	1,421 (54.3%)[f]	708 (27.1%)[f]	92 (3.5%)	19 (0.7%)	1–4	1–4
		Blastocyst	242 (15.3%)[f]	1,082 (68.2%)[f]	233 (14.7%)[f]	25 (1.6%)	1–4	1–4	1–4
Autologous oocyte, age 35–37 y	Favorable	Cleavage	116 (8.3%)[f]	1,021 (73.5%)[f]	244 (17.6%)	8 (0.6%)	1–4	0	0
		Blastocyst	947 (28.5%)[f]	2,303 (69.3%)[f]	73 (2.2%)	0	0	0	0
	Average	Cleavage	771 (14.9%)[f]	2,665 (51.6%)[f]	1,544 (29.9%)[f]	165 (3.2%)	16 (0.3%)	1–4	1–4
		Blastocyst	895 (21.1%)[f]	2,854 (67.3%)[f]	450 (10.6%)	41 (1.0%)	1–4	0	0
	Less favorable	Cleavage	343 (18.3%)[f]	759 (40.4%)[f]	619 (33.0%)[f]	139 (7.4%)[f]	16 (0.9%)	1–4	0
		Blastocyst	126 (14.7%)[f]	506 (59.1%)[f]	196 (22.9%)[f]	23 (2.7%)	5 (0.6%)	0	0
Autologous oocyte, age 38–40 y	Favorable	Cleavage	39 (4.5%)[f]	336 (39.0%)[f]	403 (46.8%)[f]	81 (9.4%)	1–4	0	0
		Blastocyst	223 (14.5%)[f]	1,137 (74.1%)[f]	166 (10.8%)	9 (0.6%)	0	0	0
	Average	Cleavage	881 (15.1%)[f]	1,743 (30.0%)[f]	2,311 (39.7%)[f]	746 (12.8%)[f]	113 (1.9%)	15 (0.3%)	10 (0.2%)
		Blastocyst	537 (16.6%)[f]	1,824 (56.4%)[f]	755 (23.3%)[f]	99 (3.1%)	16 (0.5%)	1–4	1–4
	Less favorable	Cleavage	456 (18.1%)[f]	655 (26.0%)[f]	845 (33.5%)[f]	457 (18.1%)[f]	90 (3.6%)[f]	13 (0.5%)	1–4
		Blastocyst	123 (15.3%)[f]	368 (45.8%)[f]	254 (31.6%)[f]	48 (6.0%)[f]	7 (0.9%)	1–4	1–4
Autologous oocyte, age 41–42 y	Favorable	Cleavage	13 (5.0%)[f]	39 (15.1%)[f]	85 (32.9%)[f]	65 (25.2%)[f]	47 (18.2%)[f]	8 (3.1%)	1–4
		Blastocyst	35 (11.2%)[f]	162 (51.8%)[f]	104 (33.2%)[f]	8 (2.6%)	1–4	0	0
	Average	Cleavage	576 (16.5%)[f]	768 (22.0%)[f]	912 (26.1%)[f]	736 (21.1%)[f]	409 (11.7%)[f]	78 (2.2%)	16 (0.5%)
		Blastocyst	244 (19.2%)[f]	432 (34.0%)[f]	455 (35.8%)[f]	107 (8.4%)	26 (2.0%)	8 (0.6%)	0
	Less favorable	Cleavage	300 (17.2%)[f]	420 (24.1%)[f]	419 (24.1%)[f]	343 (19.7%)[f]	202 (11.6%)[f]	43 (2.5%)[f]	13 (0.7%)

Patient group	Prognosis	Embryo stage	Number and percentage of ETs by number of embryos transferred[f]						
			1 embryo	2 embryos	3 embryos	4 embryos	5 embryos	6 embryos	7 + embryos
Donor oocyte, any age	Any	Blastocyst	80 (17.9%)[f]	123 (27.5%)[f]	171 (38.2%)[f]	51 (11.4%)[f]	17 (3.8%)	5 (1.1%)	1–4
		Cleavage	164 (8.1%)[f]	1,611 (79.8%)[f]	210 (10.4%)	29 (1.4%)	5 (0.2%)	1–4	0
		Blastocyst	2,208 (28.7%)[f]	5,199 (67.6%)[f]	255 (3.3%)	31 (0.4%)	1–4	0	0
Total			16,798 (20.0%)[f]	49,258 (58.6%)[f]	13,309 (15.8%)	3,454 (4.1%)	1,023 (1.2%)	189 (0.2%)	55 (0.1%)

Note: From National ART Surveillance System (NASS), United States, 2012.

[a] Favorable prognosis patients include those who underwent first assisted reproductive technology (ART) cycle and had extra embryo(s) cryopreserved.

[b] Average prognosis patients include those who had [1] first ART cycle and no extra embryo(s) cryopreserved, [2] previous ART cycle(s), no previous live birth(s), but extra embryo(s) cryopreserved, or [3] previous ART cycle(s) and previous live birth(s).

[c] Less favorable prognosis patients include those who had previous ART cycle(s), no previous live birth(s), and no extra embryo(s) cryopreserved.

[d] Cleavage stage embryos are defined as embryos transferred on day 2 or 3.

[e] Blastocyst stage embryos are defined as embryos transferred on day 5 or 6.

[f] Acceptable number of embryos to transfer according to 2009 American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) Guidelines on Number of Embryos Transferred (12).

[g] Numbers 1 through 4 are not shown due to confidentiality requirements to suppress small cell tabulations.

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