Original Research

Obstetric and Neonatal Outcomes After Transferring More Than One Embryo in Patients With Preimplantation Genetic Testing

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OBJECTIVE: To compare obstetric and neonatal outcomes after single embryo transfer (SET) compared with multiple embryo transfer (MET) from frozen-thawed transfer cycles of embryos that underwent preimplantation genetic testing for aneuploidies (PGT-A).

METHODS: We conducted a retrospective cohort study from the SART CORS (Society for Assisted Reproductive Technology Clinic Outcome Reporting System) national database. Clinical and demographic data were obtained from the SART CORS database for all autologous and donor egg frozen-thawed transfer cycles of embryos that underwent PGT-A between 2014 and 2016, after excluding cycles that used frozen oocytes, fresh embryo transfer, and transfers of embryos from more than one stimulation cycle. Multivariable linear and log-binomial regression models were used to estimate the relative and absolute difference in live-birth rate, multiple pregnancy rate, gestational age at delivery, and birth weight between SET compared with MET.

RESULTS: In total, 15,638 autologous egg transfer cycles and 944 donor egg transfer cycles were analyzed. Although the live-birth rate was higher with MET compared with SET in the autologous oocyte cycles (64.7% vs 53.2%, relative risk [RR] 1.24, 95% CI, 1.20–1.28), the multiple pregnancy rate was markedly greater (46.2% vs 1.4%, RR 32.56, 95% CI, 26.55–39.92). Donor oocyte cycles showed similar trends with an increased live-birth rate (62.0% vs 49.7%, RR 1.26, 95% CI, 1.11–1.46) and multiple pregnancy rate (54.0% vs 0.8%) seen with MET compared with SET. Preterm delivery rates and rates of low birth weight were significantly higher in MET compared with SET in both autologous and donor oocyte cycles and were also higher in the subanalysis of singleton deliveries that resulted from MET compared with SET.

CONCLUSION: Despite some improvement in live-birth rate, nearly half of the pregnancies that resulted from MET of embryos that underwent PGT-A were multiples. Compared with SET, MET is associated with significantly higher rates of neonatal morbidity, including preterm delivery and low birth weight. The transfer of more than one embryo that underwent PGT-A should continue to be strongly discouraged, and patients should be counseled on the significant potential for adverse outcomes.

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Assisted reproductive technology (ART) has advanced significantly since the first child was born after in vitro fertilization (IVF) in 1978.[1] In

2020, there were 165,041 embryo transfers in the United States that resulted in 79,942 neonates born, which accounts for 2% of all neonates born.[2] Though advancements in laboratory and clinical techniques have improved success rates over the years, the most common complication of ART continues to be multiple gestations due to the transfer of more than one embryo to the uterus.[3–5] In 2018, the percentage of multiple births in the United States was higher among pregnancies conceived through ART (21.4%) than among the total birth population.[6]

The risks of multiple gestations include increased prematurity, growth restriction, disability, and death in neonates, in addition to increased hypertensive disorders, gestational diabetes mellitus, and hemorrhage in mothers.[7,8] Multiple pregnancies also produce large health care costs. It has been estimated that the financial burden of ART-associated preterm deliveries is approximately $1 billion annually.[8] Given the above information, the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology began publishing guidelines in 1998 that recommend the number of embryos to transfer in IVF cycles. In 2017, the guidelines recommended elective single embryo transfer (SET) in all favorable patients aged 37 years or younger. Moreover, after a study that showed that transferring a single euploid blastocyst resulted in pregnancy rates similar to transferring two untested blastocysts while dramatically reducing the risk of twins, elective SET was recommended for all euploid embryo transfers regardless of patient age.[9,10]

Preimplantation genetic testing for aneuploidies (PGT-A) has been developed as an embryo-selection tool to identify embryos with high implantation potential and low miscarriage risk.[11–13] The research and development of PGT-A have been inherently linked to the idea of SET. Because the ASRM and the Society for Assisted Reproductive Technology recommendations are tolerant of multiple embryo transfer (MET) for some patients whose embryos have not undergone PGT-A but support only elective SET for patients with euploid embryos for transfer that have undergone PGT-A, the addition of PGT-A potentially can convert some METs to SETs. When recommendations are followed, such a strategy has been shown to decrease the risk of multiple gestations and the negative pregnancy outcomes that follow, without compromising the live-birth rate.[10–15] However, MET of embryos that have undergone PGT-A is being done, and pregnancy outcomes from national registries that result from the transfer of more than one embryo that has undergone PGT-A have not been reported.[16] For this reason, we aimed to study obstetric and neonatal outcomes after SET compared with MET from frozen-thawed transfer cycles of embryos that had undergone PGT-A. We hypothesized that MET of embryos that had undergone PGT-A would have higher rates of live births, multiple births, preterm deliveries, and low birth weights than SET of embryos that had undergone PGT-A.

METHODS

The data used for this study were obtained from SART CORS (Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART (the Society for Assisted Reproductive Technology Clinic Outcome Reporting System). Data were collected through voluntary submission, verified by the Society for Assisted Reproductive Technology, and 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). The Society for Assisted Reproductive Technology maintains Health Insurance Portability and Accountability Act–compliant business associate agreements with reporting clinics. In 2004, after a contract change with the Centers for Disease Control and Prevention, the Society for Assisted Reproductive Technology gained access to the SART CORS data system for the purposes of conducting research. In 2017, 82% of all ART clinics in the United States were Society for Assisted Reproductive Technology members.[17]

The data in the SART CORS are validated annually with 7–10% of clinics receiving onsite visits for chart review based on an algorithm for clinic selection. During each visit, data reported by the clinic were compared with information in patients' charts. In 2019, records for 2,014 cycles at 34 clinics were randomly selected for full validation, along with 213 fertility preservation cycles selected for partial validation. The full validation included review of 1,300 cycles for which a pregnancy was reported. Nine out of 11 data fields selected for validation were found to have discrepancy rates of 5% or less.[17] The exceptions were the diagnosis field, which, depending on the diagnosis, had a discrepancy rate between 2.5% and 17.8%, and the start date, which had an 8.4% discrepancy rate.[18] Obstetric outcomes from Massachusetts ART records during 2004–2008 have been validated to have more than 95% agreement with vital records.[18]

This study included freeze-all IVF stimulation cycles from 2014 to 2016 that underwent PGT-A testing on blastocyst-stage embryos from autologous

or donor oocytes. The specific PGT-A results for each embryo, and its classification as euploid, aneuploid or mosaic, are not recorded in SART CORS. The subsequent cycles in which these frozen embryos were transferred were linked to the stimulation cycles from which the embryos originated. The study was limited to the first transfer cycle per individual patient within the defined study period. Cycles that used frozen oocytes, fresh embryo transfer, or transfers of embryos from more than one stimulation cycle were excluded. Stimulation cycles with only one frozen embryo were excluded, because such patients did not have the possibility to undergo MET.

The primary outcomes were live-birth rate and multiple pregnancy rate. *Live birth* was defined as delivery of a liveborn neonate at 24 weeks of gestation or later, and the *multiple pregnancy rate* was defined as the number of multiple pregnancies among all live births. Secondary outcome measures included clinical pregnancy rate, gestational age at delivery, and birth weight. *Clinical pregnancy* was defined as ultrasonographic visualization of an intrauterine gestational sac. We additionally created two categories for prematurity (less than 37 weeks and less than 34 weeks), low birth weight (less than 2,500 g), and very low birth weight (less than 1,500 g). Other relevant demographic and clinical variables were also retrieved from the SART CORS database, including patient age at time of frozen-thawed embryo transfer, donor age at IVF cycle stimulation (donor cycles only), reason for seeking ART, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) at the time of frozen-thawed transfer, maximum follicle-stimulating hormone (FSH) level (autologous cycles only), last recorded anti-müllerian hormone (AMH) level (autologous cycles only), gravidity, prior spontaneous abortion, and parity.

To address missing data in BMI, maximum FSH level, gravidity, and parity, we created 10 imputed data sets using multiple imputation by chained equations ("mice"),[19] where missing observations for each variable were iteratively imputed through regression models using available information from other variables. Outliers in BMI were set to 99th percentile of the data to minimize their influence. Relative and absolute differences between groups were estimated using log-binomial and linear regression, respectively. Estimates from each imputed data set were pooled using Rubin's Rule,[20,21] which accounts for variance across imputed data sets. For birth weight, we used general estimating equations to account for nonindependent observations in birth weights due to multiple pregnancies. Additionally, for models related to birth weight and gestational age, we used a double robust inverse probability weighting approach to address potential live-birth bias.[22] Within each of the imputed data sets, we calculated stabilized inverse probability weights for probability of being censored (ie, live birth) and being assigned the treatment (SET vs MET), and applied the weights to the relevant models. Analysis was repeated on the subset of complete data for primary analyses to establish effects without multiply imputed data. Regression analysis was also repeated using 1:1 propensity score matching rather than inverse probability weighting.

All analyses were stratified based on autologous compared with donor oocytes. Models were adjusted for patient age, BMI, gravidity, parity, and reasons for seeking ART treatment (binary variables for male infertility, endometriosis, polycystic ovaries, diminished ovarian reserves, uterine factor infertility, ovulation disorders, and tubal factor). Autologous models were additionally adjusted for the last recorded AMH level and maximum FSH level, and donor models were additionally adjusted for donor age. To specifically compare singletons born from SET with those born from MET (and likewise for multiple pregnancies), sensitivity analyses were performed using models of birth weight and gestational age stratified by singleton compared with multiple pregnancies.

This project was conducted after internal institutional review board review and approval (Montefiore IRB 2019-9899, approved January 24, 2019). Nonidentifiable patient data were obtained from SART CORS. Patient consent was not required because this work exclusively used retrospective data from a national registry collected during routine care.

RESULTS

A total of 15,638 patients who underwent autologous egg cycles were included in analysis, with 12,932 patients who had SET and 2,706 patients who had MET. In the MET group, 17 patients had three embryos transferred and the remainder had two embryos transferred. Of all recorded pregnancies, 15 were noted to be triplet live births and 13 of the 15 triplet live births resulted from the MET group. Age, BMI, and AMH level were clinically comparable between SET and MET (Table 1). The patients in the SET group were more likely to be parous and less likely to have a history of spontaneous abortion, although the differences were small.

Estimates from multivariable models, including both relative and absolute risk differences, reflected significant differences in all clinical outcomes between SET and MET (Table 2). Clinical pregnancy rates

Table 1. Characteristics of Patients Who Had Autologous Egg Frozen Embryo Transfer of an Embryo or Embryos That Underwent Preimplantation Genetic Testing for Aneuploidies

	SET (n=12,932)	MET (n=2,706)	*P*
Demographics			
Age (y)	36.54±3.72	35.79±3.81	<.001
BMI (kg/m^2)	24.67±4.97	25.41±5.24	<.001
AMH (ng/mL)	2.41±3.04	2.65±3.29	<.001
Gravidity			<.001
0	4,895 (37.9)	898 (33.2)	
1 or more	8,022 (62.1)	1,806 (66.8)	
Parous	3,891 (30.3)	712 (26.6)	<.001
Previous spontaneous abortion			<.001
0	7,812 (60.5)	1,497 (55.4)	
1 or more	5,102 (39.5)	1,207 (44.6)	
Reason(s) for seeking ART*			
Male infertility	3,488 (27.0)	821 (30.4)	<.001
Endometriosis	729 (5.6)	186 (6.9)	.01
Polycystic ovaries	1,897 (14.7)	481 (17.8)	<.001
Diminished ovarian reserve	3,298 (25.5)	731 (27.0)	.09
Uterine factors	817 (6.3)	262 (9.7)	<.001
Ovulation disorders	3,324 (25.7)	582 (21.5)	<.001
Any tubal factors	1,139 (8.8)	293 (10.8)	.001

SET, single embryo transfer; MET, multiple embryo transfer; BMI, body mass index; AMH, anti-müllerian hormone; ART, assisted reproductive technology.
Data are mean±SD or n (%) unless otherwise specified.
* Percentages may add up to more 100% due to patients having multiple diagnoses.

were significantly higher with MET than with SET (73.8% vs 62.0%, relative risk [RR] 1.2, 95% CI, 1.17–1.23). Live-birth rates were also significantly higher in the MET group (64.7% vs 53.2%, RR 1.24, 95% CI, 1.2–1.28), along with a dramatically higher multiple pregnancy rate (46.2% vs 1.4%, RR 32.56, 95% CI, 26.55–39.92) (Table 2). Preterm delivery rates before 37 weeks of gestation (37.7% vs 12.0%, RR 2.93, 95% CI, 2.69–3.20) and before 34 weeks of gestation (10.8% vs 3.1%, RR 3.22, 95% CI, 2.68–3.89) were significantly elevated in MET cycles compared with SET cycles. Compared with SET, births from MET had a lower mean birth weight (−603.5 g, 95% CI, −644.6 to −562.3), a higher risk for low birth weight (35.7% vs 8.0%, RR 4.34, 95% CI, 3.89–4.85), and a higher risk for extremely low birth weight (5.6% vs 1.4%, RR 4.68, 95% CI, 3.41–6.43). Additionally, when restricting analysis to only singleton live births, the rate of preterm delivery and low birth weight remained statistically significantly higher in the MET group compared with the SET group (Table 3).

A total of 944 were included in the donor egg cycle analysis. This included 723 patients who had SET and 221 patients who had MET. All METs were of two embryos. Age of donor and recipient, BMI, gravidity, parity, and reason for seeking ART were clinically comparable between the two groups (Table 4). Clinical pregnancy rate was significantly higher with MET than with SET for donor egg cycles (71.0% vs 60.0%, RR 1.2, 95% CI, 1.08–1.33). The live-birth rate was also significantly higher in the MET group (62.0% vs 49.7%, RR 1.26, 95% CI, 1.11–1.43) and was accompanied by a markedly increased multiple pregnancy rate (54.0% vs 0.8%) (Table 5). Preterm delivery rates and rates of low birth weight were significantly elevated in MET cycles compared with SET cycles.

As a sensitivity analysis and alternative to direct model adjustments, we performed 1:1 propensity score matching following the same modeling strategies in both the autologous and donor egg cycles. There were no appreciable differences in the results of these models compared with our presented models. These findings included as Appendices 1–4, available online at http://links.lww.com/AOG/D482.

DISCUSSION

The development and clinical utilization of PGT-A has been strongly linked to a rise in SET.[10–16] Preimplantation genetic testing for aneuploidies has been promoted as an embryo-selection tool to identify individual embryos with high implantation potential, as well as high clinical pregnancy and live-birth rates after SET.[10–16] Nonetheless, it has not been proven in randomized trials to improve live-birth rate per single embryo transferred in patients younger than

Table 2. Pregnancy and Neonatal Outcomes Among People Receiving Autologous Egg Multiple Embryo Transfer Compared With Single Embryo Transfer of an Embryo or Embryos That Underwent Preimplantation Genetic Testing for Aneuploidies*

	SET	MET	Adjusted RR (95% CI)	Adjusted RD (%) (95% CI)	Adjusted MD [β (95% CI)]
Clinical pregnancy	8,018 (62.0)	1,997 (73.8)	1.20 (1.17–1.23)	12 (0.1–0.14)	
Live birth	6,876 (53.2)	1,750 (64.7)	1.24 (1.2–1.28)	12 (0.1–0.14)	
Transfers resulting in singleton	6,778 (52.5)	941 (34.8)	0.67 (0.64–0.71)	−17 (−0.19 to −0.15)	
Transfers resulting in multiples	98 (0.8)	809 (29.9)	40.14 (32.65–49.35)	29 (0.28–0.3)	
Multiple pregnancy rate†	98 (1.4)	809 (46.2)	32.56 (26.55–39.92)	45 (0.44–0.46)	
Birth weight (g)‡	3,335.34±608.51	2,726.52±738.09			−603.46 (−644.61 to −562.3)
Less than 2,500	552 (8.0)	904 (35.7)	4.34 (3.89–4.85)	27 (0.25–0.3)	
Less than 1,500	81 (1.2)	143 (5.6)	4.68 (3.41–6.43)	4 (0.03–0.06)	
Gestational age (wk)§	38.90±2.26	37.23±3.18			−1.63 (−1.76 to −1.5)
Less than 37	828 (12.0)	659 (37.7)	2.93 (2.69–3.20)	25 (0.23–0.27)	
Less than 34	211 (3.1)	189 (10.8)	3.22 (2.68–3.89)	8 (0.06–0.09)	

SET, single embryo transfer; MET, multiple embryo transfer; RR, relative risk; RD, risk difference; MD, mean difference.
Data are n (%) or mean±SD unless otherwise specified.
* All models were adjusted for age, body mass index (BMI), gravidity, parity, male infertility, endometriosis, polycystic ovaries, diminished ovarian reserve, uterine factor infertility, ovulation disorders, tubal factor infertility, last recorded anti-müllerian hormone level, and maximum follicle-stimulating hormone level.
† Defined as multiple pregnancies among only live births.
‡ Summary statistics calculated as per neonate, regardless of singleton or multiple births. For modeling, generalized estimating equation was used to account for correlation between birth weights from nonsingleton pregnancies. Reduced covariates (age, BMI) were used to help model convergence, but the inclusion of other covariates one by one did not substantively alter model estimates.
§ Restricted to pregnancies with live births.

age 35 years, largely because of the low rate of aneuploidy in younger patients.[23] However, for increasing oocyte age and particularly older than age 38 years, the live-birth rate per intended SET will be higher with PGT-A than without PGT-A.[23] Thus, by adopting SET accompanied by PGT-A, with its simultaneous increase in live-birth rate per transfer, MET of untested embryos may be replaced by SET, particularly among women older than age 35 years.

However, the reality of clinical practice as evidenced by national registry data appears to contradict this rosy picture. The mean age in this cohort was approximately 36 years for women undergoing autologous IVF cycles and 26 years for oocyte donors, implying that the majority of PGT-A in autologous cycles and almost all PGT-A in donor cycles was performed in women younger than age 38 years, for whom elective SET would have been recommended even in the absence of PGT-A. In this context, it is striking that so many METs were performed, most of which would have been not recommend even without PGT-A.

This study represents the first comprehensive analysis of the outcomes and consequences of MET of embryos that have undergone PGT-A using U.S.-based national registry data. We identified 2,927 such cases and affirm that obstetric and neonatal outcomes when multiple embryos that have undergone PGT-A are transferred are far worse than the outcomes with elective SET. Although the live-birth rate was higher in the MET group, the magnitude of increase in multiple pregnancy rate was far greater. The neonatal consequences also demonstrate a significant increase in both preterm delivery and low birth weight.

Although in the past the goal of ART was solely to maximize live-birth rates, high-quality clinical practice now also demands consideration of the health of the parent and children created through these technologies. The availability of more than one embryo suitable for transfer forces a risk benefit calculation at an emotionally difficult time. The primary analyses of this study demonstrate that, although there is improvement in live-birth rate per transfer when transferring more than one embryo that has undergone PGT-A at a time, the maternal and neonatal morbidity from a 46.2% multiple pregnancy rate in autologous egg MET and a 54.0% multiple pregnancy rate in donor egg MET must be weighed against the improvement in live-birth rate.

Table 3. Pregnancy and Neonatal Outcomes Among Singleton Live Births From Autologous Egg Multiple Embryo Transfer Compared With Single Embryo Transfer of Embryos That Underwent Preimplantation Genetic Testing for Aneuploidies*

	SET	MET	Adjusted RR (95% CI)	Adjusted RD (%) (95% CI)	Adjusted MD [β (95% CI)]
Birth weight (g)†	3,368.05 (576.45)	3,260.57 (664.80)			−100.86 (−151.87 to −49.85)
Less than 2,500	422 (6.3)	92 (9.9)	1.50 (1.19–1.88)	3 (0.01–0.05)	
Less than 1,500	57 (0.9)	23 (2.5)	2.73 (1.63–4.58)	2 (0–0.03)	
Gestational age (wk)‡	38.96 (2.19)	38.53 (2.78)			−0.39 (−0.54 to −0.24)
Less than 37	750 (11.1)	156 (16.6)	1.42 (1.22–1.65)	5 (0.03–0.07)	
Less than 34	188 (2.8)	44 (4.7)	1.49 (1.1–2.03)	1 (0–0.03)	

SET, single embryo transfer; MET, multiple embryo transfer; RR, relative risk; RD, risk difference; MD, mean difference.
Data are n (%) unless otherwise specified.
* All models were adjusted for age, body mass index (BMI), gravidity, parity, male infertility, endometriosis, polycystic ovaries, diminished ovarian reserve, uterine factor infertility, ovulation disorders, and tubal factor infertility.
† Summary statistics calculated as per neonate, regardless of singleton or multiple births. For modeling, generalized estimating equation was used to account for correlation between birth weights from nonsingleton pregnancies. Reduced covariates (age, BMI) were used to help model convergence, but the inclusion of other covariates one by one did not substantively alter model estimates.
‡ Restricted to pregnancies with live births.

We found that singleton pregnancies resulting from MET were more likely to be complicated by preterm delivery or low birth weight than singleton pregnancies resulting from SET (Table 3). Although the SART CORS database does not offer an obvious explanation for this phenomenon, we speculate that some singleton pregnancies resulting from MET were complicated by a vanishing twin, which has been shown to negatively affect perinatal outcomes in the surviving twin,[24] implying that even MET resulting in a singleton live birth may incur additional harm.

Most remarkably, MET of embryos that have undergone PGT-A did not even increase the rate of singleton live birth, largely due to the very high rate of

Table 4. Characteristics of Patients Who Had Donor Egg Frozen Embryo Transfers of an Embryo or Embryos That Underwent Preimplantation Genetic Testing for Aneuploidies

	SET (n=723)	MET (n=221)	*P*
Demographics			
Recipient age (y)	42.17±4.75	41.65±5.37	.2
Donor age (y)	26.67±3.97	25.78±3.67	.003
Recipient BMI (kg/m^2)	24.13±5.04	25.85±5.60	.007
Donor type			
Anonymous	653 (90.3)	208 (94.1)	.1
Known	70 (9.7)	13 (5.9)	
Gravidity of recipient			.94
0	325 (45.8)	98 (46.2)	
1 or more	385 (54.2)	114 (53.8)	
Parous recipient	174 (24.6)	45 (21.3)	.36
Reason(s)s for seeking ART*			
Male infertility	107 (14.8)	23 (10.4)	.12
Endometriosis	29 (4.0)	5 (2.3)	.3
Polycystic ovaries	11 (1.5)	7 (3.2)	.16
Diminished ovarian reserve	509 (70.4)	124 (56.1)	<.001
Uterine factors	43 (5.9)	17 (7.7)	.35
Ovulation disorders	422 (58.4)	83 (37.6)	<.001
Any tubal factors	31 (4.3)	6 (2.7)	.43

SET, single embryo transfer; MET, multiple embryo transfer; BMI, body mass index; ART, assisted reproductive technology.
Data are mean±SD or n (%) unless otherwise specified.
* Percentages may add up to more 100% due to patients having multiple diagnoses.

Table 5. Pregnancy and Neonatal Outcomes Among People Undergoing Donor Egg Multiple Embryo Transfer Compared With Single Embryo Transfer of Embryos That Underwent Preimplantation Genetic Testing for Aneuploidies*

	SET	MET	Adjusted RR (95% CI)	Adjusted RD (%) (95% CI)	Adjusted MD (95% CI)
Clinical pregnancy	441 (60.2)	159 (71.0)	1.20 (1.08–1.33)	11 (0.04–0.19)	
Live birth	364 (49.7)	137 (62.0)	1.26 (1.11–1.43)	13 (0.06–0.21)	
Transfers resulting in singletons	361 (49.2)	63 (28.5)	0.59 (0.47–0.74)	−20 (−0.27 to −0.12)	
Transfers resulting in multiples	3 (0.4)	74 (33.5)			
Multiple pregnancy rate†	3 (0.8)	74 (54.0)			
Birth weight (g)‡	3,211.38±609.8	2,766.76±605.0			−473.72 (−599.67 to −347.78)
Less than 2,500	41 (11.6)	68 (33.8)	3.21 (2.19–4.7)	24 (0.16–0.32)	
Gestational age (wk)§	38.51±2.2	37.03±2.5			−1.57 (−2.02 to −1.11)
Less than 37	58 (16.2)	58 (42.6)	2.79 (2.07–3.77)	31 (0.22–0.4)	

SET, single embryo transfer; MET, multiple embryo transfer; RR, relative risk; RD, risk difference; MD, mean difference.
Data are n (%) or mean±SD unless otherwise specified.
* All models adjusted for patient age, donor age, donor type (anonymous or known), patient body mass index.
† Defined as multiple pregnancies among only live births.
‡ Calculated as per neonate, regardless of singleton or multiple births. Analyses for extremely low birth weight (less than 1,500 g) not shown due to insufficient sample size.
§ Restricted to pregnancies with live births. Analyses for extreme prematurity (less than 28 weeks) not shown due to insufficient sample size.

multiple pregnancies after MET when pregnancy resulted. Patients using autologous MET actually had a lower rate of singleton live birth than those who underwent SET (34.7% vs 52.4%). Similar results were also noted with the donor oocyte transfers. Our results show that MET does not result in a higher rate of the ideal outcome of singleton live birth.

Since SET has gained popularity, there has been a shift from looking at the live-birth rate per embryo transfer to cumulative live-birth rate.[25] Prior studies have found no decline in the live-birth rate of subsequent cycles after a failed euploid embryo transfer.[25] This implies that a sequential strategy, in which a failed SET is followed by another SET, may also lead to a higher live-birth rate compared with MET of two embryos that have undergone PGT-A.[25–29] A SET-only policy with embryos that have undergone PGT-A likely would maximize cumulative live-birth rate (ie, the rate of at least one live birth) while minimizing maternal and neonatal morbidity.

In 2013, the ASRM guidelines for number of embryos to transfer did not yet include information specific to embryos that had undergone PGT-A.[30] Embryos that had undergone PGT-A were not specifically addressed until the 2017 guidelines, when it was recommended that only one euploid embryo be transferred at a time regardless of patient age or embryo stage.[9] This study includes patients who underwent treatment between 2014 and 2016, before publication of the 2017 guidelines. However, these guidelines were based on earlier literature contemporaneous with the included cycles establishing that PGT-A was meant to be used in conjunction with SET.[10] It is possible that, since the 2017 ASRM guidelines were released, the practice of transferring more than one euploid embryo has become even more rare.

This study was limited by the lack of results from PGT-A to the research team. Some included embryo transfers were potentially indeterminate, mosaic or even aneuploid. We speculate that MET was more likely to include a noneuploid embryo or an embryo of poor quality and that this may have been used to justify the MET. In this case, the data could underestimate the actual multiple pregnancy rate, which may have been higher if all embryos transferred were confirmed to be euploid. Additionally, the lack of aneuploidy testing results means we do not know whether there were additional euploid embryos available for transfer among patients who underwent SET. Future studies on data sets including embryo-level aneuploidy testing results may enable a better understanding of why physicians (and patients) choose to do MET and focus research on those specific scenarios. The study was also limited by the retrospective nature

of the national registry. Some patient characteristics, such as race and smoking, are self-reported and known to be less accurate in this data set, which is why they weren't included in this study. There remain known, albeit generally small, discrepancies in the SART CORS data set, including potential errors in, for example, reported BMI (if not measured on the day of transfer) and infertility diagnoses and the possibility of isolated data-entry errors.

Overall, this work reinforces the well-established neonatal implications of performing transfers in excess of recommendations designed to minimize multiple pregnancies.[4–6] Although no guidelines have ever endorsed MET of embryos that have undergone PGT-A, at least if they are euploid, the national registry data from 2014 to 2016 highlight that this is a common practice, at 17.3% of autologous PGT-A transfers and 23.4% of donor oocyte PGT-A transfers. Although there is a clear increase in the live-birth rate per transfer with MET compared with SET, MET is associated with an unacceptably high rate of multiple pregnancy rates, a low rate of singleton pregnancies, and a high risk of low birth weight and preterm deliveries, even among the singleton deliveries resulting from MET compared with SET. Consistent with the most recent ASRM guidelines, there appears to be no role in contemporary clinical practice for MET in euploid embryos that have undergone PGT-A.

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