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Fresh vs. frozen embryo transfer: new approach to minimize the limitations of using national surveillance data for clinical research

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Abstract

Objective: To assess the benefit of frozen vs. fresh elective single embryo transfer using traditional and novel methods of controlling for confounding.

Design: Retrospective cohort study using data from the National Assisted Reproductive Technology Surveillance System.

Setting: Not applicable.

Patient(s): A total of 44,750 women aged 20–35 years undergoing their first lifetime oocyte retrieval and embryo transfer in 2016–2017, who had ≥4 embryos cryopreserved.

Intervention(s): Fresh elective single embryo transfer and frozen elective single embryo transfer.

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El resumen está disponible en Español al final del artículo.

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Main Outcome Measure(s): The primary outcome was a singleton live birth. Secondary outcomes included rates of total live birth (singleton plus multiple gestations), twin live birth, clinical intrauterine gestation, total pregnancy loss, biochemical pregnancy, and ectopic pregnancy. Outcomes for infants included gestational age at delivery, birth weight, and being small for gestational age.

Result(s): The eligibility criteria were met by 6,324 fresh and 2,318 frozen cycles. Patients undergoing fresh and frozen transfer had comparable mean age (30.69 [standard deviation {SD} 0.08] years vs. 31.06 [SD 0.08] years) and body mass index (24.76 [SD 0.20] vs. 25.65 [SD 0.15]); however, women in the frozen cohort created more embryos (8.1 [SD 0.12] vs. 6.8 [SD 0.08]). Singleton live birth rates in the fresh vs. frozen groups were 51.4% vs. 48.8% (risk ratio 1.05; 95% confidence interval [CI], 1.00–1.10). After adjustment with a log-linear regression model and propensity score analysis, the difference in singleton live birth rates remained nonsignificant (adjusted risk ratio, 1.05; 95% CI, 0.97–1.14 and 1.02; 95% CI, 0.96–1.08, respectively). A novel dynamical model confirmed inherent fertility (probability of ever achieving a pregnancy) was balanced between groups (odds ratio, 1.23; 95% CI 0.78–1.95]). The per-cycle probability of singleton live birth was not different between groups (odds ratio 1.11 [95% CI 0.94–1.3]).

Conclusion(s): In this retrospective cohort study of fresh vs. frozen elective single embryo transfer, there was no statistically significant difference in singleton live birth rate after adjustment using log-linear models and propensity score analysis. The successful application of a novel dynamical model, which incorporates multiple assisted reproductive technology cycles from the same woman as a surrogate for inherent fertility, offers a novel and complementary perspective for assessing interventions using national surveillance data.

Abstract

Analizar los beneficios de la transferencia electiva de un embrión congelado vs. uno fresco utilizando métodos tradicionales y novedosos para controlar factores de confusión.

Estudio de cohorte retrospectiva utilizando datos del Sistema Nacional de Vigilancia de Técnicas de Reproducción Asistida (“National Assisted Reproductive Technology Surveillance System”).

No aplicable.

Un total de 44.750 mujeres entre 20 y 35 años sometidas a su primera captación ovocitaria y transferencia embrionaria en 2016–2017 que tuvieron ≥4 embriones criopreservados.

Transferencia electiva de un único embrión en fresco y transferencia electiva de un único embrión congelado.

El resultado primario fue el recién nacido vivo único. Entre los resultados secundarios se incluyeron las tasas de nacimiento vivo totales (gestaciones únicas y múltiples), de nacimiento vivo gemelar, de gestación clínica intrauterina, de pérdida de gestación total, de gestación bioquímica y de gestación ectópica. Los resultados para los niños incluyeron la edad gestacional al parto, el peso al nacer, y ser pequeño para la edad gestacional.

Los criterios de elegibilidad se cumplieron en 6.324 ciclos en fresco y en 2.318 ciclos congelados. En las pacientes que se transfirieron el embrión fresco o congelado tuvieron comparables tanto la edad media (30.69 [desviación estándar {SD} 0.08] años vs. 31.06 [SD 0.08] años) como el índice de masa corporal (24.76 [SD 0.20] vs. 25.65 [SD 0.15]). Sin embargo, las mujeres de la cohorte

de congelados generaron más embriones (8.1 [SD 0.12] vs. 6.8 [SD 0.08]). Las tasas de recién nacido único en los grupos de fresco vs. congelado fueron de 51.4% vs. 48.8% (riesgo relativo 1.05; intervalo de confianza del 95% [CI], 1.00–1.10). Tras el ajuste con un modelo de regresión lineal logarítmico y con el estudio de la puntuación de propensión, la diferencia en las tasas de recién nacido vivo único se mantuvieron no significativas (razón de riesgo ajustada, 1.05; 95% CI, 0.97–1.14 y 1.02; 95% CI, 0.96–1.08, respectivamente). Un novedoso modelo dinámico confirmó que la fertilidad inherente (probabilidad de conseguir una gestación en algún momento) estaba equilibrada entre los grupos (razón de probabilidad, 1.23; 95% CI 0.78–1.95]). La probabilidad de un recién nacido vivo por ciclo no fue diferente entre los grupos (razón de probabilidad 1.11 [95% CI 0.94–1.3]).

En este estudio retrospectivo de cohortes de transferencias de embrión único fresco vs. congelado, y utilizando modelos de regresión lineal logarítmicos y el estudio de la puntuación de propensión, no hubo diferencias estadísticamente significativas en las tasas de recién nacido vivo único. La aplicación con éxito de un novedoso modelo dinámico, que incorpora múltiples ciclos de técnicas de reproducción asistida en la misma mujer, como sustituto de la fertilidad inherente, ofrece una perspectiva novedosa y complementaria para valorar intervenciones, utilizando datos de vigilancia nacionales.

Keywords

Frozen embryo transfer; fresh embryo transfer; real-world data; national database; modeling

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It has been hypothesized that there is a benefit of delaying embryo transfer (often called a “freeze all” in vitro fertilization [IVF] cycle) relative to performing an immediate (“fresh”) transfer. In a “freeze all” cycle, all viable embryos are cryopreserved to delay embryo transfer until the supraphysiologic hormone levels, induced by ovarian stimulation, have resolved, potentially improving pregnancy rates. If true, this would represent a dramatic shift in the standard approach to IVF. A recent randomized controlled trial (RCT) (1) comparing live birth rates after frozen (delayed) vs. fresh (immediate) elective single embryo transfer performed in China demonstrated a modest benefit of frozen embryo transfer; however, the generalizability of these findings is limited (2, 3).

Although arduous in all fields, RCTs are especially challenging to conduct in reproductive medicine because exclusion from federal research funding and unique ethical concerns pose added barriers (4). As a result, RCTs involving assisted reproductive technologies (ARTs), including IVF, are especially rare (5). Well-powered observational studies using national ART databases have become a common methodologic approach to assess interventions in a real-world setting (6). However, concerns linger regarding the quality of these data, the effects of unmeasured covariates, and the potential for confounding by indication (7).

Although some factors that contribute to a woman’s fertility can be measured (e.g., age and ovarian reserve), it is also possible that women have a differential “inherent fertility” (probability of ever achieving a pregnancy) (8). If true, this latent variable has the potential to impact the type of fertility treatment a woman receives as well as the outcome of fertility treatment, representing a source of unmeasured confounding. Because many women

undergo multiple embryo transfers to achieve a live birth, and success or failure after a single (index) embryo transfer will not alter a woman's inherent fertility, we hypothesized that inherent fertility could be estimated using longitudinal data from subsequent fertility treatment cycles. This information could then be used to control for inherent fertility when examining factors that contribute to the success in the index embryo transfer, in conjunction with current methods to control for confounding.

Using data from the National ART Surveillance System (NASS), this study aims to assess the benefit of delaying embryo transfer using both traditional analytic approaches that address confounding and a novel dynamical model to account for the latent variable of "inherent fertility." The availability of population level surveillance data provides a unique opportunity to investigate this clinical question in a real-world setting.

MATERIALS AND METHODS

Data Source

The Centers for Disease Control and Prevention (CDC) maintains NASS, which includes data from approximately 98% of IVF cycles performed in the United States (9). Reporting to NASS has been federally mandated since 1992, and 547,692 ART cycles were reported from 2016–2017 (10). Moreover, NASS collects information on patient characteristics, treatment parameters, and IVF cycle outcomes. Annual data validation was performed in 7%–8% of reporting clinics during the study period and found very low discrepancy rates (<4%) (9, 11). As of 2016, NASS allows embryo transfer cycles to be linked to the corresponding oocyte retrieval cycle. Epidemiological research of NASS data was approved by the Institutional Review Board at the CDC.

Study Design

Our study population comprised all women who underwent their first oocyte retrieval and embryo transfer (index transfer) in 2016 or 2017. Women aged 20–35 years who underwent a single embryo transfer with cryopreservation of additional embryos (elective single embryo transfer) were eligible. To facilitate the comparison with the recent RCT (1), we applied similar eligibility criteria. The RCT was restricted to ovulatory patients, as the investigators had previously studied a polycystic ovarian syndrome population. Consequently, cycles with a diagnosis of ovulatory dysfunction were excluded from this analysis. Cycles for uterine factor infertility were also excluded. Although preimplantation genetic testing (PGT) use is common among younger women, inclusion of PGT cycles would introduce bias in favor of the frozen embryo transfer cohort; PGT cycles were excluded from the clinical trial and this analysis (12). The population was further restricted to cycles that resulted in ≥4 embryos using an antagonist IVF protocol (Fig. 1). Application of these restrictive eligibility criteria ensured that the study population was limited to patients with a favorable prognosis (e.g., age <35 years with multiple embryos available for cryopreservation) who are most likely to have the opportunity to delay embryo transfer.

Eligible women who underwent a frozen single embryo transfer were considered exposed (frozen cohort) and were compared with those who underwent a fresh single embryo transfer

(fresh cohort). All cycles that met eligibility criteria were included to maximize statistical testing power.

Outcomes

The primary outcome was a singleton live birth. Secondary outcomes included rates of total live birth (singleton plus multiple gestations) (Supplemental Fig. 1, available online), twin live birth, clinical intrauterine gestation, total pregnancy loss, biochemical pregnancy, and ectopic pregnancy. Outcomes for infants included gestational age at delivery, birthweight, and being small for gestational age.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) and between cohort differences were compared by the Student's *t* test. Categorical variables were represented as frequency and percentage; differences in these variables were assessed using Pearson's correlation coefficient test. Between cohort differences in outcomes were also compared with Pearson's correlation coefficient test and crude risk ratios were calculated without adjustment for potential confounders.

Adjusting for confounding.—The crude analysis was adjusted using a log-linear model and propensity score analysis. Risk ratios for singleton live birth were calculated by fitting a log-linear regression model using Poisson regression, with inference based on a robust variance estimator rather than the Poisson regression variance (13). Adjusted risk ratios controlled for a predetermined set of potential confounders, which included patient characteristics (age, body mass index (BMI), race and ethnicity, duration of infertility, reason for ART, gravidity, parity, and antimüllerian hormone [AMH] level) and cycle characteristics (days of stimulation, total gonadotropin dose, number of oocytes retrieved, use of intracytoplasmic sperm injection, number of embryos created, and development of moderate or severe ovarian hyperstimulation syndrome [OHSS]). Four variables (BMI, race and ethnicity, AMH level, and duration of infertility) with moderate (»20%) to high levels of missingness (≥40%) were imputed and 5 different imputed data sets were created (Supplemental Methods). Indicators for missing values of these variables were also included as covariates in the model fitting using imputed data (14). The adjusted risk ratios from the 5 imputed datasets were combined to obtain final estimates and estimated variance (SAS Inc. Cary, NC) (15).

In addition, a propensity score analysis was used to calculate the likelihood of a singleton live birth for the 2 treatment groups, standardized to the overall (study) population. The propensity score is a balancing score; in a set of women all of whom have the same propensity score, the distribution of observed baseline covariates remains the same between the exposed and unexposed. Propensity scores were estimated using logistic regression including all aforementioned covariates with the outcome being the exposure (fresh or frozen embryo transfer). Missing data were handled in a similar way as in the log-linear modeling. For those with missing data, imputed values and indicators of missingness were included to estimate the propensity scores (16). The propensity score model was fit for each of the 5 imputed replicate datasets. The data were subdivided into 20 strata defined by

quantiles of the propensity score for each replicate dataset. Stratification on the propensity score involves stratifying women into mutually exclusive subsets based on their estimated propensity score. Within each propensity score stratum, exposed and unexposed patients will have roughly similar values of the propensity score. Therefore, when the propensity score has been correctly specified, the distribution of measured baseline covariates will be approximately similar between exposed and unexposed subjects within the same stratum. In this analysis, covariate balance between the cohorts was confirmed using a mean propensity score. Data from each replicate dataset were standardized to the overall study population to ensure that the distribution of covariates was the same in both groups (17, 18). For each replicate dataset, an estimator of the risk ratio and its variance were calculated. These estimates were combined to produce a single estimator of the risk ratio and its variance (eMethods).

Dynamical model.—A novel dynamical model was developed, based on the model proposed by Kaplan et al. (19), which assumes an inherent fertility probability and a per-cycle probability of live birth and allows these quantities to vary for each woman as a function of her covariates (eMethods). The probability of *inherent fertility* represents the chance that a woman with a given set of baseline covariates is ever capable of achieving a live birth. Conversely, the *per-cycle probability of a live birth* depends on time-varying covariates for each cycle, although the coefficient governing the effect of each variable was considered to be the same at each cycle (Supplemental Fig. 2).

The baseline (time-invariant) covariates considered predictive of a woman's inherent fertility were age, BMI, race/ethnicity, AMH level, duration of infertility, number of previous spontaneous abortions, gravidity, parity, and reason for ART, number of oocytes retrieved, number of embryos created, and type of embryo transfer (fresh or frozen) in their index cycle. Conversely, the cycle-specific (potentially time-varying) covariates were age, BMI, days of stimulation, diagnosis of moderate or severe OHSS, use of intracytoplasmic sperm injection, number of embryos created, number of embryos transferred, and the type of embryo transfer. Each parameter was modeled on the logit scale. Indicators for the 20 propensity score strata (using the mean propensity score) were included in the models for each parameter to account for confounding by variables included in the construction of the propensity score.

Effect of population restriction.—To assess the effect of specific inclusion criterion on the strength of association for fresh vs. frozen transfer and singleton live birth, crude risk ratios were calculated for subpopulations created as the eligibility criteria were applied. To increase restriction and thus improve prognosis, these 4 subpopulations were: all women who underwent index embryo transfer in 2016–2017; women aged 20–35 who underwent index embryo transfer in 2016–2017; women who underwent index embryo transfer in 2016–2017 and had an elective single embryo transfer; and women who underwent index embryo transfer in 2016–2017 and created at least 4 embryos during their fresh IVF cycle.

Expanded population.—As a second analysis, all models were fit to an expanded population of women who transferred one or more embryos but met all other eligibility criteria.

RESULTS

Characteristics of the Final Study Population

Between 2016 and 2017, 44,750 women aged 20–35 years underwent an elective single embryo transfer as their index transfer (Fig. 1). Of these, 6,324 fresh and 2,318 frozen cycles met the eligibility criteria. Patients undergoing frozen transfers had higher gravidity, parity, and AMH levels compared with the women undergoing a fresh transfer. Women undergoing a frozen transfer also had more oocytes retrieved, embryos created, and a high incidence of moderate or severe OHSS during ovarian stimulation (Table 1).

Pregnancy outcomes for each cohort are presented in Table 2. There was no statistically significant difference in the proportion of women who achieved a singleton live birth with frozen embryo transfer compared with those who underwent fresh embryo transfer (51.4% vs. 48.8%, P=.09 [Table 2]; risk ratio [RR] 1.05, 95% confidence interval [CI] 1.00–1.10 [Fig. 2]). The secondary outcomes of total pregnancy loss rate, total live birth rate, and gestational age at delivery were also similar. A high mean singleton birth weight was observed in the frozen cohort (3391.46 g [SD 19.02]) compared with the fresh cohort (3232.87g [SD 9.38]) (P<.0001).

Adjusting for Confounding

After fitting a log-linear Poisson regression model, the difference in the chance of achieving a singleton live birth remained nonsignificant (RR, 1.05; 95% CI, 0.97–1.14). Similarly, using a 20-strata propensity score analysis yielded an RR of 1.02 (95% CI, 0.96–1.08) for singleton live birth (Fig. 2).

Dynamical Model

Because the dynamical model relies on longitudinal data, the subset of patients who underwent at least one subsequent embryo transfer during the study period were identified. Of the 2,318 patients in the frozen cohort, 559 (24.1%) underwent a second transfer and 140 (6.0%) underwent a third transfer during the study period. Conversely, in the fresh cohort (n = 6,324), 1,989 (31.5%) underwent a second transfer and 359 (5.7%) underwent a third.

There was no statistically significant difference in inherent fertility between groups after controlling for confounding variables included in the propensity score (odds ratio [OR], 1.23; 95% CI, 0.78–1.95) (Supplemental Table 1, available online). The estimated inherent fertility of the frozen and fresh embryo transfer groups was 91.7% and 90.0%, respectively.

The per-cycle probability of singleton live birth for the 2 groups was compared after adjusting for confounding variables. The probability of singleton live birth was not found to be statistically different between the frozen and fresh groups (OR, 1.11; 95% CI, 0.94–1.31) (Fig. 2 and Supplemental Table 1).

Effect of Population Restriction

In the crude analysis of subpopulation 1 (n = 121,805), the least restricted group, there was a statistically significant benefit to frozen transfer (crude RR, 1.45; 95% CI, 1.43–1.47).

This benefit was mitigated in subpopulation 2 (n = 68,278); (RR, 1.27; 95% CI, 1.25–1.29). For subpopulation 3 (n = 53,940), an even more modest benefit of frozen embryo transfer was observed (RR, 1.17; 95% CI, 1.15–1.19). Lastly, the group with the most favorable prognosis, subpopulation 4 (n = 57,065) had the lowest treatment effect (RR, 1.13; 95% 1.11–1.15) (Supplemental Fig. 3).

Expanded Population

The above analyses were applied to a population not restricted to single embryo transfers (n = 3,718 frozen; n = 9,406 fresh). The mean number of embryos transferred per cycle was 1.38 (SD 0.02) in the expanded frozen transfer cohort and 1.33 (SD 0.03) in the expanded fresh cohort (P=.06). Patients undergoing frozen transfers were younger, had lower BMIs, and higher gravidity, parity and AMH levels compared with women undergoing a fresh transfer (Supplemental Table 2).

Pregnancy outcomes for each expanded cohort are presented in Supplemental Table 3. More women achieved a singleton live birth with frozen compared with fresh embryo transfer (45.6% vs. 43.1%, P=.04; (Supplemental Table 3); RR, 1.04; 95% CI, 1.01–1.08) (Fig. 2). The secondary outcomes of total pregnancy loss rate, total live birth rate, and gestational age at delivery were similar. Mean birth weight was higher in the frozen cohort (3373.39g [SD 15.18]) compared with the fresh cohort (3225.68g [SD 9.88] (P<.0001).

The RR for singleton live birth after fitting a log-linear Poisson regression model was 1.08 (95% CI, 1.01–1.15). Similarly, the RR after fitting a 20-strata propensity score analysis re-fit for this population was 1.07 (95% CI, 1.01–1.12) (Fig. 2).

Of the 3,718 index frozen embryo transfers in this cohort, 1,197 (32.2%) patients underwent a second transfer during the study period and 335 (9.0%) underwent a third. Of the 9,406 fresh transfers, 3,291 (35.0%) patients underwent a second transfer and 803 (8.5%) underwent a third.

The inherent fertility of the expanded cohorts was balanced (OR, 1.25; 95% CI, 0.95–1.65) (Supplemental Table 4). There was a high per-cycle probability of live birth in the expanded frozen cohort (OR, 1.21; 95% CI, 1.07–1.37) (Fig. 2).

DISCUSSION

Analysis of population-based, national ART surveillance data did not demonstrate a statistical difference in achieving a singleton live birth for frozen elective single embryo transfer compared with fresh elective single embryo transfer. This finding was consistent among the crude analysis, log-linear model, and propensity score adjusted analyses. The application of a novel dynamical model, which allowed for the possibility of differences in inherent fertility across cohorts, suggested that confounding was controlled by demonstrating that inherent fertility was balanced between the 2 cohorts. The dynamical model's ability to adjust for time-dependent covariates allowed for the estimation of per-cycle probability of live birth by incorporating data from multiple cycles of an individual woman.

These results differ from those of the RCT from China, which demonstrated a benefit of frozen embryo transfer with similar patient and cycle characteristics (RR, 1.26; 95% CI, 1.14–1.41), but are consistent with a Cochrane meta-analysis of 8 RCTs that found little or no difference in cumulative live birth rates between the “freeze all” and conventional IVF strategies (OR, 1.08; 95% CI, 0.95–1.22]) (20). Possible explanations for these disparate results include differences in the study populations, laboratory techniques (e.g., timing of embryo cryopreservation, method of cryopreservation, and embryo developmental stage at transfer), indication for number of embryos transferred, and the limited generalizability of RCTs. The higher singleton birth weight observed in the frozen embryo transfer cohort is consistent with previous literature (21), including the aforementioned RCT (1).

The results for the per-cycle probability of live birth parameter of the dynamical model are not directly comparable to the RRs. The dynamical model controls for inherent fertility (determined post hoc to the index transfer), and thus considers the effect of treatment on the per-cycle chance of live birth among women who are inherently fertile. The per-cycle chance of live birth estimated in the dynamical model may be a better estimate of the efficacy of embryo transfer type, as it describes the likelihood of success only in women who are inherently fertile. The observed probabilities of inherent fertility are consistent with the existing literature (22). Conversely, the RRs of the index cycle represent the effectiveness of transfer type in a population in which some women are inherently infertile.

This analysis suggests that the treatment effect of frozen vs. fresh transfer may be dependent on underlying prognosis of the patient. As the population was restricted to patients with a more favorable prognosis, the difference in success rates comparing frozen to fresh embryo transfer was reduced. In addition, we demonstrated a modest benefit of frozen embryo transfer in case the population was not restricted to a single embryo transfer. This may represent confounding by indication as patients with a favorable prognosis are more likely to undergo frozen transfer as their index transfer (23). In the study population, log-linear model and propensity score analysis results were similar to those of the crude analysis, suggesting that confounding was minimal after restricting the study population by the eligibility criteria we used.

The strengths of this study include the use of a national ART surveillance data, which allowed for a robust sample size despite the very restrictive eligibility criteria. Further, the introduction of functionality in 2016 that links oocyte retrievals and embryo transfers allowed cycle-to-cycle changes (time-varying covariates) to be included in the model. A limitation of our analysis is that, unlike an RCT, NASS was not designed for research purposes. As such, several relevant covariates were absent or incompletely captured necessitating the use of imputed data. Two such variables are reasons for the cryopreservation of all embryos and embryo stage at transfer, which are not reported to NASS. Although we could not control for embryo stage, we believe nearly all transfers were at the blastocyst stage because the study population was restricted to women who underwent their first IVF cycle in 2016 or 2017 and cryopreserved at least 4 supernumerary embryos. Although, because we limited our analysis to women with such a favorable prognosis, our findings may not be generalizable to the broader population of women undergoing IVF.

CONCLUSIONS

In an analysis of comprehensive, national ART surveillance data we find modest or no difference between outcomes from frozen and fresh embryo transfer after purposeful embryo cryopreservation in a population restricted to women with good prognosis. We also demonstrate that future investigations can be effectively performed with robust databases, such as NASS, but methods for adjustment (i.e., log-linear models and propensity score analysis) will likely be necessary. Further, the successful application of a novel dynamical model allows for the utilization of longitudinal data on multiple ART cycles from the same woman and offers a unique and complementary perspective for assessing interventions and controlling for unmeasured confounding. These methodologies provide effective ways to overcome the limitations of observational IVF data allowing for interrogation of interventions unlikely to be investigated by a gold standard RCT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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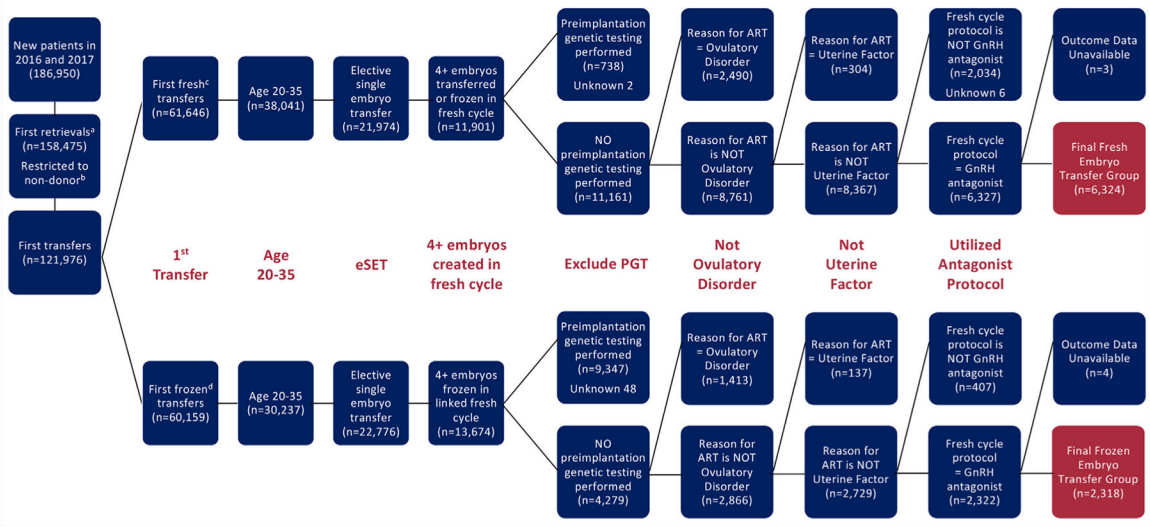

FIGURE 1.

Identification of the study population

[a] First retrieval: patient's first in vitro fertilization cycle and oocyte retrieval procedure

[b] Nondonor: autologous cycle with patient's own oocytes

[c] Fresh transfer: transfer immediately after ovarian hyperstimulation

[d] Frozen transfer: delayed transfer of previously cryopreserved embryo after supraphysiologic hormonal levels induced by ovarian stimulation have resolved. eSET = elective single embryo transfer, PGT = preimplantation genetic testing, ART = assisted reproductive technology, GnRH = gonadotropin-releasing hormone.

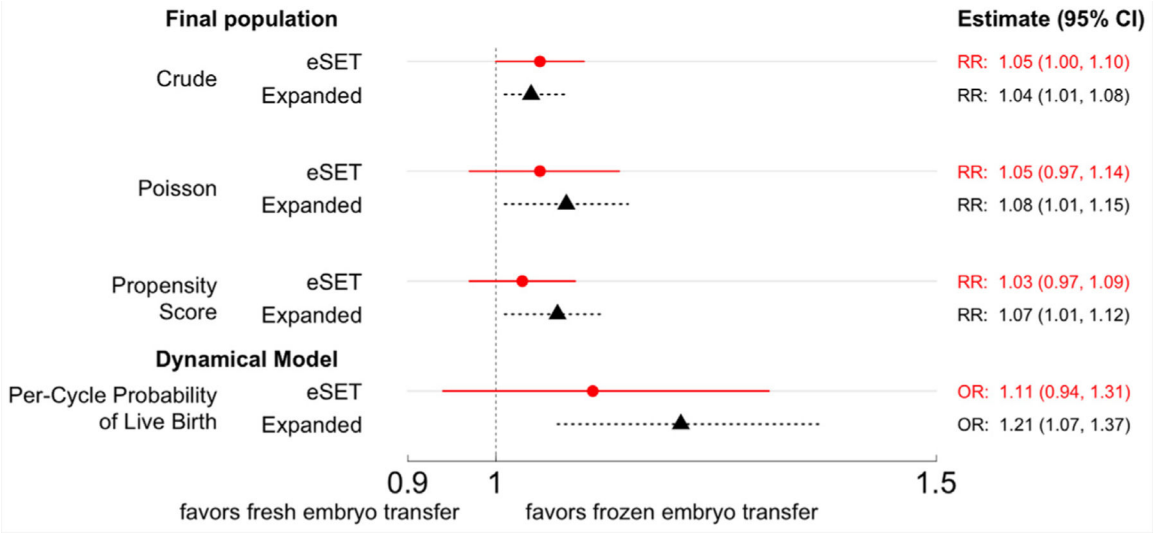

FIGURE 2.

Forest plot of singleton live birth for elective single embryo and expanded populations. Point estimate >1 favors frozen embryo transfer. The *top panel* compares the crude risk ratio with those adjusted by the Poisson regression and propensity score matched approaches for both the elective single embryo and expanded populations. The *bottom panel* displays the per-cycle probability of live birth parameter of the dynamical model (eMethods) which is reported as an odds ratio between frozen/fresh embryo transfer.

TABLE 1

Patient demographics and cycle characteristics

	Frozen embryo transfer (n = 2,318)	Fresh embryo transfer (n = 6,324)	*P* value
Age, mean (SD), (y)	30.69 (0.08)	31.06 (0.08)	<.0001
Body mass index, mean (SD), (kg/m^2)	24.76 (0.20)	25.65 (0.15)	.0001
Missing[a], No. (%)	368 (15.9)	832 (13.2)	.3726
Race/ethnicity, No. (%)[b]			.3300
Non–Hispanic white	973 (42.0)	2,825 (44.7)	
Non–Hispanic black	109 (4.7)	330 (5.2)	
Hispanic	255 (11.0)	511 (8.1)	
Asian	<110 (4.6)	250 (4.0)	
Other	**[c]	12 (0.2)	
Missing[a]	872 (37.6)	2,396 (37.9)	
Duration of infertility[d], mean (SD), (mo)[e]	6.95 (1.11)	9.22 (0.94)	.0832
Missing[a], No. (%)	1,608 (69.4)	4,092 (64.7)	.0002
Reason for ART[f], No. (%)			
Tubal factor	384 (16.6)	1,025 (16.2)	.7781
Male factor	1,022 (44.1)	2,560 (40.5)	.0975
Unexplained infertility	543 (23.4)	1,916 (30.3)	.0001
Combined factors	2,272 (98.0)	6,294 (99.5)	.0001
Other	272 (11.7)	505 (8.0)	.0039
Previous pregnancies, No. (%)			.0018
0	1,603 (69.2)	4,092 (64.7)	
1	403 (17.4)	1,313 (20.8)	
2+	312 (13.5)	919 (14.5)	
Previous live births, No. (%)			.0137
0	1,997 (86.2)	5,286 (83.6)	
1	237 (10.2)	802 (12.7)	
2+	84 (3.6)	236 (3.7)	
Previous spontaneous abortions, No. (%)			.1657

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	Frozen embryo transfer (n = 2,318)	Fresh embryo transfer (n = 6,324)	*P* value
0	1,973 (85.1)	5,317 (84.1)	
1	247 (10.7)	770 (12.2)	
2+	98 (4.2)	237 (3.7)	
Antimüllerian hormone, mean (SD), ng/mL [d]	5.32 (0.24)	4.14 (0.11)	<.0001
Missing[a], No. (%)	1,325 (57.2)	4,130 (65.3)	.0120
Days of stimulation, mean (SD), (d)	9.67 (0.08)	9.53 (0.07)	.1008
Total gonadotropin dose, mean (SD), (IU)	2611.40 (60.53)	2631.23 (70.88)	.7611
Endometrial thickness on day of trigger, mean (SD), (mm)	5.97 (0.34)	7.29 (0.34)	.0004
Number of oocytes retrieved, mean (SD)	22.42 (0.38)	17.76 (0.33)	<.0001
Intracytoplasmic sperm injection[g], No. (%)	1,784 (81.0)	4,398 (71.7)	.0006
Number of embryos created, mean (SD)	8.09 (0.12)	6.83 (0.08)	<.0001
Quality of transferred embryo(s), No. (%)			.1784
Good	1,359 (87.7)	5,533 (90.5)	
Fair	182 (11.7)	551 (9.0)	
Poor	8 (0.5)	27 (0.4)	
Missing[a]	769 (33.2)	213 (3.4)	<.0001
Number of embryos cryopreserved, mean (SD)	8.09 (0.12)	5.83 (0.08)	<.0001
Moderate or severe ovarian hyperstimulation syndrome, No. (%)	65 (2.8)	45 (0.7)	.0001

[a]Missing = n (%) of women for whom this data was not available.

[b]Race/ethnicity and ethnicity categories were self-reported by patients to individual clinics. The category of “other” includes Native Hawaiian or other Pacific Islander, American Indian, and Alaska Native individuals as well as patients who reported “part” for their race/ethnicity/ethnicity.

[c]To protect confidentiality, cells with values <10 are suppressed, as are data that can be used to derive cell values of <10. These values are included in totals.

[d]The duration of infertility variable is calculated among those with a prior pregnancy, i.e. women with secondary infertility.

[e]Variable that was added to the National ART Surveillance System in 2016 and, as a result, has high level of missingness during the study period (2016–2017) as clinics were just beginning to update reports to include this data.

[f]Reason for ART categories: tubal factor refers to the fallopian tubes being blocked or damaged; ovulatory infertility refers to conditions in which the ovaries are not producing oocytes normally; male factor refers to reduced sperm concentrations or other issues related to sperm function that make it difficult for a sperm to fertilize an oocyte under normal conditions; “unexplained” includes patients who have completed an evaluation with no obvious explanation for their infertility; “combined factors” refers to a patient for whom multiple reasons apply; “other” incorporates diagnoses that did not undergo ART for any of the above reasons.

[g] Intracytoplasmic sperm injection refers to cycles in which the sperm is directly injected into the oocyte for fertilization. No. = Number, ART = assisted reproductive technology, SD = standard deviation.

TABLE 2

Live birth, clinical pregnancy, and miscarriage rates in fresh and frozen embryo transfers

	Frozen embryo transfer (n = 2,318)	Fresh embryo transfer (n = 6,324)	*P* value
Pregnancy			
Singleton live birth rate	51.4% (1192/2318)	48.8% (3089/6324)	.0944
Twin live birth rate	0.7% (16/2318)	0.9% (56/6324)	.3706
Total live birth rate	52.1% (1208/2318)	49.7% (3146/6324)	.1293
Clinical intrauterine gestation rate	61.2% (1418/2318)	58.0% (3670/6324)	.0001
Delivery Information			
Gestational age, mean (SD), (wk)	38.74 (0.08)	38.81 (0.04)	.4484
Birthweight, mean (SD), (gm)			
Singleton	3391.46 (19.02)	3232.87 (9.38)	<.0001
Twin	2013.14 (185.84)	2214.55 (81.68)	.3239
Small for gestational age rate[a]	1.2% (14/1180)	2.4% (76/3114)	.0083
Pregnancy Loss			
Total pregnancy loss rate[b]	25.5% (422/1657)	24.2% (1047/4319)	.3479
Biochemical loss rate	13.8% (229/1657)	13.4% (579/4319)	.7041
Ectopic pregnancy rate	0.6% (10/1657)	1.6% (70/4319)	.0008

Note:

[a]The proportion of infants who were small for gestational age (i.e., born at <10th percentile of birthweight for gestational age)

[b]Calculated as sum of stillbirths and spontaneous abortions divided by total number of pregnancies.