Intracytoplasmic sperm injection versus conventional in vitro fertilization in unexplained infertility

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Objective: To compare cumulative live birth rate (CLBR) and cost-effectiveness of intracytoplasmic sperm injection (ICSI) vs. conventional in vitro fertilization (cIVF).
Design: Retrospective cohort study of cycles reported to the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System.
Setting: Society for Assisted Reproductive Technology (SART) member IVF clinics in the United States.
Patient(s): Patients with unexplained infertility who underwent first autologous retrieval cycles between January 2017 and December 2019 with linked fresh and frozen embryo transfers through December 2021.
Intervention(s): ICSI vs. cIVF.
Main Outcome Measure(s): The primary outcome was CLBR, defined as ≤1 live birth from a retrieval cycle and all linked embryo transfers. Secondary outcomes included two pronuclear (2PN) per oocyte retrieved, miscarriage rate, and total number of transferred or frozen embryos per 2PN. Subsamples with and without preimplantation genetic testing for aneuploidy (PGT-A) were analyzed. Outcomes were adjusted for age, body mass index, number of oocytes retrieved, length of follow-up, and clinic ICSI use rate.
Result(s): A total of 18,805 patients with unexplained infertility were included. No difference in CLBR was found among cycles without genetic testing (54.4% ICSI vs. 57.5% cIVF) and with PGT-A (47.6% ICSI vs. 51.8% cIVF). Intracytoplasmic sperm injection cycles without genetic testing had a higher miscarriage rate (16.4% vs. 14.4%) but no difference was seen in cycles with PGT-A (13.9% ICSI vs. 13.2% cIVF). Intracytoplasmic sperm injection cycles had a significantly lower ratio of 2PN per oocyte retrieved without genetic testing (59.7% vs. 60.9%) and with PGT-A (63.3% vs. 65.8%). The ratio of embryos transferred or frozen per 2PN was not significantly different in cycles without genetic testing (49.4% vs. 49.6%) or with PGT-A (54.2% vs. 55.2%). Total fertilization failure occurred in 216 patients (4%) who underwent cIVF and in 153 patients (1.1%) who used ICSI.

Compared with cIVF alone, an estimated additional $11,011,500 was charged to patients for ICSI without genetic testing and $9,010,500 was charged to patients for ICSI with PGT-A over 2 years by Society for Assisted Reproductive Technology clinics. On the basis of total fertilization failure rates, 35 patients would require treatment with routine ICSI to avoid a single cycle of total fertilization failure with cIVF.
Conclusion(s): Routine use of ICSI in unexplained infertility is not warranted due to the additional cost and lack of CLBR benefit. (F S Rep® 2024;5:263–71. ©2024 by American Society for Reproductive Medicine.)
Key Words: Conventional IVF, ICSI, cumulative live birth rate, unexplained infertility

Intracytoplasmic sperm injection (ICSI) was introduced in 1992 as a promising technique for couples who had not been able to become pregnant by traditional in vitro fertilization (IVF) because of severely impaired sperm parameters (1). Since then, ICSI has been used at an increasing rate and expanded to non-male factor infertility cases. Currently, ≤30% of couples experiencing infertility are diagnosed with unexplained infertility (2). In vitro fertilization with ICSI has been proposed as a treatment for unexplained infertility to bypass fertilization barriers that might occur in these cases (3), and of the 64,073 people diagnosed with unexplained infertility between 2008 and 2012, 25,253 (39%) underwent conventional IVF (cIVF) and 38,820 (61%) underwent ICSI (4).

In the 2020 evidence-based guideline for the treatment of unexplained infertility, the Practice Committee of the American Society for Reproductive Medicine stated that there is no difference in clinical pregnancy and live birth rates between ICSI and conventional IVF (2). Whereas some studies show ICSI is associated with a lower risk of complete fertilization failure

and a higher fertilization rate when compared with cIVF, others show improved implantation, clinical pregnancy, as well as live birth rates with conventional fertilization (5–8). Given inconclusive evidence of benefit, there has been a call for further studies evaluating the role of ICSI in an unexplained infertility population (3).

Cumulative live birth rate (CLBR), evaluating whether a live birth occurred from any embryos resulting from a single egg retrieval cycle, provides a comprehensive measure of IVF clinical outcomes. The purpose of our study was to look at CLBR using ICSI vs. cIVF using recent national data and to provide a cost analysis comparing the two fertilization methods. We hypothesize that there will be no significant difference in the cumulative live birth rate between ICSI and cIVF when used in the setting of unexplained infertility.

MATERIALS AND METHODS

This retrospective analysis was performed using primary IVF clinic data collected by the Society for Assisted Reproductive Technology (SART). All data are collected by SART, validated and audited annually, as well as 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).

Study population

The dataset included patients who underwent their first IVF autologous oocyte retrieval cycles between January 2017 and December 2019. We linked subsequent fresh and frozen embryo transfers occurring through December 2021 that used only embryos from the initial retrieval to determine the CLBR. Cycles using donor sperm, frozen sperm, using frozen oocytes, cycles without any retrieved oocytes, or using 2nd-day ICSI because of oocyte immaturity were excluded. Patients with a male factor diagnosis in a subsequent cycle, using genetic testing other than preimplantation genetic testing for aneuploidy (PGT-A [PGT for monogenic/single gene disorders and PGT for chromosome structural rearrangements]), with transfers of embryos less than Day 5, unclear ICSI use, and with more embryos reported thawed in linked cycles than reported frozen in the initial cycle were excluded (Fig. 1).

Outcomes

The primary outcome was the CLBR after cIVF or ICSI for patients undergoing their first retrieval. Cumulative live birth is the preferred outcome measure when reporting success with a single IVF cycle (9). The CLBR was defined as all associated fresh and subsequent linked frozen transfer cycles from a single retrieval cycle up to the first resulting live birth per female patient (10). Secondary outcomes included two pronuclear (2PN) per oocyte retrieved, miscarriage rate, and total number of transferred or frozen embryos per 2PN. Subsamples with and without PGT-A were analyzed. Outcomes were adjusted for age, body mass index (BMI), number of oocytes retrieved, length of follow-up, and clinic ICSI use rate. Subanalyses by female age group <35, 35–37, 38–40, and >40 were per-

formed. Finally, a subanalysis was performed comparing cumulative live birth rates among clinics that perform a high level of ICSI, which we defined as clinics performing ICSI for >80% of their cycles, and low level of ICSI, which we defined as clinics performing ICSI for ≤80% of their cycles.

Covariates

We analyzed demographic and clinical data reported in patients' first retrieval cycle in the SART database. Body mass index was calculated using the reported heights and weights of the patients. We classified patients into seven racial categories (White, Black, Hispanic/Latina, Asian, American Indian/Alaskan Native, Native Hawaiian/other Pacific islander, and other/Multiracial) on the basis of clinic-reported patient race. Although only unexplained infertility diagnosis cycles were analyzed, causes of infertility in subsequent cycles were evaluated and these included endometriosis, polycystic ovarian syndrome, diminished ovarian reserve, tubal factor, uterine factor, unexplained, other, and multiple diagnoses (excluding those who reported male factor infertility). Treatment characteristics from the retrieval cycle and subsequent linked transfer cycles were summarized in Table 1.

Statistical analysis

We performed a priori power analyses to determine the degree of difference we would be powered to detect in CLBR, on the basis of the sample size and ratio of ICSI to cIVF within our dataset for cases with and without genetic testing. Assuming a CLBR rate of 39.2% among cIVF cases (4), setting alpha at 0.05, with our sample of 11,630 cases without genetic testing, we would have 99.8% power to detect an absolute difference of 4.5% in CLBR. Applying the same assumptions to our PGT-A group, with our sample of 7,175 cases we would have 80% power to detect an absolute difference of 4.5% in CLBR.

Sample descriptive statistics were calculated using t tests, Mann–Whitney U tests, and χ^2 with post hoc z tests. Adjusted odds ratios for CLBR and miscarriage were calculated using a log-binomial model, as well as 2PN per oocyte was retrieved and total embryos were transferred or frozen per 2PN using a binomial distribution. Outcomes were adjusted for age, BMI, number of oocytes retrieved, length of follow-up, and clinic ICSI use rate. These variables were selected a priori on the basis of the literature and the clinical experience of the research team. Race was not included in the regression model because a large proportion of the sample was missing data on race. Due to the number of cycles with missing BMI values, demographic and cycle characteristics of cycles with missing BMI values were compared with cycles with reported BMI for cycles with blastocyst transfer. Body mass index was assumed to be missing at random and a complete case analysis was used for regression modeling.

Analyses of covariance were used to assess the relationship of ICSI with the ratio of 2PN per oocyte retrieved and the ratio of total transferred or cryopreserved embryos per fertilized oocyte while controlling for age, BMI, and number

FIGURE 1
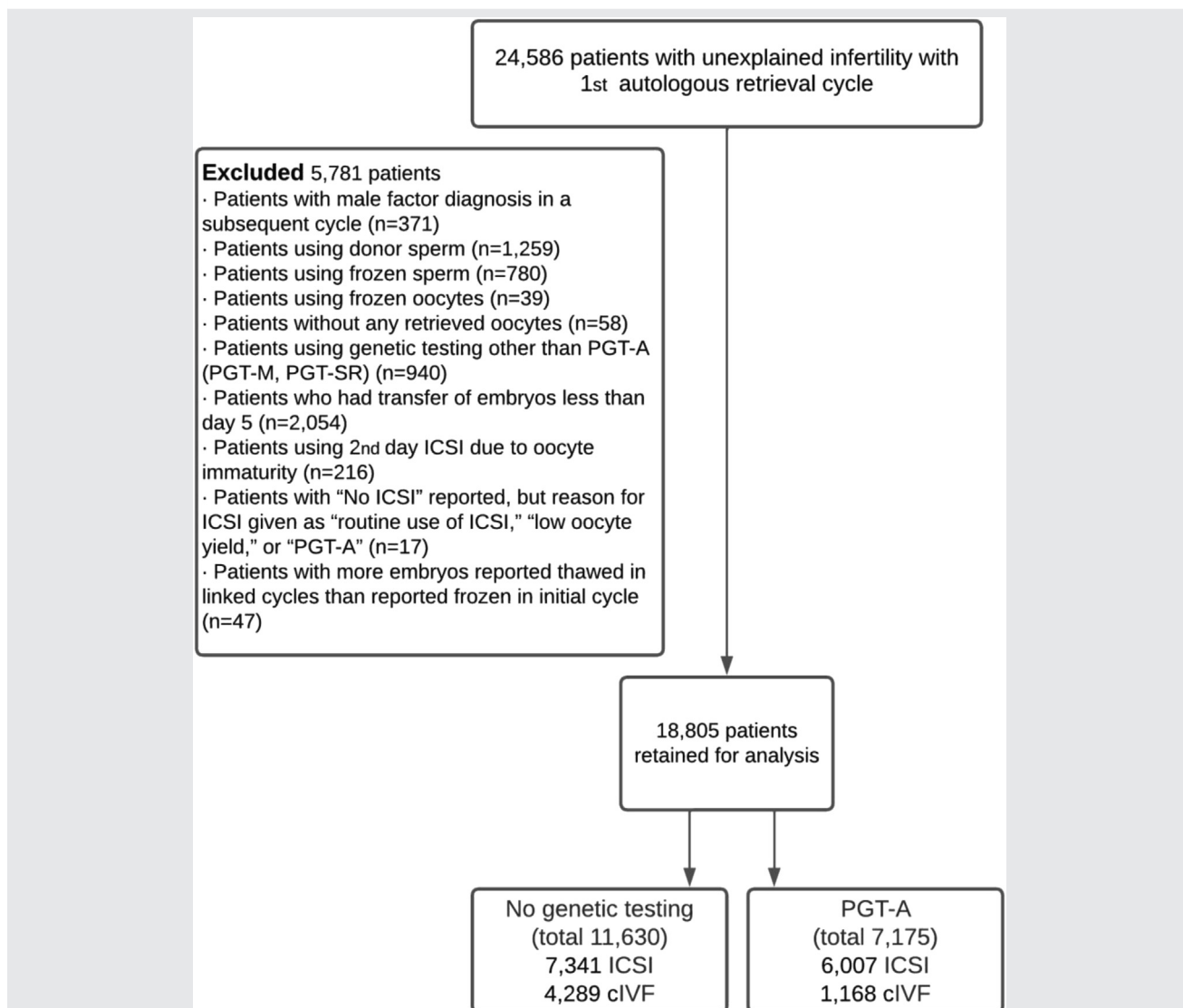
Study flow diagram. cIVF = conventional IVF; ICSI = intracytoplasmic sperm injection; PGT-A = preimplantation genetic testing for aneuploidy; PGT-M = preimplantation genetic testing for monogenic/single gene disorders; PGT-SR = preimplantation genetic testing for chromosome structural rearrangements.

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of oocytes retrieved, length of follow-up, as well as clinic ICSI use rate. Data were assessed for multicollinearity, normality, homogeneity of variance, homogeneity of regression, and linearity to confirm that analyses of covariance assumptions were met.

To assess the remaining reproductive potential at the end of the study period for participants who did not have a live birth, the percentage of embryos used was calculated by dividing the total number of embryos transferred across all study cycles by the total number frozen and transferred in the initial cycle. t tests were used to compare the percent of embryos used between ICSI and cIVF groups. The log-binomial models were performed in SAS v9.4. All other statistical analyses were performed in SPSS version 26.

Ethics

The Institutional Review Board of the University of Iowa exempted this project from further review as data used in the study was completely de-identified. (Determination of Human Subjects IRB ID# 201608711).

RESULTS

A total of 24,586 patients with unexplained infertility were found to be undergoing their first autologous retrieval cycle between January 2017 and December 2019. After the exclusion of patients using donor sperm, frozen sperm or oocytes, without any retrieved oocytes, with male factor diagnosis in a subsequent cycle, using genetic testing other than PGT-A

TABLE 1

Demographic and clinical characteristics of study population and treatment characteristics by fertilization method.

	No genetic testing			Preimplantation genetic testing for aneuploidy (PGT-A)		
	ICSI n = 7,341	cIVF n = 4,289	*P*	ICSI n = 6,007	cIVF n = 1,168	*P*
Age	33.4 ± 4.0	33.5 ± 3.8	.079	35.2 ± 3.82	35.5 ± 3.78	.004
Race						
White	3897 (53.1)	2002 (46.7)	<.0001	2580 (43)	362 (31)	<.0001
Black	259 (3.5)	151 (3.5)		114 (1.9)	14 (1.2)	
Hispanic/Latina	364 (5.0)	164 (3.8)		242 (4)	30 (2.6)	
Asian	779 (10.6)	433 (10.1)		1046 (17.4)	146 (12.5)	
American Indian, Alaskan Native	6 (0.1)	1 (0)		4 (0.1)	1 (0.1)	
Native Hawaiian or other Pacific Islander	11 (0.1)	4 (0.1)		7 (0.1)	1 (0.1)	
Multiracial	68 (0.9)	33 (0.8)		39 (0.6)	6 (0.5)	
Body mass index (BMI)	25.81 ± 6.39 (n = 6407)	25.48 ± 5.72 (n = 3912)	.007	24.42 ± 5.06 (n = 5408)	24.51 ± 4.94 (n = 1040)	.614
Smoker	113 (1.5)	56 (1.3)	.350	76 (1.3)	21 (1.8)	.192
Infertility Diagnosis in Subsequent Cycles[a]						
No new causes	7117 (96.9)	4131 (96.3)	.073	5617 (93.5)	1083 (92.7)	.356
Endometriosis	14 (0.2)	12 (0.3)	.437	34 (0.6)	3 (0.3)	.260
Polycystic Ovarian Syndrome	112 (1.5)	77 (1.8)	.301	116 (1.9)	38 (3.3)	.006
Diminished Ovarian Reserve	44 (0.6)	25 (0.6)	1.00	74 (1.2)	18 (1.5)	.473
Tubal Factor	29 (0.4)	26 (0.6)	.195	28 (0.5)	2 (0.2)	.214[d]
Uterine Factor	19 (0.3)	18 (0.4)	.188	28 (0.5)	7 (0.6)	.713
Recurrent Pregnancy Loss	21 (0.3)	17 (0.4)	.402	33 (0.5)	5 (0.4)	.762
Multiple diagnoses	53 (0.7)	32 (0.7)	1.00	87 (1.4)	20 (1.7)	.583
Gravidity	0.58 ± 0.95	0.64 ± 0.98	.002	0.68 ± 1.06	0.80 ± 1.14	.004
Nulliparous	6047 (82.4)	3492 (81.4)	.202	4845 (80.7)	891 (76.3)	<.001
Full-term births	0 (0–1)	0 (0–1)	.450	0 (0–1)	1 (0–1)	.021
Preterm births	0 (0–0)	0 (0–0)	.227	0 (0–0)	0 (0–0)	.117
Spontaneous Abortions	0 (0–1)	0 (0–1)	.970	1 (0–1)	1 (0–1)	.416
Clinic Characteristics[b]						
ICSI cycles/Insemination cycles (%)	90.59 ± 12.84	64.90 ± 19.75	<.001	93.12 ± 10.47	56.96 ± 20.09	<.001
Total Insemination cycles	864 ± 1001	1019 ± 1118	<.001	717 ± 811	663 ± 560	.005
Treatment Characteristics						
Oocytes retrieved in stimulated cycles	14.9 ± 8.42	15.0 ± 8.66	.255	16.6 ± 9.01	16.7 ± 9.04	.875
Total 2PN	8.8 ± 5.65	9.1 ± 6.06	.006	10.3 ± 6.02	10.8 ± 6.40	.020
Ratio of 2PN/oocyte retrieved (%)	59.65 ± 21.03	60.91 ± 24.52	.006	63.27 ± 18.35	65.77 ± 19.64	<.001
Number of embryos transferred and frozen	4.4 ± 3.70	4.5 ± 3.74	.356	5.5 ± 3.94	5.8 ± 4.30	.009
Ratio of embryos transferred and frozen / 2PN (%)	49.37 ± 28.78	49.58 ± 26.47	.691	54.19 ± 25.42	55.24 ± 26.00	.208
Number of embryos transferred[c]	1 (1–2)	1 (1–2)	.537	1 (0–1)	1 (0–1)	.784

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TABLE 1

Continued.

	No genetic testing			Preimplantation genetic testing for aneuploidy (PGT-A)		
	ICSI n = 7,341	cIVF n = 4,289	P	ICSI n = 6,007	cIVF n = 1,168	P
Number of embryo transfers (fresh and frozen)	1.20 ± 0.84	1.29 ± 0.88	<.001	0.90 ± 0.80	0.94 ± 0.86	.142
Number of embryos transferred in live birth cycle	1 (1–2)	1 (1–1)	<.001	1 (1–1)	1 (1–1)	.047
Frozen embryos not used in linked cycles	2.8 ± 3.48	2.9 ± 3.55	.227	4.5 ± 3.73	4.8 ± 4.03	.012

Note: cIVF = conventional IVF, ICSI = intracytoplasmic sperm injection, PGT-A = preimplantation genetic testing for aneuploidy; 2PN = .
Values are presented as mean ± SD, Median (Inter Quartile Range), or n (%). The P-value for t test, Mann–Whitney U test, or χ^2 except when otherwise noted.
Smokers are defined as those who smoked 3 months before any cycle within the dataset.
Missing data for <0.5% of cases on clinic characteristics. Missing data for 32.1% of cases on race, and 10.8% of cases on BMI.
[a] Clinic characteristics are annual rates or totals for the reporting year of the patient's initial cycle.
[b] All patients in the dataset had a sole diagnosis of unexplained infertility in the initial cycle. Diagnoses listed in subsequent cycles are given here. Patients may have had multiple diagnoses in subsequent cycles; totals of diagnosis categories will not sum to 100%.
[c] Total number of embryos transferred across all cycles for each patient.
[d] P-value for Fisher's exact test.

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(PGT for monogenic/single gene disorders and PGT for chromosome structural rearrangements), with a transfer of embryo before Day 5, using 2nd-day ICSI for oocyte immaturity, with unclear ICSI use, and with more embryos reported thawed in linked cycles than initially frozen, a total of 18,805 patients with unexplained infertility were included for analysis. Of those included, 71% underwent ICSI and 29% underwent conventional IVF (Fig. 1).

The demographic and clinical characteristics of the patients undergoing IVF without genetic testing or with PGT-A are depicted in Table 1. All patients in the dataset had a sole diagnosis of unexplained infertility in their initial cycle, however, there were various diagnoses listed in their subsequent cycles. Age, BMI, and gravidity were clinically similar in both groups, although noted to have statistically significant differences. The rate of nulliparous women using ICSI vs. cIVF without genetic testing was not statistically significant, however, the rate of nulliparous women who used ICSI with PGT-A was significantly higher than those using cIVF with PGT-A (P< .001). Full-term births in the ICSI and cIVF groups undergoing PGT-A were clinically similar, although noted to have a statistically significant difference. There were no statistically significant differences in full-term births in the group without genetic testing, or in preterm births or spontaneous abortions in either group. In both groups without genetic testing and PGT-A, the patients utilizing ICSI were found to be treated in clinics with significantly higher rates of ICSI per insemination cycle. There were no statistically significant differences in the number of oocytes retrieved per stimulated cycle. Conventional IVF was associated with significantly higher ratios of 2PN per oocyte retrieved in both groups without genetic testing and PGT-A.

Of the 11,630 patients without genetic testing, 63% underwent ICSI and 37% underwent cIVF. The CLBR was 54.4% for ICSI and 57.5% for cIVF among the cycles without genetic testing, a difference that was not significantly different after adjustment for covariates (adjusted odds ratio [AOR], 0.91; 95% confidence interval [CI], 0.82–1.02). Of the 7,175 patients who underwent PGT-A, 84% underwent ICSI and 16% underwent cIVF. The CLBR was 47.6% for ICSI cycles and 51.8% for cIVF cycles with PGT-A, a difference that was not significantly different after adjustment for covariates (AOR, 0.98; 95% CI, 0.79–1.21) (Table 2). When comparing the CLBR of clinics that perform a high level of ICSI, which we defined as clinics performing ICSI for > 80% of their cycles, and low level of ICSI, which we defined as clinics performing ICSI for ≤ 80% of their cycles, there was no significant difference in CLBR in cIVF and ICSI cycles with PGT-A and without genetic testing (Supplemental Table 1, available online). The miscarriage rate was significantly higher among patients utilizing ICSI without genetic testing compared with cIVF (16.4% vs. 14.4%; AOR, 1.27; 95% CI, 1.06–1.53). There was no difference in miscarriage rates in ICSI and cIVF cycles with PGT-A (13.9% ICSI vs. 13.2% cIVF; AOR, 0.922; 95% CI, 0.62–1.37). As depicted in Table 3, ICSI cycles without genetic testing had a significantly lower ratio of 2PN per oocyte retrieved (59.7 vs. 60.9%; AOR, 0.95; 95% CI, 0.93–0.97). Similarly, ICSI cycles with PGT-A had a significantly lower ratio of 2PN per oocyte retrieved

TABLE 2

Cumulative live birth rates and miscarriage rates.

| Outcome | Without genetic testing (n = 11,630) | | | | With PGT-A (n = 7,175) | | | |
	ICSI	cIVF	OR (95% CI)	AOR (95% CI)[c]	ICSI	cIVF	OR (95% CI)	AOR (95% CI)[c]
Cumulative live birth rate (CLBR) (%)[a]	54.4	57.5	0.881 (0.817–0.951)	0.910 (0.815–1.016)	47.6	51.8	0.845 (0.746–0.958)	0.981 (0.791–1.217)
Miscarriage rate (%)[b]	16.4	14.4	1.166 (1.022–1.332)	1.274 (1.059–1.533)	13.9	13.2	1.069 (0.835–1.3668)	0.922 (0.621–1.368)

Note: Values are presented as n (%) or Median (interquartile range). AOR = adjusted odds ratio; BMI = body mass index; CI = confidence interval; cIVF = conventional IVF; ICSI = intracytoplasmic sperm injection; OR = odds ratio; PGT-A = preimplantation genetic testing for aneuploidy.
[a] Cumulative live birth rate is defined as the first resulting live birth from all associated fresh and subsequent linked frozen transfer cycles from a single retrieval cycle per female patient. N is the number of patients who had a pregnancy in the initial or any subsequent cycle, regardless of the outcome. Patients may have had a miscarriage and gone on to have a live birth in a future cycle.
[b] Miscarriage rate is defined as miscarriage per clinical pregnancy. N are patients who had a miscarriage in the initial or any subsequent cycle.
[c] Adjusted for age, BMI, number of oocytes retrieved, length of follow-up, and clinic ICSI use rate.

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(63.3% vs. 65.8%; AOR, 0.89; 95% CI, 0.86–0.92). The ratio of embryos transferred or frozen per 2PN was not significantly different between ICSI and cIVF in cycles without genetic testing (49.4% vs. 49.6%; AOR, 1.02; 95% CI, 0.99–1.04) and with PGT-A (54.2% vs. 55.2%; AOR, 0.97; 95% CI, 0.93–1.01). There were no significant differences in the number of total embryos remaining among patients utilizing ICSI and cIVF in both groups without genetic testing and with PGT-A (Supplemental Table 2). A subanalysis by female age group <35, 35–37, 38–40, and >40 found similar outcomes to our initial analysis including females of all ages (Supplemental Table 3). However, when dividing our data by age, our sample sizes were not sufficient to run adjusted odds ratios and adjusted rate ratios. Among the groups undergoing PGT-A, 4,118 patients (68.6%) in the ICSI group and 808 (69.2%) in the cIVF group underwent ≥ 1 embryo transfer, a difference that was not statistically significant (P=.699). Among all cycles, 369 had outcomes of zero 2PNs, representing 369 cycles with total fertilization failure. Total fertilization failure occurred in 216 of the 5,457 patients (4%) who underwent cIVF and in 153 of the 13,348 patients (1.1%) who used ICSI.

Through literature and online searches, ICSI was found to cost an estimated additional $1500 when compared with cIVF alone, and each cycle costs an estimated $12,400 (11–13). Assuming the actual additional cost of ICSI when performed in the setting of IVF is within 10% of this estimate ($1,350–$1,650), an estimated additional $11,011,500 ($9,910,359–$12,112,650) was charged to patients for ICSI without genetic testing and an additional $9,010,500 ($8,109,450–$9,911,550) was charged to patients for ICSI with PGT-A over 2 years by SART clinics. If an inflated 10% total fertilization failure rate is assumed with cIVF, and the cost of a subsequent IVF cycle for the 10% of the couples who experienced total fertilization failure is considered, after subtracting the cost of an additional cycle for 10% of the cIVF cases still leads to an additional cost of $5,049,790–$5,693,140, depending on whether ICSI or cIVF is used in the subsequent cycle, charged by SART member clinics for ICSI in cycles without genetic testing over this 2-year time frame. Similarly, with an overestimated 10% total fertilization failure rate for cIVF with PGT-A, SART member clinics are charging an additional

$7,386,980–$7,562,180 to patients with the use of ICSI routinely.

In our study, total fertilization failure occurred in 216 of the 5,457 patients (4%) who underwent cIVF and in 153 of the 13,348 patients (1.1%) who used ICSI. From our data regarding the total fertilization failure rate, we found that 35 patients would need to be treated with routine ICSI to avoid 1 cycle of total fertilization failure with cIVF. If all patients with unexplained infertility are routinely treated with ICSI to avoid total fertilization failure, the cost difference between routine ICSI and routine cIVF, with one subsequent episode of ICSI per 35 patients for total fertilization failure, is $38,600 for every 35 patients or $1,103 per patient.

DISCUSSION

Our study, which included a large national cohort of unexplained infertility cycles, found that the use of ICSI added no benefit to CLBR for both cycles without genetic testing and cycles utilizing PGT-A. Previous randomized control trials comparing the outcomes of ICSI and cIVF in patients with unexplained infertility have been mixed on whether ICSI use is beneficial for this patient population (5–8, 14). Some have found no improvement in fertilization rates using ICSI for unexplained infertility, and others have shown lower complete fertilization failure rates with ICSI compared with cIVF with an unexplained infertility diagnosis (6–8). Bhattacharya et al. (8) and Foong et al. (14) found that there was no difference in pregnancy rates between cIVF and ICSI among couples diagnosed with unexplained infertility. However, these prior studies are limited by small sample sizes, are several decades old during which many changes in IVF practices have occurred, and focus on outcomes that are less meaningful for patients than the CLBR. Our study includes thousands of cycles across the nation using recent data and focuses on CLBR as the primary outcome.

Among cycles without genetic testing and with PGT-A, ICSI was associated with a lower ratio of 2PN per oocyte retrieved, our surrogate measure for fertilization rate. This may be due to the practice of inseminating only mature oocytes with ICSI, whereas some immature oocytes may mature overnight in culture and fertilize by cIVF, thus increasing the

TABLE 3

Two pronuclear per oocyte retrieved, embryos transferred and frozen per two pronuclear among patients utilizing intracytoplasmic sperm injection vs. conventional in vitro fertilization.

Outcome	Without genetic testing (n = 11,630)				With genetic testing (n = 7,175)			
	ICSI Adjusted mean[a]	cIVF Adjusted mean[a]	OR (95% CI)	AOR (95% CI)	ICSI Adjusted mean[a]	cIVF Adjusted mean[a]	OR (95% CI)	AOR (95% CI)
2PN/oocytes retrieved (%)	59.65 ± 21.03	60.91 ± 24.52	0.958 (0.939–0.978)	0.945 (0.925–0.965)	63.27 ± 18.35	65.77 ± 19.64	0.895 (0.866–0.924)	0.888 (0.858–0.918)
Embryos transferred or frozen/2PN (%)	49.37 ± 28.78	49.58 ± 26.47	1.022 (0.99–1.048)	1.015 (0.988–1.043)	54.19 ± 25.42	55.24 ± 26.00	0.953 (0.917–0.990)	0.966 (0.927–1.006)

Note: Values presented as mean ± SD. AOR = adjusted odds ratio; BMI = body mass index; CI = confidence interval; cIVF = conventional in vitro fertilization; ICSI = intracytoplasmic sperm injection; OR = odds ratio; 2PN = 2 pronuclear.
[a] Adjusted for age, BMI, number of oocytes retrieved, length of follow-up, and clinic ICSI use rate.

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total pool of oocytes available for fertilization by standard insemination. This is consistent with prior findings by Johnson et al. (5) that the fertilization rate per oocyte before assessment of oocyte maturity is similar between ICSI and cIVF. It has previously been hypothesized that there are theoretical procedural risks associated with ICSI including disturbance of ooplasm or meiotic spindle, injection of biochemical contaminants, transmission of genetic defects possibly related to the underlying male factor infertility, injection of sperm mitochondrial deoxyribonucleic acid, injection of chromosomally anomalous sperm (15). These factors may also contribute to our finding of a lower ratio of 2PN per oocyte retrieved associated with ICSI cycles. On the other hand, cIVF is beneficial in that it is less costly for the patient and less time-intensive for embryologists in IVF laboratories (16, 17). Past studies have found that the fertilization rate per oocyte retrieved and blastocyst formation rate were higher with cIVF, when compared with ICSI, because of natural selection's ability to choose the most robust sperm with the best fertilization capacity (17). During cIVF, there is also less risk of mechanical damage to the oocytes, allowing embryologists to avoid cases of oocyte degeneration (18). The ratio of transferred or frozen embryos per 2PN using cIVF and ICSI was not statistically different, signifying that the proportion of usable embryos resulting from the 2PNs was similar between ICSI and cIVF. In this study, we found that PGT-A cycles were significantly more likely to use ICSI than cycles without genetic testing ($P<.001$). Although recent studies by De Munck et al. (19) and Kim et al. (20) have found that PGT-A with cIVF and ICSI result in similar outcomes, we believe some programs choose to retain the policy of using ICSI for PGT-A cases in their laboratories as a precaution to avoid contamination of biopsies with deoxyribonucleic acid from supernumerary sperm.

Prior studies on outcomes after ICSI and cIVF have not specifically analyzed differences in miscarriage rate. It has been hypothesized that by bypassing natural selection, ICSI may lead to higher aneuploidy risk (21). Others have found no significant difference in the frequency of chromosomal abnormalities found among miscarriages after ICSI, cIVF, and spontaneous conception (22, 23). In our study, ICSI was associated with a higher miscarriage rate in cycles without genetic testing when compared with that of cIVF. Although it may be argued that a 2% difference in miscarriage rate may not be clinically meaningful, this outcome may confirm that in fact, mother nature is superior at selection compared with ICSI and further studies investigating this possible outcome should be performed.

Many clinics perform ICSI to avoid total fertilization failure. However, total fertilization failure is uncommon, occurring in 5%–10% of cIVF cycles, and is especially rare in cases of non-male factor infertility (17, 24). A meta-analysis in 2013 found that for couples with well-defined unexplained infertility, the use of ICSI significantly decreases the relative risk of total fertilization failure (5). Total fertilization failure occurred in 4% of patients who underwent cIVF and in 1.1% who used ICSI in our study, confirming more cases of total fertilization failure in cIVF cycles ($P<.001$). Although total fertilization failure is a devastating event, this was still rare

among cIVF cycles and the use of ICSI did not eliminate this event. This 4-fold difference in fertilization failure rate is understandably a reason some may choose ICSI over cIVF. Importantly, fertilization does not always lead to good-quality embryos, and the most clinically meaningful outcome, CLBR, was not different between groups.

Our cost analysis estimates that an additional $11,011,500 was charged to patients undergoing ICSI without genetic testing and an additional $9,010,500 was charged to patients undergoing ICSI with PGT-A over 2 years by SART member clinics. Some may argue that expedited treatment with the routine use of ICSI could potentially help bypass cIVF cycles with failed fertilization. Even if we assume an inflated 10% rate of total fertilization failure with cIVF and take into consideration the cost of a subsequent IVF cycle with or without ICSI for 10% of the couples using cIVF, an additional $5,049,790–$5,693,140 is being charged to patients for IVF without genetic testing and an additional $7,386,980–$7,562,180 is being charged to patients for IVF with PGT-A over 2 years.

From our data regarding total fertilization failure using ICSI and cIVF, we found that 35 patients would need to be treated with routine ICSI to avoid 1 cycle of total fertilization failure. If ICSI is routinely performed for patients with unexplained infertility to avoid total fertilization failure, the cost difference between routine ICSI and routine cIVF with one subsequent episode of ICSI for total fertilization failure is $38,600 for every 35 patients or $1,103 per patient. Therefore, it is evident that clinics that perform routine ICSI are not saving costs in their attempt to avoid total fertilization failure. However, these costs do not take into account the emotional and physical burden that patients may undergo from the subsequent cycles of IVF. Furthermore, it is difficult to account for the burden caused by the delay in time to childbearing which may be caused by failed fertilization cycles.

The restricted period of time between retrieval cycles occurring between January 2017 and December 2019 and the transfers occurring through December 2021 is a limitation of this study. A longer period of follow-up may allow for more cycles of embryo transfers, each with the potential of resulting in a live birth. However, we determined that there was no statistically significant difference in the total number of remaining embryos among patients who underwent ICSI and cIVF both without genetic testing and with PGT-A. Therefore, it is unlikely that additional time would have provided a significant benefit in the CLBR in either group. Our analysis was also limited by the data available, as is the case with all retrospective studies. Approximately 32% of data on race was missing from the cycles in our dataset. Similarly, approximately 10% of BMI data were missing from the cycles in our dataset. When analyzing our adjusted models with and without BMI, the results were not noticeably different so multiple imputation was not performed on the observations with missing BMI values. We did not have any information regarding cytogenetic testing on products of conception among patients who underwent miscarriages. Although this study exclusively used data collected by SART, there has been no evaluation of the consistency of laboratory techniques used among the SART member clinics. We were unable

to assess the number of suitable cryopreserved embryos after PGT-A testing. Given the differences and variability in what suitable may mean between patients and clinics, it is not possible to make this assessment with the database. Furthermore, we found no difference in the number of patients who underwent ≥ 1 transfer after PGT-A testing in the cIVF and ICSI groups. In addition, with the use of the data collected by SART, we assume that all SART member clinic providers are correctly diagnosing unexplained infertility. Although we adjusted for variables including, age, BMI, number of oocytes retrieved, length of follow-up, and clinic ICSI use rate, there are many other factors that may contribute to the success of IVF. The strengths of our study include a large cohort of unexplained infertility patients across the nation, and the evaluation of CLBRs as well as additional costs charged to patients, both of which are important and clinically meaningful outcomes for our patients.

CONCLUSION

The routine use of ICSI among patients with unexplained infertility is not warranted as it does not increase the CLBR and adds additional cost. On discussing the risks and benefits, weighing the emotional, physical, as well as financial costs associated with each insemination method, the decision to pursue conventional IVF or ICSI must be made on a case-to-case basis as a shared decision with the patient.

CRediT Authorship Contribution Statement

Aya Iwamoto: Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Karen M. Summers:** Writing – review & editing, Formal analysis, Data curation. **Amy Sparks:** Writing – review & editing, Supervision, Project administration, Data curation, Conceptualization. **Abigail C. Mancuso:** Writing – review & editing, Supervision, Conceptualization, Project administration, Formal Analysis.

Declaration of Interests

A.I. has nothing to disclose. K.M.S. has nothing to disclose. A.S. has nothing to disclose. A.C.M. has nothing to disclose.

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