Comparing reproductive outcomes between conventional in vitro fertilization and nonindicated intracytoplasmic sperm injection in autologous embryo transfer cycles: a Society for Assisted Reproductive Technology Clinic Outcome Reporting System Study

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Objective: To compare clinical outcomes between nonindicated intracytoplasmic sperm injection (ICSI) and conventional insemination.
Design: Autologous cycles performed from 2014–2017 were identified, excluding frozen oocyte cycles. Outcomes were compared between conventional insemination (in vitro fertilization [IVF]) and nonindiated ICSI and analyzed separately for fresh, frozen-thawed preimplantation genetic testing (PGT) and frozen-thawed non-PGT cycles.
Setting: US-based fertility clinics reporting to the Society for Assisted Reproductive Technology.
Participants: A total of 187,520 patients underwent 318,930 cycles, 57,516 (18.0%) using conventional IVF and 261,414 ICSI (82.0%).
Interventions: Intracytoplasmic sperm injection, with or without indications (male factor, prior fertilization failure or any PGT [2012 recommendations]/single-gene PGT [2020 recommendations]).
Main Outcome Measures: Odds ratios (ORs) for live birth rates and clinical pregnancy rates were calculated after multivariable adjustment for maternal age, body mass index, infertility etiologies, prior IVF births, and number oocytes retrieved.
Results: Intracytoplasmic sperm injection was indicated in 151,627 (58.0%) of cycles according to 2012 American Society for Reproductive Medicine Practice Committee recommendations, and 108,895 (41.7%) according to 2020 recommendations. In multivariable models, nonindicated ICSI among fresh cycles was associated with reduced odds of completing a blastocyst-stage transfer (OR, 0.72; 95% confidence interval [CI] [0.7, 0.75]; $P<.001$), resulting in reduced odds of live birth (OR, 0.80; 95% CI [0.78, 0.83]; $P<.001$). Among completed fresh transfers, clinical pregnancy and live birth rates were comparable between nonindicated ICSI and IVF. Nonindicated ICSI in frozen-thawed cycles with PGT and without PGT was associated with comparable live birth and clinical pregnancy rates with IVF in multivariable models.
Conclusion: Nonindicated ICSI was associated with reduced blastocyst availability in fresh cycles compared with IVF, leading to lower live birth rates. Outcomes from completed transfers were clinically comparable. (Fertil Steril Rep® 2024;5:23–32. ©2023 by American Society for Reproductive Medicine.)
Key Words: Intracytoplasmic sperm injection, assisted reproduction, national registry, non-male factor infertility, live birth rate

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Intracytoplasmic sperm injection (ICSI) was developed to facilitate fertilization in couples with male factor infertility undergoing in vitro fertilization (IVF) or after a prior fertilization failure (1, 2). Nonetheless, since its development in 1992, ICSI has been proposed for use in many other clinical cases, including unexplained infertility, poor-quality or limited oocyte yield, advanced maternal age, in combination with preimplantation genetic testing (PGT), and some have even suggested use of ICSI for all cycles (3). One obvious benefit of ICSI for patients planning genetic testing is that only one sperm is ever exposed to the ovum, limiting the theoretical possibility of contamination with genomic material from other sperm. This may be particularly relevant when PGT is performed, particularly for single-gene disorders.

The American Society for Reproductive Medicine (ASRM) Practice Committee issued a committee opinion in 2012 recommending against ICSI for unexplained infertility, low-oocyte yield, and advanced maternal age and only recommended its use for male factor infertility, planned PGT, in vitro maturation of oocytes, and previously cryopreserved oocytes (3). This committee opinion was updated in 2020, which affirmed the previous findings while narrowing the recommended indications for use of ICSI in PGT to "cases where contamination of extraneous sperm could affect the accuracy of test results" (4).

Despite these relatively strict recommendations, ICSI remains widely utilized in the United States among patients without the above indications. One study using Centers for Disease Control and Prevention national assisted reproduction surveillance data reported significant regional variation in ICSI usage, but no correlation between the rate of male factor infertility diagnoses within a clinic and its use of ICSI (5). Moreover, nationwide ICSI rates among IVF patients increased from 46.3% ± 6.1% to 70.0% ± 7.1% between 2000 and 2014 despite no increase in the reported rate of male factor infertility among them (5), with no improvement in postfertilization outcomes among all fresh transfers performed in the United States from 2008–2012 (6).

No large US-based cohort has rigorously evaluated how often ICSI was performed according to clinical recommendations. Moreover, the potential clinical consequences of nonindicated ICSI have never been evaluated for frozen-thawed transfers and stratified by use of PGT.

We therefore conducted a review of the Society for Assisted Reproductive Technology (SART) national registry to track recent use of ICSI and its indications compared with recent practice guidelines and compare the clinical outcomes between patients receiving conventional insemination against those receiving nonindicated ICSI.

METHODS

SART Database

The study dataset was obtained from the SART Clinic Outcome Reporting System (SART CORS). Data were collected from participating clinics through voluntary submission, verified by SART, 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 & Accountability Act-compliant business associates agreements with reporting clinics. In 2019, 81% of all assisted reproductive technology (ART) clinics in the United States reporting 90% of all IVF cycles were SART members (7). Participating clinics are expected to prospectively report cycles (within 4 days of gonadotropin start or before any embryo thaw). Although retrospective reporting is accepted, it is discouraged by prominently displaying prospective reporting rates on public-facing clinic summary reports.

The data in the SART CORS are validated annually with some clinics receiving on-site visits for chart review. During each visit, data reported by the clinic were compared with information recorded in patients' charts. In 2021, records for 1,945 cycles at 33 clinics were randomly selected for full validation, along with 262 fertility preservation cycles selected for partial validation. Nine of ten data fields selected for validation were found to have discrepancy rates of $\leq 5\%$ (7). The exception was the diagnosis field, which, depending on the diagnosis, had a discrepancy rate between 0.7% and 9.1% (7). Obstetric outcomes in SART CORS, including live birth/fetal death, plurality, birth date, and singleton birthweight were validated in a study comparing 9,092 ART deliveries in Massachusetts in 2004–2008 with state vital records of live birth and fetal death certificates. The SART-reported outcomes from Massachusetts ART records were validated to have >95% agreement with vital records (8).

Patient Inclusion/Exclusion Criteria

To measure adherence to Practice Committee recommendations for use of ICSI for non-male factor indications and the associated implications, we searched the SART CORS retrospective cohort for all autologous IVF cycles performed between 2014 and 2017.

The cycles were restricted to those resulting in oocyte retrieval, with at least one oocyte retrieved. Mixed donor cycles, cycles using frozen oocytes, and transfers entailing gamete intrafallopian transfer or zygote intrafallopian transfer were excluded. Cycles lacking clinical outcome data, cycles with unknown ICSI or IVF status, and cycles without all relevant covariates (age, body mass index [BMI], prior ART live births, and male infertility status) were excluded. Fresh transfers from cycles reporting use of PGT for all embryos were excluded given concerns for the accuracy of such labels.

Group Assignment Definition

Embryos fertilized via conventional insemination (IVF without ICSI) were considered the reference control group. Embryos fertilized via ICSI were classified based on whether the ICSI was recommended by the 2012 ASRM Practice Committee guidelines and whether the ICSI was recommended by the 2020 ASRM Practice Committee guidelines. Intracytoplasmic sperm injection was considered indicated by 2012 guidelines if the partner had a recorded history of male infertility, the cycle entailed PGT for some or all embryos, or the couple

experienced a prior failed fertilization. Intracytoplasmic sperm injection was considered nonindicated otherwise. For 2020 definitions, ICSI was considered indicated if the partner had history of male infertility, the couple experienced a prior failed fertilization, or if PGT was performed for single-gene analysis, human leukocyte antigen typing, or for known carrier state of the partners. Intracytoplasmic sperm injection was considered nonindicated when none of these indications were present.

Measured Covariates and Outcomes

Measured variables included patient age at start of oocyte retrieval cycle (classified as <35, 35–37, 38–40, and ≥41 years), female infertility etiology, male infertility etiology, BMI (classified as <18.5, 18.5–24, 25–29, 30–34, 35–39, and ≥40 kg/m^2), history of prior IVF birth, and number oocytes retrieved. Female infertility etiology was classified into binary categories based on the presence of: polycystic ovary syndrome or ovulatory disorders; tubal factors or endometriosis; diminished ovarian reserve (DOR), defined as high follicle stimulating hormone or high estradiol in the early follicular phase or during a clomiphene challenge test, or reduced ovarian volume (note, the SART CORS database does not define "high" or "reduced"); or other female infertility (including uterine factor or hypothalamic amenorrhea). Male factor infertility was diagnosed based on clinic-reported indication(s) for ART, because more specific male factor diagnoses based on the semen analysis and workup were not introduced into SART CORS until 2016. Multiple infertility diagnoses were possible for each couple undergoing IVF.

The primary outcome was live birth rate, with secondary outcomes of clinical pregnancy rate and spontaneous abortion rate. Outcomes from transfers are expressed and analyzed on an intended-transfer basis to capture intended fresh cycles and intended embryo thaws not resulting in transfers. Live birth was defined as delivery of a fetus after 20 weeks' gestational age with more than fleeting signs of life. Clinical pregnancy was defined as sonographic visualization of an intrauterine gestational sac. Spontaneous abortions were defined as losses before 20 weeks of completed gestation.

Statistical Analysis

Summary statistics were computed as mean ± SD for continuous data and number and percent for categorical data, after removal of missing demographic data. Summary statistics for clinical outcomes were tabulated after stratifying patients by age groups (detailed above) and use of ICSI according to 2020 guidelines.

Outcomes were analyzed for all patients. Intended fresh embryo transfers, intended frozen-thawed embryo transfers among embryos not receiving PGT, and intended frozen-thawed embryo transfers after PGT were analyzed separately. Analysis was repeated after stratifying based on the presence of a male factor infertility to estimate the effect of use of ICSI against a reference population undergoing conventional IVF with male factor infertility and a reference population undergoing IVF without male factor infertility.

An additional subanalysis was performed on single blastocyst-stage embryo transfer cycles (i.e., completed transfers).

To account for multiple cycles per person, odds ratios (ORs) and 95% confidence intervals (CIs) were computed from multivariable generalized estimating equations with binomial link, adjusting for a set of prespecified covariates: patient age at cycle start, BMI, female infertility binary categories (as detailed above), male infertility, and prior IVF live birth. Analyses of fresh transfers were further adjusted for number of retrieved oocytes. P values of $<.05$ were considered statistically significant.

Statistical analysis was performed using R 4.2.0 (9).

Informed Consent and Institutional Review Board Approval

This project was conducted after internal Institutional Review Board review and approval (Montefiore IRB 2021-12639, approved February, 23, 2021). Nonidentifiable patient data were obtained from SART CORS. Patient consent was not required, because this work exclusively utilized retrospective data from a national registry collected during routine care.

RESULTS

The study cohort included 187,520 patients undergoing autologous cycles, 34,233 of whom generated embryos fertilized via conventional IVF during their first treatment cycle. For the remaining 153,287 patients who created embryos via ICSI, ICSI was considered indicated among 92,134 (60.1%) by 2012 recommendations and among 63,337 (41.3%) by 2020 ASRM Practice Committee recommendations (Table 1). Patient age, BMI, parity, prior ART live births, and number of prior spontaneous abortions were clinically comparable between conventional IVF and nonindicated ICSI groups, although small differences met statistical significance ($P<.001$ for all comparisons) because of the large sample size (Table 1).

Overall, 318,930 ART cycles were analyzed, representing 57,516 (18.0%) conventional IVF and 261,414 ICSI (82.0%) cycles. Among the ICSI cycles, ICSI was indicated in 151,627 (58.0%) according to 2012 recommendations, whereas it was indicated in 108,895 (41.7%) according to 2020 ASRM Practice Committee recommendations (Supplemental Table 1, available online).

Because male factor infertility was considered an indication for ICSI, none of the nonindicated ICSI cycles had a male factor infertility diagnosis. However, a male factor infertility diagnosis was reported in 5,336 (9.3%) of the conventional IVF cycles (Supplemental Table 1). Patients with DOR or ovulatory disorders were more likely to undergo nonindicated ICSI compared with IVF, whereas those with tubal factor infertility were less likely to undergo nonindicated ICSI compared with conventional IVF (Supplemental Table 1, $P<.001$ for all comparisons).

Intended fresh cycles were more likely to result in a completed transfer if conventional IVF was used compared

TABLE 1

Demographic information on 187,520 participants included in this study.

Characteristic	Conventional IVF (n = 34,233)	Indicated ICSI by 2012 Guidelines (n = 92,134)	Nonindicated ICSI by 2012 Guidelines (n = 61,153)	*P* Value[b]	Indicated ICSI by 2012 Guidelines (n = 63,337)	Nonindicated ICSI by 2020 Guidelines (n = 89,950)	*P* Value[b]
Age[a] (mean [SD])	34.82 (4.55)	34.43 (4.37)	35.42 (4.89)	<.001	34.04 (4.49)	35.38 (4.61)	<.001
BMI[a] (mean [SD])	26.32 (5.95)	25.95 (5.75)	26.36 (6.04)	<.001	26.34 (5.89)	25.96 (5.85)	<.001
Parity [N (%)]				<.001			<.001
0	24,414 (71.3)	67,852 (73.6)	45,039 (73.6)		47,627 (75.2)	65,264 (72.6)	
1	7,050 (20.6)	18,189 (19.7)	11,508 (18.8)		12,065 (19.0)	17,632 (19.6)	
2	1,661 (4.9)	4,079 (4.4)	2,584 (4.2)		2,456 (3.9)	4,207 (4.7)	
3+	1,077 (3.1)	1,815 (2.0)	1,812 (3.0)		1,070 (1.7)	2,557 (2.8)	
Missing	31 (0.1)	199 (0.2)	210 (0.3)		119 (0.2)	290 (0.3)	
Prior ART live births (N [%])				<.001			<.001
0	32,785 (95.8)	86,717 (94.1)	58,447 (95.6)		59,143 (93.4)	86,021 (95.6)	
1	1,325 (3.9)	4,803 (5.2)	2,414 (3.9)		3,742 (5.9)	3,475 (3.9)	
2	115 (0.3)	556 (0.6)	257 (0.4)		411 (0.6)	402 (0.4)	
3+	8 (0.0)	58 (0.1)	35 (0.1)		41 (0.1)	52 (0.1)	
Spontaneous abortion (N [%])				<.001			<.001
0	25,027 (73.1)	70,362 (76.4)	45,185 (73.9)		51,371 (81.1)	64,176 (71.3)	
1	5,966 (17.4)	13,985 (15.2)	10,422 (17.0)		8,616 (13.6)	15,791 (17.6)	
2	2,059 (6.0)	4,850 (5.3)	3,482 (5.7)		2,290 (3.6)	6,042 (6.7)	
3+	1,157 (3.4)	2,832 (3.1)	1,958 (3.2)		973 (1.5)	3,817 (4.2)	
Missing	24 (0.1)	105 (0.1)	106 (0.2)		87 (0.1)	124 (0.1)	
Prior failed fertilization	0 (0.0)	333 (0.4)	0 (0.0)	<.001	333 (0.5)	0 (0.0)	<.001

ART = assisted reproductive technology; BMI = body mass index; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization.
[a] For frozen cycles, data were taken from the linked original cycle,
[b] between conventional IVF and nonindicated ICSI.

Gingold. IVF vs. nonindicated ICSI in SART CORS. Fertil Steril Rep 2024.

TABLE 2

Relative 2PN count and odds ratio of transfer attempt among fresh cycles.

	2PN embryos			Transfer Attempted		
Subgroup	**Difference**	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**
All						
Conventional IVF		Ref			Ref	
All ICSI	−0.13	−0.17, −0.08	<.001	0.83	0.81, 0.85	<.001
2012/2020 guidelines[a]						
Indicated ICSI	0.80	0.65, 0.94	<.001	1.90	1.78, 2.04	<.001
Nonindicated ICSI	−0.30	−0.34, −0.25	<.001	0.72	0.7, 0.75	<.001
Diagnosed male fertility						
Conventional IVF		Ref			Ref	
All ICSI[b]	1.14	0.98, 1.31	<.001	2.00	1.86, 2.15	<.001
No male infertility						
Conventional IVF		Ref			Ref	
All ICSI	−0.30	−0.34, −0.25	<.001	0.73	0.71, 0.75	<.001
2012/2020 guidelines[a]						
Indicated ICSI	−0.55	−0.77, −0.33	<.001	1.52	1.28, 1.8	<.001
Nonindicated ICSI	−0.29	−0.34, −0.25	<.001	0.72	0.7, 0.74	<.001

Note: All models adjusted for age, BMI, male infertility (yes/no), female infertility (binary categories for PCOS or ovulatory disorders, tubal factors or endometriosis, DOR, or other factors [uterine or hypothalamic amenorrhea]), prior IVF live birth (0/1), and number of total retrieved oocytes.
2PN = 2-pronuclear; CI = confidence interval; DOR = diminished ovarian reserve; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; OR = odds ratio; PCOS = polycystic ovarian syndrome; PGT = preimplantation genetic testing.
[a] The 2012/2020 guidelines are equivalent as fresh cycles with PGT were excluded.
[b] All cases of diagnosed male infertility are considered indicated ICSI.

Gingold. IVF vs. nonindicated ICSI in SART CORS. Fertil Steril Rep 2024.

with nonindicated ICSI (62% vs. 55%), whereas indicated ICSI in intended fresh cycles was associated with clinically comparable transfer rate (61%) (Supplemental Table 2). Intended frozen-thawed transfers, with or without PGT, culminated in transfers in >99% of all cases (Supplemental Table 2).

Generating 2-Pronuclear Embryos and Completing a Fresh Blastocyst Transfer

Among fresh cycles, nonindicated ICSI was associated with fewer 2-pronuclear (2PN) embryos (mean difference −0.30; 95% CI [−0.34, −0.25]; $P<.001$) and lower odds of completing a blastocyst-stage transfer (OR 0.72; 95% CI [0.7, 0.75]; $P<.001$) compared with conventional IVF after multivariate adjustment (Table 2). In contrast, among patients with male factor infertility, indicated ICSI was associated with generation of more 2PN embryos (mean difference, 1.14; 95% CI [0.98, 1.31]; $P<.001$) and higher odds of completing a transfer (OR, 2.00, 95% CI [1.86, 2.15]; $P<.001$) compared with conventional IVF among patients with male infertility after multivariate adjustment (Table 2). Among patients with non-male factor infertility but with other indications for ICSI, indicated ICSI was associated with generation of fewer 2PN embryos (mean difference −0.55; 95% CI [−0.77, −0.33], $P<.001$) but higher odds of completing a transfer (OR, 1.52; 95% CI [1.28, 1.80], $P<.001$) compared with having non-male factor indications for ICSI but still proceeding with conventional IVF (Table 2). Similar analysis could not be performed on frozen-thawed transfers, because such cycles were only registered after an embryo was available for transfer and other sources of patient dropout were minimal (Supplemental Table 2).

Clinical Outcomes in Fresh Cycles

Among intended fresh embryo cycles, nonindicated ICSI was associated with significantly lower odds of clinical pregnancy (OR, 0.79; 95% CI [0.77, 0.82]; $P<.001$), live birth (OR, 0.80; 95% CI [0.78, 0.83]; $P<.001$), and spontaneous abortion (OR, 0.84; 95% CI [0.79, 0.89]; $P<.001$) compared with conventional IVF after multivariate adjustment (Table 3).

On stratified analysis, nonindicated ICSI for non-male factor indications was also associated with lower odds of clinical pregnancy (OR, 0.79; 95% CI [0.77, 0.82]; $P<.001$), live birth (OR, 0.80; 95% CI [0.78, 0.83]; $P<.001$), and spontaneous abortion (OR 0.84; 95% CI [0.79, 0.89]; $P<.001$) compared with conventional IVF for non-male factor indications (Table 3). Indicated ICSI for non-male factor indications showed similar trends suggesting potentially lower pregnancy, live birth, and abortion rates compared with conventional IVF for non-male factor indications, although these were not statistically significant (Table 3). In contrast, indicated ICSI for male infertility was associated with higher odds of clinical pregnancy (OR, 1.52; 95% CI [1.40, 1.66]; $P<.001$), live birth (OR, 1.45; 95% CI [1.32, 1.59]; $P<.001$), and spontaneous abortion (OR, 1.56; 95% CI [1.28, 1.90]; $P<.001$) compared with conventional IVF for patients with male infertility (Table 3).

When restricted to completed fresh single blastocyst transfers, use of nonindicated ICSI was associated with no significant difference in live birth, clinical pregnancy or spontaneous abortion compared with IVF overall or IVF for patients without male factor infertility after multivariate adjustment (Table 4). Similarly, indicated ICSI for non-male factor infertility was associated with comparable clinical outcomes to IVF for non-male factor (Table 4). Indicated ICSI for male factor infertility was also associated

TABLE 3

Odds ratios of IVF outcomes by ICSI usage and stratified by male infertility.

		Live Birth			Clinical Pregnancy			Spontaneous Abortion		
Subgroup		**OR**	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**
All cycles										
Fresh—no PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI	0.86	0.84, 0.89	<.001	0.86	0.84, 0.89	<.001	0.90	0.85, 0.95	<.001
	2012/2020 guidelines[a]									
	Indicated ICSI	1.30	1.21, 1.41	<.001	1.35	1.25, 1.45	<.001	1.34	1.16, 1.55	<.001
	Nonindicated ICSI	0.80	0.78, 0.83	<.001	0.79	0.77, 0.82	<.001	0.84	0.79, 0.89	<.001
Frozen—any PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI/indicated ICSI by 2012 guidelines	1.00	0.95, 1.05	1.00	1.04	0.99, 1.09	.15	1.12	1.02, 1.22	.02
	2020 guidelines									
	Indicated ICSI	1.04	0.96, 1.14	.33	1.08	0.99, 1.18	.10	1.11	0.95, 1.29	.20
	Nonindicated ICSI	0.99	0.94, 1.04	.73	1.03	0.97, 1.08	.33	1.12	1.01, 1.23	.02
Frozen—no PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI	1.02	0.98, 1.06	.34	1.03	0.99, 1.07	.19	1.01	0.95, 1.07	.83
	2012/2020 guidelines[a]									
	Indicated ICSI	1.00	0.89, 1.13	.96	0.96	0.86, 1.08	.52	0.90	0.76, 1.08	.26
	Nonindicated ICSI	1.02	0.98, 1.07	.29	1.04	0.99, 1.08	.10	1.02	0.95, 1.09	.57
Diagnosed male infertility										
Fresh—no PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI	1.45	1.32, 1.59	<.001	1.52	1.4, 1.66	<.001	1.56	1.28, 1.9	<.001
Frozen—any PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI	1.10	0.92, 1.31	.29	1.17	0.98, 1.4	.09	1.15	0.83, 1.58	.40
Frozen—no PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI	1.00	0.89, 1.13	.99	0.96	0.86, 1.08	.50	0.91	0.76, 1.08	.26
No male infertility										
Fresh—no PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI	0.80	0.78, 0.83	<.001	0.79	0.77, 0.82	<.001	0.84	0.79, 0.89	<.001
	2012/2020 guidelines[a]									
	Indicated ICSI	0.85	0.7, 1.03	.09	0.85	0.71, 1.01	.07	0.93	0.67, 1.29	.66
	Nonindicated ICSI	0.80	0.78, 0.83	<.001	0.79	0.77, 0.82	<.001	0.84	0.79, 0.89	<.001
Frozen—any PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI/indicated ICSI by 2012 guidelines	0.99	0.94, 1.04	.60	1.02	0.97, 1.08	.46	1.11	1.01, 1.22	.03
	2020 guidelines									
	Indicated ICSI	0.99	0.89, 1.1	.79	1.02	0.92, 1.14	.70	1.15	0.95, 1.39	.15
	Nonindicated ICSI	0.99	0.93, 1.04	.58	1.02	0.97, 1.08	.47	1.11	1.01, 1.22	.03
Frozen—no PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI	1.02	0.98, 1.07	.29	1.04	0.99, 1.08	.10	1.02	0.96, 1.09	.56

Note: All models adjusted for age, BMI, male infertility (yes/no), female infertility [binary categories for PCOS or ovulatory disorders, tubal factors or endometriosis, DOR, or other factors (uterine or hypothalamic amenorrhea)], and prior IVF live birth (0/1). Models for fresh cycles further adjusted for number of total retrieved oocytes. No individuals in the Frozen—any PGT group had DOR. Effects of indicated ICSI for patients with no male infertility could not be estimated in the Frozen—no PGT group because of insufficient sample size.

BMI = body mass index; CI = confidence interval; DOR = diminished ovarian reserve; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; OR = odds ratio; PCOS = polycystic ovarian syndrome; PGT = preimplantation genetic testing.

[a] For cycles not utilizing PGT, the 2012/2020 guidelines are equivalent.

Gingold. IVF vs. nonindicated ICSI in SART CORS. Fertil Steril Rep 2024.

with comparable clinical outcomes to IVF for male factor (Table 4).

Clinical Outcomes in Frozen-Thawed Cycles with PGT

Among intended frozen-thawed embryo transfers with PGT, ICSI for any reason (i.e., indicated by 2012 guidelines) was associated with comparable odds of clinical pregnancy and live birth but slightly higher odds of spontaneous abortion (OR, 1.12, 95% CI [1.01, 1.22]; $P=.02$) compared with conventional IVF after multivariate adjustment (Table 3). Nonindicated ICSI (by 2020 guidelines) was similarly associated with comparable odds of clinical pregnancy and live birth but increased spontaneous abortions (OR, 1.12; 95% CI (1.01, 1.23); $P=.02$) compared with conventional IVF after multivariate adjustment (Table 3).

On stratified analysis, nonindicated ICSI (by 2020 guidelines) for non-male factor infertility remained associated with comparable pregnancy and live birth rates but higher odds of spontaneous abortion (OR, 1.11; 95% CI [1.01, 1.22]; $P=.03$) compared with conventional IVF for patients without male factor after multivariate adjustment (Table 3). Indicated ICSI for non-male factor was associated with no significant differences in pregnancy, live birth, or abortion rates compared with conventional IVF for non-male factor (Table 3). Indicated ICSI for male factor infertility was also associated with no significant differences in pregnancy, live birth, or abortion rates compared with conventional IVF for male factor patients undergoing conventional IVF after multivariate adjustment (Table 3).

When restricted to completed single embryo transfers, unadjusted pregnancy, abortion, and live birth rates remained clinically comparable (Supplemental Table 3). However,

TABLE 4

Odds ratios of IVF outcomes by ICSI usage stratified by male infertility, restricted to completed single blastocyst transfers.

		Live Birth			Clinical Pregnancy			Spontaneous Abortion		
Subgroup		**OR**	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**
All cycles										
Fresh—no PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI	0.96	0.91, 1.01	.10	0.96	0.91, 1.01	.11	1.00	0.91, 1.09	.94
	2012/2020 guidelines[a]									
	Indicated ICSI	0.87	0.76, 1.01	.07	0.94	0.82, 1.09	.42	1.26	0.96, 1.66	.10
	Nonindicated ICSI	0.97	0.91, 1.02	.26	0.96	0.91, 1.01	.15	0.97	0.88, 1.07	.53
Frozen—any PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI/indicated ICSI by 2012 guidelines	0.97	0.92, 1.03	.29	1.01	0.95, 1.06	.79	1.12	1.02, 1.23	.02
	2020 guidelines									
	Indicated ICSI	1.04	0.95, 1.13	.37	1.08	0.98, 1.18	.11	1.10	0.95, 1.28	.21
	Nonindicated ICSI	0.96	0.91, 1.01	.14	0.99	0.94, 1.05	.76	1.11	1.01, 1.23	.04
Frozen—no PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI	1.06	1.01, 1.12	.03	1.07	1.02, 1.13	.006	1.03	0.95, 1.12	.460
	2012/2020 guidelines[a]									
	Indicated ICSI	0.99	0.85, 1.15	.92	0.96	0.83, 1.12	.61	0.92	0.73, 1.17	.52
	Nonindicated ICSI	1.07	1.01, 1.13	.02	1.09	1.03, 1.15	.002	1.04	0.96, 1.14	.34
Diagnosed male infertility										
Fresh—no PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI	0.88	0.75, 1.03	.11	0.96	0.82, 1.13	.62	1.31	0.95, 1.81	.10
Frozen—any PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI	1.10	0.91, 1.33	.31	1.20	0.99, 1.45	.06	1.26	0.89, 1.77	.19
Frozen—no PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI	0.98	0.85, 1.14	.83	0.97	0.84, 1.13	.70	0.96	0.76, 1.22	.76
No male infertility										
Fresh—no PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI	0.97	0.91, 1.02	.23	0.96	0.91, 1.01	.13	0.97	0.88, 1.07	.55
	2012/2020 guidelines[a]									
	Indicated ICSI	0.81	0.57, 1.15	.24	0.84	0.59, 1.19	.32	1.14	0.63, 2.06	.67
	Nonindicated ICSI	0.97	0.91, 1.02	.26	0.96	0.91, 1.01	.15	0.97	0.88, 1.07	.52
Frozen—any PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI/indicated ICSI by 2012 guidelines	0.95	0.9, 1	.06	0.98	0.93, 1.04	.47	1.11	1.01, 1.23	.04
	2020 guidelines									
	Indicated ICSI	0.97	0.87, 1.09	.61	1.01	0.91, 1.14	.81	1.18	0.97, 1.43	.10
	Nonindicated ICSI	0.95	0.89, 1	.05	0.98	0.92, 1.03	.42	1.11	1.01, 1.23	.04
Frozen—no PGT	IVF without ICSI	Ref			Ref			Ref		
	All ICSI	1.05	0.99, 1.11	.09	1.07	1.01, 1.13	.02	1.05	0.96, 1.14	.28

Note: All models adjusted for age, BMI, male infertility (yes/no), female infertility (binary categories for PCOS or ovulatory disorders, tubal factors or endometriosis, DOR, or other factors [uterine or hypothalamic amenorrhea]), and prior IVF live birth (0/1). Models for fresh cycles further adjusted for number of total retrieved oocytes. No individuals in the Frozen—any PGT group had DOR. Effects of indicated ICSI for patients with no male infertility could not be estimated in the Frozen—no PGT group because of insufficient sample size.

BMI = body mass index; CI = confidence interval; DOR = diminished ovarian reserve; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; OR = odds ratio; PCOS = polycystic ovarian syndrome; PGT = preimplantation genetic testing.

[a] For cycles not utilizing PGT, the 2012/2020 guidelines are equivalent.

Gingold. IVF vs. nonindicated ICSI in SART CORS. Fertil Steril Rep 2024.

nonindicated ICSI remained associated with slightly increased spontaneous abortions compared with IVF (OR, 1.12; 95% CI [1.01, 1.23]; $P=.02$) (Table 4). Nonindicated ICSI for non-male factor was associated with slightly increased spontaneous abortions compared with IVF for non-male factor (OR, 1.11, 95% CI [1.01, 1.23]; $P=.04$), with the live birth rate bordering on being considered significantly lower (OR, 0.95, 95% CI [0.89, 1.00]; $P=.05$) (Table 4).

Clinical Outcomes in Frozen-Thawed Cycles without PGT

Among intended frozen-thawed embryo transfers without PGT, nonindicated ICSI was associated with comparable odds of clinical pregnancy, live birth, and spontaneous abortion compared with conventional IVF after multivariate adjustment (Table 3). Indicated ICSI was similarly associated with comparable odds of clinical pregnancy, live birth, and spontaneous abortion compared with conventional IVF after multivariate adjustment (Table 3).

On stratified analysis, ICSI for non-male factor infertility was associated with comparable pregnancy, live birth, and abortion rates to IVF for non-male factor infertility (Table 3). Intracytoplasmic sperm injection among patients with male factor infertility was associated with comparable pregnancy, live birth, and abortion rates to IVF performed on patients with male factor infertility (Table 3).

When restricted to completed single frozen-thawed blastocyst transfers without PGT, unadjusted analyses suggested a potential for increase in live birth among women 38–40

years (Supplemental Table 3) with use of unindicated ICSI. Use of nonindicated ICSI was associated with slightly increased odds of clinical pregnancy (OR, 1.09; 95% CI [1.03, 1.15]; $P=.002$) and live birth (OR, 1.07; 95% CI [1.01, 1.13]; $P=.02$) compared with conventional IVF after multivariate adjustment (Table 4). However, the effect of ICSI for non-male factor infertility on live birth rate compared with IVF for non-male factor infertility was not sustained on stratified analysis (Table 4).

DISCUSSION

To our knowledge, this study is the first to use the SART national registry to understand the clinical implications of using ICSI stratified by type of embryo transfer (fresh, frozen-thawed with PGT, and frozen-thawed without PGT) and whether ICSI is indicated.

This work confirms prior randomized and large retrospective studies (10–16) suggesting that ICSI for non-male factor infertility (and nonindicated ICSI in general) offers no detectable clinical benefit in most cases, including fresh transfers and frozen-thawed transfers with PGT. Most strikingly, it suggests the potential for significant harm from nonindicated ICSI. We found that use of nonindicated ICSI in fresh cycles was associated with a reduced number of 2PN embryos and blastocysts available for transfer compared with conventional IVF (Table 2), and that this translated into reduced pregnancy and live birth rates with nonindicated ICSI during fresh cycles (Table 3). In contrast, indicated ICSI was associated with the more 2PN embryos and blastocysts for transfer, which led to higher pregnancy and live birth rates compared with conventional IVF. However, the blastocysts, once generated from either insemination procedure, indicated or not, appear to function comparably during fresh transfers (Table 4).

Prior ART surveillance data similarly reported a lower live birth rate with ICSI among fresh cycles with non-male factor infertility (6). Analysis of these cycles from 2008–2012 failed to identify significant increases in cancellations before transfer with ICSI (some ICSI subgroups even had a lower cancellation rate), but showed a lower pregnancy and live birth rate among transfers. In contrast, our study highlighted that blastocyst transfers were less likely to be completed with nonindicated ICSI compared with IVF, but that the blastocyst transfers have comparable clinical outcomes. Intracytoplasmic sperm injection also slightly reduced the number of 2PN embryos generated in all cases other than indicated ICSI for male factor, which had more available 2PNs (Table 2). It is notable that >40% of the transfers in this earlier cohort used day 3 transfers (6). Historical transfer of day 3 embryos from the ICSI group lacking the potential to progress to the blastocyst stage in the ICSI group could potentially explain this discrepancy.

This study also reinforces the unassailable benefits of ICSI for male factor infertility, with markedly improved odds of completing a transfer and having a live birth compared with conventional IVF for male factor (or even compared with all cycles utilizing conventional IVF). These benefits were also observed in prior ART surveillance studies (6).

The evidence for most other indications for ICSI remains limited. Although ICSI has been shown to prevent fertilization failure (number needed to treat = 33) from a well-designed randomized controlled trial, clinical pregnancy rates were comparable between ICSI and conventionally inseminated groups (10). These findings are essentially confirmed in our cohort, which identified higher odds of completing a fresh transfer with indicated ICSI for non-male factor, despite the slightly reduced number of 2PN embryos (Table 2), but no effect on live birth (Table 3) or live birth when restricted to completed blastocyst transfers (Table 4).

One randomized controlled trial (11) and another retrospective cohort (12) found no benefit from use of ICSI in patients with poor oocyte yield, whereas a national cohort study from 2014 actually found decreased odds of live birth with ICSI among patients diagnosed with DOR (13). A large Australian cohort study (14), a Latin American registry (16), and a large Chinese cohort (15) similarly found no difference in cumulative live birth rate when ICSI was performed for non-male factor infertility. A cohort study of patients undergoing PGT for aneuploidy with split insemination by IVF and ICSI found similar rates of mosaicism and aneuploidy, suggesting that contamination during IVF was unlikely (17). A recent study using SART registry data from 2014–2015 found that ICSI for non-male factor was not associated with improved live birth outcomes among PGT or non-PGT cycles, despite adding significant costs (18). The primary analysis of this study, analyzing outcomes from the first retrieval cycle per patient, was reported on a per-transfer basis, thus potentially excluding more challenging patients requiring multiple retrievals and not counting cycles that fail to proceed to transfer.

The structure of the SART CORS registry, in which planned frozen-thawed embryo transfers are only registered after an embryo is already created and available for transfer, precludes making conclusions about blastocyst availability among frozen-thawed cycles. Extrapolation of findings from fresh cycles raises the concern that nonindicated ICSI may similarly reduce blastocyst availability for frozen-thawed cycles, potentially also reducing live birth rates, even if such blastocyst-stage transfers have comparable clinical outcomes with or without ICSI (Table 3).

The slightly increased rate of spontaneous abortions with use of ICSI among frozen-thawed cycles with PGT defies convenient explanation, particularly because no such effect was observed in untested embryos. Although the increased losses did not clearly translate into any effect on live birth rates overall, the live birth rate for the subanalysis of nonindicated ICSI compared with IVF patients without male factor (Table 4) was of borderline significance to suggest it was slightly lower. One potential explanation is that laboratories that performed routine ICSI for patients undergoing PGT might have differed in other laboratory techniques (e.g., taking a larger trophectoderm biopsy) from those that performed PGT after conventional IVF, and that this confounding compromised embryonic growth potential after implantation, leading to increased spontaneous abortions.

Rather surprisingly, we were unable exclude the possibility that nonindicated ICSI in frozen-thawed transfers without

use of PGT may convey a small clinical benefit once the transfer is registered compared with conventional insemination. However, this finding must be interpreted with caution for several reasons. Most notably, our findings regarding fresh transfers suggest that use of nonindicated ICSI reduces embryo availability and is the dominant effect. Although it may be possible that frozen-thawed non-PGT transfers may have a slightly higher live birth rate on a per-transfer basis, even this finding is questionable. The estimated effect size is relatively small (OR, 1.07) and the 95% CI barely excludes the null effect. In fact, the effect was not significant among planned frozen-thawed transfers without PGT (Table 3). These observations collectively suggest that the association between nonindicated ICSI and higher live birth rates in only frozen-thawed transfers without PGT potentially represents a false positive and is unlikely to be clinically meaningful compared with the anticipated dramatic reduction in number of embryos available for transfer.

Overall, prior findings and our work thus support the clinical practices endorsed in recent ASRM guidelines (3, 4). Nevertheless, there may be a role for revisiting recommendations against performing ICSI for non-male factor infertility in non-PGT frozen-thawed transfers. Still, any potential benefits must also be weighed against the well-established additional costs (18) and potential risks associated with ICSI. Children conceived from ICSI (for any indication) were reported to have higher rates of malformations compared with those conceived from IVF, although most of this effect was in the urogenital system of boys, suggesting that paternal genetic factors among those with male factor infertility rather than the ICSI procedure itself are likely responsible (19). A study analyzing ART-conceived singletons born in California from fresh transfers reported a higher adjusted hazard risk ratio of autism when ICSI was used (20). Overall, the case for a wider use of ICSI outside of male factor infertility in clinical practice remains weak, although the matter remains actively debated and estimates of the absolute long-term risks from ICSI range from very small to nil (21).

This study is notable for its very large sample size, including all autologous IVF cycles performed in the United States at SART-member clinics between 2014 and 2017, with additional subanalyses restricted to single embryo transfers. The exclusion of all identifiable indications for ICSI in the nonindicated ICSI group facilitated a more rigorous comparison with those undergoing conventional insemination, whereas the large sample size permitted adjustment for multiple potential confounders.

Nonetheless, this study is limited by its retrospective nature. Use of ICSI has clear regional variation and is known to vary by fertility clinic, many of which use ICSI universally. Region-specific or clinic-specific identifiers were not available for this study, making it impossible to adjust for confounding at the laboratory or clinic level despite its potential for dramatic effects. Patients receiving nonindicated ICSI were also clearly different from those receiving IVF, including in their infertility diagnoses. Thus, effect estimates were dependent on the completeness of multivariable adjustment for known confounders. A small percentage of cases of IVF had male factor infertility, including rare cases of severe male factor infertility. Although most such cases of IVF likely represented mild cases of male factor infertility, it may also represent suboptimal patient management, for example because of lack of a skilled embryologist to perform ICSI.

Although it is reasonable to assume that almost all transfers of frozen-thawed embryos utilizing PGT were euploid, the aneuploidy status after PGT was not available in SART CORS. Potential confounding may exist if the ICSI or IVF groups disproportionately underwent transfers of mosaic or even aneuploid embryos. Because ART cycle outcomes are tracked over only a limited period, it was not possible to establish whether all embryos from a cycle were used or family building is complete. Despite regular validation of the SART CORS registry on a subset of cycles, reporting errors exist, and infertility diagnoses, including male factor infertility, are likely underreported. The effects of such underreporting on the principal findings are unclear.

CONCLUSION

Nonindicated ICSI in fresh cycles is associated with reduced pregnancy and live birth rates compared with conventional IVF because of fewer available blastocysts for transfer, but completed fresh blastocyst transfers have comparable clinical outcomes with or without ICSI. Intracytoplasmic sperm injection for male factor clearly improves blastocyst availability and live birth rate compared with conventional IVF. Frozen-thawed cycles with or without PGT appear to be largely unaffected by nonindicated ICSI, although there might be a small benefit from ICSI in frozen-thawed transfers without PGT and a small increase in losses among frozen-thawed transfers with PGT.

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Declaration of Interests

J.A.G. has nothing to disclose. H.W. has nothing to disclose. H.L. has nothing to disclose. M.S. has nothing to disclose. S.J. has nothing to disclose.

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