Clinical outcomes following ICSI cycles using surgically recovered sperm and the impact of maternal age: 2004–2015 SART CORS registry

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Abstract

Purpose The aims of this study were (1) to evaluate clinical outcomes after ICSI cycles using surgically recovered sperm and (2) to assess the influence of maternal age on those outcomes.

Methods A retrospective cohort study of 24,763 IVF cycles of fresh autologous oocytes and ICSI using surgically recovered sperm reported to the SART CORS database from 2004 to 2015.

Results and conclusions Older women had significantly longer stimulation ($p < 0.001$), a lower number of oocytes retrieved ($p < 0.001$), a lower number of 2PN zygotes ($p < 0.001$), a lower chance of having a blastocyst transferred ($p < 0.001$), and a higher number of fresh embryos transferred ($p < 0.001$). There was no significant association between the number of 2PNs per oocyte retrieved and maternal age ($p = 0.214$). Both clinical pregnancy rates and live birth rates (LBR) decreased with advanced maternal age ($p < 0.001$). LBR ranged from 50.4% in women < 30 to 7.2% in women > 42 years, and for cleavage-stage transfers, the LBR ranged from 47.3% in women < 30 to 6.3% in women > 42 years. There were no differences in gestational age at delivery, proportion of term deliveries, preterm deliveries, neonatal birth weight < 2500 g, neonatal birth weight > 4000 g and average birthweight of neonates for singleton pregnancies according to age. For twin pregnancies, women < 30 years had significantly higher number of live births, term deliveries, and lower preterm deliveries than older women. There was a similar number of female (6051) and male neonates (5858; $p = 0.2$). Overall, pregnancy outcomes with ICSI using surgically recovered sperm are reassuring and comparable to those of ICSI with ejaculated sperm.

Keywords Azoospermia · Testicular sperm · Epididymal sperm · ICSI · Pregnancy outcomes

Introduction

Over 1% of infants in the USA are conceived using assisted reproductive technology (ART) [1, 2] and, among fresh-

embryo IVF cycles, the use of ICSI increased from 36.4% in 1996 to 76.2% in 2012 [3]. Since the first children were born after intracytoplasmic sperm injection (ICSI) using testicular sperm [4, 5], the use of TESE, PESA (percutaneous epididymal sperm aspiration), and TESA (testicular sperm aspiration) has steadily increased. Pregnancies achieved by ART, particularly with ICSI procedures, are susceptible to genetic risks inherent to the male population treated and additional risks inherent to this invasive procedure. Even though very early studies indicated that the frequency of congenital abnormalities in IVF-conceived children was similar to those following natural conception [6], concerns about these children's health still persist and the routine use of ICSI, in particular, has raised some of these concerns [7]. Follow up case series reports of ICSI progeny did not reveal alarming differences compared with children from standard IVF [8, 9]. Epidemiological studies have questioned such positive interpretations, by reporting a twofold increase in ART infant's malformations [10], a concurrent reduction in birth weight [11, 12], and a possible

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association with increased phenotypic anomalies [13] including some forms of cancer [14] and imprinted disorders [15]. However, larger multicenter studies demonstrated that these anomalies are independent of ART and the procedures used and are more related to the particular genetic background of the parents such as the presence of a male factor [16]. To address these concerns, monitoring organizations prompted studies including genetic screening and longer follow-up developmental milestones to look into childhood outcomes.

Various groups have reported impaired fertility potential in cases where surgically retrieved epididymal or testicular sperm are used for ICSI compared with ejaculated sperm, though there is little consensus when comparing men with obstructive (OA) and nonobstructive (NOA) azoospermia. However, studies involving large cohorts have now shown near equivalence with samples retrieved from the epididymis or testis [17, 18], and even with sperm characterized by poor motility and morphology. In the extreme scenario of necrospemia, testicular sperm may even outperform viable ejaculated samples [19].

In evaluating outcomes of IVF/ICSI with surgically obtained spermatozoa, it is important to acknowledge the many factors affecting success. In particular, maternal age is an important confounding factor. Maternal age has a significantly detrimental effect on pregnancy rates [20], especially after age 40 [21]. In a series of ICSI for azoospermia, fertilization rates, embryo quality, and clinical pregnancies were significantly higher for cycles involving oocytes from women < 35 years and sperm from men with OA compared to men with NOA [22]. Studies are conflicting on whether younger maternal age has a positive correlation with fertilization rates [21, 23].

The aim of this study was to retrospectively (1) evaluate the clinical outcomes after ICSI cycles using surgically retrieved sperm and (2) assess the influence of maternal age on those outcomes.

Methods

The data source for the study was the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) database. The dataset for this investigation included de-identified fresh ART cycles performed from 2004 to 2015, male infertility only with surgically obtained sperm (epididymal and testicular) and ICSI with autologous oocytes. Cycles with donor eggs or donor sperm, male factors with ejaculated spermatozoa, rescue ICSI, and frozen embryos were excluded. The data source for ART data for this study was SART CORS, which contains comprehensive data from more than 90% of all clinics performing ART in the USA. Data were collected and 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). SART maintains HIPAA-compliant business associate agreements with reporting clinics. In 2004, following a contract change with CDC, SART gained access to the SART CORS data system for the purposes of conducting research. The national SART CORS database for 2004–2012 contains 1,250,545 cycles among 642,715 women, resulting in 196,912 live births. The database includes information on demographic factors (age, race/ethnicity); ART factors (infertility diagnoses, oocyte source and state, use of micromanipulation, the number of embryos transferred); treatment outcomes (the number of fetal heartbeats on early ultrasound, early pregnancy loss); and pregnancy outcomes (live born, stillborn, length of gestation, plurality, and genders). The data in the SART CORS are validated annually [1] with some clinics having on-site visits for chart review based on an algorithm for clinic selection. During each visit, data reported by the clinic were compared with information recorded in patients' charts. In 2012, records for 2045 cycles at 35 clinics were randomly selected for full validation, along with 238 egg/embryo banking cycles [1]. The full validation included review of 1318 cycles for which a pregnancy was reported. Among the non-donor cycles, 331 were multiple-fetus pregnancies. Ten out of 11 data fields selected for validation were found to have discrepancy rates of $\leq 5\%$. The exception was the diagnosis field, which, depending on the diagnosis, had a discrepancy rate between 2.1 and 9.2%.

The data were stratified into five groups based on maternal age: < 30 years, 30–34 years, 35–37 years, 38–42 years, and > 42 years. The primary outcome measure was live birth rate (LBR) per oocyte retrieval to avoid inaccuracy in cycle cancellation reporting. Additional outcomes included proportion of normal fertilization, embryo stage, embryo grading, proportion of spontaneous miscarriages, clinical pregnancy rate (CPR), gestational age at delivery, births with preterm delivery (PTD, < 37 weeks gestational age) and the proportion of neonates with low birth weight (LBW, < 2500 g). An estimate of the fertilization rate was calculated as the number of 2-pronuclei (2PN) zygotes divided by the total number of oocytes retrieved, the parameter provided by the database. Results were compared to the 2014–2015 SART CORS registry for ICSI for male factor [24]. The local Office of Regulatory Affairs allowed an exemption from Institutional Review Board approval since this project does not involve human subjects.

Descriptive statistics were computed and reported. Mean and standard deviation were calculated for continuous variables, and frequencies and percentages for categorical variables. *T* test was used for continuous variables and chi-square analysis was used for categorical variables. We used analysis of variance (ANOVA) to determine whether the means of the maternal age groups were significantly different in each variable. Post hoc pairwise comparisons were performed when maternal age groups differed significantly. Welch's test for unequal variances was employed when variances of each group differed

significantly. We used chi-square to determine whether the distribution of each categorical variable differed significantly by maternal age group. Chi-square was further used to determine the odds of variables occurring with each maternal age group in comparison to women aged < 30.

Outcomes were then compared between groups using linear regression (for continuous outcomes) or logistic regression (for categorical outcomes), adjusting for covariate factors. Statistics were performed using IBM SPSS Statistics (IBM Corp. Armonk, NY). An alpha level of 0.05 was considered statistically significant. In post hoc pairwise comparisons between the five maternal age groups, a Bonferroni corrected *P* value of 0.01 was considered significant.

Results

The total number of fresh autologous cycles of ICSI with surgically retrieved sperm performed between 2004 and 2015 was 24,763. The annual number of these cases had an initial increase after 2005 and it had remained fairly stable throughout the reported period (Fig. 1). Of these 24,763 cycles, 5304 (21.4%) were performed in the < 30-year-old age group, 9414 (38.0%) in the 30–34-year-old age group, 5399 (21.8%) in the 38–42-year-old age group and 4283 (17.3%) and 363 cycles (1.5%) in the > 42-year-old age group (Table 1). Table 1 also presents demographics according to age distribution (including BMI, baseline cycle day 3 serum FSH levels, gravity, and prior numbers of live births, preterm births, spontaneous abortions, biochemical pregnancies, and fresh cycles).

Table 2 shows ICSI cycle characteristics by maternal age. Older women had significantly longer stimulation ($p < 0.001$), a lower number of oocytes retrieved ($p < 0.001$), a lower number of 2PN zygotes ($p < 0.001$), a lower chance of having a blastocyst transferred ($p < 0.001$), and a higher number of fresh embryos transferred ($p < 0.001$). There was no

significant association between number of 2PNs per oocyte retrieved and maternal age ($p = 0.214$).

Cleavage-stage transfers represented approximately 77% and blastocyst transfers represented approximately 23% of the transfers. The odds of having a good-quality first blastocyst transferred declined as age increased (Table 3). There was a significant correlation between the grade of the first blastocyst transferred and maternal age ($p < 0.001$). Also, the mean grade of the first transferred blastocyst for mothers younger than 30 years old was significantly higher than mothers older than 38 years. In addition, the mean grade of the first blastocyst transferred in mothers aged between 30 to 34 years old was also significantly higher in quality in comparison to mothers older than 42 years old ($p = 0.014$). The grade of the second blastocyst transferred in mothers between 38 and 42 years old was significantly better than that in mothers older than 42 years old ($p = .034$). There was also a significant association between the grade of the third embryo transferred and maternal age ($p < .001$).

Pregnancy outcomes of the ICSI cycles using surgically recovered sperm are presented in Table 4. The rate of biochemical pregnancies per embryo transfer increased with maternal age for cleavage stage but not for blastocyst transfers, whereas the rate of clinical intrauterine pregnancies at 7 weeks as determined by ultrasound and live births per embryo transfer decreased by maternal age for both types of embryos ($p < 0.001$). The rate of abortions increased significantly with age, both for cleavage stage ($p < 0.001$) and for blastocyst transfers ($p < 0.001$). There were very few maternal deaths reported (total of three cases). There were no differences in ectopic pregnancies according to age. There was a similar number of female (6051) and male neonates (5858; $p = 0.2$).

Table 5 presents neonatal outcomes by maternal age for singleton pregnancies. The singleton LBR increased with advanced maternal age ($p = 0.026$) but the overall LBR (singletons and higher order combined) declined with maternal age (OR 0.87 95%CI [0.81–0.93] for 30–34 years, 0.62 95% CI

Fig. 1 Number of cycles using surgically retrieved sperm from 2004 to 2015, the SART CORS database

Table 1 Population characteristics by maternal age

	Maternal age					<i>P</i> value
	< 30 years (<i>n</i> = 5276)	30–34 years (<i>n</i> = 9360)	35–37 years (<i>n</i> = 5369)	38–42 years (<i>n</i> = 4242)	> 42 years (<i>n</i> = 360)	
BMI, mean ± sd (39.7% missing)	25.04 ± 5.08	25.21 ± 5.45	25.58 ± 5.46	25.98 ± 5.54	25.66 ± 5.80	< 0.001
BMI missing, <i>N</i> (%)	2012 (38.1)	3690 (39.4)	2200 (41.0)	1716 (40.5)	159 (44.2)	0.010
Baseline FSH, mean ± sd (27.71% missing)	6.42 ± 2.38	6.81 ± 2.47	7.24 ± 3.16	7.57 ± 3.2	9.57 ± 5.89	< 0.001
Baseline FSH missing, <i>N</i> (%)	1670 (31.7)	2640 (28.2)	1373 (25.6)	1084 (25.6)	92 (25.6)	< 0.001
Gravidity, mean ± SD	0.33 ± 0.68	0.59 ± 0.92	0.83 ± 1.12	1.01 ± 1.28	1.25 ± 1.5	< 0.001
Prior full-term births, mean ± sd	0.36 ± 0.59	0.52 ± 0.75	0.62 ± 0.84	0.68 ± 0.95	0.75 ± 1.09	< 0.001
Prior preterm births, mean ± sd	0.03 ± 0.18	0.05 ± 0.24	0.06 ± 0.28	0.07 ± 0.33	0.05 ± 0.32	< 0.001
Prior spontaneous abortions, mean ± sd	0.26 ± 0.54	0.33 ± 0.63	0.42 ± 0.73	0.51 ± 0.77	0.66 ± 0.89	< 0.001
Prior biochemical pregnancies, mean ± sd	0.04 ± 0.22	0.07 ± 0.28	0.08 ± 0.31	0.08 ± 0.31	0.06 ± 0.26	< 0.001
Prior fresh cycles, mean ± sd	0.41 ± 0.92	0.66 ± 1.09	0.86 ± 1.28	1.04 ± 1.48	1.86 ± 2.48	< 0.001

[0.58–0.68] for 35–37 years, 0.68 95% CI [0.34–0.40] for 38–42 years, and 0.08 95% CI [0.05–0.12] for > 42 years gestational age at delivery (*p* 0.21), proportion of term deliveries (*p* 0.69), preterm deliveries (*p* 0.69), neonatal birth weight < 2500 g (*p* 0.57), and neonatal birth weight > 4000 g (*p* 0.99) and average birthweight of neonates (*p* 0.33) were not affected by age for singleton pregnancies.

The neonatal outcomes of twin pregnancies according to maternal age are shown in Table S6. The twin LBR decreased with maternal age (*p* < 0.001). As expected, twin term deliveries were higher in the younger population (*p* < 0.001) as preterm deliveries (PTD) increased with age (*p* = 0.001). There were no differences in birthweight, low birth weight, or high birth weight according to maternal age.

Table S7 presents a comparison between pregnancy outcomes for ICSI with surgically recovered sperm (SART CORS 2004–2015) vs all-male factor ICSI cases (SART CORS 2014–2015), grouped by maternal age. The OR for live births in surgically recovered sperm was lower for women of advanced maternal age (OR 1.16 95% CI [1.11–1.22] for <

35 years, 1.29 95% CI [1.20–1.40] for 35–37 years, 1.24 95% CI [1.13–1.37] for 38–42 years and 0.80 95% CI [0.43–1.49] for > 42 years). This trend was not seen for clinical pregnancy rate. The miscarriage rate was generally lower for surgically recovered sperm and this trend reached significance for the 35–37- and 38–42-year age groups. The odds ratio for preterm delivery trended lower for all age groups, and this trend reached significance for the < 35- and 3537-year age groups.

Discussion

This study aimed to evaluate clinical outcomes of the 24,763 ICSI cycles using surgically recovered sperm (combined epididymal and testicular) reported to SART between 2004 and 2015 and to assess the influence of maternal age on those outcomes. Older women had significantly longer stimulation, a lower number of oocytes retrieved, a lower number of 2PN zygotes, a lower chance of having a blastocyst transferred, and a higher number of fresh embryos transferred but a similar

Table 2 ICSI cycle characteristics by maternal age

	Maternal age					<i>P</i> value
	< 30 years (<i>n</i> = 5276)	30–34 years (<i>n</i> = 9360)	35–37 years (<i>n</i> = 5369)	38–42 years (<i>n</i> = 4242)	> 42 years (<i>n</i> = 360)	
Days of ovarian stimulation, mean ± sd	11.6 ± 2.4	11.7 ± 2.2	11.9 ± 2.6	11.9 ± 2.7	12.1 ± 3.4	< 0.001
Number of oocytes retrieved, mean ± sd	16.2 ± 8.0	14.71 ± 7.6	13.1 ± 7.4	11.6 ± 7.3	9.0 ± 6.1	< 0.001
Total 2PN, mean ± sd	7.0 ± 5.4	6.6 ± 5.3	5.8 ± 4.9	5.1 ± 4.4	3.8 ± 3.8	< 0.001
2PN per oocyte retrieved (%), mean ± sd	43 ± 27	44 ± 28	43 ± 29	44 ± 28	40 ± 29	0.214
Fresh embryos transferred, mean ± sd	2.1 ± 0.7	2.2 ± 0.8	2.4 ± 0.9	2.8 ± 1.2	3.5 ± 2.2	< 0.001
Blastocyst transfer, <i>N</i> (%)	1329 (25.1%)	2127 (22.6%)	1014 (18.8%)	608 (14.2%)	21 (5.8%)	< 0.001
Fresh embryos cryopreserved, mean ± sd	2.2 ± 3.2	1.8 ± 3.1	1.3 ± 2.7	0.8 ± 2.1	0.2 ± 0.9	< 0.001
Day of transfer, mean ± sd	3.9 ± 1.1	3.8 ± 1.2	3.65 ± 1.1	3.5 ± 1.0	3.2 ± 0.9	< 0.001

Table 3 Odds of good quality embryo by maternal age compared with good quality embryo at age < 30 for patients who underwent blastocyst or cleavage-stage transfers

		Maternal age				
		< 30 years (ET = 1326)	30–34 years (ET = 2125)	35–37 years (ET = 1014)	38–42 years (ET = 608)	> 42 years (ET = 21)
First blastocyst grade	Good, <i>N</i> (% of reported)	799 (73.5)	1232 (72.2)	541 (67.3)	326 (65.1)	14 (73.7)
	Fair, <i>N</i> (% of reported)	243 (22.4)	397 (23.3)	222 (27.6)	146 (29.1)	3 (15.8)
	Poor, <i>N</i> (% of reported)	45 (4.1)	78 (4.6)	41 (5.1)	29 (5.8)	2 (10.5)
	Not reported, <i>N</i> (% of total)	239 (18.0)	418 (19.7)	210 (20.7)	107 (21.4)	2 (9.5)
	Odds ratio (95% CI)	1	0.93 (0.79–1.11)	0.74 (0.61–0.90)	0.67 (0.53–0.84)	1.01 (0.36–2.83)
		< 30 years (ET = 3348)	30–34 years (ET = 6229)	35–37 years (ET = 3768)	38–42 years (ET = 3050)	> 42 years (ET = 254)
First cleavage stage embryo grade	Good, <i>N</i> (% of reported)	1354 (71.8)	2512 (71.0)	1445 (66.7)	1254 (68.8)	98 (60.9)
	Fair, <i>N</i> (% of reported)	455 (24.1)	842 (23.8)	598 (27.6)	440 (24.1)	47 (29.2)
	Poor, <i>N</i> (% of reported)	76 (4.0)	186 (5.3)	122 (5.6)	128 (7.0)	16 (9.9)
	Not reported, <i>N</i> (% of total)	1463 (43.7)	2689 (43.2)	1603 (42.5)	1228 (40.3)	93 (36.6)
	Odds ratio (95% CI)	1	0.96 (0.85–1.08)	0.79 (0.69–0.90)	0.87 (0.75–1.00)	0.61 (0.44–0.85)

number of 2PNs. Both clinical pregnancy rates and live birth rates decreased with advanced maternal age, while there were no differences in gestational age at delivery, number of term deliveries, and neonatal birthweight for singletons according

to maternal age. Even though some studies suggested an altered sex ratio when using ICSI [25, 26], these data set demonstrated that the proportion of male to female neonates is not altered by the use of ICSI with surgically retrieved sperm.

Table 4 ICSI cycle outcomes by maternal age for blastocysts and cleavage stage transfers

		Maternal age					
		< 30 years (ET = 1326)	30–34 years (ET = 2125)	35–37 years (ET = 1014)	38–42 years (ET = 608)	> 42 years (ET = 21)	<i>P</i> value
Number blastocysts transferred <i>n</i> = 5094		1.84 (0.51)	1.85 (0.55)	1.96 (0.62)	2.30 (0.78)	2.76 (1.30)	< 0.001
Treatment outcome	Not pregnant, <i>N</i> (% per ET)	359 (27.1)	609 (28.7)	325 (32.1)	244 (40.1)	11 (52.4)	< 0.001
	Biochemical, <i>N</i> (% per ET)	102 (7.7)	190 (8.9)	96 (9.5)	51 (8.4)	2 (9.5)	0.61
	Clinical IUP, <i>N</i> (% per ET)	853 (64.3)	1305 (61.4)	581 (57.3)	309 (50.8)	8 (38.1)	< 0.001
	Ectopic, <i>N</i> (% per ET)	11 (0.8)	20 (0.9)	10 (1.0)	3 (0.5)	0	0.76
Pregnancy outcome	Live Birth, <i>N</i> (% per ET)	771 (58.1)	1149 (54.1)	486 (47.9)	227 (37.3)	4 (19.0)	< 0.001
	Number live born, mean (SD)	1.37 (0.53)	1.35 (0.52)	1.29 (0.48)	1.24 (0.47)	1.0 (0)	0.002
	Still Birth, <i>N</i> (% per IUP)	4 (0.5)	10 (0.8)	1 (0.2)	1 (0.3)	0	0.45
	Abortion, <i>N</i> (% per IUP)	78 (9.1)	143 (11.0)	92 (15.8)	81 (26.2)	4 (50.0)	< 0.001
		< 30 years (ET = 3348)	30–34 years (ET = 6229)	35–37 years (ET = 3768)	38–42 years (ET = 3050)	> 42 years (ET = 254)	<i>P</i> value
Number cleavage embryos transferred <i>n</i> = 16,649		1.75 (1.07)	1.84 (1.14)	2.04 (1.29)	2.44 (1.56)	2.87 (2.44)	< 0.001
Treatment outcome	Not pregnant, <i>N</i> (% per ET)	1302 (38.9)	2575 (41.3)	1745 (46.3)	1684 (55.2)	201 (79.1)	< 0.001
	Biochemical, <i>N</i> (% per ET)	234 (7.0)	461 (7.4)	313 (8.3)	295 (9.7)	21 (8.3)	0.001
	Clinical IUP, <i>N</i> (% per ET)	1791 (53.5)	3153 (50.6)	1681 (44.6)	1049 (34.4)	32 (12.6)	< 0.001
	Ectopic, <i>N</i> (% per ET)	19 (0.6)	40 (0.6)	28 (0.7)	18 (0.6)	0	0.74
Pregnancy outcome	Live birth, <i>N</i> (% per ET)	1583 (47.3)	2763 (44.4)	1367 (36.3)	770 (25.2)	16 (6.3)	< 0.001
	Number live born, mean (SD)	1.33 (0.52)	1.30 (0.50)	1.26 (0.49)	1.21 (0.46)	1.25 (0.45)	< 0.001
	Still Birth, <i>N</i> (% per IUP)	8 (0.4)	21 (0.7)	10 (0.6)	5 (0.5)	0	0.53
	Abortion, <i>N</i> (% per IUP)	186 (10.4)	345 (10.9)	294 (17.5)	274 (26.1)	16 (50.0)	< 0.001

*Six heterotopic pregnancies were seen, three in the cleavage stage and three in the blastocyst stage transfers

Table 5 Neonatal Outcomes by Maternal Age for Singleton Pregnancies

	Maternal Age					<i>P</i> value
	< 30 years	30–34 years	35–37 years	38–42 years	>42 years	
Number of live births (% of total live births)	1574 (66.8)	2708 (69.1)	1368 (73.7)	790 (79.2)	16 (80)	0.026
Gestational age at delivery (days), mean $\pm$ sd	271.5 $\pm$ 17.7	272.2 $\pm$ 16.0	271.4 $\pm$ 17.5	270.5 $\pm$ 18.7	270.9 $\pm$ 12.5	0.21
Numbers of term delivery, <i>N</i> (%)	1182 (87.7)	2033 (89.1)	1019 (88.2)	597 (87.9)	14 (100)	0.69
Numbers of preterm delivery, <i>N</i> (%)	165 (12.3)	248 (10.9)	136 (11.8)	82 (12.1)	0	0.69
Birthweight ^a (grams), mean $\pm$ sd	3236.0 $\pm$ 622.6	3265.6 $\pm$ 593.5	3256.2 $\pm$ 604	3220.2 $\pm$ 606.4	3296.2 $\pm$ 477.8	0.33
Birthweight ^a < 2500 g, <i>N</i> (%)	139 (8.8)	207 (7.6)	118 (8.6)	70 (8.9)	0 (0)	0.57
Birthweight ^a > 4000 g, <i>N</i> (%)	113 (7.2)	192 (7.2)	100 (7.3)	58 (7.3)	1 (6.3)	0.99

^a Birthweight reported as average of both neonates

The main strength of this study is the large number of cases reported nationwide with a sufficient sample size to allow for subgroup analysis. Some of the limitations, besides being a retrospective study, are not being able to link cycles for patients undergoing more than one cycle, to differentiate between reason for azoospermia (OA vs NOA) or effect of paternal age as these variables were not collected by the SART database [24] during the time frame studied.

Many investigators have explored the relationship between sperm acquisition source and fertility outcomes. Ghazzawi et al. [27] did not find any difference in fertilization rates (69–79%) and pregnancy rates (21–28%) from use of ejaculated versus epididymal and testicular sperm in ICSI cycles. However, some studies have shown that live births per embryo transfer were significantly lower in NOA compared with the OA [28]. It is theorized that these sperm's immaturity, as they are extracted from the epididymis, decreases their chance of successful fertilization and implantation [28]. Research has focused on more sophisticated rubrics of sperm quality in order to understand and optimize IVF-ICSI outcomes. Reactive oxygen species and DNA damage have been two areas of intense investigation. Preliminary research has also shown that sperm quality, especially in terms of DNA integrity, may decrease in some patients as the spermatozoa transit through the male reproductive tract [21, 29]. As a result, some couples may benefit from testis-derived sperm even in the presence of viable sperm in the ejaculate.

From our study, we were able to determine that the estimated fertilization rate in women undergoing ICSI for male factor with surgically retrieved sperm did not significantly differ with maternal age, with rates ranging between 40 to 44%. These fertilization rates are underestimated since they were calculated as the number of 2PNs divided by the total number of oocytes aspirated (mature and immature, as provided by SART database). Despite this underestimation, these calculated rates are comparable, and not inferior, to reported IVF fertilization rates of 44 to 59% [21] and to the fertilization

rates of surgically recovered sperm between 45 and 80% per injected oocyte [22, 30–32].

The grade of the first blast transferred was significantly associated with maternal age, where younger women had a higher grade embryo. Heitmann et al. [33] previously demonstrated using a univariate binary logistic regression analysis that the SART embryo grading was significantly correlated with both implantation (OR 2.33, 95%CI 1.30–4.10) and live birth (OR 2.07, 95%CI 1.14–3.76). It is well known that monthly fecundity gradually decreases from the mean age of 30 years [32], as well as increasing frequency of chromosomal abnormalities with worsening embryo quality [34, 35].

In these group of patients, the overall, CPR per embryo transfer ranged from 56.7% in the < 30-year age group to 14.5% in the < 42-year age group. Despite the majority of the embryo transfers having been performed at the cleavage stage (76.6%) during the studied time frame, these ranges are in accordance with the 26–57% reported in the literature for ICSI cases for azoospermia, both for day 2–3 transfer [22, 28, 30] and for blastocyst transfer [36]. Another expected finding was the increasing risk of miscarriage with advanced maternal age (10% in < 30 years and 50% in > 42 years).

Our study also showed that overall LBR significantly decreased with advanced maternal age, with ranges of 50.4% in < 30 years to 7.2% in > 42 years, which is also consistent with the reported ranges of 18–54% [37]. The fact that singleton LBR increased with maternal age could be due to the very low number of cases (16 only) in the older than 42-year age group. Stillbirths and maternal deaths were very rare events, occurring less than 1% and not related to maternal age.

Interestingly, this study shows that, for singleton pregnancies, neither the percentage of term deliveries nor PTD vary significantly with maternal age, pointing to the male factor as the main reason for infertility. Cleary-Goldman et al. [38] demonstrated that women older than 40 had an adjusted OR 1.4 (95% CI 1.1–1.7) of PTD. Numerous studies have shown associations between ART and risk of PTD and LBW [29, 30, 39,

40]. Further, in a systematic review, ICSI was associated with a lower risk of PTD than conventional IVF [41]. However, in a large study, there was no impact of severe male factor in IVF/ICSI on obstetrical/perinatal outcomes including birth weight, rate of PTD, and rate of congenital malformations [42].

The literature does suggest an emerging theme in surgically retrieved sperm used for ICSI. Impaired fertilization and early embryo development is seen, but pregnancy rates appear to be preserved once a blastocyst is obtained for transfer proving that achievement of high pregnancy rates in couples with severe male factor infertility is dependent primarily upon female and not male factors [43]. Understanding more about factors that affect ICSI outcomes with surgically retrieved sperm will not only help us predict patients' outcomes but it can help us educate and better counsel our patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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