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GYNECOLOGIC ENDOCRINOLOGY AND REPRODUCTIVE MEDICINE

Should Intra Cytoplasmic Sperm Injection (ICSI) be the primary insemination method in women undergoing IVF cycles with donor sperm?

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Abstract

Purpose To compare efficacy of Intra Cytoplasmic Sperm Injection (ICSI) with conventional in vitro fertilization (IVF) on treatment outcome in women undergoing in vitro fertilization with donor sperm.

Methods We examined retrospectively the outcome data from 203 patients undergoing fresh cycles of conventional IVF (cIVF) or ICSI and an additional 77 frozen-thawed embryo transfer (FET) cycles during 2003–2014, all using donor sperm. Fertilization, cleavage, pregnancy and live birth rates and number of high-quality embryos were compared between cIVF and ICSI.

Results Altogether 185 women underwent 479 transfer cycles of fresh embryos (237 cIVF vs. 224 ICSI and 18 "rescue ICSI" cycles). In addition, 77 FET cycles were compared (24 cIVF vs. 53 ICSI cycles). No differences were found between cIVF and ICSI in fertilization, cleavage, pregnancy and live birth rates (92.6% vs 92.2%, 73.4% vs 72.4%, 25.3% vs 27.2% and 13.1% vs 14.7%, respectively). Pregnancy and life birth rates remained similar even when FET cycles were included (25.8% vs 26.2% and 13.1% vs 13.7%, respectively). The use of ICSI was associated with lower rates of high-quality embryos (52.7% vs. 63.3%, $P<0.0001$). A multivariate logistic regression analysis found that patients' age, number of transferred embryos and smoking were independently associated with the chance to conceive. Patient age correlated inversely with fertilization rate ($r=-0.13$, $P<0.006$).Non-smokers were more likely to become pregnant (OR = 2.23, $P<0.012$).

Conclusions Our results show that ICSI does not bypass the age-related decrease in oocyte quality in patients using donor sperm for IVF. Use of ICSI was associated with lower rates of high-quality embryos. The findings imply that ICSI should not be the primary method of insemination in patients undergoing IVF with donor sperm.

Keywords IVF · ICSI · Fertilization · Pregnancy · Donor sperm

Introduction

The use of sperm from donors in fertility treatments is an increasingly common procedure in many fertility centers. The main indications for the use of donor sperm are either couples with azoospermia of the male partner, lack of viable spermatozoa in testicular/epididymal sperm retrieval techniques, or single women (or female couples) seeking pregnancy with the aid of a sperm bank. When repeated cycles of conventional fertility treatments with donor sperm do not yield pregnancy or in cases of mechanical infertility, patients are referred to IVF.

Intra cytoplasmic sperm injection (ICSI) micromanipulation technique has been practiced widely since 1992 [1] as a mean to overcome fertilization failure after conventional IVF (cIVF) or in cases of severe oligoasthenoteratospermia. However, the practice of ICSI has since been extended to surgically retrieved spermatozoa from testis or epididymis, preimplantation genetic testing, insemination of vitrified oocytes and more [2]. Although the practice of ICSI has significantly increased during recent years among fresh IVF cycles in the USA, (the largest relative increase among cycles without male factor

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infertility), its use was not associated with improved post-fertilization reproductive outcomes, irrespective of male factor infertility diagnosis [3]. ICSI in IVF cycles with donor sperm is being routinely practiced by some IVF units [4] to avoid cryopreservation-induced damage to spermatozoa [5] whereas in other units, cIVF is practiced in the first IVF cycle, based on the good sperm parameters, a prerequisite for sperm donors. Several studies have addressed the issue of a possible benefit of ICSI in older population. De brucker et al. [6] compared the outcome of fertility treatments with donor sperm between ICSI vs. repeated intrauterine inseminations, and found, that time to delivery was shorter when ICSI was used. Some studies found a benefit for ICSI compared with cIVF among women aged 40–42 years old even when the indication for ICSI was male infertility [7]. On the other hand, Seng et al. [8] did not find any benefit for ICSI in older women. When the use of ICSI with donor sperm is not routinely practiced, possible indications for its use may be fertilization failure in the previous cycle, low number of oocytes retrieved or an unexpectedly low post-processing motility of sperm on the day of oocyte aspiration [9].

The growing population of single women undergoing fertility and IVF treatment using donor sperm is characterized by relatively older age than that of patients seeking fertility [10]. Consequently, chances for conception in this population are relatively lower compared to the average infertile population. In addition, unless a mechanical factor infertility is present, most recipients of donor sperm who undergo cIVF treatment have failed to conceive after repeated cycles of ovulation induction with gonadotropins and intrauterine insemination, despite good sperm parameters. Therefore, this specific sub-population poses a special challenge for fertility caretakers. It is possible, that the use of the ICSI technique, which bypasses some stages of the sperm-oocyte interaction (binding to and penetrating of the zona pellucida [11], fusion with oocyte vitelline membrane and entrance to the ooplasma), will be able to overcome the age-mediated obstacles to fertilization and implantation. By controlling for the sperm parameter in sperm–oocyte interaction (using high-quality sperm from donors) it may be possible to isolate the oocyte factor. Comparison ICSI to cIVF with donor sperm has never been addressed. Thus, the objective of this preliminary study was to compare parameters of treatment outcome in ICSI vs. cIVF cycles among patients using donor sperm.

Materials and methods

In the present retrospective analysis, 648 consecutive IVF cycles using donor sperm performed throughout 2003–2014 at Carmel Medical Center were analyzed. The study was approved by the Institutional Review Board.

Fresh cycles

Patients underwent long or short protocol treatment [12]. Insemination of oocytes was performed with use of cIVF or ICSI procedures according to indications and sperm quality [13]. Thawed donor sperm was treated according to standard procedures [14]. As mentioned in Fig. 1, we excluded from our study all ICSI cases that were due to low post-thawed sperm parameters ($\leq 5 \times 10^6$ motile spermatozoa). In some cases, ICSI was performed (in the presence of good sperm parameters) to avoid cryopreservation-induced damage to spermatozoa or potential fertilization failures.

Fallowing fertilization and cleavage, embryo selection for transfer was performed according to standard morphologic assessment methods [15].

Frozen-thawed embryo cycles

Patients underwent either a natural cycle protocol or a hormonal replacement protocol to achieve a receptive endometrium [16].

Demographic, clinical and laboratory parameters of the treatment cycles including treatment outcome were

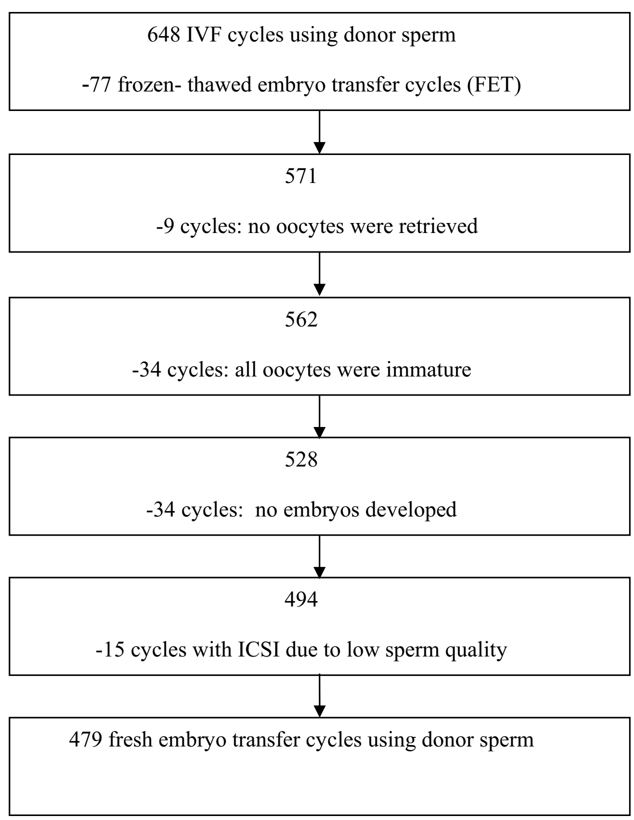

Fig. 1 Flowchart of study enrollment (fresh embryos)

recorded and compared between the two insemination methods, cIVF vs. ICSI.

Statistical analysis

Statistical analysis was performed using IBM statistics SPSS22 package for Windows (SPSS Inc., Chicago, Illinois, USA).The continuous variables were presented by mean ± SD, or median and range. The categorical variables were presented in percentages. To check if there are differences in demographical and clinical characteristics between 2 groups (cIVF vs. ICSI), Chi square test was used for the categorical variables and independent t-test or Mann–Whitney, as appropriate, for the continuous variables. Generalized estimating equation method using the binominal distribution was used to identify the factors that are related to pregnancy controlling for repeated measures (women who had more than one cycle) The significant variables in the univariate analysis were entered into a multivariate model. OR with 95%CI are presented. $P<0.05$ was considered statistically significant.

Since our data included repeated measurements (patients undergoing more than one treatment cycle), we employed an additional model for repeated measurement, generalized estimating equation for logistic regression, adjusted for repeated measures. Analysis of the results was performed twice and presents as OR and adjusted OR in the tables.

Results

During the study period, 648 IVF cycles using donor sperm were analyzed, consisting of 571 (88.1%) ovarian stimulation cycles and 77 (11.9%) frozen-thawed embryo transfer (FET) cycles. The mean and median cycle number of fresh cycles was 2.7 ± 2.1 (1–15) and 2 cycles, respectively. Altogether 203 women participated in the study. Patients underwent ovarian stimulation by administration of gonadotropins after pituitary desensitization with GnRH agonists or short protocol with GnRH antagonists (Table1). Oocytes were retrieved in 562/571 cycles (98.4%) and 528/562 (93%) were mature. In 494/526 (93.5%) cycles, fresh embryos were transferred.

In 15/528 (2.8%) cases, all embryos were cryopreserved as cautionary measure to prevent ovarian hyperstimulation syndrome. In another 19/528 (3.5%) cases, no embryos were transferred due to failure of embryo development. Altogether, fresh embryos were transferred in 494 cycles. In 15 cycles of embryo transfer ICSI was performed due to post-thaw reduction in motile sperm ($\leq 5\times10^6$ motile spermatozoa). These cycles were omitted from analysis.

Final comparison was therefore performed between cIVF and ICSI in 479 embryo transfer (ET) cycles: 237 cycles with cIVF, 224 cycles using elective ICSI and 18 cycles (3.6%) in which emergency ICSI procedure (“Rescue ICSI”) was performed 18–20 h post insemination due to total fertilization failure by cIVF (Fig. 1).

Altogether 1129 fresh embryos were transferred. In 127/494 (25.7%) cycles, 551 surplus embryos were cryopreserved. Mean and median patient's age were 37.5 ± 5.3 and 38.4 years respectively (range: 20–45). No difference was found between the number of retrieved and mature oocytes between cIVF vs. ICSI cycles (8.1 ± 4.9 vs. 8.0 ± 5.1, 4.3 ± 3.0 vs. 4.7 ± 3.3, respectively).

Ninety one percent (186/203) of the patients were unwed, of which 55% (112/186) were single. Comparison of descriptive data including demographic, clinical and laboratory parameters is summarized in Table 1. No differences were found between cIVF and ICSI cycles regarding patient's age, basal FSH levels, smoking status, treatment protocol and number of retrieved and mature oocytes (Table 1). Higher

Table 1 Comparison of demographic, clinical and laboratory parameters of the study groups

Parameter	Total ($n=479$)	cIVF cycles ($n=237$)	ICSI cycles ($n=224$)	Rescue ICSI ($n=18$)	*P*
Age (years) (mean ± SD)	37.5 ± 5.3	37.4 ± 5.3	37.6 ± 5.3	37.6 ± 4.6	0.919
Basal FSH (IU/L) (mean ± SD)	7.1 ± 3.3	7.3 ± 3.6	7.0 ± 2.9	6.7 ± 3.1	0.487
Smoking status: number (%)	92 (19.2)	37(15.6%)	51(22.8%)	4(22.2%)	0.141
IVF Protocol					
1. Long GnRH agonist	295 (61.6)	151 (63.7)	130 (58.0)	14 (77.8)	0.162
2. GnRH antagonist	184 (38.4)	86 (36.3)	94 (42.0)	4 (22.2)	
Number of ampoules of Gonadotropin used (mean ± SD)	179.8 ± 108.6	158.3 ± 99.9	205 ± 111.7	145 ± 113.5	0.0001
No. of retrieved oocytes (mean ± SD)	8.1 ± 4.9	8.1 ± 4.9	8.0 ± 5.1	8 ± 5.1	0.936
No of mature oocytes (mean ± SD)	4.5 ± 3.2	4.3 ± 3.0	4.7 ± 3.3	3.5 ± 2.5	0.251

doses of gonadotropins were used in cIVF cycles compared with ICSI cycles (179.8 vs. 158.3 IU/D, $P<0.0001$) (Table 1). No difference was found when ICSI and cIVF cycles were compared in number of fertilized oocytes, cleave, transferred and cryopreserved embryos, fertilization, cleavage, pregnancy and live birth rates (Table 2). The rate of high-quality embryos was lower in ICSI compared with cIVF cycles (52.7% vs. 63.3%, $P<0.0001$, Table 2). Additional analysis was performed regarding 77 FET cycles using donor sperm. Two hundred and fifty eight embryos were thawed and 189 were transferred in 70 FET cycles. In 7 (10%) of cycles, no embryo survived thawing. No differences were found between cIVF and ICSI regarding mean number of thawed and transferred embryos, mean survival rate, pregnancy and live birth rates (Table 3). Even when FETs were added to the transfer cycles of fresh embryos, no difference was found between cIVF and ICSI cycles in pregnancy and live birth rates (Table 4).

Using the logistic regression analysis model, no association was found between the insemination procedure (cIVF vs. ICSI) and the occurrence of pregnancy for any number of embryos transferred. Twenty-five women underwent an cIVF cycle followed by a next cycle with ICSI. Fertilization rates were comparable between these cycles (92.2% vs. 94.3%, $P<0.670$). Patient's age was found to be inversely correlated with fertilization rate ($r=-0.13$, $P<0.006$). The factors that were found to affect the chance for pregnancy were patient's age, number of mature oocytes retrieved, number of transferred embryos and smoking status (Table 5). Using multivariate logistic regression analysis, patients' age,

Table 2 Comparison between outcome parameters in cIVF vs. ICSI cycles in fresh embryos

Parameter	Total $N=479$	cIVF $N=237$	ICSI $N=224$	Rescue ICSI $N=18$	P
No of fertilized oocytes (mean ± SD)	4.1 ± 2.9	3.97 ± 2.9	4.2 ± 3.0	3.1 ± 2.1	0.201
Fertilization rate (% ± SD)	92.5 ± 15.3	92.6 ± 15.5	92.2 ± 15.2	93.5 ± 16.3	0.862
Median (Interquartile range)	100 (100, 100)	100 (100, 100)	100 (96.3, 100)	100 (100,100)	
Cleavage rate (% ± SD)	72.8 ± 28.1	73.4 ± 27.6	72.4 ± 28.6	70 ± 27	0.840
No of embryos developed (mean ± SD)	3.33 ± 2.5	3.36 ± 2.6	3.4 ± 2.4	2.3 ± 2.2	0.026[a]
Number and rate of high-quality embryos (%)	578/1129 (57.8%)	346/547 (63.3%)	289/548 (52.7%)	18/34 52.9%	0.0001[b]
No of embryos transferred (mean ± SD)	2.36 ± 0.9	2.31 ± 0.8	2.45 ± 0.9	2.45 ± 0.9	0.029 [c]
No of cryopreserved surplus embryos (mean ± SD)	$N=127$ 4.3 ± 2.2	$N=64$ 4.4 ± 2.2	$N=61$ 4.2 ± 2.1	$N=2$ 4 ± 1.7	0.99
Pregnancy rate (%)	122 (25.5)	60 (25.3)	61 (27.2)	1(5.6)	0.12
Live birth rate (%)	65 (13.6)	31 (13.1)	33 (14.7)	1 (5.6)	0.538

[a]Sig difference after Bonferroni correction ($P<0.016$) between cIVF & Rescue ICSI & between ICSI & Rescue ICSI

[b]Sig difference after Bonferroni correction (0.0001) between cIVF & ICSI

[c]No Sig difference after Bonferroni correction

Table 3 Comparison between treatment outcome parameters in cIVF vs. ICSI cycles in FET cycles

Parameter	Total ($n=70$)	cIVF ($n=23$)	ICSI ($n=47$)	P
Number of thawed embryos (mean ± SD)	3.6 ± 1.4	3.6 ± 2.1	3.6 ± 1.5	0.49
Number of transferred embryos (mean ± SD)	2.7 ± 0.9	2.5 ± 1	2.7 ± 0.9	0.14
Mean embryo survival rate (%)	77 ± 21%	74.2 ± 24.5	78.3 ± 20.6	0.491
Pregnancy rate (%)	17 (24.3)	7 (30.4)	10 (21.3)	0.401
Live birth rate (%)	7 (10.0)	3 (13.0)	4 (8.5)	0.676

Table 4 Comparison between treatment outcome parameters in cIVF vs. ICSI cycles in fresh and frozen—thawed embryos

Parameter	Total $N=549$	cIVF $N=260$	ICSI $N=271$	Rescue ICSI $N=18$	P
Pregnancy rate (%)	139 (25.3)	67(25.8)	71(26.2)	1 (5.6%)	0.151
Live birth rate (%)	72 (13.1)	34 (13.1)	37 (13.7)	1 (5.6)	0.657

number of transferred embryos and smoking status independently affected the chance to conceive (Table 6). Both univariant and multivariant analysis were performed also according to the model adjusted for repeated measurements. Implementation of this model did not affect the results (Tables 4, 5).

The odds ratio for pregnancy for a non-smoker was 2.2 compared with smoker ($P < 0.012$) (Table 6). The performance of rescue ICSI was associated with lower success rates compared with both cIVF and ICSI methods (Tables 2, 4, 5).

Discussion

Since the development of the ICSI technique for improvement of fertilization rates in cases of fertilization failure in cIVF or severe male factor infertility, many attempts have been made to expand the indications for its use in assisted reproduction technologies. Nowadays, ICSI is applied more than 70% of all IVF cycles [3]. Whereas the superiority of ICSI over cIVF in cases with extremely low sperm parameters [17, 18] or prior failed fertilization

Table 5 Factors affecting the occurrence of pregnancy

Parameter	No pregnancy ($n = 357$)	Pregnancy ($n = 122$)	OR 95%CI	Adjusted OR	*P*
Age (years) (mean ± SD)	37.8 ± 5.1	36.1 ± 5.6	0.94 (0.90–0.97)	0.94 (0.90–0.97)	< 0.0001
Basal FSH (IU/L) (mean ± SD)	7.3 ± 3.4	6.8 ± 2.9	0.96 (0.89–1.03)	0.95 (0.89–1.03)	0.197
Number of mature oocytes (mean ± SD)	4.34 ± 3.2	5.02 ± 3.0	1.06 (1.0–1.13)	1.07(1.01–1.14)	0.039
Treatment Type *N* (%)					
cIVF	177 (49.6)	60 (49.2)	Ref	Ref	
ICSI	163 (45.7)	61 (50.0)	1.1 (0.73–1.67)	1.12 (0.71–1.78)	0.617
Rescue ICSI	17 (4.8)	1 (0.8)	0.17 (0.02–1.3)	0.17(0.02–1.3)	0.086
Fertilization rate (%) (mean ± SD)	92.8 ± 15.4	91.7 ± 15.2	1.0 (0.98–1.0)	1.0 (0.98–1.01)	0.515
Number ET					
$n = 1$ *n* (%)	78 (87.6)	11 (12.4)	Ref	Ref	
$n \geq 1$(2–5) *n* (%)	279 (71.5)	111 (28.5)	2.8 (1.4–5.5)	2.78 (1.5–5.2)	0.001
Smoking status					
No *n* (%)	280 (78.4)	107 (87.7)	1.96(1.08–3.56)	1.93 (0.99–3.8)	0.055
Yes *n* (%)	77 (21.6)	15 (12.3)	Ref	Ref	

Adjusted OR- analysis of results according to the generalized estimating equation for logistic regression, adjusted for repeated measures

Table 6 Multivariant logistic regression analysis: factors affecting the occurrence of pregnancy

	Multivariate		
	OR 95%CI	Adj OR 95%CI	*P*-value
Age (years) (mean ± SD)	0.94 (0.90–0.98)	0.94 (0.90–0.98)	0.001
Basal FSH (IU/L) (mean ± SD)	1.00 (0.93–1.07)	1.00 (0.93–1.07)	0.953
Number of mature oocytes (mean ± SD)	1.00 (0.93–1.08)	1.0 (0.93–1.09)	0.932
Treatment Type *N* (%)			
cIVF	Ref	Ref	
ICSI	1.16(0.76–1.8)	1.17 (0.72–1.88)	0.533
Rescue ICSI	0.22 (0.03–1.7)	0.22 (0.03–1.7)	0.146
Fertilization rate (%) (mean ± SD)	1.0 (0.99–1.01)	1.0 (0.98–1.01)	0.863
Number ET			
$n = 1$ *n* (%)	Ref	Ref	
$n \geq 1$(2–5) *n*(%)	2.4 (1.15–4.9)	2.4 (1.18–4.8)	0.015
Smoking status			
No *n* (%)	1.87 (1.01–3.4)	1.9 (0.96–3.6)	0.065
Yes *n* (%)	Ref	Ref	

Adjusted OR- analysis of results according to the generalized estimating equation for logistic regression, adjusted for repeated measures in cIVF [19] has been demonstrated in numerous studies, there is no consensus regarding the use ICSI vs. cIVF for other indications. Some investigators found improved fertilization rates with ICSI compared to cIVF in unexplained or non-male factor infertility [20, 21]. Artini et al. [22] compared the use of ICSI vs. cIVF in poor responder patients in the absence of male infertility. They found that cIVF was superior to ICSI among women younger than 38 years old regarding implantation and pregnancy rates. Beyond this age, no differences were found between the two groups of patients. In a Cochrane database, van Rumste et al. [23] did not find any benefit for the performance of ICSI in cases with non-male subfertility. Most of the studies evaluating the effectiveness of ICSI procedure were performed in couples suffering from infertility, necessitating assisted reproduction techniques. In these cases, even when the indication for performing ICSI was not due to male factor infertility or failed fertilization in cIVF, one cannot exclude, theoretically the possible existence of an occult male factor, not evident by sperm parameters, fertilization or embryo development rates, but which may influence pregnancy rates. On the other hand, in cIVF cycles with donor sperm, the male factor is excluded since most of the sperm donors have proven fertility. Hence, we can better isolate the "egg factor" effect. The population of women undergoing IVF with donor sperm is relatively older than the average fertility patients (a larger fraction of single women). As a result, there is higher incidence of age-related infertility. In addition, most of the patients who needed IVF with donor sperm failed to conceive with repeated cycles of intrauterine insemination as a primary treatment strategy, so this selected population may present an occult egg factor infertility.

The design of the present study, defining only female factors and excluding male factor enables us to analyze whether ICSI may overcome the age-related egg factor infertility, commonly among patients using donor sperm in IVF. Although our study is retrospective, the two study groups (cIVF vs. ICSI) were comparable in demographic and almost all of cycle parameters (Tables 1 and 2), accept differences in the number of ampoules of Gonadotropin that were in use (Table 1) which could act as a confounder. We found that for every number of embryos transferred, ICSI procedure by itself did not influence fertilization, cleavage, embryo quality, pregnancy and live birth rates as compared with cIVF. These findings were persistent also for frozen-thawed embryos. This may imply that ICSI procedure should not be performed as a first choice for the insemination of oocyte in women undergoing IVF with donor sperm. The use of ICSI was associated with lower rates of development of high-quality embryos, in contrast to the findings of Khamsi et al., who demonstrated higher rates of high-quality embryos at 48 h after ICSI compared with cIVF. However, different study populations may explain the conflicting results. In addition, some studies have demonstrated an increased risk for major congenital malformations among children born after ICSI compared with cIVF although this issue is controversial [24].

An interesting finding in our study was the inverse correlation between patients' age and fertilization rate. This issue is in debate in the literature. Some studies [25] have found an age-dependent decrease in fertilization rate. It is possible that our results apply to the specific population or relatively older recipients of donor sperm undergoing IVF. Factors found to affect the chance of pregnancy were patient's age, number of mature oocytes (similar to the results of Mokdad et al. [26]), number of transferred embryos and smoking. In a logistic regression multivariate analysis, smoking was independently associated with decrease pregnancy rates by half. This finding is in line with previous studies that reported a detrimental effect of smoking on ovarian reserve [27], oocyte fertilization [28], embryo development (as evident by morphokinetics using time lapse analysis [29]) and healthy term delivery in IVF patients [30]. Women who are candidates for cIVF using donor sperm should be strongly advised to stop smoking prior to treatment, to improve reproductive outcome, which may be compromised due to older age and reduced quality of oocytes.

Although our work is retrospective and needs validation by a large, randomized, controlled, prospective study, our results imply that ICSI has no advantage over cIVF and should not be used routinely for women undergoing IVF using donor sperm.

Authors contributions ZW-M: Conception and design of the manuscript, Critical revision of the manuscript for important intellectual content. AD: Acquisition of data, Statistical analysis. HG: Critical revision of the manuscript for important intellectual content. SL-B: Analysis and Interpretation of data. IB: Analysis and Interpretation of data. MK: Analysis and Interpretation of data. MD: Supervision.

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Availability of data and material All data and study materials are available if needed.

Code availability Not applicable.

Declarations

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

Ethical approval The study was approved on 28.1.2014 by the institutional ethical review board. IRB number 0074–13-CMC.

Consent to participant Not applicable.

Consent for publication Not applicable.

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