

Sibling Oocytes Randomly Assigned to Either Conventional Fertilization or Intracytoplasmic Sperm Injection Demonstrate Equivalent Fertilization and Blastulation Rates

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Abstract

Background: To determine the difference in fertilization and blastulation rates between sibling oocytes randomly assigned to either Conventional Fertilization (CF) or Intracytoplasmic Sperm Injection (ICSI) in patient couples with normal semen analysis parameters.

Methods: A retrospective review of embryologic and clinical outcomes from patients undergoing their first In Vitro Fertilization (IVF) cycle that randomly assigned one-half of sibling oocytes to either CF or ICSI. Randomization occurred prior to removal of the oocyte cumulus cells which allows identification of metaphase II oocytes eligible for ICSI. All male partners met normal semen analysis parameters and normal fertilization was anticipated for the IVF cycle. Each patient served as their own control.

Results: A total of 682 oocytes were included and were assigned to either CF or ICSI. The CF had a significantly higher fertilization rate compared to ICSI (67.9% versus 60%) when immature (non-metaphase II) oocytes were included in the analysis; however this difference diminished when only those oocytes eligible for ICSI were included. There was no difference in the day-3 embryo progression, the blastulation rate, the mean number of oocytes fertilized and the mean number of blastocysts per IVF cycle. Additionally, there was no significant difference in the pregnancy related outcomes between the two groups.

Conclusions: These studies demonstrates that in patient couples with normal semen analysis parameters, undergoing their first IVF cycle and who have anticipate normal fertilization, randomly assigning oocytes to CF or ICSI does not improve fertilization or blastulation. To confirm these findings, larger prospective studies are required.

Keywords: Intracytoplasmic sperm injection; ICSI; Fertilization; Sibling; Oocyte; IVF; Blastulation

Introduction

The success of In Vitro Fertilization (IVF) relies upon the acquisition of mature metaphase II oocytes, fertilization and survival of the fertilized oocyte to the cleavage or blastocyst stage of embryonic development. At the inception of IVF, successful fertilization was entirely reliant upon the ability of ejaculated sperm to penetrate the outer boundaries of the oocyte, including the corona radiata (outer layer of cells surrounding the oocyte) and the zona pellucida [1]. The zona pellucida, which is the oocyte's primary boundary, permits or inhibits sperm from releasing its genetic material in to the cytoplasm (ooplasm) of the oocyte. Following penetration, the zona pellucida prevents additional sperm from entering the oocyte. If the sperm, through its own motile forces, cannot penetrate the zona pellucida, fertilization will not occur. Failure of fertilization with IVF was observed primarily in patient couples with male factor infertility for which an insufficient quantity or quality of the sperm could not fertilize the mature oocyte. To overcome this Intracytoplasmic Sperm Injection (ICSI) was developed [2].

ICSI is a micromanipulation technique in which a single sperm is injected directly into the cytoplasm of a mature oocyte. As opposed to Conventional Fertilization (CF) which mixes an aliquot of sperm with the oocyte within culture media, ICSI offers the ability to bypass the zona pellucida, which in some cases can pose as a barrier to fertilization [3].

ICSI was first successfully reported with human pregnancies by Palermo *et al* in 1992 for the treatment of male factor infertility due to poor semen quality [4]. The utility of ICSI has since been expanded to include a variety of fertility diagnoses [5-8]. In 2008 the American Society for Reproductive Medicine created a list of indications for ICSI,

which included the treatment of male factor infertility and selected types of female infertility [5]. However, a complete consensus regarding the defined role of ICSI in fertility centers has yet to be realized and remains controversial [9].

Since the broad expansion of the use of ICSI to most fertility centers, the rate at which ICSI is applied in IVF cycles has increased dramatically. The Society for Assisted Reproductive Technology (SART) reported that in 2012, 67% of the 165,172 IVF cycles completed in the United States used ICSI to complete fertilization. The high proportion (67%) of ICSI used contrasts the 34% of all IVF cycles performed for male factor infertility, which have a clear indication for its use [10].

An additional contributing factor to the expanded role of ICSI is the reported high fertilization and pregnancy rates associated with ICSI cycles [3,11-13]. These encouraging outcomes have contributed to ICSI becoming the standard method for fertilization in many IVF centers. Despite the current high frequency that ICSI is used for fertilization, major professional societies have not endorsed the universal application

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of ICSI in all patients undergoing IVF and the wide-spread application of this technology remains controversial [5]. Some experts criticize the universal application of ICSI to all IVF patients for multiple reasons. Firstly, ICSI adds significant financial costs and increases the consumption of laboratory resources. Additionally, while ICSI is generally considered to be a safe technology, it is associated with both documented and theoretical risks [14-16].

Due to the valid criticisms directed at the general application of ICSI, CF continues to be used by many IVF centers, if no barrier to fertilization is predicted. To avoid complete fertilization failure, many centers randomly divide sibling oocytes between CF and ICSI. As early as 1996, Yang *et al* published the first results of randomly assigned sibling oocytes to either ICSI or CF and demonstrated that similar rates of fertilization and pregnancy occurred in the sample of 13 couples with a total of 280 oocytes [17]. Additional studies have analyzed this approach in patients with a variety of diagnoses and have demonstrated mixed results regarding fertilization, total fertilization failure, morula development, implantation and clinical pregnancy [11,18-32]. The most consistent finding from prior studies is a decrease in the total fertilization failure per IVF cycle in the ICSI groups [11,21]. Currently all but one of the studies evaluating the randomization of sibling oocytes to either CF or ICSI stopped embryo evaluation at 48 hours following fertilization or at the cleavage stage of embryonic development. At this time only one prior study [32] has analyzed the rate of blastulation of fertilized oocytes randomly assignment to ICSI or CF in couples with normal semen analysis parameters; and thus the information available on the effect of ICSI as compared to CF on blastulation in randomly assigned sibling oocytes is very limited.

The aim of this study was to determine the difference in fertilization and blastulation rates in sibling oocytes that have been randomly assigned to either CF or ICSI from patient couples with no indication for ICSI.

Materials and Methods

We conducted a retrospective review of all first-time IVF cycles in which oocyte fertilization was accomplished by randomly assigning sibling oocytes to either an ICSI group or CF group. Randomization was performed prior to removal of the cumulus layer of cells from the oocyte (stripping) which allows identification of metaphase II oocytes that are eligible for ICSI. The study design was approved by the Johns Hopkins Medical Institutions Institutional Review Board. This fertilization strategy is utilized in our clinic for patients undergoing their first IVF cycle and have no specific indication for the use of ICSI, but nonetheless desire the use of ICSI. All clinical management decisions for these IVF cycles were made by the reproductive endocrinology and infertility physicians. All women underwent controlled ovarian hyperstimulation following a gonadotropin/gonadotropin-releasing hormone antagonist protocol with Human Chorionic Gonadotropin (hCG) trigger in an outpatient academic fertility center. Oocyte retrieval was performed with ultrasound-guided trans-vaginal puncture 36 hours after administering the hCG injection. Retrieved oocytes surrounded by Cumulus and Corona Cells (OCC) were placed in culture followed by allocation to CF or ICSI groups. OCC allocated to the ICSI group were characterized for maturity following stripping of the OCC and only metaphase II oocytes were injected with a single sperm. Empty, immature and nonviable oocytes were discarded. Semen analysis parameters were defined as normal using the standards established by the World Health Organization [33].

For this review, exclusion criteria included IVF cycles performed for male factor infertility, couples who underwent a previously IVF

cycle and IVF cycles in which all embryos were cryopreserved. Data was obtained for each oocyte retrieved and its clinical course and ultimate disposition: discarded, cryopreserved or transferred. Additionally, pregnancy outcomes following the fresh embryo transfer was analyzed including implantation rate, overall pregnancy rate (positive hCG), and ongoing clinical pregnancy (sonographic evidence of cardiac activity by 6-7 weeks of embryonic gestation). In all cases, the embryos with the highest morphologic grade were used for uterine transfer.

The oocyte outcomes including: fertilization, blastulation, day-3 progress, fertilization failure and blastulation failure were analyzed using both the total number of oocytes randomized to either CF or ICSI and the outcomes of the ICSI group recalculated including only those oocytes that identified as metaphase II oocytes eligible for ICSI.

Data were compiled in Microsoft Excel (Microsoft Corporation, Redmond, Washington) and statistical analysis was performed using STATA 13 (StataCorp LP, College Station Texas). Proportional values with a dichotomous outcome, were compared using the chi-square test and mean values were compared using the Student's t-test. Statistical significance was considered to be a p-value of ≤ 0.05 .

A total of 58 patient couples underwent their first IVF treatment cycle from June 2009 to June 2012 and met the above inclusion criteria for review with sibling oocytes randomized to either CF or ICSI. Fourteen of the 58 couples were excluded from the blastulation rate calculations due to the intention to transfer cleavage stage embryos at the time of initiating the IVF cycle, leaving 44 couples available for assessing blastulation rates. The mean female age was 35 ± 6 years with a range of 25 to 43 years. This was the first attempted IVF cycle for all couples. Indications to undergo IVF treatment included: unexplained infertility (n=28), diminished ovarian reserve (n=20), tubal factor (n=5) and endometriosis (n=5). All patient couples had normal semen analysis parameters [33] that were evaluated prior to initiating the IVF cycle. Fresh sperm was used for 53 of the IVF cycles and the remaining 5 cycles used a previously cryopreserved semen due to the use of donor sperm or a social indication (i.e. travel of the male partner on the day of retrieval). All patients underwent controlled ovarian hyperstimulation with a combination of recombinant follicle stimulating hormone and purified human menopausal gonadotropins (mean: 3500 ± 1300 units). In all patients transvaginal oocyte retrieval was performed 36 hours following administration of the hCG trigger (Figure 1).

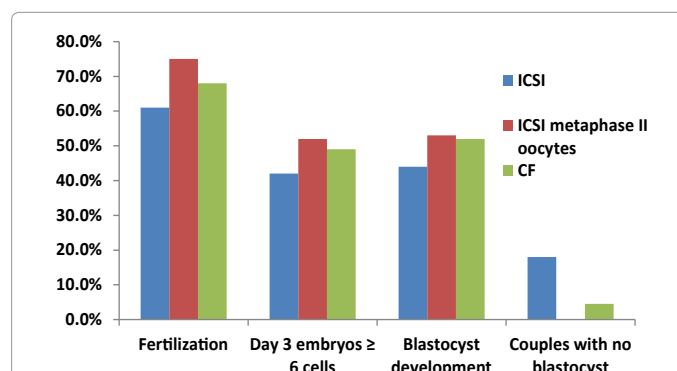


Figure 1: Title: Blastulation Rates Comparing Intracytoplasmic Sperm Injection with Conventional Fertilization.

A comparison of intracytoplasmic sperm injection (ICSI) with conventional fertilization (CF) with regard to the percentage of oocytes fertilized, cleavage stage embryos with ≥ 6 cells on day-3 of development, blastocyst development rate and the percentage of couples who no blastocysts development with ICSI or CF. Also compared separately from the ICSI group are those oocytes that were mature metaphase II.

Results

From a total 58 IVF cycles 682 oocytes were collected (mean: 11.9 ± 8 oocytes per patient cycle) and are summarized in Table 1. The allocation of oocytes to either ICSI or CF was performed prior to identifying if an oocyte was a mature metaphase II oocyte appropriate for ICSI. A total of 355 oocytes were randomized to CF and 327 were randomized to ICSI; the difference between the mean numbers of oocytes allocated to each group per patient couple was not statistically significant ($p > 0.05$). Of all 327 sibling oocytes assigned to undergo ICSI, 80% (262/327) were mature metaphase II oocytes and underwent the ICSI procedure. The fertilization rate of the oocytes

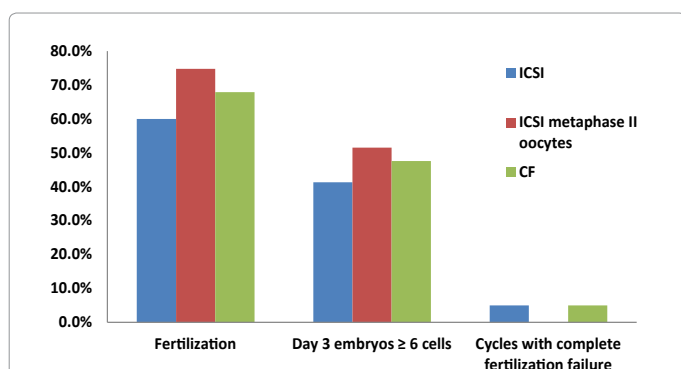


Figure 2: Title: Fertilization Rates Comparing Intracytoplasmic Sperm Injection with Conventional Fertilization.

A comparison of intracytoplasmic sperm injection (ICSI) with conventional fertilization (CF) of oocytes from 58 patient couples with 682 oocytes. Also compared separately from the ICSI group are those oocytes that were mature metaphase II. Outcomes demonstrated are the rates of fertilization and cleavage stage embryos with ≥ 6 cells on day-3 of development. Also compared was the percentage of couples who had complete fertilization failure with ICSI or CF.

that underwent CF was 67.9% (241/355) as compared to a fertilization rate of 60% (196/327) ($p < 0.05$) for the oocytes assigned to the ICSI group. However, this fertilization rate includes those oocytes that were non-metaphase II and thus ineligible to undergo ICSI within the ICSI group. The difference in the rate of fertilization between the CF and ICSI groups was not statistically significant when the non-metaphase II oocytes were excluded, increasing the fertilization rate of the ICSI group to 74.8% (196/262) ($p > 0.05$) (Figure 2).

Embryos were next evaluated on day-3 following fertilization for the number of cells present. A total of 6 or more cells were considered an appropriate level of progress and indicative of a “high quality” cleavage stage embryo. There was no significant difference ($p > 0.05$) identified between day-3 embryos; observed at 47.6% (169/355) for CF and 41.3% (135/327) for ICSI. The rate of > 6 cell day-3 embryos increased to 51.5% (135/262) for the ICSI group when only metaphase II embryos were included ($p > 0.05$). Of all 58 IVF cycles, both the CF and ICSI groups had 3 cycles in which all allocated oocytes to either ICSI or CF resulted in complete fertilization failure. However, in the ICSI group, all 3 groups with complete fertilization failures resulted when only one oocyte was eligible for ICSI following allocation of the sibling oocytes. The means calculated for oocyte fertilization, per IVF cycle for CF and ICSI was 4.2 ± 3.0 and 3.4 ± 2.6 respectively ($p > 0.05$).

The 44 cycles intended for blastocyst transfer included 549 oocytes with 285 allocated to CF and 264 to ICSI (summarized in Table 2). Of the 264 allocated to ICSI, 81% (215/264) were metaphase II oocytes eligible for ICSI. There was no statistical difference between the CF group and ICSI group with regard to the rate of fertilization, the mean number of oocytes fertilized per IVF cycle and the development of > 6 cell day-3 embryos. In addition, the differences between the CF and ICSI groups were not significant when the analysis was adjusted for the use of only metaphase II oocytes in the ICSI group; however the ICSI outcomes improved in all parameters measured following

	ICSI	ICSI metaphase II oocytes	CF	P value	P value metaphase II oocytes
No. of oocytes (mean \pm std)	327 (5.6 \pm 3.6)	262 (4.5 \pm 2.8)	355 (6.1 \pm 4.3)	$P > 0.05^a$	$P < 0.05^a$
Fertilization	60.0% 196/327	74.8% (196/262)	67.9% (241/355)	$P < 0.05^b$	$P > 0.05^b$
Day-3 embryos ≥ 6 cells	41.3% (135/327)	51.5% (135/262)	47.6% (169/355)	$P > 0.05^b$	$P > 0.05^b$
Cycles with complete fertilization failure	5% (3/58)		5% (3/58)		

CF=conventional fertilization, ICSI=Intracytoplasmic Sperm Injection, Std=standard deviation. Statistical analysis performed with ^aStudents t-test or ^bchi-square test.

Table 1: Fertilization and day-3 embryo development of sibling oocytes treated by CF or by ICSI intended for day 3-or day-5 transfer or cryopreservation in 58 patient couples with 682 total oocytes.

	ICSI	ICSI metaphase II oocytes	CF	P value	P value metaphase II oocytes
No. of oocytes (mean \pm std)	264 (6.0 \pm 3.7)	215 (4.9 \pm 3.0)	285 (6.5 \pm 4.6)	$P > 0.05^a$	$P > 0.05^a$
Fertilization	61% (162/264)	75% (162/215)	68% (195/285)	$P > 0.05^b$	$P > 0.05^b$
Day-3 embryos ≥ 6 cells	42% (112/264)	52% (112/215)	49% (139/285)	$P > 0.05^b$	$P > 0.05^b$
Blastocyst development	44% (115/264)	53% (115/215)	52% (149/285)	$P < 0.05^b$	$P > 0.05^b$
Couples failed to develop blastocyst	18% (8/44)		4.5% (2/44)	$P < 0.05^b$	
Fertilization per couple (mean \pm std)	3.7 \pm 2.7		4.4 \pm 3.0	$P > 0.05^a$	
Blastulation per couple (mean \pm std)	2.6 \pm 2.2		3.39 \pm 2.4	$P > 0.05^a$	

CF=Conventional fertilization, ICSI=intracytoplasmic sperm injection, std=standard deviation. Statistical analysis performed with ^aStudents t-test or ^bchi-square test.

Table 2: Fertilization and blastocyst development from sibling oocytes treated by CF or by ICSI with the intention for blastocyst transfer in 44 couples with 549 oocytes.

	ICSI	CF	P-value	CF and ICSI*	Overall
#Couples with fresh blastocyst(s) embryo transfer	8	14		15	37
Pregnancy rate	62.5% (5/8)	64% (9/14)	P > 0.05 ^a	60% (9/15)	62% (23/37)
Implantation rate	44% (7/16)	48% (13/27)	P > 0.05 ^a	33% (11/33)	41% (31/76)
On-going clinical pregnancy rate	50% (4/8)	36% (5/14)	P > 0.05 ^a	47% (7/15)	43% (16/37)

CF=conventional fertilization, ICSI=intracytoplasmic sperm injection. Statistical analysis performed with ^achi-square test. *This group included a double or triple-embryo transfer that included sibling embryos that were fertilized by separate methods.

Table 3: Pregnancy outcomes of couples with outcomes separated by embryo transfers that included embryos fertilized by ICSI alone, CF alone and multiple-embryo transfers which combined embryos fertilized by both methods. The differences in pregnancy rates, implantation rates and on-going clinical pregnancy rates were not statistically significant.

the adjustment (Table 2). The blastocyst development rate was 52% (149/285) for the CF group and 43% (115/264) for the ICSI group ($p < 0.05$). However, when only metaphase II oocytes were included in the ICSI group the blastocyst development rate increased to 53% (115/215) and no statistical significance was identified ($p > 0.05$). In addition, there was no significant difference identified in the mean number of blastocysts per IVF cycle, 3.4 ± 2.4 and 2.6 ± 2.2 for CF and ICSI respectively ($p > 0.05$). Of the oocytes allocated to CF, only 2 cycles had no blastocysts develop, however of the ICSI cycles, 8 failed to develop a single blastocyst ($p < 0.05$). Although the ICSI group had a higher number cycles with complete failure to develop blastocysts, following adjustment for non-metaphase II oocytes in the ICSI group, 4 of the 8 complete failures had only 1 oocyte eligible for ICSI.

Next we analyzed pregnancy rates; however, not all patients underwent a fresh embryo transfer at the blastocyst stage (Table 3). Of the 44 cycles planned for blastocyst transfer, 84% (37/44) underwent a fresh embryo transfer. Two cycles had a single-embryo transfer, 31 cycles had a double-embryo transfer and 4 cycles had a triple-embryo transfer. In addition, 15 cycles transferred sibling blastocysts from both the CF and ICSI group making identification of which fertilization method resulted in the pregnancy not possible. The overall pregnancy rate per blastocyst(s) transfer was 62% (23/37). Excluding those cycles that used a multiple-embryo transfer of embryos that were from both fertilization cohorts, the overall pregnancy rates for ICSI and CF were 62.5% (5/8) and 64% (9/14) respectively. The overall implantation rates were 44% (7/16) for ICSI and 48% (13/27) for CF. The on-going clinical pregnancy rate, defined as cardiac activity at 6 to 7 weeks gestational age, was 50% (4/8) for ICSI and 36% (5/14) for CF. All pregnancy related parameters demonstrated no statistical significance ($p > 0.05$) when comparing the differences measured between the ICSI and CF groups.

Discussion

In this study we compared sibling oocytes that were randomized to either CF or ICSI. The results demonstrate that ICSI did not confer a benefit to oocyte fertilization, the cell number of day-3 cleaved stage embryos, and blastulation and pregnancy rates in couples with normozoospermic semen undergoing their first IVF cycle. Remarkable, the CF group seemed to demonstrate an overall trend for improvement over the ICSI group in the parameters measured, however, this trend diminished when the non-metaphase II oocytes were excluded from the ICSI group.

To our knowledge, only one prior study evaluated the ability of randomly assigned oocytes to CF or ICSI to reach the blastocyst

stage in patient couples with normozoospermic semen parameters [32]. In the study performed by Komsky-Elbaz et al. patient couples with endometriosis underwent IVF with sibling oocytes randomized to CF or ICSI and identified that the ICSI group had higher rates of fertilization, a higher mean number of day-2 embryos, and an overall higher mean number of embryos available for cryopreservation. However, blastulation and pregnancy rates did not differ significantly between the CF and ICSI groups [32], which concur with the findings from our study. The slight variation in the results from their study as compared to ours can be potentially explained by the differences in the female patient population included in their study. All patients included in the Komsky-Elbaz et al. study had severe endometriosis, as compared to our study which included only 5 (9%) patients with endometriosis.

In addition, the overall results from our study correspond with similarly conducted studies reviewing fertilization and day-2 or day-3 embryo quality prior to embryo transfer. The earliest similarly conducted study which randomized sibling oocytes to CF or ICSI in couples with normal semen analysis parameters found no difference in fertilization; however the increase of total failure of fertilization in the CF group was statistically significant [19]. Similar findings, identifying no increase in fertilization or embryo quality with the use of ICSI were also confirmed in later studies. Contradicting this study, as well as the prior listed studies, Khamisi *et al* concluded that ICSI increased fertilization and embryo quality.

Unfortunately confounding an accurate comparison of the different studies is the inclusion of non-metaphase II oocytes to the randomized ICSI groups. Oocytes randomized to the ICSI group in some studies remained in the "ICSI group" regardless of the ability to perform ICSI [11,21,31]. Other studies included only randomized oocytes that qualified to undergo ICSI to be included in the analysis [19,32]. By comparing only oocytes that qualified to undergo ICSI with the oocytes assigned to CF, a selection bias is introduced in favor of the ICSI group. Our goal in this study was to avoid the selection bias for ICSI by performing both the analysis for all oocytes allocated to ICSI as well as an analysis of the ICSI group with only metaphase II oocytes eligible for ICSI.

The strengths of this study include comparing oocytes by using patients as their own control. Furthermore, oocytes were randomly assigned, prior to removal of the cumulus cells of the oocyte, to ICSI versus IVF so that mature oocytes were not pre-selected to ICSI group. Limitations of this study include the small sample size that was not powered adequately to evaluate pregnancy outcomes. In addition, the pregnancy outcomes listed are influenced by other factors apart from the insemination procedures, mainly the varying number of embryos transferred. In addition, the analysis of this data is retrospective and the allocation of the oocytes to either CF or ICSI is performed by embryologists as part of routine clinical care and as such is not subject to an objective systematic blinding process to prospectively randomized oocyte allocation. This allows the potential bias for allocating embryos to one group or the other. As our data suggests improved outcomes for CF, poorer quality oocytes may have been allocated to the ICSI procedure as an attempt to improve overall fertilization for the cycle; however this would give the appearance of ICSI being less effective. Another limitation of this study is that it did not evaluate embryos that underwent uterine transfer following cryopreservation. To improve the accuracy of this data, a rigorous prospective oocyte allocation protocol needs to be used at the time of oocyte retrieval.

Although a rigorous prospective protocol for randomly assigning sibling oocytes could further elucidate the outcomes of ICSI and IVF of sibling oocyte allocation, randomized trials of patient couples have

been conducted that accord with our results. In these prospective trials entire patient couples with normal semen analysis parameters were randomized to either complete CF or ICSI on all oocytes rather than sibling oocytes. The overall findings suggest that no definitive benefit of ICSI over CF was identified regarding embryo and pregnancy outcomes [22,34-36]. In order to make a more global assessment of ICSI versus CF in couples with non-male subfertility, a Cochrane review was conducted and determined that only one study [34] met the quality standards to be included in their analysis, which reported no significant advantage of ICSI over CF with their data suggestive of improved implantation and pregnancy rates in the CF group, although the difference was not statistically significant. The Cochrane review concluded that whether ICSI should be preferred to IVF for cases of non-male factor subfertility remains an open question and further research is required [37].

Additional support of the findings that ICSI does not improve outcomes over CF in infertile couples with normal semen analysis parameters was demonstrated in a retrospective review of pregnancy outcomes from centers that use ICSI on the majority IVF cycles. Using the SART database, Hodes-Wertz et al., compared outcomes from clinical IVF centers that utilized ICSI in greater than 90% of IVF cycles to centers which used ICSI in only 40% of IVF cycles and found that the increased use of ICSI did not convey an increase in live birth rates [38].

Despite a large number of studies demonstrating that CF outcomes are equivalent to ICSI in the absence of an indication for ICSI, there is an increasing trend for the routine use of ICSI. The SART national database demonstrates that since 2003 the use of ICSI has steadily increased by 22% in 2012 (55% to 67%). However, in that same time there is a paucity of non-conflicting data that clearly demonstrates the need to increase the use of ICSI [5].

There are a variety of reasons that ICSI plays such a dominant role in IVF. Firstly, data from couples suffering from male-factor infertility clearly demonstrate benefits from the use of ICSI [4,5,24,39]. Secondly, many clinics that currently utilize ICSI at a high rate demonstrate excellent pregnancy results. However, these two factors alone are insufficient to definitively show the inferiority of CF in the absence of well-established indications for the use of ICSI [5]. Accumulating data seems to show no clear benefit for the general application of ICSI over CF. Additionally, ICSI is not without potential drawbacks. The most apparent being that ICSI is associated with increased costs. Furthermore, ICSI carries with it potential risks, both demonstrated and theoretical, although there are many limitations to this data [40-42]. These potential risks should be a deterrent to the universal utilization of ICSI until definitive studies are complete. While ICSI has a role in maximizing fertility success in certain populations, the evaluation of universally applying ICSI in all IVF cycles should continue.

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