Use of intracytoplasmic sperm injection (ICSI) in normospermic men may result in lower clinical pregnancy and live birth rates

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Abstract

Background: While ICSI was developed for overcoming male infertility, it is increasingly being used for non-male factor indications, without consensus regarding the safety and efficacy of this approach.

Aims: Does ICSI offer any benefit compared to standard in vitro fertilization (IVF), in the setting of normal semen parameters?

Materials and Methods:

Retrospective analysis of reproductive outcomes in 3363 stimulated cycles (IVF=1661; ICSI=1702), in patients treated between 2009 –2015, was performed. Selected couples had no male factor infertility. Couples with abnormal semen parameters (based on WHO 2010 guidelines), presence of anti-sperm antibodies and low oocyte yield of ≤ 4 oocytes, were excluded. The outcomes analysed include 1) Fertilisation rate (FR) 2) Clinical pregnancy rate (CPR) and 3) Live birth rate (LBR), by method of fertilisation used (IVF vs ICSI) and controlling for significant confounders.

Results:

FR, CPR and LBR were significantly higher in the IVF group compared with ICSI (67.1% vs 62.3%, 23.06% vs 16.8%, 17.22% vs 13.2%, respectively). Pregnancy rate with ICSI was

approximately 30% lower than with IVF, even when controlling for significant factors such as day of embryo transfer and number of embryos transferred. This translates to one less pregnancy in every 15 cycles where ICSI was used without clear indication.

Conclusions:

Our data suggests that ICSI may be detrimental to clinical outcomes and contributes to the wider understanding of use of ICSI in normospermic men.

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Introduction

Intracytoplasmic sperm injection (ICSI) was introduced in 1992 to improve fertility outcomes in the setting of male-factor infertility and has revolutionized treatment options, with improved outcomes ^{1, 2}. However, its use has expanded to other areas, including poor

responders (≤ 4 harvested oocytes), advanced maternal age and in the setting of previously failed IVF cycles. Some centres use ICSI indiscriminately^{3, 4}. At present, these are not included as standard indications for ICSI and are not supported by professional bodies⁵.

In Australia and New Zealand the use of ICSI in all cases of assisted reproductive technology (ART) increased from 59.1% in 2008 to 63% in 2015⁶. This increase parallels the current global trend toward increased ICSI utilization, with a similar pattern is seen in the United States, where the proportion of cycles using ICSI rose from 36.4% to 72.6% between 1996 and 2012⁷. Some countries, such as Italy, are using ICSI almost exclusively, accounting for 98% of cycles in 2008^{8, 9}. Interestingly, this increase is occurring despite a stable proportion of patients diagnosed with male infertility overall, thus representing application of ICSI, not supported by current medical evidence¹⁰.

The growing use of ICSI in the presence of normal semen analysis has raised concern, as studies aimed at verifying the efficacy of ICSI over IVF in this setting are inconsistent. Some studies demonstrate no difference in outcomes between the two modalities¹¹⁻¹⁴, whilst others demonstrate conflicting advantages in one application over the other¹⁵⁻¹⁸. Adding further complexity, interpretation of these studies is problematic as there is a lacking focus on meaningful clinical outcomes, with most research focusing on surrogate markers, such as fertilisation rate (FR), total fertilisation failure (TFF) and implantation rate (IR). While these are important reproductive markers, they may not reflect desired clinical outcomes, specifically pregnancy and live birth¹⁹.

In addition to efficacy there are safety concerns. Despite its widespread application, ICSI has not been subjected to ethical review, animal studies or rigorous testing in humans to assess biological impact and overall safety²⁰. The procedure bypasses natural selection safeguards, which may affect offspring and future generations²¹⁻²³. Chromosomal damage may occur due to the injection of non-capacitated, acrosome intact spermatozoa, which with natural fertilization would never enter the oocytes. Furthermore, it is possible that incubation and pre-treatment of spermatozoa during ICSI results in DNA damage²⁰. Some studies have demonstrated an increase in genetic abnormalities, birth defects and developmental delay with the use of ICSI²²⁻²⁶.

It is noteworthy that these studies review outcomes in offspring following all ICSI, not specifically normospermic couples. Abnormalities in semen analysis, motivating the

application of ICSI, may be the underlying cause for offspring health impact. This is an area of ongoing research.

Another consideration is that ICSI is a more costly and resource-dependent technique, compared with conventional IVF²⁷, placing extra economic burden on public funding and/or patients.

Given the inconsistencies in the literature, safety concerns and resource demands of ICSI use, we sought to retrospectively analyse outcomes from our centre, with large cycle numbers, to add to existing evidence and encourage evidence-based trends in clinical practice.

Materials and Method:

Study Design:

We performed a retrospective cohort study, including couples attending Melbourne IVF for treatment between July 2009 and December 2015. Ethics approval was granted by Melbourne IVF Human Research and Ethics Committee (reference number 42/15-MIVF). We received no funding for this study. There are no conflicts of interest.

A total of 3363 stimulated cycles, performed in patients with non-male factor infertility, were reviewed in this analysis. Only embryos produced from the first egg collection were included in the analysis. Of these cycles, 1661 (49.4%) were IVF and 1702 (50.6%) were ICSI. All cycles underwent standard stimulation protocols, which included antagonist, gonadotrophin releasing hormone agonist (GnRHa) short and long down-regulation cycles. All cycles utilised conventional IVF or ICSI.

For cycles utilising ICSI, there was no identifiable indication for its use over IVF.

Participant characteristics:

Commonly accepted indications for the use of ICSI are abnormal semen analysis, presence of anti-sperm antibodies, poor fertilization in past IVF attempts and low oocyte yield. Couples with these indications were excluded. Only those undergoing first cycle of IVF in our centre

were included, to eliminate those with poor fertilization in prior cycles. To control for poor responders and diminished ovarian reserve (DOR), we excluded cycles with ≤ 4 oocytes collected. All eligible couples had normal semen analysis and absent sperm antibodies. The cause for infertility included anovulation, tubal factor, age-related and unexplained infertility. Cycles utilizing donor gametes or preimplantation genetic testing (PGT) were excluded.

As per the World Health Organisation (WHO) 2010 criteria, we defined the minimum normal semen analysis as concentration >15 mil/ml, motility $>40\%$, progressive motility $>32\%$, normal morphology $>4\%$ and volume $>1.5\text{ml}$ ²⁸.

Outcome measures:

Primary outcomes included fertilisation rate (FR), clinical pregnancy rate (CPR) and live-birth rate (LBR). All collected oocytes in the IVF group were subjected to insemination. For ICSI, only metaphase II or metaphase I who progressed to metaphase II were injected.

Statistical analysis

Statistical analysis was performed using STATA 9.2. Where comparison between groups was performed (IVF vs ICSI group), continuous variables were normally distributed and expressed as Mean and Standard Deviation, using Student's t-test. Categorical variables were expressed as percentages and the difference between groups analysed using Chi square test. Logistic regression analysis was performed with clinical pregnancy rate being the outcome variable. Variables that reached $p < 0.1$ on the multivariate analysis were included in the final multivariate model, with $p < 0.05$ considered statistically significant.

Results:

Reproductive outcomes from 3363 IVF/ICSI cycles were reviewed, with proportion of IVF and ICSI almost equal (IVF = 49.4%; ICSI = 50.6%).

Baseline female characteristics are shown in Table 1. The two groups were similar, with respect to age, body mass index (BMI) and duration of FSH stimulation. FSH start dose was significantly higher in the ICSI cohort.

The semen analyses for included couples were within normal parameters WHO criteria. Sperm concentration, motility, progressive motility and morphology were significantly lower

in the ICSI group, but importantly they were still within pre-defined normal limits (115.3 ml vs 87.5 ml $p<0.0001$; 60% vs 57.7% $p<0.0001$; 53.2% vs 50.3% $p<0.0001$; 12.1% vs 8.2% $p<0.0001$, respectively) (Table 1).

Clinical outcomes are shown in Table 2. The FR was significantly higher in the IVF group (67.1% vs 62.3% $p<0.0001$). There is no difference in outcomes following day 2 or day 5 embryo transfers between IVF and ICSI. As expected, day 5 transfers had better outcomes in both groups. Patients in the ICSI group were more likely to have two embryos transferred compared with IVF. Both CPR and LBR were significantly higher with IVF (26.83% vs 19.85% $p<0.001$) and (17.22% vs 13.2% $p=0.001$), respectively.

Results of the univariate analysis, with clinical pregnancy being the outcome of interest, are presented in Table 3. Unsurprisingly, women in the pregnant cohort were significantly younger and had more eggs collected, fertilised and frozen, and a higher percentage of day 5 transfers when compared to the non-pregnant cohort. With respect to fertilisation method, pregnant women were more likely to have utilised IVF compared to ICSI ($p<0.001$). Variables that achieved a p-value of less than 0.1 were included in the logistic regression model, with clinical pregnancy being the outcome variable.

The multivariate analysis is shown in Table 4. ICSI appears to have a detrimental effect on clinical pregnancy rates compared to IVF. The magnitude of this effect is in the order of about 30% reduction in pregnancy rate with ICSI. Transferring a day 5 embryo compared to a day 2 embryo increases clinical pregnancy by 17% (OR=1.17). Transferring two embryos instead of one improves pregnancy rate by 32% (OR=1.32). Not surprisingly increasing age above 35 years old, FSH dose and duration of FSH stimulation all reduce the OR of clinical pregnancy. Conversely, every additional embryo that is frozen in a stimulated cycle increases the odds of clinical pregnancy by 10% (OR=1.1). It is important to note that none of the semen parameters achieved statistical significance.

Discussion:

While the application of ICSI for abnormal semen parameters has clearly demonstrated improved fertility outcomes, this is not the case in normospermia. Studies aimed at analysing its efficacy in this setting are inconsistent. This is a topic of great interest as worldwide rate of ICSI use in normospermic couples continues to rise, representing a significant deviation from evidence-based practice.

Bhattacharya and Eftekhari supported the use of IVF over ICSI in this patient population. A randomised control trial (RCT) by Bhattacharya et al in 2001 reviewed outcomes from 415 normospermic couples randomly assigned to conventional IVF or ICSI. They demonstrated a significantly higher FR per oocyte retrieved (58% vs 47% $p<0.0001$) and IR (30% vs 22% $p=0.03$) with IVF. CPR was also slightly higher in the IVF group, however this failed to reach statistical significance (33% vs 22% $p=0.11$). IVF was also associated with significantly shorter laboratory time, making it a more efficient application¹⁵. Eftekhari et al supported these findings in 2012, demonstrating a significant improvement in FR (66.22% and 57.46% $p=0.036$), IR (16.67% and 11.17% $p=0.049$) and CPR (35.7% and 21.5% $p=0.031$) in the IVF group compared with ICSI¹⁶.

On the other hand, Fishel and Khamsi demonstrated better outcomes with ICSI. A prospective RCT by Fishel et al in 2000 reviewed clinical outcomes between conventional IVF and ICSI using sibling metaphase II oocytes in 221 patients. They demonstrated a significantly higher FR (79% vs 60% $p<0.015$) and lower TFF with ICSI. Despite these findings, the authors advised against its routine application in all cycles due to a lack of knowledge concerning its safety at the time of publication¹⁷. Khamsi et al demonstrated similar findings in their small prospective study whereby the sibling oocytes of 35 normospermic couples were randomly assigned to conventional IVF or ICSI. They demonstrated higher FR (71.3% and 57.2% $p=0.005$) and embryo quality in the ICSI cohort¹⁸.

A small prospective RCT by Foong et al in 2005 reviewed outcomes in sixty couples with normal semen analysis and unexplained infertility and found no statistically significant difference between IVF and ICSI in relation to FR, IR, CPR or LBR¹¹.

In agreement with the findings of Bhattacharya and Eftekhari, we present a clear advantage with the use of IVF over ICSI, in patients with normal semen parameters. Specifically, we have demonstrated an improvement in all primary outcomes, including FR, CPR and LBR, with absolute difference of 4.8%, 6.98% and 4.02% respectively, with use of IVF in this patient population. The lower pregnancy rate in the ICSI group is of potentially even greater clinical significance, as there were more double embryo transfers (48.3% IVF vs 55.1% ICSI).

The basis for observed lower fertilisation, CPR and LBR in the ICSI group is unknown and may reflect the exclusion of natural selection, where conception occurs with 'chosen' rather

than biologically fit sperm. Despite embryologists selecting sperm based on ideal phenotypic attributes, it may be of lower genetic quality when compared to other spermatozoa present in the sample, resulting in failed fertilisation or the development of a poorer-quality embryo. An alternative explanation is damage from the ICSI procedure itself, via mechanical injury, introduction of unwanted material during the ICSI process or exposure to various synthetic mediums.

There is a possibility, that due to the retrospective nature of this study ICSI patients are somehow different, in unidentified ways we have not controlled for, resulting in this group having a worse baseline fertility than the IVF population. The higher FSH start dose in the ICSI cohort may support this theory. The small 26.2 IU statistically significant difference ($p < 0.001$) however, is of doubtful clinical significance.

To address ovarian reserve differences between the two groups, we excluded those with ≤ 4 oocytes harvested. The number of oocytes collected represents a more useful indicator of ovarian reserve, compared to surrogate markers such as AMH or day 2 FSH. This eliminates the important confounder of a higher rate of poor responders in the ICSI group.

Semen characteristics (Table 1), do demonstrate a statistically significant difference in sperm parameters, specifically concentration, motility, progressive motility and morphology, with lower values in the ICSI population. This is of doubtful clinical significance, as these parameters fall within the normal defined reference ranges, and regardless, would be overcome with the use of ICSI. To explore the possible impact these variances had on pregnancy, we compared semen characteristics between the pregnant and non-pregnant populations. As shown in Table 3, there was no significant difference in any of the semen characteristics between pregnant and non-pregnant patients, further supporting this theory.

Given the current guidelines, we questioned why ICSI had been utilised and did not find any documented indications. In 2010 the WHO published new criteria for 'normal' semen analysis, with lower acceptable ranges compared with those published in 2009. Given that our data collection spans 2009 to 2015, this may represent use of previous guidelines, or a delay in clinicians adopting updated criteria. Alternately, clinicians may have chosen to apply ICSI to patients whose semen analysis, whilst falling within normal limits, may be approaching borderline acceptable values. Given the conflicting outcomes in published studies, clinicians may also be misinformed or potentially overly optimistic regarding ICSI's

potential in this subset of patients, resulting in its application outside of present indications. Another potential confounder may be that whilst we have only included patients undergoing their first ART cycle with our clinic, it is not known if these patients have undergone cycles elsewhere. Previously failed cycles, or patient request, may have also been an underlying factor in the clinicians' decision to use ICSI. The results of our study support IVF for non-male factor infertility. Although the findings are limited by its retrospective design, we have demonstrated that ICSI likely has a detrimental effect on clinical outcomes. Caution is advised when considering the use of ICSI in normospermic couples given these results, safety concerns and cost effectiveness. We encourage further clinical trials, specifically large prospective RCT's, to further evaluate the role of ICSI in non-male factor infertility.

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1 Table 1 - Baseline Characteristics

Variable	IVF (n=1661)	ICSI (n=1702)	p-value
	No. %/Mean(SD)(CI)	No. %/Mean(SD)(CI)	
Age at OPU (years)	37.4(4.5)(37.2-37.6)	37.5(4.5)(37.3-37.7)	0.6
BMI (weight/height ²)	24.5(4.7)(24.2-24.7)	24.3(24.1)(24.1-24.6)	0.46
FSH start dose (IU)	255.5(110.5)(250.1-260.8)	281.7(123.7)(275.8-287.6)	<0.0001
FSH duration (days)	9.3(1.98)(9.2-9.4)	9.3(1.92)(9.3-9.4)	0.68
Semen characteristics			
Concentration (mil/ml)	115.3(77)(111.6-119)	87.5(63.5)(84.5-90.6)	<0.0001
Days of abstinence	3.7(2.1)(3.6-3.8)	3.5(1.9)(3.5-3.6)	0.093
Volume (ml)	3.4(1.5)(3.3-3.5)	3.4(1.5)(3.4-3.5)	0.3
Motility (%)	60(8.3)(59.6-60.4)	57.7(8.5)(57.4-58.2)	<0.0001
Progressive Motility (%)	53.2(9)(52.7-53.6)	50.3(9.5)(49.9-50.8)	<0.0001
Normal Morphology (%)	12.1(5.3)(11.9-12.4)	8.2(4.7)(8-8.5)	<0.0001

OPU – Oocyte pick up; BMI – Basal metabolic index. FSH – Follicle Stimulating Hormone

Table 2 – Clinical Outcomes

	IVF (n=1661)	ICSI (n=1702)	p-value
	No. %/Mean(SD)(CI)	No. %/Mean(SD)(CI)	
No. oocytes harvested	8.75(5.6)(8.48-9)	8.96(5.6)(8.69-9.2)	0.28
No. fertilised normally	5.64(3.9)(5.5-5.8)	5.38(3.8)(5.2-5.6)	0.06
Fertilisation Rate(%)	67.1	62.3	<0.0001
No. embryos frozen	1.99(2.6)(1.86-2.11)	1.71(2.4)(1.6-1.82)	0.0013
Day2/day5 ET (%)	49.3/50.7	49.6/50.4	0.91
ETx1/ETx2 (%)	51.7/48.3	44.9/55.1	<0.001
CPR (%)	26.83	19.85	<0.001
LBR (%)	17.22	13.2	0.001

ET – Embryo transfer; CP – clinical pregnancy rate; LBR – Live birth rate

Note – Fertilisation rate includes abnormal fertilisation

Table 3 – Univariate analysis: clinical pregnancy

Univariate analysis	Not pregnant n= 2568 (76.7%)	Pregnant n= 780 (23.3%)	p-value
	Number(%)/Mean(SD)(SI)	Number(%)/Mean(SD)(SI)	
BMI	24.5(5)(24.3-24.7)	24.2(4.4)(23.8-24.4)	0.09
Age at OPU	38.7(3.3)(38.6-38.9)	37.3(2.8)(37.1-37.5)	<0.0001*
Start FSH dose	278.8(120.7)(274.1-283.5)	235.6(102.8)(228.4-242.8)	<0.0001*
FSH duration	9.4(2)(9.3-9.4)	9.2(1.9)(9.1-9.4)	0.09 *
Number of Eggs collected	8.5(5.5)(8.3-8.7)	10.2(5.8)(9.8-10.6)	<0.0001*
Eggs fertilised	5.2(3.7)(5.1-5.4)	6.5(4.1)(6.2-6.8)	<0.0001*
Fertilisation rate(%)	64.5%	65.3%	0.37

Number of embryos frozen	1.6(2.4)(1.6-1.7)	2.6(2.8)(2.4-2.8)	<0.0001*
ET day - % of day 5	18.9%	28.6%	<0.0001*
Number transferred - %of DET	35.6%	30.3%	<0.0001*
Concentration	101.3	101.2	0.95
Days of abstinence	3.6	3.6	0.8
Volume	3.4	3.5	0.18
Motility	58.7	59.5	0.02*
Prog Motility	51.6	52.2	0.08*
Morphology	10	10.6	0.02*
ICSI %	52.8%%	43.1%	<0.001*

*Variables that reached $p < 0.1$ were included in the multivariate analysis (Table 4)

Table 4 – Multivariate analysis: Clinical pregnancy (CP)

Variable	Odds Ratio for CP	p-value (95% CI)
BMI	1	0.94 (0.98-1.02)
Number of eggs collected	1	0.81 (0.98-1.03)
Average Progressive Motility	0.99	0.36 (0.96-1.02)
Normal Morphology	1	0.36 (0.99-1.03)
Number fertilised	0.98	0.2 (0.95-1.01)
Motility	1	0.16 (0.997-1.02)
Age above 35	0.885	<0.001 (0.86-0.91)*
FSH dose	0.999	0.001 (0.998-0.999)*
FSH duration	0.94	0.003 (0.89-0.98)*
Number of embryos frozen	1.1	<0.001 (1.06-1.13)*
ET day	1.17	<0.001 (1.09-1.24)*
Number of embryos transferred	1.32	0.006 (1.08-1.6)*
ICSI compared to IVF	0.696	<0.001 (0.589-0.824)*

*Variables that reached significance of $p < 0.05$ on multivariate logistic regression analysis, with CP being the outcome variable

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