Human Reproduction Open, pp. 1–5, 2017
doi:10.1093/hropen/hox013

human reproduction open

ORIGINAL ARTICLE

Is there a reason to perform ICSI in the absence of male factor? Lessons from the Latin American Registry of ART

Juan-Enrique Schwarze[1,2,*], Rodrigo Jeria[2], Javier Crosby[3], Sonia Villa[1], Carolina Ortega[1], and Ricardo Pommer[1]

[1]Reproductive Medicine Unit, Clinica Monteblanco, Camino a Farellones 18780, Lo Barnechea, Santiago 7690000, Chile [2]Obstetrics and Gynecology, Universidad de Santiago, Av Libertador Bernardo O'Higgins 3363, Santiago, Estación Central, Chile [3]Reproductive Medicine Unit, Clinica Las Condes, Estoril 450, Las Condes, Santiago, Chile

*Correspondence address. Reproductive Medicine Unit, Clinica Monteblanco, Santiago, Chile Tel: +56-991005611; E-mail: schwarze@monteblancoivf.cl

Submitted on May 14, 2017; resubmitted on June 19, 2017; editorial decision on July 12, 2017; accepted on August 9, 2017

STUDY QUESTION: Does the use of ICSI offer any outcome advantage over IVF in patients with non-male factor infertility?

SUMMARY ANSWER: We did not find any outcome improvement that justifies the routine use of ICSI over IVF in non-male factor ART cycles.

WHAT IS ALREADY KNOWN: Since its introduction in Latin America, the use of ICSI has increased substantially, even among patients without male factor infertility. However, it is not clear whether ICSI provides an advantage over IVF in non-male factor infertility.

STUDY DESIGN SIZE, DURATION: A retrospective cohort study of fresh cycles performed in 155 ART clinics located in 15 Latin American countries between 2012 and 2014. Records were assessed for 49,813 ART cycles (39,564 ICSI and 10,249 IVF) performed in infertile couples who did not have male factor infertility. Student's *t*-test was used to analyze normally distributed data, Wilcoxon test to analyze non-normally distributed data, and Fisher's exact test for categorical data. Logistic regression was used to quantify the effect of ICSI on delivery rate, adjusting for age of female partner, number of oocytes inseminated, number of embryos transferred, and transfer at blastocyst stage as possible confounding factors. Poisson regression analysis was used to quantify the effect of ICSI on fertilization rate, adjusting for age of female partner.

PARTICIPANTS/MATERIALS, SETTING, METHOD: Cycles with the diagnosis of male factor and use of cryopreserved semen and with a freeze-all strategy were excluded.

MAIN RESULTS AND THE ROLE OF CHANCE: After correcting for age of female partner, number of oocytes inseminated, number of embryos transferred and transfer at blastocyst stage, we found that the use of ICSI was associated with a significant decrease in the odds of delivery compared to IVF (odds ratio 0.88, 95% CI 0.84 to 0.93; $P < 0.0001$).

LIMITATIONS REASONS FOR CAUTION: An important limitation of this study is the lack of randomization owing to its retrospective nature. This could result in selection bias, i.e. couples with the worst prognosis undergoing ICSI, or patients with a history of fertilization failure in IVF cycles undergoing ICSI. More than one cycle from the same couple may be included in the study.

WIDER IMPLICATIONS OF THE FINDINGS: The lack of an outcome benefit—and, indeed, a reduced likelihood of delivery—following ICSI in non-male factor infertile couples suggests that ICSI may not be the most appropriate clinical approach in these patients.

STUDY FUNDING/COMPETING INTEREST(S): None.

Key words: IVF / ICSI / non-male factor infertility / ART / delivery rate / fertilization failure

WHAT DOES THIS MEAN FOR PATIENTS?

Although ICSI was originally intended to help with male fertility problems, it is often used more widely instead of standard IVF. This paper asks whether there are any advantages to using ICSI instead of IVF when there are no male fertility issues.

The researchers carried out a study looking at the outcomes of treatment performed in 155 fertility clinics in 14 Latin American countries over a period of 2 years. In Latin America, many centres offer ICSI to everyone needing assisted conception rather than IVF in the hope of improving the chances of success. The outcomes of more than 49,000 cycles were considered and the figures show that if people had ICSI instead of IVF when there was no male fertility problem, the treatment was actually less likely to be successful.

ICSI is also sometimes suggested for women who are older or those who have not produced many eggs in an earlier cycle. The study found no increase in the chance of fertilization when these women were given ICSI either.

The study was looking at existing data, which means the reasons why individual couples had ICSI rather than IVF are not known, and this could affect the findings. Even taking this into account, the researchers conclude that there is no evidence for offering ICSI instead of IVF if there are no male fertility problems as it is less likely to work.

Introduction

ICSI was developed as an ART method in order to treat couples with severe male factor infertility, enabling them to produce a biological child (Palermo *et al.*, 1992; Boulet *et al.*, 2015; Grimstad *et al.*, 2016). In 1992, ICSI was introduced in Latin America; in the last two decades, its use has increased substantially, even among patients without male factor infertility (Zegers-Hochschild *et al.*, 2011).

Despite its increasing use in non-male factor infertility cases, an advantage of ICSI over IVF has not yet been demonstrated in these cases. In a RCT that included 415 couples with non-male factor infertility, conventional IVF was associated with better fertilization rates and implantation rates than ICSI, although live birth rates were comparable (Bhattacharya *et al.*, 2001). In a retrospective analysis of 745 women over 40 years undergoing ART, no advantage in terms of delivery rate was demonstrated (Tannus *et al.*, 2017). Furthermore, a retrospective analysis of 350 women with a low response to stimulation did not find any improvement in fertilization or delivery rates (Luna *et al.*, 2011).

Nonetheless, many centres in Latin America perform only ICSI. This preference might reflect a desire of both physicians and infertile couples to optimize the outcome of ART cycles since treatments are often paid out-of-pocket by patients. ICSI is also pursued with the hope that it might diminish the risk of total fertilization failure and increase the number of embryos available (Kim *et al.*, 2007; Tannus *et al.*, 2017).

We wished to determine empirically whether the use of ICSI is associated with an improvement in the outcome of non-male factor infertile couples undergoing ART. The findings of this study could have implications for standard practice in the clinical approach to assisted reproduction in cases of non-male factor.

Materials and Methods

The Latin American Registry of ART (RLA) keeps a database, tracking individual data from 155 centres located in 15 Latin American countries. Data recording begins with the controlled ovarian hyperstimulation protocol and continues to the birth of the neonate(s).

Data analysed for our study were proportioned by the RLA; as part of the accreditation procedure performed regularly by two independent professionals, all centres state in their consent form that the data collected may be published in epidemiological studies, which will maintain anonymity of patients. Patients can request to have their data removed from the database. For these reasons, no Institute Review Board/Ethics Committee approvals were needed.

Biomedical data for fresh IVF and ICSI cycles were extracted from cycles initiated between 1 January 2012 and 31 December 2014. Since our objective was to compare the outcomes associated with the type of insemination in couples without male factor infertility, we excluded cycles with the diagnosis of male factor and use of cryopreserved semen. Furthermore, we excluded cycles with a freeze-all strategy. It is possible that more than one cycle from the same couple is included in the study.

Retrieved data included: diagnoses, age of female partner in completed years, number of oocytes retrieved, number of oocytes inseminated, number of oocytes fertilized, stage of embryo development at embryo transfer (cleaving embryo or blastocyst), outcome (no pregnancy, spontaneous miscarriage, delivery of a live infant), number of babies born (singletons, twins, triplets and more), gestational age in completed weeks of amenorrhoea, perinatal outcome, and birthweight. We used the International Committee for Monitoring Assisted Reproductive Technology revised glossary of ART terminology.

When appropriate, we present the difference between proportions or means (ICSI result minus IVF result) with the corresponding 95% CI. We performed logistic regression analysis, adjusting for female age in completed years, embryo development at the time of transfer (blastocyst stage and cleaving embryo), number of embryos transferred and number of oocytes inseminated to compare the effect of ICSI over IVF on the odds of delivery per embryo transfer (odds ratio, OR). Similarly, logistic regression, adjusted for female age, was used to compare the effect of ICSI over IVF on the odds of spontaneous miscarriage. To compare the effect of ICSI over IVF on fertilization rate, we performed Poisson regression analysis, adjusting for female age. The Kolmogorov–Smirnov test was used to determine if there was a normal distribution of data. The Student's *t*-test was used to analyse continuous (normally distributed) data, Wilcoxon test to analyse non-normally distributed data, and Fisher's exact test for categorical data. A *P*-value of less than 0.05 was considered as statistically significant.

All statistical analyses were performed with STATA (Statcorp, TX, USA).

Results

We reviewed a total of 49,813 cycles: 39,564 ICSI cycles and 10,249 IVF cycles. Baseline cohort characteristics are described in Table I. ICSI and IVF groups were similar in terms of female age and female BMI. The diagnosis of infertility owing to tubal factor was more common in the IVF group (23.8%) than in the ICSI group (18.1%).

Table I Baseline characteristics in ART cycles for non-male factor infertile couples in the RLA, 2012–2014.

Characteristic	ICSI (*n* = 39,564)	IVF (*n* = 10,249)	*P*-value**
Female age in years, mean (SD)	36.9 (4.4)	36.3 (4.4)	<0.0001
Female BMI (kg/m^2)			<0.0001
<18.50	1.46%	1.28%	
18.50–24.99	42.48%	41.91%	
25.00–29.99	14.37%	18.20%	
≥30.00	41.69%	38.62%	
Cause of infertility (%)(*)	*n* = 54,642	*n* = 15,603	<0.0001
Unexplained	36.4%	33.1%	
Tubal factor	18.1%	23.8%	
Endocrine	8.0%	9.1%	
Endometriosis	12.5%	11.0%	
Ovarian insufficiency	15.0%	16.4%	
Other	9.0%	6.8%	

(*)Women may have had up to two diagnoses per cycle.
**Fisher's exact test.
RLA, Latin American Registry of ART.

Table II Comparison of outcomes of ART cycles among non-male factor infertile couples, RLA 2012–2014.

Number of cycles	ICSI (*n* = 39,564)	IVF (*n* = 10,249)	Difference (95% CI)(**)
Oocytes retrieved, mean (SD)	7.91 (5.68)	8.24 (5.9)	−0.33 (−0.46 to −0.21)
Fertilization rate, (%)	73.84%	73.55%	0.28% (−0.29% to 0.85%)
Fertilization failure, *n* (%)	1775 (4.49%)	345 (3.37%)	1.12% [0.71% to 1.52%](*)
Mean number of embryos transferred (SD)	2.07 (0.7)	2.2 (0.7)	−0.14 (−0.16 to 0.12)
Blastocyst stage transfer (%)	17.90%	32.00%	−14.1 (−15.14 to −13.06)(*)
Miscarriage rate, *n* (%)	2195 (19.19%)	646 (17.75%)	1.44% [0.00 to 2.87]
Live birth rate per cycle, *n* (%)	9093 (22.99%)	2948 (28.76%)	−5.78% [−6.74 to −4.81](*)
Singleton	7265 (79.0%)	2196 (74.0%)	(*)
Twins	1748 (15.9%)	703 (23.8%)	
Triplets and higher	80 (1.2%)	49 (1.6%)	
Birthweight (g), mean (SD)			
Singleton	3064.6 (512.8)	2993 (479.5)	71.58 [44.15 to 99.01](*)
Twins	2294 (473.8)	2282 (460.9)	12.74 [−19.41 to 44.89]
Triplets and higher	1698 (412.9)	1703 (440.6)	−5.14 [−105 to 95.61]
Duration of gestation (Weeks Amenorrhoea), mean, (SD)			
Singleton	37.6 (2.14)	37.3 (2.07)	0.28 [0.18 to 0.4]
Twins	35.2 (2.7)	35.1 (2.5)	0.07 [−0.18 to 0.33]
Triplets and higher	32.1 (2.7)	32.1 (3.3)	0.01 [−1.13 to 1.14]
Birth < 37 weeks (%)			
Singleton	1020 (14.04%)	373 (16.99%)	−2.95% (−4.71% to −1.18%)
Twins	948 (54.23%)	435 (61.88%)	−7.65% (−11.93% to −3.36%)
Triplets and higher	66 (86.84%)	43 (87.76%)	−0.92 (−12.83% to 10.99%)

(*)$P < 0.0001$.
(**)Fisher's exact test; Student's *t*-test when appropriate.

We did not find a clinically relevant, statistically significant difference in the mean number of oocytes retrieved, total fertilization failure, mean number of embryos transferred, or miscarriage rate (Table II). We also did not find a difference in the mean gestational age between babies born after ICSI or IVF, or the proportion of preterm deliveries. Nor did we find a clinical significant difference in the mean weight at delivery (Table II).

Overall, we found a difference in the proportion of total fertilization failure, however of little clinical significance (Table II). Furthermore, we compared the proportion of total fertilization failure when four or fewer oocytes were inseminated. We found that ICSI was associated with an increase in the proportion of total fertilization failure compared to IVF: 9.70% versus 8.43% respectively, for a difference of +1.27% (95% CI 0.25% to 2.29%, $P = 0.019$). We also compared the proportion of total fertilization failure in women 40 years of age or older. ICSI was associated with a significant increase in the proportion of total fertilization failure compared to IVF: 7.06% versus 5.96% respectively, for a difference of +1.10% (95%CI 0.15% to 2.05%, $P = 0.030$).

Live birth rate per initiated cycle was significantly lower in the ICSI group, with a difference of −5.78% (95%CI −6.74 to −4.81, $P < 0.0001$). After correcting for age of female partner, number of oocytes inseminated, number of embryos transferred and transfer at blastocyst stage, we found that the use of ICSI was associated with a significant decrease in the odds of delivery (OR 0.88, 95%CI 0.84 to 0.93; $P < 0.0001$). In the case of women 40 years of age or older, the live birth rate per initiated cycle was also significantly lower in cycles with ICSI (11.42%) than with IVF (15.05%), for a difference of –3.63% (95%CI −5.00% to −2.25%, $P < 0.0001$).

To test for the effect of ICSI over IVF in the number of fertilized oocytes, we performed an age-corrected Poisson regression analysis. We found that ICSI was associated with an increase in the incidence rate ratio of fertilization of 1.04 (95%CI 1.03–1.05; $P < 0.001$).

After correcting for age of female partner, the use of ICSI was not associated with a significant change in the odds of miscarriage (OR 1.05, 95%CI 0.95 to 1.16; $P = 0.301$). In the case of women 40 years of age or older, the miscarriage rate increased significantly when ICSI was used (32.54%) compared to IVF (26.19%), for a difference of +6.35% (95%CI 2.43% to 10.27%, $P = 0.002$).

Discussion

After correcting for known confounding factors, such as age of female partner, number of embryos transferred, and embryo stage at transfer, we found that ICSI was associated with a decrease in the likelihood of delivering a baby.

One of the main strengths of our study is the number of cycles analysed. To our knowledge, we have performed the largest retrospective study to date comparing ICSI and conventional IVF in couples without male factor infertility. The database used analysed in this study covers more than 80% of ART cycles carried out in the region (Zegers-Hochschild *et al.*, 2011), thus our results are generalizable to all Latin American countries. The data provided are checked by the RLA central office before inclusion in the database (Zegers-Hochschild *et al.*, 2016), therefore the clinical information is considered reliable. Finally, the thoroughness of the database also enabled us to correct for confounding factors.

Our results were similar to those of previous studies in terms of pregnancy and fertilization rates (Bukulmez *et al.*, 2000; Bhattacharya *et al.*, 2001; Kim *et al.*, 2007; Grimstad *et al.*, 2016; Tannus *et al.*, 2017). Furthermore, we found that the use of ICSI does not reduce the risk of total fertilization failure, even in the case of poor ovarian response, as did Luna *et al.* (2011), or in the case of women 40 years of age or older. Nevertheless, it is reassuring to corroborate that ICSI is not associated with a change in the prognosis of neonates, in terms of birthweight and prematurity.

An important limitation of this study is the lack of randomization owing to its retrospective nature. This could result in selection bias, i.e. couples with the worst prognosis undergoing ICSI, or patients with a history of fertilization failure in IVF cycles undergoing ICSI. Nevertheless, we have corrected for confounding factors in our analysis, thus reducing the risk of bias.

In summary, we found no data that justify the routine use of ICSI in non-male factor ART cycles. Indeed, the use of ICSI in these couples was associated with a poorer outcome. Therefore, we suggest that the first approach offered should be IVF.

Acknowledgements

We would like to thank the Latin American Registry of ART, especially its director, Fernando Zegers-Hochschild, for their thorough work to keep this registry running.

Authors' roles

J-ES contributed to the conception of the work; the acquisition, analysis, interpretation of data for the work; drafting the work; final approval of the version to be published; and agreement to be accountable for all aspects of the work. RJ contributed to the acquisition, analysis, interpretation of data for the work; drafting the work; and final approval of the version to be published. JC contributed to the design of the work; the acquisition, analysis, interpretation of data for the work; drafting the work; final approval of the version to be published; agreement to be accountable for all aspects of the work, and final approval of the version to be published. SV contributed to the design of the work; drafting the work; final approval of the version to be published. CO contributed to the design of the work; the acquisition, analysis, interpretation of data for the work; drafting the work; final approval of the version to be published; agreement to be accountable for all aspects of the work and final approval of the version to be published. RP contributed to the design of the work; the acquisition, analysis, interpretation of data for the work; drafting the work; final approval of the version to be published; agreement to be accountable for all aspects of the work and final approval of the version to be published.

Funding

None.

Conflict of interest

None declared.

References

Bhattacharya S, Hamilton MP, Shaaban M, Khalaf Y, Seddler M, Ghobara T, Braude P, Kennedy R, Rutherford A, Hartshorne G *et al.* Conventional

in-vitro fertilisation versus intracytoplasmic sperm injection for the treatment of non-male-factor infertility: a randomised controlled trial. *Lancet* 2001;**357**:2075–2079.

Boulet SL, Mehta A, Kissin DM, Warner L, Kawwass JF, Jamieson DJ. Trends in use of and reproductive outcomes associated with intracytoplasmic sperm injection. *JAMA* 2015;**313**:255–263.

Bukulmez O, Yarali H, Yucel A, Sari T, Gurgan T. Intracytoplasmic sperm injection versus in vitro fertilization for patients with a tubal factor as their sole cause of infertility: a prospective, randomized trial. *Fertil Steril* 2000;**73**:38–42.

Grimstad FW, Nangia AK, Luke B, Stern JE, Mak W. Use of ICSI in IVF cycles in women with tubal ligation does not improve pregnancy or live birth rates. *Hum Reprod* 2016;**31**:2750–2755.

Kim HH, Bundorf MK, Behr B, McCallum SW. Use and outcomes of intracytoplasmic sperm injection for non-male factor infertility. *Fertil Steril* 2007;**88**:622–628. Elsevier.

Luna M, Bigelow C, Duke M, Ruman J, Sandler B, Grunfeld L, Copperman AB. Should ICSI be recommended routinely in patients with four or fewer oocytes retrieved? *J Assist Reprod Genet* 2011;**28**:911–915.

Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. *Lancet* 1992;**340**:17–18.

Tannus S, Son W-Y, Gilman A, Younes G, Shavit T, Dahan M-H. The role of intracytoplasmic sperm injection in non-male factor infertility in advanced maternal age. *Hum Reprod* 2017;**32**:119–124.

Zegers-Hochschild F, Schwarze JE, Crosby JA, Musri C, Urbina MT, Latin American Network of Assisted Reproduction (REDLARA). Assisted reproductive techniques in Latin America: the Latin American Registry, 2013. *Reprod Biomed Online* 2016;**32**:614–625. Elsevier.

Zegers-Hochschild F, Schwarze MJE, Crosby JA, do Carmo Borges de Souza M. Twenty years of assisted reproductive technology. *JBRA Assist Reprod* 2011;**15**:15–30.