Journal of Assisted Reproduction and Genetics, Vol. 17, No. 9, 2000

REVIEW

The Status of Controlled Prospective Clinical Trials for Efficacy of Intracytoplasmic Sperm Injection in In Vitro Fertilization for Non-Male Factor Infertility

FIROUZ KHAMSI,[1,2,4] YALCIN YAVAS,[1] SILVIE ROBERGE,[1] IARA C. LACANNA,[1] JEREMY C. WONG,[1,3] and MAXINE ENDMAN[1]

Submitted: January 5, 2000
Accepted: May 3, 2000

***Purpose**: Intracytoplasmic sperm injection (ICSI) of some sibling oocytes may have a beneficial effect in couples going through in vitro fertilization for causes of infertility not related to the male factor. Our purpose was to critically appraise the randomized controlled studies done in this area and arrive at some recommendations.*
***Methods**: The four controlled trials done so far have utilized similar methodology, i.e., they randomly allotted sibling oocytes to ICSI versus standard insemination in patients going through in vitro fertiliztion and embryo transfer.*
***Results**: In the first trial reported in 1995 there was no difference in fertilization rate, whereas the later trials reported in 1997, 1999, and 2000 showed improvement with ICSI that reached statistically significant level in the last two studies.*
***Conclusions**: Total fertilization failure of an in vitro fertilization cycle can be prevented and fertilization can be improved if half of sibling oocytes are subjected to ICSI.*

KEY WORDS: Intractoplasmic sperm injection; in vitro fertilization; sibling oocytes; embryo transfer.

[1] Toronto Fertility Sterility Institute, Toronto, Canada.
[2] Division of Endocrinology and Metabolism, Toronto General Hospital, University Health Network, Department of Medicine, University of Toronto, Toronto, Canada.
[3] Department of Obstetrics and Gynecology, University of Toronto, Sunnybrook Health Science Centre, Toronto, Canada.
[4] To whom correspondence should be addressed at Toronto Fertility Sterility Institute, 66 Avenue Road, Toronto, Ontario M5R 3N8, Canada.

INTRODUCTION

Originally, intracytoplasmic sperm injection (ICSI) was developed for treatment of male-factor infertility (1). It was subsequently discovered that when there is total fertilization failure in an in vitro fertilization (IVF) cycle, subsequent IVF with ICSI may lead to fertilization and pregnancy (1). Therefore, IVF-ICSI was advocated for such cases with a normal spermatogram. For a woman going through the physical, emotional, and financial burden of an IVF cycle, total fertilization failure is devastating. Such women may have had many oocytes retrieved and it may be advisable to do ICSI on some of the retrieved oocytes. If there is total fertilization failure of inseminated oocytes, fertilization may be achieved with oocytes subjected to ICSI in the same cycle. This concept has led four groups to investigate the place of ICSI in IVF cycles done for non-male-factor infertility (2–5). All investigators used random allocation of retrieved oocytes to IVF without or with ICSI. Comparison of the fertilization and embryo development of these sibling oocytes is providing some answers to the place of ICSI in all IVF cycles, including those done for tubal factor, infertility of undetermined cause, endometriosis, and so forth. In this article, we have reviewed all parameters in the four reports in order to provide a clearer picture.

REVIEW OF THE METHODOLOGY

The four studies were done in the last 6 years (2–5).

1058-0468/00/1000-0504$18.00/0

Table I. Patients' Profiles and ICSI Fertilization Rate per Injected Mature Oocyte

Variable	Aboulghar *et al.* (2)	Ruiz *et al.* (3)	Jun *et al.* (4)	Khamsi *et al.* (5)
No. cycles	22	70	103	35
Age	33	31.9	NR	33.9
Length of infertility	8.6	NR[a]	NR	5.2
Cause of infertility				
Unknown	22	63	19	12
Tubal	—	—	37	18
Endometriosis	—	7	17	2
Donor sperm	—	—	—	4
Donor oocyte	—	—	—	1
ICSI fertilization rate (per injected oocyte)	63	78.4	NR	81.7

[a] NR, Not reported.

Causes of infertility are shown in Table I. Aboulghar *et al.* (2) studied infertility of undetermined cause, Ruiz *et al.* (3) included mild endometriosis, and Jun *et al.* (4) included tubal causes as well. Khamsi *et al.* (5) included aforementioned causes as well as four cases of therapeutic donor insemination. These four cases would have had ICSI if any sperm had been found in husband's ejaculate; but since no sperm could be found, donor sperm was used (with prior informed consent). In addition, Khamsi *et al.* (5) had one case of oocyte donation (without male factor). All investigators utilized a standard gonadotropin-releasing hormone (GnRH) long-term down-regulation with subsequent human menopausal gonadotropin (hMG) [or pure follicle-Stimulating hormone (FSH)]. Intracytoplasmic sperm injection was performed using standard techniques described previously (1). In all four studies, some of the oocytes were randomly allotted to ICSI. The results are reported as fertilization rate per oocyte assigned to each treatment group. In the case of ICSI, only oocytes at metaphase II stage were injected; therefore, some oocytes were not injected because they were either immature or postmature, but they were still counted so that a bias was not created in favor of ICSI. However, three of the four studies also reported their fertilization rate per mature injected oocyte (Table I).

The four groups appeared to have a fairly successful IVF-ICSI program as far as pregnancy rates were concerned. However, pregnancy rates are not reported here as a mixture of embryos resulting from the two treatments were transferred.

REVIEW OF THE OUTCOME OF THE TRIALS

Table I shows the ICSI fertilization rate per mature oocyte injected. It can be seen that with progression of the year of study there has been an improvement in fertilization rate, ranging from 63% to 81.7%. Table II compares the fertilization rates based on number

Table II. Fertilization Rate in Oocytes Subjected to IVF Insemination or ICSI

Variable	Aboulghar *et al.* (2)	Ruiz *et al.* (3)	Jun *et al.* (4)	Khamsi *et al.* (5)
IVF				
No. oocytes	138	551	350	187
No. fertilized oocytes	70	298	184	107
Fertilization	50.7%	54%	52.5%	57.2%
ICSI				
No. oocytes	160	589	456	188
No. fertilized oocytes	80	356	299	134
Fertilization rate (per assigned oocyte)	50%	60.4%	65.6%	71.3%
Statistical significance for fertilization rate (P)	NS[a]	NS	<0.01	0.005

[a] NS, Not significant.

of oocytes assigned to treatments. The earliest study reported in 1995 (2) showed no difference in fertilization rate based on the number of oocytes assigned to treatments (50.7% for standard IVF vs. 50% for ICSI). The second study reported in 1997 (3) showed a difference in fertilization rate between IVF and ICSI, that is, 54% versus 60.4%, respectively, but this was not significant. The third study done in 1998 (4) showed a difference in fertilization rate between IVF insemination and ICSI (52.5% vs. 65.6%) that reached a statistical significance ($P < 0.01$). The last study of Khamsi *et al.* (5) also showed a highly significant difference in fertilization rate between IVF insemination and ICSI (57.2% vs. 71.3%; $P = 0.005$).

The results of good and fair embryo formation are shown in Table III. Ruiz *et al.* (3) showed no difference, whereas Jun *et al.* (4) and Khamsi *et al.* (5) reported very similar figures that were statistically significant ($P < 0.01$). The percentages of good and fair embryos over the number of oocytes allotted to IVF and ICSI were 49.2% and 59.2% (4), and 47.1% and 64.4% (5), respectively. The similarity between these two studies is most interesting.

There was one factor that all four studies were in agreement, that is, the difference in the incidence of total fertilization failure between the two groups. The first three investigators reported a total fertilization failure of 22.7%, 11.4%, and 6.8%, respectively, for standard IVF insemination and no fertilization failure for the ICSI group (Table IV). Khamsi *et al.* (5), however, reported a fertilization failure of 14.3% (5/35) and low fertilization rate of 20.0% (7/35) for IVF (total 34.3%; 12/35), and fertilization failure of 2.9% (1/35) for ICSI.

CONCLUSION BASED ON THE FOUR TRIALS

The four controlled and prospective trials are unanimous in their conclusion that if some of the sibling oocytes are subjected to ICSI, we can avoid the problem of total fertilization failure with conventional IVF insemination, that is, no embryo transfer in an IVF cycle. Considering that often there are many oocytes retrieved, it seems logical to subject some of the oocytes to ICSI. Chronologically, the last two of the four studies showed statistically significant benefit of ICSI both in fertilization and good–fair embryo development. The failure of the earlier studies may be related to improvement in the ICSI technique over the last 5 years. This is demonstrated by the fact that fertilization rate per mature injected oocyte was 63% in the first study and increased to 81.7% in the last study.

The above studies point to the benefit of performing ICSI on some of retrieved oocytes regardless of the cause of infertility. Are there any disadvantages to this proposal? Does the addition of ICSI to standard IVF increase the chance of congenital abnormalities? The most detailed study in this respect (6) showed a malformation rate of 3.3% for ICSI, which was similar to figures from national registries for spontaneous pregnancies. Similar malformation rate (3.6%) was reported for IVF cycles (7). Performing ICSI will result in a higher cost for a patient who would have good fertilization without ICSI. However, it is definitely cost-saving for a patient who may have very low fertilization or no fertilization

Table III. Fair and Good Embryo Formation in Oocytes Subjected to IVF Insemination or ICSI

Variable	Aboulghar *et al.* (2)	Ruiz *et al.* (3)	Jun *et al.* (4)	Khamsi *et al.* (5)
IVF				
No. oocytes	138	551	350	187
No. embryos	NR[a]	265	150	88
Fair–good embryo formation rate	NR	48.1%	49.2%	47.1%
ICSI				
No. oocytes	160	589	456	188
No. embryos	NR	309	270	121
Fair-good embryo formation rate	NR	52.5%	59.2%	64.4%
Statistical significance for embryo formation rate (P)	NR	NS	<0.01	0.001

[a] NR, Not reported; NS, not significant.

Table IV. Total Fertilization Failure per Patient Whose Sibling Oocytes Were Subjected to IVF Insemination or ICSI

Variable	Aboulghar *et al.* (2)	Ruiz *et al.* (3)	Jun *et al.* (4)	Khamsi *et al.* (5)
IVF				
No. cycles	22	70	103	35
No. failures	5	8	7	5
Percent	22.7	11.4	6.8	14.3
ICSI				
No. cycles	22	70	103	35
No. failures	0	0	0	1
Percent	0	0	0	2.9
Statistical significance	NR[a]	<0.01	NR	NR

[a] NR, Not reported.

without ICSI. This matter will have to be discussed with the couple in order to arrive at an informed consent.

In a laboratory where ICSI is performed for every IVF cycle, the general level of expertise and dexterity of the embryologists will improve. This is an additional benefit of performing ICSI on some of the oocytes of all patients. Are there subgroups of patients that may benefit from ICSI, that is, those with infertility of undetermined cause versus tubal disease? Aboulghar *et al.* (2) reported earlier that ICSI did not help patients with tubal disease. However, Khamsi *et al.* (5) had at least one patient with tubal cause who had no fertilization with standard IVF insemination (0/6) versus 50% (4/8) fertilization for sibling oocytes subjected to ICSI. The controlled studies of Khamsi *et al.* (5) are ongoing, and eventually an analysis could be made pertaining to patients with each cause of infertility.

Intracytoplasmic sperm injection may now have a role in IVF cycles offered to patients with non-male-factor infertility. Whether success with ICSI is related to abnormalities of spermatozoa or oocyte can only be the subject of speculation now, but this can be further investigated by more detailed examination of the spermatozoa and oocytes of the patients using techniques such as electron microscopy.

REFERENCES

1. Van Steirteghem AC, Nagy Z, Joris H, Liu J, Staessen C, Smitz J, Wisanto A, Devroey P: High fertilization and implantation rates after intracytoplasmic sperm injection. Hum Reprod 1993;8:1061–1066
2. Aboulghar MA, Mansour RT, Serour GI, Sattar MA, Amin YM: Intracytoplasmic sperm injection and conventional in vitro fertilization for sibling oocytes in cases of unexplained infertility and borderline semen. J Assist Reprod Genet 1996;13:38–42
3. Ruiz A, Remohi J, Minguez Y, Guanes PP, Simon C, Pellicer A: The role of in vitro fertilization and intracytoplasmic sperm injection in couples with unexplained infertility after failed intrauterine insemination. Fertil Steril 1997;68:171–173
4. Jun JH, Lim CK, Kim JW, Son IP, Koong MK, Song IO, Song JH, Yoo KJ, Kang IS: Comparison of fertilization and embryonic development between conventional insemination and ICSI treatment in the sibling oocytes of non-male factor infertility [abstract no. O-014]. Am Soc Reproduct Med 1999; 72(Suppl.1):S6
5. Khamsi F, Yavas Y, Roberge S, Wong J, Lacanna IC, The BL, Endman M: Intracytoplasmic sperm injection increased fertilization and good-quality embryo formation in patients with non-male indications for in vitro fertilization. A prospective randomized study. 2000; accepted, Fertil Steril
6. Boundelle M, Legein J, Buysse A, Van Assche E, Wisanto A, Devroey P: Prospective follow-up study of 432 children born after intracytoplasmic sperm injection. Hum Reprod 1996;11: 101–107
7. Schattman G, Rosenwaks Z, Berkely A: Congenital malformations in children born utilizing the assisted reproductive technologies. *In* Serono International Symposium on Genetics of Gametes and Embryos. New York, 1995, p 36