ICSI vs. IVF: the correct choice

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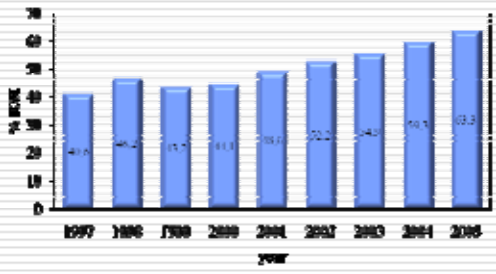
Developments preceding ICSI

- IVF - in vitro fertilization (Steptoe and Edvards, 1978) :
  - less efficient for severe male infertility.
- PZD-partial zona disection (Cohen et al., 1988),
- SUZI-subzonal insemination (Ng et al., 1988)
  - percentage of normal fertilization too low.
- ICSI-intracytoplasmatic sperm injection (Palermo et al., 1992)
  - fertilization was significantly better.

Development in the use of ICSI versus IVF in Europe (EIM 1997-2005)



IVF and ICSI cycles in European countries (EIM 2005)

	Number of cycles	% ICSI
France	55526	58.2
German	38380	70.3
Italy	33203	72.9
UK	31858	45.0
Spain	26739	83.4
Turkey	25577	97.2
Belgium	15185	75.0
The Nederland	14995	40.7
Russia	13842	34.3
Sweden	9865	49.0
Slovenia	2225	67.2

Trends in the use of intracytoplasmatic sperm injection marked variability between countries

Anders Nybo Andersen[1], Elisabeth Carlsen and Anne Loft

Possible reasons why the use of ICSI has increased:

- declining sperm quality
- declining tubal infertility
- advanced age
- indication non male factor infertility.

Differences in the use of ICSI between regions and countries:

- medical causes (IUI before ICSI)
- non-medical causes (re-imbursement system).

Intracytoplasmic sperm injection (ICSI) in 2006: Evidence and Evolution

The ESHRE Capri Workshop Group[1]

Table 1: Current indications for ICSI

- Ejaculated spermatozoa
  - Oligozoospermia
  - Asthenozoospermia (caveat for 100% immotile spermatozoa)
  - Teratozoospermia
  - (≤4% normal morphology by strict criteria—caveat for globozoospermia)
  - High titres of antisperm antibodies
  - Repeated fertilization failure after conventional IVF-ET
  - Autoconserved frozen sperm from cancer patients in remission
  - Ejaculatory disorders (eg, electro-ejaculation, retrograde ejaculation)
- Epididymal spermatozoa
- Testicular spermatozoa

Indication for ICSI- severe male infertility

Postwash total progressively motile sperm count:

<500.000 progresive motile spermatozoa (Devroy et al.,1998),

<1 milion progresive motile spermatozoa (Rhemrev et al.,2001).

Sperm morphology:

≤4% normal morphology by strict criteria (Coetzee at al., 1998).

Antisperm immunity:

high titres of antisperm antibodies (ESHRE Capri Workshop Group, 2006).

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Conventional in vitro fertilization versus intracytoplasmic sperm injection in patients with borderline semen: a randomized study using sibling oocytes

Lucette van der Westerlaken, M.Sc., Nico Naaktgeboren, Ph.D., Harjo Verburg, M.D., Sandra Dieben, M.D., and Frans M. Helmerhorst, Ph.D.

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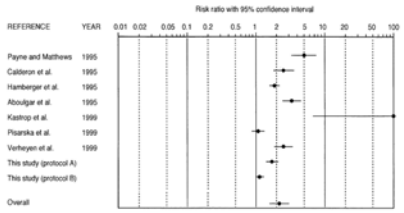
106 cycles and 1518 inseminated oocytes

	N	%
Fertilization after both IVF and ICSI	78	73
Fertilization after ICSI only	26	25
Fertilization failure IVF and ICSI	2	2

Conclusion(s): Performing ICSI on at least some of the oocytes will avoid unnecessary fertilization failure in patients with borderline semen.

Meta-analysis comparing fertilization in vitro after conventional IVF and ICSI in patients with moderate male subfertility

332 cycles and 4,199 inseminated oocytes



Tournaye. IVF vs. ICSI for male infertility. Fertil Steril 2002.

Meta-analysis comparing fertilization in vitro after conventional IVF and ICSI in patients with moderate male subfertility

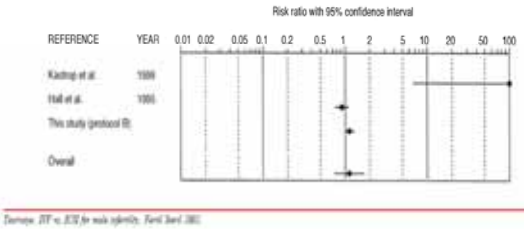
332 cycles and 4,199 inseminated oocytes

	IVF	ICSI	RR
Fertilization rate (%)	35.7	62.8	1.9 (1.4-2.5)
Fertilization failure (%)	33.7	3	7.5 (3-20)

The number of ICSI procedures required to avoid a complete fertilization failure after IVF (number needed to treat, NNT) was 3.1 (95% CI, 2–12)

Tournaye. IVF vs. ICSI for male infertility. Fertil Steril 2002.

Meta-analysis comparing fertilization in vitro after conventional IVF and ICSI in cycles in which ≥0.8 X 106/mL motile spermatozoa are used to inseminate the oocyte



Comparison of fertilization from sibling oocytes subjected to two protocols of conventional insemination (IVF) and ICSI i

73 cycles and 986 inseminated oocytes

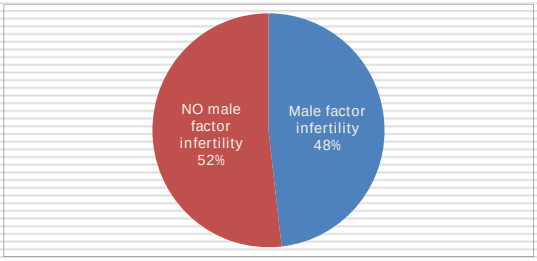
	Cycles (N)	Fertilization after IVF, n (%)	Fertilization after ICSI n (%)	Fertilization failure–IVF, n (%)	Fertilization failure–ICSI n (%)	Pregnancies (%)
Protocol A (5,000 sperm per oocyte)	35	37.4	64.3	25.7	0	42.8
Protocol B (20,000 sperm per oocyte)	38	59.6	67.6	5.3	0	42.1

High insemination concentration can improve fertilization after conventional IVF in cases with moderate male subfertility and may be an alternative to ICSI.

Tournaye. IVF vs. ICSI for male infertility. Fertil Steril 2002.

Proportion of ICSI cycles with diagnosis of male factor infertility (US - 2006 ART Report, CDC 2008)

99199 fresh-nondonor cycles, 62.2 % ICSI



ICSI for non-male inferility factors

- unexplained infertility
- fertilization failure after IVF
- poor responders
- advanced age
- all indications

Should ICSI be used in non-male factor infertility?

Yasser Orief et al., *Reproductive BioMedicine Online 2004*

ICSI has become increasingly popular, and is gradually being adopted for standard in-vitro insemination for non-male factor indications. This has arisen because of the increasing expectation from infertile couples of obtaining a successful pregnancy.

IVF can be bypassed by ICSI in order to reduce the incidence of fertilization failure in standard IVF, and this includes cases of defective sperm and normozoospermia.

Moreover, the removal of the cumulus cells provides the physicians with more direct feedback on the quality of their stimulation, giving the use of ICSI in patients with few or poor morphology oocytes a much higher chance of success.

In summary, both the safety and scientific viewpoints strongly support the use of ICSI for all indications and are confident that it will replace other methods.

Fertilization rate in sibling oocytes allocated to IVF or ICSI in non-male infertility factor

	N	Fertilization rate IVF (%)	Fertilization rate ICSI (%)	TFF IVF (%)	TFF ICSI (%)
Khamsi et al, 2001	35	57.2	71.3	11.4	2.9
Ruiz et al, 1997	70	54.0	60.4	11.4	0
Staessen et al, 1999	56	53.0	62.0	12.5	3.6
Hwang et al, 2005	60	44.8	72.3	15.0	0
Jaroudi et al, 2003	124	51.6	61.0	19.2	0.8
Hershlag et al, 2002	60	48.1	65.3	16.7	0
Aboulghar et al, 1996	22	50.7	63.0	22.7	0

Randomized controlled studies compared the efficacy of IVF vs. ICSI in couples with non-male infertility

	N	Fertilization rate (%)		Pregnancy rate (%)	
		IVF	ICSI	IVF	ICSI
Aboulghar et al., 1996	116	64.8	53.3	31.0	32.8
Bukulmez et al., 2000	76	67.3	69.3	21.5	21.5
Poehl et al., 2001	89			33.0	23.0
Bhattacharya et al., 2001	415	58	48	33.0	26.0
Foong et al., 2006),	60	77.2	82.4	50.0	50.0

ICSI versus conventional techniques for oocyte insemination during IVF in patients with non-male factor subfertility: a Cochrane review

M.M.E.van Rumste[1,3], J.L.H.Evers[1] and C.M.Farquhar[2]

[1]Department of Obstetrics and Gynaecology, Academic Hospital Maastricht, P. Debyelaan 25, Postbus 5800, 6202 AZ Maastricht, The Netherlands and [2]Department of Obstetrics and Gynaecology, National Women's Hospital, Claude Road, Epsom, Auckland, New Zealand

- Identified 15 controlled studies
- Only one study met the criteria of optimal study design
- Identified study showed no difference in pregnancy rates
- Concluded use of ICSI for non-male factor infertility remains an open question
- Further research should focus on live-birth rates and adverse events

Human Reproduction Vol.19, No.2 pp. 223–227, 2004

Articles

Conventional in-vitro fertilisation versus intracytoplasmic sperm injection for the treatment of non-male-factor infertility: a randomised controlled trial

S Bhattacharya, M P H Hamilton, M Shaaban, Y Khalaf, M Seddler, T Ghobara, P Braude, R Kennedy, A Rutherford, G Hartshorne, A Templeton

	IVF (n=206)	ICSI (n=209)	95% CI
Fertilisation rate (per oocyte retrieved)	58%	47%	8·5 to 14·5
Fertilisation rate (per oocyte inseminated/injected)	58%	65%	-10·0 to -4·0
Failed fertilisation	5%	2%	-0·3 to 7·5

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S Bhattacharya, M P H Hamilton, M Shaaban, Y Khalaf, M Seddler, T Ghobara, P Braude, R Kennedy, A Rutherford, G Hartshorne, A Templeton

	IVF (n=219)	ICSI (n=204)	RR (95% CI)
Implantation rate*	30%	22%	1·35 (1·04–1·76)
Clinical pregnancy rate	33%	26%	1·27 (0·95–1·72)
Multiple pregnancy rate	24%	30%	0·78 (0·43–1·40)

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S Bhattacharya, M P H Hamilton, M Shaaban, Y Khalaf, M Seddler, T Ghobara, P Braude, R Kennedy, A Rutherford, G Hartshorne, A Templeton

Subgroup analysis among 100 patients with unexplained infertility

	IVF (n=61)	ICSI (n=50)	RR (95% CI)
Fertilisation rate (per oocyte retrieved)	61%	50%	(5–17)
Fertilisation rate (per oocyte inseminated/injected)	61%	70%	(2–14)
Failed fertilisation	1.6%	0%	
Clinical pregnancy rate	32%	38%	0.83(0.48-1.45)

A prospective randomized trial of conventional in vitro fertilization versus intracytoplasmic sperm injection in unexplained infertility

	IVF (n=30)	ICSI (n=30)
Fertilization rate	77.2%	82.4%
Fertilization failure	6.7%	0%
Live birth rate	46.7%	50.0%

Foong et al., Journal of Assisted Reproduction and Genetics, Vol. 23, No. 3, March 2006

Intracytoplasmic sperm injection as a treatment for unexplained total fertilization failure or low fertilization after conventional in vitro fertilization

Lucette van der Westerlaken, M.Sc., Frans Helmerhorst, M.D., Ph.D., Sandra Dieben, M.D., and Nico Naaktgeboren, Ph.D.

Department of Reproductive Medicine, Leiden University Medical Center, Leiden, The Netherlands

	Previous IVF with TFF (N=24)	Previous IVF with low fertilization (N=17)
Fertilization rate IVF	29.3%	42%
Fertilization rate ICSI	55.6%	62%
Fertilization after ICSI only	66.7%	50%

Performing ICSI on at least part of the oocytes will avoid unnecessary total fertilization failure.

Fertility and Sterility® Vol. 83, No. 3, March 2005

Human Reproduction vol.13 no.8 pp.2126–2129, 1998

Intracytoplasmic sperm injection as a routine indication in low responder patients

Carlos Moreno[1], Amparo Ruiz[1], Carlos Simón[1,2], Antonio Pellicer[1,2] and José Remohí[1,2,3]

[1]Instituto Valenciano de Infertilidad (IVI), and [2]Department of Pediatrics, Obstetrics and Gynaecology, Valencia University School of Medicine, Valencia, Spain

	IVF (n=52)	ICSI (n=52)
Fertilization rate	58.8%	56.5%
Fertilization failure	11.5%	11.5%
Pregnancy rate/cycle	17.3%	21.1%

We conclude that the technique of fertilization is not related to the reproductive outcome of low responders, and the routine use of ICSI is not indicated.

Comparing intracytoplasmic sperm injection and in vitro fertilization in patients with single oocyte retrieval

Itai Gazhan, B.Sc.,[a] Alon Dor, B.Sc.,[b] Betty Farber, M.Sc.,[c] Dror Meirow, M.D.,[c] Shira Feinstein, M.D.,[c] and Jacob Levron M.D.[c]

[a]Miller School of Medicine, University of Miami, Miami, Florida; [b]Brandeis University, School of Arts and Sciences, Waltham, Massachusetts; and [c]IVF Unit, Division of Obstetrics and Gynecology, The Chaim Sheba Medical Center, Tel Hashomer, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

	patients ≤39 years old		patients >39 years old	
	IVF	ICSI	IVF	ICSI
Number	73	24	95	17
Fertilization rate (%)	67.1	75.0	68.4	82.4
Pregnancy rate (%)	8.2	0	1.1	0

Fertility and Sterility® Vol. 87, No. 3, March 2007

P-336 Poster ICSI vs IVF with normal semen: any advantage?

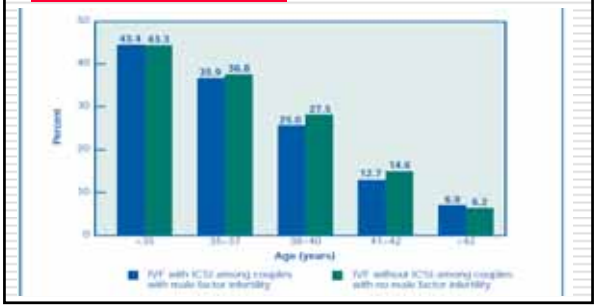
D. Barnabe[1], A.P. Ferraretti[1], C. Magli[1], E. Pescatori[1], G. Colpi[2], L. Gianaroli[1]
[1]S.I.S.Me.R. s.r.l., Reproductive Medicine Unit, Bologna, Italy, [2]ISES, Istituto per la Sterilità e Sessualità, Milano, Italy

Abstracts of the 24th Annual Meeting of the ESHRE, Barcelona, Spain, 7–9 July, 2008

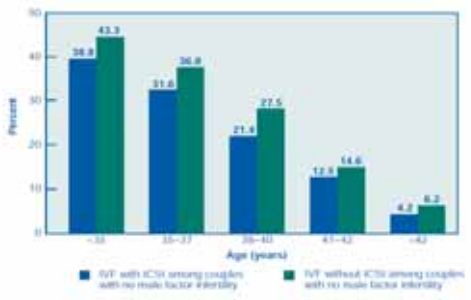
	IVF (n=141)	ICSI (n=81)
Fertilization rate	78.2%	75.6%
Fertilization failure	8.2%	11.1%
Pregnancy rate/ET	27.9%	20.3%
Delivery rate/cycle	21%	11%

When a limited number of eggs can be inseminated, the use of ICSI in the presence of normospermic samples did not increase the FR and PR.

Live births rates among couples diagnosed with male factor infertility who used IVF with ICSI, compared with couples not diagnosed with male factor infertility who used IVF without ICSI (US - 2006 ART Report, CDC 2008)



Percentages of retrievals that resulted in live births among couples not diagnosed with male factor infertility, by use of ICSI (US - 2006 ART Report, CDC 2008)



ICSI and safety

The risk of adverse perinatal outcome seems to be comparable to that of standard IVF (Kallen et al., 2005).

Two meta-analyses have demonstrated the same pattern for congenital malformations (Hansen et al., 2005; Lie et al., 2005),

ICSI pregnancies compared with IVF pregnancies had a higher rate of chromosomal abnormalities, even though the average maternal age was lower（Gjerris et al., 2008)

Studies are needed to clarify whether newborn and long-term health of ICSI offspring differ from typical births in the population, and if so, whether those differences are common to both IVF and ICSI (ESHRE Capri Workshop Group, 2007)

ICSI and cost

ICSI cycle in average costs 8.5 – 30% more than an IVF cycle (Kjellberg et al., 2006, Kovacs et al. 2004, Bouwmans et al., 2008).

Ola et al. (2001) found a cost difference of about £600 per fresh cycle between IVF and ICSI and estimated that £60 000 (cost needed to treat, CNT) would be needed to gain one additional live birth when ICSI was used for patients requiring IVF.

Total actual costs per started IVF and ICSI cycle were E 2381 and E 2578, respectively, but the costs per ongoing pregnancy were E446 less for ICSI compared with IVF (Bouwmans et al., 2008).

Good Clinical Treatment in Assisted Reproduction - *An ESHRE position paper*

eshre

EXECUTIVE SUMMARY June 2008

INTRACYTOPLASMIC SPERM INJECTIONS (ICSI)

ICSI should be considered in the presence of severe sperm abnormalities or a history of fertilisation failure in conventional IVF attempts. It must be emphasised that ICSI does not represent the most suitable treatment for female pathologies such as poor ovarian response or previous implantation failures.