What Is the Best Strategy for Using Embryos and Presenting Results in Assisted Reproductive Technology? A Strategy for Valid Comparisons of Results

Presentation of results is now an important facet of assisted reproductive technology (ART), for quality control, counseling of patients, research and development, accreditation of clinics, and establishment of national and international registers (1). Results can also have a financial impact on clinics, especially in countries such as the United Kingdom, where publication and public scrutiny of clinical results are requirements for accreditation by the Human Fertilization and Embryology Authority (HFEA), or in countries in which there is vigorous commercial competition between clinics.

An enormous number of factors influence ART results: cultural, financial, ethical, clinical, and administrative practices and clinical factors such as female age at treatment, etiology of infertility, ovarian stimulation regimes, patient history, previous treatment cycles, treatment modality, number of oocytes available for insemination, number of embryos transferred, and embryo selection (2–4). One cannot, and therefore should not, make comparisons of results unless equivalent data sets are being compared. The introduction of undue vari-

ance due to uncontrolled factors can skew the results and suggest differences that do not exist, and this in turn can lead to misinformation and unwarranted changes in clinical practice. For example, one should not compare in vitro fertilization (IVF) pregnancy rates for the United States, where it is common practice to transfer three, four, or five or more embryos, with those for other countries where only two embryos are routinely transferred, because the pregnancy rate is correlated with the number of embryos transferred (4).

Another perception that arises from invalid comparisons is that one form of treatment is more effective than another. A good example of this is intracytoplasmic sperm injection (ICSI). The high initial pregnancy rates achieved after the widespread introduction of ICSI (5–7) prompted some practitioners to speculate that we should inject all oocytes and abandon routine IVF insemination. This was short-sighted for several reasons, not least of which was that it completely ignored the issue of congenital abnormalities and the developmental outcome of children produced by ICSI (8) at a time

Table I. Selection Criteria Used to Control for Clinical Factors Known to Influence ART Pregnancy Rates Adversely

Control for	Selection criterion
Female age	<37 years at oocyte retrieval
Ovarian stimulation	Leuprolide + hMG ^a only
Repeated failure of implantation	Stimulated cycle No. 1 or 2
Poor ovarian response	≥6 mature oocytes recovered
Poor fertilization, oocyte defects	≥50% fertilization rate
Poor embryo development	≥1 embryo frozen
Number of embryos transferred	2 or 3 embryos transferred

^a Human menopausal gonadotropin.

when ICSI was still very much an experimental technique.

At the Reproductive Medicine Unit in Adelaide, we also recorded higher pregnancy rates per transfer with ICSI than IVF (35 versus 25%, respectively) after the routine introduction of ICSI in May 1993. Hence, we decided to compare critically IVF and ICSI results to determine whether the perceived difference was real or merely an artifact due to uncontrolled factors. While the two patient groups were not identical, strict cycle selection criteria were used to minimize the impact of uncontrolled clinical factors (other than etiology) and thereby essentially analyze the effect of one variable, mode of insemination.

IVF and ICSI cycles performed at the Reproductive Medicine Units at The Queen Elizabeth Hospital and Wakefield Clinic between May 1993 and April 1996 were analyzed to control for procedural changes over time. The cycle selection criteria listed in Table I were used to control for clinical

factors that are known to influence ART pregnancy rates adversely.

Of the 3387 IVF and ICSI cycles performed during the 3-year study period, 398 IVF cycles and 339 ICSI cycles met the cited selection criteria and were included in the analysis. The results are summarized in Table II. Some of the data were not normally distributed, so data sets were compared using the Mann-Whitney *U* test and Fisher's exact test, and *P* < 0.05 was considered significant.

There were no significant differences in the implantation rate per embryo transferred, clinical pregnancy rate, live birth rate, miscarriage rate, or biochemical pregnancy rate. This indicates that, once uncontrolled clinical factors have been excluded, there is no clinical advantage of ICSI over IVF as the mode of insemination and one should expect similar success rates and outcomes. This has also been demonstrated in a randomized, prospective controlled trial (9). This should not really come as any great surprise, because after all, ICSI is nothing more than another means of producing a fertilized oocyte. Why it should produce better clinical results has never been demonstrated.

The results also show that the use of ICSI is slightly less efficient and more wasteful of oocytes than routine IVF. There was a reduced number of oocytes inseminated by ICSI, despite higher numbers retrieved, and a reduced number of cryopreserved embryos after ICSI. Immature oocytes, destruction of oocytes during or after injection, and a slightly reduced fertilization rate all contribute to this wastage.

The best way to answer these questions, however, is to perform prospective, randomized controlled trials. This may be difficult to do, but clinics

Table II. Results for 398 IVF and 339 ICSI Cycles During the 3-Year Study Period^a

	IVF	ICSI	<i>P</i>
Number of cycles	398	339	—
Female age	31.5 ± 3.5	30.9 ± 3.5	0.026
Oocytes retrieved	13.6 ± 5.8	14.8 ± 6.4	0.01
Oocytes inseminated	13.5 ± 5.8	12.1 ± 5.3	0.0008
Fertilization rate per inseminated oocyte	80.3 ± 14.2	77.8 ± 14.2	0.011
Embryos transferred	2.5 ± 0.5	2.4 ± 0.5	ns
Embryos cryopreserved	4.8 ± 3.2	3.5 ± 2.6	<0.0001
Implantation rate per embryo transferred	17.8%	17.3%	ns
Clinical pregnancy rate	33.4%	32.2%	ns
Biochemical pregnancy rate	5.0%	0.9%	ns
Miscarriage rate	30.8%	22.9%	ns
Live birth rate	23.1%	24.8%	ns

^a Some values are expressed as mean ± SD. Biochemical pregnancies were assumed to be one implantation. ns, not significantly different.

should collaborate to perform these trials and put aside their competitive instincts. This enables a higher degree of objectivity and the results from similar trials can be combined for more powerful meta-analyses such as those undertaken by the Cochrane Collaboration (10,11).

At the very least we must compare apples with apples, and this can be done by eliminating uncontrolled variables so that only comparable sets of ART results are analyzed and compared. The selection criteria outlined above can be used to select a "gold standard" subset which can then be used as in this example, to compare treatment modalities, or for routine clinical and laboratory quality control. Furthermore, the outcome parameters outlined in Table II provide a range of important clinical and laboratory end points with which to evaluate treatment efficiency and outcomes. Pregnancy rates alone can be misleading and other parameters, especially implantation rate per embryo, should always be presented. An option is to include results from frozen-thawed embryos, which provides an indication of the outcome potential from one stimulated cycle of ART treatment.

ACKNOWLEDGMENTS

We would like to thank the staff of the Reproductive Medicine Units at The Queen Elizabeth Hospital and Wakefield Clinic, especially Barbara Godfrey.

REFERENCES

1. Lancaster PA: Registers of in-vitro fertilization and assisted conception. *Hum Reprod* 1996;11 (Suppl 4):89-104
2. Check JH, Lurie D, Callan C, Baker A, Benfer K: Comparison of the cumulative probability of pregnancy after in vitro fertilization-embryo transfer by infertility factor and age. *Fertil Steril* 1994;61:257-261
3. Giorgetti C, Terriou P, Auquier P, Hans E, Spach JL, Salzmann J, Roulier R: Embryo score to predict implantation after in-vitro fertilization: based on 957 single embryo transfers. *Hum Reprod* 1995;10:2427-2431
4. Roseboom TJ, Vermeiden JP, Schoute E, Lens JW, Schats R: The probability of pregnancy after embryo transfer is affected by the age of the patient, cause of infertility, number of embryos transferred and the average morphology score, as revealed by multiple logistic regression analysis. *Hum Reprod* 1995;10:3035-3041
5. 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
6. Palermo GD, Cohen J, Alikani M, Adler A, Rosenwaks Z: Intracytoplasmic sperm injection: A novel treatment for all forms of male factor infertility. *Fertil Steril* 1995;63:1231-1240
7. Payne D, Matthews CD: Intracytoplasmic sperm injection—Clinical results from the reproductive medicine unit, Adelaide. *Reprod Fert Dev* 1995;7:219-227
8. Bonduelle M, Wilikens A, Buysse A, Van-Assche E, Wisanto A, Devroey P, Van-Steirteghem AC, Liebaers I: Prospective follow-up study of 877 children born after intracytoplasmic sperm injection (ICSI), with ejaculated epididymal and testicular spermatozoa and after replacement of cryopreserved embryos obtained after ICSI. *Hum Reprod* 1996;11 (Suppl 4):131-55
9. Aboulghar MA, Mansour RT, Serour GI, Amin YM, Kamal A: Prospective controlled randomized study of in vitro fertilization versus intracytoplasmic sperm injection in the treatment of tubal factor infertility with normal semen parameters. *Fertil Steril* 1996;66:753-756
10. Bero L, Rennie D: The Cochrane Collaboration. Preparing, maintaining, and disseminating systematic reviews of the effects of health care. *JAMA* 1995;274:1935-1938
11. Hughes EG: Systematic literature review and meta-analysis. *Semin Reprod Endocrinol* 1996;14:161-169

Sean P. Flaherty

Dianna Payne

Robert J. Norman¹

Reproductive Medicine Unit
Department of Obstetrics and Gynaecology
The University of Adelaide
The Queen Elizabeth Hospital
Woodville, South Australia 5011

¹ To whom correspondence should be addressed.