SHORT COMMUNICATION

MELBOURNE, AUSTRALIA

Can dissenting findings regarding the comparative effectiveness of ICSI and IVF be explained by a learning curve?

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Purpose: To determine whether between-trial heterogeneity in relative risk of fertilisation for intracytoplasmic sperm injection (ICSI) compared to *in vitro* fertilisation (IVF) can be explained by learning or by between-trial variation in patient characteristics.

Methods: Systematic review and meta-analysis of trials comparing fertilisation outcomes for ICSI and IVF (without surgical sperm retrieval). Meta-regressions to identify associations between treatment effect and trial characteristics.

Results: Coefficients on individually significant covariates from the meta-regressions confirm that the ICSI versus IVF treatment effect is increased when patients are “unsuited for IVF” but reduced as semen quality improves and when IVF insemination concentrations are increased. However, the relative risk of fertilisation varies *inversely* with publication date; contrary to the hypothesised learning effect.

Conclusion: While it is recognised that publication date might proxy for unobserved covariates, the possibility of a learning effect in favour of ICSI is not supported by the meta-regression.

KEY WORDS: Health technology assessment; ICSI; IVF; meta-regression.

INTRODUCTION

Intracytoplasmic sperm injection (ICSI) is an assisted reproduction technique that involves injecting a single sperm into the cytoplasm of an oocyte. ICSI was developed to provide a new treatment option for couples with severe male factor infertility who could not be helped by conventional *in vitro* fertilisation (IVF). It has recently been suggested that conventional techniques, such as IVF, should be abandoned

and that ICSI should become the sole technique for treating infertility (1).

The safety, effectiveness and cost-effectiveness of ICSI (without surgical sperm retrieval) were evaluated by a team of researchers at Monash University. The purpose of the evaluation was to inform the Medical Services Advisory Committee (MSAC) of Australia in its decision to allocate public funding for new technologies. In evaluating the effectiveness of ICSI without surgical sperm retrieval, three patient groups were considered:

- “Unsuited for IVF”: patients with a near-zero probability of successful fertilisation using standard or modified IVF;
- “Subnormal semen”: infertile couples where the male partner has moderate to severe abnormalities on semen analysis but does not require surgical sperm retrieval; and
- “IVF failure”: infertile couples presenting after failure of standard IVF in at least one cycle (<30% fertilisation).

During the course of the review it was suggested that the between-trial heterogeneity in the ICSI versus IVF treatment effect might be attributable to a learning curve such that earlier trials were underestimating the steady-state treatment effect. The purpose of the current study is to determine whether between-trial heterogeneity with respect to relative risk of fertilisation for ICSI compared to IVF can be explained by a learning curve or by between-trial variation in patient characteristics. Only one trial reported valid comparisons with respect to either live births or clinical pregnancies (10), an insufficient sample size to permit a valid test of the learning curve hypothesis with respect to final outcomes.

METHODS

A systematic review and meta-analysis of fertilisation rates in controlled trials comparing ICSI and IVF (without surgical sperm retrieval) was performed. Potentially relevant studies to January 2003 were identified from a number of electronic databases including the Cochrane Database of Systematic Reviews (CDSR), CENTRAL and MEDLINE. An internet search of relevant websites and online databases was also undertaken. The search included the MeSH terms: Sperm injections, intracytoplasmic/and Infertility, male/and Ejaculation/and Fertilisation *in vitro*/as well as a

number of keywords including: intra?cytoplasm\$ and (sperm\$ adj inject\$) and (Infertil\$ adj male).

Primary experimental studies and systematic reviews that compared ICSI (without surgical sperm retrieval) and an appropriate existing practice comparator in one of the three relevant patient groups were eligible for inclusion in the review. For couples unsuited for IVF and who may have been treated in the past via subzonal insemination (SUZI) or partial zona dissection (PZD), "no treatment" was identified as the appropriate existing practice comparator. Conventional IVF was identified as the appropriate existing practice comparator in patients for whom IVF offers a non-zero probability of fertilisation. Comparisons against high insemination concentration *in vitro* fertilisation (HIC IVF) were also included to test the hypothesis that variation in IVF fertilisation rates was due to variation in IVF insemination concentration. The outcome of interest was singleton live-births at full-term but evidence regarding rates of fertilisation, implantation/pregnancy, miscarriage and congenital malformation was also reviewed.

Influence analysis was performed to determine whether the pooled relative risk was significantly different after deletion of selected trials. Trials were then categorised according to various trial charac-

teristics including the *maximum* IVF insemination concentration used and/or permitted in the trial, the minimum percentage of motile sperm observed in male-partners admitted to the trial, the maximum percentage of sperm with normal morphology observed in male-partners admitted to the trial and publication date for the trial. Missing values for these trial characteristics were replaced for minimum percentage motile sperm (missing: 0%), maximum percentage normal morphology (missing: 30%: WHO Threshold for "normal") and maximum IVF insemination concentration (missing: standard IVF = 0.15, HIC IVF = 1.0). A set of dichotomous variables was also created to denote the patient group in which the trial was conducted: "unsuited for IVF indication," "subnormal semen indication" and "mixed indication." Finally, a series of meta-regressions was performed to identify associations between estimates of treatment effect and trial characteristics.

RESULTS

Two systematic reviews and 21 primary studies met the eligibility criteria and were appraised to determine the relative effectiveness of ICSI compared

Table I. Fixed and Random Effects Meta-Analyses for RR of Per Oocyte Fertilisation^{a, b}

Study	RR	95% CI	Weights	
			Fixed	Random
Payne-94 (2)	4.98	3.89, 6.37	63.32	5.02
Fishel-95_GrpA (3)	1.58	1.17, 2.11	44.36	4.85
Aboulghar-95 (4)	3.32	2.80, 3.95	129.52	5.23
Hamberger-95 (5)	1.85	1.62, 2.11	220.87	5.32
Calderon-95_Grp1&2 (6)	2.53	2.02, 3.19	73.10	5.07
Hall-95 (7)	0.87	0.70, 1.09	82.43	5.11
Fishel-95_GrpA (3)	0.94	0.67, 1.32	33.60	4.69
Aboulghar-96a_Grp2 (8)	1.72	1.35, 2.21	63.59	5.02
Pisarka-99_GrpB (9)	1.38	1.11, 1.72	79.67	5.10
Kastrop-99 (10)	107	1.79, 6390	0.23	0.22
Verheyen-99 (11)	2.44	1.94, 3.07	73.15	5.07
Pisarka-99_GrpA (9)	1.06	0.86, 1.32	82.15	5.11
Fishel-00_Grp5 (12)	1.93	1.50, 2.48	60.91	5.00
Griffiths-00_S2 (13)	0.87	0.68, 1.12	61.64	5.01
Fishel-00_Grp1 (12)	1.80	1.50, 2.16	114.85	5.20
Plachot-02_Main (14)	1.44	1.23, 1.68	163.17	5.27
Tournaye-02_PrtB (15)	1.13	0.98, 1.31	174.75	5.29
Plachot-02_SubGrp (14)	0.99	0.82, 1.18	121.80	5.22
Tournaye-02_PrtA (15)	1.72	1.45, 2.02	140.94	5.25
Hershlag-02_Grp2 (16)	1.03	0.90, 1.17	234.96	5.33
M-H pooled RR	1.53	0.47, 1.60	Test of RR = 1: $z > 4.556$ $p = 0.000$	
R-E pooled RR	1.59	1.30, 1.94		

^aTest for heterogeneity: $Q = 364.466$ on 19 df ($p = 0.000$).

^bMoment-based estimate of between studies variance = 0.183.

Table II. Random Effects Meta-Regression for RR of Per Oocyte Fertilisation

	Coef	SEM	$p > z $	95% CI
Max IVF insemination concentration	-0.2897	0.25	0.256	-0.79, 0.21
Max percent normal morphology	0.0032	0.00	0.329	-0.00, 0.01
Publication date	-0.1000	0.03	0.002	-0.16, -0.04
Mixed indication	-0.5036	0.25	0.043	-0.99, -0.02
Unsuited for IVF indication	6.9699	3.25	0.032	0.60, 13.34
Constant	200.4957	63.31	0.002	76.4, 324.6

to existing practice. Table I summarises the fixed and random effects meta-analyses for trials reporting the rate of 2PN zygotes per oocyte. One trial reported a relative risk of per oocyte fertilisation equal to 107 (95% CI: 1.79, 6390) (10) but this was considered an outlier. The relative risk of per oocyte fertilisation in remaining trials varied from 0.87 (95% CI: 0.70, 1.09) (7) to 4.98 (95% CI: 3.89, 6.37) (2). Tests for heterogeneity suggested that different trials drew samples from different underlying distributions of treatment effect ($Q = 364.466$, $df = 19$, $p = 0.000$). The influence analysis confirmed that the pooled relative risk was significantly different after excluding selected trials (4, 16).

Table II summarises results from the random effects meta-regression. Residual heterogeneity was minimised ($\tau^2 = 0.1347$) after adjusting for the covariates: Publication date, maximum IVF insemination concentration, maximum percentage normal morphology, “unsuited for IVF indication” (denoting the outlier) and “mixed indication.” The covariates publication date ($p = 0.002$), “mixed indication” ($p = 0.043$) and “unsuited for IVF indication” ($p = 0.032$) were individually significant in explaining between-trial variation in the relative risk of per oocyte fertilisation. The coefficients on individually significant covariates suggest that relative risk of per oocyte fertilisation (ICSI versus IVF) varies inversely with publication date and is lower for “mixed indication” trials and higher for “unsuited for IVF indication” trials.

DISCUSSION AND CONCLUSION

Results from the meta-regression confirm the importance of careful subgroup analysis in rationing public funding for new technologies. The relative

value ICSI and IVF for assisted fertilisation depends on the characteristics of each technology and of the target population. While it is recognised that publication date might proxy for any number of unobserved variables, there is no evidence to suggest that between-study variation in treatment effect can be explained by a lack of experience with ICSI in earlier trials. In fact, treatment effect is *inversely* related to publication date such that results from earlier trials tend to favour ICSI and results from more recent trials tend to favour IVF. The possibility of a learning effect in favour of ICSI is therefore not supported by the meta-regression.

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