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DEBATE—continued

Should ICSI be the treatment of choice for all cases of in-vitro conception?

Considerations of fertilization and embryo development, cost effectiveness and safety

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There is now considerable discussion whether intracytoplasmic sperm injection (ICSI) should be used in all cases of IVF. A critical and balanced view of the current literature is presented. The difficult question is how to identify men with apparently normal semen who are likely to fail to achieve a pregnancy using IVF. In conclusion, from both the safety and scientific viewpoint, ICSI should only be used in cases where success at IVF is regarded as unlikely.

Key words: budget impact analysis/cost needed to treat/fertilization failure/intracytoplasmic sperm injection (ICSI)/number needed to treat

Introduction

The indication to perform intracytoplasmic sperm injection (ICSI) in the earlier days was male factor infertility. Today, this have been expanded to include fertilization failure after conventional IVF (Kastrop *et al.*, 1999; Fishel *et al.*, 2000), ejaculatory dysfunction, immunological infertility and treatment for cancer patients who have had chemo/radiotherapy (Naysmith *et al.,* 1998; Horne *et al.*, 2001). Conventional IVF on the other hand is performed in cases of tubal disease, anovulation, unexplained infertility, and previous failed treatment by other methods. The insemination concentration is usually about 50 000 motile spermatozoa per oocyte. However, there are reports of the use of much higher insemination concentrations (HIC) in selected groups of patients to avoid the use of ICSI (Kastrop *et al.,* 1999; Fishel *et al.,* 2000). In contrast to ICSI, IVF preserves the natural selection of spermatozoa, which occurs at the sperm–oocyte interface during penetration of the oocyte vestments.

Recent data from Fishel and colleagues have examined the concept that ICSI should be offered to all patients needing IVF because of the significantly higher fertilization rate (Fishel *et al.,* 2000). ICSI has become more developed as a technique and popularized to a stage of routine laboratory service. For example, in the UK the Human Fertilisation and Embryology Authority (HFEA) reported a 14% rise in the use of ICSI in 1998/1999 compared with the previous year. Almost half of fresh embryo transfers (median 47% range 16–74%) in this period were a result of ICSI treatment (Human Fertilisation and Embryology Authority, 2000). This is consistent with data from the European register where 43% of the transfers were from ICSI (EIM/ESHRE, 2001). Clearly, the use of ICSI is rising throughout the world and in some clinics it is the exclusive treatment of choice. Therefore, the issue of whether to use ICSI for all in-vitro inseminations needs to be critically discussed.

In this debate, we examine the arguments for and against the use of ICSI in cases where IVF would normally be used (non male-factor infertility). The issues discussed are fertilization rate, total failure of fertilization, embryo damage/blastocyst formation, cost effectiveness and safety.

Fertilization rate as a measure of effectiveness

One group has performed a randomized, prospective, multicentred trial using sibling metaphase II oocytes in 221 patients to try to address the question of whether ICSI should be advocated for all couples (Fishel *et al.,* 2000). The patients were divided into five groups. These included: Group 1 (37 patients): idiopathic previous failed IVF, where HIC was compared with ICSI using the partners' spermatozoa; Group 2 (18 patients): idiopathic previous failed IVF with HIC, where conventional IVF was compared with ICSI using donor spermatozoa; Group 3 (36 patients): patients unsuitable for conventional IVF (male infertility), where IVF using donor spermatozoa was compared with ICSI using partner's spermatozoa; Groups 4 and 5 had metaphase II oocytes that had failed to fertilize by IVF and were re-inseminated by either HIC or ICSI. The clinical bottom line for groups 2 and 3 was that conventional IVF had a fertilization rate of 65.4% and ICSI 75.6%, with an absolute treatment effect of 0.102 [95% confidence interval (CI) 0.025–0.179], generating a number needed to treat (NNT) of 10 (95% CI 6–40). The NNT is the number of sibling MII oocytes that need to be inseminated by ICSI to derive one additional zygote, compared with IVF. Although this figure is statistically significant, in clinical terms it means that, in this group of patients where normal spermatozoa were used in IVF, for every 10 sibling MII oocytes inseminated by ICSI, only one extra zygote is produced compared with insemination by conventional IVF.

In other studies, a lack of significant difference has been demonstrated in the fertilization rates obtained with ICSI and

IVF in patients with non-male factor infertility (61 versus 67%) (Yang *et al.*, 1996) and unexplained infertility (60.4 versus 54%) (Ruiz *et al.*, 1997). Nevertheless, we need to be cautious in the interpretation of the results presented by some of these studies, as for example, at the design stage, power and sample size statistics were often not sufficiently emphasized, thereby exposing the results to possible random errors (Fishel *et al.,* 2000). In addition to this, some studies (Ruiz *et al.*, 1997) are not randomized controlled trials. Closer scrutiny often shows that the only control possible due to ethical considerations was the use of sibling metaphase II (MII) oocytes. Often, in these studies, no explicit descriptions were made of what happened to oocytes allocated to ICSI, but found not to be MII after denudation (i.e. was intention-to-treat analysis performed?), or how investigators who randomized and performed in-vitro inseminations were blinded to embryo grading. These potential sources of error may serve to reduce the strength of evidence presented by the authors (NHS Centre for Reviews and Dissemination, 1999). The implication is that often, what is presented as level Ib evidence in favour of ICSI (or in fact against) may, on critical appraisal, be found to be no better than level II or III. Therefore, larger carefully conducted studies are required on non male-factor patients to confidently address the question whether ICSI does result in significantly higher fertilization rates (and embryo development) in men with apparently normal semen.

Fertilization rate: an interim outcome measure

The use of fertilization rate instead of total failure of fertilization, or indeed clinical pregnancy rate as an outcome event has drawbacks. Fertilization rate is an interim outcome measure in an IVF programme, which may have little effect on the final outcome of a fresh cycle or that of a subsequent frozen embryo transfer. It is therefore difficult to judge whether or not to advocate ICSI over IVF based on fertilization rate alone. To illustrate the point, imagine a scenario with a mean recovery of 10 MII oocytes, fertilization rate of 65% from IVF, and 75% from ICSI. In the UK, a maximum of three embryos can be replaced in a treatment cycle. Frozen embryo–thaw success rates of 81–90% for IVF and 88–91% for ICSI have been described in prospective randomized studies (Damario *et al.*, 1999; Hu *et al.*, 1999). Consequently, this would allow approximately the same number of frozen embryo transfer cycles for IVF or ICSI. It would therefore seem apparent that, if decision analysis was performed based on the above scenario, an improved fertilization rate alone might not be enough to advocate ICSI over IVF per cycle of treatment.

Total failure of fertilization

From the clinician and patients' points of view, the rate of total failure of fertilization is a more useful outcome measure than fertilization rate. ICSI has an advantage, which in the UK is in the form of an HFEA regulation, requiring that only MII oocytes, assessed after cleaning the oocyte–cumulus–complex, be injected. There is a prescribed oocyte quality and therefore a time limit to when insemination has to be accomplished during ICSI. For conventional IVF however, metaphase I (MI), MII, or luteinized post-maturity oocytes can be used.

Several studies have attempted to demonstrate a superiority of ICSI over IVF based on failed fertilization rates. For example, in a controlled study of 70 couples with either unexplained infertility or endometriosis who had failed to respond to intrauterine insemination, Ruiz and his colleagues, (Ruiz *et al.,* 1997), found a clear benefit of ICSI over IVF (failed fertilization rates of 0 versus 11%) despite the lack of significant difference in the fertilization rates between the two methods (60.4 versus 54%). In this study, whereas metaphase II oocytes were used for ICSI, this was not the case for the IVF group, thus exposing the results to bias. In another example, an 'auto-controlled' study of 662 sibling MII oocytes from patients with tubal disease and normozoospermic partners, found rates of total failure of fertilization of 3.6% (95% CI = 0.4 to 12.3) for ICSI and 12.5% (95% CI = 5.2–24.1) for IVF (Staessen *et al.*, 1999). This would appear to present a real difference, although the small sample size may have introduced type II error. These potential sources of error may have served to reduce the strength of evidence presented by the authors, and when considered may mean that the superiority described in favour of ICSI over conventional IVF may be a chance occurrence.

However, whilst scientific rigour indicates that the above studies have potential errors it does look as though ICSI may be of benefit in cases of fertilization failure with conventional IVF that can be predicted before treatment. Data from Liu and Baker illustrate this point (Liu and Baker, 2000). They have reported on 160 patients who have apparently normal semen but either fail to bind to the zona pellucida (ZP) or do not acrosome react (AR) in response to the ZP (disordered ZP-induced AR) and thus fail to have successful IVF conceptions. They estimate that, in their patient population, up to a third of normozoospermic men have disordered ZP-induced AR. Interestingly, ICSI was found to overcome these defects resulting in live births (Liu and Baker, 2000).

In contrast, in our clinic, which is a tertiary referral centre, we do not see a high incidence of fertilization failure with IVF. The total failed fertilization rate for treatments between January 1999 and July 2000 was 1.5% (95% CI 0.04–3.8) for ICSI and 2.1% (95% CI 1.0–3.8) for IVF (Table I). Our data suggest that improved but flexible clinical and laboratory protocols can reduce the incidence of total failure of fertilization, although it is possible that in our centre we do not have a high incidence of normozoospermic men with dysfunctional spermatozoa (see Liu and Baker above) which may account for our low incidence of failed fertilization.

Embryo damage and blastocyst formation

ICSI is associated with reduced blastocyst formation (Shoukir *et al.,* 1998; Dumoulin *et al.*, 2000; Griffiths *et al.,* 2000) and a higher miscarriage rate (Aytoz *et al.,* 1999). These negative influences on development have primarily been attributed to the poor quality of injected spermatozoa. There is no doubt that the spermatozoa used for ICSI have higher levels of defects which are likely to have an adverse effect on embryo development e.g. higher levels of DNA damage (Sakkas *et al.*,

Table I. Comparisons between ICSI and IVF: January 1999–July 2000 at the Assisted Conception Clinic, Birmingham Women's Hospital, UK

	*ICSI (271 fresh cycles)	*IVF (478 fresh cycles)
Number of oocytes recovered (mean ± SD)	13.7 ± 9.8	14.2 ± 9.4
Number of normally fertilized oocytes (mean ± SD)	6.5 ± 5.2	7.7 ± 5.7
[b]Total failed fertilization rates (% and 95% CI)	1.5 (0.04–3.8)	2.1 (1.0–3.8)
Clinical pregnancy rates (% and 95% CI)	30.6 (25.2–36.5)	28.2 (24.2–32.5)

*In 271 ICSI patients, the injected spermatozoa were prepared from fresh ejaculates in 83.2%, fresh surgical sperm retrievals (SSR) in 6.5%, frozen SSR in 9.2% and from donated samples in 1.1%.
[a]The female patients in each group were similar for age, down-regulation, super-ovulation and luteal support protocols. Mean and median numbers of recovered and fertilized oocytes were similar.
[b]Two patients who underwent IVF and had total failed fertilization due to sperm infection were not included.
CI = confidence interval.
ICSI = intracytoplasmic sperm injection.

Table II. Cost analysis comparing cost benefit and cost effectiveness of ICSI with IVF using HFEA 1998–1999 UK national data

	[a]HFEA live birth rates (Cost per pregnancy)	[b]Cost benefit
ICSI (average cost of £2700 per cycle)	22.6%	£11 946.90
IVF (average cost of £2100 per cycle)	21.6%	£9 722.22
ATE = 0.22–0.21	0.01	
NNT to gain an extra pregnancy if ICSI was preferred to IVF (NNT = 1/ATE)	100	
[α]Cost needed to gain an *extra* pregnancy if ICSI preferred to IVF [CNT = (£2700–£2100) ×NNT]	£60 000	
[χ]Budget impact analysis (BIA)	29	

[a]HFEA live birth rates are derived from published UK national statistic based on 18 042 ICSI and 27 616 IVF fresh cycles of treatment in which embryos were transferred.
[b]It costs approximately £2000 more per pregnancy by ICSI.
[c]It will cost £60 000 for every *extra* pregnancy gained if ICSI were preferred to IVF.
[d]BIA defines the number of cycles of conventional IVF that the CNT would have funded i.e. £60 000/£2100.
ATE = absolute treatment effect.
CNT = cost needed to treat.
ICSI = intracytoplasmic sperm injection.
NNT = number needed to treat.

1999) and increased levels of aneuploidy (Bernardini *et al.*, 1997). However, the technique itself may have a negative effect on development. This was illustrated by Griffiths and colleagues who showed a significantly lower ($P < 0.01$) development to the blastocyst stage in ICSI compared with IVF when semen from the same semen samples was used for each technique (Griffiths *et al.*, 2000). Perhaps this is not surprising as apart from the physical damage that may occur during and/or after injection (Dumoulin *et al.*, 2001), there are clear differences in the synchrony of fertilization events in ICSI compared with IVF e.g. changes in the pattern of Ca^{2+} induced transients (Tesarik, 1998) and decondensation of the spermatozoon which may specifically lead to abnormal development. For example, in both rhesus monkeys (Hewitson *et al.*, 1999) and humans (Bourgain *et al.*, 1998; Terada *et al.*, 2000) there is atypical decondensation of the nucleus and delayed replication of the male genome. In addition, the non-random positioning of the chromosomes in the nucleus, combined with the atypical nuclear decondensation, may lead to higher levels of aneuploidy (Luetjens *et al.,* 1999; Terada *et al.*, 2000). Thus, the ICSI procedure itself may make a contribution to the poorer embryo development in ICSI embryos as compared with IVF. Clearly, more comprehensive studies are required to address this specific issue. These must include, where possible, follow up data including conception rates, as one randomized controlled study which compared ICSI with IVF in non male-factor cases concluded that implantation and pregnancy rates were not different (Aboulghar *et al.*, 1996).

Economic analysis based on live birth rates

In the reporting period between 1998 and 1999, the HFEA showed an overall live birth rate per fresh treatment cycle for ICSI of 22.6% (4082/18042) significantly higher ($P = 0.01$) than the rate of 21.6% (5969/27617) for IVF.

However, ICSI is substantially more expensive than IVF. In our clinic, as in many parts of the UK, the cost difference is about £600 per fresh cycle completed (Philips *et al.*, 2000). In the UK 25% of treatments are funded by the National Health Service (NHS) (Kerr *et al.*, 1999). We suggest that recommending the use of ICSI for all those needing IVF is unlikely to be considered a judicious use of scarce resources.

Table III. Live birth rate (LBR) depending on fertilization rate and number of embryos available for transfer with conventional IVF in comparison with ICSI

	Fertilization rate			
	IVF			ICSI[c]
	<25%	<40%	⩾50%	70%
No. embryos available for transfer	2	3	⩾4	⩾4
LBR per treatment cycle started[a] (%)	14.3	20	28	28
No. embryos available for cryopreservation	0	0	⩾2	⩾2
LBR from frozen transfer per embryo transfer[b] (%)	0	0	6[(1)] 12[(2)]	6[(1)] 12[(2)]

Live birth rates (LBR) estimated using Human Fertilisation and Embryology Authority UK national database (Human Fertilisation and Embryology Authority, 2000). Assuming 10 oocytes recovered.
[a]Estimates of LBR per treatment cycle started calculated from published data (Templeton and Morris, 1998) i.e. odds ratio of birth of 0.5 if two oocytes fertilized and two embryos available [14.3% LBR; 0.7 if three or four oocytes fertilized and three embryos available (20% LBR)]. LBR taken as 28.6% when more than four embryos were created from fresh stimulated IVF and two embryos replaced (Human Fertilisation and Embryology Authority, 2000). It was assumed for 20% LBR at <40% fertilization rate that three embryos would be replaced as this provides a greater chance of a live birth compared to two embryos replaced.
[b]Specific data on frozen embryo transfers are not available for number of embryos transferred. The average LBR/embryo transfer from frozen embryo transfer is 13.4% (ICSI and IVF—where up to three embryos could be transferred). Data in the HFEA report show the overall LBR from one, two and three embryos replaced (fresh and frozen) as 8% for one embryo and 22% for two or three embryos. We would assume at least a 50% reduction in the LBR if only one frozen embryo was replaced compared to two. Thus we have taken a figure of 6% LBR for one embryo and 12% for two embryos.
[c]We have assumed that ICSI would result in ~70% fertilization rate in these patients (Fishel *et al.*, 2000; see also text).
[(1)]one embryo transferred; [(2)]two embryos transferred.

To illustrate this, we used the HFEA 1998/99 data, assuming that the advantage of ICSI was sustained even when performed on the population of couples who would have had IVF for female or unexplained factors. We used the data comparing live birth rates per fresh cycle to derive the absolute treatment effect (ATE = 0.01), and NNT (NNT = 100) (see Table II). Cost benefit analyses show that each live birth produced by ICSI costs £2000 extra. The main cost implication however is the incremental cost effectiveness or cost needed to treat (CNT). This shows that £60 000 will be needed to gain one *additional* live birth when ICSI is advocated for all patients requiring IVF. Budget impact analysis (BIA) shows that CNT (£60 000) can treat an extra 29 cycles of conventional IVF.

Safety

Several reports suggests that our initial fears about an increased incidence of major congenital malformations and possible imprinting disorders in the offspring following ICSI are unfounded (Bonduelle *et al.,* 1999; Loft *et al.,* 1999; Manning *et al.*, 2000; Wennerholm *et al.,* 2000). However, it is important to remember that we still do not know the long-term effects of the ICSI procedure and that many of the putative follow-up studies contain insufficient numbers of patients and often have a relatively high incidence of patients lost to follow up (Hawkins and Barratt, 1999; Hawkins *et al.*, 1999). Clearly more comprehensive, long-term and possibly national studies are necessary.

It is probable that the increases in congenital abnormalities observed in some ICSI children, such as sex chromosome abnormalities, are due to the use of sub-optimal male gametes. However, the technique itself may play a role in the formation of these abnormalities. In addition, there is experimental evidence that provides caution against the widespread use of ICSI, for example, the incorporation of exogenous DNA into spermatozoa and subsequent transmission to the offspring (Perry *et al.*, 1999; Chan *et al.,* 2000). Experiments in mice have shown an enhancement of a genetic defect (sperm morphology) through ICSI (Akutsu *et al.*, 2001). The incorporation of foreign DNA combined with the possible enhancement of defects by bypassing the natural selection mechanisms now needs rigorous experimentation in the human.

The difficult question

The arguments above do not support the routine use of ICSI in all IVF treatments. However, there is a clear group of patients, e.g. those with normal but dysfunctional spermatozoa, that have zero or significantly reduced fertilization success at IVF (Barratt and Publicover, 2001). Such patients can be successfully treated by ICSI. Whilst it is possible, using sophisticated sperm function assays such as zona binding, to predict which men may have reduced success at IVF, such assays are impossible to use on a routine basis (Whitmarsh *et al.,* 1996). The question that all clinics therefore face is: at what IVF fertilization rate does ICSI become a more effective treatment than IVF? The answer is not clear-cut. We have attempted to address this by using the HFEA data (Templeton and Morris, 1998; Human Fertilisation and Embryology Authority, 2000). Table III illustrates three scenarios where the IVF fertilization rate and number of embryos created, which have significant effects on live birth rate (LBR) varies.

In these examples an IVF fertilization rate of <40% would only result in a maximum 20% LBR with no embryos available for freezing. Thus, the use of ICSI will result in a significantly higher LBR per fresh cycle and allow the possibility of 2–3 embryos for transfer in a subsequent cycle. Under such circumstances, it would be better to advise ICSI. However, the situation becomes less obvious when the fertilization rate is ⩾50% as the LBR for fresh transfers are comparable with ICSI (28%) and, depending on the exact fertilization rate, a number of embryos are available for freezing. Of course, in these examples we have assumed that the spermatozoa look normal but are defective thus, embryos and pregnancies can be achieved by ICSI whereas conventional IVF would have been unsuccessful (Liu and Baker, 2000). This is not always the case and our examples in Table III only apply to such cases where ICSI can circumnavigate the use of defective male gametes.

Conclusion

Using the currently available clinical, scientific and economic data, there appears to be no advantage to using ICSI instead of IVF for all patients requiring IVF. However, there are some situations where ICSI may be of benefit. These are generally where there is fertilization failure or significantly reduced fertilization success (see Table III). In clinics where these two factors are prominent, and cannot be corrected by other means, then the use of ICSI represents an effective tool. However, the real challenge is to identify, prospectively, which cases (men) are likely to give poor success at IVF.

In summary, from both the safety and scientific viewpoints, ICSI should only be used in cases where success at IVF is regarded as unlikely.

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Note added at proof

After completion of this manuscript Bhattacharya and colleagues reported on a trial comparing ICSI and IVF in non-male factor and mild male factor infertility. Although live birth rates were not reported, implantation rates were similar between the two groups (Battacharya *et al*., 2001).

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