

## Review

# Should ICSI be used in non-male factor infertility?



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## Abstract

There is general agreement that intracytoplasmic sperm injection (ICSI) should be used in male factor infertility cases, such as oligoastheno-teratozoospermia, presence of anti-sperm antibodies, or azoospermia, these cases being diagnosed through abnormal semen analysis. There are no randomized clinical trials comparing ICSI with IVF (or other interventions) where semen quality is so poor that IVF would not achieve fertilization. It is accepted that ICSI is the only treatment option in those circumstances. The role of ICSI where IVF can be expected to give a reasonable fertilization rate is the question that needs to be answered. The argument is whether or not ICSI should be used for all cases of infertility. This paper proposes and strongly supports the use of ICSI for all indications. Considerations of fertilization and embryo development, cost effectiveness and safety will be clearly discussed.

**Keywords:** assisted conception, ICSI, infertility, IVF

## Introduction

IVF was initially developed for female infertility due to tubal disease. Using this technique, fewer spermatozoa are required to obtain oocyte fertilization than with natural intercourse or intrauterine insemination. This feature of IVF has made it an attractive option even in male factor patients in whom surgical or pharmacological therapy has failed or is inapplicable. However, conventional IVF is not very successful in the presence of compromised semen parameters. In these cases, high insemination concentration (HIC) has been shown to be beneficial (Baker *et al.*, 1993; Fishel *et al.*, 1993; Tucker *et al.*, 1993).

Currently, several male factor abnormalities, including varying degrees of oligozoospermia, asthenozoospermia, oligoasthenozoospermia and teratozoospermia, are best treated by intracytoplasmic sperm injection (ICSI).

ICSI, with its high fertilization and pregnancy rates, has gradually replaced conventional IVF and other types of

micromanipulation as first-line therapy in couples with severe male factor infertility. Since the report of the first human pregnancies achieved by the injection of a single spermatozoon into a human oocyte (Palermo *et al.*, 1992), this technique has been applied extensively world-wide. ICSI ensures high fertilization and pregnancy rates regardless of sperm concentration, motility or morphology, even when epididymal or testicular spermatozoa are used (Devroey *et al.*, 1994; Nagy *et al.*, 1995; Silber, 1995), with the resultant extension of this technique to patients for whom conventional IVF may be an option, including infertile partners with unexplained infertility (Aboulghar *et al.*, 1996a).

Considering the high success rate of ICSI, it is reasonable to consider this technique for all cases requiring in-vitro conception, with a limitation for some cases of female infertility but specifically taking into consideration the age of the woman (Oehninger *et al.*, 1995), and notwithstanding cost and the need for qualified laboratory personnel and facilities (Yang *et al.*, 1996).

In contrast, some authorities advocate the use of ICSI only when previous fertilization failure with IVF has occurred, or the number and/or quality of available spermatozoa is not appropriate for IVF; others have expressed the view that the main aim should always be to use the simplest and least expensive procedure, with the greatest long-term chance of healthy children (Baker *et al.*, 1993; Tucker *et al.*, 1993).

Previous studies comparing IVF and ICSI have given inconsistent results. Due to the use of different insemination concentrations, divergent rates of fertilization were demonstrated after IVF. Although the rates of fertilization observed with ICSI were significantly higher (Payne *et al.*, 1994; Calderon *et al.*, 1995; Aboulghar *et al.*, 1996a,b), it was reported in one study (Hall *et al.*, 1995) that there was no significant difference in implantation and pregnancy rates between ICSI and IVF with high insemination concentrations.

ICSI has become more developed as a technique and popularized to the stage of routine laboratory service. For example, in the UK, the Human Fertilization 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 Fertilization 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.

This review examines 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, safety and potential risks and cost effectiveness.

## Fertilization rate as a measure of effectiveness

In standard IVF, complete failure of fertilization occurs in 10–15% of treatments. Although the causes may be unclear, many studies indicate that sperm defects appear to be the major contributors (Mahadevan and Trounson, 1984; Jeulin *et al.*, 1986; Kruger *et al.*, 1988; Liu and Baker 1992a,b,c; Franken *et al.*, 1993; Oehninger *et al.*, 1997).

Oocyte immaturity or abnormalities can also contribute to failure of fertilization. Where the majority of oocytes fertilize, the few that do not fertilize often have defects (Bedford and Kim, 1993; Van Blerkom *et al.*, 1994). However, oocyte factors appear to be uncommon causes for complete failure of fertilization. Standard follicle stimulation treatments rarely produce uniformly abnormal or immature oocytes.

Fishel *et al.* have performed a randomized, prospective, multi-centre 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 partner's 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, 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. 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, caution is required 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 analysis 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 provided 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 against ICSI 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 (Damarico *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 clinical point 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 the 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 (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 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 = 0.4–12.3) 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.

In a study carried out by Hariprashad *et al.* (2002) to determine if ICSI is an effective method for improving pregnancy rates among patients who had previously unsuccessful IVF cycles resulting from poor or total fertilization failure, it was found that fertilization, clinical pregnancy and implantation rates were all significantly higher after the use of ICSI. The ongoing pregnancy rate between the ICSI and insemination group were significantly different; 34.1 and 10.7% respectively. It was concluded that ICSI can overcome certain factors that may cause abnormally low or no fertilization, and that even in cases where semen parameters are normal, ICSI can be useful and give a positive result.

However, whilst scientific analysis 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.

Although most of the patients with failure of fertilization in standard IVF can now be treated by ICSI (Van Steirteghem *et al.*, 1993), diagnosing the causes of failure of fertilization in standard IVF is important. Ideally, they should be detected before IVF is started. It is known that sperm–zona pellucida (ZP) interaction is important in human fertilization (Overstreet and Hembree, 1976; Yanagimachi, 1994).

Tests for sperm–ZP binding and penetration have been developed and the results are highly correlated with fertilization rates *in vitro* (Burkman *et al.*, 1988; Franken *et al.*, 1993; Liu and Baker 1994).

The ZP-induced AR is highly correlated with sperm–ZP penetration and fertilization rate in conventional IVF in patients with normal semen analysis (Liu and Baker 2000, 2003a,b; Bastiaan *et al.*, 2003).

The study that most supports this argument is that from Liu and Baker, (2000). They have reported on 160 patients who have apparently normal semen but either fail to bind to the ZP or do not show an acrosome reaction (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. They also stated that patients with unexplained infertility with ZP-induced AR <16% have average fertilization rates of <30% with conventional IVF. Interestingly, ICSI was found to overcome these defects resulting in live births (Liu and Baker, 2000).

These studies show that in the absence of any male factor problem, the incidences of fertilization after conventional IVF and ICSI are comparable; however, ICSI offers the advantage of bypassing the barriers responsible for any block in the process of fertilization, which may be of oocyte origin, and especially if of spermatozoan origin, and the risk of complete fertilization failure is minimized.

In summary, these authors suggest that 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.

## Safety and potential risks

Several reports suggest that initial fears about an increased incidence of major congenital malformations and possible imprinting disorders in the offspring following ICSI are unfounded (Manning *et al.*, 2000; Wennerholm *et al.*, 2000). However, it is important to remember that the long-term effects of the ICSI procedure are still unknown, 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.

The potential concerns regarding ICSI offspring relate to four general areas of investigations: the obstetrical outcomes of pregnancies resulting from ICSI, chromosomal abnormalities associated with the offspring of ICSI pregnancies, congenital malformations of the newborns resulting from the ICSI procedure, and the developmental abnormalities in children born as a result of ICSI.

The potential risks associated with the ICSI procedure can be divided into two main groups, as outlined by Patrizio (1995). The risks include both those that are independent of, and those that are dependant on the ICSI process. Risks independent of ICSI include potential fertilization of male gametes that carry either genetic anomalies or structural defects. In addition, there is the potential for incorporating sperm mitochondrial DNA or fertilizing anomalous female gametes that would be otherwise bypassed by natural selection. Either process could result in congenital malformations or male related infertility in resulting offspring.

The second group includes those risks that are dependant on the ICSI procedure itself. These include injection of foreign substances or contaminants, disruption of the ooplasm or the meiotic spindle apparatus, and the embryologist's improper selection of the incompetent sperm for injection. The introduction of these risks could result in birth defects or genetic abnormalities in offspring.

## Obstetrical outcome

Regarding obstetrical outcome, the possibility remains that despite apparently normal in-vitro development, delayed aberrations from ICSI may result in birth defects. One such outcome is the rate of miscarriage. An increased rate of pregnancy loss may be indicative of an ICSI-related abnormal outcome. The 1999 Society for Assisted Reproductive Technology data for the United States reported rate of spontaneous abortion of ICSI pregnancies at 17.6%, which was similar to the reported rate for IVF non-ICSI pregnancies of 16.7% (ASRM/SART, 2002). This would suggest no clinical effect severe enough to cause a loss of pregnancy from ICSI in the first trimester.

Several retrospective series have looked at specific obstetrical delivery data related to ICSI. Wisanto *et al.* (1995) reviewed the first consecutive 424 pregnancies resulting from ICSI for severe male factor infertility at their centre in Belgium. Evaluation of singleton gestation (69%) revealed a prematurity rate of 7.6%, a rate of low birth weight of 10.3%, and a perinatal mortality of 13.5/1000. These rates were reported to be similar to those in a comparable IVF patient population and slightly higher than those for spontaneous pregnancies when controlled for multiple pregnancies.

Govaerts *et al.* (1996) demonstrated in a retrospective study, pregnancy outcome of 145 ICSI pregnancies was matched with a similar number of IVF pregnancies. Results showed no difference in the rates of preclinical (15%) and clinical abortions (11 versus 15%). Four ectopic pregnancies were observed in the IVF group and none in the ICSI group. In the ICSI group, two therapeutic abortions were performed for poly-malformations and suspicion of cystic fibrosis. In the IVF group, one therapeutic abortion for neural tube malformation

was performed. The rate of aborted embryonic sacs before 16 weeks of gestation was not significantly lower in ICSI compared with the IVF group (13.7 versus 20%). The rate of multiple gestations was also similar in both groups (35% for ICSI and 31% for IVF).

These results are reassuring, but because of the size of the study, caution should still be observed.

Shieve *et al.* (2002) reported on a large population-based retrospective analysis of birth in the United States to assess more completely the relationship between assisted reproduction and low birth weight. This study has the power of over 42,000 assisted reproduction deliveries and calculated expected odds ratios from over 3 million naturally conceived deliveries in 1997. Examining both singleton and multiple births, they determined that the overall risk for low birth weight of term infants conceived by assisted reproduction was 2.6 (95% confidence interval, 2.4–2.7) compared with the risk of infants conceived naturally. It is interesting that this increased risk was not further increased for multiple births. When the group was stratified by ICSI and IVF, low birth weight infants were less common in the ICSI than in the IVF group. This interesting sub-analysis suggest that some aspects of assisted reproduction independent of ICSI (i.e. medications, infertility history, or the IVF procedure itself) may put these infants at greater risk of low birth weight.

In late 2002, Ludwig and Diedrich (2002) stated that molecular biological studies might support the idea that increased risks for pregnancy course following IVF and ICSI especially premature birth and low birth weight, are not related to the techniques used, but to parental background factors. Therefore, there are more infertility related problems than those related to the technique; however, a risk related to the technique itself cannot be excluded completely by currently available data.

These studies have addressed the potential effects of ICSI on obstetrical outcomes from early pregnancy to late in the gestation. The results are complicated by the patients' older age and increased multiple gestations in both undergoing both IVF and ICSI. When attempts are made to control for these confounding variables, the overall rate of lower birth weight appears to be the single most consistent risk to offspring from both ICSI and IVF. ICSI thus does not appear to impose any additional obstetrical detriment over conventional IVF to the developing fetus.

## Chromosomal abnormalities

Other arguments against the use of ICSI include questions about the safety of the technique and the possibility of the technique inducing damage or chromosomal abnormalities.

ICSI enables direct vision of oocytes and evaluation of their maturation state, thereby determining female factors. Concerns over germinal arrest or metaphase I have been eliminated because this technique allows us to see these conditions, along with the quality of the oocytes.

Regarding the spermatozoa, there is no relation between sperm morphology and genetic condition, meaning that it is not

guaranteed that spermatozoa with good morphology do not have any genetic abnormalities, and *vice versa*, that spermatozoa with bad morphology do have genetic abnormalities (Bianchi *et al.*, 1996).

If good morphology means good genetic quality, then there would be no abortions in normozoospermia cases, but there are. Even more significant than this is, how can there be more concern over genetic abnormalities in normozoospermia than of those in cases of severe male factor cases – cases where there is a much greater risk of genetic abnormalities? Regarding post-zygotic events leading to chromosome abnormalities induced by the actual procedure itself, Bonduelle *et al.* (2002), in their recent study using prenatal testing in ICSI pregnancies, concluded that there is a higher risk of de-novo chromosomal anomalies that is mainly related to a higher level of sex chromosomal anomalies and also to a higher level of de-novo structural anomalies, and not to the actual procedure of ICSI.

Several studies have reported an increase in adverse perinatal outcome of pregnancies obtained after ICSI–embryo transfer (Rizk *et al.*, 1991; Alsalili *et al.*, 1995). However, different studies have shown no additional risk after ICSI (Bonduelle *et al.*, 1995; Govaerts *et al.*, 1996). Although congenital malformations and sex chromosome abnormalities seem to be slightly higher after ICSI, a statistically significant difference has not been identified (Liebaers *et al.*, 1995).

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.*, 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 (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).

Thus, the ICSI procedure itself may contribute 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.*, 1996c).

Taken together, these studies imply that offspring from ICSI indeed carry an increased rate of chromosomal aberrations. These abnormalities seem to be related to the underlying parental risk of abnormality and not to the ICSI procedure itself. Therefore, genetic counselling must incorporate pre-ICSI screening of couples. Discussion of both macro-abnormalities (karyotype) and micro-abnormalities (gene microdeletions) should be included.

## Congenital malformations

Several centres have evaluated the implication that congenital malformations may arise secondary to ICSI. The first report by Bonduelle *et al.* (1995) prospectively followed 130 ICSI offspring and compared the results with those for 130 IVF offspring. The rate of congenital malformations was 3.2% for the ICSI group versus 4.6% for the IVF group. Reassuringly, the ICSI malformations appeared to be distributed evenly without clustering in any organ system.

Recently, Bonduelle *et al.* (2004) concluded that infertility treatment by ICSI does not adversely affect growth during childhood and the children's general health seems satisfactory. They investigate the physical outcome in 5-year-old children born after ICSI and compare them with children born after spontaneous conception. Three hundred singleton children from Belgium, Sweden and the USA, born after ICSI, were matched by maternal age, child age and gender. In one centre, matching was also performed for maternal education. The main end point was growth. Secondary end points were general health, e.g. common diseases, chronic illnesses, surgical interventions and physical/neurological examinations. Growth assessed as stature at follow-up was similar in the two groups, despite a higher rate of preterm birth and low birth weight in the ICSI children. Common diseases and chronic illnesses occurred at similar rates in both groups. More ICSI children underwent surgical interventions and required other therapy, e.g. physiotherapy and dietary therapy. Physical/neurological examinations revealed few abnormalities in either group.

Ludwig *et al.* (2001; Ludwig and Katalinic, 2002) reported on the German ICSI experience at the American Society of Reproductive Medicine 2001 meeting. They looked at 2809 pregnancies following ICSI in 59 German IVF centres in a prospective fashion and classified malformations according to the European Registry of Congenital Anomalies and Twins (EUROCAT). They found a rate of major malformations in controls of 7.2% from a national birth registry and a rate of ICSI offspring of 9.1%. This difference was not statistically significant. They found no clustering of defects. They did find that maternal risk (i.e. occupational exposure or family history of malformations) statistically increased the malformation rate independent of ICSI. Multivariate analysis confirmed that ICSI was not an independent risk factor for congenital malformations.

In an attempt to address the shortcomings of the prior studies, Anthony *et al.* (2002) compared the congenital malformation rates for offspring of IVF ( $n = 4224$ ) and offspring of natural conception ( $n = 314,605$ ) in the Netherlands. The strength of this study was the use of the same database for the both cases and controls and a cohort that was large enough to allow subgroup analysis. Their results showed a slight increased risk of any malformation (major and minor) for IVF offspring (OR, 1.20; 95% CI, 1.01–1.43) compared with the natural conception group. This difference was, however, no longer statistically significant when confounding variables such as maternal age, parity and ethnicity were controlled (OR, 1.03; 95% CI, 0.86–1.23).

Unfortunately, the investigators were not able to separate out the ICSI children from the IVF study population. The fact that there was only a small increase in the malformation rate in a variety of organ systems makes it much less likely that some procedural aspect of IVF was responsible. The lack of a correlation between malformations and IVF treatment was further substantiated by the fact that the differences could be completely accounted for by maternal risk factors.

Thus, the issue regarding congenital malformations and CSI remains clouded by the inherent biases of each observational study. The vast majority of studies have found no increased rate of malformations associated with ICSI. In addition, it is reassuring that there is no clustering of any specific major malformation. The inability to randomize treatments in a prospective fashion and the inherent difficulty in finding ideal controls limits the capacity to determine potential minor differences in the ICSI population given the present state of knowledge.

## Developmental abnormalities

Bonduelle *et al.* (1998) assessed mental development in 201 ICSI offspring as compared with 131 IVF offspring and 1238 normal children. This was a prospective study with follow-up of 2 years. The most important thing in this study was the use of a single blinded paediatrician to test all of the ICSI and IVF children. Unfortunately, the follow-up at 2 years was somewhat low, at 25%. The overall mental scores were similar for all groups.

Sutcliffe and his group (1999) looked at mental development at 12 and 24 months of age of 123 singleton children from ICSI and 123 conceived naturally. A single observer assessed all children and follow-up was 90%. These children were matched for social class, maternal education level, religion, sex and race but not for maternal age. They found no difference in the average mental age and in the overall development as expressed by the Griffiths quotient.

In addition, there was no difference in four of five Griffiths sub-quotients: locomotor, personal and social, hearing and speech, and performance. Offspring of ICSI, however, performed worse in high-level hand–eye coordination tasks. The investigators commented that this difference in hand–eye coordination is ‘unlikely to be of functional significance’.

Developmental assessment of ICSI children has been sparse at best, with only short follow-up of the children. It does appear that there are no major developmental delays, either motor or

mental, but to decipher potential minor abnormalities a larger prospective effort of many institutions will need to be undertaken.

## Cost

The answer to the argument that ICSI is more expensive than IVF, resulting in worries over the practice of ICSI by clinics with profit rather than the patient in mind, is quite simple: make the cost of ICSI the same as that of IVF.

As regard the financial aspect of IVF and ICSI, a good choice is the model of the RCOG Guidelines (RCOG Guidelines, 2004)

For IVF, the age-specific costs per live birth are very similar for ages 24–33 years, after which they rise steeply with increasing age. The costs per live birth were £11,917 at 24 years, £12,931 at 35 years and £20,056 at 39 years. The total costs after three cycles of treatment based on 1000 couples at the start of treatment and using the baseline cost of IVF treatment and a discontinuation rate of 17.7% were £6.2 million in women aged 24 years, £6.3 million in women aged 35 years and £6.9 million in women aged 39 years. The percentage of couples who achieved a live birth after three cycles of treatment were 52% at 24 years, 49% at 35 years and 34% at 39 years. The cost-effectiveness ratios (cost per live birth) presented here can be compared with cost effectiveness ratios reported for other countries using evidence from randomized clinical trials of clinical efficacy. The results suggest far higher cost-effectiveness ratios (cost of IVF per delivery) in the USA (as might be expected), but similar results in Scandinavian countries (Granberg *et al.*, 1998)

The data reported below are for the year 1994: Sweden £10,295; Denmark £11,858; Norway £13,413; Finland £11,211; and Iceland £7400. Comparing these results with the cost per live birth for couples undergoing ICSI using the baseline cost of ICSI treatment (£2936) and an OHSS incidence rate of 0.2%, the cost per live birth was £14,002. The total cost after three cycles of ICSI treatment was £6.5 million, with 48% of couples achieving a live birth. At a lower cost per ICSI treatment (£1936, which excludes drugs) the cost per live birth was £9056.

## Conclusion

ICSI has become increasingly popular, and although it was intended primarily to treat male factor infertility, the procedure 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. 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. Finally, the adoption of preimplantation genetic diagnosis by an increasing number of centres requires the generation of embryos by ICSI, to exclude the risk of interference of contaminating spermatozoa.

Examination of the available data from thousands of ICSI children reveals that it is largely a safe procedure and should

continue to be offered to couples for whom no other method of assisted reproduction can offer success.

There are no data suggesting that ICSI should not be performed in all cases of in-vitro conception. In all cases, female factor or male factor (normal or abnormal spermatozoa), the use of ICSI bypasses most dysfunctions, eliminating the majority of barriers to fertilization. If fertilization does still not occur, then there is a greater chance of it being a genetic reason, and the risk of genetic abnormalities in normal spermatozoa should not be of greater concern than those in abnormal spermatozoa.

There appears to be no increase in prematurity and perinatal mortality in ICSI pregnancies compared with IVF pregnancies when studies are appropriately controlled.

There is probably an increased rate of sex chromosome abnormalities in offspring from ICSI pregnancies. This finding appears to be related either to inherited paternal karyotypic abnormalities or to abnormal spermatogenesis, and not to de-novo acquisition. In addition, a high percentage of azoospermic and severely oligospermic men have microdeletion of the Y chromosome.

There appears to be no significant increase in congenital malformations, and it is also reassuring that there appears to be no increase of malformations of any specific organ system after ICSI.

The effect on psychomotor development remains difficult to assess in children born from ICSI procedure. Follow-up studies were performed at early ages, and the predictive value of such early age testing for school performance and later development in life remains questionable. However, it appears that psychomotor development of such children is probably normal.

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.

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