# Minimum standards for ICSI use, screening, patient information and follow-up in WA fertility clinics

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## 1. BACKGROUND

ICSI has been shown to be effective for male factor infertility and it also brings advantages in relation to PGD procedures and in the avoidance of transmission of infectious diseases.

To date studies reporting long term follow up of children conceived by ART are few and the available evidence concerning difference in outcomes between those conceived by IVF compared to ICSI are conflicting. In deciding to continue to limit the routine application of ICSI in IVF, the Council notes that the following concerns remain with the use of both ICSI and IVF:

1.1 Plural births present the greatest risk of mortality and morbidity following both IVF and ICSI (Devroey and Van Steirteghem, 2004).

1.2 ICSI and IVF infants are more likely to be born preterm and of low birthweight compared to spontaneously conceived infants (Bonduelle et al, 2004; Schieve et al, 2002).

1.3 An increased risk of birth defects following ART treatment has been previously suggested but remained controversial (Hansen et al, 2002). The Council has noted that a recently published systematic review supports the existence of an increased risk of birth defects. The review examined 25 studies from around the world that compared birth defects in IVF and/or ICSI infants to spontaneously conceived infants (Hansen et al, 2005). Two thirds of the studies reviewed showed a 25% or greater risk of birth defects in IVF or ICSI babies. Meta-analysis of the study results suggested a statistically significant 30-40% increased risk of birth defects associated with assisted reproductive technology. Unfortunately there are limited data examining the risk of birth defects in ICSI infants separately. A sub-group analysis of the 5 studies with ICSI data revealed a 30% increased risk of birth defects in ICSI compared to spontaneously conceived infants. However, this sub-group analysis included only 4000 ICSI births, 85% of which were contributed by a single study.

1.4 The European multi-centre cohort study of ICSI infants (published since the meta-analysis was performed) found that ICSI infants were 2.54 (95% CI 1.13-5.71) times more likely to be diagnosed with a major malformation by 5 years of age than spontaneously conceived infants after adjusting for maternal age, educational level, social class, maternal smoking and drinking and number of previous pregnancies. ICSI boys in particular had an excess risk of uro-genital malformations. These may be attributable to paternal genetic factors rather than the ICSI procedure itself (Bonduelle et al, 2005).

1.5 There is evidence for an increased risk of imprinting disorders in ICSI and IVF children, although these disorders remain extremely rare (Cox et al, 2002; De Baun et al, 2003; Halliday et al, 2004).

1.6 Assessment of a number of ICSI and IVF cohorts at 5 years of age have shown that these children experienced greater morbidity in the first 5 years and had significantly more surgical interventions compared to spontaneously conceived children. Hearing, vision and growth were similar for both groups (Bonduelle et al, 2004; Bonduelle et al 2005).

There is potential for ICSI to lead to the inheritance of conditions associated with male infertility (eg mutations in the cystic fibrosis gene and micro deletions on the Y chromosome) that in turn affect fertility of male offspring. Prenatal testing has provided evidence of a significant increase in *de novo* sex and autosomal chromosome aberrations after ICSI, which is related to low sperm counts (Devroey and Van Steirteghem, 2004). Although ICSI is allowed in the treatment of male infertility appropriate investigations into the cause of the infertility and counselling about the risk of infertility in male offspring are recommended.

The Council will continue to request that the Department of Health's Reproductive Technology Unit (RT Unit) routinely monitor birth outcomes through data linkage, at the time of annual reporting. The Council will also request that the RT Unit monitor longer term outcomes from time to time, where this may be carried out through linkage to other databases available in the health system, and do what it can to promote and endorse this research.

**REFERENCES:**

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Hansen et al, 2005 Assisted reproductive technologies and the risk of birth defects – a systematic review. Human Reproduction 20(2): 328-338.

Schieve et al, 2002 Low and very low birth weight in infants conceived with use of assisted reproductive technology. The New England Journal of Medicine 346(10): 731-737.

## 2. CURRENTLY ACCEPTABLE MINIMUM STANDARDS FOR ICSI USE (INCLUDING THE USE OF RETRIEVED SPERM)

2.1 Given the range of concerns, current knowledge of ICSI does not support its use in all cases of IVF for the time being.

2.2 The HRT Act has been clarified to allow the use of IVF to avoid the transmission of a genetic abnormality or a disease (including infectious diseases) and ICSI may be used under these circumstances. However other aspects of the procedures will require approval from the Council as innovative practices.

2.3 The use of ICSI prior to pre-implantation genetic diagnosis is now permitted under these standards. The use of ICSI prior to polymerase chain reaction (PCR) is strongly recommended and it is an acceptable alternative to conventional insemination for fluorescence in situ hybridisation (FISH) cases.

2.4 ICSI may be used in the treatment of severe male factor infertility, including cases with -

- Very low numbers of motile sperm with normal appearance
- Unexplained azoospermia; azoospermia due to ejaculatory disorders (eg retrograde ejaculation, aspermia); or acquired testicular failure (eg mumps, orchitis, radiotherapy or chemotherapy)
- Absence of sperm secondary to blockage or abnormality of the ejaculatory ducts
- Frozen sperm collected prior to cancer treatment that may be limited in number and quality
- A history of polypronuclear oocytes

2.5 ICSI may also be used in cases where there the following have been documented-

- Problems with sperm binding to and penetrating the egg
- Antisperm antibodies of sufficient quantity and /or quality to prevent fertilisation
- Prior repeated low fertilisation rate or fertilisation failure with standard IVF culture and fertilisation methods.

2.6 ICSI may be used in cases where there is an expectation that only one or two oocytes will be available for attempted fertilisation. This includes cases where participants choose to have single or dual oocyte collection.

2.7 ICSI is to be a clinical decision made in advance and it is not appropriate for the matter to be raised with the patients for the first time in the emergency situation, especially by laboratory staff on the day of oocyte retrieval. Emergency ICSI is to be allowed only if this possibility has been foreshadowed and discussed at the time of clinical examination and counselling, so that the patients are able to give effective consent to the procedure.

2.8 Use of immature sperm

It is currently a condition of all Practice Licences that any surgically retrieved sperm from the epididymis or testis used in ICSI by a WA clinic is independently motile, released from the seminiferous epithelium by spontaneous spermiation, with normal head morphology (regular oval shape lying within the parameters 3-5 microns long and 2-3 microns wide).

2.9 'Rescue ICSI'
At present, because of the risk of undetected polyspermia and an increased risk of cytogenetic abnormalities, it is not appropriate to use ICSI to re-fertilise eggs that have failed to fertilise by conventional IVF.

2.10 'Split fertilisation'
Where a clinic is to carry out 'split fertilisation', with some oocytes being subjected to standard IVF and some to ICSI, this should be indicated on the fertilisation form in response to the question about micro-manipulation, including comments on why this is being carried out. Where an embryo transfer involves mixed ICSI and non-ICSI embryos these should be left out of any follow-up of ICSI outcomes carried out by the RT Unit.

2.11 Any clinic seeking to vary these limitations should make a specific application for approval by the Council.

## 3. MINIMUM STANDARDS FOR REQUIRED SCREENING PRIOR TO ICSI

3.1 For all cases where there is an unexplained low sperm count (below WHO guidelines for normality), because of the potential link between male infertility and other genetic conditions, every effort should be made to obtain a three generation genetic history from the client. The privacy of others involved must be respected during this process.

3.2 For all cases where there is unexplained azoospermia or severe oligozoospermia (<1 million sperm/ml) patients should be strongly advised to have karyotyping and testing for micro y deletion and CFTR testing. The outcome of these tests will assist the couple in giving informed consent prior to undergoing ICSI.

3.3 For all cases where ICSI is considered and the participants are of advanced age, participants be informed of the merits of undergoing pre-natal genetic testing should a pregnancy result, with information on complications associated with these tests and the implications of multiple pregnancies. Genetic counselling should be routinely offered.

## 4. MINIMUM STANDARDS FOR FOLLOW-UP OF ICSI USE BY LICENSEES

4.1 The clinics should continue to report to the Council any matters of concern arising from their own experience or from the literature.

4.2 Clinics are also encouraged to design and carry out their own additional follow-up studies.

4.3 In accordance with Direction 2.6 of the *Human Reproductive Technology Act* (1991) licensed clinics are required to report each ART cycle to the Commissioner of Health, including whether ICSI was used in the cycle.

## 5. PROTOCOLS REGARDING ICSI TO BE SET OUT IN A PROTOCOL MANUAL

5.1 Where ICSI is to be carried out in the permitted circumstances, Licensees need to ensure that the procedures to be followed are set out in the detailed manual for which Council approval is obtained (Directions 9.2 and 9.3).

5.2 Documentation is to be provided to the Council (on request) showing that the procedure to be adopted:

- complies with relevant professional standards, such as of the NHMRC and RTAC
- has not been rejected by a relevant HREC
- is used in other reputable, nationally or internationally recognised clinics
- is reported in international peer-reviewed literature, indicating safe and successful outcome, based on good research
- is expected to be, or is currently, successful in the local clinic (eg. details of results or relevant staff training undertaken)
- is considered a necessary element of the routine practice in the clinic.