

Use of ICSI

Strategic delivery: Safe, ethical, effective treatment Consistent outcomes and support Improving standards through intelligence

Details:

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Output:

For information or decision? For information

Recommendation The Committee is asked to:

- Consider the progress of research around the use of ICSI and possible risks associated with this technique;
- Advise the Executive if they are aware of any recent developments; and
- Consider whether the Executive needs to update the HFEA's patient information or guidance to clinics.

Resource implications N/A

Implementation date N/A

Communication(s) N/A

Organisational risk Low Medium High

Annexes

1. Background

- 1.1.** Intracytoplasmic sperm injection (ICSI) is the process of injecting a single sperm into an egg. Currently around two thirds of IVF cycles carried out in Europe involve ICSI. In recent years, experts have been debating whether ICSI is being used appropriately.
- 1.2.** In 2009 SCAAC considered the use of ICSI and the potential risks. The HFEA issued guidance to licensed fertility clinics regarding the information they should provide to patients about the risks involved with ICSI (e.g. risks of eggs being damaged in the procedure, risk of embryos/children having genetic abnormalities, imprinting disorders and male infertility being passed on to the next generation). Research exploring the impacts of ICSI has continued to develop and SCAAC has monitored this through its horizon scanning functions looking at health outcomes in children born following assisted reproduction.
- 1.3.** Paragraph 21.1 of the 8th Edition of the Code of Practice outlines the information that should be provided to patients on the risks associated with ICSI:

Before treatment is offered, the centre should give the woman seeking treatment and her partner, if applicable, specific information about the risks of ICSI which might lead to:

a) a reduced number of eggs being available for treatment (compared to IVF), due to eggs being immature or damaged by the process of ICSI

b) children conceived having inherited genetic, epigenetic or chromosomal abnormalities (including cystic fibrosis gene mutations, imprinting disorders, sex chromosome defects and heritable sub-fertility).

- 1.4.** The HFEA website also provides [information to patients](#) on the following possible risks associated with the use of ICSI:
- Genetic and developmental defects (the patient information also highlights that any increased risk could also be due to underlying male factor infertility)
 - The possibility of boys inheriting their father's infertility
 - An increased risk of miscarriage because the technique uses sperm that would not otherwise have been able to fertilise an egg
 - A low sperm count caused by genetic problems being passed on to a male child.
- 1.5.** The National Institute for Health and Care Excellence (NICE) provides some recommendations about fertility treatments in their '[Fertility problems: Assessment and treatment](#)' clinical guideline. The guideline states that the recognised indications for treatment by ICSI include:
- Severe deficits in semen quality
 - Obstructive azoospermia
 - Non-obstructive azoospermia

The NICE guideline also recommends that “*couples should be informed that ICSI improves fertilisation rates compared to IVF alone, but once fertilisation is achieved the pregnancy rate is no better than with IVF*”.

- 1.6.** The International Committee for Monitoring Assisted Reproductive Technologies world report: Assisted Reproductive technology 2008, 2009 and 2010 was published by Dyer et al. in 2016. The report showed that ICSI was used in around 66% of aspiration (egg collection) cycles, however, ICSI was used in 100% of cycles in the Middle East, compared with 55% in Asia and 65% in Europe. The authors noted that investigation into why ICSI is a preferred fertilisation technique in a number of countries, particularly in Latin America and the Middle East, is warranted.
- 1.7.** The use of ICSI was identified as a high priority issue for SCAAC in 2016. The Committee decided to consider a detailed literature review on the topic upon publication of new relevant professional body guidance. This guidance has not yet been published, so the Committee agreed to consider the use of ICSI during 2017. This paper precedes a broader piece of work by the Executive, using Register data to look at the use of ICSI in the UK and exploring whether the technique is being used appropriately.
- 1.8.** This paper will outline research carried out relating to the use of ICSI, with a particular focus on the last five years.

2. Birth defects and health outcomes

- 2.1.** Davies et al. (2012) linked assisted reproduction treatment data from South Australia with a registry of births and terminations with a gestation period of at least 20 weeks or a birth weight of at least 400g and registries of birth defects (including cerebral palsy and termination for defects at any gestational period). The study reported that both IVF and ICSI treatments were associated with an increased risk of birth defects. After adjusting for confounders, the increased odds of birth defects following IVF treatment was no longer statistically significant. The increased odds of birth defects following ICSI remained statistically significant after adjusting for confounders, however, the authors did not rule out the possibility that this effect could be due to the underlying male infertility factors that led to ICSI being used.
- 2.2.** Belva et al. (2012) measured obesity levels and body fat distribution in 14 year old teenagers who were conceived by ICSI. Body composition data was collected for 217 ICSI conceived singletons (116 boys, 101 girls) and 223 singletons born following spontaneous conception (115 boys, 108 girls). No difference in body composition measurements was found between ICSI and spontaneously conceived boys. However, when only boys with more advanced pubertal stages were included in the analysis, ICSI conceived boys were found to have a significantly higher sum of peripheral skin folds. ICSI conceived girls were found to have significantly higher central, peripheral and total body fat (adiposity). The authors recommended continued monitoring of body fat patterns in teenagers born following assisted reproduction.

- 2.3.** In 2015, Massaro et al. carried out a systematic review and meta-analysis looking at IVF and ICSI treatments and the risk of genitourinary congenital malformations. 22 studies were included in the review which showed that ICSI is associated with a slightly higher risk of genitourinary congenital malformations compared to IVF. However, when only the high-quality studies were analysed, the difference in risk was no longer statistically significant.
- 2.4.** A recent systematic review by Rumbold et al. (2017) explored whether different fertility treatments affected cognitive ability in school aged children. 35 studies were included in the review, of which seven were rated as high quality. The authors reported that amongst the high-quality studies, there were inconsistent findings relating to the effects of ICSI on cognitive ability; one study found a lower IQ on average amongst ICSI conceived children compared to spontaneously conceived children (5 to 7 points, on average), whilst another two studies found no difference. Three studies compared ICSI conceived children to children born following conventional IVF; one study found increased risk of mental retardation in ICSI conceived children, one found a small difference in IQ between the two groups (ICSI conceived children having an IQ 3 points lower, on average), and one study found no difference. The variation in findings between high quality studies indicates that further research is required to properly understand any impacts of ICSI on cognitive ability in children.
- 2.5.** Xiong et al. (2017) used data from the Society for Assisted Reproductive Technology (SART) database to carry out a retrospective cohort study of 141 030 women conceiving using ART between 2006 and 2010. The authors reported that over the study period, overall ICSI use increased from 68.9% to 73.1%, with the greatest increase in use occurring in women with no male factor infertility problem. ICSI pregnancies were found to be associated with an increased risk of birth defects compared to IVF alone (adjusted odds ratio 1.2, 95% confidence interval 1.2 to 1.3). The increase in risk of birth defects was found in women having ICSI treatment with and without male factor infertility.

3. Heritable infertility

- 3.1.** In 2016, Belva et al. published the first assessment of fertility in men aged between 18 and 22 years, who were conceived using ICSI for severe male factor infertility. The study reports the results of a single semen sample analysis in 54 adult men who were conceived by ICSI and 57 spontaneously conceived men. The men conceived by ICSI were found to have significantly lower median sperm concentration, total sperm count and total motile sperm count compared to their spontaneously conceived peers. Although the sample size for this study was small, it provides the first indication that male infertility may be passed on to the next generation when boys are conceived by ICSI.
- 3.2.** Another study looking at the same cohort of men conceived by ICSI because of severe male factor infertility investigated reproductive hormone levels to gain insights into the gonadal function of ICSI conceived men. Belva et al. (2017, a) measured circulating levels of follicle stimulating hormone (FSH), luteinising

hormone (LH), inhibin B and testosterone. They reported comparable levels of these hormones between the two groups. ICSI conceived men were found to be more likely to have low inhibin B and high FSH, although these results did not reach statistical significance. Despite the small sample size in this study, the authors suggest that further exploration of the reproductive status of ICSI conceived men is warranted.

- 3.3.** A further study by Belva et al. in 2017(b) compared reproductive hormone levels and antral follicle count (measured using ultrasound) in women conceived by ICSI due to male factor infertility and women born after spontaneous conception. This study followed 71 women aged between 18 and 22 years and 81 spontaneously conceived women of the same age. The authors report that antral follicle count and circulating reproductive hormone levels were similar between the two groups. These results provide some indication that women born following ICSI may not inherit infertility from their fathers. However, this was a small study and further research is needed to confirm the results.

4. Epigenetic effects

- 4.1.** Epigenetics refers to the information in the genome over and above that contained in the DNA sequence. Epigenetic activity is closely linked with critical developmental steps which occur around the time of conception. One example of an epigenetic modification is DNA methylation, which can change the activity of a gene without changing the DNA sequence itself.
- 4.2.** Hajj et al. (2017) investigated whether ICSI induces DNA methylation changes in the resulting children. Umbilical cord blood samples were obtained from healthy newborn singletons conceived spontaneously (n=53), through ICSI (n=89) or through IVF (n=34). DNA samples from 48 ICSI pregnancies and 46 control pregnancies were used for genome-wide analyses and the DNA methylation patterns were compared. The authors reported that significant differences in DNA methylation were seen at 0.11% of the sites that were analysed. However, they also note that although the epigenetic changes were widespread between the ICSI and control groups, none of the changes had a large effect size and the observed patterns for ICSI conceived newborns and controls were within the normal range of methylation variation. Finally, the authors note that only healthy newborns were included in their study and larger epigenetic changes in newborns with severe medical problems cannot be ruled out.

5. Effectiveness compared to IVF alone

- 5.1.** A study by Hodez-wertz et al. in 2012 determined whether the use of ICSI in couples who previously underwent ICSI cycles elsewhere could be decreased without compromising the pregnancy rate. The group retrospectively analysed the records of 149 fresh, in vitro fertilisation-embryo transfer cycles in patients who underwent ICSI elsewhere and subsequent fertilisation by insemination

only (all insemination group) or half insemination and half ICSI. They compared fertilisation, implantation, and clinical pregnancy and live birth rates. The group found no statistically significant difference in the live birth rate between the two groups. This study therefore suggests that stringent criteria for ICSI may not compromise the clinical outcome and fertilisation can be achieved whether or not ICSI is used.

- 5.2.** Bhattacharya et al. (2013) used anonymised HFEA Register data to investigate factors associated with treatment failure as well as poor outcomes at each stage of an IVF treatment cycle. The study showed that failed fertilisation was more common in IVF cycles compared to ICSI (4.7% compared to 2.2%). When only women who had successful fertilisation or who reached embryo transfer were included in the analysis, treatment using ICSI was independently associated with a slightly increased risk of failure to achieve a live birth. The authors reported that the intention to perform ICSI was associated with a decreased risk of treatment failure in women starting an IVF cycle. However, this association reversed at a later stage once fertilisation was confirmed which suggests that the lower chance of treatment failure was not due to increased chance of implantation of ICSI embryos.
- 5.3.** In 2015, Boulet et al. analysed data from the US National Assisted Reproductive Technology Surveillance System to explore trends in the use of ICSI between 1996 and 2012. They identified 1,395,634 fresh IVF cycles, of which 908,767 (65.1%) used ICSI and 486,867 (34.9%) used conventional IVF. Male factor infertility was identified in 35.8% of fresh IVF cycles. The team found that in the presence of male factor infertility, reproductive outcomes of fresh IVF cycles using ICSI were similar to outcomes using conventional IVF. In cycles using ICSI without male factor infertility, the team identified “small but significant” reductions in implantation, pregnancy, live birth and multiple live birth, compared with cycles using conventional IVF without male factor infertility.
- 5.4.** A Cochrane Review published in 2016 (Cissen et al., 2016) aimed to explore the safety and effectiveness of different fertility treatments in couples with abnormal sperm parameters. The fertility treatments examined were expectant management, timed intercourse, intrauterine insemination, IVF and ICSI. 10 studies were included in the review and the authors reported that no studies were found which compared ICSI with timed intercourse, intrauterine insemination or IVF. This suggests that further research is needed to determine the comparative safety and effectiveness of different fertility treatments aimed at treating male subfertility.
- 5.5.** Tannus et al. (2017) investigated whether ICSI improves reproductive outcomes compared with conventional IVF when used for non-male factor infertility in women aged 40 years and older. This retrospective, single centre study included a total of 745 women: 490 women underwent ICSI and 255 had conventional IVF. All women were at least 40 years old at the beginning of ovarian stimulation and their male partner had normal sperm parameters according to World Health Organisation criteria. The results showed that, after

controlling for confounders, the live birth rates between the ICSI and conventional IVF groups were similar. The authors suggest that there is no advantage of ICSI over conventional IVF in women aged 40 years and over when used for non-male factor infertility. This study, whilst retrospective in nature, and with a small sample size, prompts the question of why ICSI is being used in couples where there is no male factor infertility.

6. Conclusions

- 6.1. Since SCAAC last considered the use of ICSI in 2009, research has continued to develop in this area and has continued to suggest an association between the use of ICSI and various health impacts on the children born. However, it is still unclear whether these impacts are caused by the ICSI treatment itself, or by the underlying infertility in the couple seeking treatment.
- 6.2. Several studies have investigated the effectiveness of using ICSI in the absence of male factor infertility. Initial evidence suggests that the use of ICSI where there is no male factor infertility is no more effective than IVF alone. This is an area which requires further research to ensure that patients are not being asked to pay for potentially unnecessary treatments which may come with additional risks.

7. Recommendations

- 7.1. The Committee is asked to:
 - Consider the progress of research around the use of ICSI and possible risks associated with this technique;
 - Advise the Executive if there are aware of any recent developments; and
 - Consider whether the Executive needs to update the HFEA's patient information or guidance to clinics.

8. References

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