

HUMAN FERTILISATION AND EMBRYOLOGY AUTHORITY

SCIENTIFIC AND CLINICAL ADVANCES GROUP

Committee:	Scientific and Clinical Advances Group
Meeting Date:	24 November 2005
Agenda Item:	6
Paper Number:	SCAG (11/05)02
Paper Title:	<i>In vitro</i> maturation of oocytes
Author:	Chris O'Toole
For Information or Decision?	Decision
Resource Implications:	
Recommendation to the Committee:	Members are asked to decide whether IVM should be offered as a treatment service and, if so, to decide the categories of patients to which this service should be offered.

Aim

1. The aim of this paper is to seek the views of the Scientific and Clinical Advances Group on whether *in vitro* matured oocytes should be used in treatment services.

Introduction

2. *In vitro* maturation (IVM) is process whereby oocytes are matured in the laboratory from the germinal vesicle (GV) stage of development to the metaphase II stage. The recovery of immature oocytes followed by *in vitro* maturation and *in vitro* fertilisation (IVF) could be an attractive alternative to conventional *in vitro* fertilisation especially for women with polycystic ovaries or polycystic ovarian syndrome who may be a greater risk of developing ovarian hyperstimulation syndrome following treatment with gonadotrophins. Furthermore, IVM could also be used in cases where women, who have regular menstrual cycles, are referred for IVF due to severe male infertility.
3. A review of the literature shows that more than 300 healthy children have been born following immature oocyte retrieval and *in vitro* maturation. In general, the clinical pregnancy and implantation rates are 30-35% and 10-15% respectively (Chain, *et al.*, Curr Opin Obstet Gynecol. 2004; 16(3):211-219). The pregnancy outcomes from five centres that carry out IVM is summarised in Table 1 below.

Table 1. Summary of pregnancy outcomes from five centres with *in vitro* maturation programmes

Hospital / Group	Cycles (n)	Implantation Rate (%)	Clinical Pregnancies % (n)
McGill Reproductive Centre, Montreal, Canada	254	11.1	24.0 (61)
Maria Infertility Hospital, Seoul, Korea	419 (Day 3 transfer)	11.6	32.7 (137)
	80 (Day 5 transfer)	27.2	53.8 (43)
Maria Medical Centre, Seoul, Korea	94	6.9	27.1 (23)
Herlev University Hospital, Herlev, Denmark	12		23
Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan	68	10.5	33.8 (23)
Hospital Antoine Beclere, Clamart, France	45	10.9	20.0 (9)

(sources: Papanikolaou, *et al.*, Reproductive Medicine Online 2005; 10(5):587-592. Le Du, *et al.*, Human Reproduction 2005; 20(2):420-424)

4. The Scientific and Clinical Advances Group, at its meeting on 13 September 2004, reviewed two reports relating to the clinical aspects of *in vitro* maturation of oocytes. The information was supplied by MediCult (a company that supplies a wide range of products for use with Assisted Reproduction Technologies). The first report summarised published research reporting the outcome of treatment using *in vitro* matured eggs and states that over 140 children have been born following *in vitro* fertilisation using *in vitro* matured oocytes. The second was a dissertation on studies carried out at a hospital in Denmark between 1997 and 2000. This study reported 36 pregnancies and 25 live births, with the exception of one child who was born with a soft cleft palate, all children were healthy.
5. All other studies that have followed-up the children born following IVF with *in vitro* matured oocytes have reported that all the children were healthy.

6. One study has reported an increase in embryo aneuploidy following *in vitro* oocyte maturation and subsequent delayed fertilisation using ICSI. This study used *in vitro* maturation to mature immature oocytes collected as part of IVF cycles and then injected them with sperm collected 16-24 hours previously. The study reported that embryos created after *in vitro* maturation and delayed intracytoplasmic sperm injection contain an increase in aneuploidy (79.7%) compared with control embryos (60.5%) (Emery, *et al.*, Fertility and Sterility 2005; 84(4): 1027-1029).

Background

7. In January 2001 the HFEA's Working Group on New Developments in Reproductive Technologies (WGNDRT) considered *in vitro* maturation of oocytes (IVM) and the use of *in vitro* matured eggs in treatment. In particular, the Group recognised that clinics in Denmark, Canada and Korea were already using *in vitro* matured oocytes in treatment and that one group (Mikkelsen *et al.*, 1999) had reported a pregnancy rate of 25% per embryo transfer and that another group (Cha *et al.*, 1999) had reported that 20 babies had been born to women with polycystic ovary syndrome following IVM.
8. The Group noted that the professional bodies (RCOG, BFS and ACE) agreed that *in vitro* maturation of oocytes might prove useful but its introduction into clinical treatment should proceed with caution. Therefore, the Working Group decided to recommend that IVM should be limited to the treatment of three groups of patients:
 - Women with polycystic ovary syndrome;
 - Women with PCO like multicystic ovaries, and
 - Women who have shown evidence of hyperstimulation in previous hormone treatment.
8. The Working Group also recommended that only Centres with research experience in IVM should be licensed to use IVM clinically. In particular, Centres would need to demonstrate the ability, on site, to create mature human oocytes i.e. Centres would need to show competence in creating Metaphase II oocytes and that suitable protocols were in place.
9. In conclusion the Working Group agreed to recommend to the Authority that the use of *in vitro* matured eggs be allowed in treatment, subject to the following conditions:
 - that only Centres with research experience, in IVM, should be licensed to use IVM clinically;
 - that Centres would need to demonstrate ability, on site, to create mature human oocytes. In particular, Centres would need to show

competence in creating Metaphase II oocytes and that suitable protocols are in place;

- that IVM should be limited to three categories of patients:
 - a) women with polycystic ovary syndrome,
 - b) women with PCO like multicystic ovaries, and
 - c) women who have shown evidence of hyperstimulation in previous hormone treatment;
 - that patients should be fully informed of the nature of the procedure both in written and orally delivered;
 - that centres should submit a report after one year of licensed treatment detailing:
 - a) the categories of patients treated,
 - b) the number of eggs collected,
 - c) the proportion of eggs that matured to metaphase II,
 - d) the treatment outcome i.e. the implantation rate, the pregnancy rate and the percentage of live births per treatment cycle, and
 - that the long-term follow-up of children born as a result of IVM should be strongly encouraged.
10. The HFEA has not received any applications for a licence to carry out IVM but the Executive is aware of that one Centre is in the process of submitting an application.

Issues for decision

11. Is there sufficient knowledge about embryos created using *in vitro* matured oocytes especially in relation to chromosome number and gene expression to allow these embryos to be used in treatment services? If not, what further information is needed?
12. If Members are satisfied that there is sufficient evidence on the safety and efficacy of IVM then Members are asked whether, pending an application, IVM should be offered as a licensed treatment and, if so, whether it wishes to make or amend the same recommendations as made by the WGNDRT listed in paragraph 8 above.
13. If the Scientific and Clinical Advances Group decide to make the same recommendations as listed above then it is recommended that the HFEA should only licence a Centre to carry out IVM as part of a clinical trial.