acart
Advisory Committee on Assisted Reproductive Technology

Consultation on the Use of In Vitro Maturation in Fertility Treatment

Discussion document

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Chair's Foreword

In 2005 the Human Assisted Reproductive Technology Order in Council (the HART Order) published a list of procedures that could be undertaken by health professionals without the need for review by the Ethics Committee on Assisted Reproductive Technology. Such procedures are referred to as 'established procedures'.

The HART Order explicitly excluded the collection of immature eggs and the use of eggs that have been matured by in vitro maturation from the list of established procedures. This was because, at that time, the procedure was relatively new and the expert group set up to advise on the established procedures considered that there was insufficient information on the safety of the procedure.

In early 2008 ACART commissioned an expert review of the literature and, based on that review, came to the preliminary view that the information now available indicates that it is safe for the collection of immature eggs and the use of eggs that have been matured by in vitro maturation to be declared an established procedure.

This discussion document sets out the reasons for this preliminary view and asks for your opinion on whether you agree or not, as well as your opinion on related matters. Please take the time to consider the questions included in this document. We would welcome your comments on these, or any other aspect of the document. Although ACART has set out its proposed advice to the Minister, it is open to changing its views. Your comments will help ACART to finalise its advice to the Minister.

Sylvia Rumball
Chair, Advisory Committee on Assisted Reproductive Technology

How to Have Your Say

Your feedback is important to help ACART finalise its advice on the use of in vitro maturation. Please take this opportunity to have your say. You may make a submission on your own behalf or as a member of an organisation. A summary of submissions will be released along with ACART's advice to the Minister.

ACART welcomes your views on any or all of the issues raised. However, there are some key questions we would like you to think about and comment on. These questions are set out in a detachable submission form at the back of this document.

You can contribute your views by:

1. emailing a completed submission form or your comments to acart@moh.govt
2. writing down your views on the submission form and posting it to:
   ACART Secretariat
   PO Box 5013
   Wellington.

The closing date for submissions is 16 March 2009.

All submissions will be considered and ACART will revise the guidelines as appropriate. Consultation must then take place with the Minister of Health before the guidelines are issued to ECART.

Additional copies of this discussion paper are available from the ACART website www.acart.health.govt.nz or from:

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Executive Summary

The Human Assisted Reproductive Technology Order 2005 established a list of procedures that could be undertaken by health professionals without the need for review by the Ethics Committee on Assisted Reproductive Technology (ECART). It also explicitly excluded some procedures, including any procedure that involves the collection of immature eggs or the use of eggs that have been matured by in vitro maturation.

The Advisory Committee on Assisted Reproductive Technology (ACART) has reviewed recent evidence and considered the risks, benefits and ethical issues associated with the use of in vitro maturation (IVM). ACART proposes to recommend to the Minister of Health that the collection of immature eggs and the use of eggs that have been matured by IVM now become an established procedure. Following are the key points noted by ACART:

- There is a reduction in the risk to women of ovarian hyperstimulation and related complications compared with conventional in vitro fertilisation (IVF).
- IVM may provide a preferred treatment option for women with polycystic ovarian syndrome in particular, but also for couples where male infertility is the only identified cause of infertility, and for women who respond poorly to or wish to reduce or avoid ovarian stimulation.
- IVM has an implantation rate approximately half that of conventional IVF, a miscarriage rate approximately double that of conventional IVF and a birth rate approximately half that of conventional IVF. However, evidence suggests that the risks to the resulting child are no greater than those associated with conventional IVF and intracytoplasmic sperm injection (ICSI).
- Informed consent is a key ethical issue associated with the use of IVM.
- The best way to manage the few ethical issues associated with the use of IVM is through direct discussions between clinicians and patients.
- There has been a reasonable uptake of the technology worldwide, with 300 to 400 babies born following IVM. It appears that outcomes are similar to IVF and ICSI babies, although there have not yet been enough babies born to determine absolute risks for specific health abnormalities.
- Only the United Kingdom has specifically approved IVM for use and no country requires ethical review, as it is largely seen as a variation on conventional IVF.

ACART considers that if the use of IVM in fertility treatment is approved as an established procedure, it will be important to monitor the outcomes for children born following IVM in New Zealand and around the world. ACART has the responsibility for such monitoring in New Zealand.

1 Introduction

ACART's role

ACART's role under the Human Assisted Reproductive Technology Act 2004 (HART Act 2004) is to:

- issue guidelines and advice to the Ethics Committee on Assisted Reproductive Technology (ECART) on any matter relating to any kind of assisted reproductive procedure or human reproductive research
- provide the Minister with advice on aspects of, or issues arising out of, different kinds of assisted reproductive procedures or human reproductive research
- monitor the application and health outcomes of assisted reproductive procedures and established procedures and developments in human reproductive research.

Scope of this document

Under the HART Act 2004 ACART could recommend that the use of IVM in fertility treatment be:

- an established procedure
- subject to ethical approval on a case-by-case basis (therefore requiring guidelines)
- subject to a moratorium
- prohibited.

ACART has previously been advised by the Ministry of Health that it is not an option under the HART Act to classify the use of a fertility treatment, however novel, as 'human reproductive research' or 'innovative practice', and therefore make it subject to guidelines and ECART review. The understanding is that 'human reproductive research' refers only to research on or involving gametes or embryos, but not research involving gametes or embryos and human participants. This is, however, not obvious from the definition in the HART Act and ACART has sought further advice from the Ministry of Health.

An established procedure is a procedure that is declared established under section 6 of the HART Act 2004 and that can be routinely undertaken by fertility clinics without the clinics having to seek ethical approval from ECART on a case-by-case basis.

ACART has decided that when it considers any new technology it will follow the process set out in the HART Act 2004 for determining if a procedure should become an established procedure. In giving its advice to the Minister of Health, ACART is required by the HART Act 2004 to provide the Minister with a report that sets out:

- information about the procedure or treatment
- an assessment, drawn from published and peer-reviewed research, of the known risks and benefits to health of the procedure or treatment
- advice on whether, in its expert opinion, the known risks to health resulting from the procedure or treatment fall within a level of risk that is acceptable in New Zealand

- an ethical analysis of the procedure or treatment
- advice on whether, in its expert opinion, the Minister should recommend that the procedure or treatment be declared an established procedure.

This document follows the above format.

Abbreviations and terms used

Assisted reproductive technology is a complex topic and this document uses a number of technical terms. In the following discussion, where a technical term is used in the text for the first time it is given in **bold type** and you will find its meaning explained in the glossary on page 13.

Where a term that has a commonly accepted abbreviation is used frequently, the first instance of the abbreviation will include the full spelling of the term and subsequent uses will rely on the abbreviation alone. Some of the most common abbreviations found in this document are:

ACART	Advisory Committee on Assisted Reproductive Technology
ECART	Ethics Committee on Assisted Reproductive Technology
HART Act 2004	Human Assisted Reproductive Technology Act 2004
IVF	in vitro fertilisation
IVM	in vitro maturation

2 Information about IVM

What is IVM?

In vitro maturation (IVM) involves removing immature eggs that have yet to complete their growth, and subsequently maturing these eggs in the laboratory. It is a process that is added prior to in vitro fertilisation (IVF) to replace the maturation process the eggs would normally undergo within the **ovary**. Once mature, the eggs undergo insemination and are used as in conventional IVF.

The major differences between conventional IVF and IVF with IVM are:

- IVM patients receive little or no ovarian hormonal stimulation, whereas in conventional IVF the patient's ovaries are stimulated with large doses of hormones to release a number of mature eggs. Hormonal stimulation is associated with a risk of **ovarian hyperstimulation syndrome** (OHSS) which can adversely affect a woman's health.
- in conventional IVF eggs mature within the ovaries, whereas with IVM eggs are matured ***in vitro*** for one to two days, prior to being used in IVF treatment.

Use of IVM

IVM is at an early stage of acceptance as part of fertility treatment. In most countries it is permitted but rarely practised. Generally, it has not been 'approved' for use because it is largely seen as a variation on conventional IVF, and so is not separately regulated. Only the United Kingdom has specifically approved the use of IVM as an adjunct technology to IVF.

The first IVM baby was born in the United States in 1983. During the 1980s and 1990s there were relatively large numbers of IVM treatment cycles, but few pregnancies. In contrast, the current decade has seen a reasonable number of babies born following IVM, particularly in Scandinavia and Asia. At this stage 300 to 400 babies have been born worldwide following IVM.

IVM in New Zealand

In March 2005 the Advisory Group on Assisted Reproductive Technology (AGART)[1] recommended that because of the relatively novel nature of IVM and the lack of evidence available on the associated health outcomes, it should continue to be monitored and not, at that stage, placed on the list of established procedures.

[1] AGART was convened in June 2004 to provide the Director-General of Health with an assessment of the risks and benefits associated with assisted reproductive procedures. Its work resulted in the list of established procedures set out in the Human Assisted Reproductive Technology Order 2005. ACART, a different committee, was subsequently established under the HART Act to undertake ongoing work in relation to assisted reproductive technology.

The Human Assisted Reproductive Technology Order 2005 subsequently set out the established procedures. It also explicitly excluded some procedures, including any procedure that involves the collection of immature eggs or the use of eggs that have been matured by IVM.

Options for the use of IVM eggs

If IVM is approved for use in New Zealand following public consultation and ACART's advice to the Minister of Health, eggs that have been matured by IVM could, in addition to being used by a woman for her own fertility treatment, be donated to others for use in fertility treatment or donated for use in research.

Donation for use in fertility treatment

Currently, women may donate fresh eggs to other women whose own eggs are not viable. Donors may be personal donors who donate to friends or relatives, or they may be clinic-recruited donors who do not know the recipient. Potentially, the donation to others of eggs matured by IVM could also be allowed. Donation of in vitro matured eggs between family members other than sister and sister or cousin and cousin would be subject to the *Guidelines on Donation of Eggs or Sperm between Certain Family Members* and would require ECART approval.

Donation for use in research

All **human reproductive research** must proceed under guidelines and with review by ECART.

Interim guidelines for ECART regarding research on **gametes** and non-viable embryos were approved by the former Minister of Health, Hon Annette King, under section 83 of the HART Act 2004. The guidelines allow eggs, sperm and non-viable embryos to be donated for research purposes, provided ECART has given specific approval for each research proposal.

ACART expects to review these guidelines within the next 18 months. Public consultation will be undertaken as part of this review, as required by the HART Act.

3 Assessment of Known Risks and Benefits to Health Associated with the Use of IVM

This section summarises the known risks and benefits associated with the use of IVM in fertility treatment. The information is discussed in more detail in Appendix B.

Risks

Egg collection

There is an increased incidence of ovarian bleeding associated with the collection of immature eggs. This is because the collection procedure differs from that used in conventional IVF. With IVM the eggs are usually more embedded in the follicle wall and have to be scraped off, and as a result it is associated with more ovarian bleeding than egg collection in conventional IVF. There is, however, no publication of an adverse event arising from egg collection during an IVM treatment cycle.

Egg development

IVM does not lead to any observable damage to the eggs. They mature readily and have fertilisation rates comparable with eggs in conventional IVF. However, IVM eggs appear to have significant levels of spindle (the part of a cell that holds the chromosomes in place ready for fertilisation) and/or chromosomal defects. This damage is reflected in the impaired developmental potential of embryos formed with IVM eggs (see below), which may be a contributing factor to lower implantation and higher miscarriage rates compared with conventional IVF.

Embryo development

IVM compromises subsequent embryo development rates. The reasons for this are complex and not yet fully understood. The best measure of embryo development is the implantation rate. In IVM, the implantation rate is approximately half that of conventional IVF, most likely due to an increase in spindle and chromosome damage in developing eggs. Possibly for the same reason, miscarriage rates are approximately double that of conventional IVF and the live birth rate half that of conventional IVF.

This topic is the subject of intense research. Embryo development rates following IVM of eggs are slowly, but consistently, improving with time.

Outcomes for children born following IVM

There is limited information on obstetric and postnatal outcomes following IVM as the children are still young and, although there has been a reasonable uptake of the technology, there are still too few births to determine absolute risks for specific health abnormalities.

From the published data there appears to be no major neonatal or infant health complications following IVM compared with conventional IVF and **intracytoplasmic sperm injection (ICSI)**. Gestational age, growth restriction, **Apgar scores**, birth weights and sex ratios are all comparable with births resulting from IVM, IVF and ICSI. No major chromosomal abnormalities have been reported in children born following IVM, and the rate of congenital abnormalities appears consistent with that of IVF generally. Physical and neurological development in children born following IVM also appear to be normal.

Reports, therefore, indicate very few obstetric or child health conditions following IVM, and at this stage it appears that outcomes are similar to those for IVF and ICSI babies. However, the data published is preliminary, and ongoing monitoring as more studies are published will be necessary to assess the risks associated with IVM.

Benefits

The major benefit of IVM is for women with **polycystic ovarian syndrome** (PCOS) or polycystic ovaries. Women with PCOS are at particular risk of developing **ovarian hyperstimulation syndrome** (OHSS) as a result of the hormones used to stimulate the ovaries into releasing a number of mature eggs. IVM therefore provides an alternative, safer option for these women. OHSS occurs in approximately 5 percent of women undertaking an IVF cycle. It is usually mild and self-limiting, but in some cases urgent medical attention is needed, and the condition can be life threatening.

IVM may also benefit couples with male factor infertility, and women who respond poorly to or who wish to reduce or avoid the high doses of hormones used in conventional IVF. IVM is also a cheaper option due to the use of no or lower doses of hormones.

At this stage, however, most women will likely opt for conventional IVF because its success rate in producing a live birth is considerably higher than with IVM.

Monitoring

The lack of evidence discussed above highlights the need for data collection on the application of IVM and the outcomes for children born in New Zealand following IVM. ACART has the statutory responsibility to monitor the application and health outcomes of assisted reproductive procedures and established procedures, and will work with the Ministry of Health to determine the best means of undertaking this function.

The HART Act contains regulation-making powers to require those performing procedures to keep and report information to ACART, any duly authorised representative of ACART, or the Director-General of Health. An outcome of discussions with the Ministry of Health may be the making of regulations.

1. Given these risks and benefits, what is your opinion on ACART's proposed advice to the Minister of Health? Please give reasons for your views.

4 Acceptability of the Risks Associated with the Use of IVM

ACART has developed a framework to help assess the acceptability of risks associated with a particular procedure or treatment. This framework has been used here to consider the acceptability of the risks associated with the collection of immature eggs and the use of eggs that have been matured by IVM in fertility treatment.

This section summarises ACART's views on the acceptability of the risks associated with IVM. The full risk analysis is set out in Appendix A.

There are very few known health risks associated solely with the use of IVM, and ACART's analysis indicates that the known risks are at a level that may be acceptable in New Zealand.

- IVM provides a safer treatment option for women with PCOS, couples with male factor infertility and women who respond poorly to or wish to reduce or avoid the high doses of hormones that are used in conventional IVF.
- Although IVM has an implantation rate approximately half that of conventional IVF, a miscarriage rate approximately double that of conventional IVF, and about half the birth rate of conventional IVF, outcomes for babies appear, at this stage, to be similar to those associated with the use of conventional IVF and ICSI.
- There has been a reasonable uptake, which enables a developing picture of outcomes associated with the technology and approximately 300 to 400 births in other countries.
- No country has banned IVM, the United Kingdom has explicitly approved IVM, and most countries allow it as a variation on conventional IVF.
- There are few ethical issues associated with the use of IVM, and ACART considers these issues are best dealt with in discussions between the clinician and the patient.
- ACART considers the use of IVM to be consistent with the purposes and principles of the HART Act 2004.

There is, however, a lack of data on outcomes for children born following IVM. Implementation of a monitoring framework will, therefore, be an important part of ACART's recommendations to the Minister.

5 Ethical Analysis

Overall, ACART considers that there are few ethical issues associated with the use of IVM. This section discusses these issues.

Informed consent

The HART Act 2004 requires that no assisted reproductive procedure be performed on an individual unless the individual has made an informed choice and given **informed consent**.

Fertility services and associated health professionals are subject to the Code of Health and Disability Services Consumers' Rights 1996, which confers 10 rights on consumers of health and disability services, including the right to make an informed choice and give informed consent.

In addition, more detailed requirements for informed consent, specific to assisted reproduction, are set out in the **Fertility Services Standard**. This standard sets out the regulations under which fertility professionals are required to operate. The standard requires that:

- full information be provided, both in writing and verbally, on all aspects of the treatment, including:
  - an acknowledgement that the treatment may be unsuccessful
  - suggestions for any alternative options
  - details of the components of the procedure
  - a list of all risks and possible side effects or complications
  - an explanation of all terminology
- information be provided about the experimental nature of the treatment and the lack of evidence about the health of children born following IVM
- adequate time and opportunity be provided for patients to discuss their treatment with competent staff.

Donating eggs matured by IVM for treatment purposes

At present egg donation is an established procedure under the HART Act 2004. The established procedure does not specify whether the donated eggs may have been matured by IVM.

ACART considers that the use of eggs matured by IVM should not be restricted to a woman's own use. ACART sees no reason to prohibit the donation of eggs matured by IVM for use in fertility treatment, provided that women receiving donated eggs matured by IVM are informed of the risks associated with their use and of the procedure's relative novelty as a form of treatment.

Māori perspectives

The HART Act requires that everyone exercising powers or performing functions under this Act must be guided by its principles, including the principle that 'the needs, values, and beliefs of Māori should be considered and treated with respect'.

Māori perspectives are diverse and are likely to differ both between and within iwi, hapū and whānau. Although it is unlikely there will be a single Māori view on the use of IVM in fertility treatment, there may be common concerns that arise from within **te ao Māori** (the Māori world view). This section outlines some of the fundamental values and beliefs of Māori that are relevant to fertility treatment.

Knowledge and protection of **whakapapa** is a key concern that has been expressed to ACART due to the potential implications for entitlement to resources, such as land, and for wider whānau relationships. Some Māori are concerned that whakapapa would be disrupted through the use of some assisted reproductive procedures. The HART Act requires that information about donors be kept by providers and the Registrar-General of Births, Deaths and Marriages. The Act specifies that ethnicity and any relevant cultural affiliation must be recorded, along with, in the case of Māori donors, the donor's whānau, hapū and iwi affiliations.

Some Māori have raised concerns over who has the **mana** to make decisions about the use of assisted reproductive technology. Recognition of mana through the potential involvement of whānau in decision-making is important because it:

- gives whānau an opportunity to explore ways to address infertility (an expression of **whanaungatanga**)
- provides a space in which to discuss the cultural implications of assisted reproduction, including rights of acknowledgement, access to information beyond that set out in the HART Act, the use of surnames, and claims to resources to which the donor's family may be beneficiaries.[2]

The Fertility Services Standard provides for the involvement of whānau in fertility treatment.

In the context of assisted reproduction, **tino rangatiratanga** involves the right to self-determination at both an individual and collective level, and the ability to express **kaitiakitanga** (guardianship). Eggs remain under the mana of the woman from whom they have been taken and, if subsequently donated, this remains true until they enter the **whare tangata** (womb). In this case, the responsibility to protect whakapapa resides with the Registrar-General of Births, Deaths and Marriages, and with whānau, hapū and iwi.

ACART hopes that this discussion will encourage Māori to consider **tikanga** (protocols) that are relevant to assisted reproduction, and appropriate ways to respect the values and beliefs of Māori in the development of policy and the provision of services to treat infertility.

[2] M Hudson, C Henry, A Shelling, et al. 2008. *Recognising the Needs, Values and Beliefs of Māori in Assisted Reproductive Technologies*. Paper presented to the Bioethics Conference, Dunedin.

‘Surplus’ embryos

Contemporary New Zealand is home to a variety of religions. For some the use of any assisted reproductive treatment may be unacceptable. Others agree with some forms of treatment, but regard as unacceptable embryo freezing and the dilemma of decisions about the fate of embryos that are surplus to reproductive requirements. IVM produces fewer eggs because it uses no or low doses of hormones to stimulate the ovaries. As a result there are fewer embryos for implantation, thus reducing the numbers of surplus embryos to be frozen. IVM may, therefore, provide a more acceptable alternative to conventional IVF for people who have these concerns.

Equity

Another issue relevant to the use of IVM concerns access to the technology. Due to the reduced use of hormones it costs less than conventional IVF. This may help increase equity of access to fertility treatment.

2. Has ACART identified all of the ethical issues relevant to the use of IVM in fertility treatment? Do any of the issues identified above, or any other ethical issues, affect ACART’s proposed advice that the use of IVM should be allowed in fertility treatment? If so, how?

6 Conclusion: Proposed Advice to the Minister

ACART proposes to recommend to the Minister that the collection of immature eggs and the use of eggs that have been matured by in vitro maturation become an established procedure for individual treatment purposes and donation for treatment purposes.

ACART's reasons for its recommendations are as follows.

- Although IVM is still a relatively new technique, the available evidence suggests that the risks to the resulting child associated with the use of IVM are similar to those associated with the use of conventional IVF and ICSI.
- For some women, particularly those with PCOS, IVM may be the preferred option available to preserve their fertility due to their increased risk of OHSS.
- There appear to be few ethical issues associated with the use of IVM, and ACART considers that these issues can best be managed in discussions between clinician and patient.

If the Minister approves the use of IVM as an established procedure, it will be ACART's responsibility to monitor the health outcomes of children born following IVM.

3. Should the use of IVM in fertility treatment become an established procedure? If not, why, and how should the use of IVM be regulated?
4. Should the use of in vitro matured eggs in fertility treatment be limited to the individuals the eggs came from, or should the eggs be able to be donated to others for use in fertility treatment?

Glossary

Advisory Committee on Assisted Reproductive Technology (ACART)	The advisory committee established under New Zealand's Human Assisted Reproductive Technology Act 2004.
Advisory Group on Assisted Reproductive Technology (AGART)	The group convened in June 2004 to provide the Director-General of Health with an assessment of the risks and benefits associated with assisted reproductive technologies. The group's work resulted in the list of established procedures.
Apgar score	A summary score to evaluate the health of a newborn baby whereby five simple criteria are scored on a scale from zero to two and the scores are added.
Assisted reproductive procedure	The Human Assisted Reproductive Technology Act 2004 defines an assisted reproductive procedure as a procedure performed for the purpose of assisting human reproduction that involves: • the creation of an in vitro human embryo, or • the storage, manipulation or use of an in vitro human **gamete** or an in vitro human embryo, or • the use of cells derived from an in vitro human embryo, or • the implantation into a human being of human gametes or human embryos.
Embryo	This includes a **zygote** and a cell or group of cells that has the capacity to develop into an individual, but does not include stem cells derived from an embryo.
Established procedure	A procedure that is declared established under section 6 of the Human Assisted Reproductive Technology Act 2004 and therefore does not require approval from ECART.
Ethics Committee on Assisted Reproductive Technology (ECART)	The ethics committee established under New Zealand's Human Assisted Reproductive Technology Act 2004.
Fertility Services Standard	A standard issued under the Health and Disability Services (Safety) Act 2001 that sets out the safety and quality measures that all fertility services provided by New Zealand fertility clinics must meet. This standard will come into force in 2009.
Gamete	An egg or sperm, whether mature or not, or any other cell (whether naturally occurring or artificially formed or modified) that (i) contains only one copy of all or most chromosomes and (ii) is capable of being used for reproductive purposes.
Human Assisted Reproductive Technology Act 2004 (HART Act 2004)	An act to secure the benefits of, and regulate, assisted reproductive technology and human reproductive research.
Human reproductive research	Research that uses or creates a human gamete, a human embryo or a hybrid embryo.
Informed consent	A person's voluntary agreement, based on adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic or preventive procedure.

Intracytoplasmic sperm injection (ICSI)	A procedure in IVF where one selected sperm is injected into the cytoplasm of an egg to achieve fertilisation.
In vitro	In relation to an embryo, a foetus, gamete or cell, means an embryo, a foetus, gamete or cell that is outside a living organism.
In vitro fertilisation (IVF)	The uniting of egg and sperm outside the body (in the laboratory).
Kaitiakitanga	Guardianship.
Mana	A concept that implies authority, influence and prestige, as well as the recognition of these qualities.
National Ethics Committee on Assisted Human Reproduction (NECAHR)	An ethical review and policy body that was established in 1993 to manage some aspects of assisted reproductive technologies before the passing of the Human Assisted Reproductive Technology Act 2004.
Ovarian hyperstimulation syndrome (OHSS)	A complication of some forms of fertility medication.
Ovary	The egg-producing reproductive organ found in females.
Polycystic ovarian syndrome (PCOS)	A disorder that affects approximately 5 percent of women. Symptoms can include lack of regular ovulation and/or menstruation. It is a leading cause of infertility.
Te ao Māori	Māori world view.
Tikanga	Protocols or the 'right ways' of dealing with issues that arise in relation to a topic.
Tino rangatiratanga	The right to self-determination at both an individual and a collective level.
Whakapapa	The genealogical descent of all living things from the gods to the present time.
Whanaungatanga	The obligation of care and support among relatives.
Whare tangata	Womb.
Zygote	The product of the fusion of an egg and a sperm. It contains two copies of each chromosome, one from each parent. The zygote develops into an embryo.

Appendix A: Risk-acceptability Analysis of the Collection of Immature Eggs and the Use of Eggs that have been Matured by In Vitro Maturation

This analysis uses information drawn from the report *The Use of In Vitro Maturation* (IVM) (see Appendix B).

Summary

There are few known risks associated with the collection of immature eggs and the use of eggs that have been matured by IVM. Analysis of these risks indicates that the known risks to health associated with IVM may be acceptable at this stage. In summary:

- IVM provides a treatment option for women with polycystic ovarian syndrome, couples with male factor infertility, and women who respond poorly to or wish to reduce or avoid ovarian stimulation regimes used in conventional IVF
- IVM has an implantation rate approximately half that of conventional IVF and a miscarriage rate approximately double that of conventional IVF
- the live birth rate is probably half that associated with conventional IVF
- there has been a reasonable uptake of the technology worldwide, with 300 to 400 children recorded as having been born following IVM
- IVM is not prohibited in any country
- only the United Kingdom has specifically approved IVM for use, and no country requires ethical review, because it is largely seen as a variation on conventional IVF
- there are few ethical issues associated with IVM, indicating that these issues are best dealt with between clinician and patient
- the use of IVM appears to be consistent with the principles of the HART Act.

There is, however, a lack of information on neonatal and long-term developmental outcomes for children born following IVM as it is still at an early stage of use as a treatment for infertility. Ongoing monitoring of outcomes is needed to assess the long-term risks of the procedure.

Risk

'Risk' is a combination of two concepts:

- the likelihood of an effect occurring

- the consequences of an effect if it occurs.

Likelihood and consequences can be described qualitatively or quantitatively.

Likelihood

To consider the likelihood of risks associated with the collection of immature eggs and the use of eggs that have been matured by IVM, ACART used the following categories.

	Category	**Description**
A	Frequent	Is expected to occur again either immediately or within a short period of time (likely to occur most weeks or months)
B	Likely	Will probably occur in most circumstances (several times a year)
C	Possible	Possibly will recur – might occur at some time (may happen every one to two years)
D	Unlikely	Possibly will recur – could occur at some time in two to five years
E	Rare	Unlikely to recur – may occur only in exceptional circumstances (may happen every five to 30 years)

Consequences

To assess the consequences of the risks associated with the collection of immature eggs and the use of eggs that have been matured by IVM, ACART used the following descriptors of consequences.

Descriptor	**Descriptions (risks and costs)**
Serious	Patients whose death is unrelated to the natural course of the illness and differs from the immediate expected outcome of patient management
Major	Patients suffering a major permanent loss of function (sensory, motor, physiological or psychological) unrelated to the natural course of the illness and differing from the expected outcome of patient management
Moderate	Patients with permanent reduction in bodily function (sensory, motor, physiological or psychological) unrelated to the natural course of the illness and differing from the expected outcome of patient management, or any of the following: • increased length of stay as a result of the incident • surgical intervention required as a result of the incident
Minor	Patients requiring an increased level of care, including review and evaluation, additional investigations or referral to another clinician
Minimum	Patients with no injury or increased level of care or length of stay

Comparing the risks

ACART has used the following table to quantify and compare the risks associated with the collection of immature eggs and the use of eggs that have been matured by IVM. Known risks associated with adjunct procedures, such as IVF, are included in the table for additional information.

Likelihood	Consequences				
	Serious	**Major**	**Moderate**	**Minor**	**Minimal**
A (frequent)	E	E	H	M	M
B (likely)	E	E	H	M	L
C (possible)	E	H	H	M Miscarriage rate higher than conventional IVF	L Increased ovarian bleeding compared with mature egg removal in conventional IVF
D (unlikely)	E	H	M	L	L
E (rare)	H	M No major malformations in children born, beyond those found generally in IVF and ICSI	M	L	L

Notes:
E = extreme risk
H = high risk
M = moderate risk
L = low risk

In addition, IVM compromises subsequent embryo development. The reasons for this are complex and still not fully understood. This leads to an implantation rate and a live birth rate that are approximately half that of conventional IVF. Success rates have been improving slowly over time and are expected to continue to improve.

Relevant principles of the Human Assisted Reproductive Technology Act 2004

ACART is guided in its decision-making by the principles of the HART Act 2004. All of these principles are relevant to a risk-acceptability analysis. The principles can be divided into health and ethical principles.

Health principles

- The health and wellbeing of children born as a result of the performance of an assisted reproductive procedure or an established procedure should be an important consideration in all decisions about that procedure.

- The human health, safety and dignity of present and future generations should be preserved and promoted.
- Although all persons are affected by assisted reproductive procedures and established procedures, women, more than men, are directly and significantly affected by their application, and the health and wellbeing of women must be protected in the use of these procedures.

The collection of immature eggs and the use of eggs that have been matured in vitro appear to be consistent with the health principles of the HART Act.

Three to four hundred children have been born worldwide following IVM. From the studies reported in the literature there is no noticeable increase in abnormalities in these children. There are, however, too few children to calculate the absolute risks for specific abnormalities found in pregnancy and birth.

The primary benefit of IVM is to the women being treated. Compared with conventional IVF, IVM removes the need to administer to women large doses of follicle stimulating hormone, which can lead to ovarian hyperstimulation syndrome (OHSS). OHSS occurs in approximately 5 percent of women undertaking an IVF cycle. It is usually mild and self-limiting, but in some cases urgent medical attention is needed and the condition can be life-threatening.

Women with polycystic ovaries or polycystic ovarian syndrome (PCOS) would particularly benefit from IVM because they have an increased risk of OHSS.

Ethical principles

- No assisted reproductive procedure should be performed on an individual and no human reproductive research should be conducted on an individual unless the individual has made an informed choice and given informed consent.
- Donor offspring should be made aware of their genetic origins and be able to access information about those origins.
- The needs, values and beliefs of Māori should be considered and treated with respect.
- The different ethical, spiritual and cultural perspectives in society should be considered and treated with respect.

The collection of immature eggs and the use of eggs that have been matured in vitro appear to be consistent with the ethical principles of the HART Act.

IVM is an emerging technology. It is less successful in terms of pregnancy and birth rates than IVF, and the outcomes for children are not well known, although they appear to be similar to outcomes for children born following conventional IVF and ICSI. Informed consent is a key ethical principle associated with IVM. It would be essential that those considering using IVM fully understand the current limitations of this technology.

Under the HART Act, the donor register will facilitate any child born from donated eggs becoming aware of his or her genetic origins. This will ensure that children born from donated IVM eggs are able to learn about their genetic origins.

Māori perspectives are diverse and are likely to differ both within and between iwi, hapū and whānau. However, there are likely to be common concerns within te ao Māori.

IVM may be more acceptable to those whose ethical and spiritual perspectives mean that they are opposed to the disposal of surplus embryos associated with conventional IVF, because fewer eggs, and therefore fewer embryos, result due to the absence of hyperstimulation.

Effect of data uncertainty

IVM is an emerging technology, so there are a number of uncertainties in the information.

IVM compromises subsequent embryo development rates. This is evident in nearly all human and animal studies, but the reasons for this are complex and not yet fully understood. The best measure of embryo development rate is implantation rate. Implantation rates from IVM eggs are usually about half those of conventional IVF eggs, most likely due to an increase in spindle and chromosome damage in developing eggs. Using current technology, miscarriage rates following IVM are approximately double those of conventional IVF, and live birth rates approximately half those of conventional IVF.

There is limited information on the obstetric and postnatal outcomes of IVM pregnancies because the technology is relatively new, the children are still young and there have been relatively few births. Although reports indicate very few obstetric or perinatal conditions from IVM pregnancies, ongoing monitoring of international data will be essential to assess the risks associated with this procedure as more studies are published.

These limitations in the information highlight the importance of ongoing monitoring if IVM is approved for use in New Zealand.

Effect of cumulative risk

The risks as set out above are an increase in ovarian bleeding and an increased miscarriage rate compared with conventional IVF. However, compared with conventional IVF, the overall risks may be lower due to the reduced use of gonadotrophins.

Revealed preferences

If the risks of this technology are similar to those of other, more common, assisted reproductive technologies, this might indicate that people would consider that the risks associated with the technology are acceptable.

Because the success rate of IVM is considerably less than that of IVF it is relatively infrequently used internationally. It has not been undertaken in New Zealand because it was explicitly excluded from the established procedures set out in the HART Order in Council 2005 due to its novelty at the time.

Countries from which there are peer-reviewed published studies of pregnancies or births from IVM are: Australia, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, South Korea and Sweden. There are also non-peer-reviewed reports of its use in China, Ireland, Israel, the Middle East, the United States and Vietnam. IVM is not banned in any country and does not require ethical review in any country. In most countries it is considered an add-on to IVF, although in the United Kingdom it has been explicitly approved for use. It is commonly used in Asia and Scandinavia. Three to four hundred babies have so far been born worldwide following IVM.

There has been some interest within New Zealand in the use of IVM, including an application to NECAHR immediately prior to the passing of the HART Act, and, subsequently an application to ECART, media coverage, parliamentary questions and a direct letter to ACART from a potential consumer. The interest in using IVM has primarily been in relation to women with polycystic ovarian syndrome (PCOS).

Risk reduction/management

The risks associated with the use of assisted reproductive technologies can be mitigated or managed by using clinical indicators. However, there are no obvious patient exclusion criteria specific to IVM. In contrast with conventional IVF, patients with PCOS or polycystic ovaries may benefit from IVM because of their increased risk of OHSS.

There is little information about neonatal and long-term developmental outcomes for children born from IVM eggs, so it would be important, if IVM were to be approved, for ACART to monitor outcomes in New Zealand and internationally.[3]

Benefits

Although section 6(c) of the HART Act 2004 only requires ACART to assess the risks of the procedure, some consideration of the benefits of the procedure may help to assess the acceptability of those risks. If the benefits are important, these benefits may make the risks associated with the technology more acceptable.

The benefits associated with the collection of immature eggs and the use of eggs that have been matured through IVM are considerable for women with polycystic ovaries and PCOS. Women with PCOS are at increased risk of OHSS, which is associated with the use of conventional IVF. IVM may be the best option for these women to bear children. In addition, couples with male factor infertility and women who respond poorly or wish to reduce or avoid ovarian stimulation regimes used in conventional IVF may benefit from IVM.

[3] Under section 35(2)(a) of the HART Act 2004, ACART is responsible for monitoring the application and health outcomes of assisted reproductive procedures and established procedures.

Decision-maker

From the ethical analysis presented above there appear to be very few ethical issues associated with the collection of immature eggs and the use of eggs that have been matured by IVM, with the key issue being informed consent. It may even reduce some ethical concerns for some people in that fewer embryos are created compared with conventional IVF.

IVM is likely to be used by few women at this stage because it results in about half the rate of live births when compared with conventional IVF. Although birth rates remain relatively low, it may be the preferred option for women with PCOS in particular.

A technology that has very few attendant ethical issues does not require oversight by ECART. If the majority of issues are those that are better dealt with in discussion between the clinical team and the patient/s, this might indicate that the risks are acceptable for the purpose of making that procedure an established procedure.

In the past ACART has generally considered that it is those procedures that involve third parties that require ethical review, particularly with a view to ensuring informed consent has been given.

In the case of the collection of immature eggs and the use of eggs that have been matured by IVM, the ethical issues are such that a reasonable individual, in that individual's position, could weigh up and decide on the risks themselves, in discussion with their clinical team. Therefore, it may be appropriate to make the collection of immature eggs and the use of eggs that have been matured through IVM an established procedure. This would be consistent with ACART's pre-consultation view on the regulation of the use of frozen eggs.

Alternatively, because the procedure is still emerging, it could be treated as innovative practice and guidelines developed for ECART to consider applications to use the procedure as part of an intervention study. Note that several submitters have come to this conclusion in relation to the use of frozen eggs. These submitters are concerned at the experimental nature of the use of frozen eggs and the importance of consistent information for women, and the need to monitor the application and outcomes of the use of frozen eggs.

Note also that, at the time the HART Act was passed, ACART was advised by the Ministry that treating a procedure as innovative practice or research were not options under the Act. ACART has recently questioned this and written to the Ministry seeking clarification.

Appendix B:
The Use of In Vitro Maturation

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Executive summary

In vitro maturation (IVM) of human oocytes provides options in the treatment of infertility. As an adjunct procedure to conventional *in vitro* fertilisation (IVF), IVM provides a treatment option for women with Polycystic Ovarian Syndrome (PCOS), for couples where male factor infertility is the only identified cause of infertility, and for women who respond poorly or wish to reduce/avoid ovarian stimulation regimes used in conventional IVF. IVM is practised in numerous countries throughout the world and is not prohibited anywhere.

Analysis of the literature shows that the adoption of IVM has been limited in particular by poor embryo survival and pregnancy rates following embryo transfer. Implantation rates are approximately 50% of, and miscarriage rates approximately double that of, conventional IVF, but some laboratories are now reporting much improved results. Consequently, multiple embryo transfer is commonly performed without a notable increase in multiple births above conventional IVF. Couples' expectations of success of treatment also need to be more carefully managed with IVM.

Despite the reduced embryo implantation rate and increased miscarriage rate, there is little evidence that IVM is associated with perturbations in fetal and neonatal growth, chromosomal abnormalities, congenital malformations, or cognitive development, over and above that encountered in conventional IVF and intra cytoplasmic sperm injection (ICSI) offspring. This is confirmed in the animal literature, where IVM also reduces initial embryo viability but established pregnancies deliver apparently normal offspring.

There is a clear reduction in the risk to women of ovarian hyperstimulation and related complications when undertaking IVM treatment as compared to conventional IVF. In countries where there is no subsidisation of treatment, especially for the cost of hormones, there are also reduced costs per cycle to couples.

There are deficiencies in the available data, especially dealing with neonatal and long-term developmental outcomes following IVM, where the number of recorded children born from IVM is still less than 500. There is no central registry of IVM offspring and there are no easily identifiable long-term studies in progress.

Our conclusion is that IVM as a therapy is at an early stage of adoption. Further research is required to improve success rates, and further neonatal and post-natal data are required to assess long-term risk of the technique. There is enough preliminary evidence to suggest that if there is a greater risk to neonatal health, then this is relatively small. In contrast, there are immediate health benefits from the reduction in hormone administration to women undergoing IVM as compared with conventional IVF.

Abbreviations used

ART	assisted reproductive technologies
FSH	follicle stimulating hormone
hCG	human chorionic gonadotrophin
HFEA	Human Fertilisation and Embryo Authority (UK)
IU	international units
IVF	*in vitro* fertilisation
IVM	*in vitro* maturation
LH	luteinising hormone
OHSS	Ovarian Hyperstimulation Syndrome
PCO	polycystic ovaries
PCOS	Polycystic Ovary Syndrome

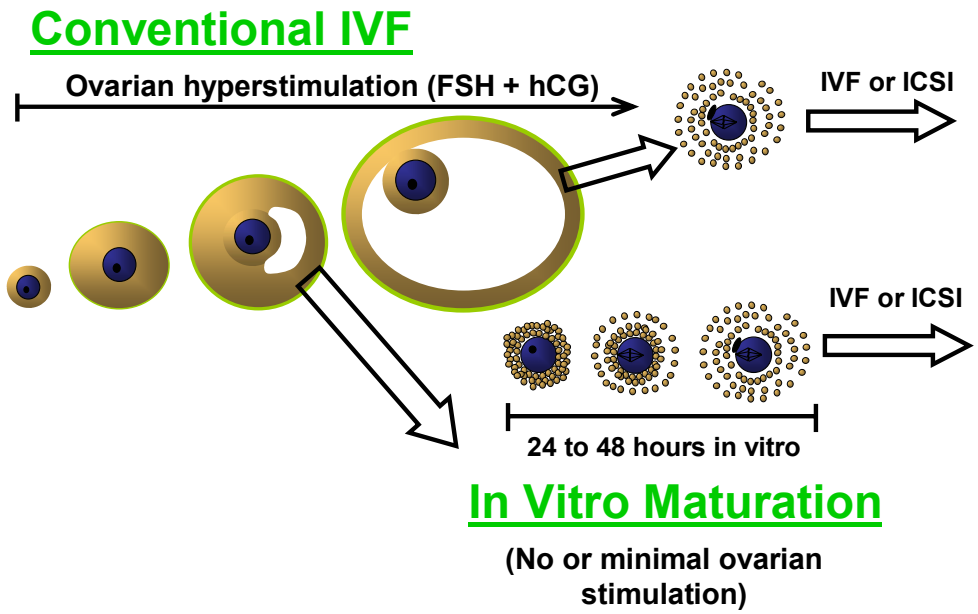
Background

In vitro maturation (IVM) of human oocytes is an adjunct treatment to the process of conventional *in vitro* fertilisation (IVF) within the field of assisted reproductive technologies (ART) used to treat couples that require treatment to resolve their infertility.

What is the process of oocyte in vitro maturation (IVM)?

In vitro maturation (IVM) of oocytes refers to the practice of removing immature cumulus-oocyte complexes from follicles that have yet to complete their growth, and subsequently maturing these oocytes *in vitro*. Figure 1 illustrates the major differences between IVM and conventional IVF.

Figure 1: Schematic of the major differences between IVM and conventional IVF



Note: Firstly, for IVM, patients receive no or minimal ovarian hormonal stimulation, whereas in IVF patients' ovaries are hyperstimulated with large doses of gonadotrophins. Secondly, in IVF, oocyte maturation occurs *in vivo*, whereas in IVM, oocyte maturation occurs *in vitro* for 1–2 days, prior to standard fertilisation procedures.

Which clinical processes are different in IVM?

The majority of the indications for treatment, many aspects of patient treatment and care, and most laboratory practices are common for IVM and IVF. IVM is an additional procedure that is added prior to IVF, which replaces a process that oocytes undertake within ovarian follicles. Within routine IVF procedures this process is manipulated by the administration of exogenous gonadotrophin hormones. The main differences between IVM and IVF treatment cycles are outlined below.

- **Patient preparation:** Women undergoing IVM either completely forgo ovarian hormonal stimulation prior to egg collection or receive minimal stimulation. This is the single largest benefit of IVM and makes the technology particularly attractive to PCOS and PCO patients (see clause 7). There are number of significant clinical variations on IVM.
  - **No stimulation:** patients receive no hormonal stimulation prior to egg pick-up. This protocol is widely practised in Scandinavia and is particularly used with PCOS and PCO patients, but can also be used for non-PCOS patients.
  - **FSH priming:** patients receive minimal FSH stimulation (3–6 days of low-dose FSH) prior to egg pick-up. This protocol is not widely practised.
  - **hCG priming:** patients receive no FSH and receive one bolus dose of 10,000 IU hCG 36 hours prior to egg pick-up. This protocol is widely practised in Canada and South Korea [1] and is particularly used with PCOS and PCO patients, but can also be used for non-PCOS patients.
  - **FSH + hCG priming:** a combination of (b) and (c) above. This protocol is alternatively called 'minimal stimulation IVF' although it usually involves some of the IVM laboratory procedures listed below. This is an emerging trend in ART towards this protocol as IVF success rates continue to increase [2, 3].

- **Laboratory practices:** The process of IVM of human oocytes in the laboratory requires the same equipment and many of the same laboratory standards as other aspects of laboratory practices for the production of embryos in routine IVF cycles. Differences between the IVF process and IVM are:
  - **oocyte pick-up:** there is a slight variation on the oocyte pick-up procedure from routine IVF: IVM oocyte pick-up uses a slightly different needle, reduced aspiration pressure, and is usually associated with increased ovarian bleeding (see clause 12)
  - **use of an IVM medium:** oocytes are cultured *in vitro* for 24–48 hours in a special oocyte maturation medium; once mature, oocytes undergo insemination by ICSI (see clause 12).

A Current status of procedure/treatment

1 Indicate if IVM has been 'approved' for human use in other countries; or alternatively, indicate if IVM has not been banned and is being used for reproductive purposes in other countries

To the best of our investigations, IVM is not banned in any country to date and is commonly practised in some countries (see clause 4). In most countries, such as Australia and USA, IVM is permitted but is rarely practised. IVM is particularly common throughout Asia.

'Approval' for the use of IVM, as such, is rare as in most countries it is regarded as a variation of conventional IVF and so the practice is not separately regulated. This is the situation for the vast number of countries. The only known country where IVM has been identified as an adjunct technology to IVF is the United Kingdom.

2 If it has been approved (or is in use), specify:

(a) which countries, and

IVM has been approved for human clinical use by the UK regulatory body, the Human Fertilisation and Embryo Authority (HFEA). See 2b below for countries in which it is in use.

(b) when approval was given / use began

IVM was approved by the HFEA in its letter CE(00)05 (2 June 2000), where it stated that 'any centre wishing to use this technique in clinical treatment would need first to apply to the HFEA for a licence'. This policy was reiterated as explained in CH(07)01 (5 February 2007), but then altered on 30 November 2007 (CH(07)04), whereby IVF centres were simply to notify their HFEA inspector that they wish to conduct IVM and were required to comply to an amended Code of Practice (G.5.14).

Table 1 documents the chronology of the development of IVM by country, based on peer-reviewed published studies. This table does not contain all human IVM publications, but it includes a large proportion and the most significant studies. The first IVM baby was born in 1983 in the USA. The 1980s and 1990s were characterised by relatively large numbers of IVM treatment cycles with few pregnancies. In contrast, the current decade has generated a higher number of IVM offspring, most notably in Asia and Scandinavia.

(c) the extent or conditions of the approval/use

See 2b above.

3 If it has been banned (or has proven to be controversial), specify

(a) which countries

To the best of our investigations IVM has not been banned in any country. We contacted numerous government regulatory agencies, fertility societies and individual colleagues from around the world and determined IVM is not banned in any country. Most reported no specific regulation of IVM.

Table 1: Peer-reviewed evidence of IVM cycles and births

Year	Cycles (*n*)	Births (*n*)	Country	Reference
1983	44	1	USA	[4]
1985	90	NR	Japan	[5]
1987	11	NR	France	[6]
1987	40	NR	USA	[7]
1991	85	NR	USA	[8]
1991	23	3	South Korea	[9]
1993	40	NR	Spain	[10]
1994	42	1	Australia	[11]
1994	66	NR	USA	[12]
1995	1	1	Australia	[13]
1995	56	NR	Belgium	[14]
1996	20	NR	Australia	[15]
1996	1	1	Belgium	[16]
1997	1	1	Australia	[17]
1997	26	NR	Israel	[18]
1997	1	1	Saudi Arabia	[19]
1997	1	1	USA	[20]
1997	14	1	USA	[21]
1998	NR	NR	Taiwan	[22]
1998	92	NR	Belgium	[23]
1998	59	2	USA	[24]
1998	72	17	South Korea	[25]
1998	20	NR	Saudi Arabia	[26]
1999	2804	1	Belgium	[27]
1999	2	4	Canada	[28]
1999	25	9	Canada	[29]
1999	21	2	Saudi Arabia	[30]
1999	32	5	Denmark	[31]
2000	87	9	Denmark	[32]
2000	94	20	South Korea	[33]
2000	24	6	Canada	[34]
2001	36	3	Denmark	[35]
2001	177	20	Canada	[36]
2001	132	12	Denmark	[37]
2001	63	6	South Korea	[38]
2002	107	17	Canada	[39]

Year	Cycles (*n*)	Births (*n*)	Country	Reference
2003	68	21	Taiwan	[40]
2005	203	24	South Korea	[41]
2005	45	6	France	[42]
2005	239	36	Finland	[43]
2005	47	29	South Korea	[44]
2008	152	66	China	[45]
2008	89	29	China	[46]
Totals	**5252**	**355**		

Note: NR = not reported or not carried out.

Table 2: Non-peer-reviewed data from 2007 on IVM births

Region	Country/group	No. of deliveries and ongoing pregnancies
Europe	Scandinavia	150
	Italy	77
	France	40
	Germany	20
	Rest of Europe	33
Subtotal		320
Asia	South Korea	457
	Japan	100
	China (including Hong Kong)	60
	Vietnam	26
	Middle East	21
	Rest of Europe	15
	Australia	5
Subtotal		684
North America	Canada	120
	USA	5
Subtotal		125
Total		**1129**

Source: H Ingolf Nielsen (Medicult, Denmark), presented at The Second International Symposium on *In vitro* Maturation of Oocytes, Lyon France, 2007 (A Medicult sponsored symposia, details of which can be retrieved from: http://www.medicult.com/Home/News%20And%20Events/2007/July/IVM%20Symposium%20presentations.aspx.

(b) Why it was banned/proved controversial?

Not applicable.

4 Indicate the number of individuals who have used IVM and/or the number of individuals studied who have used IVM

It is difficult to report this information with any degree of accuracy. There is no central worldwide registry of IVM pregnancies/offspring, and a large proportion of units practising IVM do not report or publish results or pregnancies. Hence, the numbers reported here, whether they are from peer- or non-peer-reviewed sources, are certainly an underestimate of actual numbers.

Peer-reviewed numbers

While it is very difficult to obtain information on the number of 'individuals' who have used IVM, most studies report 'number of cycles'; ie, the number of patient treatment cycles (including individual repeat cycles). Table 1 above summarises the bulk of the known published data on number of cycles and number of live births from IVM, divided by country (this is not meant to be a definitive list).

Another source of data on IVM cycles and pregnancies is the European Society of Human Reproduction and Embryology (ESHRE) publication on European data on ART. The 2004 statistics were published in 2008 [47]. This report details that in 2004 there were 170 IVM treatment cycles across Europe (Finland 96, Poland 2, Russia 34, Serbia and Montenegro 2, Slovenia 34) resulting in 17 pregnancies.

Non-peer reviewed numbers

Table 2 above presents non-peer-reviewed data from HI Nielsen presented at The Second International Symposium on *In vitro* Maturation of Oocytes, Lyon France, 2007, and is perhaps the best estimate available of the world status of the number of IVM pregnancies.

5 Describe the information that is available on the outcomes of using IVM

This information is described in detail at clause 9 below.

6 Describe the information that is available on the risks of IVM

This information is described in detail at clauses 10 and 11 below.

7 Describe the information that is available on the benefits of using IVM, including whether there are potential recipients of the technology who would otherwise have no available option

Benefit to the patient

The major benefit of IVM is that the procedure removes the need to administer to women large multiple doses of follicle stimulating hormone (rhFSH) normally used in conventional IVF treatment. Women undergoing IVM receive either substantially reduced levels of gonadotrophins or no gonadotrophins (see section 'Patient preparation' in Background above). Exogenous FSH can lead to a condition of ovarian hyperstimulation syndrome (OHSS), which occurs in approximately 5–10% of women undertaking IVF cycles. OHSS is usually mild and self-limiting. In some cases, urgent medical attention is required. When severe, the condition can be potentially life threatening, requiring hospitalisation, intravenous fluids, pain relief, and other medication. Pulmonary embolism from a clot in the leg or complications of severe dehydration may occur in rare cases. **Hence, a very important benefit of IVM is the elimination of risk of OHSS** (Table 3). As women with the condition of Polycystic Ovarian Syndrome (PCOS) are at least double the risk of developing OHSS in response to FSH, these patients require IVM in preference to conventional IVF.

Table 3: Incidence of OHSS in IVM vs IVF in women with PCOS

	IVM (n = 107)	IVF (n = 107)	*P*
Total units FSH injected	0	2355 ± 833	< 0.01
Moderate or severe ovarian hyperstimulation syndrome	0%	11.2%	< 0.01

Source: Adapted from [39]

IVM can also be applied to women whose preference is to minimise ovarian hyperstimulation during infertility treatment. IVM is also more convenient to the patient as it requires less drug administration, which is usually performed by the patients themselves. There is currently a resurgence in interest in 'natural cycle IVF' or minimal stimulation IVF, and IVM represents an important technology in this area [3, 48, 49]. There is data suggesting the use of gonadotrophins for ovarian stimulation is associated with increased health risks including: increased risk to women for ovarian, breast and endometrial cancers (eg, [50], [51]) and increased risk of stroke (eg, [52]), although many of these claims are disputed [53]. Hence, the reduced use of gonadotrophins in IVM may be associated with a reduced risk of long-term adverse health outcomes, relative to conventional IVF.

Due to the reduced use of gonadotrophins, the other **major advantage of IVM over conventional IVF is a substantial reduction in cost**. Hence, in low-income families, in countries where infertility treatment is not publicly subsidised and in some developing countries, IVM is likely to provide treatment opportunities to couples who would otherwise have none. In this sense, IVM could be viewed as being more socially equitable than conventional IVF. These factors are likely contributing to the high rate of IVM usage in Asia.

Finally, an intriguing and unique situation in Italy has sparked a substantial increase in IVM usage in that country. In 2004 the Italian government introduced a new law that prevents the use of more than 3 oocytes per IVF cycle and the freezing of embryos, such that low stimulation IVF or natural cycle IVM/IVF may become the first choice of infertility treatment in Italy [54].

In summary, IVM is likely to increase treatment options and access to ART in:

- women with PCOS
- women who wish to avoid ovarian hyperstimulation
- low-income patients
- developing countries.

Benefit to oocyte/embryo/resulting child

There are no immediate benefits to the oocyte/embryo or resulting child as a result of IVM treatment. The benefit of IVM lies primarily with the woman being treated.

8 Describe any areas where there is deficient information about IVM (ie, potential risks, benefits and outcomes)

Benefits

There is no deficiency in information in this area. The cost, financial, sociological and health benefits (particularly to PCOS patients) of IVM are clear (see clause 7 above).

Potential risks and outcomes

As IVM is an emerging ART, there are considerable deficits in information on human IVM. Specific deficits in information include:

- prospective controlled studies on the efficacy of IVM compared to conventional IVF (as of 18 September 2008 the *Cochrane Review* '*In vitro* maturation in sub fertile patients with polycystic ovarian syndrome undergoing assisted reproduction' remains at 'protocol' status)
- IVM culture conditions required for human oocytes
- risk of oocyte spindle and chromosomal damage as a result of IVM
- risk of epigenetic damage to the oocyte as a result of IVM
- risk of congenital defects in IVM children
- risk of physical or psychomotor impairment in IVM children
- no centralised register of IVM results or offspring, leading to significant under-reporting of worldwide IVM activities.

Most notably, because IVM is a relatively new ART, with few offspring born to date, all of whom are young, there are very few (< 5) follow-up studies on the health and development of IVM children.

B Information from human studies

1 Outline the efficacy of IVM, including

In general terms, to gauge the efficacy of IVM, the technique is best compared to conventional IVF procedures using fresh mature eggs obtained after standard ovarian hyperstimulation procedures. However, it is important to note that **there are still very few genuine prospective controlled trials in humans directly comparing IVM to IVF**. By far the bulk of published peer-reviewed reports on IVM do not compare IVM to IVF, but rather examine IVM efficacy within different patients populations or compare various IVM laboratory procedures.

(a) Fertilisation rates

Fertilisation rates of IVM oocytes are generally comparable to those obtained in conventional IVF cycles. This is because IVM oocytes are generally fertilised by ICSI, which largely overcomes any potential impediments to fertilisation. In the direct comparison between IVM and IVF cycles in table 4 below, fertilisation rates were identical (78%) and cleavage rates were 74% and 72% ($P > 0.05$) in IVM and IVF oocytes, respectively [39]. From reviews summarising the 13 major studies of modern IVM, fertilisation rates typically range between 69% and 79% [1, 55].

Table 4: Fertilisation rate from IVM vs IVF in women with PCOS

	IVM (n = 860)	**IVF (n = 1244)**	***P***
Fertilisation rate	78%	78%	n.s.

Source: Adapted from [39]

(b) Survival rate of the oocyte following IVM

Please compare with fresh mature eggs.

Oocyte 'survival rates' following IVM are rarely if ever reported. The best indication of oocyte survival or oocyte viability is its capacity to, (1) mature or reach metaphase II (MII) and, (2) fertilise (see 9a) and support embryo (see 9c) and fetal development (see 9d). Maturation rates following IVM are typically slightly lower than oocytes from IVF cycles, as typified in Child *et al* [39] in the table below. Typical MII rates range between 73% and 79% [1, 55].

Table 5: Metaphase II rate from IVM vs IVF in women with PCOS

	IVM (n = 1102)	**IVF (n = 1594)**	***P***
Metaphase II rate	76%	80%	< 0.01

Source: Adapted from [39]

(c) Embryo development rates

There is no doubt that IVM compromises subsequent embryo development rates [1]. There is ample and consistent evidence of this phenomenon in nearly all human and animal studies. The reasons for the impaired developmental potential of IVM oocytes, compared to IVF oocytes are complex and not yet fully understood. This topic is the subject of intense animal research, and embryo developmental rates post-IVM are slowly, consistently improving with time.

Embryo development rates *per se* of human oocytes post-IVM are rarely thoroughly reported as embryos are usually transferred back to the uterus on D2 or D3. There is still very limited blastocyst culture of embryos from human IVM oocytes. As a consequence, the best measure of embryo development rate in human IVM oocytes is 'implantation rate', which is defined as the number of gestational sacs at 6 weeks divided by the number of embryos transferred. Implantation rates from IVM oocytes are usually ~ ½ those of IVF oocytes as typified in the table below (Table 6) from [39]. Table 7 summarises some of the major studies of modern IVM, and implantations are consistently just above 10%: ~13% in non-PCOS patients and 11.6% in PCOS patients [1, 55].

Table 6: Implantation rate from IVM vs IVF in women with PCOS

	IVM	IVF	*P*
Implantation rate	9.5%	17.1%	< 0.01

Source: Adapted from [39]

Table 7: Embryo development and implantation rates after IVM

Cycles (*n*)	Cleavage rate (%)	Embryos transferred (mean)	Implantation rate (%)	Reference
94	88	4.9	6.9	[33]
24	95	2.7	15.7	[34]
36	60	1.8	15.0	[35]
121	93	3.2	9.3	[36]
68	88	3.8	10.5	[40]
203	N/A	5.0	5.5	[41]
45	96	2.5	10.9	[42]
48	75	1.6	18.5	[43]
140	90	3.2	15.4	[45]

(d) Pregnancy rates

Please compare to use of fresh mature eggs in IVF.

Pregnancy rate is usually defined as the percentage of cycles commenced producing a positive hCG result, confirmed at 6–8 weeks by the presence of a fetal heart beat by ultrasound. Pregnancy rates are confounded by the number of embryos transferred per cycle, as many clinics compensate for poor embryo developmental potential by transferring more embryos. As IVM oocytes have a lower developmental potential (see 9c above), it has been common practice to transfer more embryos than would be transferred in an IVF cycle. Indeed, in Child *et al* [39] significantly ($P < 0.01$) more embryos in IVM cycles were transferred (3.2) than in IVF (2.7). With time and with improvements in IVM technologies, the number of embryos transferred in IVM cycles is steadily declining, consistent with the trend in conventional IVF.

In Table 8 below from Child *et al* [39], IVM generates ~ 2/3 the pregnancy rate of IVF. Although in this case this is not significantly different, it is reasonable to conclude that currently IVM has a lower pregnancy rate than IVF. Elective single embryo transfer is currently not recommended.

Table 8: Pregnancy rate from IVM vs IVF in women with PCOS

	IVM (n = 107)	IVF (n = 107)	*P*
Pregnancy rate	21.5%	33.7%	n.s.

Source: Adapted from [39]

Table 9: Pregnancy and miscarriage rates in PCO and PCOS undergoing IVM

Cycles (*n*)	Pregnancy rate (%)	Miscarriage rate (%)	Reference
94	27	20	[33]
24	33	25	[34]
36	23	57	[35]
121	27	40	[36]
68	34	22	[40]
203	22	37	[41]
45	23	33	[42]
48	42	36	[43]
89	41	21	[46]
140	40	9	[45]

Table 9 above summarises the major recent studies of IVM and pregnancy rates, which are approximately 26% in PCOS patients and typically ~20% in non-PCOS patients [1, 55]. However, it is perhaps noteworthy that the two most recent studies from 2008 [45, 46], both from China, are reporting IVM pregnancy rates of around 40%.

Table 9 also illustrates that miscarriage rates after IVM range from 20 to 57%. With very few adequately controlled studies it is difficult to determine if miscarriage rates are significantly higher than in IVF or ICSI. However, this seems likely given the well-established precedent for this phenomenon in animal studies (see section C, 19d), and is likely to be a reflection of combined poorer oocyte/embryo developmental potential and suboptimal endometrial preparation [56]. In support of this conclusion, a recent study by Brackett *et al* [57] (Table 10) compared pregnancy losses between IVM, IVF and ICSI within a single clinic and found a significantly higher miscarriage rate in IVM pregnancies compared to IVF and ICSI. It is important to bear in mind that the women receiving IVM were predominantly PCOS (80%), unlike the other two groups.

Table 10: Miscarriage rate from IVM, IVF and ICSI

	IVM (n = 99)	IVF (n = 705)	ICSI (n = 502)	*P*
Miscarriage rate	25.3%	15.7%	12.6%	< 0.05

Source: Adapted from [57]

(e) Live birth rates

Please compare to use of fresh mature eggs in IVF.

Live birth rate is defined as the percentage of cycles commenced resulting in at least one live offspring. As with pregnancy rates, live birth rates are affected by the number of embryos transferred and the inherent developmental potential (implantation rate and miscarriage rate) of the embryo. As can be seen from the data in Table 11 [39], IVM generates approximately half the live birth rate of IVF. Although in this case this is not significantly different, it is reasonable to conclude that currently IVM has a lower live birth rate than IVF.

Table 11: Live birth rate from IVM vs IVF in women with PCOS

	IVM (n = 107)	IVF (n = 107)	*P*
Live birth rate	15.9%	26.2%	n.s.

Source: Adapted from [39]

A true measure of efficiency of an ART is the **cumulative delivery rate**, which measures the live birth rate per treatment cycle using all the embryos generated from one oocyte collection. Hence this measure includes cumulative live birth rate per pick-up from fresh and subsequent frozen embryo transfer cycles. Such data is scarce. However, estimates of cumulative delivery rates from IVF (~60%) are substantially higher than from IVM (~15%) [56]. This is particularly a reflection of the lower average number of oocytes collected in IVM and the poorer embryo development rates, such that less supernumerary embryos are generally available for cryopreservation in IVM cycles [56].

Table 12: Estimates of cumulative delivery rate from IVM vs IVF

	IVM	IVF
Estimated cumulative delivery rate	~13%	~60%

Source: Adapted from [56]

(f) Diagnostic accuracy of the procedure (if applicable)

Not applicable.

10 Detail any risks to health through the use of IVM, including (but not limited to)

(a) any potential side effects (please compare to use of fresh mature eggs in IVF)

There are no obvious or major side effects from IVM to women being treated. In fact there are substantially fewer side effects compared to using mature eggs in IVF because IVM patients receive substantially less or no gonadotrophins (see Table 3).

The collection procedure for immature oocytes differs slightly from collecting mature oocytes in IVF. While both procedures involve ultrasonography-guided trans-vaginal ovarian follicle aspiration, oocytes are easier to aspirate in IVF. In IVM, the cumulus-oocyte complex is usually more embedded in the follicle wall, so the cumulus-oocyte complex is usually scrapped from the follicle wall using the bevel of the aspiration pipette. Hence, an IVM oocyte pick-up is usually associated with more ovarian bleeding than an IVF pick-up. However, there are no publications outlining an adverse event arising from oocyte pick-up during an IVM cycle.

The technique of oocyte collection for IVM can take longer and it has been suggested it is more painful. However, there is a published study demonstrating that pain level actually experienced during the collection procedure was less than expected prior to the procedure [58].

(b) Health outcomes for female patients (if applicable) – this includes both short term and long term (eg, the treatment could increase the risk of cancer many years later)

There are no obvious or major adverse health outcomes for female patients being treated with IVM. There is substantially less risk of major adverse short-term outcomes (such as OHSS) or long-term outcomes (such as the risk of cancers) due to the reduced administration of gonadotrophins (see clauses 7 and 24).

Because of the reduction in pregnancy rates and live-births following IVM, there may be a need to manage couples' expectations of success of the procedure, especially if they compare against published rates of success for IVF. Such management of patients' expectations should reduce any additional anxiety that may occur through treatment from IVM, rather than having IVF treatment. Nevertheless, there is no published data for an increased anxiety over treatment for couples undertaking IVM.

(c) Any suggested exclusions of potential patients based on clinical indicators (eg, cancer, diabetes, previous OHSS)

There are no obvious patient exclusion criteria specific to IVM. As an adjunct procedure to IVF, in general, the same patient exclusion criterion applies to both techniques. The notable exception to this is PCOS and PCO patients who, because of their increased risk of ovarian hyperstimulation syndrome (OHSS), may be excluded from conventional IVF but not from IVM.

(d) Health outcomes for male patients (if applicable)

There are no health risks to male patients specifically as a consequence of using IVM. Procedures undertaken by male patients are identical in IVM and IVF cycles.

(e) Observed damage to the oocyte

Morphological damage: IVM does not lead to any 'observable' or obvious visible damage to the oocyte. Under appropriate culture conditions, oocytes rarely degenerate during IVM, they undergo maturation to MII quite readily (see 9b above), they undergo comparatively normal cumulus cell expansion, and they generally exhibit comparable fertilisation rates to IVF oocytes (see 9a above). However, IVM undoubtedly compromises the oocyte at the sub-cellular and molecular level in ways that are still not understood. This is reflected in consistent impaired post-IVF developmental potential of embryos generated from IVM (see 9c above).

Spindle and chromosome damage

Table 13: Normality of spindle and chromosomal configurations in IVM and *in vivo* maturated oocytes from PCOS patients

Oocyte group	No. (%) of oocytes with spindle configuration		No. (%) of oocytes with chromosome configuration	
	Normal	Abnormal	Normal	Abnormal
In vitro matured (n = 48)	27 (56.3)	21 (43.7)[a]	32 (66.7)	16 (33.3)[a]
In vivo matured (n = 22)	19 (86.4)	3 (13.6)	20 (90.9)	2 (9.1)

a P < 0.05 oocytes matured *in vivo*.

Source: Adapted from Li *et al* [59]

Several studies have investigated spindle and chromosome defects following IVM using either immature or partially matured oocytes recovered post-hCG from ovarian-stimulated cycles. Such oocytes should be regarded as having suboptimal developmental competence and therefore it is unsurprising to note that these oocytes appear to have significant levels of spindle and/or chromosomal defects following IVM (eg, [60, 61]). However, Li *et al* [59] utilised immature oocytes from unstimulated PCOS patients and compared spindle and chromosome configurations with those within *in vivo*-matured oocytes from a similar patient group but who did undergo conventional ovarian stimulation. They described significantly more abnormal spindles and chromosome configurations in the IVM group (Table 13).

Nevertheless, these results stimulated debate regarding the value of such observations; such abnormal oocytes could be removed prior to fertilisation using suitable microscopic techniques [62, 63]. If there were to be a genuine increase in spindle and chromosomal abnormalities in IVM oocytes, this may contribute to the increased incidence of miscarriage from IVM (see clause 9d).

Epigenetic modifications to the oocyte: There is a lack of information regarding the epigenetic state of oocytes following IVM, especially for oocytes collected from unstimulated cycles. Borghol *et al* [64], using germinal-vesicle arrested oocytes collected post-hCG from an ovarian-stimulated cycle and subsequently *in vitro* matured, found 15/20 oocytes with normal methylation status for an imprinted differentially methylated region of the gene *H19*, but 5 oocytes from two patients had disturbed methylation patterns. These oocytes, however, are highly compromised as they have failed to mature *in vivo* following gonadotrophin stimulation. Khoureiry *et al* [65] have examined the methylation of another imprinted region of the *KCNQ1OT1* gene. They found no differences in the level of methylation between *in vivo* or *in vitro* matured oocytes from PCOS-patients. However, they did observe less methylation in both IVM and *in vivo* derived oocytes from ovarian stimulated cycles compared with oocytes retrieved from unstimulated PCOS patients, suggesting that follicle stimulation with gonadotrophins may also be a cause of disrupted methylation patterning.

11 Detail the obstetric outcomes (risks and/or benefits to health), including (but not limited to)

It is important to note that there is very limited information available on the obstetric and post-natal outcomes of IVM pregnancies. This is because, (1) the technology is relatively new and so the children are still young, and (2) the relatively low number of IVM children born so far. It is believed there are around 300 to 400 reported IVM-conceived children worldwide and this is not an adequate number to calculate absolute risks for specific health abnormalities.

However, as a general statement for this clause 11(a–h), **reports so far indicate very few obstetric or perinatal complications from IVM pregnancies**. In a recent review of the topic, Suikkari and Sonderstrom-Anttila [56] conclude: ‘More than 300 children have been born and follow-up studies have reported no major concerns about the pregnancies, deliveries or health of the babies’.

(a) Observed damage to the oocyte or embryo

See 10e above.

(b) Neonatal/infant complications

From the preliminary data published so far, in general there appears to be no major neonatal or infant health complications from IVM compared to conventional IVF or ICSI [55, 56, 66, 67]. Gestational age, growth restriction, Apgar scores, birth weights and sex ratios are all comparable between births resulting from IVM, IVF or ICSI [55, 56, 66, 67]. (See also clause11h.)

Table 14: Perinatal clinical characteristics of IVM births

Characteristic	IVM# (n = 21)	Control* (n = 21)	*P*
Gestational age at birth (weeks)	38.1 ± 1.5	38.1 ± 1.5	n.s.
Birth weight (g)	3075 ± 489	3134 ± 287	n.s.
Birth height (cm)	49.6 ± 1.4	49.9 ± 0.9	
Head circumference at birth (cm)	33.5 ± 0.8	34.1 ± 0.9	
Sex (n)			
Male	11	13	n.s.
Female	10	8	n.s.
Size for gestational age (n)			
Appropriate	20	21	
Small	1	0	
Mode of delivery (n)			
Caesarean	14	17	
Vaginal	7	4	
Apgar score (n > 6 at 5 minutes)	21	21	n.s.

Children from PCOS mothers undergoing gonadotrophin priming, IVM and ICSI-ET.

* Children from spontaneous pregnancies.

Note: Values are means ± standard deviations.

Source: Adapted from [67].

(c) Chromosomal abnormality

Karyotyping of IVM children has not been carried out systematically. However, of the three reports in the literature to date, none have reported major anomalies. Shu-Chi *et al* [67] reported no abnormal karyotypes in 21 IVM children (table 15), and in the other studies, two insignificant abnormal karyotypes were reported, both inherited from one of the parents [68, 69]. Recently Buckett *et al* [57] have also reported no chromosomal abnormalities in 99 IVM children.

Table 15: Karyotype of IVM children

	IVM# (*n* = 21)	Control* (*n* = 21)	*P*
Abnormal karyotype	0	0	n.s.

Children from PCOS mothers undergoing gonadotrophin priming, IVM and ICSI-ET.

* Children from spontaneous pregnancies.

Source: Adapted from [67].

(d) Congenital malformations (ie, birth defects)

Of the ~300 IVM children reported in the literature, there are reports on approximately half of these in terms of congenital abnormalities at birth. Approximately 5% of children born from IVM have some form of congenital defect (Table 16, [55]), which is similar to rates reported within the general population (≈5%). Due to the very low numbers of IVM infants, it is impossible at present to determine accurately whether IVM is associated with an increased risk of chromosomal abnormalities or congenital birth defects. However, a major malformation rate of 5% associated with IVM (Table 16) is comparable with rates reported for ICSI (7.4% [70], 4.9% [71], 8.6% [72]). In support of this, Buckett *et al* [66] recently examined 432 ART children compared to age- and parity-matched controls, and concluded that all ART pregnancies are associated with an increased risk of congenital abnormalities, but that IVM is not associated with any additional risk.

Table 16: Summary of congenital defects from major IVM studies, 1995–2006

Period of study [reference]	IVM children born (*n*)	Congenital defects
1995–98 [33]	20	- 0
1995–01 [41]	28	- 1 hydrops fetalis (terminated) - 1 omphalocele (45X/46XY mosaicism) - 1 cleft palate
1999–04 [69]	47	- 1 soft palate - 1 still birth at 42.3 weeks
1998–06 [66]	48	- 1 VSD - 1 hip dislocation
2002–03 [42]	5	- 0
Totals	**148**	**7/148 (4.7%)**

(e) Child development (physical, psychomotor and cognitive)

The first reports on follow-up data on IVM children appeared in 2006, and to date there are only two publications in the literature [67, 68]. Based on these very preliminary studies, IVM children appear to have normal physical and neurological development rates from 0 to 2 years of age.

In a study that tracked growth parameters including, body weight, body height and head circumference from 0 to 2 years of age, IVM children were within normal limits [67]. In the same study, all IVM children had normal neurological development (Table 17 [67]).

Table 17: Psychomotor and cognitive development of IVM children aged 6–24 months

Index	IVM# (*n* = 21)	Control* (*n* = 21)	*P*
Bayley Mental Development Index	92.7 ± 10.5	97.2 ± 8.9	P = 0.07
Bayley Psychomotor Development Index	96.7 ± 8.9	96.2 ± 7.1	n.s.

\# Children from PCOS mothers undergoing gonadotrophin priming, IVM and ICSI-ET.

* Children from spontaneous pregnancies.

Note: Values are means ± standard deviations.

Source: Adapted from [67]

In a separate follow-up study of 46 IVM children [68], obstetrics and perinatal outcomes including birth weight were within the normal range. At six months of age, none were assessed as having considerable development disorder and 3 (7%) had minor development disorder. By 12 months, 19% of children had minor development disorder and one child had considerable development disorder (further investigation revealed this child had a glioma of the optic nerve). By two years of age, neuropsychological development of the cohort was within the normal range: 97% of children with a Bayley Mental Development Index > 85 and one child (3%) with an index between 70 and 84 [68].

(f) Psychological outcomes for child and family

Apart from the neuropsychological data on IVM infants presented above (11f), no further data is available on the psychological wellbeing of IVM offspring or their families.

(g) Epigenetic disorders (ie, imprinting)

There is no information whatsoever on the incidence of epigenetic disorders in IVM children. No studies to date have examined epigenetic markers in IVM offspring of imprinted genes that are known to be involved in development. There are a limited number of recent studies examining imprinting in human oocytes during IVM (see clause 10e).

A number of recent studies have reported an increased incidence of imprinting disorders such as Beckwith-Wiedemann and Angelman syndromes in children conceived using ART procedures (conventional IVF and ICSI) (reviewed in [73]). Although such an association remains controversial, it emphasizes the need for follow-up studies of ART children, including IVM children. However, it is important to note that with such imprinting disorders having an incidence of < 1% in ART children [74], even with such follow-up studies it will be decades before robust data will becomes available on the risk of epigenetic disorders in children conceived by IVM.

(h) Maternal outcomes (including complications)

The significant increase in IVM miscarriage rates is reported in clause 9d above. In general, in terms of maternal obstetric outcomes, IVM pregnancies are comparable to conventional IVF and ICSI pregnancies. Multiple pregnancy rates, mode of delivery, cord pH and pregnancy complications are all comparable between births resulting from IVM, IVF or ICSI [55, 56, 66, 67]. ART pregnancies in general are associated with an increased risk of multiple pregnancy (twins: IVM 21%, IVF 20%, ICSI 17%) and Caesarean delivery (IVM 39%, IVF 36%, ICSI 36%) compared to non-ART pregnancies (twins: 1.7%; Caesarean 26.3%), but compared to IVF and ICSI, IVM is not associated with any additional risk [66].

Consistent with this, in a separate report from 43 IVM pregnancies, 35% were delivered by Caesarean section and 9% were pre-term deliveries (< 37 weeks) [68]. The ectopic pregnancy rate is not significantly higher from IVM than conventional IVF or ICSI (Table 18).

Table 18: Ectopic pregnancy rate from IVM, IVF and ICSI

	IVM (n = 99)	**IVF (n = 705)**	**ICSI (n = 502)**	***P***
Ectopic rate	1.0 %	2.3 %	1.8 %	n.s.

Source: Adapted from [57].

12 Indicate if the use of IVM introduces any medicines to be used in a new way (if it involves a new medicine it will have to go to the Health Research Council of New Zealand's Standing Committee on Therapeutic Trials (SCOTT)); if yes, please address the following

New medicines

IVM does not require any additional medicines from a conventional IVF procedure. A feature of IVM is that it uses less medicine (gonadotrophin hormones) than conventional IVF (recombinant FSH in particular).

New device – IVM medium

IVM requires a chemical solution to support the oocyte maturation process, specifically by supporting the surrounding cumulus cells, which, in turn, support the oocyte during the maturation process.

The composition of this medium differs in some respects to media used for conventional IVF. The purpose of the IVM medium is to provide an environment in a clinical laboratory that mimics the follicular fluid that bathes the cumulus–oocyte complex. The action of the medium is to support the final maturation of the oocyte. The timing of this process of final maturation *in vitro* can occur between 24 hours and 48 hours. Once a matured cumulus–oocyte complex (which contains the oocyte surrounded by somatic cells that support the nutrition of the oocyte, known as cumulus cells) has been obtained by the IVM procedure, the process leading to the production of an embryo is identical to existing procedures for conventional IVF practices.

As the components of the medium mimic the natural environment within the follicle, there is negligible risk to the oocyte and ensuing embryo. In particular, as the components of the medium are there to support cumulus cell function, and have little direct contact with the oocyte itself, then the concept of adverse risk to the oocyte from a component of the medium is negligible. Recent reviews by [75, 76] describe the physiological attributes of components within IVM media.

Salts

The medium is a mixture of inorganic salts, such as Na^+, K^+, Ca^{2+}, Cl^- and HPO_4^{2-}, SO_4^{2-}, and an HCO_3^- ion pH buffering system, which requires an increase in CO_2 in the gas phase to equilibrate at the appropriate pH and closely represents the chemical nature of the follicular environment that the cumulus–oocyte complex would experience. This is typical of most cell culture media and such ions are widely used in embryo culture media.

Energy substrates

The energy substrates glucose and the metabolite of glucose, pyruvic acid (in the form of a Na-salt), are both included to provide substrates for energy generation and essential building blocks for cellular function. These are widely used in a variety of cell culture media and are essential in embryo culture media.

Amino acids

Amino acids are also included in the formulation, which includes glutamine. A further amino acid, the sulphated 2-mercaptoethylamine, may be added to assist in the stability of another amino acid, cysteine. The function of these amino acids is to: provide additional energy substrates; provide the building blocks for protein synthesis; and act as molecules known to have wide housekeeping (homeostatic) roles in maintaining the cell in a viable state. Amino acids are widely used in cell culture media, and most embryo culture media contain a variety of amino acids.

Peptide hormones

- Recombinant human follicle stimulating hormone (purified)
- Human chorionic gonadotrophin (purified from urinary sources)
- Recombinant human insulin (purified)

These three peptides are all commonly used in *in vitro* maturation formulations. Exposure to these peptides is restricted to the IVM period. Following maturation, an 18-hour fertilisation period and a subsequent 24–48 hour embryo culture period occurs. Therefore, as the cumulus cells are removed either prior to or following *in vitro* fertilisation, and the oocytes themselves are not in direct contact with the IVM medium, it is highly unlikely that the oocyte is exposed directly to these peptides. As these peptides interact with the cumulus cells and, in general, do not interact with the oocyte itself, the risk that the oocyte is in contact with physiologically significant levels of these peptides is negligible. Therefore, there is likely to be negligible risk to either the oocyte or the patient posed by the inclusion of these peptides.

All three are ligands for membrane-bound receptors and elicit a number of cellular events via intracellular signalling pathways that are very well characterised. All are represented in the follicular fluid directly, or in analogue form. Therefore, the purpose of these peptides is to replace those found in follicular fluid during *in vivo* maturation of the cumulus–oocyte complex so that normal cumulus cell function can occur during *in vitro* maturation. However, their presence highlights a major difference between IVM medium and embryo culture medium, as no receptor-ligand peptides are used in commercially prepared embryo culture media. Nevertheless, the activity of these peptides is not directly on the oocyte, but on the cumulus cells which surround the oocyte to support their function, which in turn supports the oocyte.

Very few controlled human studies have been conducted on the efficacy of adding these three peptide hormones to IVM medium. A recent study showed no beneficial effect of adding recombinant hCG in the IVM medium on pregnancy outcomes [46].

In all IVF laboratories, whether oocytes have been collected and cultured for IVM or via more conventional IVF protocols, the removal of cumulus cells (using a combination of chemical and mechanical means) occurs either before insemination by intra-cytoplasmic sperm injection or following insemination in routine IVF treatment. This is not altered with the incorporation of the IVM procedure. Thus, there is no involvement of the IVM medium, its components or the cells that interact directly with the IVM medium from the point where fertilisation of the oocyte has occurred, which includes embryo culture and embryo transfer. Thus, there is no carry-over of IVM components or cumulus cells into the process of embryo production from the time the oocytes are removed from IVM and fertilised. This is made even more unlikely by the extensive washing of oocytes and embryos in fertilisation and embryo culture media that occurs following maturation, fertilisation and embryo culture.

(a) Toxicity

As there are no new medicines, there are no toxicity effects. Indeed, the reduction in gonadotrophin hormone use lessens the risk of ovarian hyperstimulation.

(b) Interactions

As there are no new medicines, there are no interactions.

(c) Long-term effects of medications

Not applicable.

13 Indicate if other treatment (eg, for cancer) might be delayed as a result of IVM

As IVM is an adjunct treatment to conventional IVF, there are no additional delays for other therapies. Furthermore, IVM may be required to enable fertility in girls and women who have ovarian tissue frozen or oocytes frozen at the immature germinal vesicle stage prior to chemotherapy.

14 Indicate the potential age range of this treatment

18–45 years.

15 Indicate if IVM can increase the risk of other disease (eg, cancer)

Unknown at this stage due to lack of epidemiological data on IVM children.

C Information from animal studies

16 Introduction

As described by [77] and [78], early work in the development of *in vitro* fertilisation and culture in all species studied to that time was successful only when *in vivo* maturation of oocytes occurred (ie, gonadotrophin stimulation of ovaries and induction of maturation, usually with hCG or GnRH injection). The first demonstration that oocytes matured *in vitro* could be fertilised and cultured *in vitro*, and produce live offspring after embryo transfer in any species, was achieved using mouse oocytes [79]. As expected, the efficiency of this process was relatively poor by today's standards: only 60% matured, 23% fertilised and cleaved, and of those, 34% developed to the blastocyst stage. Nevertheless, five normal progeny from 11 transferred blastocysts were born and survived following transfer (see Appendix 1). Despite efforts, it was more difficult to achieve such a success in other species. For example, the first publication reporting successful IVM/F/C in domesticated species (sheep and pigs) occurred in 1986 [80].

There are many thousands of papers dealing with experimental IVM where the end point of the experiment is meiotic maturation, early cleavage or blastocyst development [75]. The great majority of research publications involving IVM in animal species describe experiments into the genetic and biochemical mechanisms involved in the final maturation stages of mammalian oocytes. This is mostly performed to generate a greater understanding of the regulatory mechanisms surrounding maturing oocytes. Furthermore, IVM is a platform technology for the production of embryos by somatic cell nuclear transfer (cloning), which is attractive to animal breeding industries utilizing highly valuable animals, and to conservationists protecting rare breeds and species (eg, Enderby Island cattle [81]). Indeed, much recent work investigating the efficiency of the IVM process using animal oocytes has been performed using parthenogenetically activated oocytes (oocytes activated to cleave as embryos in the absence of fertilisation). Clinical IVM in animal species is largely restricted to cattle.

Just as in clinical infertility practice, IVM is very rarely used in isolation of other *in vitro* techniques required to generate an embryo. These other techniques (*in vitro* fertilisation and culture of embryos) also significantly impact on parameters covered in clauses 18–21. Both *in vitro* fertilisation and, most significantly, *in vitro* culture of embryos are known to have profound effects on the developmental trajectory of embryos, both prior to transfer and, more significantly, on post-transfer survival and on neonatal outcomes. This is nicely demonstrated by Rizos *et al* [82], who examined embryo development comparing different combinations of either *in vivo* or *in vitro* maturation, fertilisation and culture.

Published manuscripts were examined (Appendix 1) when there was clear evidence that post-transfer data of IVM oocytes was compared with *in vivo* matured (ie, 'fresh') oocytes. This significantly reduced the number of papers reported here in Appendix 1.

17 Indicate if IVM has been used in animals; if so, please specify what species and address clauses 18–20 for each species

Table 19 outlines many of the species in which IVM has been performed. This list is by no means complete. The breadth of species that have had oocytes matured *in vitro* is now extremely wide, with some quite controversial examples, such as Minke whales [83]. There is also a continuing introduction of new species to IVM technology. The major reason is the application of conservation biology utilizing either *in vitro* embryo production or somatic cell nuclear transfer (cloning) to assist in preserving rare breeds or species [81].

Table 19: Species identified in which *in vitro* maturation of oocytes has been performed

Genus	Species	Example reference
Primates	Macaque, Cynomolgus monkey Marmoset monkey Rhesus monkey	[84] [85, 86] [87]
Rodent	Laboratory mouse Laboratory rat Golden hamster Rabbit	[88] [89] [90] [91]
Bovine	*Bos taurus* (eg, Hereford) *Bos indicus* (eg, Brahman) River buffalo Murah buffalo	[92] [93] [94] [95]
Ovine	Sheep	[96]
Caprine	Goat	[97]
Porcine	Pig	[98]
Equine	Horse	[99]
Cervine	Red deer/Wapiti Reindeer	[100] [101]
Canine	Domestic dog Red fox Blue fox	[102] Review [103] Review [103]
Feline	Domestic cat Lion	[104] [105]
Camelids	Dromedary camel	[106, 107]
Exotic species	Mohor gazelle Rhinoceros Elephant Minke whale	[108] [109] [109] [83]

There are several species that encapsulate the great majority of literature on IVM. These are the mouse, cow and pig. Significant work has also been conducted on sheep, and increasing levels of research are conducted on the horse. The domesticated species are primarily studied due to their economic value and the availability of oocytes from abattoir-recovered ovaries. Appendix 1 displays data for species where there is clear evidence of comparison between *in vivo* matured and *in vitro* matured oocytes and where subsequent transfer of the embryos has taken place to provide pregnancy and neonatal data. The data presented in Appendix 1 represents a snapshot of the total literature available.

18 Specify the number of animals studied which have used IVM

Appendix 1 comprises a list of published studies, which include those that quote numbers of animals used. However, the vast majority of experimental IVM publications dealing with mice, cows, pigs and sheep do not quote animal numbers. For the domestic species, this is due to the use of abattoir-collected ovaries, which are a valuable source of experimental oocytes for research purposes, whereas the routine nature of mouse IVM experimentation is such that only numbers of oocytes collected and utilised are quoted.

19 Outline the efficacy of using IVM

(a) Fertilisation rates

As can be seen in Appendix 1, fertilisation rates within most species (especially the most researched species) are similar compared to *in vivo* matured oocytes. In species where this is not so, a possible reason is the lack of understanding regarding the conditions required for sperm capacitation and fertilisation.

(b) Survival rate of the oocyte following IVM

As with human IVM, very few studies quote oocyte survival rates following IVM. Instead of oocyte survival, an alternative criterion which is more often expressed is the proportion of matured oocytes; ie, the proportion of oocytes that progressed successfully to the metaphase II stage of meiosis (hence have completed the first stage of meiotic resumption prior to fertilisation, where meiotic resumption of the egg is completed). However, some work using rare or exotic species do quote survival rates. For example, in the study of [95] using buffalo oocytes, rates of survival were approximately 90%.

Nearly all mammalian species undergo spontaneous nuclear maturation during *in vitro* maturation, therefore it is not uncommon for relatively high levels of oocyte maturation rates (ie, greater than 70%) to be achieved following *in vitro* maturation. The exception appears to be the canids (dogs, foxes), where generally very few (less than 20%) oocytes complete spontaneous meiotic maturation *in vitro* (reviewed by [103]). Maturation of canid oocytes *in vivo* is also unique, as the oocytes are ovulated early in meiosis and not at the MII stage [103]), and this may contribute to the difficulty of maturing oocytes *in vitro* in these species.

(c) Embryo development rates

Embryo production rates are generally lower for IVM oocytes compared to those *in vivo* derived (Appendix 1). In another example, [82] demonstrated that *in vitro* matured bovine oocytes produce about 30% fewer cow blastocysts than *in vivo* matured oocytes. The reasons for this are poorly understood, despite much continuing research, and involve the lack of follicular environment during final maturation and the nature of the association between cumulus cells and the oocyte (reviews [110, 111]). Nevertheless, progress has been made, as demonstrated by more recent publications outlined in Appendix 1.

(d) Pregnancy rates (please compare to use of fresh mature eggs)

Initial pregnancy rates, especially in the major three species that have been studied, are generally not different between *in vivo* matured and *in vitro* matured oocytes (see Appendix 1). However, IVM and embryo culture-derived embryos have relatively high pregnancy losses relative to *in vivo*-derived embryos (see Appendix 1 and Table 20.)

(e) Live birth rates (please compare to use of fresh mature eggs)

As for human IVF, live birth rates are invariably lower following IVM and embryo culture in animals. This is well demonstrated by [112] with cattle embryo transfer using IVM and embryo culture-derived embryos, where survival following transfer progressively decreases throughout pregnancy (see table 20). Again, the contribution of IVM to pregnancy loss, especially when matured oocytes have also been fertilised and cultured *in vitro*, is not known.

Table 20: Pregnancy and calving results from six different bovine embryo culture systems (all using IVM) conducted in three different European laboratories

Embryo culture system	No. embryos transferred	No. recipients	Recipients pregnant (%)			
			Day 21	Day 35	> Day 90	Calves born
A	47	32	7 (22)	7 (22)	7 (22)	9 (19)
B	16	16	5 (31)	5 (31)	5 (31)	5 (31)
C	24	24	14 (58)	9 (38)	8 (33)	8 (33)
D	9	9	1 (11)	1 (11)	0 (0)	0 (0)
E	129	129	73 (57)	61 (47)	51 (40)	49 (38)
E	110	55	30 (55)	27 (49)	24 (44)	21 (19)
E	188	94	58 (62)	50 (53)	46 (49)	62 (33)
F	49	49	36 (73)	29 (59)	17 (35)	16 (33)

Source: Taken and modified from [112]

(f) Diagnostic accuracy of the procedure (if applicable)

Not applicable.

19 Detail any risks to health of using IVM, including (but not limited to)

(a) Any potential side effects

The most widely recognised abnormality with IVM and embryo culture-derived embryos is the high degree of early developmental arrest before and immediately following embryo transfer (see Appendix 1 and Table 20).

Other than this early embryonic loss, there appears to be no significant side effects as a result of IVM in many species. In ruminants, there is a condition known as 'Large Offspring Syndrome', which is a complication as a result of the *in vitro* culture of embryos. This syndrome is characterised by a significant skew to heaviness in birth weight above the normal population. There are also other complications, such as an increased gestation length, increased neonatal mortality (usually due to the increased incidence of dystocia), skewed allometry of organ development within fetuses and abnormalities in the placental development (for reviews see: [113] [114] [115]).

Large Offspring Syndrome is usually attributed to the period of embryo culture prior to transfer. In fact, it was first identified using *in vivo*-matured and -fertilised oocytes that were subsequently cultured *in vitro* and transferred (reviewed in [116]). Also, significantly, Thompson *et al* [117] showed that birth weight of some lambs was high regardless of whether the oocytes were derived from *in vivo* maturation or *in vitro* maturation when all embryos were cultured under 'high birth weight inducing conditions' (ie, the presence of serum in culture medium). Nevertheless, IVM may contribute or exacerbate this condition when combined with *in vitro* culture of cattle and sheep embryos, as suggested by the data of Holm *et al* [118].

In the mouse, *in vitro* culture of embryos is known to reduce fetal growth and placental development and lower birth weight (eg, [119]). Any effect of *in vitro* maturation is largely unknown and may also exacerbate this phenomenon. However, [88] have recently found that, in comparison with *in vivo* maturation, there was no difference in implantation rates following IVM under different oxygen concentrations, but did observe small, subtle differences in placental and fetal weight in comparison with *in vivo* matured oocytes (Table 21). It is unknown if such subtle differences pose a risk to ongoing health.

Table 21: Development following transfer of IVM vs *in vivo*-matured oocytes subsequently fertilised and cultured *in vitro*

	IVM treatment			***In vivo***
	2% O_2	**5% O_2**	**20% O_2**	
Implantation rate[A] (%)	69.7 ± 10.5	56.9 ± 9.0	80.0 ± 5.4	65.0 ± 10.1
Viable fetuses/blastocyst implanted[B] (%)	45.0 ± 10.3	49.3 ± 8.8	42.0 ± 9.0	39.7 ± 10.4
Fetal weight (mg)	870.2 ± 26.7^{ab}	823.3 ± 28.1^{a}	928.5 ± 26.1^{b}	879.3 ± 32.3^{ab}
Fetal crown-rump length (mm)	18.4 ± 1.0	19.9 ± 0.3	20.1 ± 0.3	19.3 ± 0.4
Placental weight (mg)	98.7 ± 5.5^{ab}	87.4 ± 4.0^{a}	100.1 ± 5.5^{ab}	104.5 ± 5.4^{b}
Fetal:placental weight ratio	9.1 ± 0.4	9.8 ± 0.5	9.6 ± 0.5	8.8 ± 0.5

A Implantation rate: number of fetal/placental units or resorptions present as a percentage of the number of embryos transferred.

B Viable fetuses/blastocyst implanted: percentage of implanted embryos that developed into a viable fetus. Number of uterine horns per treatment group, six embryos transferred per horn, 2%: n = 11; 5%: n = 12; 20%: n = 10; *in vivo*: n = 10.

Notes: Different superscripts within a row represent statistically significant differences, $P < 0.05$.

Data are represented as mean ± SEM.

Source: Taken from Banwell *et al* [88]

(b) Health outcomes for male subject (if applicable)

There is data concerning the differential post-natal growth of males over females following embryo culture and transfer [119], and there is even evidence that embryo culture *in vitro* favours the development and survival of male embryos [120] [121]. However, these have all been associated with embryo culture *in vitro* [121] and not specifically with IVM. There is no direct evidence for health outcome differences following IVM to males in the animal literature.

(c) Ongoing development of offspring born as a result of the procedure

There is no data concerning long-term developmental outcomes from IVM-derived offspring, and this is seen as a major deficiency in both animal models and clinical studies [75].

21 Detail the obstetric outcomes (risks and/or benefits to health), including (but not limited to)

(a) Neonatal/infant complications

See the answer to clause 20 for details. Newborn calves born from *in vitro*-produced embryos (which includes the IVM process) also have blood chemistry differences compared with normally conceived calves [122], but this appears to be due to the increased size of calves under some culture conditions, as this was not observed when calf size at birth was normal [123].

(b) Chromosomal abnormality

In animal species, aneuploidy occurs with much less frequency than for human oocytes [124], with perhaps the exception of the cow, where approximately 7–15% of oocytes are of mixed ploidy [125]. Searches for key words such as *in vitro* maturation and aneuploidy revealed little, especially with respect to work conducted in animals. Furthermore, [126] have concluded that there is 'no significant difference of meiotic spindle organisation, chromosome alignment and aneuploidy between *in vivo* and *in vitro* matured oocytes derived from naturally cycling and stimulated mice'. Nevertheless, one condition reported to increase aneuploidy is very high FSH levels (10–1000 x more than normal) during *in vitro* maturation of mouse oocytes [127]. In contrast, [128] found that mixoploidy in bovine blastocysts following IVM compared with *in vivo* maturation is doubled. Similarly, [129] found that blastocyst embryos from IVM and embryo culture in their system were associated with high levels of mixoploidy (72%) compared with *in vivo*-derived blastocysts (25%).

(c) Congenital malformations (ie, birth defects)

There appears to be a small absolute increase in incidences of birth defects following IVM and embryo culture, but no data concerning specific events arising from IVM of oocytes. Large Offspring Syndrome is usually attributed to the embryo culture phase (see answer to clause 20), and this is associated with an increase in the incidence of abnormalities, mostly hydroallantois (3.2% vs 0.7%, [130]. [131] reported a globosus amorphous from an IVM and embryo culture-derived and transferred bovine embryo, which was twin with a normal fetus.

(d) Offspring development (physical, psychomotor and cognitive)

There is no data on the long-term development of IVM-derived offspring in animals. There is data concerning the longer-term development of offspring derived specifically from transfer of *in vivo*-matured and -cultured embryos, compared with naturally conceived offspring, which suggests psychomotor and cognitive differences as a result of the period of embryo culture and transfer (eg, [132]). Again, the question of whether IVM could exacerbate such effects remains unanswered.

(e) Epigenetic disorders (ie, imprinting)

There is no evidence that IVM *per se* promotes epigenetic modification. There is evidence that ageing of meiotically matured mouse oocytes by culture *in vitro* will promote hypermethylation of at least one gene (*Ped*), but this is an 'aged oocyte' model [133]. Furthermore, parthenogenetic pig embryos have nearly an indistinguishable methylation profile compared to *in vivo*-derived embryos, suggesting that methylation status as a result of IVM and parthenogenetic activation has not deviated from the normal patterns [134]. In contrast, different IVM conditions are known to alter gene expression patterns in oocytes [135], and this is correlated to subsequent blastocyst development.

D General

22 Specify any alternative procedures or treatments that could be used to gain the same result (ie, preserve fertility); if so, please detail

23 List any alternatives methods/treatments to the use of IVM and

(a) Discuss how the benefits to health of the alternative procedures/treatments compare to the benefits of IVM

(b) Discuss how the risks to health of the alternative procedures/treatments compare to the risks of IVM

It was agreed that clauses 22 and 23 deal with the same matters and therefore should be answered similarly.

IVM occupies a niche in the treatment of infertility, which lies on a treatment continuum between artificial insemination and conventional IVF. In particular, it may be attractive to couples where male infertility is the only cause of infertility and females have good prognosis of establishing a pregnancy following embryo transfer, as intra cytoplasmic sperm injection can be performed on IVM oocytes. For female infertility as a consequence of polycystic ovaries, IVM offers the opportunity to mature oocytes in the absence of conventional gonadotrophin treatment. It may also be a useful alternative for women who respond poorly to conventional IVF.

Alternative methods that lie at a similar point to IVM in the treatment continuum are natural cycle or modified natural cycle IVF [136]. Advantages include providing nil (in the case of natural cycle IVF) or a reduced exposure to gonadotrophins (therefore minimising the risk of hyperstimulation syndrome) and potentially reducing costs. Furthermore, the maturation of the oocyte within the follicle in the absence of exogenous hormone stimulation should provide the optimal environment for the oocyte to achieve developmental competence.

Both these options require more complex monitoring of the patient by ultrasound and through blood plasma hormone analysis, especially for natural cycle IVF compared with conventional IVF. Even so, there is a high risk of missing the endogenous LH surge, especially in natural cycle IVF, which invariably would mean a failed cycle. Furthermore, these alternatives would not apply to patients with polycystic ovaries.

24 Specify and detail any additional information related to the risks or benefits to health of IVM, not canvassed in the above clauses, that should be considered when making an assessment of the risks and benefits to health of the use of eggs that have been matured by IVM

There is data suggesting the use of gonadotrophins for ovarian stimulation is associated with increased health risks, including:

- increased risk to women for ovarian, breast and endometrial cancers (eg, [50], [51])
- increased risk of stroke (eg, [52]).

However, many of these claims remain under dispute [53]. Nevertheless, the use of IVM, with the reduced requirement for gonadotrophin stimulation, may alleviate concerns that women may have with placing themselves at risk of disease due to ovarian stimulation.

25 Outline any long-term follow-up studies presented to date and any planned for the future

Neonatal consequences of IVM have been described as a part of section B, clause 11.

There are no long-term studies as yet within the literature. However, at the 2nd International Symposium on *in vitro* maturation of oocytes, Lyon, France, 2007, several proposals were discussed to establish an international registry of IVM-derived children. Furthermore, Associate Professor Thompson has received an email request from Professor Ri-Cheng Chian of McGill University, Canada, for a collaborative venture initiated to provide such data, with preliminary results planned to be released in November 2008.

26 Comment on the quality of the published research

The literature used within this report is of high quality, derived mostly from well-recognised and cited journals in the fields of obstetrics and gynaecology and reproductive biology. There are clear areas of deficiency in the literature to specific questions raised in this report, especially in regard to follow-up studies associated with children derived from clinical IVM. There is also a lack of literature concerning the same question from animal data. In particular, there is a lack of studies in animals which compare the outcomes of IVM as a stand-alone treatment with *in vivo*-derived oocytes, and the subsequent long-term development of offspring born from IVM vs *in vivo*-matured oocytes. These areas should be supported by research funding agencies with interests in child health and development.

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Appendix 1: Efficacy of *in vitro* maturation of mammalian oocytes (mostly compared with *in vivo* maturation) as a technology across different species where pregnancy/live births have been established

Q 17	Q 17				Q 18	Q 19b	Q 19a	Q 19c	Q 19c	Q 19d	Q 19e		
Genus	**Species**	**IVM alone and transfer**	**IVM in conjunction with IVF/IVC**	**Fresh mature oocyte controls?**	**No. animals used**	**Embryonic outcome measures**				**Post-transfer outcomes**		**Comments**	**References**
						Oocyte survival following IVM	**Fertilisation rate (from oocytes inseminated)**	**Early cleavage rate (from oocytes inseminated)**	**Blastocyst rate (from cleaved oocytes)**	**Pregnancy rate (from animals transferred)**	**Live-birth rate (from embryos transferred)**		
Rodent	Mouse	–	Y	Y	N/A	N/A	N/A	*72–75% (IVM) cf 84% (in vivo)	*77–82% (IVM) cf 84% (in vivo)		*13–24% (IVM groups) cf 17% (in vivo)	No. animals not reported. * Involves different IVM treatments	[137]
		–	Y	Y	N/A	#80–97%	#88–96%	#82–87%	#55–68%	#57% (IVM) cf 83% (in vivo)	*#42–49% (IVM) cf *39% (in vivo) *D18 fetuses	No. animals not reported. # Involves different IVM treatments.	[88]
		–	Y	N	N/A	60%	N/A	23%	34%	N/A	5/11		[79]
Bovine	Cow	–	Y	Y (in vivo produced blastocysts)	N/A (abattoir)	75%	N/A	61–67%	13–20%	9/18 (best IVM) cf 9/16 (in vivo)	7/18 (best IVM) cf 9/16 (in vivo)	Different IVM treatments applied	[138]
		Y (+ IVF and culture in heifer oviduct)	N	Y (+ IVF and culture in heifer oviduct)	3 (in vivo maturation) ? IVM	N/A	84% (IVM) cf 66% (in vivo)	57% (IVM)	N/A	0/20 (IVM) cf 2/6 (in vivo)	N/A		[139]
		Y (+ IVF and culture in heifer oviduct)	N	N	10	N/A	70%	N/A	36%	1 of 2	1 ongoing at 4 mo		[140]
		Y (+ IVF and culture in ewe oviduct)	N	N		57–74%		71–92%	39–74%	14/19	12/18 (Day 69+)		[141]

Q 17	Q 17				Q 18	Q 19b	Q 19a	Q 19c	Q 19c	Q 19d	Q 19e		
Genus	**Species**	**IVM alone and transfer**	**IVM in conjunction with IVF/IVC**	**Fresh mature oocyte controls?**	**No. animals used**	**Embryonic outcome measures**				**Post-transfer outcomes**		**Comments**	**References**
						Oocyte survival following IVM	**Fertilisation rate (from oocytes inseminated)**	**Early cleavage rate (from oocytes inseminated)**	**Blastocyst rate (from cleaved oocytes)**	**Pregnancy rate (from animals transferred)**	**Live-birth rate (from embryos transferred)**		
	Murah buffalo	–	Y	N	6	N/A	*64–71%	60–66%	23–52%	4/14	0#	*Control and selected treatment # 1 aborted male calf @ 4.5 mo	[95]
Ovine	Sheep	N	Y	Y (+ fert in vivo)	30	N/A	N/A	61%/70% IVM cf 90%/93% (in vivo)	24%/32% IVM cf 55%/78% (in vivo)	20/29 IVM cf 21/34 (in vivo)	18/29 IVM cf 20/33 (in vivo)	Two different media used for embryo culture	[117]
		Y (+IVF and culture in rabbit oviduct)	Y	Y	53	N/A	N/A	*61–75% IVM cf *75–79% (in vivo)	N/A	#2/4 (IVM) cf #4/20 (in vivo)	Ongoing preg (>3 mo) were 1 (IVM) and 2 in vivo) respectively	* Various IVF treatments # 2–5 embryos transferred to each ewe	[142]
		–	Y	N	N/A	N/A	80%	N/A	–	7/16	10 lambs		[80]
Caprine	Goat	–	Y	N	75	N/A	N/A	72%	–	40/50 (80%)	38/50 (72%)	Donors were goats > 7 y o	[97]
		–	Y	Y	23	61–100% (IVM)	44–68% (IVM) cf 19–46% (in vivo)	11–40% (IVM) cf 8–15% (in vivo)	N/A	3/9	0/9*	*Resorptions occurred by 3.5 mo	[143]
Porcine	Pig	–	Y	N	N/A (abattoir ovaries)	72%	75% (22% mono-spermic)	N/A	20%	2/4	Each farrowed, 4 and 7 piglets, respectively	Data from best treatment group; all piglets grew to healthy adults	[144]
		–	Y	N	N/A (abattoir ovaries)	82%	50–75%	N/A	15–20%	2/4	2/4		[80]
		–	Y	N	N/A (abattoir ovaries)	N/A	78% (47% mono-spermic)	39%	N/A	4/8	9 live piglets, 1 still born from one pregnancy	1 animal aborted, 2 ongoing pregnancies	[145]

Q 17	Q 17				Q 18	Q 19b	Q 19a	Q 19c	Q 19c	Q 19d	Q 19e		
Genus	**Species**	**IVM alone and transfer**	**IVM in conjunction with IVF/IVC**	**Fresh mature oocyte controls?**	**No. animals used**	**Embryonic outcome measures**				**Post-transfer outcomes**		**Comments**	**References**
						Oocyte survival following IVM	**Fertilisation rate (from oocytes inseminated)**	**Early cleavage rate (from oocytes inseminated)**	**Blastocyst rate (from cleaved oocytes)**	**Pregnancy rate (from animals transferred)**	**Live-birth rate (from embryos transferred)**		
Equine	Horse	–	Y	N	N/A (abattoir ovaries)	68–75%	N/A	*86–95%	*13–27%	*5/15	*3/15	* Involves different embryo culture treatments	[99]
		Y (+ IVF and culture in sheep oviduct)	Y	N	N/A	N/A	N/A	89% (IVM only) cf 69% (in vivo)	50% (IVM only) cf 14% (in vivo)	4/6 (IVM only) cf 8/11 (in vivo)	2/11 (IVM only) cf 5/11 (in vivo)	IVM only = IVM followed by culture within sheep oviduct prior to transfer	[146]
Felines		–	Y	Y	N/A	84% (IVM) cf 94% (in vivo)	N/A	41% (IVM) cf 65% (in vivo)	29% (IVM) cf 41% (in vivo)	3/9	2/9*	*3rd pregnancy ended on Day 62 gestation – possibly from placental separation	[147]
Ungulates	Mohor gazelle	–	Y	N	6	43–65%	82–84%	36–44%	0%#	0/3	–	# remaining cleaved oocytes following transfer	[108]
Camelids	Dromedary camel	–	Y	Y	36	84% (IVM) cf 93% (in vivo)	N/A	68% (IVM) cf 72% (in vivo)	35% (IVM) cf 32% (in vivo)	5/12 (IVM) cf 7/13 (in vivo)	0 (IVM) cf 1/13 (in vivo)	Also an in vivo matured and fertilised group	[106]
		–	Y	N	N/A	N/A	N/A	59–72%	20–35%	15/37 (47%)	7/37 (19%)		[107]

Submission Form

Please provide your contact details below.

Name:	
If this submission is made on behalf of an organisation, please name that organisation here:	
Please provide a brief description of the organisation if applicable:	
Address/email:	
Interest in this topic (eg, user of fertility services, health professional, member of the public):	

Please note that all correspondence may be requested by any member of the public under the Official Information Act 1982 (the Act). If there is any part of your correspondence that you consider should be properly withheld under the legislation of the Act, please make this clear in your submission, noting the reasons why you would like the information to be withheld.

If information from your submission is requested under the Act, the Ministry of Health (the Ministry) will release your submission to the person who requested it. However, if you are an individual, rather than an organisation, the Ministry will remove your personal details from the submission if you check the following box.

☐ I **do not** give permission for my personal details to be released to persons under the Official Information Act 1982.

All submissions will be acknowledged by ACART, and a summary of submissions will be sent to those who request a copy. The summary will include the names of all those who made a submission. In the case of individuals who withhold permission to release personal details, the name of the organisation will be given if supplied.

Do you wish to receive a copy of the summary of submissions?

☐ Yes

☐ No

Questions

Question 1:

Given the identified risks and benefits, what is your opinion on ACART's proposed advice to the Minister of Health? Please give reasons for your views.
(See chapter 3 for a discussion of risks and benefits, and chapter 6 for the proposed advice.)

Question 2:

Has ACART identified all the ethical issues relevant to the use of IVM in fertility treatment? Do any of the identified, or any other ethical issues, affect ACART's proposed advice that the use of IVM should be allowed in fertility treatment? If so, how?
(See chapter 5 for a discussion of the ethical issues, and chapter 6 for the proposed advice.)

Question 3:

Should the use of IVM in fertility treatment become an established procedure? If not, why, and how should the use of IVM be regulated?

Question 4:

Should the use of in vitro matured eggs in fertility treatment be limited to the individuals the eggs came from, or should the eggs be able to be donated to others for use in fertility treatment?

Question 5:

Do you have any further comments to share with ACART?