Consultation on the Use of Frozen Eggs in Fertility Treatment:

Discussion document

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Chair's foreword

Human assisted reproductive technologies are advancing rapidly. These technologies offer many potential benefits to infertile couples, but there are also uncertainties and risks. The Advisory Committee on Assisted Reproductive Technology (ACART) has been established to formulate policy advice specific to New Zealand in relation to this controversial field.

The collection and freezing of eggs was declared to be an established procedure in New Zealand in 2005. This means that eggs can be collected and frozen routinely in fertility clinics without requiring case-by-case approval by the Ethics Committee on Assisted Reproductive Technology (ECART).

When ACART was established, the then Minister of Health, Hon Annette King, asked, among other things, for advice on the use of frozen eggs in fertility treatment. Before ACART advises the Minister of Health, it is required to consult on the proposed advice.

ACART proposes that the use of frozen eggs in fertility treatment become an established procedure. The reasons for this are set out in the following pages of this discussion document.

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 recommendations to the Minister on the use of frozen eggs in fertility treatment.

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 frozen eggs. 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 of Health.

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 5 September 2008.

All submissions will be considered before ACART's advice to the Minister of Health is finalised.

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

In June 2005 the collection and cryopreservation (freezing) of human eggs was declared to be an established procedure, meaning that it could be routinely offered by fertility clinics. However, the subsequent use of frozen eggs was specifically excluded from this established procedure because the risks could not be adequately assessed due to the novelty of the technique.

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 frozen eggs. ACART proposes to recommend to the Minister that the use of frozen eggs now become an established procedure, for the following reasons:

- Evidence suggests that the risks to a resulting child associated with the use of frozen eggs are no greater than the risks associated with the use of frozen embryos or in-vitro fertilisation (IVF) generally, given that damaged eggs will be identified and discarded or will fail to fertilise.
- Egg freezing and subsequent use is the only option available for preserving the fertility of some women, particularly those undergoing cancer treatment.
- Egg freezing and subsequent use offers an alternative to those who, for religious or spiritual reasons, find the freezing of embryos unacceptable.
- Egg freezing and subsequent use may also have benefits where embryos cannot be formed due to the absence of sperm for fertilisation.
- The few ethical issues associated with the use of frozen eggs can be better managed in direct discussions between clinicians and patients.

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

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

When ACART was established, the then Minister of Health, Hon Annette King, asked ACART, among other things, for advice on the use of eggs frozen at the mature stage, following collection for fertility treatment. Under the HART Act 2004 ACART could recommend that the use of frozen eggs for fertility treatment be:

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

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 clinic 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, 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.

Note that the established procedure of egg collection and freezing is outside the scope of this document. Also outside the scope of the document is the use of eggs frozen at the very immature stage in pieces of ovary (ovarian tissue freezing).[1]

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**. You will also find its meaning explained in the glossary on page 14.

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.

[1] Ovarian tissue freezing is a new technology that has been developed for preserving reproductive potential in young women with malignant disease who are often rendered menopausal following chemotherapy and radiotherapy. In 2005 ovarian tissue cryopreservation was declared an established procedure because it offers a holding mechanism for women and girls about to undergo cancer treatment. However, the subsequent use of ovarian tissue in fertility treatment was not included in the established procedure due to its novelty at the time. ACART has commissioned a report on the safety issues associated with in vitro maturation and will consult on this later in 2008.

2 Information about egg freezing

What is an egg?

At birth, the female reproductive gonad (**ovary**) contains all the eggs for a woman's reproductive life. At any one time the majority of these eggs lie dormant, in a very immature state. During each menstrual cycle a few of these eggs start to develop as a result of hormonal changes in the woman, and in most cases one of these eggs will continue to develop and be released (ovulated) each month. By the time of **ovulation** the egg is over three times its original size and is primed ready for fertilisation – it is now referred to as a mature egg. The drugs used in **in-vitro fertilisation (IVF)** treatments can allow more than one of these mature eggs to be produced in a single cycle.

Egg freezing as a procedure

Human **embryo** freezing has been used as an important part of fertility treatment for over 15 years, and thousands of healthy babies have been born around the world from this technology. The same cannot be said for human egg freezing, which is still a relatively new procedure.

There are two basic ways for eggs to be frozen: controlled rate freezing and vitrification. These techniques are discussed in detail in Appendix 1.

- **Social reasons:** for example, women who do not have a partner or who want to focus first on their career may wish to preserve their fertility by freezing some of their eggs for use at a later date.

Egg freezing in New Zealand

In March 2005 the **Advisory Group on Assisted Reproductive Technology (AGART)**[2] recommended that egg freezing be declared an **established procedure** as 'it alone offers a holding mechanism for women about to undergo cancer treatment'. The group also recommended that the established procedure exclude the subsequent use of frozen eggs in treatment because 'the risks associated with this have not been able to be adequately assessed due to the novelty of the technique'.

The current established procedure, which covers the freezing of eggs, does not set down the reasons for which freezing can be undertaken, and so women may freeze their eggs for any reason. However, reasons for egg freezing generally fall into one of three categories.

- **Medical reasons:** women at risk of losing their fertility through early menopause, cancer treatment or other illness may freeze their eggs in the hope of later being able to use them to reproduce.
- **Spiritual, religious or ethical reasons:** those undergoing fertility treatment may object to storing their embryos but may have no objection to storing their eggs and sperm.

[2] 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.

Options for the use of frozen eggs

Once eggs have been frozen they might be thawed and used for research purposes or, if approved, for fertility treatment.

Use for fertility treatment

As we have seen, women who have had eggs removed and frozen to preserve their fertility could go on to use these previously frozen eggs in their own fertility treatment at a later date. 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 of frozen eggs to others could also be allowed.

Use for research purposes

Interim guidelines for the **Ethics Committee on Assisted Reproductive Technology (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.

3 Assessment of known risks and benefits to health associated with the use of frozen eggs

This section summarises the known risks and benefits associated with the use of frozen eggs in fertility treatment. The information is discussed in more detail in Appendix 1.

Risks

Risks to the egg

The controlled-rate freezing procedure (using the **cryoprotectants** propanediol and sucrose) is similar to the process used for embryo freezing and has been used successfully in that context for over 15 years, resulting in the birth of thousands of healthy babies. However, this success has not been translated into egg freezing, mainly due to the vulnerable state of the mature egg, together with its large size and high water content.

The inability of an egg to respond to changes in the environment (both within the egg and its surroundings) during freezing and thawing has resulted in:

- rupture of the cell membrane
- rupture of components within the egg (cortical granules) that are involved in the fertilisation process
- alterations to the fine filamentous structures that form the **cytoskeleton** just under the surface of the egg
- damage to the spindle, a part of the egg that holds the chromosomes in place ready for fertilisation.

Any one of these kinds of damage reduces an egg's ability to be fertilised and could result in abnormal chromosome numbers after fertilisation.[3] However, from the evidence available, ACART concludes that although egg freezing and thawing can cause some changes to the egg, the changes that occur are usually transient or able to be detected, allowing permanently affected eggs to be discarded.

[3] Much of this damage reported in studies has been attributed to the use of an inferior cryoprotectant (DMSO), which has since been replaced by another cryoprotectant (propanediol), and also to differences in eggs between the different species used in research.

Outcomes for children born from frozen eggs

There has been no genetic or developmental follow-up study of babies born from frozen eggs, possibly because so few babies have been born in any single fertility centre. Neither has there been any systematic reporting of pregnancy and birth data.

One study of 13 babies reported normal birthweight, normal karyotypes (chromosome numbers) and no malformations in any of the babies. In another study no chromosomal abnormalities were observed following **amniocentesis** sampling of five pregnancies. Another study reported 48 healthy babies born, with no major malformations, following the double sucrose method. No information has been found on birth outcomes following the vitrification method (see Appendix 1).

The above studies report on only a small proportion of the total number of babies born from frozen eggs, which would currently be over 160.[4] Future monitoring information on these births should more accurately assess the longer-term health outcomes for these babies.

There is a large amount of literature on the ongoing development of children born as a result of IVF. Although the data from that research shows a slight increase in congenital anomalies in children conceived as a result of IVF, there is no difference between children conceived with a fresh embryo transfer and children conceived as a result of the transfer of frozen embryos. It is also possible that the increased incidence of abnormalities is related to the genetic background of the individuals/couples involved in the treatment rather than the IVF procedure itself.

If the incidence is in fact related to the IVF procedure, then a similar profile for early childhood development could be expected in children born as a result of using frozen eggs. However, many more children need to be born and studied before any meaningful conclusions can be drawn.

ACART concludes that the evidence at this stage suggests that health outcomes for children born from the use of frozen eggs are similar to those for children born as a result of other IVF procedures. However, this is based on a limited number of studies, and further research is needed in this area.

Maternal health outcomes

No maternal complications have been reported following the use of frozen eggs, although miscarriage does occur. Whether the incidence is increased relative to IVF is difficult to tell at present. One group using the altered salt and low sucrose method reported that three out of six pregnancies were lost before 12 weeks' gestation. Another group reported a level of 20 percent loss using the initial low sucrose method and three losses from 18 pregnancies with the triple sucrose method. Although these latter miscarriage rates are not significantly different from those associated with embryo freezing, the numbers are too low to make a meaningful comparison at this stage.

[4] Although the births of more than 160 babies are reported in the published literature, the consensus at the ASPIRE Conference (Singapore, May 2008) was that the number is now between 500 and 600.

Benefits

Embryo freezing and the use of frozen embryos in fertility treatment have been well established for many years and are relatively successful techniques. Although it is unlikely that the results for egg freezing will surpass those for embryo freezing in the near future, there are situations where the freezing and subsequent use of frozen eggs is preferable to embryo freezing, including:

- where embryos cannot be formed due to there being no sperm for fertilisation
- in the case of young single women with malignant conditions or related treatments that threaten their fertility
- where the individual/couple undergoing fertility treatment objects to creating and storing multiple embryos.

These benefits are only possible if the subsequent use of frozen eggs is permitted.

Monitoring

The lack of evidence discussed above highlights the need for data collection on the outcomes for children born in New Zealand as a result of assisted reproductive procedures. ACART is currently investigating the best ways to collect this data.

For the use of frozen eggs, ACART considers that the following information would be necessary to monitor the procedure adequately:

- freezing method used
- original reason for freezing
- fertilisation method used
- number of clinical pregnancies and deliveries
- frequency of multiple births
- birthweight
- gestational age
- gender
- age of mother at birth
- frequency of congenital abnormalities
- perinatal mortality (stillbirths and neonatal mortality).

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.
   (See chapter 3 for a discussion of risks and benefits, and chapter 6 for the proposed advice.)
2. What is your view on the information that ACART suggests should be collected to monitor the use of frozen eggs in fertility treatment?

4 Acceptability of the risks associated with the use of frozen eggs

ACART has developed a framework to help assess the acceptability of risks associated with a particular procedure or treatment, and this has been used here to consider the acceptability of the risks associated with the use of frozen eggs in fertility treatment. Note that the risks associated with the *collection and freezing* of eggs are not considered because the freezing of eggs is an established procedure and is outside the scope of this document. This section summarises ACART's view on the acceptability of the risks associated with the *use* of frozen eggs. The full analysis of the risks associated with the use of frozen eggs is set out in Appendix 2.

There are very few known health risks associated solely with the use of frozen eggs, and ACART's analysis indicates that the known risks fall within a level of risk that is acceptable in New Zealand, for the following reasons.

- For some women (particularly those undergoing treatment for cancer), egg freezing and the subsequent use of those frozen eggs will be the only option available to them to have genetically related children.
- The miscarriage risk is similar to the miscarriage risk associated with the use of frozen embryos (though numbers are too small to make a meaningful comparison at this stage).
- There has been a reasonable uptake of the technology and approximately 160[5] births in other countries.
- No country has banned egg freezing, although the Hungarian Ministry of Health is considering a moratorium pending further research.
- There are few ethical issues associated with the use of frozen eggs, and ACART considers these issues are best dealt with in discussions between the clinician and the patient.
- ACART considers the use of frozen eggs 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 from eggs that have previously been frozen. Implementation of a monitoring regime will, therefore, be an important part of ACART's recommendations to the Minister.

[5] Although the births of more than 160 babies are reported in the published literature, the consensus at the ASPIRE Conference (Singapore, May 2008) was that the number is now between 500 and 600.

5 Ethical Analysis

Overall, ACART considers that there are few ethical issues associated with the use of frozen eggs. 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 use of frozen eggs, including:
  - an acknowledgement that the use of frozen eggs 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 using frozen eggs and the lack of evidence about the health of children born from frozen eggs
- adequate time and opportunity be provided for patients to discuss their treatment with competent staff.

Posthumous use of frozen eggs

The technology of egg freezing potentially allows for the future use of eggs from a woman who has died since having her eggs frozen. This issue is especially pertinent if egg freezing is used to preserve the fertility of cancer patients who later die. Under the Reproductive Technology Accreditation Committee's (RTAC's) code of practice, fertility clinics' consent forms to freeze eggs must state what is to be done with those eggs if the consenting person dies or becomes incapable of varying their consent. The Fertility Services Standard also requires providers to have procedures in place for dealing with situations where the consenting person dies or becomes incapable of varying their consent. ACART considers that the use of frozen eggs after the death of a woman is covered by these requirements.

Donating frozen eggs 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 must be fresh or frozen.

ACART considers that the use of frozen eggs should not be restricted to a woman's own use. Provided that the women receiving donated frozen eggs are informed of the risks associated with their use, and of the procedure's relative novelty as a form of treatment, ACART sees no reason to prohibit the donation of frozen eggs for use in fertility treatment. At present, fresh eggs are preferred, but occasionally it may be necessary to use frozen eggs for egg donation (for example, to make it easier to synchronise with the recipient's cycle).

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 frozen eggs 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 and, 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.[6]

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

[6] Hudson M, Henry C, Shelling A, et al, Recognising the needs, values and beliefs of Māori in assisted reproductive technologies, paper presented to the Bioethics Conference, Dunedin, 2008.

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). Frozen 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 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.

Human rights issues

In New Zealand the Human Rights Act 1993 prohibits discrimination on the basis of a variety of factors, including gender, age and religious belief.

Gender

For several decades men have been able to preserve their fertility, for whatever reason, by freezing their sperm. They have then been able to use their frozen sperm without specific approval from an ethics committee. It could be argued that women should also have access to this technology without constraint.

Age

The technology of egg freezing, thawing and subsequent use may allow women to freeze their eggs and use them to bear children when they are of an advanced age or post-menopausal. This may, however, be only theoretical as eggs may only be stored for a maximum of 10 years, unless a specific extension is granted by ECART, based on guidelines that are to be developed by ACART. Given the upper age at which it would be sensible to collect and freeze eggs for reproductive use, the 10-year limit will restrict the age at which most women could use frozen eggs to reproduce.

Religious belief

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 find embryo freezing and the dilemma of having to decide what to do with embryos that are surplus to reproductive requirements unacceptable. The use of frozen eggs would provide a more ethically acceptable alternative to the use of frozen embryos for people who have these concerns.

Equity

Another issue relevant to the use of frozen eggs concerns access to the technology. The freezing and future use of frozen eggs is likely to include paying for the following services:

- ovarian stimulation
- egg collection
- egg freezing
- storage of eggs (annual fee)
- use of eggs in treatment (up to two cycles of IVF are now publicly funded)
- other associated costs.

It is likely that these costs will restrict who is able to access this technology. In addition, it is probable that the above services will only be available in larger centres around the country, limiting access to the technology for those who live in smaller centres in New Zealand.

Use of eggs for social reasons

A woman might want to freeze and use her eggs to preserve her fertility for personal reasons (for example, where she does not have a current partner or lacks the material resources to support a child at present). Specifically freezing and using frozen eggs for personal reasons raises questions about reproductive autonomy and the rights of the individual versus community acceptability of technologies.

ACART considers that current evidence would not support a woman's belief that she would be preserving her fertility, given that the birth rate from the use of frozen eggs remains relatively low. ACART considers that the freezing of eggs is at best a backstop measure for those who are at risk of losing their fertility altogether, and that it would be unwise for women to rely on egg freezing for social reasons. Decisions on egg freezing are, however, best clarified between the clinician and the patient to ensure that a woman (or couple) is given full information on the procedure and is able to make an informed choice.

3. Has ACART identified all the ethical issues relevant to the use of frozen eggs in fertility treatment? Do any of these issues affect ACART's proposed advice that the use of frozen eggs 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 use of frozen eggs become an established procedure for:

- individual treatment purposes (use of frozen eggs in fertility treatment by the woman who originally stored them)
- donation for treatment purposes (use of frozen eggs by other women in fertility treatment)
- donation for use in research.

ACART's reasons for its recommendations are as follows.

- The collection and freezing of eggs is currently an established procedure, and so there would have to be strong reasons to prevent women from subsequently using their frozen eggs.
- Although it is still a relatively new technique, the available evidence suggests that the risks to the resulting child associated with the use of frozen eggs are no greater than those associated with the use of frozen embryos or IVF generally, given that damaged eggs will be identified and discarded or will not fertilise.
- For some women, particularly those undergoing cancer treatment, egg freezing and subsequent use will be the only option available to preserve their fertility.
- Egg freezing and subsequent use also offer an alternative to those who, for religious or spiritual reasons, find the freezing of embryos unacceptable.
- There appear to be few ethical issues associated with the use of frozen eggs, and ACART considers that these issues can be managed in discussions between clinician and patient.
- Although it is preferable to use donated fresh eggs because of their greater rate of success, allowing the use of frozen donated eggs means that the cycles (of both the donor and the receiver) can be better synchronised where necessary.
- Allowing the use of frozen eggs puts women on an equal footing with men, who are free to use their frozen sperm for fertility treatment.

If the Minister approves the use of frozen eggs as an established procedure, it will be ACART's responsibility to collect information to monitor the health outcomes of children born as a result of the use of frozen eggs.

4. Should the use of frozen eggs in fertility treatment become an established procedure? If not, why, and how should the use of frozen eggs be regulated?
5. Should the use of frozen eggs in fertility treatment be limited to the individuals the eggs came from, or should frozen eggs be able to be donated to others for use in fertility treatment?
6. Should frozen eggs be able to be donated for research purposes?

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.
Amniocentesis	The sampling of the amniotic fluid (the fluid that encloses an embryo) by inserting a hollow needle into the fluid to determine the condition of the embryo.
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.
Cryopreservation	The freezing and storage of tissues and cells at extremely low temperatures.
Cryoprotectant	A solution that will crystallise in a controlled way at a subzero temperature.
Cytoskeleton	The series of protein skeletal elements found in a living cell that gives shape and coherence to the cell.
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.
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.
Ovary	The egg-producing reproductive organ found in females.
Ovulation	The process in the menstrual cycle by which a mature ovarian follicle ruptures and discharges an egg that participates in reproduction.
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 1: Report on Egg Freezing for ACART

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An overview of egg freezing

Why cryopreserve human eggs?

Although human embryo cryopreservation (freezing) has been used as an important adjunct to fertility treatment for over 15 years and thousands of normal babies have been born around the world from this technology, the same cannot be said for human egg (oocyte) freezing. The potential clinical benefits of oocyte cryopreservation include (but are not restricted to) preservation of fertility options for women of reproductive age who are at risk of losing their ability to produce eggs as a result of toxic anticancer treatments but have no partner and are, therefore, unable to benefit from routine embryo freezing procedures [1].

Although three babies were born from egg freezing in the 1980s, the technology was never systematically used for clinical material until the late 1990s. The more vulnerable state of the egg and the poor initial success rate were the major contributors to the lack of clinical application. Many of the concerns regarding egg freezing were based on animal studies, but subsequent evidence from research using human eggs has indicated that these may be unfounded and relate specifically to species difference. These human studies together with a number of recent clinical egg freezing programs suggest that the technology is a viable option for appropriate patients (recent review [2]).

What is an egg?

At birth, the female reproductive gonad (ovary) contains the total complement of eggs for the female reproductive life. At any point during reproductive life, the majority of these eggs lie dormant in a very immature state. Each menstrual cycle, a few of these eggs start to develop as a result of hormonal changes in the woman and, in most cases, one of these developing eggs will continue to develop and be released (ovulated) each month. By the time of ovulation the egg is over three times its original size and is primed ready for fertilisation – this is referred to as a mature egg. The drugs used in IVF treatments can allow more than one of these mature eggs to be produced in a single cycle. The mature egg, prior to being fertilised, is in a dynamic state in which it is potentially vulnerable to any changes in its environment. Exposure to any inappropriate environment may render the mature egg unable to proceed through the processes of fertilisation and subsequent division into an embryo consisting of multiple cells and, therefore, prevent a resultant pregnancy. If not applied in an appropriate way, egg cryopreservation may have this effect.

Egg freezing

Generally eggs are frozen at two of the above developmental stages – at the very immature stage in pieces of ovary and at the mature stage following collection for IVF. The freezing of eggs within pieces of the ovary is a new technology that has been developed for storing reproductive potential in young women with malignant disease who are often rendered menopausal following chemotherapy and radiotherapy [3–6]. Although the freezing of the pieces of ovary is promising, very little information is available regarding the clinical potential of this technology [7–11]. Two births have been reported from this technology recently [12, 13]. The remainder of this report will concentrate on the freezing of mature eggs.

There are two basic processes by which cells can be frozen – controlled rate techniques or vitrification.

Controlled rate freezing

To successfully achieve survival after controlled rate freezing, water within the egg cell must be removed and replaced with a solution that will crystallise in a controlled fashion at a subzero temperature. This solution is referred to as a cryoprotectant.

To assist with the removal of water from the egg, a second cryoprotectant (sucrose) is also added, but this does not enter the egg. After sufficient time for displacement of the water, the egg is placed in a sealed plastic straw. The temperature is slowly reduced to the crystallisation temperature and then further reduced at an even slower rate to −196°C. The eggs remain at this temperature in liquid nitrogen storage tanks until required. To thaw the eggs, the procedure is essentially reversed, bringing the egg quickly back to body temperature and replacing the cryoprotectant inside the egg with water.

Vitrification

In this case, the egg is exposed to a combination of very concentrated cryoprotectants, often for only 30 seconds, and then the temperature is dropped very quickly to –196°C.

The major difference in this procedure compared to controlled rate freezing is that there is no crystallisation. Due to the high concentration of the cryoprotectants and the ultra-rapid rate at which the temperature is reduced, the surrounding solution and that inside the egg never crystallise and form a glass-like (vitrified) state.

Again, to thaw the egg, a reverse procedure is applied. It appears, from experience with the vitrification of other types of cells that minor variations in the time of exposure to the cryoprotectant (sometimes as little as a few seconds) can result in damage. Previously, vitrification has been used mainly for animal embryos; however, more recently it has been applied to clinical egg and embryo storage.

Current status of the procedure

Has egg freezing been banned?

Unlike embryo freezing, which has been banned in Germany for a number of years and in Italy since 2004 [14], based on ethical reasons, there appears to be no specific legislation in any country banning egg freezing at present.

Is approval required for egg freezing?

A survey of IVF groups in a number of major countries (Australia, United States, United Kingdom, Canada, France, Sweden, Finland, Italy) indicated that there is also no requirement for specific approval of egg freezing.

Although there is a general consensus that this technology should be available for young women with cancer, there is controversy relating to its use for extending female fertility. The Practice Committees of the Society for Assisted Reproductive Technology (USA) and the American Society for Reproductive Medicine were of the opinion that "oocyte cryopreservation is an experimental procedure that should not be offered or marketed as a means to defer reproductive aging". They further stated that "oocyte cryopreservation is not an established medical treatment". However, this was subsequently qualified when they suggested a number of guidelines for providing information to women who may wish to insure against declining fertility. They also suggested that institutional board approval be required.

Controversy about banning

Although there are no bans on egg freezing at present, a recent article [15] indicated that the Hungarian Ministry of Health is currently working on a proposal that intends to ban egg freezing in Hungary temporarily. The standpoint taken is that the safety of the technology has not been proven and that there is a high risk to the genetic material within the egg, which translates to a significantly increased risk to the offspring. The Ministry is requesting further animal experimentation to clarify the probability of permanent lesions to the spindle and alterations of the genetic material. They also believe that, at present, suspension is justified due to the low efficiency of the procedure, which has reached the level required for clinical adoption.

Information provided in the subsequent sections of this report will show that many of the animal studies do not correlate with the conditions for human egg freezing and that species differences in the egg have a major impact on the results obtained for egg freezing. It is the author's opinion that more weight should be given to studies using the exact material that would be frozen in the clinical situation, that is, the human mature egg, and not to animal studies. The report will also show that, at present, the efficiency of egg freezing with new developments is approaching that observed for other assisted reproductive technologies.

Number of patients

In the mid 1980s when egg freezing was first introduced as a clinical procedure, only four patients were reported, and these were all patients achieving a pregnancy [16–18]. Egg freezing resurfaced some 10 years later, following the report of a baby born [19] using a new procedure; the procedure currently used. Again, the number of patients for which the procedure had been used were small – generally pilot studies or case reports of successful pregnancies (56 patients).

Although this trend has continued for the use of egg freezing in a small population of specific patients, for example, couples in which no sperm was obtained during IVF treatment, the change to the law in Italy suggests that in Italian clinics that use egg freezing to overcome the limitation of creating only three embryos, the majority of IVF patient would have eggs frozen in every cycle. At least in Italy this will translate over the next few years into an exponential increase in the number of patients using egg freezing. The national Italian data for 2005, presented at the recent Second World Congress on Human Oocyte Cryopreservation 2007, reported that only 12 percent of patients had frozen eggs, which translates to 12,689 eggs.

In the literature at present, there are reports of egg freezing from clinics in 15 countries (United States, Australia, Canada, Spain, Germany, Hungary, Czech Republic, Brazil, Argentina, Colombia, China, Taiwan, Korea, Japan and Italy). From these reports, it can be seen that over 2,600 patients have frozen more than 16,818 eggs [15, 20–80].

Outcome

For all assisted reproductive technologies, the ultimate outcome is measured as the number of live births achieved. In the above studies, 220 babies were reported from the thawing of 16,818 eggs, which equates to 1.3 babies for every 100 oocytes thawed. Similarly, the Italian data for 2005 (some of which would have been also reported in the above publications) resulted in at least 133 babies born from the thawing of 12,689 eggs (1.0 baby/100 eggs). In comparison, in Victoria, Australia, for the year 2004, from 56,986 fresh eggs collected, 1271 babies were born following transfer of fresh embryos (2.2 babies/100 eggs). The additional contribution of frozen embryos increased the figure to three babies per 100 eggs collected (data for IVF procedures collected by the State Government of Victoria, Australia).

One confounding factor in reporting the total number of births from egg freezing is that, in many of the above reports, the final outcome was only measured as foetal heart detection (of which 507 have been reported), and therefore the above calculation of 1.3/100 is an underestimation of the outcome. Theoretically, assuming a 20 percent miscarriage rate, which many of the controlled rate freezing procedure papers report, the reduction from foetal heart detection to birth (406) would result in 2.4 babies/100 eggs, which is approaching the result for frozen embryos.

Other confounding factors are that the data has been generated using two extremely different procedures; controlled rate freezing and vitrification, with a number of modifications applied to both, and that miscarriage rates may be higher with some procedures. A more accurate assessment of the outcomes and efficiency of each of the procedures will be described further on in this report.

Risk of using frozen eggs

The controlled rate freezing procedure, using the cryoprotectants propanediol and sucrose, is similar to the process used for embryo freezing and has been used successfully for over 15 years, resulting in the birth of thousands of babies. However, this success has not been translated into egg freezing, mainly due to the vulnerable state of the mature egg together with its size and water content.

An inability to respond to changes in the environment both within the egg and its surroundings during freezing or thawing results in rupture of the cell membrane, which is indicated by the survival rate. These conditions during freezing are also thought to cause rupture of components within the egg that are involved in the fertilisation process; the cortical granules [81].

Similarly, fine filamentous structures that form the cytoskeleton just under the egg surface are also altered when exposed to the chemicals used in freezing; the cryoprotectant [82]. Another component, the spindle, which holds the chromosomes in place ready for fertilisation, is sensitive to reduced temperature [83]. Damage to these components would compromise the egg's ability to be fertilised and could result in abnormal chromosome numbers after fertilisation.

However, much of this damage reported in these studies has been attributed to the use of an inferior cryoprotectant (DMSO), which has since been replaced by another cryoprotectant (propanediol), and also to differences in eggs between species. This will be discussed in more detail further on in this report.

Benefits of using frozen eggs

Embryo freezing has been well established for many years and is a highly successful technique for maximising the chance of pregnancy from a population of eggs while reducing the risk of multiple pregnancy. It is difficult to see that, in the near future, the results for egg freezing will surpass embryo freezing due to the ability to select embryos and the pressure to achieve a pregnancy quickly [84].

Clearly there is a benefit in freezing eggs in the situation where embryos cannot be formed due to absence of sperm for fertilisation [1] or in the case of young single women who have malignant conditions that threaten their fertility [85]. There is also a benefit in freezing donated eggs for synchronisation with the recipient [52]. At present, these are the main situations in which egg freezing is used in all countries apart from Italy. However, the main benefit of egg freezing lies in the ethical problems associated with the creation and storage of multiple embryos. Egg freezing eliminates the dilemma patients face when discarding embryos, or legal issues relating to ownership of embryos following separation.

Lack of information

As stated previously, many of the earlier studies dealt with small numbers of patients, but this has recently altered with many of the Italian groups reporting egg freezing using a controlled rate method in larger numbers of patients (50–100).

Similarly, although the interest in vitrification of human eggs is increasing, the reports in the literature are of small series of patients, which are generally a selected group of patients who have good quality eggs (egg donors). Larger numbers of non-selected patients are required to validate the procedure. There is also an absence of basic biological studies with human eggs assessing the cellular structures in which damage may occur following vitrification.

The literature lacks a comparison between fresh eggs and frozen eggs within the same clinic in which all other factors apart from the freezing of the egg are uniform. Attempts to provide this comparison have been presented in a couple of recent studies, but these studies are deficient in meaningful embryo quality assessment between fresh and frozen eggs. Data regarding any follow-up of postnatal and childhood development is completely absent.

Information from human studies

Efficacy

Survival, fertilisation, embryo development and implantation following egg freezing

The ultimate success of any assisted reproductive technology must be defined in terms of babies born. However, a number of other crucial criteria must be applied in order to fully understand the value and shortcomings of egg freezing. The controlled rate freezing procedure, using the cryoprotectants propanediol and sucrose [86], heralded the reintroduction of egg freezing as a clinical procedure and culminated in the report of a normal live birth following thawing, fertilisation and transfer [19].

In these initial studies [87, 88], approximately 50 percent of frozen eggs survived when thawed, 50 percent of these were able to be fertilised by a sperm in the laboratory and go on to produce an embryo. However, only 25 percent of these embryos continued cleaving to the implantation stage (blastocyst). This freezing procedure has been the most widely used clinical approach to date, resulting in 43 births from over 460 women treated [19, 21–37, 57, 89–91]. Just over 4000 eggs have been frozen and thawed, with 50 percent surviving the procedure.

Following a procedure in which the sperm is directly injected inside the egg (Intra cytoplasmic sperm injection (ICSI)), the normal process of fertilisation occurred in 54 percent of the surviving eggs.

ICSI is the preferred method of fertilising frozen eggs. The vast majority (85 percent) of these fertilised eggs subsequently formed early stage (2–8 cells) embryos that were transferred to the patient. The proportion of embryos transferred that subsequently go on to form a detectable foetus is referred to as the implantation rate. This is an early stage of pregnancy defined by the detection of a foetal heartbeat, using ultrasound scanning. The implantation rate of embryos formed from frozen eggs was approximately 10 percent. So, based on the numbers of surviving eggs, the number of those that fertilised and developed and the number of embryos that formed a foetus when transferred to the patient, it can be estimated that approximately two foetuses would result from the thawing of 100 frozen eggs. Based on published data from approximately the same time period [92], this can be compared to approximately six foetuses from 100 non-frozen eggs if they were exposed to sperm and the embryos were transferred or approximately four foetuses from 100 non-frozen eggs if they were exposed to sperm, frozen and thawed as embryos and transferred.

Using this model, it could be considered that egg freezing is approximately half as effective as embryo freezing and a third as effective as the use of fresh eggs.

New methods

Recently a number of modifications to this original method have been reported. These have aimed at improving the efficiency of removing water (dehydration) before freezing by using higher levels of the cryoprotectant sucrose. Although the number of eggs frozen using some of these modifications is lower, there is a general trend towards improved results. Doubling the sucrose level has achieved an improved survival rate of 71 percent and a higher fertilisation rate of 80 percent [38, 40–44, 60, 93, 94].

A slightly higher proportion of the fertilised eggs form embryos relative to the low sucrose method, and the above improvements result in double the number of embryos (53) produced per 100 eggs compared to the low sucrose procedure (23) and more of these embryos implant (implantation rate of 17 percent). This attrition rate would result in nine foetuses from 100 frozen eggs, which is equivalent to the outcome from non-frozen eggs observed with recent improvements in culture methods (unpublished observation). Again, more recent in-house data would be required to make a meaningful comparison. The major group using this procedure has had 50 babies born from this procedure (personal communication).

Further increasing the sucrose level to three times that reported in the initial procedure has been trialled more extensively [15, 36, 47–53, 59, 61, 63–67]. Again, higher survival (73 percent) and fertilisation (73 percent) rates are achieved. Although a high number of embryos are generated (48 per 100 eggs), fewer of the embryos implant, reducing the final outcome to three foetuses per 100 thawed eggs. To date, 54 babies have been born using this modification.

Another approach has been to alter the salt solution the eggs are exposed to in combination with sucrose at each of the above concentrations; 0.1M [54], 0.2M [55, 62] and 0.3M [55, 68, 69]. Altering the salt solution produced no further improvement in the survival, fertilisation and embryo development rates above that for the corresponding sucrose level alone. However, the implantation rates differ when compared to the corresponding sucrose alone. The 0.1M and 0.3M sucrose levels together with the salt modification resulted in a two-fold improvement in the implantation rate compared to sucrose alone. In contrast, a lower implantation rate was achieved when the double sucrose combined with the salt modification was used (11 percent) relative to the double sucrose alone. Finally, the culmination of these rates for both the 0.1M and 0.3M sucrose in the modified salt media, results in six foetuses/100 eggs thawed.

Caution should be exercised in interpreting these results since all modified salt studies are on relatively small numbers of eggs (~ 200) and only 16 births have been reported.

Vitrification

Although previously the same could have been said of vitrification, at the recent American Society for Reproductive Medicine meeting (October 2007), 173 births were reported from a vitrification procedure using similar cryoprotectants to the controlled rate freezing procedure (propanediol [PROH] and sucrose) together with another cryoprotectant; ethylene glycol (EG) [95].

A further 39 births have been reported following vitrification in a solution where the propanediol has been replaced with dimethyl sulphoxide (DMSO) [70, 71, 73, 75–77, 79, 80, 96]. Previously, all studies reported were on small numbers of eggs (< 100) [71, 73, 75, 77]. This together with minor differences in methodology, which may have a significant impact on the outcome, made meaningful comparisons difficult. However, there appear to now be three main streams of methodology and a significant number of eggs (> 200) vitrified with each (1. EG, 2. EG + DMSO, 3. EG + PROH).

Survival and fertilisation rates are slightly lower in both the EG and EG + PROH (~75 percent for each) compared with the EG + DMSO procedure (93 percent and 87 percent respectively). With one of these procedures (EG + PROH), only half the fertilised eggs formed embryos, therefore generating only 30 embryos/ 100 eggs and four implantations/ 100 eggs, which is similar to some of the controlled rate freezing procedure results.

Although better development rates were observed with the other procedures, only slightly more implantations, that is, five/ 100 eggs would be generated with the EG method due to a lower implantation rate of 10 percent. At present, the EG + DSMO procedure is achieving the highest rates, generating 75 embryos and 12 implantations/100 eggs. In contrast to the controlled rate and other vitrification studies, eggs vitrified in the EG + DMSO procedure were all obtained from young donors and are highly likely to be of higher quality than those from older infertile women, which may bias the data. Although suggestive of a marked improvement, only 22 babies have been reported from the EG + DMSO procedure.

Much larger studies using these vitrification methods are needed to establish whether these improvements can be maintained for all patients and whether the pregnancies reported continue to term deliveries.

Live birth

As stated previously, many of the studies generally report pregnancies, and if births have occurred prior to publication these are also included. Therefore, the numbers of births are always significantly lower than the numbers of pregnancies. It is important to establish that the new methods result in pregnancies that progress to full term. However, the small numbers of babies born from each modification make it difficult to generate meaningful birth rates for each modification. At present, the only number that provides a reasonable indication of live birth rate is the overall total, which is 1.3 births per 100 eggs. This is approximately half the rate estimated for the use of fresh eggs.

Health risks

Potential side effects from using frozen eggs.

The potential side effects that occur in the process of collecting eggs for freezing are similar to IVF. The stimulation protocol to induce multiple follicular development is identical to that utilised in the IVF programme. Consequently, the side effect or risk profile is the same as for the IVF programme up to and including the egg collection procedure. Risks associated with the process of ovarian hyperstimulation and egg collection can include an adverse reaction to the medication or over response to the medication. An excessive response to the ovulatory stimulants may subsequently lead to the ovarian hyperstimulation syndrome.

The ovarian hyperstimulation syndrome is characterised by abdominal distension, fluid retention and associated alteration of kidney, liver and blood clotting functions. In approximately 5 percent of patients, we would expect to obtain 20 or more eggs from the procedure. It is estimated that about 5 percent of those patients will require hospitalisation for pain control, fluid replacement and maintenance until the hyperstimulation phase passes [138].

The risk of ovarian hyperstimulation in these patients will be less than for the general IVF population. The reason for this is that if a transfer procedure utilising fresh embryos is undertaken and a pregnancy occurs, then this exacerbates the syndrome. In effect, the freezing of eggs will reduce the incidence of severe and later stage ovarian hyperstimulation.

Potential risks and side effects at the time of the egg collection procedure include pelvic infection, which may lead to ovarian abscess, peritonitis and/or pelvic abscess. The occurrence of these side effects is rare, with a reported incidence of less than one in five thousand cases [115]. Vaginal and/or pelvic bleeding and the need for a blood transfusion and/or abdominal or other surgery are rare.

The reported incidence of the serious side effects of damage to ovaries, bowel, bladder or other internal organs adjacent to the ovaries and subsequent need for abdominal or other surgery is rare at less than one per ten thousand cases [115].

Potential side effects following an egg collection procedure would include deep venous thrombosis or pulmonary embolism.

As discussed above, the occurrence of risk from these procedures is anticipated to be the same as the occurrence of risk for the IVF procedure given the common pathway with regard to ovarian hyperstimulation and egg collection procedure [97].

Health outcomes for female patients

The health outcome for patients is anticipated to be similar to that of the IVF procedure, excluding the chance of pregnancy. Most female patients can expect their menstrual cycle to return to normal within six weeks of having the procedure. The hyperstimulated ovary is expected to return to normal size and endocrine pattern within one month of the egg collection procedure. Patient symptoms attributable to fluctuating hormone levels can be anticipated during that time. In addition, there may be symptoms of pelvic discomfort and pain in the immediate post-operative period due to swelling and bleeding that had occurred within the ovary after the egg collection procedure.

In the longer term, studies have looked at the incidence of hormonally related cancers in female patients undertaking the IVF procedure. There is no increased incidence of breast, ovarian or uterine cancer in those patients who have had cycles of ovarian hyperstimulation. The Australian study for breast cancer following ovarian hyperstimulation showed no increased risk for the incidence of breast cancer with five to 15 years of follow-up after the treatment was undertaken [98–100].

Exclusion of potential patients based on clinical indicators

Possible exclusion from treatment would be based upon a clinical scenario. This would include:

i. patients in whom the risk of ovarian hyperstimulation would adversely impact the diagnosis, that is, the increased levels of hormone, particularly oestrogen, in women diagnosed with breast cancer. There have been recent reports in the literature of patients having ovarian stimulation with an aromatase inhibitor so as to retrieve oocytes but limit the production of oestrogen from the follicles producing the egg [101]. Whilst the oestrogen level is reduced compared to a normal cycle of ovarian hyperstimulation, there is still the issue of the delay in commencing chemotherapy whilst undergoing ovarian hyperstimulation and oocyte collection. In addition, if there is an over-response to the medication and the ovarian hyperstimulation syndrome develops, then chemotherapy would need to be deferred until the haemo-dynamic situation had resolved

ii. the potential for the initial diagnosis to worsen during the time that it would take to arrange and undertake the procedure of ovarian stimulation and egg harvesting, that is, an aggressive tumour or cancer that could advance in the four to six weeks that may be required to complete the cycle of treatment

iii. patients in whom the procedure of ovarian hyperstimulation may worsen the underlying medical condition, that is, chronic and/or severe renal disease

iv. patients in whom the underlying medical condition would preclude a pregnancy. In medical conditions such as severe pulmonary hypertension, the mortality rate may be in excess of 50 percent if a pregnancy is attempted. However, there would be little point in retrieving the eggs and freezing them for later use in the patient if a pregnancy was absolutely contra-indicated in her, except if a surrogacy arrangement was planned or anticipated.

Damage to the egg

Although the rupture of the cortical granules has been reported following exposure to cryoprotectants [81, 102], others have reported the converse, that is, a normal population of these granules following freezing [86, 103].

The release of these granules would result in an inability to fertilise, but normal fertilisation following insemination occurred in a similar proportion of frozen to non-frozen eggs [87]. This study clearly established that cortical granule discharge is not a concern with the current slow-controlled rate freezing of human eggs. Although this has not been specifically assessed following vitrification, the introduction of a sperm directly into the egg (ICSI) would overcome the impact of this damage.

Alterations to other minute structures within the egg involved in moving molecules and energy metabolism are apparent in eggs frozen in the high sucrose (0.3) procedure [102].

Initial studies showed that the spindle that anchors the chromosomes in place dissolved at low temperatures and reformed on subsequent return to body temperature [83, 104]. During this process, chromosomes were displaced from the spindle and detected scattered through the egg, which would result in an abnormal chromosome number in the subsequent embryo. This scattering of the chromosomes was only observed in mouse eggs and not observed in human eggs examined under the same conditions [105].

The addition of the cryoprotectant propanediol protected the spindle during the reduction in temperature both in the mouse [106, 107] and the human egg [86]. In the human egg, no stray chromosomes were detected whether the spindle was abnormal or normal [86] after freezing. Further studies showing that human frozen eggs with an abnormal spindle were prohibited from fertilising normally and that normal chromosome numbers were present in those that fertilised [87] confirmed that this was not a major concern in human eggs but associated specifically with mouse oocytes.

New technology has allowed direct visualisation of the spindle in living eggs and has verified normal spindle reformation after controlled rate freezing in human eggs [108, 109].

Assessment of embryos for normal chromosome number detected similar proportions of abnormal chromosomes in both fresh and frozen eggs (~25 percent) [110].

Direct visualisation of eggs after vitrification has also shown the spindle to reform [111], however no chromosomal assessment has been made of embryos derived from vitrified eggs.

Alterations to the cytoskeleton filaments have been observed after controlled rate freezing procedures and vitrification in some animal eggs [82, 112, 113]. These cytoskeleton filaments must function normally for movement of male and female DNA during fertilisation and cleavage. The lack of artificial activation [88] high normal fertilisation [87] and formation of embryos in the human egg following controlled rate freezing [88] indicate that, if alteration to the cytoskeleton is occurring, it is only transient and not impacting on the subsequent process. Although fertilisation and embryo development occur following vitrification of eggs, studies to dismiss the concerns regarding alteration of the cytoskeleton and artificial activation have not been undertaken at present.

Obstetric outcomes

Egg damage

As explained above, eggs in which the spindle has been damaged are unlikely to proceed through fertilisation. Similarly, damage to the cytoskeleton would prohibit fertilisation and normal embryo development. In both situations, this abnormal material is detected and discarded during the treatment and not transferred to the patient, thereby having no impact on obstetric outcome.

Neonate development

At the recent Second World Congress on Human Oocyte Cryopreservation (2007), an international database aimed at collating outcomes from all forms of egg freezing was initiated. This should provide a systematic reporting of pregnancy, miscarriage and birth data, which does not exist in the present publications.

Unfortunately, at present, there is limited information regarding genetic status or developmental follow-up of babies born from egg freezing, presumably due to the fact that so few babies have been born in any single centre. In the publications mentioned above, very little information is given regarding the pregnancies and/or births apart from an occasional report of term pregnancy, sex of offspring and birthweight.

However a recent abstract attempted to assess outcomes from all publications up to July 2006 [114]. A similar miscarriage rate to that observed with embryo freezing was reported (~20 percent). Two-thirds of these miscarriages were karyotyped, and all were chromosomally normal. Of the 197 babies born, only one-quarter were subsequently karyotyped; again all were normal. One infant was reported with ventricular septal defect. Health status at birth was reported for two-thirds of the babies and recorded as normal in all, however, subsequent health status at 6–36 months of age was only reported on one-third of infants, but again all were normal.

Two of the larger groups in Italy have also reported outcomes of 165 babies in total [115, 116]. Two women underwent elective abortions, one for trisomy 21 and one for Turners syndrome. Two malformations were detected, one infant with Choanae Atresia and the other with Rubinstein–Taybi syndrome, all others were normal.

Another group in the United States reported that 50 babies have been born. Malformations observed were; a set of twins, one born with absence of one ear opening, the other with V.A.T.E.R.; two siblings with autism (these have a naturally conceived sibling with Rubinstein–Taybi syndrome); a ventricular septal defect occurred in two children, one has repaired on its own, and the other has required surgical repair (personal communication).

Limited information has been reported with respect to the outcome from vitrified eggs [95]. No miscarriage rate, genetic information or health status was given, but no adverse perinatal outcome was reported (173 babies).

Although some of the births from these four studies would have been included in the summary data, the outcomes would not have been included. There is a large amount of literature to review with regard to ongoing development of children born as a result of IVF. Whilst that data shows a slight increase in congenital anomalies in children conceived as a result of IVF, there is no difference between children conceived with a fresh embryo transfer versus a conception after the transfer of frozen embryos. It is possible that the increased incidence of abnormalities is related to the genetic background of the couple on treatment rather than the IVF procedure per se. If that were the case, then a similar profile for early childhood development could be expected in children born as a result of utilising frozen eggs. There will obviously need to be many more children born and followed up before any meaningful conclusions can be drawn.

Maternal outcome

Again no maternal complications have been reported following egg freezing, although miscarriage does occur. Whether the incidence is increased relative to IVF is difficult to ascertain at present. One group, using the altered salt and low sucrose method reported that three out of six pregnancies were lost before 12 weeks gestation [54]. However, a number of other studies using controlled rate freezing [15, 42, 50, 63, 91] and one using vitrification [80] have reported 20–25 percent miscarriage rates. Although more numbers are needed to make a meaningful comparison, these latter rates do not appear to be significantly different from those associated with embryo freezing. No adverse obstetric outcomes have been reported. The mean gestational age at delivery for vitrification and the controlled rate freezing procedure for singleton births was 37 [95] and 39 weeks [115] respectively, and for multiple births 36 weeks. Mean birthweight was slightly lower with vitrification (singleton 2.9 kilograms and multiple 2.2 kilograms) relative to the controlled rate freezing procedure (3.3 and 2.6 kilograms respectively), but this needs to be compared to age and ethnic population matched data.

Delay of other treatments

Patients requiring egg freezing to preserve their fertility may need to delay other treatments such as chemotherapy until eggs have been collected. In those cases in which this is not advised following consultation with other medical specialists, the alternative procedure of freezing ovarian tissue could be offered to eliminate the delay.

Age range

In most clinical studies reported above, the majority of the patients are less than 38 years of age. The application of egg freezing to older patients with, on average, lower numbers of eggs following ovarian stimulation, together with lower implantation rates and a higher risk of chromosomal abnormalities is not advisable. Ovarian tissue has been collected and frozen from young children (two years of age) [117] and, at Melbourne IVF, as young as four months old.

Risk of other disease

There has been no report of any other diseases that has resulted or occurred following egg freezing. It would be expected that the risk associated with egg freezing would be similar to that with IVF. No evidence was found when reviewing the available literature that the use of frozen eggs increased the risks of other diseases such as cancer.

Animal studies

Species

The major species studied have been the mouse, rabbit, cattle and pig. There are a number of limitations with summarising the animal data:

1. Although often the cryoprotectant used is the same, the procedure varies between studies for the same species.
2. Variation in the egg size and the rate at which water moves between species indicate that a procedure that gives high results in one species may not be appropriate in different species.

3. In domestic species the eggs used are at a different stage of development and are either frozen at this stage or matured in culture (IVM) before freezing. Eggs collected at this immature stage appear to be compromised in their ability to form a normal spindle, to undergo normal fertilisation and produce embryos, which are often of poor quality.

In contrast to the human studies, in the animal studies, vitrification is used in preference to controlled rate freezing. Also development to the foetal stage and beyond has only been assessed in mice.

Numbers and efficacy of using frozen eggs

Mouse

An example of the impact of minor technical variation is reported using two types of containers in which the eggs are frozen (n = 338) with one type resulting in a higher survival (80 percent compared to 60 percent). However, fewer normal spindles were present (21 percent compared to 78 percent) [118]. In another study comparing freezing eggs by the controlled rate freezing procedure (240) and vitrification (170), both using the same cryoprotectant (DMSO), the survival rate was better with vitrification relative to controlled rate (94 percent versus 69 percent) and more eggs were obtained with a normal spindle following vitrification (87 percent versus 72 percent for controlled rate freezing) [119].

A similar result was observed with controlled rate freezing of 1837 mouse eggs, whether using the cryoprotectant DMSO or the one use for human controlled rate freezing (propanediol). Both resulted in similar survival (60 percent) and fertilisation (50 percent) [120].

Subsequent development following vitrification using the cryoprotectant used for human vitrification (EG) in over 2600 eggs resulted in an average survival of 70 percent, half of which fertilised (50 percent), and just over half of these developed to the implantation stage embryo (60 percent). Following transfer of these, half continued to foetal development.

Unfortunately the study was not continued to live births, and no distinction was made between normal and abnormal developing foetuses. However, using this procedure, 20 foetuses resulted from 100 vitrified eggs compared to 48 per 100 fresh eggs [121].

Vitrification of 260 mouse eggs using a similar method resulted in 97 percent survival, of which 70 percent fertilised and half of these grew to the implantation stage of development and, following transfer, 10 percent resulted in live pups. This corresponds to three births per 100 frozen eggs, which is half the number for fresh eggs [122].

Foetal development or live births have been reported following freezing in a number of early studies. The methods used for freezing in these have since been improved, but very few of the recent studies continue development through to the foetal stage. In one of the early studies, over 500 mouse eggs were frozen using DMSO and controlled rate freezing (no rate for survival was reported); 36 percent fertilised, 67 percent implanted and half of these developed to live foetuses [123]. Another study reported that, following the freezing of over 900 mouse eggs, 37 foetuses developed and 24 live pups were born (three live births per 100 frozen eggs) [124]. In a comparison of vitrification and controlled rate freezing 37 live pups were born from 1700 vitrified eggs and 46 pups from 745 frozen eggs (two per 100 vitrified and six per 100 frozen eggs) [125].

Rabbit

Applying this vitrification procedure with slight modifications to1758 rabbit eggs also resulted in a high survival rate (80 percent). However, only one-third of the eggs contained a normal spindle, which translated into a poor fertilisation rate of less than 10 percent, and less than half of those subsequently formed embryos [126]. Overall, only two eggs out of 100 vitrified resulted in an embryo compared to 53 embryos from 100 fresh eggs.

Cattle

A study using a large number of cattle immature eggs that were matured (IVM) prior to vitrification (over 1000) achieved slightly better results [127]. Survival was consistently greater than 90 percent, however, only half of these fertilised and formed embryos, resulting in only three out of 100 eggs frozen continuing to cleave up to the implantation stage, in contrast to 25 per 100 fresh eggs. Again a slight modification and the use of a different freezing container resulted in lower survival (60 percent), but a higher proportion cleaved to the implantation stage – 10 per 100 frozen eggs [128].

Pig

Two studies of 682 pig IVM eggs using a similar vitrification procedure to those above resulted in survival of 60 percent of eggs, however, none of these subsequently developed to the implantation stage of development. In contrast, 27 fresh eggs formed these embryo from 100 fresh eggs [129, 130].

Risks using frozen eggs

Spindle damage

As stated above, studies involving freezing of animal eggs often assess the spindle and normal configuration of the chromosomes. Damage to these appears more common in eggs that have been collected at the immature stage and frozen at this stage or following maturation. In pig eggs, following vitrification, only 10 percent of the eggs had a normal spindle and, in over 60 percent of the eggs, the chromosomes were either dispersed throughout the egg or not detected [130]. This level of damage to the spindle was confirmed by another study of vitrified pig eggs, but chromosomes were retained on the spindle in more of the eggs (60 percent) [129].

Controlled rate freezing of IVM cattle eggs resulted in a similar rate of both spindle damage and normal chromosome appearance [131]. Care must be taken in interpreting these results; this damage does not appear to be specific to the mechanism of freezing but is probably due to the reduced temperature and/or the cryoprotectant together with the immature nature of the egg. In all of these studies, a correspondingly low proportion of the eggs continued to develop through fertilisation and cleavage.

In contrast, 70 percent of mouse eggs following the controlled rate freezing procedure and 80 percent following vitrification had normal spindles [119]. Another study has confirmed this high proportion with normal spindle after vitrification (80 percent). However, the same procedure in a different container resulted in only 20 percent normal [118]. Both of these studies showed that time is required after thawing for the spindle to regain its normal appearance.

This is the likely reason for the observation of a high proportion of eggs with an abnormal spindle after exposure to a reduced temperature reported in earlier studies [83, 104, 105, 132, 133].

In all of these comparative studies between controlled rate freezing and vitrification, there is a delay of around one hour at 22°C before returning to the temperature at which the spindle reforms (37°C) in the controlled rate studies but not in vitrification. These differences may be eliminated by maintaining the temperature at 37°C during the dehydration and rehydration steps for the controlled rate freezing, which has been the aim of the 0.2M sucrose procedure used for human eggs. Similarly cytoskeleton filaments require time and the appropriate temperature to regain normality following freezing and thawing [119].

Chromosomal abnormalities

The disruption of the spindle following freezing may result in eggs with abnormal chromosome distribution. However, the rate of aneuploidy (which would be expected to be higher due to more abnormal spindles following controlled rate freezing) was observed to be the same in all conditions (9 percent) [134]. It is, however, unlikely that these eggs would subsequently fertilise and form normal embryos considering the above data. Two studies assessing the embryos formed following freezing or exposure to 0°C reported a similar level of chromosomal abnormalities in embryos from fresh or frozen eggs (1.5 percent) [106, 123]. Using the same freezing procedure another study showed a three-fold increase in chromosomal abnormalities in embryos derived from frozen mouse eggs (fresh: 12 percent compared with frozen: 32 percent) [125]. Eggs were also vitrified in this study, and 38 percent of the embryos that developed were chromosomal abnormal.

On subsequent assessment of the foetuses that developed following vitrification four abnormal foetuses (one anencephaly, three hydrocephalies) were detected, and none were observed in either the fresh or controlled rate freezing group.

Development

Metabolism in mouse eggs has been shown to be reduced following both types of freezing but to a lesser extent following vitrification than controlled rate freezing [135]. The proteins present within mouse eggs may also be altered after freezing [136].

Again, these changes may relate to the temperature eggs are exposed to during thawing, and whether either of these impact on subsequent development is unknown.

There have been no reports of any potential side effects from the freezing of eggs in any animal.

No ongoing development of offspring has been reported using frozen eggs in any animal species.

General

Alternative procedures

An alternative procedure to freezing mature eggs is to freeze the eggs at a very young stage embedded within the ovarian tissue [117, 137] as discussed above.

This procedure requires no preparation of the tissue (no need for hormones before collecting the tissue). This technology is generally used in the situation where the patient urgently requires chemotherapy or radiotherapy, and there is no time to undergo an ovarian stimulation cycle to collect mature eggs. A similar risk would be associated with obtaining the ovarian tissue to freeze and freezing mature eggs. Due to their specific medical condition, some of these patients will be at greater risk during and following either procedure.

Concluding remarks

The review of animal studies using frozen eggs has highlighted the difficulties associated with using an animal model to develop freezing technology for the human egg. The mouse egg, which was originally used and associated with much of the damage reported with egg freezing, is a completely inappropriate model for the human egg. Studies with human mature eggs have indicated that this damage is generally reversible and subsequent development from damaged human eggs is unlikely. Although there is variability amongst procedures used for human egg freezing, there are now a large number of eggs frozen (16,000) and a reasonable number of births (220) to suggest that there is no elevated risk associated with freezing human eggs. Obviously, a follow-up study on the development of children from egg freezing is required to confirm this.

While initial reports suggested that egg freezing may be significantly less efficient than embryo freezing, recent improvements appear to offer more promise. At present, the results are compromised by the lack of data comparing egg freezing to embryo freezing within the same clinic; which is required to overcome the variation that exists between units, reported in the results from many forms of assisted reproductive technology.

Recent improvements in embryo culture methods would also be expected to improve the overall outcome from egg freezing.

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Appendix 2: Risk Assessment of the Use of Frozen Eggs

'Risk' is a combination of two concepts:

- the likelihood of an effect occurring
- the consequences of an effect if it occurs.

Likelihood and magnitude can be described qualitatively or quantitatively.

Likelihood

To consider the likelihood of risks associated with the use of frozen eggs, ACART has used the following categories.

	Descriptor	**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 use of frozen eggs, ACART has 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 the patient's 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 each aspect of the risk associated with the use of frozen eggs. Known risks associated with 'adjunct procedures' (such as the collection of eggs for storage and IVF) are included in the table for additional information.

	Consequences				
Likelihood	**Serious**	**Major**	**Moderate**	**Minor**	**Minimum**
A (frequent)	E	E	H	M	M
B (likely)	E	E	H	M	L
C (possible)	E	H	H	M	L
D (unlikely)	E	H	M	L Miscarriage rate: • using salt/low sucrose method: three of six pregnancies lost before 12 weeks • using initial low sucrose method: 20% miscarriage • using triple sucrose method: three losses from 18 pregnancies The latter two rates are not significantly different from those associated with embryo freezing, though the numbers are too low to make meaningful comparisons.	L
E (rare)	H	No major malformations in children born following the use of frozen eggs have been reported, though studies do indicate a general increased risk of malformations in children born through IVF (using both fresh and frozen embryos). Because of the potential damage to egg chromosomes, the risk of congenital malformations should be monitored.	M	L	L

Legend:

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

It should also be noted that a number of eggs do not survive the freeze/thaw process intact. Eggs in which the spindle has been damaged are unlikely to proceed through fertilisation. Similarly, damage to the cytoskeleton would prohibit normal fertilisation and development of the embryo. In both situations this abnormal material is discarded and not transferred to the patient, thereby having no impact on the obstetric outcome.

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 between health and ethics.

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.

ACART considers that the use of frozen eggs is consistent with the above principles. In particular, ACART has considered the health and wellbeing of children born as a result of the use of frozen eggs and considers that, at this stage, the evidence does not indicate increased risks to those children above those associated with IVF alone. Although there is some evidence that transient chromosome changes to eggs can occur during the freezing/thawing processes, at this stage there is no evidence to suggest that these changes remain beyond embryo formation. Eggs that are permanently damaged during a freeze or thaw process are likely to be discarded.

Allowing the use of frozen eggs ensures that women who have frozen eggs to preserve their fertility have the opportunity to use those eggs, thereby protecting their health and wellbeing.

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.

Given the relative novelty of using frozen eggs, it is important that individuals considering using frozen eggs are informed about all aspects of the eggs' use.

ACART considers that frozen eggs should also be able to be donated. Under the HART Act 2004, the donor register will ensure that any child born from a donated egg will be made aware of his or her genetic origins.

Allowing for eggs to be both frozen and used takes account of the various ethical, spiritual and cultural perspectives that couples undergoing fertility treatment may hold, by allowing the freezing and use of eggs where embryo freezing may be unacceptable to them.

Effect of data uncertainty

This discussion document identifies the following issues with the current data.

- There has been no genetic or developmental follow-up of babies born following egg freezing, and in other studies very little information is given regarding the pregnancies or births (apart from some reporting of the term of pregnancy, sex of offspring and birthweight).
- A confounding factor in reporting the total number of births from frozen eggs is that, in many reports, the final outcome was only measured as foetal heart detection (and not actual live birth), and this data was generated using two different freezing techniques.
- Many of the early studies related to small groups of patients.
- The literature lacks comparison between fresh eggs and frozen eggs within the same clinic, in which all factors apart from the freezing are the same.
- Where studies have attempted to compare fresh and frozen eggs, the studies are deficient in meaningful embryo quality assessment between fresh and frozen eggs.
- Data collected by the National Perinatal Statistics Unit (Australia and New Zealand fertility outcomes) does not currently report analysis of data collected from the use of frozen eggs.[7]

ACART considers that the above uncertainties point to a need to ensure ongoing monitoring and research on births from frozen eggs.

Effect of cumulative risk

At this stage the only known risk directly associated with the use of frozen eggs is the miscarriage rate outlined above. As noted, there are some risks associated with the egg collection procedure, but this procedure is separated in time from the actual use of the frozen eggs, and the risks are therefore not really cumulative.

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 of the availability of more effective technologies, egg freezing (and therefore use) is still relatively rare. In the literature at present there are reports of egg freezing in 15 countries (United States, Australia, Canada, Spain, Germany, Hungary, Czech Republic, Brazil, Argentina, Colombia, China, Taiwan, Korea, Japan and Italy). These reports indicate that over 1820 patients have frozen more than 11,693 eggs. In these studies, 160 babies have been reported from the freezing of 11,248 eggs, which equates to 1.4 babies for every 100 eggs frozen.

The numbers are comparatively low compared to IVF or other reproductive technologies. However, this is likely due to the availability (in most countries) of embryo freezing and the use where possible of fresh embryo transfer. However, the change to the law in Italy to prohibit embryo freezing could result in an exponential increase in the number of patients using egg freezing.

Although there are currently no overseas prohibitions on egg freezing, a recent article indicated that the Hungarian Ministry of Health is currently working on a proposal

[7] AIHW National Perinatal Statistics Unit, 2004, *Assisted Reproduction Technology in Australia and New Zealand 2004*, http://www.npsu.unsw.edu.au/NPSUweb.nsf/resources/ART_2003-04/$file/ART10+report.pdf

that may place a moratorium on egg freezing in Hungary. The concern is that the safety of the technology has not been proven and that there is a high risk to the genetic material within the egg, which translates to a significantly increased risk to the offspring.

There has not been a high uptake of egg freezing worldwide. However, a number of people (at least 1820) clearly consider the risks associated with the technology to be acceptable.

In New Zealand, a handful of women hold frozen eggs with fertility providers. It is difficult from such small numbers to assume that these women consider the risks associated with the use of those eggs to be acceptable or that there is a demand in New Zealand for the technology to become available.

Risk reduction/management

The risks associated with the use of frozen eggs can be mitigated or managed by using clinical indicators. Appendix 1 of this discussion document notes that the exclusion of potential patients would be based on clinical indicators (for example, those patients for whom the risk of ovarian hyperstimulation would adversely affect the prognosis. These clinical indicators are already used by clinics when offering egg freezing.

Carefully monitoring the pregnancies of women who conceive using previously frozen eggs may also reduce the risks to the unborn child and the mother. It will also be important for ACART to monitor any outcomes of births from the use of frozen eggs in New Zealand.

Benefits

Although section 6(d) of the HART Act 2004 only asks ACART to provide an assessment of 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 significant, these benefits may make the risks associated with the technology more acceptable.

The benefits associated with the use of frozen eggs are no different from the benefits offered by other assisted reproductive technologies, such as IVF, or the use of fresh eggs. It is simply another potential path for a person to take in an attempt to conceive a child. For women who have frozen eggs before cancer treatment, the use of those eggs in treatment may be their only option for bearing children that are genetically related.

However, there are a number of additional benefits associated with the overall technology of freezing and subsequently using frozen eggs, including:

- being able to freeze eggs where embryos cannot be formed due to absence of sperm for fertilisation
- potentially preserving the fertility of a young single woman with a malignant condition that threatens her fertility
- freezing donated eggs to better synchronise with the recipient's cycle
- for some people, eliminating the ethical and religious issues associated with creating and storing multiple embryos, including the dilemmas patients face when discarding embryos, or legal issues relating to the use of embryos following separation.

In general, ACART considers that the benefits associated with the use of frozen eggs are significant and outweigh the risks associated with the procedure.

Decision-maker

From the ethical analysis provided above, there appear to be very few issues associated with the use of frozen eggs. Indeed, allowing eggs to be frozen may eliminate some difficult ethical or religious issues for some people.

Egg freezing is a technology that is likely to be used in only a small number of cases. At this stage, freezing embryos is a far better option. However, for a small number of people, egg freezing is desirable for medical, ethical/religious or social reasons.

A technology that has very few attendant ethical issues does not require oversight by ECART. If the majority of risks are those that are better dealt with in discussion between clinician and patient, this might indicate that the risks are 'acceptable' for the purpose of making that procedure an established procedure. In terms of the use of frozen eggs in fertility treatment, ACART considers that the risks and 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. ACART proposes that the use of frozen eggs, therefore, should be an established procedure.

Appendix 3: Members of ACART

Sylvia Rumball (Chairperson)

Sylvia Rumball is Assistant to the Vice Chancellor (Ethics and Equity) at Massey University. She has a PhD in chemistry and for many years taught chemistry and undertook research in structural biology at Massey University.

She has extensive international, national and local experience on ethics committees through past membership with the UNESCO International Bioethics Committee, the Health Research Council Ethics Committee and the Massey University Human Ethics Committee; current membership of the Ethics Advisory Panel of the Environmental Risk Management Authority and the MASH Trust Ethics Committee; as past Chair of the National Ethics Committee on Assisted Human Reproduction; and as current Chair of the Massey University Human Ethics Chairs Committee.

Professor Rumball is also a member of the recently established International Council for Science Committee on Freedom and Responsibility in Science, a member of the Massey University Council and an auditor for the New Zealand Universities Academic Audit Unit.

In 2007 she was made a Companion of the New Zealand Order of Merit for services to science. She is also the recipient of a Palmerston North City Council Civic Award, a Distinguished Alumni Award from the University of Canterbury and a New Zealand Science and Technology medal.

Gareth Jones

Gareth Jones is Deputy Vice Chancellor (Academic and International) at the University of Otago, where he is also Professor of Anatomy and Structural Biology. He qualified in medicine and neuroscience (BSc Hons, MBBS) at University College London (UCL) and has DSc and MD degrees from the University of Western Australia and the University of Otago, in science and bioethics respectively. He was made a Companion of the New Zealand Order of Merit in 2004 for his contributions to science and education. He has published extensively in neuroscience, anatomy education and bioethics. His recent publications include: *Speaking for the Dead: Cadavers in biology and medicine* (2000), *Stem Cell Research and Cloning* (editor, 2004), *Medical Ethics* (co-author, 4th edition, 2005) and *Designers of the Future* (2005).

John Forman

John Forman is a parent of adult twins with a rare genetic disorder, alpha mannosidosis, and his family experience with physical and intellectual disability has drawn him into a range of health and disability sector networks over the past 30 years. He has also spent many years in disability support service provision, mainly in community mental health. Since the late 1990s John has focused on the development of patient/family support networks in New Zealand and internationally, with an emphasis on partnership with health professionals, policy agencies and researchers to promote prevention, treatments and cures for rare disorders.

He has volunteer roles on the boards of several local and international advocacy groups. His paid role is Executive Director of the New Zealand Organisation for Rare Disorders, where he advocates for the increased application of genome knowledge and biotechnology to control health and disability problems, with a sharp eye on the ethical issues to ensure safety for the patients and their families.

Richard Fisher

Richard Fisher is a gynaecologist with a sub-specialty practice in reproductive medicine. He is a co-founder of Fertility Associates and has been an active advocate for infertile couples for 20 years. He is the only New Zealander to have been elected President of the Fertility Society of Australia. Richard is a member of a number of professional associations and is a member of the Institute of Directors in New Zealand Inc. He is married and has four children. Richard brings a medical professional's viewpoint to ACART, which is tempered by a recognition of the need for community involvement and decision-making in this area.

Christine Rogan

Christine Rogan has worked to actively promote health for 15 years. She is a past President and life member of the Auckland Infertility Society and became the first National Development Officer for the New Zealand Infertility Society (now called Fertility NZ). She currently works as a health promotion advisor with a non-government public health organisation. In addition, Christine is a non-medical Performance Assessment Committee Member for the Medical Council of New Zealand and the Dental Council of New Zealand. Christine has a tertiary qualification in social sciences from Massey University and lives on the North Shore of Auckland with her daughter.

Ken Daniels

Ken Daniels is Adjunct Professor in the School of Social Work and Human Services at the University of Canterbury. He was appointed to establish social work education and training at Canterbury in 1975 and retired in 2004. For over 30 years he has been actively involved in studying, writing, counselling and policy development in the psychosocial aspects of assisted reproductive technology (ART). His particular focus has been on the children and families that result from ART.

He served for nine years on NECAHR – the last three as Deputy Chair. Professor Daniels has carried out research in a number of countries and has been used as a policy consultant in several overseas jurisdictions. He has published extensively, and his book *Building a Family with the Assistance of Donor Insemination* is used by parents and professionals throughout the world. Professor Daniels is also a board member of the Richmond Fellowship of New Zealand.

Mark Henaghan

Mark Henaghan is Professor and Dean of Law at the University of Otago and Principal Investigator of the Human Genome Project, Law and Ethics for the Future, which is sponsored by the Law Foundation New Zealand. Professor Henaghan's primary research interests are family law and medico-legal law involving children.

Andrew Shelling

Associate Professor Andrew Shelling is head of the Medical Genetics Research Group, which is primarily interested in understanding the molecular changes that occur during the development of genetic disorders, focusing on infertility and reproductive cancers, but also including cardiac disorders and inflammatory bowel disease. He is currently an associate editor for the journal *Human Reproduction* which is one of the leading journals in the area of reproductive research.

Dr Shelling has a special interest in understanding the cause of premature menopause, and his research is internationally recognised for identifying genetic causes of this common cause of infertility. He initiated the development of a support group for women with premature menopause in New Zealand. Dr Shelling is currently Deputy Head of the Department of Obstetrics and Gynaecology, University of Auckland, and is extensively involved in teaching reproduction, genetics and cancer at the university. Dr Shelling has recently served as President of the New Zealand branch of the Human Genetics Society of Australasia. He has also recently been appointed as a trustee for the Nurture Foundation for Reproductive Research (Nurture).

Ian Hassall

Ian Hassall is a New Zealand paediatrician and children's advocate. He was New Zealand's first Commissioner for Children from 1989 to 1994. His career has entailed working for children and their families as clinician, strategist, researcher and advocate. He is at present Senior Lecturer in the Children and Families Programme of the Institute of Public Policy at Auckland University of Technology (AUT).

Dr Hassall teaches the Master of Arts (Children and Public Policy) at AUT. He is a member of the Steering Group and Project Team for Every Child Counts, a coalition of child advocacy and service organisations, whose aim is to place children centrally in government decision-making. He is married to Jenny, is father to four children and grandfather to five. He is the Children's Commissioner's nominee to ACART.

Cilla Ruruhira Henry

Cilla Ruruhira (QSM JP) grew up under the mantle of the kīngitanga movement, deeply entrenched in Waikato kawa (protocol) and tikanga (teachings). Her hapū connections are Ngāti Wairere. Her other tribal connections are Hauraki, Ngāti Hako. Cilla has three children and five mokopuna. From the early years of Playcentre as a young mother, Cilla moved on to join the Department of Social Welfare as a residential social worker working with teenaged adolescents. In her capacity as a healer she has worked with potential teenage suicide victims and their parents in South Auckland. Over the years Cilla has shared her knowledge and expertise with various social services groups, both government and iwi based.

Cilla's passion is children, and she is a Resource Panel Member for the care and protection of children and their families services through the government agency Child, Youth and Family (CYF). She is a Māori specialist consultant, Bicultural Therapy Model (BTM), Department of Corrections Psychological Services, Hamilton, working with Māori inmates at Waikeria Prison. Cilla is also the Māori Women's Welfare League branch representative on the National Council of Women of New Zealand (NCWNZ).

Maui Hudson

Maui Hudson lives in Rotorua, and his iwi affiliations are with Whakatohea, Ngā Ruahine and Te Mahurehure. Maui has professional qualifications from Auckland University of Technology (AUT) in physiotherapy, ethics and Māori health, and currently works for the Institute of Environmental Science and Research Ltd (ESR) in a Māori development position. In this role he is responsible for internal development, providing cultural and ethical advice to researchers, and establishing research relationships with Māori and Pacific communities. Maui is a JP and has previously been a member of the Ethics Committee on Assisted Reproductive Technology (ECART) and the Auckland Regional Health and Disability Ethics Committee. He is married and has three children.

Robyn Scott

Robyn's background is in both not-for-profit management and education. She studied at Wellington College of Education (now the Faculty of Education, Victoria University of Wellington) and Victoria University of Wellington before embarking on a career in primary school teaching and the teaching of speech and drama and music. From there she moved to managing a not-for-profit organisation, working particularly in the area of health support and health advocacy.

Robyn is currently Executive Director of Philanthropy New Zealand and is charged with leading and developing the key organisation that works to motivate and inspire philanthropists and grant makers.

Robyn lives in Wellington with her husband and two school-aged children. Outside work she enjoys a range of mostly family activities that tend to centre around children's sport and cultural events, and also enjoys travel and reading. She is an alumna of Leadership New Zealand, having graduated in 2006.

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 (for example, 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 these 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:

What is your view on the information that ACART suggests should be collected to monitor the use of frozen eggs in fertility treatment?
(See chapter 3.)

Question 3:

Has ACART identified all the ethical issues relevant to the use of frozen eggs in fertility treatment? Do any of these issues affect ACART's proposed advice that the use of frozen eggs 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 4:

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

Question 5:

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

Question 6:

Should frozen eggs be able to be donated for research purposes?

Question 7:

Do you have any further comments to share with ACART?