

**Report to the
Director-General of Health
on the Risks and
Benefits Associated with
Assisted Reproductive
Technologies**

The Advisory Group on Assisted
Reproductive Technologies

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Executive Summary

The Advisory Group on Assisted Reproductive Technologies (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.

AGART reviewed the existing available evidence and also commissioned a systematic review. AGART noted that the evidence available was limited and often of a poor quality, but new research is being published regularly, which means that a subsequent review will be required.

The existing evidence suggests an increased risk of major birth defects associated with assisted reproductive technologies (ART), and this is a concern. Nevertheless, AGART considered the increased risks to be acceptable as they are not greatly increased above those for the general population and in general the procedures offer benefits to those parents who might not otherwise conceive children naturally. There is also a link between ART and poorer neonatal and maternal health outcomes, but some of this can be attributed to maternal age and infertility.

While acknowledging that it considers the majority of risks associated with these procedures to be acceptable, AGART considers it essential for information on the health of children born as a result of ART to be collected on an ongoing basis. AGART makes suggestions in this report as to how this might be done.

Recommendations

The Advisory Group on Assisted Reproductive Technologies (AGART) recommends that the Director-General of Health:

1. **Note** that under the Human Assisted Reproductive Technology Act 2004 (HART Act), the Director-General of Health is deemed to be the advisory committee and must provide advice to the Minister of Health on the procedures that should be declared to be 'established procedures' under the HART Act.
2. **Note** that AGART was convened in June 2004 to provide the Director-General of Health with advice on the risks associated with assisted reproductive technologies (ART) and an assessment of the acceptability of those risks.
3. **Note** that the group met three times over 2004 and 2005 and bases the following recommendations on systematic reviews carried out by the New Zealand Guidelines Group and literature searches and updates carried out by New Zealand Health Technology Assessment.

Risks associated with assisted reproductive technologies (ART)

4. **Note** that babies born as a result of ART are more likely to be born preterm,¹ be of lower birthweight² and be a twin or higher order multiple than their non-ART counterparts.³
5. **Note** that there is a 2.6–4.2% risk of major birth defects associated with ART.⁴ The risk of major birth defects in the general population is 2–3%.
6. **Note** that there are many risks associated with multiple pregnancies, but there is conflicting evidence as to whether ART procedures adversely affect the outcome of multiple births in comparison to naturally conceived multiple births.

In vitro fertilisation (IVF)⁵

7. **Note** that IVF has been in use for more than 25 years, and in New Zealand in 2002, there were 228 deliveries following IVF alone.
8. **Note** that singleton children born as a result of IVF are more likely to be born early,⁶ be of low birthweight⁷ and have poorer neonatal health outcomes⁸ than naturally conceived children. There also appears to be a link between IVF and major birth defects.⁹
9. **Note** that there is some evidence of slightly increased risks of poorer maternal health outcomes in relation to IVF as compared to natural conception, but the evidence is limited and of poor quality. Some of the outcomes are likely to be related to the age of the woman.

¹ 72.7% of babies conceived by ART in 2002 were born at full term compared with 88.6% of babies born in 2002 at full term in the general population.

² In 2002 the average birthweight was 2985 grams compared with an average birthweight in the general population of 3011 grams.

³ 18.7% of ART births in 2002 involved the delivery of twins or higher order multiples, as compared with around a 1% chance of conceiving twins in the general population.

⁴ 'Major malformation' is defined by the International Clearinghouse for Birth Defects Monitoring Systems (www.icbd.org).

⁵ In vitro fertilisation (IVF) is where egg and sperm are combined in the laboratory for fertilisation outside the body and the resulting embryo is replaced in the uterus.

⁶ The risk of preterm delivery for singletons conceived as a result of IVF is around twice that of natural conception.

⁷ For singletons conceived as a result of IVF, the risk of being born weighing less than 1500 grams is around three times that of natural conception.

⁸ Neonatal, perinatal and infant mortality rates are twice as high for babies conceived by IVF as for natural conceptions.

⁹ See Recommendation 4. There are very few studies that report health outcomes for children born as a result of IVF alone – most studies also report on intracytoplasmic sperm injection (ICSI) and gamete intra fallopian transfer (GIFT) – so it is difficult to disentangle the results from IVF for these.

10. **Note** that AGART considers that the increased risks to the mother and infant posed by IVF are acceptable because the risks are not greatly increased above those for the general population and there are potential benefits to individuals who otherwise might not have the opportunity of accessing this technology to conceive a child.
11. **Agree** to recommend to the Minister of Health that IVF be placed on the list of established procedures under the HART Act.

Intracytoplasmic sperm injection (ICSI)¹⁰

12. **Note** that children born as a result of ICSI do not appear to be at any greater risk of adverse obstetric outcomes than children born as a result of IVF.¹¹
13. **Note** that ICSI and IVF are comparable with respect to overall neonatal complications, though when multiple births are considered separately, ICSI has a significantly lower complication rate than IVF and a significantly lower incidence of neonatal/infant death.
14. **Note** that there is no difference between ICSI and IVF in relation to the risk of miscarriage, ectopic pregnancy and Caesarean delivery.
15. **Note** that children conceived by ICSI appear to have a three- to four-fold increase in risk over natural conception of both inherited and de novo chromosomal abnormalities.¹²
16. **Note** that the de novo chromosomal abnormalities in ICSI fetuses consist mainly of an increased number of sex chromosomal abnormalities, though structural abnormalities are also increased above population rates.
17. **Note** that the sons conceived by ICSI of men with a Y-chromosome microdeletion will inherit the same deletion and will be infertile. They will require ICSI themselves if they wish to father a child.
18. **Note** that there is no significant difference between ICSI and IVF in the rate of major malformations diagnosed during the first year of life, but a recent case-control study has raised the possibility that children conceived by ICSI, especially boys, may be more likely to have urogenital or other malformations diagnosed later in childhood.¹³

¹⁰ Intracytoplasmic sperm injection (ICSI) is where a single sperm is injected directly into a single oocyte. The resulting embryos are then transferred into the woman's uterus.

¹¹ Obstetric outcomes include: miscarriage, ectopic pregnancy, stillbirth and low birthweight.

¹² Inherited chromosomal abnormalities are those chromosomal abnormalities that are passed on from the parents. De novo chromosomal abnormalities are newly occurring (not inherited) chromosomal abnormalities. With respect to natural conceptions, the risk of a de novo chromosomal abnormality diagnosed prenatally is around 0.5%, as compared with 1.6% for ICSI conceptions.

¹³ Major malformations may be caused by chromosomal abnormalities but will not always be.

19. **Note** that AGART considers that the risks associated with ICSI are acceptable because the risks:
- are not greatly increased above the risks associated with natural conception
 - are generally acceptable to couples who have undertaken ICSI
 - in most cases are similar to the risks associated with IVF
 - are able to be mitigated through prenatal diagnosis and the provision of information to prospective parents.
20. **Agree** to recommend to the Minister of Health that ICSI be placed on the list of established procedures under the HART Act.

Assisted hatching¹⁴

21. **Note** that assisted hatching has been in use since the early 1990s, and in New Zealand in 2002, there were 40 cycles performed using assisted hatching with a result of 10 deliveries.¹⁵
22. **Note** that there is some evidence to suggest that for some women assisted hatching can improve pregnancy rates.
23. **Note** that there is limited evidence available on the health outcomes associated with assisted hatching.
24. **Note** that AGART considers that because the use of assisted hatching is limited to a small number of selected cases where outcomes of previous IVF attempts have been poor, any risks associated with assisted hatching are acceptable at this stage.
25. **Note** that the information on assisted hatching will continue to be monitored by AGART.
26. **Agree** that the Ministry of Health work with fertility providers to develop a clinical guideline for the use of assisted hatching so that its use is limited to those circumstances where assisted hatching is most appropriate.
27. **Agree** to recommend to the Minister of Health that assisted hatching be placed on the list of established procedures under the HART Act.

¹⁴ Assisted hatching is the mechanical, chemical or laser disruption of the zona pellucida prior to embryo replacement.

¹⁵ This is a delivery per cycle rate of 25%.

In vitro maturation¹⁶

28. **Note** that in vitro maturation is a relatively new technique used in conjunction with IVF or ICSI, and there is limited evidence available as to its risks and benefits.
29. **Agree** that, given the novelty of and limited evidence available on in vitro maturation, it not be placed on the list of established procedures under the HART Act at this stage.

Blastocyst culture¹⁷

30. **Note** that blastocyst culture has been used in New Zealand for over 15 years, and in New Zealand in 2002, there were 58 blastocyst transfer cycles resulting in 18 deliveries.¹⁸
31. **Note** that there are some technical difficulties associated with blastocyst culture, and there is a risk that it could result in the loss of all embryos.
32. **Note** that there is limited evidence available on the health outcomes associated with blastocyst culture.
33. **Note** that AGART considers that because the use of blastocyst culture is limited to few indicated cases and because it is a long-standing procedure with clinical benefit, the risks associated with blastocyst culture are acceptable at this stage.
34. **Note** that the information on blastocyst culture will continue to be monitored by AGART.
35. **Agree** that the Ministry of Health work with fertility providers to develop a clinical guideline for the use of blastocyst culture, so that its use is limited to those circumstances where blastocyst culture is most appropriate.
36. **Agree** to recommend to the Minister of Health that blastocyst culture be placed on the list of established procedures under the HART Act.

¹⁶ In vitro maturation of oocytes can be defined as the act of culturing and maturing oocytes that have been harvested at an immature state.

¹⁷ Blastocyst culture is a process used within IVF and ICSI where there is prolonged culture of embryos in vitro for around five days. By this time, the least viable embryos will have succumbed leaving the most viable available for transfer, therefore theoretically increasing the transplantation rate.

¹⁸ This is a delivery per cycle rate of 31%.

Gamete intra fallopian transfer (GIFT)¹⁹

37. **Note** that GIFT has been in use since the early 1980s, and in New Zealand in 2002, no GIFT cycles were carried out.
38. **Note** that the evidence suggests a small increased risk over natural conception of delivering a small-for-gestational-age or very-small-for-gestational-age baby and also of delivering preterm associated with GIFT.
39. **Note** that the above risks could be associated with patient characteristics (eg, maternal age or infertility) and multiple pregnancies.
40. **Note** that AGART considers that these risks are acceptable because the risks are similar to natural conception and because GIFT offers an alternate option for fertility treatment to those who have moral or religious objections to the in vitro creation of embryos.
41. **Agree** to recommend to the Minister of Health that GIFT be placed on the list of established procedures under the HART Act.

Intra-uterine insemination (IUI)²⁰

42. **Note** that IUI has been in use since the early 1980s and is the common method of inseminating donor sperm. In New Zealand in 2002, there were 680 donor insemination cycles, resulting in 91 deliveries.²¹
43. **Note** that there is some evidence that suggests that IUI is associated with an increased risk over natural conception of preterm delivery and low birthweight.
44. **Note** that the above risks could be associated with patient characteristics (eg, maternal age or infertility) and multiple pregnancies.
45. **Note** that AGART considers that the above risks are acceptable because they are relatively low as compared to natural conception and other ART procedures and because IUI is a commonly used method of donor insemination.
46. **Agree** to recommend to the Minister of Health that IUI be placed on the list of established procedures under the HART Act.

¹⁹ Gamete intra fallopian transfer (GIFT) is a technique that involves combining eggs and sperm outside the body and immediately placing them into the fallopian tubes to achieve fertilisation. GIFT is used in less than 1% of fertility treatments in New Zealand.

²⁰ Intra-uterine insemination (IUI) is the artificial insemination of sperm, which have been washed free of seminal fluid, into the uterine cavity. IUI is a relatively simple technique. It is the common method of inseminating donor sperm, which in 2002 accounted for 9.4% of all ART treatments in Australia and New Zealand.

²¹ This is a delivery per cycle rate of 13%.

Cryopreservation²²

47. **Note** that cryopreservation is often used in conjunction with ART procedures, whereby gametes and embryos arising from the IVF and ICSI methods can be frozen and used in subsequent ART treatment.

Sperm

48. **Note** that AGART considers that the risks associated with the cryopreservation of sperm and subsequent use of thawed sperm in treatment are minimal.
49. **Note** that AGART considers that any risks associated with sperm cryopreservation and subsequent use in treatment are acceptable on the basis that such risks are minimal and sperm cryopreservation offers benefits for sperm donation and males about to undergo cancer treatment.
50. **Agree** to recommend to the Minister of Health that the cryopreservation of sperm and its subsequent use in treatment be placed on the list of established procedures under the HART Act.

Oocytes

51. **Note** that oocyte cryopreservation alone offers a holding mechanism for women about to undergo cancer treatment.
52. **Note** that there is limited data available on the risks of the subsequent use of cryopreserved oocytes.
53. **Note** that AGART considers that the risks associated with oocyte cryopreservation alone are those associated with the retrieval procedure and are minimal.²³
54. **Note** that AGART considers that the risks associated with oocyte cryopreservation alone are acceptable because they are minimal and because oocyte cryopreservation offers potential benefits to women about to undergo cancer treatment.
55. **Agree** to recommend to the Minister of Health that oocyte cryopreservation be placed on the list of established procedures under the HART Act.
56. **Note** that this established procedure should exclude the subsequent use of cryopreserved oocytes in treatment, as the risks associated with this have not been able to be adequately assessed due to the novelty of the technique.

²² Cryopreservation is the maintenance of the viability of excised tissues or organs by freezing at extremely low temperatures.

²³ These risks include the risks associated with ovarian hyperstimulation and laparoscopy. Laparoscopy is used very rarely to collect oocytes.

Ovarian tissue

57. **Note** that ovarian tissue cryopreservation, while a new technology, offers a holding mechanism for those women and girls who are about to undergo cancer treatment.
58. **Note** that AGART considers that the risks associated with ovarian tissue cryopreservation alone are those associated with the surgery to retrieve the tissue and are thus minimal.
59. **Agree** to recommend to the Minister of Health that ovarian tissue cryopreservation be placed on the list of established procedures under the HART Act.
60. **Note** that this established procedure should exclude the subsequent use of ovarian tissue in treatment, as the safety of such use has not been adequately assessed due to the novelty of the technique.
61. **Note** that in the past, proposals for the collection and cryopreservation of ovarian tissue in minors were referred to the National Ethics Committee on Assisted Human Reproduction (NECAHR) for approval. AGART notes that there are consent and ethical issues associated with collection of ovarian tissues in minors but feels that specifying an age limit for consent to medical treatment is inconsistent with current medical practice and the intent of the Care of Children Act 2004.

Embryos

62. **Note** that in New Zealand in 2002 there were 132 deliveries from 818 attempted thawed embryo cycles with embryos derived from both IVF and ICSI.
63. **Note** that there is evidence to show that embryos can be affected or damaged by the cryopreservation process.
64. **Note** that this damage can reduce the implantation potential of the embryos but has not been found to adversely affect the health of the resulting offspring any more than the risk associated with IVF or ICSI.
65. **Note** that AGART considers that the above risks are acceptable because the risks are not raised above the risks for IVF or ICSI alone and embryo cryopreservation offers some benefits to those couples undergoing fertility treatment in that their embryos may be cryopreserved for later use.
66. **Agree** to recommend that embryo cryopreservation and subsequent use of cryopreserved embryos in treatment be placed on the list of established procedures under the HART Act.

Preimplantation genetic diagnosis (PGD)²⁴

67. **Note** that the NECAHR has recently developed guidelines on the use of PGD and the Minister of Health approved these guidelines for implementation in March 2005.
68. **Note** that without PGD, the risk for some couples of having a child with a serious genetic disorder is up to 50%.
69. **Note** that the risks associated with PGD are not markedly higher than those associated with IVF or ICSI.
70. **Note** that AGART considers that the risks associated with PGD are acceptable because the risks are not raised above those risks for IVF alone and PGD offers potential benefits for those who are genetically predisposed to having a child with a genetic disorder.
71. **Agree** to recommend to the Minister of Health that PGD be placed on the list of established procedures under the HART Act.
72. **Note** that NECAHR's guidelines on PGD must be followed when recommending the appropriate parameters of the established procedure of PGD.

Information keeping

73. **Note** that concern has been expressed internationally and is shared by AGART about the health of children born as a result of ART. Therefore, AGART considers it important for information to be collected on the health of children born as a result of ART.
74. **Note** that currently fertility clinics collect information on all babies born as a result of ART.²⁵
75. **Note** that this information is currently supplied to the Australia and New Zealand Assisted Reproduction Database and feeds into the National Perinatal Statistics Unit annual report.
76. **Note** that the New Zealand Birth Defects Monitoring Programme collects information on any child born with a birth defect.
77. **Note** that AGART considers that if National Health Index (NHI) numbers were collected by fertility service providers, the NHI numbers and method of conception (eg, IVF, ICSI) could be supplied to the Ministry of Health to be matched against the Birth Defects Register.

²⁴ PGD is where one to two cells are removed from an embryo and tested for specific genetic conditions. An embryo that is unaffected by the genetic conditions tested for is then transferred to a woman's uterus.

²⁵ The information such clinics collect includes pregnancy and birth outcomes, mode of delivery, birth status, birthweight, gestational age, plurality, perinatal mortality, congenital malformation and maternal morbidity.

78. **Note** that there may be ethical and privacy issues associated with this type of data matching.
79. **Agree** that the Ministry of Health carry out further work on the possibility of matching data and putting in place systematic monitoring of health outcomes for children born as a result of ART. This is likely to include discussions with fertility clinics, seeking advice regarding any privacy issues and ensuring the Birth Defects Monitoring Programme is suitable.

Background

There are currently six fertility service providers throughout New Zealand. In 2002, the Australia and New Zealand Assisted Reproduction Database (ANZARD) recorded 3524 assisted reproductive technology (ART) treatment cycles in New Zealand (Bryant, Sullivan et al. 2004).²⁶ These treatments comprised the majority of ART procedures. Only intra-uterine insemination (IUI), the simplest ART, is not reported to ANZARD. From the remaining treatments, 863 live babies were born in New Zealand in 2002. Approximately 300 babies were born from IVF treatment, 300 from intracytoplasmic sperm injection (ICSI), 200 from using frozen embryos and the remainder from all other ARTs.

In 2003, in anticipation of the passing of the Human Assisted Reproductive Technology Act 2004 (HART Act), the Ministry of Health made an initial assessment of the health risks associated with ART. This assessment was based on a review of overseas literature and the preliminary findings of a meta-analysis currently being undertaken by Australian researchers.²⁷ The Ministry's initial assessment was that the existing evidence indicated there is an increased risk of birth defects associated with ART.

In May 2004, an Advisory Group on Assisted Reproductive Technologies (AGART) was established to provide the Director-General of Health with the following.

- 'An in-depth assessment of the possible health risks to children and the mother, including intergenerational health risks, associated with ART. The assessment will take account of current research data and knowledge on health risks associated with these procedures and of gaps in the basic science of human fertilisation and sperm selection, and heritable traits linked to sub-fertility.
- An assessment of the level of elevated risk of adverse health outcomes for children, the mother and subsequent generations associated with the use of ART:
 - focusing on those procedures currently available in New Zealand or likely to be available in the near future
 - an assessment of whether the level of risk associated with each of those procedures is acceptable
 - recommendations on whether those procedures should be approved as "established procedures" for the purposes of the HART Act 2004.
- Broad scientific advice on monitoring and research needs in relation to ART (retrospective or prospective), including surveillance, epidemiology and data collection. This will involve providing advice on:
 - the usefulness of the data currently collected by fertility clinics in terms of assessing the health risks associated with particular ART and on what, if any, additional information is needed
 - management of the information (eg, governance arrangements, anonymisation of data)
 - what, if any, research could usefully be undertaken in New Zealand, including long term follow-up of ART children.²⁸

²⁶ A treatment cycle is defined as all ART cycles initiated with the intention of treating a patient. These include cycles with: (1) attempted or successful oocyte retrieval (stimulated or unstimulated); (2) thawing of cryopreserved embryos; (3) artificial insemination using donated sperm and (4) cancellation where follicle stimulating hormone (FSH) has been administered.

²⁷ NZHTA (2003). Health outcomes for children born via assisted human reproduction. Christchurch, New Zealand Health Technology Assessment Group; Michele Hansen, personal communication.

²⁸ Terms of Reference, Advisory Group on Assisted Reproductive Technologies.

The methodologies used to collect and analyse the information contained in this report are outlined in Appendix 1. Information on the members of AGART is outlined in Appendix 2.

Under section 5 of the HART Act, an ‘assisted reproductive procedure’:

- (a) means a procedure performed for the purpose of assisting human reproduction that involves:
 - i. the creation of an in vitro human embryo; or
 - ii. the storage, manipulation or use of an in vitro human gamete or an in vitro human embryo; or
 - iii. the use of cells derived from an in vitro human embryo; or
 - iv. the implantation into a human being of human gametes or human embryos; but
- (b) does not include an established procedure.

Under section 6 of the HART Act, the Governor-General may, by Order in Council made on the recommendation of the Minister of Health given after advice tendered by the advisory committee, declare any of the following to be an established procedure for the purposes of the definition of an ‘assisted reproductive procedure’.

- (a) A medical, scientific or technical procedure
- (b) A medical treatment
- (c) An application of a medical, scientific or technical procedure
- (d) An application of a medical treatment.

Procedures available in New Zealand

AGART considered the risks associated with the following procedures, which are available in New Zealand currently.

- In vitro fertilisation (IVF)
- Intracytoplasmic sperm injection (ICSI)
- Assisted hatching in conjunction with IVF or ICSI
- Blastocyst culture in conjunction with IVF or ICSI
- Gamete intra fallopian transfer (GIFT)
- Intra-uterine insemination (IUI)
- Cryopreservation of gametes, embryos and ovarian tissue, and use of thawed gametes and embryos.

AGART also considered the risks associated with the following procedures, which they considered are likely to be or may be available in the near future.

- Preimplantation genetic diagnosis (PGD)
- Use of thawed ovarian tissue
- In vitro maturation within IVF or ICSI.

This report excludes procedures involving donated gametes and embryos and surrogacy as the procedures involved for these are outlined above (eg, IVF or IUI) and the issues associated with donation and surrogacy are largely ethical rather than clinical. The Code of Practice for Assisted Reproductive Technology Units (the RTAC Code) outlines best practice in relation to donor selection, screening, consent and collection/retrieval processes. The RTAC Code makes it mandatory for donors to be screened for:

- human immunodeficiency virus (HIV types 1 and 2)
- hepatitis C virus
- hepatitis B virus
- human T-cell lymphotropic virus type 1
- syphilis
- microbiological contamination testing.

What is 'risk'?

'Risk' is the chance of something happening that will have an impact upon objectives. It is measured in terms of consequences and likelihood. Risk is a combination of the likelihood of an adverse event occurring and the magnitude of the consequences of that event. It is sometimes subdivided into statistical, predicted, perceived and real risk. A risk analysis is the systematic use of available data to determine how often specified events may occur and the magnitude of their consequences.

In this report, the risks associated with the various ART procedures are outlined both in terms of consequences and statistical likelihood.

How did AGART determine what level of risk was acceptable?

Four approaches are generally used to assess acceptability of risk. They are cost-benefit analysis, revealed preferences, expressed preferences and natural standard.

- *Cost-benefit analysis* would deem a technology to be safe if its benefits outweighed its cost.
- *Revealed preferences* would deem a technology to be safe if its risks were no greater than those of currently tolerated technologies of equivalent benefit.
- *Expressed preferences* would deem a technology to be safe if people said that its risks were acceptable.
- *Natural standards* would deem a technology to be safe if its risks were no greater than those accompanying the natural development of the human species (Slovic 2000).

No approach to acceptable risk is clearly superior to the others. To exploit the contributions each of these methods can make, careful consideration must be given to the social and political world in which they are used and to the natural world in which we all live (Slovic 2000). AGART used a combination of the above methods, to view each technology.

A measure of the success of any analysis is its ability to inform (as well as to reflect) our beliefs and values. To this end, AGART used a programme called VIDE developed by Professor David Seedhouse²⁹ to elicit some of the values and beliefs in the AGART members' decision-making process. VIDE makes decisions transparent by exposing value judgements hidden within technical problem-solving structures. VIDE systems guide decision-makers through the evaluative elements of their decision-making, helping them make their 'judgement calls' explicit. Furthermore, by pooling records of values-based decisions, we are able to detect otherwise invisible trends with accuracy and efficiency.

²⁹ Professor Seedhouse is Director of the National Centre for Health and Social Ethics at Auckland University of Technology.

AGART members saw the VIDE software as a mechanism for beginning their discussions on risk and risk acceptability and did not see the results of VIDE as conclusive. It was noted that each member of the group brought different perspectives and beliefs to the discussion, and one way of eliciting these perspectives in a non-threatening manner was through this software. The results of the VIDE analysis are contained in Appendix 3.

From the results of the VIDE analysis, members of AGART could see that there was a threshold beyond which some members of AGART and some members of the control group felt risk was no longer acceptable. This was when the risk of having a child with birth defects was raised to around 7% (a hypothetical case example was used).

AGART also used a combination of the four risk analysis methods outlined above. AGART considered that while a cost-benefit analysis may have been useful, it would have been very difficult to carry out as it is difficult to assign a score to each of the costs and benefits. A 'revealed preferences' analysis was used particularly in relation to procedures such as intra-uterine insemination (IUI), assisted hatching and gamete intra fallopian transfer (GIFT).

AGART also considered all the technologies from an 'expressed preferences' perspective. A number of the technologies considered by AGART have been in common use for many years, and clearly, those individuals using the technology consider the risks associated with it to be acceptable.

However, people's perception of, and willingness to accept risk varies over time. It is important to review trends and re-evaluate this advice in light of better risk knowledge and changing social and cultural norms. Publication of this report is the first step in this process, and it is hoped this report will contribute to community-wide discussion of this issue. AGART also notes that one of its functions is to continue to monitor the health outcomes of assisted reproductive procedures and established procedures.

Risks and outcomes associated with ART in general

The 2002 Australian and New Zealand Assisted Reproduction Database (ANZARD) report, whilst comprising some separate Australian and New Zealand data, presented most information as total events for both countries together (Bryant et al 2004). It is clear that ART is a very common practice, with a total 36,483 treatment cycles taking place in both countries in 2002. Proportionally Australia has more babies born as a result of ART because of the greater availability of the technologies. In New Zealand in 2002, there were 53,589 live babies born in hospital to 53,037 mothers. Of these, 863 (1.6%) were conceived as a result of ART.

Maternal health outcomes

Of the 7577 pregnancies resulting from the use of ART in Australia and New Zealand in 2002, 998 (13.2%) reported a complication. Pregnancy-induced hypertension was reported in 144 (1.9%) of all pregnancies, gestational diabetes in 135 (1.8%), placenta praevia in 83 (1.1%) and antepartum haemorrhage in 72 (1.0%). Other complications, such as premature rupture of membranes (67), intra-uterine growth retardation (42) and pre-eclampsia (46), occurred in less than 1.0% of pregnancies (Bryant, Sullivan et al. 2004).

The pregnancy morbidity information is self-reported to ANZARD by patients and, if relevant, validated with hospital records by fertility centre staff. It is possible that there is incomplete

reporting of this information. These morbidities are common in pregnancy and are not elevated above those associated with pregnancies achieved through natural conception.

In the same cohort however, there were 2807 Caesarean deliveries of babies of at least 20 weeks gestation. This represents almost half (48.0%) of all deliveries after ART. In New Zealand in 2002, 22.7% (12,531) of all hospital births were by Caesarean section (NZHIS 2004). The increase is probably related to the high proportion of multiple pregnancies and the higher age of the mother.

In 2002 for the Australia/New Zealand cohort, there were 246 cases in which women were admitted to hospital with complications of ART treatment, representing 0.7% of all treatment cycles. Of these, 192 (78%) were hospitalised for symptoms of ovarian hyperstimulation syndrome. Other treatment-related complications in 2002 included abdominal pain, bleeding and infection (Bryant, Sullivan et al. 2004).

Treatment-related maternal risks

The principal risk with ART lies with the use of gonadotrophins to hyperstimulate the ovary or to induce ovulation when this treatment is administered in conjunction with IUI. The gonadotrophins used comprise the group of recombinant human follicle-stimulating hormone drugs (rFSH). Although ovarian hyperstimulation is the goal in IVF, the ovarian response is controlled, and treatments will stop if the risk of ovarian hyperstimulation is excessive. This excessive response is called the ovarian hyperstimulation syndrome (OHSS), and the 2002 ANZARD report described 192 cases (0.5%) where the women were admitted to hospital. Another 54 cases were admitted for bleeding, pain or infection related to the oocyte collection (that is usually performed by transvaginal ultrasound). The risk of death is very low, and there has been only one case in New Zealand in the last 20 years where a woman has died (for other medical reasons).

Very uncommonly, laparoscopy is required for oocyte collection and for gamete intra fallopian transfer. Laparoscopy is a relatively safe procedure, with the risk of major complications being about 1:1000 cases.

Early pregnancy complications

In 2002, a total of 7577 pregnancies as a result of ART were reported in Australia and New Zealand, of which 902 were from New Zealand centres.³⁰ Approximately 18% of all pregnancies in Australia and New Zealand in 2002 resulted in miscarriage, 1.9% in ectopic pregnancy and 0.8% in reduction or termination.

³⁰ As noted above, there were 863 babies born as a result of these 902 pregnancies.

Preterm birth

The average gestational age for all babies of at least 20 weeks gestation in the 2002 ART conception cohort was 37.2 weeks. 72.7% of babies in the 2002 ART cohort reached full-term gestation of at least 37 weeks. This is a higher proportion than the 67.4% of ART babies that were born at full term in the 2000 cohort. 21.1% of babies in the 2002 ART cohort were born at 32–36 weeks, and a further 6.1% at 20–31 weeks (Bryant, Sullivan et al. 2004). For 2002, 88.6% of babies born in New Zealand hospitals were of a gestational age of between 37–41 weeks (Bryant, Sullivan et al. 2004).

The proportion of preterm babies is possibly related to the high incidence of multiple births resulting from ART pregnancies. While the average gestational age for singletons was 38.4 weeks, for twins, this was reduced to 35 weeks, and for triplets, 30.5 weeks. Similarly, while only 11.1% of singletons were born preterm, this increased to 59.8% for twins and 100% for triplets.

However, even when multiple pregnancies are excluded from consideration, studies comparing singleton pregnancies conceived by ART with those conceived spontaneously have shown higher rates of antenatal complications, prematurity, low birthweight, small-for-gestational-age babies and perinatal mortality compared to the general population (Doyle, Beral et al. 1992; Tan, Doyle et al. 1992; Olivennes, Rufat et al. 1993; Verlaenen, Cammu et al. 1995; Schieve, Meikle et al. 2002). These complications may reflect the older age of the mother.

Low birthweight

The average birthweight for all babies of at least 20 weeks gestation in the 2002 conception cohort was 2985 grams. Live-born ART babies had an average birthweight of 3011 grams. The average birthweight for ART babies was less than the average of 3362 grams for the Australian population in 2001. Of all ART babies in 2002, 21.7% were classified as having low birthweight (<2500 grams) (Bryant, Sullivan et al. 2004). This is compared to 6.5% of all babies born in New Zealand weighing less than 2500 grams at birth.

Neonatal, perinatal and infant outcomes

Perinatal mortality refers to fetal deaths (stillbirths) of at least 20 weeks gestation or 400 grams and the death of neonatal babies occurring within 28 days of birth. The National Perinatal Statistics Unit reported that, in the Australia/New Zealand 2002 conception cohort, there were 121 reported perinatal deaths, giving a perinatal death rate of 17.3 deaths per 1000 ART births in Australia and New Zealand (Bryant, Sullivan et al. 2004). Note that this is higher than the 10.0 deaths per 1000 births reported in the Australian population in 2001 (Laws and Sullivan 2004). In New Zealand in 2000, there were 9.5 perinatal deaths per 1000 total births.³¹ There were 0.7 late neonatal deaths per 1000 total births in 2000 (NZHIS 2002).

³¹ For this dataset, perinatal deaths are fetal deaths (20 weeks gestation or 400 grams birthweight) plus infant deaths within 168 completed hours (seven days) after birth (early neonatal deaths).

Bryant et al noted that perinatal mortality in the Australia/New Zealand 2002 cohort correlated with plurality of ART pregnancies. Singletons had the lowest perinatal mortality rate: 10.9 deaths per 1000 births. Twins had a higher rate: 29.3 deaths per 1000 births, and triplets reported the highest rate: 60.6 deaths per 1000 births (Bryant et al 2004).

Multiple pregnancies

The rate of multiple pregnancies in the general population is approximately 1.7%. In 2002, of the 7577 ART pregnancies reported in Australia and New Zealand, 75.7% resulted in the delivery of one or more live babies. Of these, 81.3% were live singleton deliveries and 18.7% involved the delivery of two or more live babies. The majority of pregnancies in 2002 resulted from treatment cycles transferring two embryos. Most twins came from two embryo transfers, although a small proportion arose from single-embryo transfers, meaning they were naturally conceived monozygotic twins. Most triplets arose from two-embryo transfers, also suggesting the occurrence of monozygotic twinning (Bryant, Sullivan et al. 2004).

New Zealand fertility clinics are now moving towards single-embryo transfer, which is expected to reduce the number of multiple pregnancies arising from ART.

The New Zealand Guidelines Group note in their report (Marjoribanks, Farquhar et al. 2005) that Bonduelle et al (Bonduelle, Van Assche et al. 2002) analysed multiple ART births separately from ART singletons for the outcome of major congenital malformations and reported that there were significantly more malformations in multiple births than in singletons in children conceived by both ICSI and IVF.

Multiple births have been shown to cause a higher incidence of first trimester bleeding, and for both naturally conceived and ART conceived multiple pregnancies, patients face an increased risk of losing one of the fetuses. This risk is higher than the risk of losing all fetuses (Seoud, Toner et al. 1992). The incidence of premature labour increases with an increased number of fetuses, and premature labour is the most frequent complication in the second and third trimester (Ibid).

The risk of pre-eclampsia is two times more likely in multiple pregnancies, and 20% of pregnancy-related maternal deaths are from complications of pre-eclampsia. Lynch et al found that in their study of pre-eclampsia in multiple gestations, the relative risk of pre-eclampsia was statistically significant only among mothers who conceived using ART (Lynch, McDuffie et al. 2002). They also found that there was a five-fold increase in the risk of severe pre-eclampsia amongst ART women than in naturally conceived multiple births (Ibid). One explanation for this finding is that mothers who undergo ART treatment are of a significantly older age, with 75% of mothers in this study being over the age of 35. Pre-eclampsia is a risk factor in naturally conceived multiple pregnancies, but when factoring in the increased age of mothers undergoing ART, this risk factor is increased (Lynch, McDuffie et al. 2002).

Multiple ART births are also likely to result in low birthweights. In the Australia and New Zealand statistics for 2002, 48.4% of ART twins were classified as low or very low birthweight, and their average birthweight was 2397 grams (Bryant, Sullivan et al. 2004). The New Zealand Guidelines Group also note that obstetric and neonatal outcomes are consistently worse for multiple conceptions: for example, twins have a shorter gestation and lower birthweights than singletons – these being two of the leading predictors of fetal and neonatal wellbeing. Twins also have a higher risk of cerebral palsy and of developmental delay than singletons (Kurinczuk 2003).

It has been found that there is an increase in parental stress and depression in ART multiple gestation pregnancies, and there is an increase in hospital admissions due to post-natal depression (Scholz, Bartholomaeus et al. 1999). It has also been found that children born in multiples are more likely to face difficulties socialising and face developmental delays and behavioural problems (D'Alton 2004).

The infant mortality rate in multiple pregnancies is significantly higher than in singleton pregnancies (Garne and Andersen 2004). In the Australia/New Zealand 2002 ART cohort, twins had a perinatal mortality rate of 29.3 deaths per 1000 birth, and triplets had a perinatal mortality rate of 60.6 deaths per 1000 births (Bryant, Sullivan et al. 2004).

Summary

The New Zealand Guidelines Group note that even when multiple pregnancies are excluded from consideration, studies comparing singleton pregnancies conceived by ART with those conceived naturally have shown higher rates of antenatal complications, prematurity, low birthweight, small-for-gestational-age babies and perinatal mortality compared to the general population (Doyle, Beral et al. 1992; Tan, Doyle et al. 1992; Olivennes, Rufat et al. 1993; Verlaenen, Cammu et al. 1995; Schieve, Meikle et al. 2002).

There are clearly increased risks associated with multiple pregnancies, irrespective of the way in which the pregnancy was conceived. Some studies conclude that twins conceived by ART are at a significantly increased risk of prematurity and associated neonatal morbidity and mortality than naturally conceived twins (Moise, Laor et al. 1998). However, others have concluded that ART twins are at no greater risk than their non-ART counterparts (Helmerhorst, Perquin et al. 2004; Pinborg, Loft et al. 2004a). There is some evidence to suggest that ART multiples are more likely than ART singletons to be born with congenital malformations.

It should also be noted that gonadotrophic treatment, used in conjunction with ART procedures, carries some risks to the woman undergoing the treatment.

In Vitro Fertilisation (IVF)

In vitro fertilisation (IVF) is where eggs and sperm are combined in the laboratory for fertilisation outside the body, and the resulting embryos are replaced in the uterus. The first baby conceived through IVF was born in 1978. In Australia and New Zealand in 2002, IVF accounted for 37% of fresh and 44.2% of frozen ART procedures per number of cycles started (Bryant, Sullivan et al. 2004). In New Zealand in 2002, there were 228 deliveries following 798 IVF treatment cycles (personal communication, ANZARD, 17 March 2005).

Infants conceived following IVF are more likely to be born preterm, have low birthweights and to be twins or higher order multiples than naturally conceived infants (Beral and Doyle 1990; Helmerhorst, Perquin et al. 2004; Jackson, Gibson et al. 2004).

Preterm delivery

Singleton IVF pregnancies are at an increased risk of preterm delivery in comparison with spontaneous pregnancies. This may be attributed to various infertility co-factors such as uterine malformations and history of pelvic infection rather than the IVF procedure itself (Perri, Chen et al. 2001). Wang et al found that the risk of premature birth for IVF pregnancies is more than double the risk for spontaneous pregnancies (Wang, Norman et al. 2002).

Low birthweight

Koudstaal et al found that there is a decrease in gestational age of around five days and an increase in small-for-gestational-age in IVF pregnancies (Koudstaal, Braat et al. 2000). However, a study by Olivennes et al found that the majority of children in their study who were born small-for-gestational-age caught up in their growth (Oliviennes, Kerbrat et al. 1997). Subfertility has been found to be a risk factor for low birthweight rather than the IVF procedure itself.

Placental weight is comparable to that of naturally conceived children. There are also no differences in the structure of the placentae observed between IVF and naturally conceived children (Daniel, Schreiber et al. 1999). Thus, the small-for-gestational-age rate is not due to placental insufficiency, and it is therefore unclear whether the small-for-gestational-age rate is due to the IVF technique, ovarian stimulation or infertility factors (Koudstaal, Braat et al. 2000). There is a slightly increased risk of abnormal umbilical cord development in the IVF group. There may be adverse consequences to this, such as vasa praevia, fetal haemorrhage and fetal abnormalities. There is an increased risk for marginal cords and bilobate placental shape, which can increase the risks of a congenital malformation (Gavrill, Jauniaux et al. 1993). It is thought that these placental findings may be due to multiple embryo transfer (Koudstaal, Braat et al. 2000).

Maternal health outcomes

Some studies have suggested that there are poorer maternal health outcomes associated with IVF. It has been suggested that there is an increased risk of antepartum haemorrhage throughout IVF pregnancies. There is also an increased risk of intrahepatic cholestasis of pregnancy (Koivurova, Hartikainen et al. 2002). It has also been shown that there are increased risks of gestational diabetes mellitus and mild to moderate pregnancy-induced hypertension, although these are probably related to the age of the woman (Maman, Lunenfeld et al. 1998). The size of these risks are not well characterised but are relatively small.

Congenital malformations

Subsequent to a systematic review, Hansen et al (2005) concluded that pooled results from all suitable published studies suggest that children born following ART (both IVF and ICSI) are at increased risk of birth defects compared with natural conceptions. The results of meta-analyses of the seven reviewer-selected studies and of all 25 studies in this review suggest a statistically significant 30–40% increased risk of major birth defects associated with ART. This means that the risk of having a child with a major birth defect is in the range of 2.6–4.2%, as compared with a 2–3% risk for natural conception.

The birth defects found to occur more frequently in IVF babies than in the general population include both chromosomal and musculoskeletal defects.

It has been suggested that there is a small increased risk of neurological disability, impairment or handicap amongst children conceived by IVF, especially cerebral palsy (Stromberg, Dahlquist et al. 2002).

There is considerable evidence that imprinting disorders occur, but there is conflicting evidence as to the incidence of imprinting disorders. Genetic imprinting is a mechanism of gene regulation in which only one of the parental copies of a gene is expressed. This process is mediated through DNA methylation (the introduction of the methyl group into the DNA helix, which is thought to prevent transcription of that section of DNA) and plays a critical role in embryogenesis and development (Schieve, Rasmussen et al. 2004).

The Liggins Institute in Auckland are currently conducting a study of children conceived following IVF. Miles and Hofman (2005) speculate that IVF has altered imprinting in these children and that aspects of this alteration are manifest in growth and lipid regulating genes. They are evaluating healthy, pre-pubertal children conceived by IVF and born at term following singleton pregnancy. Subjects comprise 50 children conceived using IVF with fresh embryo transfer and 60 naturally conceived controls. Anthropometric measurements, bone age, full body scan, fasting serum glucose, insulin, lipid profile and other relevant tests were taken. Children born following IVF were born earlier, with a lower birthweight standard deviation score. Children born following IVF were taller than controls when corrected for mid-parental height, with girls being taller than boys. There was no significant difference in fasting insulin or body composition. This study is ongoing.

The New Zealand Guidelines Group (2005) found three studies that suggested a link between ART (IVF or ICSI) and Beckwith-Wiedemann syndrome (BWS), which is a congenital disorder associated with overgrowth and a predisposition to embryonic cancer and is caused by an imprinting disorder in about 60% of cases.

- DeBaun et al (2003) reported finding seven children conceived by ART among children in a United States BWS registry set up to monitor cancer incidence. After noting that four patients on the register were born after ART, the researchers specifically requested data about ART for patients joining the register from 2001. A further three children with BWS were identified out of 65 joining the register from 2001, giving a prevalence of 5% among children conceived by ART compared to 0.8% among the background population, thus suggesting a six-fold increased prevalence in ART children. In five of the six cases for which samples were available, BWS was associated with an imprinting mutation. Five of the seven cases were conceived by ICSI, which was used in 42% of IVF cycles in the general population (the study was too small to determine whether ICSI increased the risk of BWS over and above IVF alone).
- Maher et al (2003) reviewed the notes of patients referred to a United Kingdom BWS group for whom detailed clinical information was available. They reported that 6 out of 49 had been conceived by ART, three after ICSI and three after IVF alone. Estimating that 1% of children resulted from ART conceptions, the authors estimated a three-fold increase in the expected prevalence of BWS among such children. Two cases were assessed for imprinting errors, and both were positive.

- Gicquel et al (2003) reported strikingly similar results, with 6 out of 149 BWS patients diagnosed at their reference centre in France having been born following ART, two out of six after ICSI. In accordance with Maher et al (2003), Gicquel et al suggested a three-fold increase in risk associated with ART, based on a prevalence of 4% in ART patients in their series compared with 1.3% in the general French population. All six patients in this study had BWS associated with imprinting defects.

Ericson and Kallen (2001) found a specific risk increase after IVF or ICSI for malformation conditions in the following groups: neural tube defects, alimentary tract atresia, and omphalocele. Similar major malformations were noted by Westergaard et al (1999) in a cohort group of 2245 of children conceived by either ICSI or IVF.³² Other malformations that have been noted to occur more frequently among children conceived by IVF include anencephalus, spina bifida and hydrocephalus (Beral and Doyle 1990).³³

It should be noted that many of the studies outlined above include results for children born as a result of both IVF and ICSI.

Long-term health outcomes

It has been found that children born as a result of IVF are more frequently admitted to hospital and spend more time in neonatal intensive care units than children who are naturally conceived. The main increased utilisation of health care by children conceived by IVF occurs during the first year of life. This could be due to a large extent to the increased incidence of multiple births in IVF groups (Leslie, Gibson et al. 1998). Children conceived by IVF do not over-utilise health care beyond the first year of life.

It has been found that there is no evidence of an increased or decreased risk for childhood cancer in IVF groups when compared to the general population (Klip, Burger et al. 2001). In a study by Doyle et al., it was found that cancer incidence among 2507 children born from 1978 to 1991 after IVF did not differ from that in the general population of Britain (Doyle, Bunch et al. 1998).

Behavioural, psychological and psychosocial outcomes for children and parents

It has been shown that children conceived by IVF have normal psychological development with no adverse effects as a result of their status as children conceived by IVF (Montgomery, Aiello et al. 1999). There are also no differences in mental, motor, social and expressive language development or in test-taking behaviour between children conceived by IVF and first-born singleton children from naturally conceiving mothers (Gibson, Ungerer et al. 1998). Children conceived by IVF function well and do not differ from adoptive or naturally conceived children on any assessments of social or emotional adjustment. Children conceived by IVF do not show difficulties in psychological development at early adolescence arising from the method of their conception (Golombok, MacCallum et al. 2001).

³² Malformations included anencephalus, hydrocephalus, spina bifida, situs inversus, atrial septal defects type II, ventricular septal defect, other cardiovascular defects, hypospadias, cryptorchidism, palatoschisis, cheiloschisis, oesophageal atresia, pyloric stenosis, trisomy 21, Edward's syndrome.

³³ In the cohort assessed by Beral and Doyle, there were also IVF children born with rare disorders or syndromes. These included craniostenosis, Russell-Silver syndrome, osteogenesis imperfecta, persistent cloaca and absent genitalia, partial albinism in a singleton child and twins described as having extensive areas of depigmentation.

There have been no findings of any significant difference in IQ or cognitive performance between children conceived by IVF and naturally conceived children. However, in a paper by Hahn, children conceived by IVF were rated lower by teachers in socio-emotional adjustment and reported themselves to be more anxious, depressed and more aggressive than their peers (Hahn 2001).

Parental adjustment and stress

IVF mothers and fathers report predominantly comparable general psychological and parenthood-specific adjustment at one-year postpartum relative to naturally conceiving parents from a similar background (Gibson, Ungerer et al. 2000). However, mothers who conceived by IVF did tend to report more behaviour problems and difficult temperaments in their children. This could be due to underlying anxiety and concerns about the well-being and adjustment of their child during the first year of life in particular (Gibson, Ungerer et al. 1998).

Stress levels are significantly higher for first-time mothers with a history of infertility than naturally conceiving mothers. Health is also shown to be affected with a decrease in psychosocial well-being (Colpin, De Munter et al. 1999). However, IVF mothers are seen as more dependable than natural mothers, obtaining higher ratings of overt affection towards their children (Golombok, MacCallum et al. 2001). IVF mothers are also considered to view their children as more vulnerable and 'special' and can therefore sometimes form an over-protective motherly role (Gibson, Ungerer et al. 2000).

Despite the reported increase in parental stress for IVF conceived twins, studies have found that there is no difference in parenting quality and child behaviour when compared with non-IVF twins (Cook, Bradley et al. 1998). In most cases, the parent-child interaction is not adversely affected for ART twins or naturally conceived twins. Therefore, the influence of the method of conception does not seem to be a major factor in the long-term outcome of pregnancy. However, it may be important to provide specific counselling and support to first-time mothers of twins, in particular those with a history of infertility (Colpin, De Munter et al. 1999).

Summary

IVF has been in use for more than 25 years, and in New Zealand in 2002, there were 229 deliveries following IVF treatment. Children born as a result of IVF are more likely to be born preterm, have low birthweights and be twins or higher order multiples. IVF also appears to be linked to poorer maternal and perinatal health outcomes. There is also evidence that IVF is linked to congenital malformations and chromosomal abnormalities, although many studies that have reported on these outcomes considered IVF and ICSI births together.

Advancements in technology have given society the ability to monitor pregnancies very closely. Prenatal diagnosis, through the use of amniocentesis, chorionic villus sampling and ultrasound, can provide a maternity carer and prospective parents with information about the health of the fetus. AGART understands that prenatal diagnosis is recommended for any parent concerned about the risks of ART.

AGART considers the above risks, while raised, to be acceptable on the basis that they are not greatly increased above those associated with natural conception, and there are strategies available for mitigating the risks, such as single-embryo transfer and prenatal diagnosis.

Intracytoplasmic Sperm Injection (ICSI)

After prior assessment of the literature, AGART identified the need for an in-depth assessment of the possible risks associated with ICSI and contracted the New Zealand Guidelines Group to undertake this assessment. The New Zealand Guidelines Group subcontracted the Auckland-based Cochrane Menstrual Disorders and Subfertility Group to prepare a systematic review. The review aimed to assess the safety of ICSI for mother, child and family and, where possible, quantify the health risks of ICSI versus IVF and/or natural conception. Some of the following has been excerpted from the New Zealand Guidelines Group's report, which is attached will be available on their website <http://www.nzgg.org.nz>

ICSI is a fertilisation technique whereby a single sperm is injected directly into a single oocyte. The resulting embryo(s) are then transferred into the woman's uterus. ICSI was initially developed for male factor infertility, but it is increasingly used for unexplained infertility and where fertilisation has failed with conventional IVF. In New Zealand in 2002, there were 239 deliveries from 819 ICSI treatment cycles.

Obstetric outcomes

ICSI and IVF resulted in comparable rates of miscarriage, ectopic pregnancy, stillbirth and low birthweight. Prematurity rates are also comparable among singletons, though there was evidence in one large study of an increased prematurity rate among multiple births in the ICSI group. The reason for this finding was uncertain as, although the ICSI mothers were older and more likely to be primagravidae, other outcomes were similar (Bonduelle, Van Assche et al. 2002). The studies provided little evidence about Caesarean section rates or multiple pregnancy rates. However, as noted above, rates of multiple pregnancy are determined largely by the number of embryos transferred.

Neonatal outcomes

ICSI and IVF were also comparable with respect to overall neonatal complications measured by intervention rates. However, when multiple births were considered separately, the only study of reasonable quality found that ICSI had a significantly lower complication rate than IVF. This was based on an analysis of 2754 multiple births (Ibid). Moreover a meta-analysis of Bonduelle, Van Assche, et al (2002) with another large cohort study (Bryant, Sullivan et al. 2004) found a significantly lower incidence of neonatal/infant death in the ICSI group. This was partly attributable to high death rates among multiple pregnancies in the IVF group in one of the studies, but the risk remained significantly lower in the ICSI group when singletons were considered separately (Bonduelle, Liebaers et al. 2002).

Chromosomal and genetic abnormalities

Bonduelle, Liebaers et al (2002) compared karyotypes among 1437 ICSI and 493 IVF fetuses and found the rates similar (2.9% versus 3%). However this finding is of questionable value given the low uptake of prenatal testing, especially in the IVF group. The case series published by the same group (Bonduelle, Liebaers et al 2002) found a three- to four-fold increase in inherited and de novo (newly occurring) chromosomal abnormalities among ICSI fetuses compared to general population rates. This study reported that de novo chromosomal abnormalities particularly affected the sex chromosomes and were related to sperm concentration and motility.

A higher rate of congenital abnormalities was found in ICSI fetuses after early miscarriage compared to IVF. Lathi and Milki (2004) and Aboulghar et al (2001) found a significantly increased chromosomal abnormality rate in children conceived by ICSI compared to spontaneously conceived children.

Chromosomal abnormalities in ICSI offspring may be inherited or de novo. An inherited anomaly is commonly a structural defect exactly the same as that carried by one of the parents. The children may be phenotypically normal at birth but may be subject to a slight increase in mental retardation and/or malformation due to minor chromosomal imbalances secondary to the structural anomaly (Bonduelle, Van Assche et al. 2002).

De novo chromosomal abnormalities in ICSI offspring are often sex chromosomal aneuploidies, which are probably associated with sperm defects, even though the father may be karyotypically normal. Children born with sex chromosomal abnormalities usually have a normal physical appearance and an IQ within the normal range, but they are often infertile, and there is also a moderate risk of developmental problems in the areas of speech, motor skills and learning abilities. De novo structural abnormalities may be less benign and carry more risk of mental retardation (Bonduelle, Joris et al. 1998; Bonduelle, Van Assche et al. 2002).

Careful genetic screening for chromosomal abnormalities and Y-chromosome microdeletions is recommended for couples contemplating ICSI, along with the offer of prenatal diagnosis where pregnancy is achieved. Other interventions such as preimplantation genetic diagnosis (PGD) or even use of donor gametes (eggs or sperm) may be the best option in some cases (Bonduelle, Van Assche et al. 2002; Kurinczuk 2003).

It appears that all sons of men with Y-chromosomal microdeletions will inherit the anomaly and are thus likely to be infertile themselves. It had been assumed until recently that infertility was the only problem likely to ensue, but there are some concerns that more serious chromosomal disorders undetectable by standard karyotyping may be found in association with Y-chromosome microdeletions. Similarly, congenital absence of the vas deferens may be the only clinical symptom of mutations in the cystic fibrosis gene, which could be inherited by ICSI offspring in a more severe form if the mother is also a carrier (Kurinczuk 2003).

Congenital malformations

The evidence on congenital malformation rates is difficult to interpret. Rates of major malformations diagnosed during the first year of life were similar after ICSI and IVF. However, there were no cohort studies measuring this outcome beyond two years of age, and the only higher quality study with longer follow-up, a case-control study, found that although there was no statistically significant difference between the groups at five years of age, relatively more congenital malformations had become evident in the children conceived by ICSI. The additional malformations were mainly urogenital abnormalities in boys (Bonduelle, Wennerholm et al. 2005).

One study (Ericson and Kallen 2001) reported a statistically significant increase in hypospadias in ICSI two-year-olds. However, this study was limited by ascertainment bias, and no other study found a statistically significant increased risk of hypospadias or any other specific abnormality.

For the outcome of *any* malformation (major or minor), meta-analysis of two large studies showed evidence of a significantly higher rate in the IVF group at birth. However, this finding apparently related to heart problems in multiples in the IVF group in the largest study (Bonduelle, Liebaers et al. 2002), these being short-term problems that resolved spontaneously. Two large registry studies also found higher rates of major and/or minor malformations in children after ICSI compared to IVF, but one was poorly reported with only the abstract currently available (Weisel, Stolz et al. 2003), and the other reported problems with ascertainment (Ericson and Kallen 2001).

Several studies have investigated whether outcomes for children conceived by ICSI differ according to the pathology underlying infertility or the quality of sperm used. Three studies found that obstetric outcomes were generally similar regardless of the sperm origin, sperm quality or fresh/frozen status (Aytoz, Camus et al. 1998; Aytoz, Van den Abbeel et al. 1999; Wennerholm, Bergh et al. 2000), though one of these studies reported a higher rate of intra-uterine death in the ICSI group when ejaculated sperm of very poor quality was used (Aytoz, Camus et al. 1998). For the outcome of congenital malformations, no differences were found in relation to the indication for ICSI (Ludwig, Katalinic et al. 2003; Vernaeve, Bonduelle et al. 2003) or the origin of the sperm (ejaculated, epididymal or testicular) (Bonduelle, Liebaers et al. 2002; Ludwig, Katalinic et al. 2003). When sperm parameters were investigated, some studies found no differences in malformation rates in relation to sperm concentration (Ludwig 2002; Wennerholm and Bergh 2004) or sperm morphology (Bonduelle, Liebaers et al. 2002). However, one study found that major congenital malformations were more frequent where sperm motility was below 50% (Bonduelle, Liebaers et al. 2002) and another found a higher frequency of chromosomal abnormalities where sperm motility and/or concentration were low (<50% and <20X10⁶ respectively) (Bonduelle, Van Assche et al. 2002).

Although, as noted above, no reliable studies have shown a significantly increased risk of congenital malformations after ICSI compared to IVF, there is increasing evidence of a significantly increased risk of major malformations after ICSI compared to natural conception. Two recent higher quality publications, one a systematic review, calculated odds ratios of 2.0 (95% CI 1.3–3.2) and 2.77 (95% CI 1.41–5.46) respectively for major congenital malformations (Bonduelle, Wennerholm et al. 2005; Hansen, Bower et al. 2005). Hansen et al (2005) suggest that clinicians counselling their patients should calculate their absolute risk of a congenital malformation in terms of the number needed to harm and should base this on a 30–40% increase of risk over and above the baseline prevalence for their population. The baseline prevalence varies according to the population and the definition of malformation used. In New Zealand, the congenital malformation register publishes a rate of major malformations of around 2–3% in the general population (personal communication, Dr Barry Borman, 8 March 2005).

Child development

There was very little reliable evidence available for this outcome, with only two higher quality studies measuring child development in children conceived by ICSI beyond the age of two (Barnes et al 2004; Bonduelle et al 2005; Ponjaert-Kristoffersen et al 2004; Leslie et al 2003).

From the evidence available, children conceived by ICSI appear to be similar to children conceived by IVF in their physical development and use of health care resources, though compared to naturally conceived children they are significantly more likely to have had a major childhood illness or need health care resources (Bowen, Gibson et al. 1998; Leslie, Gibson et al. 2003; Barnes, Sutcliffe et al. 2004; Pinborg, Loft et al. 2004; Ponjaert-Kristoffersen, Tjus et al. 2004; Pinborg, Loft et al. 2004a; Bonduelle, Wennerholm et al. 2005).

Although one study reported that one-year-old children conceived by ICSI were more likely to experience developmental delay, a follow-up study five years later was reassuring (Bowen, Gibson et al. 1998; Leslie, Gibson et al. 2003). No other studies found evidence of any major difference between the ICSI and IVF groups with respect to motor or cognitive development. Regression analysis in one study showed that the factors influencing cognitive development in two-year-old singletons were sex, pregnancy duration, parity and child's age (method of conception and sperm parameters were not significant factors) (Bonduelle, Ponjaert et al. 2003).

Psychological outcomes

In the single higher quality study reporting this outcome, parents reported similar temperaments and levels of behaviour problems in their children regardless of their mode of conception (IVF, ICSI or spontaneous). Nor did mode of conception affect the incidence of marital difficulties, mental health problems or family stress (Barnes, Sutcliffe et al. 2004).

Epigenetic disorders

It is unclear from the handful of case reports and small studies published to date whether ART increases the frequency of epigenetic abnormalities and if so whether ICSI is specifically implicated. As all such disorders are rare, a sample large enough to detect minor increases is likely to require links between multiple, large population-based, disease registers to population-based registers of ICSI offspring (Kurinczuk 2003). It is feasible that imprinting errors may account for a wider spectrum of ART-related complications than is currently recognised. As such disorders may only manifest themselves in older children or adults, long-term follow-up will be required. Further studies will also help to explain the pathogenesis of epigenetic disorders.

A recent, large, controlled study compared the incidence of BWS in ART versus spontaneously-conceived children, using Australian registry data and matching mothers for age. BWS was nine times more common in the ART population than in the general population, which was statistically significant ($p=0.06$). This study did not report what proportion of the ART children had been conceived using ICSI. The authors note that the overall risk of BWS in children conceived using ART remains low and that BWS is in most cases associated with good outcome (Halliday, Oke et al. 2004).

Summary

In New Zealand in 2002, there were 239 deliveries from 819 ICSI treatment cycles. Children conceived by IVF and ICSI both have an increased risk of adverse obstetric and perinatal outcomes compared to naturally conceived children. This is mainly due to the high rate of multiple births in ART pregnancies, associated with multiple embryo transfer. However, the risk is also increased for ART singletons, who have a higher rate of prematurity and low birthweight than spontaneously-conceived singletons. This applies even after adjustment for maternal age and other background variables (Wennerholm and Bergh 2004). Children conceived by ICSI do not appear to be at any greater risk than children conceived by IVF of adverse obstetric and perinatal outcomes.

Children conceived by ICSI may have a higher rate of chromosomal abnormalities than those conceived by IVF, but there have been no large well-controlled studies reporting this outcome. Based on comparison with population data, children conceived by ICSI were found to have a three- to four-fold increase in risk of inherited or de novo chromosomal abnormalities compared to spontaneously-conceived children. The individual's risk of inherited abnormality can generally be assessed if the parental karyotypes are known, but the risk of a de novo chromosomal abnormality is less predictable – it appears to be higher where sperm concentration and motility are low. The absolute risk of a de novo chromosomal abnormality diagnosed prenatally is around 1.6% for ICSI conceptions versus 0.5% for natural conceptions (Bonduelle, Van Assche et al. 2002).

De novo chromosomal abnormalities in ICSI fetuses consist mainly of an increased number of sex chromosomal abnormalities, though structural abnormalities are also increased. Such abnormalities are frequently relatively mild, and affected children are usually phenotypically normal at birth, but they have an increased risk of developmental problems and infertility, which is difficult to quantify. Couples having ICSI require careful genetic counselling and may choose to undergo prenatal testing, particularly where the male partner has low sperm concentration. In some cases, preimplantation genetic diagnosis (PGD) may be appropriate (Bonduelle, Van Assche et al. 2002).

The ICSI sons of men with a Y-chromosome microdeletion will inherit the same deletion and are likely to be infertile. They will require ICSI themselves if they wish to father a child. It is currently unclear whether other abnormalities may also be associated with Y-chromosome deletions.

There is reasonably good evidence that there is no significant difference between ICSI and IVF in the rate of major malformations diagnosed during the first year of life, but a recent case-control study has suggested that children conceived by ICSI, especially boys, may be more likely to have malformations diagnosed later in childhood (Bonduelle, Wennerholm et al. 2005). However, there is reasonably good evidence of a 30–40% increased risk of birth defects associated with ART compared to natural conception (Hansen, Bower et al. 2005). This could be due to differences between the ART population and the general population, but there could also be an independent procedure-related risk.

With respect to epigenetic abnormalities, currently very little is known about human epigenetic regulation. It is suspected that ART children are prone to rare imprinting disorders, and a large case-control study has shown a significant link between BWS and ART (Halliday, Oke et al. 2004). Although BWS is in most cases associated with a good long-term outcome and the absolute risk of BWS for ART children remains low (around 1 per 4000 births), imprinting disorders can cause severe disability, and other large controlled studies will be required to confirm the extent of risk to ART children and indicate whether ICSI increases the risk of such disorders above IVF alone. Moreover, it has been suggested that epigenetic errors may also account for a wider spectrum of ART-related complications such as low birthweight (De Rycke, Liebaers et al. 2002; Halliday, Oke et al. 2004).

These conclusions are based on the very limited evidence that is currently available, much of which derives from a single research group (Bonduelle et al) which had the foresight to initiate prospective clinical follow-up of all couples in their ICSI and IVF programmes. The long-term safety of ICSI cannot be reliably assessed without properly controlled and adequately powered studies with ongoing follow-up. However, the evidence to date suggests that most children conceived by ICSI are healthy and their growth and cognitive development are comparable with both IVF and spontaneously-conceived children.

Summary of Evidence

The table below provides a summary of the evidence in relation to IVF and ICSI. It should be noted that this overview is highly simplified.

Outcome	ICSI vs IVF	ICSI vs natural conception
Obstetric outcomes	ICSI similar	ICSI worse ¹
Neonatal outcomes	ICSI similar or better ²	ICSI worse ¹
Chromosomal abnormalities	ICSI probably worse	ICSI worse
Congenital malformations	ICSI similar at birth ³	ICSI/IVF worse
Child growth	ICSI similar	ICSI similar
Child physical development	ICSI similar	ICSI worse ⁴
Child cognitive development	ICSI similar	ICSI similar
Psychological outcomes	ICSI similar	ICSI similar
Epigenetic disorders	No evidence	ICSI/IVF probably worse ⁵

Notes:

1. Mainly due to high multiple rate in ART.
2. Evidence of lower neonatal complication and death rate in ICSI group – unclear why.
3. More data needed on older children, among whom there is an unproven possibility of increased abnormalities.
4. Higher likelihood of childhood illness and higher use of health resources.
5. Far more data needed to clarify risk and which specific disorders are involved.

Assisted Hatching

Assisted hatching is one of several interventions applied during IVF treatments in an attempt to improve pregnancy rates. It involves the mechanical, chemical or laser disruption of the zona pellucida prior to embryo replacement. It has been practised in New Zealand since 1996 and is limited to cases where previous IVF treatments have failed because of poor fertilisation.

There is some evidence to suggest that assisted hatching can improve pregnancy, implantation and ongoing pregnancy rates, particularly in patients with a poor prognosis undergoing IVF or ICSI and those with repeated IVF or ICSI failures (Sallam, Sadek et al. 2003). In New Zealand in 2002, there were 40 treatment cycles involving assisted hatching, resulting in 10 deliveries (personal communication, ANZARD, 17 March 2005).

In a study group of 134, Kanyo and Konc found no increase in the major congenital malformation rate (2.2%), which is comparable to a rate of 2–3% for the general population. No increase in chromosomal aberrations was observed and neither was a difference in minor congenital malformations between the treated group and all deliveries at the hospital (Kanyo and Konc 2003).

A systematic review involving 23 randomised-controlled trials provided insufficient data to investigate the impact of assisted hatching on several important outcomes, including monozygotic twinning, embryo damage and congenital and chromosomal abnormalities (Edi-Osagie, Hooper et al. 2005).

AGART considers that assisted hatching is acceptable on the basis that it is limited to a small number of selected cases where outcomes have been poor and that, although information about risks is still lacking, they do not appear to be any greater than that expected for IVF and ICSI. AGART recommends that the Ministry of Health work with fertility providers to develop a clinical guideline for the use of assisted hatching so that its use is limited to those circumstances where assisted hatching is most appropriate.

In Vitro Maturation of Oocytes

In vitro maturation of oocytes can be defined as the act of culturing and maturing oocytes that have been harvested at an immature state. It is a new and experimental technique that is used in conjunction with IVF or ICSI. Pregnancies have been reported using in vitro matured oocytes that were retrieved immature following conventional ovarian hyperstimulation (Chian, Buckett et al. 1999).

Because of the relatively novel nature of this technique and the lack of evidence available as to the health outcomes associated with it, AGART recommends that IVM continue to be monitored. AGART considers that IVM should not be placed on the list of established procedures at this stage.

Blastocyst Culture

Blastocyst culture is a process used within IVF and ICSI where there is prolonged culture of embryos in vitro for around five days. By this time, the least viable embryos will have succumbed, leaving the most viable available for transfer and therefore theoretically increasing the transplantation rate (Hartshorne and Lilford 2002). It has been used in New Zealand for over 15 years, and in New Zealand in 2002, there were 58 blastocyst transfer cycles resulting in 18 deliveries (personal communication, ANZARD, 17 March 2005). Not all clinics use blastocyst culture because of technical difficulties.

A study by Kausche et al found that delaying the transfer of embryos to the advanced blastocyst stage of development (fully expanded with or without signs of hatching), rather than transferring the fastest-cleaving embryo that reached the blastocyst stage by day 5, does not lead to a significant shift in the sex ratio compared with transfer of early cleavage stage embryos. Furthermore, no increase in birthweight could be demonstrated for infants resulting from the transfer of advanced blastocyst stage embryos compared with the transfer of early-cleavage stage embryos (Kausche, Jones et al. 2001).

Because blastocyst culture is a long-standing procedure with clear clinical benefit in selected cases, AGART considers that blastocyst culture should be placed on the list of established procedures but be continued to be monitored. AGART recommends that the Ministry of Health work with fertility providers to develop a clinical guideline for the use of blastocyst culture so that its use is limited to those circumstances where blastocyst culture is most appropriate.

Gamete Intra Fallopian Transfer (GIFT)

GIFT is a technique that involves combining eggs and sperm outside the body and immediately placing them into the fallopian tubes (through laparoscopic surgery) to achieve fertilisation. It is usually only used where a couple has moral or religious reasons for not wanting to try IVF. In 2002 for the Australia/New Zealand cohort, GIFT accounted for 1% of fresh ART procedures per number of cycles started (Bryant, Sullivan et al. 2004). In New Zealand in 2002, there were no GIFT procedures undertaken (personal reference, ANZARD, 17 March 2005). GIFT has been in use since the early 1980s. As outlined earlier, there are some risks associated with the laparoscopic procedure.

Beral and Doyle (1990) looked at 1581 children (from 1092 deliveries) who were conceived by IVF or GIFT between 1978 and 1987 and born in England, Scotland or Wales. Of the 1092 deliveries included, 6% were from GIFT conceptions. Multiple pregnancies were more commonly associated with GIFT (38%) than IVF (22%). In this cohort, the gestational ages and birthweights were similar for babies conceived by IVF and GIFT and the prevalence of preterm delivery and low birthweight as well as the mean gestational age and birthweight were strongly related to multiplicity. Beral and Doyle reported on congenital malformations detected in this cohort but did not separate IVF from GIFT for this outcome (Beral and Doyle 1990).

AGART considers that the risks associated with GIFT are acceptable on the basis that it is a procedure that is carried out relatively rarely in New Zealand, and the risks do not appear to be raised above those associated with IVF. It is also a technique that involves minimal manipulation and handling of the gametes prior to placing them back into the uterus.

Intra-Uterine Insemination (IUI)

IUI is the artificial insemination of sperm, which have been washed free of seminal fluid, into the uterine cavity. IUI is the common method of inseminating donor sperm. 9.4% (3419) of ART treatment cycles in Australia and New Zealand in 2002 involved artificial insemination using donated sperm. ANZARD does not collect information on IUI treatments unless used for donor sperm.

IUI is often combined with ovarian stimulation and remains a widely used treatment option for couples with male factor infertility, ovulatory dysfunction, mild endometriosis or unexplained infertility. IUI is a simpler, less invasive, cheaper first-line treatment than IVF for subfertility, resulting in a pregnancy rate of 12–20% per cycle. There can be wide variation in the degree of ovarian stimulation used and in the criteria for cancelling insemination because too many follicles have developed. This has some effect on the incidence of twins but can have a profound effect on the incidence of triplets.

It has been found that IUI treatment increases the risk of preterm birth in singleton pregnancies by around 50% when compared to naturally conceived pregnancies (Wang, Norman et al. 2002). In a study by Nuojua-Huttunen et al, the obstetric and perinatal outcomes of pregnancies after IUI were evaluated. It was found that IUI treatment did not appear to increase obstetric or perinatal risks compared with matched spontaneous or IVF pregnancies. However, the mean birthweight of the IUI singletons was significantly lower than for naturally conceived singletons but was no different when compared to the IVF group. It was considered that most problems were associated with patient characteristics and multiple pregnancies (Nuojua-Huttunen, Gissler et al. 1999).

AGART considers the risks posed by IUI to be acceptable, on the basis that they are not raised above the risks associated with IVF. IUI does not involve any manipulation of oocytes and only minimal manipulation of the sperm prior to insemination. AGART thus recommends that IUI be placed on the list of established procedures under the HART Act.

Cryopreservation

Cryopreservation is the maintenance of the viability of excised tissues or organs by freezing at extremely low temperatures. Cryopreservation is often used in conjunction with ART procedures, whereby embryos arising from the IVF and ICSI methods can be frozen and used in subsequent ART treatments where they are thawed and transferred to the uterus. Sperm, oocytes and ovarian tissue can also be cryopreserved for later use in fertility treatment.

For the New Zealand/Australia ART cohort for 2002, 13.7% (1554) of all cycles started (11,370), using frozen non-donor embryos, resulted in a live delivery. This compares with 18.3% (3,640) of all cycles started (19,883), using fresh non-donor embryos. 14.8% (1554) of all frozen embryo transfers (10,505) resulted in a live delivery. This compares with 23.5% (3640) of all fresh embryo transfers (15,482), which resulted in a live delivery (Bryant, Sullivan et al. 2004). In New Zealand in 2002, there were 132 deliveries from 818 attempted thawed embryo cycles. These embryos are derived from both IVF and ICSI treatments.

Cryopreservation requires the addition of chemicals to prevent or control ice crystal formation while the solution containing the gametes or embryos is cooled. Damage may come from the chemicals themselves, from the flow of water across cell membranes causing the cell to burst, from ice crystal formations that physically pierce cell membranes or from changes in the cells while they cool. For each type of freezing and thawing regimen, these risks are addressed by the identity, combination and concentration of cryoprotectants used, the speed at which they are added or removed, the cooling rates and how ice crystal formation is 'seeded' (Ledda, Leoni et al. 2000; Callejo, Salvador et al. 2001; Revel and Laufer 2002).

Under the Reproductive Technology Accreditation Committee Code of Practice, ART units must develop policies and procedures for the safety, identification and location of cryopreserved material. It is mandatory for ART units to develop policies and procedures to limit the storage period of gametes and embryos.

Sperm cryopreservation and subsequent use of sperm in treatment

Cryopreservation of human spermatozoa is the most widely applied aspect of cryobiology in reproductive medicine. Cryopreserved-banked sperm carries the least risk of transmitting DNA damage and possible genetic defects (Brison 2002).

Of paramount importance for spermatozoa cryopreservation is retaining not only structural integrity but also functional integrity as motility and the acrosomal reaction are implicit for normal function (Kelly, Buckett et al. 2003). The significance of cell death from freeze-thawing is less important for sperm than for oocytes or embryos because nearly always relatively large numbers of sperm are available for freezing. It has been shown that in cases of men with obstructive azoospermia, the use of fresh or frozen-thawed sperm will yield equivalent fertilisation rates following ICSI. It is possible to successfully freeze and thaw epididymal, testicular as well as ejaculatory sperm (Bredkjaer and Grudzinskas 2001).

Oocyte cryopreservation

In addition to intrinsic problems with freezing any type of cell, chilling injury is the main obstacle to successful short-term and long-term preservation of mammalian oocytes. It has been suggested that chilling injury affects the membrane, the microtubules, the cytoskeletal organisation and the zona pellucida (Ledda, Leoni et al. 2000).

Where embryo freezing is not an option for technical, religious or regulatory reasons, oocyte cryopreservation offers an alternative. In a study by Oktay et al., 26 pregnancies were reported, resulting in delivery of 21 babies using cryopreserved oocytes (Oktay, Kan et al. 2001). Another study, cited in Kelly et al 2003, states that from the largest long-term study there were only nine births from over 1500 thawed and subsequently inseminated oocytes, giving a pregnancy rate of only 0.7%. Therefore, pregnancy rates are low for oocyte cryopreservation, and this has been a factor limiting its widespread adoption.

It has long been recognised that the mature oocyte is particularly susceptible to cryoinjury. Primordial follicles are thought to be less susceptible to cryoinjury compared to both mature and immature oocytes (Kelly, Buckett et al. 2003). The problem lies in the difficulty in producing mature oocytes from these primordial follicles (Shaw, Oranratnachai et al. 2000) and hence in assessing the degree of damage.

The number of follicles including primordial follicles found per square millimetre of ovarian cortex falls with age, especially after 37 years. This means the number of eggs available for freezing in older women is limited, and the quality of those eggs also declines with age (Siebzehnruhl, Kohl et al. 2000).

There is clearly limited data available on the risks of the subsequent use of cryopreserved oocytes. AGART considers that the risks associated with oocyte cryopreservation alone are those associated with the retrieval procedure and are minimal.³⁴ AGART considers that the risks associated with oocyte cryopreservation alone are acceptable because they are minimal and because oocyte cryopreservation offers potential benefits to women about to undergo cancer treatment.

Ovarian tissue banking and subsequent use of ovarian tissue in treatment

An alternative to cryopreserving mature human oocytes is to cryopreserve ovarian tissue that contains immature oocytes within the ovarian cortex (Yeung and Ng 2000).

Although human ovarian banking has been performed for several years, no ensuing pregnancy has been verified. There is the possibility of a very recent birth in Europe with ovarian-banked tissue, however, as this is a fairly new technological advance, future studies may need to determine its success (Revel and Schenker 2004). Thawed ovarian tissue samples can be grafted back to the original donor (autografting) or to the histocompatible recipient (xenografting). However, patients who have banked their ovarian tissue may in fact still be undergoing treatment and have therefore not attempted any ART procedure with the banked ovarian tissue. An added concern of ovarian tissue banking is the possibility of transferring cancer cells after treatment (Kim, Battaglia et al. 2001).

A great advantage of ovarian tissue cryopreservation over oocyte or embryo cryopreservation is that it can be offered to young girls. In a study by Poirot et al., the youngest patient was 2.7 years old, and 16 patients were under the age of 18 (Poirot, Vacher-Lavenu et al. 2002). Furthermore, the chance of restoring fertility should be higher in young girls as their ovarian cortex clearly contains more primordial and primary follicles, which are thought to survive the cryopreservation process better. It should be noted that there are ethical issues relating to ovarian tissue collection in minors.

It is considered that more work needs to be undertaken in the area of ovarian tissue banking as there is little information available in regard to hormonal function from transplanted ovarian tissue in humans (Callejo, Salvador et al. 2001).

³⁴ These risks include the risks associated with ovarian hyperstimulation and laparoscopy. Laparoscopy is used very rarely to collect oocytes.

Embryo cryopreservation and use of cryopreserved embryos in subsequent treatment

Embryo cryopreservation is a widely used and relatively well-established procedure (Shaw, Oranratnachai et al. 2000). Embryos may be cryopreserved at either pronucleate, cleavage or blastocyst stages of development. In general, where a large number of embryos are obtained, the preference is to freeze a number of pronucleate stage embryos that are more resistant to cryoinjury compared to cleavage stage embryos. Implantation rates for pronucleate stage embryos are superior to that of cleavage stage embryos, probably as a result of the lower risk of cryoinjury. However, pregnancy rates from frozen-thawed embryos are lower than those for fresh embryos (Kelly, Buckett et al. 2003).

Embryos that survive cryopreservation and thawing with all blastomeres intact could be a marker of superior intrinsic embryonic potential. Embryonic morphology before cryopreservation is positively correlated with embryonic survival after thawing; the better the morphology before cryopreservation, the better the survival after thawing. However, it is suggested that infertile couples may not have good embryonic morphology, and therefore the chances of their embryos surviving cryopreservation is reduced (Burns, Gaudet et al. 1999). A study by Tachataki et al examining the pattern of gene expression in frozen human preimplantation embryos found that morphology alone is a limited indicator of the effect of cryopreservation on an embryo. Their research showed that intact frozen-thawed embryos are not equivalent to fresh embryos, at least soon after thawing. It may also be the case that embryos are more susceptible to the freezing process at different times. This study highlighted that day 2 embryos are more vulnerable to temperature change than day 3 embryos (Tachataki, Winston et al. 2003).

Embryo cryopreservation adversely affects embryo quality but does not have detrimental effects on the implantation or pregnancy potential of high quality embryos. It has been demonstrated that more embryos of higher quality and of an advanced cell age are transferred fresh than after cryopreservation. Therefore, an overall decline in embryo morphological grading after freeze-thaw is a demonstrable detrimental effect of cryopreservation. Cryopreservation can also damage the embryo due to intracellular ice formation and osmotic shock. However, implantation rates after freeze-thaw are similar to those of fresh embryos (Selick, Hofmann et al. 1995).

Outcomes for children

It has been found that the cryopreservation process does not adversely affect the growth and health of children during infancy and early childhood. There is no increase in physical or psychomotor impairment compared with children born after either standard IVF or spontaneous pregnancies (Wennerholm, Albertsson-Wikland et al. 1998). In formal testing by Sutcliffe et al., development in children from cryopreserved embryos was not significantly different when compared with other children conceived normally and of similar social class. Their study found that children from cryopreserved embryos did not have neurological abnormalities at follow-up, and none of the children in their study had major disabilities such as cerebral palsy or developmental delay (Sutcliffe, D'Souza et al. 1995b).

However, it has been found in some animal studies that freezing of mouse embryos may affect fetal and postnatal development, and pronuclear transfer can lead to a decrease in growth. Therefore, human in vitro fertilisation technologies involving human embryo culture may give rise to reduced weight at birth (Khosla, Dean et al. 2001). It is also possible, however, that the effects of embryo freezing may have delayed consequences, and as many studies only have a short-term follow-up period, the full effect of cryopreservation on human embryos may not yet be known (Dulioust, Toyama et al. 1995).

Malformations

ART techniques using cryopreserved embryos do not produce more children with malformations than ART techniques using fresh embryos. In a study by Sutcliffe et al., it was found that the proportion of children born from cryopreserved embryos with a major congenital malformation was similar to the proportions found with IVF/ICSI procedures (Sutcliffe, D'Souza et al. 1995b).

Cancer

Sperm or oocyte cryopreservation has important applications in the field of oncological medicine. Because it halts the cell cycle, cryopreservation has already been extensively applied for fertilised oocytes at pronucleate or embryo stages. Chemotherapeutic agents may induce azoospermia in males and cause premature ovarian failure in women (Al-Fozan and Tulandi 2004). The cryopreservation of sperm has been a well-proven and practical clinical option for many years. However, there is less evidence on the cryopreservation of oocytes, which has low pregnancy rates associated with it. This could be due to the fragile nature of oocytes and that fact that the cryopreservation process may damage the oocytes (Al-Fozan and Tulandi 2004).

Summary

AGART considers that the risks posed by sperm and embryo cryopreservation and subsequent use in treatment are acceptable as cryopreservation appears to mainly affect the fertilisation and implantation potential of sperm and embryos rather than the health of the resulting offspring. The risks of cryopreservation are therefore similar to those associated with IVF and ICSI. AGART thus recommends that the cryopreservation of sperm and embryos be placed on the list of established procedures under the HART Act.

AGART recommends that oocyte cryopreservation alone be placed on the list of established procedures under the HART Act. However, this established procedure should exclude the subsequent use of cryopreserved oocytes in treatment. This is because there is limited evidence available as to the risks of the subsequent use of cryopreserved oocytes.

AGART considers that ovarian tissue cryostorage is an experimental procedure and may give cancer victims the opportunity to retain their reproductive potential in the future. AGART recommends that cryopreservation of ovarian tissue be placed on the list of established procedures under the HART Act. However, there is limited evidence available as to the success or otherwise of the use of cryopreserved ovarian tissue in treatment. At this stage, AGART considers that it would be premature to carry out a risk analysis on the basis of the evidence available and therefore considers that at this stage the use of ovarian tissue in treatment should not be placed on the list of established procedures under the HART Act.

AGART notes that ovarian tissue storage in those persons who may be not of an age to be competent to consent to the surgery has some ethical issues associated with it and has only previously been allowed by the National Ethics Committee on Assisted Human Reproduction (NECAHR) on a case-by-case basis. AGART therefore recommends that this fact be considered by the Director-General when recommending the appropriate parameters of the established procedure of ovarian tissue storage.

Preimplantation Genetic Diagnosis (PGD)

PGD is a procedure devised to test early human embryos for serious inherited genetic conditions. PGD involves the following steps.

- The creation of an embryo via IVF
- The removal of one or two cells from the embryo
- The genetic testing of these cells for specific genetic conditions
- The subsequent transfer of unaffected embryos to a woman's uterus.

In June 2004, the Ministry of Health contracted the New Zealand Guidelines Group to carry out a systematic review of the clinical evidence about PGD. The objectives of the review included:

- to review the evidence on the clinical harms and benefits associated with PGD
- to report on the effectiveness of using PGD for each of its major indications
- to identify other conditions for which PGD has been used
- to identify clinical indicators that could be used by PGD providers to monitor the effectiveness of PGD.

Some of the following is excerpted from the report of the New Zealand Guidelines Group, which available on their website <http://www.nzgg.org.nz>

In June 2003, the Minister of Health gave approval in principle to the use of PGD in New Zealand and requested that the National Ethics Committee on Assisted Human Reproduction (NECAHR) develop guidelines on the use of this technology. NECAHR consulted on guidelines for PGD in late 2004. In March 2005, the Minister of Health approved the guidelines for implementation in New Zealand.

The European Society for Human Reproduction and Embryology (ESHRE) (2002) presented obstetric and neonatal data relating to 309 clinical pregnancies reported by 12 centres. First-trimester miscarriages occurred in 11% of pregnancies and second-trimester pregnancy losses occurred in 4% of pregnancies. The most commonly reported complications of pregnancy related to prematurity, usually in multiple pregnancies. Other complications were bleeding, hypertension and pre-eclampsia. Complications were present in 33% of the ongoing pregnancies for which data was available – however, many centres did not submit any information in the relevant field, and ESHRE suggest that there were probably no complications to report.

Strom et al (2000; 2000a) reported obstetric and neonatal outcomes in a clinic case series of 102 pregnancies and 109 infants, and they compared their results to published IVF outcomes. In all cases, pre or postnatal testing confirmed the PGD diagnosis. Rates of multiple gestation and Caesarean section were high but comparable to IVF rates (15% and 40% respectively). Other complications such as preterm delivery and low birthweight were similar. However, there was a higher rate of placenta praevia in the PGD group (4% versus 0.4%); the only known risk factor for placenta praevia for these women was prior uterine surgery.

Among the 109 infants followed up by Strom et al., six reports of birth defects were considered valid by the authors. One had part of a lower limb missing. The authors noted that an amniotic band (a fibrous strand of uterine membrane) had been noted on the ultrasound examination prenatally and that the fetus had been exposed to chorionic villus sampling. They stated that it was unclear whether chorionic villus sampling could have been responsible for the defect. One child had cerebral infarcts causing seizures, probably not of a developmental origin, and the other four had minor abnormalities, namely strawberry haemangiomas (two cases), a thickened heart valve not requiring surgery (1) and bilateral toe-webbing (1). The authors state that the rate of haemangiomas (2%) is within the reported incidence of haemangiomas in newborns (1.1–2.6%).

Forty-four of these children were over six months old. They were within normal parameters for weight and height. One 30-month-old twin was receiving speech therapy for a six-month speech delay; otherwise there were no developmental problems reported among these children, but their follow-up continues (Strom C.M., S et al. 2000).

An unpublished study from one of the large United States centres (Fischer, Escudero et al. 2002) documented the outcome of 100 PGD cycles conducted for structural chromosomal abnormalities in 72 women. Of 30 clinical pregnancies, one was terminated because the fetus had an unbalanced translocation as a result of unscreened embryos being returned to the uterus (no further explanation is given), and one pregnancy miscarried. Of 39 babies delivered, one had a familial abnormality not screened for (lymph oedema distichiasis, which can cause corneal irritation and limb swelling). Two had major congenital abnormalities: tetralogy of Fallot (a major cardiac malformation) and bilateral renal agenesis (no kidneys, fatal). Thus 7.6% (3 out of 39) babies in this study had congenital abnormalities, life threatening or fatal in 5% (2 out of 39).

Another study (Joris, Vos et al. 2003) documented neonatal outcomes for 39 children born as a result of 110 embryo replacement cycles. The mean gestational age at delivery was 39 weeks for the 21 singletons and 35 weeks for the 18 twins. Three babies, one singleton and one pair of twins, were stillborn at 21–23 weeks gestation. Another baby, a twin, died at a few days of age from chylothorax, a rare congenital lymphatic anomaly, and another low-birthweight twin has diplegia, a form of paralysis. One of the singleton children has congenital finger webbing. Thus a high proportion of these babies (15%) had adverse outcomes, being either stillborn, disabled or with a congenital abnormality. A further two children, both singletons, have a developmental delay at two years of age. The authors comment that very little data is available on PGD children with which to make any comparison.

The rate of malformations reported among babies born after PGD thus ranged from 5–6.6% (Strom 2000; Joris et al 2003, ESHRE 2002). The rate of major malformations reported in ESHRE (2002) was 3.9%, which compares with a rate of 3.8% in a cohort of nearly 3000 babies after IVF alone (Bonduelle, Liebaers et al. 2002). It is difficult to compare these rates with babies conceived spontaneously as classification systems differ and women having PGD have a high baseline risk of abnormality. The New Zealand congenital malformations register reports a congenital malformations rate of 2–3% (personal communication, Dr Barry Borman, 8 March 2005).

Summary

There are clearly some risks associated with PGD. However, these risks are not markedly higher than the risks associated with IVF, and for this reason, AGART considers that the risks associated with PGD are acceptable. AGART thus considers that PGD should be placed on the list of established procedures. AGART notes that NECAHR has developed guidelines on PGD that were recently approved by the Minister of Health for implementation. AGART therefore recommends that the Director-General of Health take these guidelines into account when recommending the appropriate parameters of the established procedure of PGD.

Information Management

In its Terms of Reference, AGART was also asked to provide broad scientific advice on monitoring and research needs in relation to ART (retrospective or prospective), including surveillance, epidemiology and data collection. This will involve providing advice on:

- the usefulness of the data currently collected by fertility clinics in terms of assessing the health risks associated with particular ART and what, if any, additional information is needed
- management of the information (eg, governance arrangements, making data anonymous)
- what, if any, research could usefully be undertaken in New Zealand, including long-term follow-up of ART children.

Currently, New Zealand fertility clinics collect information on all babies born as a result of ART. They do this by following up with both the lead maternity carer and the patient subsequent to the due date of any ART pregnancy. Compliance with a request from a fertility service provider to provide information is close to 100%, with the only exception being for those patients who leave the country before birth.

The information that fertility clinics collect is fed into the Australia and New Zealand Assisted Reproduction Database (ANZARD). The data collected is used for three purposes.

- Generation of the National Perinatal Statistics Unit (Australia) annual report
- Generation of summary data reports for the Reproductive Technology Accreditation Committee (RTAC), which is responsible for accrediting fertility clinics in both Australia and New Zealand
- To provide fertility clinics with regular internal reports of their outcomes for comparison with Australia and New Zealand-wide norms.

ANZARD includes information about the treatment methods of IVF, ICSI and GIFT. It also includes information about: treatment via the cryopreservation and thaw of embryos, donor insemination, treatment involving donated gametes or embryos and the use of technologies such as assisted hatching, preimplantation genetic diagnosis and blastocyst culture. ANZARD contains details of all pregnancy and birth outcomes, including mode of delivery, birth status, birthweight, gestational age, plurality, perinatal mortality, congenital malformation and maternal morbidity. ANZARD does not contain information about artificial insemination using partner's sperm. All data is reported on an anonymised basis. Some data, such as congenital malformations and maternal morbidity is self-reported by patients and, if relevant, validated with hospital records by fertility centre staff. It is possible therefore that there is inexact reporting of this information.

While the ANZARD data collected is useful in terms of providing good information on perinatal and maternal health outcomes, data on congenital malformations is not reported by fertility clinics.

The New Zealand Birth Defects Monitoring Programme (NZBDMP) was established in 1975. Over time, the method of ascertainment has changed from a paper-based manual operation to a computer-based system. Currently, the NZBDMP, which is operated by Public Health Intelligence, Ministry of Health, covers all live births with a birth defect delivered or treated in a New Zealand publicly funded hospital. Data on stillbirths is retrospectively added to the database together with additional cases derived from the national perinatal and mortality databases.

AGART considers that there is already a good mechanism in existence for the collection of information on ART births. To enable the information that the fertility clinics collect to be matched with children on the birth defects register, fertility clinics would also have to request the child's National Health Index (NHI) number. Every child receives an NHI number at birth, regardless of where they are born. Asking fertility clinics to also collect a child's NHI number would not create any additional compliance costs on fertility clinics, as they are already collecting information for the purposes of reporting to ANZARD.

AGART notes that under section 78 of the HART Act, regulations can be made requiring fertility clinics to keep records of information of a certain kind and requiring those fertility clinics to disclose that information to AGART or to any duly authorised representative of that committee or to the Director-General of Health.

AGART considers it important for the health outcomes of children born as a result of ART to be observed on an ongoing basis. AGART thus recommends that a voluntary information collection system be initiated, in consultation with the fertility clinics. As outlined above, there is provision for regulations to be made under the HART Act to cover this. However, at this stage, AGART recommends that it be done initially on a voluntary basis, given the likelihood of a high compliance level from fertility clinics. The fertility clinics currently supply all the information they collect to ANZARD. They would need to supply the NHI numbers of all babies born as a result of ART to the Ministry of Health.

The NHI numbers could then be matched against the New Zealand Birth Defects Register. AGART notes that there may be ethical and privacy issues raised by such data matching. AGART recommends that the Ministry of Health carry out further work on this possibility, including having discussions with fertility clinics and seeking legal advice regarding the privacy issues.

Such data matching will make it possible to conduct further research and long-term follow-up of children born as a result of ART. In particular, the numbers of children born with congenital malformations after conception through ART will be able to be tracked.

Glossary

Aneuploidy	One or a few chromosomes above or below the normal chromosome number.
Angelman syndrome	A genetic disorder characterised by severe intellectual disability, seizures, ataxic gait, jerky movements, lack of speech, microencephaly and frequent smiling and laughter.
Beckwith-Wiedemann syndrome (BWS)	A model imprinting disorder resulting from mutations or epimutations, affecting imprinted genes on chromosome 11. It results in a large tongue, organ enlargement, large body size, umbilical hernia and neonatal hypoglycaemia. Birthweight is often more than eight pounds, and complications include Wilm's Tumour, seizures, aspiration and hypoglycaemia.
Blastocyst	In mammalian development, cleavage produces a thin-walled hollow sphere, whose wall is the trophoblast, with the embryo proper being represented by a mass of cells at one side. The blastocyst is formed before implantation.
Blastomere	One of the cells produced as the result of cell division/cleavage in the fertilised egg.
Cerebral palsy	A persisting qualitative motor disorder appearing before the age of three years, due to non-progressive damage to the brain.
Cholestasis	The suppression of the flow of bile.
Chromosome aberration	Deviations from the normal number or structure of chromosomes, not necessarily associated with disease.
Cleavage	The early divisions of the fertilised egg to form blastomeres.
Congenital malformation	An anomalous or abnormal formation or structure that is present at birth as a result of either hereditary or environmental influences.
Cytoskeleton	The part of the cytoplasm that remains when organelles and internal membrane systems are removed.
Demethylation	The process of removing the methyl group from a chemical compound.
Diabetes mellitus	A disease where a relative or absolute lack of insulin leads to uncontrolled carbohydrate metabolism.
Epigenetic	Something that influences the behaviour of a cell without directly affecting its DNA or other genetic machinery, such as an environmental effect.
Gametes	Specialised haploid cells produced by meiosis and involved in sexual reproduction. Male gametes are called spermatozoa, and female gametes are called oocytes.
Genetic imprinting	A mechanism of gene regulation in which only one of the parental copies of a gene is expressed.
Hypertension	Persistently high arterial blood pressure considered a risk factor for the development of heart disease, stroke and kidney disease.
Hypospadias	An abnormality of the penis that has three features. <ul style="list-style-type: none">• The opening is not in the correct place – it is usually further back from the tip of the penis on the underside.• There is often bending or curvature of the penis, which is more pronounced during erection.• The foreskin is missing on the lower half, giving a hooded or incomplete appearance.

Maternal allele	One member of a pair or series of genes that occupy a specific position on a specific chromosome inherited from the maternal side.
Methylation	The introduction of the methyl group into a chemical compound.
Microtubules	Thin tubes, made up of protein, that are used to make structures involved in cellular movement.
Mitochondria	A small intracellular organelle that is responsible for energy production and cell respiration.
Neural tube defects	The abnormal development during embryonic life of the neural tube producing congenital malformations of the nervous system due to closure failure of the neural tube.
Oocyte	A cell from which an egg or ovum develops by meiosis, the process of cell division in sexually reproducing organisms that halves the number of chromosomes in reproductive cells.
Perinatal	Relating to the period shortly before or after birth.
Pre-eclampsia	A condition of hypertension in pregnancy, typically accompanied by oedema and proteinuria.
Vasa praevia	The presentation of the umbilical blood vessels in advance of the fetal head during labour.
Zona pellucida	A translucent, elastic, non-cellular layer surrounding the ovum.

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Appendix 1: Methodologies

Methodology – selection of initial studies

In October 2003, the Ministry of Health requested the New Zealand Health Technology Assessment (NZHTA) Group do a search on the health outcomes of children born via assisted reproductive technologies (ARTs) to identify adverse outcomes and/or increased health risks of assisted human reproductive procedures including, but not limited to:

- in vitro fertilisation (IVF)
- intracytoplasmic sperm injection (ICSI)
- embryo freezing
- preimplantation genetic diagnosis (PGD).

The sources searched by the NZHTA Group were:

- **Bibliographic databases**
 - Medline
 - Embase
 - Current Contents
 - Social Science Citation Index
 - Science Citation Index
 - Cinahl Information Systems
 - Cochrane Central Register of Controlled Trials
 - Index New Zealand
- **Review databases**
 - Cochrane Database of Systematic Reviews
 - ACP Journal Club
 - Database of Abstracts of Reviews of Effectiveness
 - NHS Economic Evaluation Database for healthcare decision makers
 - The NHS Health Technology Assessment Programme
- **Evidence-based services and websites**
 - TRIP Database
 - ATTRACT (NHS Wales)
 - ARIF: Aggressive Research Intelligence Facility (University of Birmingham)
 - Bandolier (Oxford)
 - Canadian Co-ordinating Office for Health Technology Assessment
 - United Kingdom National Coordinating Centre for Health Technology Assessment
- **Government health agencies**
 - United Kingdom Department of Health and Human Services
 - Health Canada
 - United States Centers for Disease Control and Protection
 - Australian Department of Health and Ageing
 - Australian National Health and Medical Research Council

- **Library catalogues**

- Te Puna – New Zealand Bibliographic database
- British Library public catalogue
- LocatorPlus (United States National Library of Medicine)
- World Health Organization Library and Information Networks for Knowledge
- The University of Sydney
- COPAC (UK academic libraries)

- **Other**

- European Society for Human Reproduction and Embryology (ESHRE)
- Proquest Journal Service
- Google search engine.

In July 2004, NZHTA updated its search results bibliography using Medline and Current Contents database.

Criteria for including studies

Types of study

Included: Completed studies reporting health outcomes and health risks of assisted reproductive technologies for both mother and child, including psychological and developmental outcomes.

Types of participant

- Children born as a result of assisted reproductive technology (ART).
- Women and men undergoing fertility treatment.
- Women and men with future risk of infertility undergoing gamete cryopreservation.

Types of outcome

Primary:

- Obstetric and neonatal outcomes, including complications of pregnancy and birth, congenital abnormalities, developmental delay and long-term health of offspring.
- Psychological and psychosocial outcomes for parents and children after having undergone ART treatment.

Types of interventions

Clinical application of:

- ovulation induction
- in vitro fertilisation (IVF)
- intracytoplasmic sperm injection (ICSI)
- cryopreservation of gametes and embryos for fertility treatment
- intra-uterine insemination
- gamete intra fallopian transfer (GIFT)
- in vitro maturation.

Criteria for excluding studies

Excluded:

- studies that focused primarily on ethical issues relating to ART
- studies that focused on preimplantation genetic diagnosis
- studies that focused primarily on causes for infertility, rather than health outcomes of ART.

The titles and/or abstracts of articles returned by the search were scanned for relevance and full text articles retrieved for articles of interest. Full text articles were checked against the inclusion criteria, and their eligibility was determined.

Studies were not categorised, but more recent studies were relied upon in place of older evidence.

Methodology – preimplantation genetic diagnosis (PGD)

In May 2004, the Ministry of Health sought advice from the New Zealand Guidelines Group on the quantifiable harms and benefits of PGD. The following details their methodology.

Criteria for including studies

Types of study

- Included:
 - primary ongoing or completed studies reporting clinical outcomes of PGD, including impact on quality of life
 - secondary research, comprising a systematic review or health technology assessment.
- Excluded:
 - studies without clinical outcomes
 - studies using obsolete methods
 - studies of social sexing (ie, no medical indication).

Types of outcome

- Primary:
 - Reproductive outcomes, including clinical pregnancy and birth rates, loss of pregnancy.
 - Obstetric and neonatal outcomes, including complications of pregnancy and birth, congenital abnormalities, developmental delay and long-term health of offspring.
 - Quality of life of couples undergoing PGD.
 - Diagnostic accuracy at clinical level.
- Secondary:
 - Diagnostic accuracy at experimental level (for the most common indications for PGD).

Pregnancy and birth rates are defined as one concurrently per participant/couple (ie, 'twins' equal one pregnancy and one birth with two babies).

Types of interventions

- Clinical application of PGD for any of the clinical indications mentioned above.

Criteria for excluding studies

- Where studies have no clinical outcome of interest.
- Studies of the use of PGD for social sexing.
- Studies using obsolete PGD methods (such as the use of PCR for simple sexing).

Search

Medline and Embase were searched using versions of the following search strings.

1. exp PREIMPLANTATION DIAGNOSIS/ or preimplantation.mp.
2. exp GENETICS/
3. exp Chromosomes/
4. 2 or 3
5. 1 and 4
6. limit 5 to animals
7. 5 not 6.

The reference lists of articles returned were also searched. There was no language restriction. Attempts were made to contact the authors of unpublished or ongoing controlled trials. One author, Lawrence Werlin, kindly responded with additional data.

Methods

The titles and/or abstracts of articles returned by the search were scanned for relevant and full text articles retrieved for articles of interest. Full text articles were checked against the inclusion criteria, and their eligibility was determined.

Methodology – intracytoplasmic sperm injection (ICSI)

The Ministry of Health identified a need for an in-depth assessment of the possible risks associated with ICSI and contracted the New Zealand Guidelines Group to undertake this assessment. The New Zealand Guidelines Group subcontracted the Auckland-based Cochrane Menstrual Disorders and Subfertility Group to prepare a systematic review, which aims to assess the safety of ICSI for mother, child and family and where possible quantify the health risks of ICSI versus IVF and/or spontaneous conception.

Search strategy for identifying studies

A literature search was conducted for completed primary and secondary studies reporting the health risks of ICSI for mother and child. This included the output of an NZHTA search on ART outcomes commissioned by the Ministry of Health in October 2003 and updated in July and November 2004 (see 'Search' above for details on the search strings used). It was supplemented by a search on 22 December 2004 of the Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library Issue 4 2004, and the following journals: *American Journal of Obstetrics*, *American Journal of Human Genetics*, *Journal of Fertility and Sterility*, *Journal of Human Reproduction*, *Human Reproduction Update*, *Molecular and Cellular Endocrinology*, *Placenta*, *Reproduction*, *Journal of Medical Genetics*, *Molecular Human Reproduction*, *Journal of Assisted Reproduction and Genetics*, *Fetal and Maternal Medicine*, *British Medical Journal*, *The Lancet*, *New England Journal of Medicine*. The reference lists of articles retrieved were also checked.

Criteria for considering studies for the review

Types of study

- Studies assessing the health risks to the mother, child and family associated with the use of intracytoplasmic sperm injection (ICSI).

Study design

- Included: The following types of study comparing ICSI with IVF were eligible for inclusion. The list is ranked according to the quality of evidence provided by each study design.
 - Systematic reviews of randomised controlled trials
 - Systematic reviews of cohort studies
 - Individual randomised controlled trials
 - Individual cohort studies
 - Systematic reviews of case-control studies
 - Individual case-control studies
 - Case series (for inclusion only if no controlled studies were found).

For comparisons of ICSI versus spontaneous conception, our secondary objective, we included only studies using the highest quality design available for each outcome of interest.

- Excluded:
 - studies that did not describe their design
 - studies of ART that did not consider ICSI separately from IVF or other ART techniques
 - studies not published in the English language.

Study participants

- Infertile couples and/or their offspring.

Study intervention

- ICSI.

Study controls

- IVF alone
- Spontaneous conception
- No comparison (if no controlled studies of acceptable quality were found).

Outcomes of interest

Included outcomes:

- Obstetric outcomes (ie, multiple pregnancy, miscarriage, ectopic pregnancy, Caesarean delivery, stillbirth, premature birth, low birthweight)
- Neonatal/infant complications
- Chromosomal abnormalities
- Congenital malformations (ie, birth defects)
- Child development (physical, psychomotor and cognitive)
- Psychological outcomes for child and family
- Epigenetic disorders (eg, imprinting).

Excluded outcomes

- Fertility outcomes (implantation rates, pregnancy rates, birth rates)
- Economic outcomes
- Ethical issues
- Outcomes related to use of preimplantation genetic diagnosis (PGD)
- Outcomes reported by studies but not pre-specified as primary or secondary outcomes.

Quality criteria

The following quality criteria were used.

Criteria 1–5 below were adapted from the Newcastle-Ottawa Scale for assessing the quality of non-randomised studies (Wells, Shear et al.)

1. *Selection of ICSI and non-ICSI groups*
 - a. Was the recruitment method prospective, retrospective or unclear?
 - b. Design: Was a complete conception/ birth cohort recruited?
 - c. What was the participation rate of eligibles – and were those eligible but declining to participate similar to participants with respect to prognostic variables?
2. *Comparability of groups on basis of design or analysis*
 - a. Did the study report the balance between the groups of prognostic variables, such as singleton/twin status, maternal age, parity, maternal education, etc., where it was likely to affect the outcome measured?
 - b. Were the groups balanced, matched or statistically adjusted for prognostic variables (also known as confounders)?
3. *Outcome assessment*
 - a. Were the outcomes assessors blinded to the conception method?
 - b. Were the same level of scrutiny, the same ascertainment method and the same definition of outcomes used in both groups?
 - c. Did the study use an appropriate numerator and denominator for each outcome measured?
4. *Timing of follow-up*

Was outcome assessment appropriately timed and was there sufficient length of follow-up for outcomes to occur?
5. *Completeness of follow-up*
 - a. Was a high proportion of each group followed up?
 - b. Was the group lost to follow-up similar to the group whose outcomes were known, with respect to prognostic variables?
6. *Sample size*

Was the study large enough to be likely to have the statistical power to show a clinically significant difference between the groups for the outcomes measured?

7. *Quality of reporting*

Were the trial design, methods and findings clearly reported or was important information missing or unclear?

Notes on quality assessment

Study design and selection of participants

Randomised controlled trials (RCTs) facilitate objective comparison between groups because prognostic factors (both known and unknown) are likely to be evenly split between the groups by the randomisation process. However, for ethical and logistic reasons, RCTs are rarely feasible for measuring long-term safety, and in the event no RCTs were found that measured our outcomes of interest. In this situation, controlled observational studies are the best alternative.

A prospective study was defined as one in which participants were recruited to the study before the outcome of interest had occurred and were monitored over time. Prospective recruitment reduces the risk of selection bias.

Data collection in a prospectively recruited study may be prospective or retrospective. Prospective data collection is preferable as it is likely to be more reliable than, for example, a questionnaire that relies on memory of past events.

A cohort design was defined as the comparison of a complete ICSI cohort (eg, all couples conceiving by ICSI within a defined time period) with a complete control cohort (eg, all couples conceiving by IVF within the same time period). This study design reduces the potential for selection bias and confounding.

A case-control design was defined as the comparison of an ICSI cohort with a control group selected to 'match' the ICSI cases. A case-control study could be prospective, for example, if the groups were matched for prognostic factors before the outcomes of interest had occurred. The matching process is unavoidably subjective, which increases the likelihood of a biased result compared to the cohort design.

Comparability of cohorts on basis of design or analysis

The challenge of evaluating the safety of ICSI from observational studies is that the role of the ICSI procedure may be confounded by underlying factors related to infertility itself. The ICSI population is inherently more at risk of adverse outcomes than the general population due to a higher mean maternal age, higher incidence of multiple births and whatever pathology underlies the infertility. Comparison with an IVF-alone group provides some control for these factors, but the ICSI group still differs somewhat because it comprises couples for whom IVF alone is ineffective due to severe male factor infertility or because IVF has been tried and found ineffective for unknown reasons.

In observational studies there is no ideal method of ensuring the comparability of cohorts, mainly because many potential confounding factors are unknown. Statistical adjustment for known confounders creates the risk of adjusting for variables that are actually part of a causal chain of events. Moreover, case-control designs that involve matching have to exclude ART children for whom matches cannot be found, causing information to be lost and increasing the potential for bias (Kurinczuk 2003).

Outcome assessment

The feasibility of comparing ICSI with IVF varies according to the outcome measured. It is relatively straightforward to compare obstetric outcomes such as rates of miscarriage and stillbirth, which are routinely monitored, clinically obvious and do not require extended follow-up. However, other outcome measures are more prone to participation bias, losses to follow-up and differential assessment, as discussed below.

Measurement of chromosomal abnormality rates at prenatal diagnosis are highly subject to selection bias since only a minority of couples agree to undergo prenatal diagnosis, generally those perceiving themselves most at risk.

ART children generally undergo much more intensive screening and scrutiny than spontaneously-conceived children, either because of the history of their conception or because of a clinical condition associated with prematurity or multiple birth, with the result that malformations are more likely to be diagnosed and registered in ART children (ascertainment bias) (Bonduelle et al 2005).

Outcomes assessed using registry data may be less reliable than data collected within a standardised study protocol unless the registry data is mandatory and collected prospectively. Otherwise it may be impossible to ascertain what proportion of data is missing.

Different studies use different classification systems for congenital malformations, which means that event rates cannot be compared between different studies but only within studies. Moreover both groups within the same study must be assessed using the same classification system, and the use of differing systems within the same study has been shown to bias results (Kurinczuk 2003). Similarly, event rates obtained from medical records cannot be compared to rates in population registers as a substantial number of malformations in medical notes are not contained in registers: this method would tend to overestimate the malformation rate from ICSI (Wennerholm et al 2000). Malformation rates reported by cohort studies are likely to be maximum estimates compared to studies using registry data, due to the level of scrutiny employed (Bonduelle 2002).

Timing and length of follow-up

At least 30% of congenital malformations are missed at birth (Bonduelle et al 2005). Most surveys of ART children stop at two years old, which means that problems that manifest later in development, such as some imprinting errors, may not be identified (De Rycke et al 2002). A related issue is that measures of congenital malformations should include live births, stillbirths and therapeutic terminations of pregnancy (TOPs), since an estimation based on live births alone excludes the group most at risk of having a serious or lethal defect (survivor bias) (Kurinczuk, Hansen et al. 2004).

With respect to developmental outcomes, measures of intelligence in the first two years of life tend to measure perceptual motor skills rather than true intellectual ability, and developmental delay in the first two years is not always strongly predictive of later cognitive impairment. Tools developed for older children are able to provide a more robust assessment of long-term intelligence – thus greater weight should be accorded to studies of five-year-olds than of younger children as they are more likely to reflect true differences in mental ability. Moreover measures comparing the proportion of children with developmental delay may be clinically more meaningful than comparisons of overall IQ (Leslie, Gibson et al. 2003).

Completeness of follow-up

It is likely that children followed up differ in outcome from those lost to follow-up. A high loss to follow-up may bias findings in either direction, as the loss may be due to survivor bias, which favours those with favourable outcomes, or alternatively to increased vigilance in those with abnormalities.

Power

Individual studies require a large sample size in order to achieve the statistical power to show significant results for outcomes that are relatively unusual such as congenital malformation. When comparing the safety of ICSI and IVF, a non-statistically significant difference (usually reported as a p-value >0.05) does not indicate that the interventions are equally safe if the study is underpowered (Kurinczuk 2004).

Methods

The reviewers read the abstracts of studies returned by the search, read the full text of those appearing to meet the inclusion criteria and made a final selection. Relevant data on the outcomes of interest was extracted and tabulated. Studies were assessed for quality using the criteria described above and were graded according to the overall quality of the evidence provided.

Statistical analysis

Where cohort studies compared ICSI with IVF and were rated as of higher quality, dichotomous data for each study was expressed as an odds ratio with 95% confidence intervals (CI). If there was more than one suitable study reporting the same outcome, results were combined for meta-analysis with RevMan software using the Peto Mantel-Haenszel method and a fixed effect model. Continuous data was expressed as a weighted mean difference (WMD) with 95% confidence intervals and was combined for meta-analysis using a fixed effect model.

Odds ratios were not calculated for comparisons of ICSI versus IVF in lower quality studies, nor for any primary studies comparing ICSI versus spontaneous conception, as such studies were more likely to be subject to confounding. The findings of these studies are reported solely in the text.

Appendix 2: Members of the Advisory Group on Assisted Reproductive Technology (AGART)

Susan Bidwell is Information Specialist Manager at New Zealand Health Technology Assessment Group. Susan leads and coordinates the information searching for reviews and other information work undertaken by NZHTA and is responsible for retrieval and access of documents obtained for reviews and for the standard of referencing in NZHTA publications. Susan also runs training workshops nationally and internationally on skills and resources for accessing evidence-based information. She is currently a member of the Board of Directors of Health Technology Assessment International and immediate past Chair of their Information Resources Group.

Dr Barry Borman is Manager (Epidemiologist), Public Health Intelligence, Business Unit of the Ministry of Health. Barry has extensive experience leading multi-disciplinary teams and working with national health data collections and disease registers, and in perinatal epidemiology and the investigation of clusters of non-communicable diseases, especially birth defects. Barry has also undertaken research in the areas of risk perception and communication and has published more than 50 papers on a variety of public health topics. He has been the Director of the New Zealand Birth Defects Monitoring Programme since 1988 and is the Vice-Chair of the International Clearinghouse for the Birth Defects Monitoring Systems (based in Rome).

Wayne Gillett is Associate Professor at the Dunedin School of Medicine and is a certified subspecialist in reproductive endocrinology and infertility. He is Director of the Otago Fertility Service, with a major interest in reproductive surgery using both microsurgical and laparoscopic techniques, and has worked closely with the Ministry of Health in formulating clinical priority access criteria for infertility. He is a member of the Medical Practitioners Disciplinary Tribunal and was awarded MD in 1990 for work on biology of the ovarian surface epithelium.

Sylvia Rumball is Assistant Vice-Chancellor of Equity and Ethics, and Chair of the National Ethics Committee on Assisted Human Reproduction (NECAHR). She has extensive international and local experience on ethics committees including as a member of the UNESCO International Bioethics Committee, Chairperson of the Massey University Human Ethics Committee and member of the Health Research Council Ethics Committee.

Debbie Ryan is Chief Advisor, Pacific Health, Ministry of Health. Debbie brings with her a knowledge of the Pacific health sector and a commitment to improving health outcomes for Pacific peoples and communities in New Zealand.

Robyn Scott has a background in education and Not-for-Profit Management and is currently the Executive Director of Philanthropy New Zealand. She is on the Executive Committee of Fertility New Zealand, having previously been the Executive Director of the organisation for five years. She has been a member of Fertility New Zealand for 14 years and has a significant interest in issues impacting on those affected by infertility. She is the mother of two children conceived through the use of ART.

Andrew Shelling is Senior Lecturer in Obstetrics and Gynaecology, University of Auckland. He 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, including cancer.

Pat Tuohy (Chair) is Chief Advisor, Child and Youth Health, Ministry of Health. Pat is a specialist paediatrician with a particular interest in community child health. Pat's particular interests are in the areas of child health policy and developmental and behavioural paediatrics.

Teresa Wall is Manager, Māori Health Policy, Te Kete Hauora, Ministry of Health. Teresa is of Te Rarawa and Te Aupouri descent. She is a comprehensively trained registered nurse with experience in renal nursing. She holds a Diploma in Nursing, a Diploma in Public Health and is currently completing a Masters degree in Public Health from Otago University. She previously worked as a Māori advisor for the consumer protection team within the Ministry of Health. Teresa also worked in human resources for Capital Coast Health, before joining the Ministry in 1997.

John Hobbs (Manager), Aphra Green and Jenny Hawes of the Strategic Policy on Ethics and Innovation Team, Sector Policy Directorate, Ministry of Health provided AGART with secretariat support.

Appendix 3: Results of VIDE analysis

Two cases were analysed on VIDE by members of the Advisory Group on Assisted Reproductive Technologies (AGART) and members of an anonymous control group.³⁵ The first case was analysed over a period of three weeks, from 14 February 2005 to 4 March 2005. Nine members of AGART (including the secretariat) completed the analysis.

Peter (31) and Jane (29) have been married for eight years. Peter has recently had to give up his landscape gardening business due to a chronic back injury. He is currently unemployed but re-training as a website designer. Jane is a junior-school teacher.

Peter and Jane have been trying for a child naturally for four years but have unexplained infertility. Their fertility specialist has given them a 2–3% chance of conceiving naturally over the next year. They have discussed the option of assisted reproduction (funded by the public health service) with their specialist. It is estimated that having one IVF/ICSI cycle will give Peter and Jane an 18.3% chance of having a child. Their specialist thinks that this is technically their best option, given their history.

Their specialist is aware of recent literature that states that there is a 25–40% increased risk of birth defects following IVF and/or ICSI. This means that if the treatment is successful, Peter and Jane have a 2.5–4.2% chance of having a child with birth defects, whereas the risk associated with natural conception is around 2–3%.

The most recent literature does not give a clear picture of the seriousness of the birth defects, but previous papers have stated that defects can be both chromosomal and musculoskeletal and can include disorders such as Beckwith-Wiedemann syndrome, hypospadias, neural tube defects and Angelman syndrome.

The fertility specialist has advised Peter and Jane of the new evidence and associated elevated risk. Peter and Jane are prepared to go ahead, but the specialist is unsure whether she should offer the treatment, given the new data on the risks of IVF/ICSI.

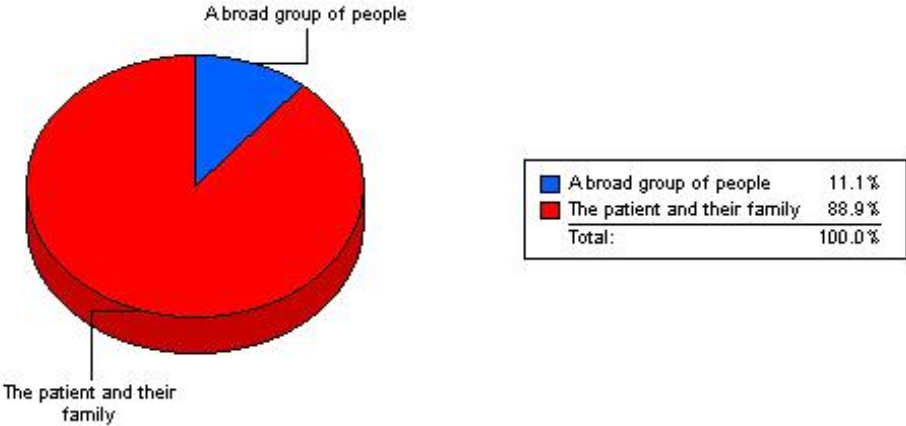
The proposal is that fertility treatment will be offered.

Each member of the advisory committee is asked to state their agreement or disagreement with the proposal, using the values-based software to express their feelings about the proposal and justify their choice.

Note: Because values-based decision-making is a very human process, each advisory committee member should assume that he or she is personally able to say yes or no to the treatment, as if he or she were the consultant.

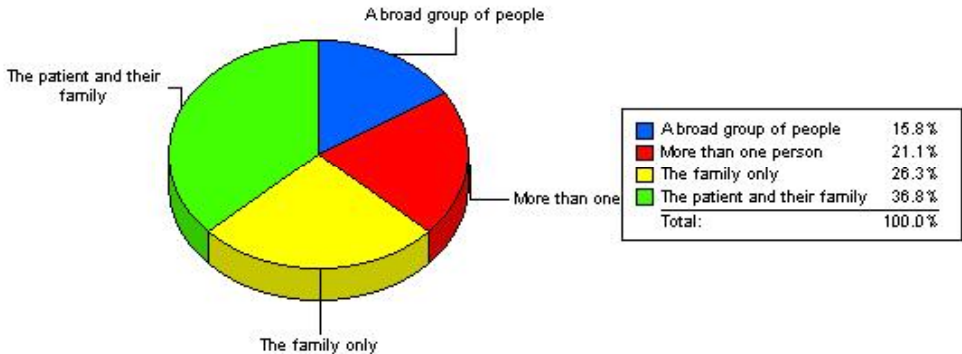
³⁵ The control group contained: three senior nurses (two fertility specialists), two philosophers, a government administrator, an ethics lecturer, a team from the Royal Australian College of Obstetricians and Gynaecologists (collective response), two learning disabilities specialists – one a senior manager, a senior osteopath, a senior lecturer in law, a public health specialist and a VIDE administrator.

For Case 1, all members of AGART agreed with the proposal that fertility treatment be offered. In the control group, 19 people completed the analysis. Seventeen members of the control group agreed with the proposal that fertility treatment be offered. Two members of the control group disagreed.



For Case 1, the majority of AGART considered that the interests of the patient and their family were the most important.

The control group had a slightly different interpretation of whose interests were of primary importance.



The second case was open for analysis between 26 February 2005 and 4 March 2005. The second case had a higher risk factor inserted into it, to see whether people’s reasoning or feelings about providing the treatment would change as a result.

Alan (31) and Karen (29) have been married for eight years. Alan is a lecturer in computer science at AUT. Karen is a preschool teacher.

Alan and Karen have been trying for a child naturally for four years but have unexplained infertility. Their fertility specialist has given them a 2–3% chance of conceiving naturally over the next year. They have discussed the option of assisted reproduction (funded by the public health service) with their specialist. It is estimated that having one IVF/ICSI cycle will give Alan and Karen an 18.3% chance of having a child. Their specialist thinks that this is technically their best option, given their history.

Their specialist is aware of very recent literature that states that there is a significantly increased risk of birth defects following IVF and/or ICSI. This means that if the treatment is successful Alan and Karen have a 6.5–7.2% chance of having a child with birth defects, whereas the risk associated with natural conception is around 2–3%.

The most recent literature does not give a clear picture of the seriousness of the birth defects, but previous papers have stated that defects can be both chromosomal and musculoskeletal and can include disorders such as Beckwith-Wiedemann syndrome, hypospadias, neural tube defects and Angelman syndrome.

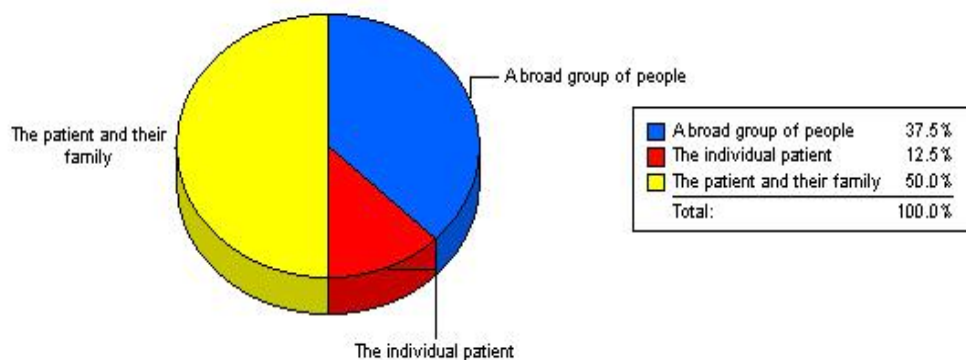
The fertility specialist has advised Alan and Karen of the new evidence and associated elevated risk. Alan and Karen are nevertheless prepared to go ahead with the treatment, but the specialist is unsure whether she should offer it, given the new data on the risks of IVF/ICSI.

The proposal is that fertility treatment will be offered.

Each member of the advisory committee is asked to state their agreement or disagreement with the proposal, using the values-based software to express their feelings about the proposal and justify their choice.

Note: Because values-based decision-making is a very human process, each advisory committee member should assume that he or she is personally able to say yes or no to the treatment, as if he or she were the consultant.

Eight people from AGART completed their analysis. Six members of AGART agreed that the treatment should be offered. Two members disagreed. AGART's interpretation of whose interests were primary shifted from the first case.



In the control group, 16 people completed the analysis. Eight people considered that the treatment should be offered, and eight people considered that the treatment should not be offered. There was a clear shift in the control group from an emphasis on the patient and their family to a broad group of people.

