Assisted reproductive technologies
Decreasing birth rates and ageing mothers ................................................................. 41
Access to ART services ............................................................................................... 42
Funding of ART ........................................................................................................... 43
  Current reimbursement arrangement ....................................................................... 43
    Medicare and ART ................................................................................................ 43
    ART and the Pharmaceutical Benefits Scheme (PBS) ........................................... 46
    Costs associated with ART under Medicare ....................................................... 46
    Government expenditure for ART services under Medicare .............................. 46
  International funding models .................................................................................. 48
Regulation of ART ....................................................................................................... 51
  Accreditation of ART .............................................................................................. 52
  ART and the Therapeutic Goods Administration (TGA) ........................................... 53
  Complementary Medicine and ART ....................................................................... 53
Outcomes of ART ......................................................................................................... 54
  Data collection ......................................................................................................... 54
  Methodological issues .............................................................................................. 55
    Predictors of ART success ..................................................................................... 55
    Discontinuation rate ............................................................................................... 55
    Spontaneous pregnancies ...................................................................................... 55
    Comparison of Australian and international ART outcomes .............................. 56
Evaluation of ART ....................................................................................................... 58
  Clinical effectiveness of ART .................................................................................. 59
    IVF ......................................................................................................................... 59
      IVF by maternal age ............................................................................................ 59
      IVF by cycle number ......................................................................................... 67
      IVF by duration of infertility ............................................................................. 71
    IUI ......................................................................................................................... 73
      IUI by maternal age ............................................................................................ 73
      IUI by cycle number ........................................................................................... 74
      IUI vs IVF .......................................................................................................... 74
    ICSI ......................................................................................................................... 76
      ICSI vs IVF effectiveness – by male factor infertility ......................................... 76
      ICSI vs IVF safety – congenital malformation rate ........................................... 79
  Other ....................................................................................................................... 84
    Frozen embryo transfer ....................................................................................... 84
    Blastocyst transfer .............................................................................................. 87
Cost-effectiveness of ART .......................................................................................... 88
  Summary of findings ............................................................................................... 88
Conclusions .................................................................................................................. 94
Tables and Figures

Figures

Figure 1. Treatment cycles started, pregnancies and live births, Australia and New Zealand, 1993–2002

Figure 2. Number of transfer cycles by ART treatment type, Australia and New Zealand

Figure 3. Distribution of treatment cycles by location for Australia and New Zealand

Figure 4. Live birth per cycle started by woman’s age for fresh, non-donor ART treatment, 2002

Figure 5. Success rates for ART by maternal age, US CDC data 2002

Figure 6. Cumulative live births and costs by number of IVF treatment programs per couples commencing
   IVF treatment – Government perspective (MBS plus Medicare Safety Net Costs)

Figure 7. Cumulative live births and costs by number of IVF treatment programs per couples commencing
   IVF treatment – Societal perspective (Total Costs)

Tables

Table 1. Medicare Benefits Schedule Items for ART

Table 2. Frequency of treatment cycles undertaken (including current cycle) for fresh non-donor ART
   treatment cycles, Australia 2002

Table 3. Frequency of treatment cycles undertaken (including current cycle) for fresh non-donor ART
   treatment cycles by maternal age group, Australia 2002

Table 4. Australian Government expenditure on assisted reproductive services 2000-2005

Table 5. ART services provided under Medicare by patient and service number 2000-2005

Table 6. Increases in numbers of patients and number of services of each year compared with preceding
   year

Table 7. Success rates of fresh, non-donor ART by maternal age, ANZARD data

Table 8. Live birth rates by maternal age for fresh, non-donor IVF cycle started, 1995-1999

Table 9. Success rates of fresh, non-donor IVF by maternal age and cycle number, ANZARD data
Foreword

Independent Review of Assisted Reproductive Technologies

The Hon Tony Abbott MP
Minister for Health and Ageing
Parliament House
CANBERRA ACT 2600

Dear Minister

I have pleasure in submitting, on behalf of the Assisted Reproductive Technologies (ART) Review Committee, the final report of the independent review of ART.

Your decision to establish an independent examination of the clinical and cost-effectiveness of ART for the purposes of public funding under the Medicare Benefits Schedule has proved timely in view of the rapidly changing environment in the area of infertility treatment in Australia and other countries.

Australia has an enviable record in the provision of safe, high quality ART services and is at the forefront of emerging technologies and quality standards; ensuring that evidence-based practice is maintained and continuously improved is imperative. ART presents important social and ethical issues and represents a significant expenditure for both governments and consumers.

Two concerns have predominated in the Committee’s deliberations; ensuring that Australians continue to have access to appropriate and effective ART services for medical infertility and that ART receives sufficient public funding in line with other health priorities. ART is a topical area of public health requiring a consistent and fair approach from governments and relevant health care providers.

The Australian Government has publicly funded ART services under the Medicare Benefits Schedule for many years. The review has sought to build on current initiatives; proposing additional measures which concentrate on adapting the classification of ART services, mechanisms to encourage national accreditation and data collection improvement, providing evidence for clinicians to determine the most clinically appropriate form of ART treatment for each individual; as well as educating the community about relevant infertility issues.

The Committee thanks all those individuals and organisations who have contributed views and information which have assisted the Committee’s understanding and its deliberations. In particular the Members of the Committee are grateful indeed for the enthusiasm and highly professional assistance of the Secretariat throughout the period of the Review.

I commend the report to you.

Yours sincerely

Ian S Fraser
Chair
28 February 2006
Terms of Reference

Assisted Reproductive Technologies Review Committee

The review will consider, and advise the Minister, on the clinical and cost-effectiveness of assisted reproductive technologies (ART) for the purposes of public funding under the Medicare Benefits Schedule.

The review will examine the evidence to determine the costs and outcomes of ART in Australia and in other comparable countries.

The review will make recommendations to the Minister on:

- The clinical appropriateness of ART interventions for the management of infertility, including societal impacts;
- The clinical effectiveness of the various methods of ART, having regard to the underlying causes of infertility;
- Suitable measures of ART outcomes for reporting purposes;
- The extent to which ART should be publicly funded, having regard to effectiveness, access and equity;
- Any other matters the review considers relevant for the Minister’s consideration.
Committee Membership

The Assisted Reproductive Technologies Review Committee:

Professor Ian Fraser (Independent Chair)
Professor in Reproductive Medicine
Department of Obstetrics and Gynaecology
The University of Sydney

Associate Professor Peter Illingworth
Acting Director
Women’s & Children’s Health
Westmead Hospital, Sydney

Dr Therese McGee
Head
Department of Obstetrics and Gynaecology
Westmead Hospital, Sydney

Dr Andrew Pesce
AMA Representative
Obstetrics and Gynaecology Services
Westmead Private Hospital, Sydney

Ms Bettina Arndt
Feature writer – Australian Consolidated Press
Regular speaker – ABC radio (Sydney, Melbourne and Canberra)

Professor John Horvath
Chief Medical Officer
Department of Health and Ageing, Canberra
Abbreviations

ABS  Australian Bureau of Statistics
AHEC  Australian Health Ethics Committee
AHTAC  Australian Health Technology Advisory Committee
AIHW  Australian Institute of Health and Welfare
ANZARD  Australian and New Zealand Assisted Reproduction Database
ART  Assisted Reproductive Technology
ASRM  American Society for Reproductive Medicine
ASSET  Australian Study of Single Embryo Transfer
BEST  Birth Emphasising a Successful Singleton at Term
BMI  Body Mass Index
BWS  Beckwith-Wiedemann Syndrome
CDC  Centers for Disease Control and Prevention
CFO  Child and Family Outcomes
CI  Confidence Interval
CMR  Congenital Malformation Rate
DET  Double Embryo Transfer
DI  Donor Insemination
eSET  Elective Single Embryo Transfer
ESHRE  European Society of Human Reproduction and Embryology
ET  Embryo Transfer
FSH  Follicle Stimulating Hormone
GIFT  Gamete Intrafallopian Transfer
GnRH  Gonadotrophin-Releasing Hormone
HCG  Human Chorionic Gonadotrophin
HFEA  Human Fertilisation and Embryology Authority
HMG  Human Menopausal Gonadotrophin
HOMBR  Higher Order Multiple Birth Rate
HOPR  Higher Order Pregnancy Rate
HTA  Health Technology Assessment
ICSI  Intracytoplasmic Sperm Injection
IUI  Intrauterine Insemination
IVF  *In Vitro* Fertilisation
LBR  Live Birth Rate
LH  Luteinising Hormone
MBS  Medicare Benefits Schedule
MSAC  Medical Service Advisory Committee
NHMRC  National Health and Medical Research Council
NICE  National Institute of Clinical Effectiveness
OHSS  Ovarian Hyperstimulation Syndrome
OPU  Oocyte Pickups
OR  Odds Ratio
PBS  Pharmaceutical Benefits Scheme
PGD  Preimplantation Genetic Diagnosis
PICO  population, intervention, comparator, outcomes
RCT  Randomised Controlled Trial
rFSH  Recombinant Human Folicle Stimulating Hormone
RR  Relative Risk
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTAC</td>
<td>(Fertility Society of Australia) Reproductive Technology Accreditation Committee</td>
</tr>
<tr>
<td>SART</td>
<td>Society for Assisted Reproductive Technology</td>
</tr>
<tr>
<td>SDR</td>
<td>Singleton Delivery Rate</td>
</tr>
<tr>
<td>SET</td>
<td>Single Embryo Transfer</td>
</tr>
<tr>
<td>TBR</td>
<td>Twin Birth Rate</td>
</tr>
<tr>
<td>TMC</td>
<td>Total Motile Sperm Count</td>
</tr>
<tr>
<td>TrBR</td>
<td>Triplet Birth Rate</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>ZIFT</td>
<td>Zygote Intrafallopian Transfer</td>
</tr>
</tbody>
</table>
Glossary

Aneuploidy: Variation in chromosome number involving one or a small number of chromosomes; commonly involves the gain or loss of a single chromosome.

Anovulation: suspension or cessation of ovulation.

Artificial insemination: placing sperm into the female reproductive tract other than through sexual intercourse.

Assisted hatching: an *in vitro* procedure in which the zona pellucida of an embryo (usually at 8-cell stage or a blastocyst) is perforated by chemical, mechanical or laser-assisted methods to assist separation of the blastocyst from the zona pellucida.

Assisted reproductive technology (ART): the application of laboratory or clinical techniques to gametes and/or embryos for the purposes of reproduction (AHEC Report, 2004).

Assisted reproductive services: clinical treatments that involved assisted reproductive technology.

ART cycle: a period of up to 30 days during which either controlled ovarian hyperstimulation has been performed with the intention of applying assisted reproductive technology, or assisted reproductive technology has been applied to patient care.

Biochemical pregnancy (pre-clinical pregnancy): evidence of conception based only on biochemical data in the serum or urine where no clinical pregnancy results.

Blastocyst: an embryo with a fluid-filled blastocele cavity (usually developing by five or six days after fertilisation).

Cancelled cycle: an ART cycle in which controlled ovarian hyperstimulation has been performed with the intention of applying assisted reproductive technology but assisted reproductive technology has not been used.

Clinical pregnancy: a pregnancy that fulfils one of the following criteria: known to be ongoing at 20 weeks; evidence by ultrasound of an intrauterine sac (with or without a fetal heart); examination of products of conception reveal chorionic villi; or a definite ectopic pregnancy that has been diagnosed laparoscopically or by ultrasound.

Clinical pregnancy rate: number of clinical pregnancies expressed per 100 treatment events. When clinical pregnancy rates are described, the precise treatment event that is being used as a denominator must be specified.

Congenital abnormality: abnormality existing at birth, regardless of cause.

---

**Controlled ovarian hyperstimulation (COH):** medical treatment to induce the development of multiple ovarian follicles.

**Cryopreservation:** freezing and storage of gametes, zygotes or embryos.

**Delivery rate:** number of deliveries expressed per 100 initiated cycles, aspiration cycles or embryo transfer cycles. When delivery rates are given, the denominator (initiated, aspirated or embryo transfer cycles) must be specified. It includes deliveries that resulted in a live birth and/or stillbirth. The delivery of a singleton, twin or other multiple pregnancy is registered as one delivery.

**Early neonatal death:** death occurring within the first seven days after delivery.

**Ectopic pregnancy:** a pregnancy in which implantation takes place outside the uterine cavity.

**Embryo:** product of conception from the conclusion of fertilisation to the end of the embryonic stage eight weeks after fertilisation.

**Embryo donation:** the giving of an embryo by either the gamete providers or the persons for whom the embryo was created to other persons for the purpose of achieving a pregnancy (AHEC Report, 2004).

**Embryo transfer (ET):** procedure in which one or more embryos are placed in the uterus or fallopian tube.

**Embryo transfer cycle:** ART cycle in which one or more embryos are transferred into the uterus or fallopian tube.

**Fertilisation:** the penetration of the ovum by the spermatozoon and fusion of genetic materials resulting in the development of a zygote.

**Fetus:** the product of conception starting from completion of embryonic development (at eight completed weeks after fertilisation) until birth or miscarriage.

**Full-term birth:** a birth that takes place at 37 or more completed weeks of gestational age. This includes both live births and stillbirths.

**Gamete intrafallopian transfer (GIFT):** ART procedure in which both gametes (oocytes and sperm) are transferred to the fallopian tubes.

**Gestational age:** age of an embryo or fetus calculated by adding 14 days (two weeks) to the number of completed weeks since fertilisation.

**Gestational sac:** a fluid-filled structure arising from trophoblastic tissue that develops early in pregnancy usually within the uterus.

**Hatching:** the process that precedes implantation by which an embryo at the blastocyst stage separates from the zona pellucida.
**Implantation:** the attachment and subsequent penetration by the zona-free blastocyst (usually in the endometrium) that starts five to seven days following fertilisation.

**In vitro fertilisation (IVF):** an ART procedure that involves fertilisation outside the body.

**Infertility:** a circumstance where there has been an inability to either conceive or carry a pregnancy to a live birth after one year of unprotected sexual intercourse, or there is a medical condition that will reduce the likelihood of either conception or carrying a pregnancy to a live birth.

**Intracytoplasmic sperm injection (ICSI):** an IVF procedure in which a single spermatozoon is injected through the zona pellucida into the oocyte. The process increases the likelihood of fertilisation when there are abnormalities in the number, quality or function of the sperm.

**Intrauterine insemination (IUI):** artificial insemination performed directly into the uterus.

**Karyotype:** the chromosome set.

**Live birth:** the birth of a live fetus after 20 weeks gestation.

**Live birth rate:** number of live births expressed per 100 treatment events. When calculating a live birth rate, more than one live birth occurring at a single delivery (i.e. from a twin or triplet pregnancy) should be counted as a single event. When live birth rates are described, the precise treatment event that is being used as a denominator must be specified.

**Malformation rate:** includes all structural, functional, genetic and chromosomal abnormalities identified in aborted tissue, or diagnosed before or subsequent to birth.

**Micromanipulation** (also referred to as assisted fertilisation): the use of special micromanipulative technology that allows operative procedures to be performed on the oocyte, sperm or embryo.

**Miscarriage:** spontaneous loss of a clinical pregnancy before 20 completed weeks of gestation.

**Neonatal death:** death within 28 days of birth.

**Oocyte donation:** the giving of oocytes by a woman to enable a recipient to have a child, of whom the recipient will be the social mother but not the genetic mother.

**Oocyte pick-up (OPU):** initiated ART cycle in which one or more oocytes are retrieved by aspiration.

**Ovarian hyperstimulation syndrome (OHSS):** a medical complication that may occur after gonadotropin use with IVF, when the ovaries have been overstimulated. The ovaries become enlarged and fluid accumulates in the abdomen.

**Preimplantation genetic diagnosis (PGD):** screening of cells from preimplantation embryos for the detection of genetic and/or chromosomal disorders before embryo transfer.
**Preterm birth:** a birth which takes place after at least 20, but less than 37, completed weeks of gestation.

**Spontaneous miscarriage:** spontaneous loss of a clinical pregnancy before 20 completed weeks of gestation or, if gestational age is unknown, a weight of 500g or less.

**Stillbirth:** the birth of a dead fetus after 20 weeks gestation.

**Subfertility:** Infertility that is not ‘absolute’, or ‘complete infertility’ – i.e. there is a chance of pregnancy but the chance of becoming pregnant (fecundability or monthly fertility) is reduced.

**Treatment cycle:** a treatment episode commencing with the first patient intervention (usually controlled ovarian hyperstimulation). An ART cycle using unstimulated ovulation is considered as commencing with the provision of ovulation monitoring services.

**Zygote intrafallopian transfer (ZIFT):** a procedure in which the zygote is transferred into the fallopian tube.

**Zygote:** a diploid cell, resulting from the completion of fertilisation of an oocyte by a spermatozoon.
Executive Summary

Assisted reproductive technologies (ART) are treatments for medical infertility, performed to assist a couple to achieve the live birth of a single healthy child. The physician is best placed to determine the clinical appropriateness of ART treatment for each woman or couple. It is estimated that one in six Australian couples suffer from some form of infertility. For the purposes of this review, the most relevant measure of the success of ART is considered to be the number of live births produced – expressed as a percentage of the number of cycles of ART treatment started.

In Australia, ART services have been reimbursed through Medicare since 1990 and associated drug therapies are funded under the Pharmaceutical Benefits Scheme. Since November 2000, there has been no restriction on the number of cycles or services that can be used by a couple.

While many other developed countries publicly fund ART to some degree, there is usually some restriction on access to funded ART services. Unlike other countries, Australia currently provides public funding for an unlimited number of ART cycles for women eligible to receive benefits under Medicare. The burden of the cost of ART therefore falls more heavily on the Australian Government than in most other countries.

Prior to the introduction of the Extended Medicare Safety Net (EMSN) in March 2004, patients were required to pay a significant percentage of costs for ART services covered by Medicare. A recent analysis suggests the average cost of an ART live birth is $32,903. This includes government, private insurance and patient out-of-pocket expenses. Previously, most of these costs were met by the patients. Under the EMSN, the Australian government now meets 80% of out-of-pocket costs for ART services provided out of hospital once a set annual threshold is reached. In 2003 Medicare expenditure for ART services was $50 million; while in 2005 expenditure totalled $108.4 million – representing a 117% increase over two years. It seems likely that these costs will continue to climb. Given the steady increase in the age of first marriages and more women delaying trying to conceive, it seems likely more women will have need of ART services in the future. With the government now liable for a significant proportion of the costs of these services, charges for ART are no longer constrained by patients’ capacity to pay. In these circumstances, the escalation of government expenditure in this area is bound to continue.

There is no national legislation that covers the regulation of ART services in Australia and the laws regarding ART services vary between the states and territories. In 1986, the Fertility Society of Australia (FSA) introduced a Code of Practice for Assisted Reproductive Technology Units and accredits units that provide ART through the Reproductive Technology Accreditation Committee (RTAC). The Research involving Human Embryos Act, 2002 requires RTAC or other accreditation for the handling of human embryos; in some states, ART legislation requires RTAC accreditation. However, there is no nationally consistent requirement for accreditation and there is no linkage between Australian Government funding and accreditation. Standardised, national accreditation requirements should be underpinned by evidence-based guidelines and an appropriately governed body.
In Australia, as in other countries, child-bearing is being delayed. The reviewed evidence provided a large quantity of data which consistently demonstrated that there is an association between declining success rates and increasing maternal age, and that this effect was maintained even after the effects of a number of other factors that influence success rates were taken into account. The decrease in the success rates of ART for women over 40 years of age was marked; an increase in maternal age was also associated with a decrease in the success rates of intrauterine insemination (IUI). An examination of Medicare data showed that utilisation of ART is increasing at a greater rate in women over 42 years of age compared to women less than 42 years of age, and suggests a need for greater public awareness of infertility issues.

The review found evidence of a general trend of decreasing birth rates with increasing numbers of successive ART cycles – although the effect of this was less marked and the effects of the cause or duration of infertility were not taken into account. Australian data indicated that the effectiveness of IVF slightly decreased in cycles two and three compared with the first cycle, without taking into account maternal age. The reason for this relationship is not known. The cycle number at which success rates decreased was inconsistent between the studies reviewed.

Although the success of IVF is reduced in women with a longer duration of infertility, the evidence shows that the size of this effect appeared to be smaller than that associated with increasing maternal age. There was very little evidence found for the comparative success rates of low-dose stimulated IUI and IVF.

Intracytoplasmic sperm injection (ICSI) is a technique that involves the injection of a single sperm into the cytoplasm of an egg to achieve fertilisation. ICSI is used in couples with male factor infertility and those with poor fertilisation using conventional IVF. There is evidence that ICSI is more effective for severe male factor infertility and failed fertilisation than IVF. High quality research comparing the success rates of these treatments in couples with mild male infertility is required.

Concern has been expressed about whether the non-natural selection of sperm used with the ICSI technique, or physical damage to the egg, could result in poorer outcomes in children conceived in this manner. Whether or not the small differences seen in the rates of malformations with ICSI and IVF in some studies are real is uncertain at this time because the evidence is conflicting. This difference was not significant in studies that examined the congenital malformation rates in ICSI versus IVF children. For couples with severe male factor infertility and failed fertilisation, ICSI is the only viable treatment option.

Review of the international literature suggests that in high quality laboratories, a high pregnancy rate can be maintained by elective single embryo transfer (SET) combined with subsequent transfer of a frozen-thawed embryo. Such a policy has the potential to prevent the serious morbidity associated with a multiple pregnancy. There have been a number of recent advances in the techniques associated with IVF, including blastocyst culture and preimplantation genetic diagnosis (PGD). Although the timelines for this review did not allow evaluation of the effectiveness of these techniques, there is a need for ongoing review of the evidence supporting the use of new and evolving technologies.
In terms of the cost-effectiveness of ART in different age groups, the results support previous findings that the cost of a live birth increases with maternal age. The findings also suggest that within younger (30-33 years) and older (42-45 years) age groups the cost per live birth increases with a greater number of treatment programs. Higher pregnancy rates in the younger age groups and the inclusion of costs associated with the pregnancy outcomes are two factors affecting the interpretation of ART cost-effectiveness.

ART items in the Medicare Benefits Schedule should be reviewed to ensure that they reflect safe, effective and cost-effective medicine that is readily accessible by all Australians. Improvements to current data collection processes and consumer information on ART practices are warranted.
Recommendations

The Committee has made a series of recommendations which have been related directly to each of the Committee’s five terms of reference:

A. The clinical appropriateness of ART interventions for the management of infertility, including societal impacts

1. That public funding of Assisted Reproductive Technologies (ART) continue to be provided by the Australian Government where ART is the clinically appropriate response to cases of medical infertility.

   - The clinical appropriateness of ART services should be determined by the treating physician/s, consistent with the national clinical practice guidelines
   - Given the success rate of less than 2% noted in the most recently available age-specific data, it is not clinically appropriate to initiate a new cycle of *in vitro* fertilisation (IVF) treatment in women using their own eggs at 44 years and over.

2. ART is an area of rapid technological change that should be subject to the existing assessment processes of the Therapeutic Goods Administration and/or the Medical Services Advisory Committee, to ensure that Australians have access to medical services that are shown to be safe and cost-effective.

3. Single embryo transfer should be used where a successful treatment outcome is likely, as determined by the treating physician/s.

4. The provision of Intracytoplasmic Sperm Injection (ICSI) (and sperm retrieval when required) is recommended in couples where infertility is due to severe male factor or where there is demonstrated fertilisation failure with conventional IVF.

B. The clinical effectiveness of the various methods of ART, having regard to the underlying causes of infertility

5. That access to Medicare Benefits Schedule (MBS) items and prescription medicines provided through the Pharmaceutical Benefits Scheme for ART services is conditional on the accreditation of the practice to provide ART services.

6. That to be accredited, an ART practice would be required to deliver services consistent with evidence-based guidelines and be subject to regular assessment and review of performance against those guidelines.

7. Mechanisms to facilitate national incident reporting of ART services should be considered.

8. The accreditation of ART practices should be conducted by an appropriately skilled and resourced body, with governance structures in line with established national standards.

---

2 Assisted Reproductive Technology (ART) is defined as: ‘The application of laboratory or clinical techniques to gametes and/or embryos for the purposes of reproduction’ (ART Review Committee Report, 2006).
C. Suitable measures of ART outcomes for reporting purposes

9. That support is provided for the improvement to data collection and reporting structures as a matter of priority, in particular, to facilitate collection of information about access to ART, clinical outcomes of ART treatment, and the costs of ART, including:
   - the generation of a patient-based database for ART services;
   - the development of linkages between ART and national perinatal databases; and
   - appropriate resources for a national ART statistics unit.

10. That advertising by ART practices to consumers should describe success rates using standardised outcome measures with the primary outcome presented being the rate of live birth-per-cycle started.

D. The extent to which ART should be publicly funded, having regard to effectiveness, access and equity

11. That Australian government funding of ART should, in consultation with the relevant health care providers, take into account evidence in relation to the success and costs of different patient groups.

12. That the Australian Government, in consultation with the relevant health care providers, revises the current arrangement of ART items in the MBS.

E. Any other matters the review considers relevant for the Minister’s consideration

13. That the Australian Government funds a national educational campaign to increase public knowledge of factors affecting both female and male infertility, with particular reference to maternal age, preventable infertility, multiple births and suitable alternative treatments.
Conduct of the Review

On 10 May 2005, the Australian Government announced that it would undertake an independent review of the clinical and cost-effectiveness of ART for the purposes of public funding under Medicare.

The purpose of this review, conducted by the ART Review Committee, was to consider and advise the Minister for Health and Ageing, the Hon Tony Abbott MP, on the clinical and cost effectiveness of ART for the purposes of public funding under the Medicare Benefits Schedule.

The ART Review Committee considered issues of access and equity, optimal health outcomes, the costs of ART, and the population to whom these services are provided, based upon the most recent national and international evidence.

Recommendations to the Minister for the appointees to the ART Review Committee were based upon relevant expertise, availability and appropriate representation.

The Chair of the ART Review Committee was Professor Ian Fraser, Professor in Reproductive Medicine, Department of Obstetrics and Gynaecology, University of Sydney. Professor Fraser was supported by Dr Andrew Pesce, Dr Terry McGee, Professor Peter Illingworth, Ms Bettina Arndt and Professor John Horvath.

Due to the short timeframe for the review, in lieu of receiving formal submissions, the ART Review Committee met with key stakeholders to provide consumer insight on the management of infertility, including societal impacts and factors involved with access and equity for consideration in the ART Review Committee’s deliberations. These included Ms Sandra K Dill AM, Chief Executive Officer and Ms Debbie Jeffrey, Chair, ACCESS Australia; Professor Michael Chapman, Chairman, IVF Directors Group; and Dr Adrianne Pope, Representative, Fertility Society of Australia.

Independent contractors were commissioned by the Department of Health and Ageing to conduct research and evidence-based literature reviews, and produce evidence-based clinical and cost effectiveness analyses for the ART Review Committee’s consideration (see Appendix A).

The ART Review Committee received data and information from the Australian Institute of Health and Welfare and several jurisdictional ART advisory bodies.

Formal correspondence on behalf of the Australian Government Chief Medical Officer to several international counterparts sought advice on the level of funding provided under other publicly funded health schemes, and provided some verification of publicly available information on comparable ART service provision and funding frameworks internationally.

The ART Review was supported by a Secretariat in the Medical and Pharmaceutical Services Division, Australian Government Department of Health and Ageing including Dr Jane Cook, Ms Roxarne Paton, Ms Susan Rackstraw and Ms Sina Capasso.
Introduction

Assisted reproductive technology (ART) is the application of laboratory or clinical techniques to gametes and/or embryos for the purposes of reproduction. The term ART has now replaced the term *in vitro* fertilisation (IVF) as ART refers to a range of techniques and services, i.e. not exclusively IVF, which are performed by specialist medical practitioners to assist people who are having difficulty naturally conceiving and carrying a baby to full term. In practice, this mainly comprises either IVF where eggs and sperm are joined outside the body prior to replacement of the embryo into the uterus, or artificial insemination, where – following laboratory preparation – sperm are placed into the reproductive tract of a woman.

The first live birth resulting from IVF worldwide occurred in England in 1978. Nowadays IVF is a well-established and accepted treatment for infertility in most developed countries. Advances in ART, including the use of donor gametes and ICSI, have led to increased numbers of infertile couples being treated with ART in recent years.

ART accounts for 1 to 3% of annual births in developed countries (Gosden et al., 2003). In 2002, 2.3% of babies born in Australia were conceived following the use of ART (Laws & Sullivan, 2004). Data from the Australian and New Zealand Assisted Reproduction Database (ANZARD) indicate that the use of ART has been steadily increasing over the ten year period, 1993–2002 (Bryant et al., 2004) (Figure 1). In this period, the use of standard IVF has not increased markedly, but significant increases in the use of ICSI and frozen embryo transfer have occurred. Over the same period, the use of GIFT has virtually disappeared.

![Figure 1. Treatment cycles started, pregnancies and live births, Australia and New Zealand, 1993–2002. Source: (Bryant et al., 2004)](image)

The number of ART services in Australia and New Zealand has also been steadily increasing over the same decade (Figure 2). The average age of women undergoing ART treatment in Australia and New Zealand in 2002 was 35.2 years (Bryant et al., 2004).
Over the past twenty years, there has been a steady decline in the number of embryos transferred in a single cycle due to growing concerns about the risk and very serious health consequences of multiple pregnancy (Bryant et al., 2004). In 1993, 55.3% of treatment cycles transferred three or more embryos. In 2002 this had decreased to 5.8% of cycles. It is now regarded as good clinical practice in Australia and New Zealand to transfer a single embryo only in women with a good prognosis for fertility.

Over this same time period, the success of ART in Australia and New Zealand has steadily increased (Bryant et al., 2004). The number of pregnancies per fresh embryo transfer cycle was 30.5% in 2002, by comparison with 16.3% in 1993. The pregnancy rate per frozen embryo transfer cycle increased from 13.5% to 19.9% in the same ten-year period. In 2002, 18.3% of all fresh, non-donor cycles started resulted in a live delivery.

The success rate as determined by the Birth Emphasising a Successful Singleton at Term (BESST) outcome, for full-term, singleton babies was 12.9% of all fresh, non-donor stimulated cycles.

In April 1998, a working party of the Australian Health Technology Advisory Committee (AHTAC) produced a report on ART treatment, *Review of assisted reproductive technology*. AHTAC’s role was to evaluate health technologies and highly-specialised services. AHTAC was subsumed by the establishment of the Medical Services Advisory Committee (MSAC) in 1998. In 1998, MSAC considered the AHTAC report and concluded it to be a comprehensive review of ART. The ART Review Committee utilised this 1998 AHTAC review of ART as a basis for the current review of ART services.
Medicare expenditure on ART services has increased significantly over recent years. Australian Government expenditure on ART almost doubled from $25.6 million in calendar year 1991, to $50 million in calendar year 2003.

From calendar year 2003 to 2004, Medicare expenditure for ART treatment increased by 57%, from $50 million to $78.6 million; from 2004 to 2005, Medicare expenditure increased by a further 38% to $108.4 million. For calendar year 2003 to 2004, PBS expenditure for ART treatment increased by 18% from $37.1 million to $43.9 million; and from 2004 to 2005, PBS expenditure increased by 9% to $47.7 million.

The EMSN may well be enabling patients to access ART who in the past could not afford to. But this dramatic rise in expenditure on ART services has not been mirrored in the number of services accessed under Medicare. Since the introduction of the EMSN, Medicare meets 80% of the out-of-pocket costs for medical services provided out of hospital, once an annual threshold is reached. The extent to which this increase in expenditure represents an increase in total charges, or a transfer of out-of-pocket gaps to MBS items numbers is unclear. Lesser factors contributing to the increase in expenditure for ART services include indexation, expected annual service growth and rapid technological advances.

It is timely that this independent review was undertaken of the clinical and cost-effectiveness of ART to ensure evidence-based delivery of appropriately funded health technologies.
Scientific Background

**Assisted Reproductive Technologies (ART)**

Assisted reproductive technology (ART) is the application of laboratory or clinical techniques to gametes and/or embryos for the purposes of reproduction. In practice, this mainly comprises either *in vitro* fertilisation (IVF), where eggs and sperm are joined outside the body prior to replacement of the embryo into the uterus, or artificial insemination, where – following laboratory preparation – sperm are placed into the reproductive tract of a woman.

In Australia, patients receiving assisted reproductive services – which include the use of ART and artificial insemination – receive reimbursement towards the costs of these treatments from the Australian government.

**Measurement of ART effectiveness**

Estimates of ART effectiveness may vary according to the definitions of treatment success and the treated population. Live birth rates provide the most clinically relevant measure of ART success. Other outcomes commonly reported in the literature include the rates of fertilisation, implantation and pregnancy. Pregnancy may be defined as the occurrence of an elevated human chorionic gonadotrophin concentration; the occurrence of a clinical pregnancy; or the presence of an on-going pregnancy beyond 20 weeks. These intermediate outcomes do not, however, represent the desired outcome of a live birth.

The European Society of Human Reproduction and Embryology (ESHRE) consensus document (2003) recommends the singleton live birth as a potential measure of ART success, given the increased risks to mother and infant associated with multiple pregnancy (Land et al., 2003).

In Australia, the Fertility Society of Australia (FSA) Code of Practice states ‘the objective of ART must be the live birth of a single healthy child’ (FSA RTAC, 2005). The outcome of a single term gestation, live baby has been referred to as Birth Emphasising a Successful Singleton at Term, or BESST (Healy, 2004; Min et al., 2004). In Australia, overall live birth rates following ART are recorded as well as the singleton and multiple live birth rates (Bryant et al., 2004).

The definition of the treated population has an impact on the calculation of the live birth rate. The inclusion of all women commencing treatment for the purpose of ART as the treated population is recommended (Bryant et al., 2004; National Center for Chronic Disease Prevention and Health Promotion et al., 2002; The Human Fertilisation and Embryology Authority, HFEA, 2003).

Studies that only report ART live birth rates per oocyte recovery or per embryo transfer cycle exclude women with failed or cancelled controlled ovarian hyperstimulation (COH) and thus may overestimate the true success rates of ART. Defining an IVF or Intracytoplasmic Sperm Injection (ICSI) treatment as the initiation of treatment with COH, allows inclusion of the results of the transfer of an initial fresh embryo and any subsequent frozen embryos stored after the initial oocyte retrieval within the same treatment cycle.
The primary effectiveness outcome considered in this review is the live birth rate per ART cycle started. An ART treatment cycle is considered as a period of up to 30 days during which either COH has been performed with the intention of applying ART; or, ART has been used.

Clinical need

In developed nations throughout the world, the total fertility rate has been declining and, in many countries, is currently below the population replacement value of 2.1 births per woman. In Australia, the total fertility rate in 2002 was 1.76, which is comparable to that in the UK, USA and Canada (Ford et al., 2005).

It is estimated that 12–25% of couples are affected by infertility, but the number of couples seeking medical advice is not accurately known (Australian Health Technology Advisory Committee, 1998b) The FSA estimates that one in six Australian couples suffer from infertility, which they define as the inability to conceive after 12 months or to carry pregnancies to a live birth (FSA, 2005a). However, there is no national data collection on infertility in Australia. A recent population-based telephone survey of Australian men (Men in Australia, Telephone Survey, MATeS) found a self-reported failure to conceive of 7.6% (Holden et al., 2005).

In developed nations, as an increasing number of women delay having children until a later age, the prevalence of infertility and need for fertility assistance services is likely to increase. The median age of child-bearing in Australian women increased from 26.8 years in 1982 to 28.7 years in 1992, and to 30.2 years in 2002 (ABS, 2005b). The average age of women bearing their first child is also increasing, from 26.2 years in 1993, to 27.6 years in 2003 (AIHW NPSU, 2005a; AIHW NPSU, 2005b).

The age-specific fertility rates of women in the age groups 20-24 and 25-29 years have been decreasing along with an increase in the age-specific fertility rates of women aged 35-39 and 40-44 years. Over a ten-year period, from 1992 to 2002, age-specific fertility rates in women aged 20-24 and 25-29 fell from 75 to 57 births per 1000 and 132 to 105 births per 1000, respectively (ABS, 2005a). Over the same period, the fertility rates of women aged 35-39 and 40-44 years increased from 38 to 52 births per1000 and from 6 to 10 births per1000, respectively. Data from the Netherlands demonstrate that the age of women registering for their first infertility consultation is increasing alongside increasing age at first birth (Snick et al., 2005).

Infertility

Infertility is defined as a circumstance where there has been either an inability to conceive or carry a pregnancy to a live birth after one year of unprotected sexual intercourse; or there is a medical condition that will reduce the likelihood of either conception or carrying a pregnancy to a live birth.

Observational studies conducted in couples using natural methods to conceive have indicated that approximately 80% of couples will conceive in the first six menstrual cycles, and an additional 10% will conceive spontaneously within the next six cycles (Gnoth et al., 2005). Of the 10% of couples classified as infertile after one year of trying to conceive, approximately half will achieve a spontaneous conception over the next three years (Gnoth et al., 2005).
Causes of infertility

A couple may be infertile due to impaired male or female fertility or a combination of factors from both partners. The dominant cause of infertility has been attributed to male factors in up to 30% of couples, female factors in up to 37% of couples, and both partners in 20 to 35% of couples (Boyle et al., 2004a). Standard practice in Australia is to undertake a full medical and sexual history and medical examination of both partners when couples present after failing to conceive after 12 months of trying. Investigation is then offered to both partners.

The purpose of these initial routine investigations is to make a diagnosis, guide management, estimate prognosis or identify patients requiring further specific investigation (Evers, 2002b). Many of the causes of infertility are reversible and are managed by non-ART treatments. In 5 to 15% of couples no cause is identified and a diagnosis of ‘unexplained infertility’ is made. Such couples are eligible for treatment using ART. The common causes of infertility are described below. These can classified under five headings based on their different cause, prognosis and non-ART treatment options: male factor infertility; ovulation dysfunction; tuboperitoneal disorders; defects in sperm-cervical mucus interaction; and unexplained (Evers, 2002c).

Risk factors

The NICE review provides detailed guidelines based upon the evidence available for known risk factors for infertility. These factors are outlined briefly below.

Female age is the major determinant of infertility. Natural female fertility falls gradually after age 30 years, with a rapid decline after age 35 years to cessation at menopause. The predictive value of female age on the success rates of reproductive services is a major focus of this review and is addressed in detail in the results section of this report.

Other factors associated with female infertility are obesity (body mass index greater than 29) and low body weight (body mass index less than 19 and irregular or absent menstruation) and smoking. Obesity has also been associated with male infertility. Excessive alcohol intake, smoking and elevated scrotal temperature due to sedentary work position, occupational heat exposure and wearing tight underwear has been associated with reduced semen quality in men, although the impact of this on male fertility is not known (NCCWCH, 2004). Prescription and recreational drugs and occupational hazards such as exposure to solvents have been associated with infertility in both males and females.
Male factor infertility

Routine investigation of male partners includes a detailed history, physical examination, semen analysis and sometimes, hormone measurement. The sperm analysis is fundamental to this assessment. A finding of no abnormality (normospermia) indicates that spermatogenesis (sperm production) is normal and the reproductive tract is patent. At the other extreme, a finding of no sperm (azoospermia) confirms male infertility. Findings between these extremes such as low sperm count (oligospermia); low sperm motility (asthenozoospermia); abnormal sperm forms (teratozoospermic) and combinations of these abnormalities are associated with male subfertility, but may only be one factor contributing to a couple’s inability to conceive.

The WHO has defined reference values for sperm count, motility and morphology, however males classified with abnormal parameters according to these guidelines may still be able to achieve conception naturally, thus the predictive value of semen analysis findings other than azoospermia are limited (WHO, 2000). Severe male factor may be regarded as either a sperm density of less than 10 x 10^6 per mL or a motility of less than 30% or a normal morphology of less than 4% (NCCWCH, 2004)

Abnormal sperm parameters may be due to problems with the production of sperm due to abnormal hormone production or testicular failure; or problems with sperm transport from the testes to ejaculation due to obstruction of the genital tract. In around one-quarter of infertile men, no underlying cause is detected (NCCWCH, 2004).

Abnormalities in sperm production may result from abnormal testicular development, secondary testicular failure, hypothalamic/pituitary failure or disorders of sperm motility or function. Abnormal testicular development is generally of unknown aetiology but can be commonly associated with conditions such cryptorchidism or abnormalities of the sex chromosomes. Testicular failure may occur secondary to conditions such as testicular torsion, trauma, orchitis or exposure to radiotherapy or chemotherapy. Hypothalamic/pituitary disease is an uncommon cause of reduced sperm production but is important because it is the only readily treatable cause. A number of congenital abnormalities of sperm morphology reduce fertility. In addition, sperm motility and function are also impaired by the presence of anti-sperm antibodies or infection.

Problems with sperm transport through the male genital tract may result from infective occlusion of the epididymis, vasectomy, or neuropathy – such as spinal injury or sexual problems.

Among cases where an underlying diagnosis can be made, varicoceles (dilation of the veins that drain the testis thought to impair fertility due to increased intratesticular temperature) and genital tract obstruction are most common (38% and 13% of diagnoses at male infertility clinics respectively) (Boyle et al., 2004a). Both these problems can be treated by surgery. Less common causes, such as sperm autoimmunity, gonadotrophin deficiency and other endocrine abnormalities are amenable to medical treatment.
Female factor infertility

Routine investigation of female partners includes a detailed history, physical examination and investigation with hormone testing to assess ovulatory function; chlamydia screening to indicate potential tubal damage; and hysterosalpingography to assess tubal patency.

Ovulatory dysfunction

Identification of ovulatory failure is made by taking a menstrual cycle history and measuring the serum concentration of progesterone. Identification of either irregular menstruation or a low progesterone concentration leads to further measurement of other hormones involved in the regulation of ovulation: follicle stimulating hormone (FSH), luteinising hormone (LH) and prolactin; as well as oestradiol produced by the ovary (Evers, 2002). The results of these tests are used to classify the causes and site of the underlying hormone disorder and determine appropriate treatment to correct the underlying cause. For example, women with a low concentration of FSH due to hypothalamic failure can be treated with gonadotropin-releasing hormones; and those with a high concentration of prolactin can be treated with dopamine antagonists and/or treatment of the underlying cause.

Women with normal hormone levels are classified as having a disturbance of the hypothalamic-pituitary-ovarian axis that determines hormone regulation. Treatment for this subgroup involves the use of ovarian stimulation drugs. No treatment is available to restore ovulation in women with premature ovarian failure (associated with a low concentration of oestradiol despite high levels of FSH). This may occur as a primary problem or secondary to chemotherapy, radiotherapy or other iatrogenic factors. Oocyte donation can be offered to achieve a pregnancy in these women.

Reproductive tract disorders

Tubal obstruction and other distortions of the pelvic anatomy can prevent natural fertilisation of the egg and sperm and transport of the embryo to the uterus for implantation. Causes include post-infectious tissue damage, post-surgical adhesions, endometriosis (the growth of endometrial tissue in areas outside the uterus) and developmental abnormalities of the uterus. Diagnosis is suggested by a history of pelvic inflammatory disease or pelvic surgery, chronic pelvic pain and clinical examination findings. A blood test to detect past exposure to the sexually transmitted disease Chlamydia trachomatis is also undertaken to assess the possibility of tubal damage. Hysterosalpingography is routinely conducted to assess tubal patency although its value as a standard investigation has been questioned (Evers, 2002). Treatment is surgical and may be performed laparoscopically. However success rates with surgery are poor (<10% for severe tubal disease) and ART offers a more effective alternative for patients with a poor prognosis for surgery.
**Endometriosis**

The association between endometriosis and infertility is complex and apparently highly variable from woman to woman. The mechanisms are not well understood, although endometriosis undoubtedly reduces the chance of conception each month in many women. There is limited level II RCT evidence and meta-analysis evidence that surgery improves fertility in women with endometriosis (Adamson & Pasta 1994; Marcoux et al, Parazzini et al, 1999), but the evidence for the role of IVF and ARTs in management is unclear (Adamson 2005). Pregnancies occur quite rapidly with IVF in women with endometriosis, but it is unclear whether one cycle of IVF is comparable to one month, six months, two years or longer of attempting to conceive naturally, or whether type or severity of endometriosis has an impact on IVF efficacy (Adamson, 2005).

**Uterine fibroids**

This is a common condition where benign smooth muscle and fibrous tumours develop in the uterine muscle. Many women with fibroids appear to have normal fertility, but limited evidence suggests that fibroids may contribute to infertility in some women (Peric and Fraser, 2006). It is likely that submucosal fibroids distorting the uterine cavity will adversely influence fertility and will reduce the likelihood of success with IVF treatment (Pritts, 2001).

**Adenomyosis**

This is another condition involving disturbance of the anatomy and function of the uterine muscle, which may interfere with fertility in some women. However, this condition generally affects women in the later years of reproductive life when fertility is less likely to be an issue. The role of ART in management is not established.

**Defects in sperm-mucus interaction**

Defects in sperm-mucus interaction are of uncertain significance. Such ‘defects’ are generally based on the post-coital test where non-motile sperm are observed in the cervical mucus. The validity of the post-coital test has been questioned and this diagnosis is not universally accepted. An abnormal post-coital test may, however, indicate the presence of anti-sperm antibodies produced by either the male or female partner with the potential to interfere with sperm motility and egg fertilisation.

**Relative frequency of different underlying causes**

The relative frequency of each diagnosis varies across different studies. The findings of studies based on couples presenting to ART clinics does not reflect the distribution of infertility causes in all couples presenting with, or treated for, infertility. However, this review is only concerned with the value of ART for infertile couples opting for ART who are not eligible for non-ART treatments.
The principal causes of infertility in this subgroup of couples can be classified as male or female factors that are not amenable to treatment or where treatment has failed (e.g. non-obstructive azoospermia, severe tubal disease and severe endometriosis) and unexplained infertility.

In 2002, the ANZARD database recorded 19,883 fresh, non-donor ART treatment cycles. The causes attributed to infertility in this population were multiple factors (31.3%), male factor only (26.4%), unexplained (16.7%), female factor only (16%; tubal disease 10%, endometriosis 6%), and other (9.7%).

**Infertility treatments**

In some couples presenting with infertility, treatment can be directed at reversing the underlying cause. As described in the aetiology section above, this may involve surgical measures to treat genital tract obstruction or endometriosis; or hormone treatment to restore ovulatory function. ART procedures are effective in cases where alternative treatments are of doubtful value; the underlying cause is not amenable to other treatments; or the infertility is unexplained.

**ART procedures**

**In vitro fertilisation (IVF)**

IVF involves a series of interventions. The five fundamental steps are: controlled ovarian hyperstimulation; oocyte retrieval; sperm retrieval and preparation; *in vitro* fertilisation; and embryo transfer. Sperm are washed, spun in a centrifuge and incubated in a specialised medium in preparation for fertilisation. Retrieved oocytes are separated from follicular fluid and classified to identify mature oocytes suitable for fertilisation. The selected samples of sperm and oocytes are combined in a culture medium in a Petri dish and inspected for fertilisation after 16 to 20 hours. Oocytes that are not fertilised or that have fertilised abnormally are discarded. At fertilisation, the resulting cell contains a pronucleus from both the oocyte and sperm (referred to as gametes) and is known as a pronuclear zygote. The two pronuclei then fuse and cell division commences, reaching a 4-cell stage at approximately 40 hours. Embryos are inspected at this stage to assess viability.

**Controlled ovarian hyperstimulation (COH)**

In the normal 28 day menstrual cycle the ovary develops approximately ten follicles, each containing an oocyte, of which one follicle develops to maturity under the influence of the pituitary hormones, FSH and luteinising hormone (LH) with ovulation around day 14 of the cycle.

COH is the use of medical treatment to induce the development of multiple ovarian follicles. Most ART cycles include COH to allow the harvest of multiple oocytes. The availability of multiple oocytes improves the likelihood that *in vitro* fertilisation will provide a range of embryos available for transfer, thus permitting the selection of embryos (on the basis of growth rates and morphology) with a higher likelihood of implanting in the uterus.

The pharmaceuticals used for COH act by raising and sustaining high FSH concentrations to allow the development of multiple mature follicles rather than one single dominant follicle.
Clomiphene citrate, an anti-oestrogen agent that increases the release of FSH from the pituitary, can be used as part of COH protocols prior to artificial insemination but, nowadays, is rarely used prior to IVF.

COH prior to IVF normally involves the use of exogenous follicle stimulating hormone to stimulate follicle development. In order to avoid premature release of LH causing premature ovulation of the oocytes, the LH concentration is normally suppressed with gonadotrophin-releasing hormone (GnRH) analogues, either agonists or antagonists.

Follicular development is monitored using serum oestradiol levels and transvaginal ultrasound. When the follicles reach a sufficient size, usually after 9 to 11 days, human chorionic gonadotropin (HCG) is administered to induce maturation of the oocytes ready for oocyte collection. The cycle may, however, be cancelled prior to oocyte collection because either an insufficient number of follicles develop to give a reasonable prospect, or too many follicles develop. In women who are repeatedly unable to develop sufficient follicles, the use of donor oocytes can be offered.

Retrieval of oocytes is undertaken within 32 to 36 hours of administering HCG and before spontaneous ovulation. This can be performed transvaginally by passing a needle into the ovary under ultrasound guidance with sedation, or by laparoscopy under general anaesthetic.

**Sperm retrieval**

Fresh sperm are retrieved from ejaculate provided by the male partner on the same day as the oocyte retrieval, although frozen-thawed sperm can also be used. If the male partner is azoospermic, percutaneous or open biopsy techniques may be used to retrieve sperm from the testes or epididymis. Percutaneous methods involve the needle aspiration of sperm from the testis, epididymus or vas. It can be performed in an outpatient setting under local or regional anaesthesia and takes approximately 30 minutes.

Open biopsy of the testis is a more invasive technique performed in an operating theatre with a general anaesthetic. It is associated with a higher risk of surgical and anaesthetic complications, but provides a greater volume of tissue – which may be needed in men with severe sperm defects or may be desired to allow storage for later ART attempts.

**Embryo transfer**

Embryo transfer takes place as an outpatient procedure either at 2 to 3 days after fertilisation, when the embryo is at the cleavage (4 to 8 cell) stage (or after 4 to 6 days if transferred at the blastocyst stage). In Australia, different gradings systems are commonly used to select the healthiest embryos for injection into the uterus transvaginally. After embryo transfer, the female is treated with progesterone or alternative regimens, daily up to week 10 of pregnancy to assist implantation and maintenance of pregnancy. The number of embryos transferred depends on the practice of the provider and the age and preferences of the treated couple.
In Australia, 94% of embryo transfers undertaken in 2002 involved single or double embryos (Bryant et al., 2004). Rates of single, double and triple/higher embryo transfer rates were 29%, 68% and 3% respectively for women less than 38 years; and 28%, 60% and 11% respectively for women aged 38 years or older (Bryant et al., 2004). Any remaining healthy embryos may be frozen for storage for thawing and transfer at a later date if needed.

**Cryopreservation and frozen embryo transfer**

The ability to preserve embryos by freezing (cryopreservation) for subsequent frozen-thawed embryo transfer in unstimulated treatment cycles has the potential benefits of increasing the number of embryo replacement cycles without additional controlled ovarian hyperstimulation and oocyte retrieval. Although the live birth rate per embryo transfer is lower for frozen than fresh cycles (14.8% versus 23.5% in Australia in 2002 (Bryant et al., 2004)), this improves the overall pregnancy rate per treatment cycle at the same time reducing the risk of ovarian hyperstimulation syndrome (OHSS).

A recent cost-effectiveness analysis from Sweden compared a single fresh embryo transfer strategy, with transfer of one additional frozen-thawed embryo if necessary, to a double fresh embryo transfer strategy (Kjellberg et al., 2006). This analysis indicated that, when maternal and paediatric complications were considered, the SET strategy was the more cost-effective approach.

In Australia, 31,253 ART treatment cycles involving embryo transfer were recorded with non-donor oocytes or embryos in 2002. Of these, 64% involved fresh embryo transfers (Bryant et al., 2004). Data from 1994 to 2002 show increasing numbers of treatment cycles resulting in the storage and thawing of frozen embryos, however data about the average number of fresh and frozen embryo transfers resulting from one COH cycle with oocyte retrieval have not been published.

Other technological advances to improve the safety and effectiveness of COH regimens, and new techniques for embryo culture, selection and transfer have contributed to the increased success rates of ART over recent times. These techniques include milder COH regimens (Pruksananonda et al., 2004; Vlaisavljevic et al., 2003), new culture media (Ben Yosef et al., 2004), transfer of embryos at the later blastocyst stage of development (at day 4 to 6) (Blake et al., 2002; Milki et al., 2003), more detailed assessment of embryo morphology prior to transfer (Rossi-Ferragut et al., 2003), and ultrasound-guided embryo transfer (Sallam et al., 2003b; Bucket, 2003).

Other new techniques such as assisted hatching (Sallam et al., 2003a; Edi-Osagie et al., 2003) and Preimplantation genetic diagnosis (PGD) for couples with known genetic diseases (Verlinsky et al., 2000) or for aneuploidy testing (Kuliev et al., 2003; Kahraman et al., 2004), offer advantages for specific indications. Research is ongoing to determine optimal therapies and techniques.
**Intracytoplasmic sperm injection (ICSI)**

Intracytoplasmic sperm injection (ICSI) is a form of ART involving the injection of a single sperm into the cytoplasm of an oocyte to achieve fertilisation. It is indicated for the treatment of couples with male factor infertility and those with poor fertilisation with conventional IVF, although some have recommended its broad use as first-line ART treatment (Abu-Hassan et al., 2003). ICSI is the only treatment option for couples with severe male factor infertility. It can be performed with ejaculated or surgically retrieved sperm. As described above for IVF, oocytes are examined after 16 hours for fertilisation, and viable embryos are transferred 1 to 3 days later (Boyle 2004).

Concerns have been raised that ICSI may be associated with an increased risk of congenital malformations and long-term genetic consequences due to the ability to produce embryos using abnormal sperm that would not otherwise be able to achieve fertilisation, including sperm from males with genetic defects (Boyle 2004).

**Gamete intrafallopian transfer (GIFT)**

Gamete intrafallopian transfer (GIFT) involves the laparoscopic aspiration of follicles and simultaneous transfer of oocytes and sperm into the fallopian tubes. Originally developed as a more physiological alternative to IVF in women with a high chance of success, the use of GIFT has declined in the last decade as the effectiveness of IVF techniques have improved. GIFT is now rarely performed in Australia (Bryant et al., 2004).

**Artificial insemination procedures**

Artificial insemination (AI) refers to procedures involving the insertion of sperm from the male partner into the vaginal vault, cervix (intracervical insemination) or uterus (intrauterine insemination, IUI, also see below) of the female partner. It may be used as a less invasive alternative to IVF or ICSI for the initial treatment of mild male factor infertility or unexplained infertility with or without ovarian stimulation (NCCWCH, 2004). Donor insemination (DI) using donor sperm may be the only treatment option available to couples with azoospermia, male genetic disorders or infectious diseases, other co-morbidities or sexual factors preventing natural insemination and conception.

**Intrauterine insemination (IUI)**

Intrauterine insemination (IUI) involves the placement of washed sperm into the uterus under ultrasound guidance to bypass the natural cervical mucus barrier. It is performed as an outpatient procedure with or without COH. It is designed to bring a high concentration of sperm into close contact with one oocyte after natural ovulation or with multiple oocytes after COH.
The main indications for IUI with COH are in the treatment of unexplained infertility, where investigations have excluded an obstructive cause (at least one open fallopian tube), and severe male factor infertility. Advantages are that the procedure is less invasive and better tolerated than IVF. Disadvantages are that the procedure has been associated with a lower success rate and higher multiple pregnancy rate than IVF. However, the use of low-dose COH regimens with abandonment of insemination when more than three dominant follicles develop may be expected to reduce the latter. In Australia, it is common practice to perform ovarian stimulation with either low-dose clomiphene citrate (usually 50-100mg daily) or FSH alone (usually 50-75 IU daily) with IUI treatment only when 1 or 2 dominant follicles are present of the day of hCG administration.

A recent report of 510 cycles of IUI with COH in an Australian IVF clinic described a live birth rate of 7% and multiple birth rate of 1% of IUI cycles started (Healy et al., 2003). In this study cycles were stopped if more than three follicles ≥14mm diameter developed. One triplet pregnancy (in 0.2% of cycles) occurred.

Key finding of the ART Review Committee:

- Since the introduction of ART and rapid technological advances, some ART procedures are now rarely used, i.e. GIFT, while other procedures such as ICSI are widely accepted.

Other

Preimplantation genetic diagnosis (PGD)

Preimplantation diagnosis is the application of genetic testing to a biopsy (usually single cell) of the embryo prior to replacement in the uterus. It may be performed for one of two reasons: to identify a specific genotype on the embryo or to screen the embryo for a lethal abnormality of the chromosomes prior to replacement. Testing of an embryo for a specific genotype is most commonly performed where the embryo has been identified in advance as having a high likelihood of a genotype associated with a specific disease state, and the couple wish to have the genetic testing performed prior to implantation to avoid either miscarriage or the need for termination of pregnancy that would be implicit part of antenatal testing after implantation. There are only a limited number of genetic tests in the MBS.

Screening of embryos for lethal aneuploidies is commonly performed in order to better select the ideal embryo for replacement and with the intention of improving the success rate of IVF. However there is little evidence from randomised controlled trials to support such a practice.
**Donor eggs/gametes**

Women may donate their oocytes to enable another woman to have a child. Use of donated oocytes is generally regarded as an effective treatment (NCCWCH, 2004). The oocyte donor normally undergoes a cycle of controlled ovarian hyperstimulation, then, following collection of the oocytes, donates the oocytes to a recipient – normally for fertilisation by the sperm of the recipient’s partner and replacement of the resulting embryo in the uterus of the recipient. This may be performed either when the recipient has no oocytes of her own – due to age, premature menopause or treatment with chemotherapy – or where the recipient’s own oocytes have proved to be unsatisfactory for treatment with IVF. In addition, donated oocytes may be used to avoid heritable genetic diseases.

There are many complex ethical issues associated with the use of donated oocytes, particularly the need for free and properly informed consent on the part of the donor as well as the use of donated oocytes in women at advanced age. Current MBS items provide for the use of donor embryos, oocytes and semen in relation to ART services.

**Donor sperm**

Men may donate their sperm for use by another man to achieve a pregnancy in his partner. Donated sperm may be used in cases where no usable sperm can be obtained from the testis or the couple may choose to have artificial insemination with donated sperm in preference to subjecting the female partner to controlled ovarian hyperstimulation and oocyte recovery. Donated sperm may also be used to achieve a pregnancy in women without a male partner.

**Gestational surrogacy**

Surrogacy involves the transfer of embryos arising from oocytes of a donor woman into the uterus of a different recipient. This situation is required when the donor of the oocytes has ovaries but no uterus (from congenital absence of the uterus or from hysterectomy) or the uterus is affected by a condition that precludes pregnancy (such as intrauterine adhesions or scarring).

The procedure was first performed in 1985 (Utian et al 1985), but few centres anywhere in the world have a large experience of this controversial procedure. Most nations either prohibit or do not utilise surrogacy, mainly as a result of cultural or religious attitudes, and the fear of financial exploitation or strong public opinion (Fasouliotis & Schnecker, 1999).

In Australia, surrogacy arrangements are not prohibited but are subject to individual state and territory legislation. Commercialisation of the surrogacy agreement is illegal; Medicare Benefits are not payable for this practice.
**Safety of ART**

Research about the safety of ART compared to spontaneous pregnancies is based on observational studies that compare outcomes for couples achieving pregnancy with ART against those achieving pregnancy spontaneously. As outlined below, these studies show that ART procedures are associated with greater health risks for the mother and child than spontaneous pregnancies. These risks are largely associated with the use of controlled ovarian hyperstimulation regimens and multiple embryo transfers in ART. For example, ovarian hyperstimulation syndrome (OHSS) and complications due to multiple pregnancies.

Other differences observed in antenatal and perinatal outcomes may reflect differences between fertile and subfertile couples, such as maternal age and paternal sperm abnormalities, rather than the independent effects of ART. However, research is ongoing to confirm or exclude an association between ART, in particular ICSI, and the risk of congenital malformations. A comparison of congenital malformation rates in ICSI and IVF offspring is considered in the results section of this report.

For infertile couples, ART may represent the only option to achieve a live birth without using donor gametes. Therefore this current review focuses on an assessment of the evidence about the relative safety and effectiveness of different ART procedures, rather than a comparison of ART versus spontaneous conception.

**Ovarian hyperstimulation syndrome (OHSS)**

OHSS is the most common and serious adverse event associated with controlled ovarian hyperstimulation. Other potential complications include pelvic pain and/or bleeding following oocyte retrieval, however these events are usually self-limited.

OHSS occurs in susceptible women who experience an excessive response to the drug treatment – resulting in increased oestrogen levels and ovarian size, increased capillary permeability and fluid imbalance. Onset occurs within nine days of oocyte retrieval, or later when it is usually associated with a pregnancy (Papanikolaou et al., 2005). In its mild form, symptoms include nausea, vomiting, diarrhoea and abdominal discomfort. More severe cases are associated with abdominal bloating. In its most severe form, severe fluid imbalance results in dehydration, breathlessness due to pleural effusions, and compromised cardiac, renal and liver function which can be life threatening. Treatment is based on rehydration, removal of excess fluid collections and prevention of thromboembolism.

The incidence of all OHSS cases in Australia is not known – as many cases will not require hospitalisation. In Australia and New Zealand, in 2002, 192 cases of OHSS requiring hospitalisation were recorded. These are likely to be the most severe cases. This represents 1.1% of 18,186 oocyte pick-ups (OPU) cycles and 0.5% of 36,483 treatment cycles including cycles with unsuccessful OPUs and embryo thaws, and donor insemination (Bryant et al., 2004).
Differences in the clinical criteria used to classify OHSS limit the indirect comparison of published rates. However, Australian and New Zealand rates appear to be broadly consistent with international experience. The ESHRE reported an overall risk of OHSS of 0.9% in 204,147 cycles of IVF and ICSI undertaken in 20 European countries in 2001 (Andersen et al., 2005).

Research is ongoing to determine the optimal regimens to prevent OHSS. A systematic review conducted by the NCCWCH for the NICE (NCCWCH, 2004) concluded that there was no evidence to support the superiority of either hMG, rFSH or urinary preparations in preventing OHSS.

There is, however, clear evidence that use of hCG for luteal support results in an increased risk of OHSS compared with either progesterone or no treatment (meta-analysis: overall incidence of OHSS with hCG 5% (n = 220) versus 0% (n = 193) with progesterone or no treatment) (Soliman et al., 1994). As a result, progesterone supplementation is normally preferable to exogenous hCG for luteal support in ART.

**Multiple pregnancy**

Multiple pregnancy is a common outcome of ART as a result of the practice of transferring more than one embryo in around 24.7% of fresh cycles and 28.8% of frozen IVF or ICSI cycles (Bryant et al., 2004). Multiple births occurred in 14.2% of all ART cycles in 2002 (Bryant et al., 2004). Intrauterine insemination with COH also exposes women to the risk of multiple pregnancy due to the maturation of multiple follicles to optimise the chance of fertilisation. Rates of multiple pregnancy following IUI are not recorded by ANZARD, and may vary according to the COH regimen and monitoring procedures used. Twin rates of around 20% and triplet rates of less than 6% following IUI with COH have been reported in Australia (Healy et al., 2003) and elsewhere (Guzick et al., 1999).

Multiple pregnancy increases the risk of adverse events for both mother and fetus, which can largely be attributed to the increased risk of preterm birth (Rao et al., 2004; Umstad & Gronow, 2003). These include a higher risk of low birth weight and perinatal mortality for infants. A retrospective cohort study of 304,466 twins and 17,696 higher order births delivered in the United States between 1995 and 1997 reported an increased risk of early death with each additional fetus (P <.001), with relative risk of 2.4 (95% CI: 2.2-2.6) for triplets compared to twins, 3.3 (95% CI: 2.5-4.4) for quadruplets, and 10.3 (95% CI: 5.0-21.4) for quintuplets (Salihu et al., 2003). Maternal complications include: anaemia, hypertension, polyhydramnios, gestational diabetes, antepartum and postpartum haemorrhage and caesarean section (Umstad & Gronow, 2003; ASRM, 2004). Multiple births also increase parenting stress (ASRM, 2004). Despite these risks, surveys have suggested that multiple pregnancies may not be viewed as an adverse outcome by women with fertility problems (NCCWCH, 2004).

The financial consequences of multiple pregnancy are high – due to the increased need for prolonged antenatal hospitalisation and neonatal care (Motohashi et al., 2004; Cassell et al., 2004; Koivurova et al., 2004; Lukassen et al., 2004). In the United Kingdom, guidelines and health service policies exist to restrict the number of embryos transferred to the uterus in order to minimise multiple births resulting from ART.
NICE guidelines recommend that prevention of iatrogenic multiple pregnancy involves the transfer of no more than two embryos for ART. The guidelines also recommend the judicious use of COH drugs and monitoring with ultrasound to chart follicular development by a specialist clinic (NCCWCH, 2004). The systematic review on which these guidelines were based did not find strong evidence that multiple pregnancy following ART resulted in poorer obstetric and neonatal outcomes than multiple pregnancy conceived spontaneously (NCCWCH, 2004). Another systematic review has suggested that the perinatal mortality rate for ART twins is lower than that for twins conceived spontaneously (Helmerhorst et al., 2004). This difference has been attributed to the higher rate of monozygotic twins conceived spontaneously and the increased rate of congenital abnormalities in monozygotic twins. A large registry study showed similar outcomes for dizygotic twins conceived by ART versus spontaneous conception (Pinborg et al., 2004b).

Despite the apparently similar multiple pregnancy rates, there is, however, a significant difference between stimulated IUI and IVF in this respect. In stimulated IUI, the response to stimulation can be variable and despite the adoption of careful ovulation induction protocols, there is still only a limited ability to control the rate of multiple pregnancies, particularly twins; the multiple pregnancy rate being as high as 20-25%. In contrast, in IVF, the multiple pregnancy rates can be very effectively controlled by limiting the number of embryos transferred. It is now being strongly argued overseas that SET is the way of the future (Barlow, 2005). In Sweden, state-funded IVF is now limited to SET – although other countries such as Belgium and the UK have taken a more flexible approach. A policy of SET in Australia would reduce multiple pregnancy rates effectively when used in association with IVF.

In Australia, no more than two embryos or oocytes can be transferred in one treatment in women less than 40 years of age (FSA RTAC, 2005). The RTAC recommends that no more than one fresh embryo or oocyte be transferred in the first attempt in women under 35 years of age.

**Key findings of the ART Review Committee:**

- There is a multiple pregnancy rate of 20-25% associated with IUI using COH.
- A policy of single embryo transfer with IVF is effective in controlling multiple pregnancy rates.

**Congenital malformations**

As maternal age increases, the risk of congenital malformations, particularly chromosomal abnormalities, increases. The frequency of trisomies increases exponentially after a maternal age of 35 years. Couples presenting for ART show a higher rate of chromosomal change than the general population (Clementini et al., 2005; Foresta et al., 2005). This has raised concerns that ART may lead to higher rates of congenital malformations, in particular following ICSI – where fertilisation is not achieved through a process of natural selection. The use of culture media to support fertilisation and embryo development has also been raised as potential causes of congenital abnormalities.
The NICE report found that, in general, the evidence about the relative safety of ART was ‘broadly reassuring’ and did not confirm a higher rate of congenital malformations, developmental abnormalities or cancer in children born following ART versus spontaneous pregnancies (NCCWCH, 2004). However, the authors also cautioned that there are no adequate randomised controlled trials to assess these issues. The observational studies identified were limited by their method of surveillance, sample size, participant attrition, length of follow-up, and lack of standardised definitions.

Furthermore, parental factors associated with infertility may confound the associations observed between the techniques used and congenital malformations. In light of these limitations, existing health technology assessment reports have all recommended long-term follow-up studies to further assess the safety implications for children born as a result of ART, in particular ICSI.

Although the NICE report concluded that there was insufficient evidence to determine whether ICSI is associated with chromosomal abnormalities in offspring of infertile couples with normal karyotypes, the authors cited a review of studies assessing fetal karyotypes (7 studies, n = 2139) which showed a significant increase in chromosomal abnormalities for ICSI offspring compared to the general neonatal population. These findings included an increase in the number of inherited structural abnormalities, most of which were inherited from infertile fathers.

The NICE report also cited observational studies that have suggested that children born after ART have a higher risk of syndromes due to genomic imprinting defects (abnormalities due to the silencing of a gene inherited from one parent). These include Beckwith–Wiedemann syndrome (BWS) which is characterised by overgrowth, enlarged tongue and abdominal wall defects. At least one Australian study has investigated this possible link (Halliday et al., 2004). This case control study (37 cases of BWS in Victoria between 1983 and 2002, and 148 matched controls) indicated that the relative risk was significantly increased in children conceived through IVF, however the uncertainty surrounding the estimate of effect was large (OR 17.8, 95% CI 1.8-432.9) (Halliday et al., 2004). The authors of the NICE report suggested that overall, the existing evidence was insufficient to confirm an association.

Since publication of the NICE report, several observational studies investigating various developmental outcomes with long-term follow-up of ARTs versus naturally conceived children have been published (Bonduelle et al., 2004; Leslie, 2004). A review of the congenital malformation rates in IVF versus ICSI offspring is presented as one of the research questions for this review (See Evaluation of ART section).

Cancer

Systematic reviews of the literature have found no association between COH regimens and cancer of the breast, thyroid, endometrium, cervix, colorectum or melanoma (NCCWCH, 2004; Klip et al., 2000; Brinton et al., 2005). However, much of the evidence is limited to small studies with short follow-up and poor reporting of the type and indications of drug use. Other limitations include the difficulty in separating the effect of other known risk-factors such as past reproductive history from the effect of the drugs used in ART (Brinton et al., 2005). Thus, further research with methodologically rigorous long-term prospective studies is required to fully investigate the potential links between COH regimens and cancer risk.
Other antenatal complications

The AHTAC review of ART (1998a) and the Alberta Heritage Foundation for Medical Research (Corabian, 1998b) both reported a higher risk of antenatal complications other than multiple pregnancies, such as pre-eclampsia (pregnancy hypertension) and placenta praevia (a placental abnormality which often leads to delivery by caesarean section) in women undergoing ART compared to women with spontaneous pregnancies. However, these risks may be associated with maternal age and obstetric history including prior pregnancy loss rather than an independent effect of ART.

The AHTAC report identified two trials using age and parity matched controls to assess the link between ART and antenatal complications, only one of which reported an association. Another systematic review has suggested that singleton pregnancies from ART have a worse perinatal outcome than non-ART singleton pregnancies (Helmerhorst et al., 2004). This question was not addressed by the recent NICE report.

A recent retrospective cohort study, based upon Australian ANZARD data, found that the transfer of fresh embryos and female-factor infertility were independently associated with preterm birth and low birth weight for singleton and twins born following ART (Wang et al., 2005). This finding was based upon 18,429 infants conceived by ART and born between 1996 and 2000, using multivariate logistic regression. The effect persisted following adjustment for maternal age and parity, cause of infertility, number of embryos transferred, type of embryos and type of procedure.

ART incident reporting

Unexpected incidents can occur in any system of medical management, for a wide range of possible reasons. Sometimes such incidents may have a negative impact on the outcome of treatment. Modern systems of risk management are geared to identify potential risk situations ahead of time and to react rapidly to reports of adverse events in order to minimise the likelihood of future recurrence. During ART treatment programmes, adverse incidents may occur during the clinical management or during embryo and gamete handling in the laboratory. Many of these potential events are well identified in the RTAC Code of Practice and recommendations are in place to prevent them. However, there is always the possibility that previously unidentified incidents may unexpectedly occur, and it is valuable to have in place a mechanism to disseminate information about such events and recommendations for future prevention.
Several individual Australian fertility programmes have such ‘in-house’ incident reporting principles in place, and consideration should be given to the establishment of a nation-wide system of laboratory and clinical incident reporting using de-identified data. It is acknowledged that there are many potential difficulties with setting up such a system, including conflicts between individual consumer privacy and other legal rights and the requirements of good quality control principles. Nevertheless, the potential benefits to quality and safety for the consumer are important and are in keeping with new directions on quality and safety within the health industry. Such an incident-reporting scheme could be set up within an appropriate accreditation body.

Impact on quality of life

Counselling is recommended for all couples accessing ART services in Australia (FSA RTAC, 2005). Infertility can be associated with feelings of stress, guilt, low self-esteem, anxiety and depression (Chen et al., 2004; van den Akker, 2005; Ragni et al., 2005b; El Messidi et al., 2004). The investigation and treatment of fertility problems can also be a cause of stress for infertile couples (Ragni et al., 2005b; van den Akker, 2005).

A prospective cohort study of educated and professional women undergoing IVF or GIFT in the USA found that women extremely concerned about the finances associated with the procedure had a high risk of not achieving a live birth (OR = 11.62, 95% CI 1.84, 73.59) (Klonoff-Cohen & Natarajan, 2004a).

Despite these stressors, there is evidence from surveys that infertile couples undergoing ART (Connolly et al., 1992) and those who have failed ART (Sydsjo et al., 2005) sustain stable relationships. Some studies have indicated that there are equal or lower levels of parenting stress in parents of IVF offspring than parents conceiving spontaneously (Glazebrook et al., 2004), including Australian evidence of positive adjustment in parents at five years following an IVF conceived birth (McMahon et al., 2003). Although it may be expected that deliveries with more than one infant result in increased parental stress (Ellison et al., 2005).
Societal Context and Consumer Perspectives

There is a scarcity of literature addressing the social, ethical, and legal issues emanating from ART. This presents specific challenges relating to public trust in science, ethical and cultural concerns, gender and the role of women. ART has become common practice in many countries today, regulated by established legislation, regulations or by committee-set ethical standards. However the law often has not responded adequately to the advances of ART. The inadequacy of standardised legislation and/or regulatory mechanisms, combined with the gap between new applications of the technology and the development of relevant law and regulatory mechanisms, has resulted in highly variable regulation internationally.

The rapid evolution and progress of these techniques has revealed certain social issues that have to be addressed. The traditional heterosexual couple, nowadays, is not considered by many as the only ‘ART appropriate patient’ since deviations from this pattern, for example, single women or same sex couples, have also gained access to these treatments. Genetic material donation, age limitation, selective embryo reduction, PGD, gestational surrogacy and cloning are interpreted differently in the various countries, as their definition and application are influenced by social factors, religion and law. Financial and emotional stresses are also often described in infertile couples.

The process of freezing eggs has been developed over the last decade and is regarded as a viable way to preserve fertility for women undergoing treatment for diseases such as cancer. More recently, however, ‘life-style’ egg freezing has emerged as an option for women who wish to delay motherhood – a process involving women that are not clinically infertile undergoing expensive and invasive ART treatment for proposed future supply of healthy eggs. This process, met by mixed views by infertility healthcare providers and consumers, contributes towards social and ethical considerations regarding access and equity of ART services.

In Australia, consumer support and information is provided by a wide-range of groups at both a national and state level. ACCESS, Australia’s National Infertility Network is an independent, non-profit, consumer-based organisation committed to being a national voice in promoting the wellbeing and welfare of infertile couples. It provides a range of member services that include fact sheets covering many aspects of infertility; support groups for people to share particular experiences (OPTIONS) and contact services; a list of infertility self-help groups established in regional areas around Australia; and also lists those clinics with RTAC accreditation. ACCESS also maintains links with other international associations through the International Consumer Support for Infertility (ICSI) network. ACCESS was also involved in promoting the lifting of the six-cycle limit on stimulated cycles of IVF in 2000. Specific support groups such as the Donor Conception Support Group for people contemplating the use of donor gametes/embryos and parents of children and children conceived using donor gametes or embryos.
**Decreasing birth rates and ageing mothers**

Fertility refers to the actual number of live births in a population relative to its size, and is generally measured by the total fertility rate (TFR). In *Recent fertility trends - Australian Social Trends* (2005)³ the ABS reports that Australia’s total fertility rate dropped below replacement level in 1976 and, to date, has further declined.

This means that the average number of babies born to an Australian woman throughout her reproductive life would not be enough to replace herself and her partner under the current age-specific fertility rates. Over the past ten years, falls in fertility rates for younger age groups (15-29 years) have not been fully offset by increases in fertility for older age groups (30-49 years).

Between 1993 and 1998, Australia experienced a slow decline in TFR from 1.86 to 1.76 babies per woman of reproductive age. In 1993, babies born to women aged 30 years or older accounted for 41% of the total fertility rate. By 2003, this proportion had risen to 51%.

There has been a trend towards women delaying births in Australia; the median age of all mothers who gave birth in 1993 was 28.9 years, rising to 29.5 years in 1998 and 30.5 years in 2003. The age at which women begin childbearing is a major determinant of lifetime family size.

Delayed childbearing reduces overall fertility in several ways:
- it reduces the period during which a woman can have children;
- women who start having children later in life tend to have fewer children during their childbearing years than those women who start earlier in life; and
- women also face the increased risk of childlessness due to delaying childbirth.

---

**Key findings of the ART Review Committee:**

- **There is an increasing trend in women delaying childbirth.**
- **Data show age specific fertility rates are decreasing and that women are presenting for the initial infertility consultation at an older age.**
- **Fertility treatment depends on the cause of infertility and individual circumstance.**

---

Access to ART services

In clinically relevant circumstances, access to a range of ART services is currently provided under Medicare without restrictions, and there are no regulations to limit the provision of services outside public funding. Due to the substantial and very advanced technological component of ART, some limitations are inevitable in relation to the equitable provision of health services to rural and remote areas; laboratory, analyses and technical support services are required to support ART facilities, even those offering a limited range of treatments.

It is not known where patients that are receiving ART treatment or those who desire access to ART treatment are located geographically, as the national data collection does not currently collect information on individual patients, but rather as episodes of treatment. This is a compelling reason to reorient the data collection to a patient-centred collection, in order to better predict demand for ART services and set up appropriate support networks for more satellite services. Figure 3 shows the distribution of treatment cycles by location for Australia and New Zealand (Bryant et al, 2004).

Figure 3. Distribution of treatment cycles by location for Australia and New Zealand

Key finding of the ART Review Committee:

- ART is technically complex and practices tend to be concentrated in areas where the necessary technical expertise and resources are available.
Funding of ART

Current reimbursement arrangement

Medicare and ART

Medicare provides financial assistance to eligible persons towards the cost of clinically relevant services that are included in the MBS and are provided by medical practitioners. A clinically relevant service is defined as one rendered by a medical practitioner that is generally accepted in the medical profession as being necessary for the appropriate treatment of the patient to whom it is rendered. In terms of ART, that means that Medicare benefits are not payable to single women or same sex couples who access ART treatments unless they are clinically infertile.

Medicare benefits are payable for ART services only where;

• the services are clinically relevant (i.e. generally accepted in the medical profession as being necessary for the appropriate treatment of the patient);
• undertaken in accordance with relevant state and territory laws; and
• not rendered in conjunction with surrogacy arrangements.

In 1990, items were introduced in the MBS to appropriately provide for ART services under Medicare. The ART items were structured and costed on the basis that an abandoned superovulated cycle, a natural cycle or a frozen embryo transfer would be significantly less than the cost and complexity of a full superovulated cycle (item 13200). Item 13203 covers both IUI and a failed superovulated cycle of less than 9 days and makes the utilisation of items difficult to interpret.

A list of the relevant MBS items and associated fee are provided in Table 1. Medicare does not provide for services such as embryo storage; blastocyst culture; ICSI; surgical sperm collection where ICSI is used; or assisted hatching.

Under Medicare, a successful ART intervention is defined as an intervention that leads to the live birth of a baby within a 12-month period of the ART intervention starting. Medicare data do not provide information about the success of an ART intervention at each stage.

For those patients who received privately provided ART and went on to deliver babies as private patients, a subset of data show:

• between 1 January 2000 and 31 December 2003, patients had an average of 3.3 interventions of ART;
• those women under the age of 42 years had an average of 3.2 interventions, while women over the age of 42 years had an average of 4.5 interventions;
• the average number of interventions per birth was 3; and
• per birth, women under the age of 42 years had an average of 2.9 interventions, while women over the age of 42 years had an average of 4.1 interventions.

---

4 This data subset is created by tracking a claim for Item 13209 (planning of a cycle) to a claim for Item 16519 (management of delivery) - or similar item - within a 12-month period.
### Table 1. Medicare Benefits Schedule Items for ART

<table>
<thead>
<tr>
<th>MISCELLANEOUS</th>
<th>ASSISTED REPRODUCTIVE SERVICES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GROUP T1 - MISCELLANEOUS THERAPEUTIC PROCEDURES</strong></td>
<td><strong>SUBGROUP 3 - ASSISTED REPRODUCTIVE SERVICES</strong></td>
</tr>
<tr>
<td><strong>ASSISTED REPRODUCTIVE SERVICES</strong> (such as <em>in vitro</em> fertilisation, gamete intrafallopian transfer or similar procedures) involving the use of drugs to induce superovulation, and including quantitative estimation of hormones, ultrasound examinations, all treatment counselling and embryology laboratory services but excluding artificial insemination or transfer of frozen embryos or donated embryos or ova or a service to which item 13203, 13206 or 13218 applies - being services rendered during 1 treatment cycle, if the duration of the treatment cycle is at least 9 days. <strong>(See paragraph T1.3 of explanatory notes to this category)</strong></td>
<td><strong>OVULATION MONITORING SERVICES</strong>, for superovulated treatment cycles of less than 9 days duration and artificial insemination - including quantitative estimation of hormones and ultrasound examinations, being services rendered during 1 treatment cycle but excluding a service to which item 13200, 13206, 13212, 13215 or 13218 applies. <strong>(See paragraph T1.3 of explanatory notes to this category)</strong></td>
</tr>
<tr>
<td>Fee: $1,730.30 Benefit: 75% = $1,297.75 85% = $1,668.80</td>
<td>Fee: $432.60 Benefit: 75% = $324.45 85% = $371.10</td>
</tr>
<tr>
<td><strong>ASSISTED REPRODUCTIVE SERVICES</strong> (such as <em>in vitro</em> fertilisation, gamete intrafallopian transfer or similar procedures), using unstimulated ovulation or ovulation stimulated only by clomiphene citrate, and including quantitative estimation of hormones, ultrasound examinations, all treatment counselling and embryology laboratory services, but excluding artificial insemination, frozen embryo transfer or donated embryos or ova or treatment involving the use of drugs to induce superovulation being services rendered during 1 treatment cycle but only if rendered in conjunction with a service to which item 13212 applies. <strong>(See paragraph T1.3 of explanatory notes to this category)</strong></td>
<td>**PLANNING and MANAGEMENT of a referred patient by a specialist for the purpose of treatment by assisted reproductive technologies including <em>in vitro</em> fertilisation, gamete intrafallopian transfer and similar procedures, or for artificial insemination payable once only during 1 treatment cycle. <strong>(See paragraph T1.3 of explanatory notes to this category)</strong></td>
</tr>
<tr>
<td>Fee: $741.50 Benefit: 75% = $556.15 85% = $680.00</td>
<td>Fee: $74.05 Benefit: 75% = $55.55 85% = $62.95</td>
</tr>
<tr>
<td><strong>OOCYTE RETRIEVAL</strong> by any means including laparoscopy or ultrasound guided ova flushing, for the purposes of assisted reproductive technologies including <em>in vitro</em> fertilisation, gamete intra-fallopian transfer or similar procedures - only if rendered in conjunction with a service to which item 13200 or 13206 applies <strong>(Anaes.).</strong> <strong>(See paragraph T1.3 of explanatory notes to this category)</strong></td>
<td>**TRANSFER of EMBRYOS or both ova and sperm to the female reproductive system, by any means but excluding artificial insemination or the transfer of frozen or donated embryos - only if rendered in conjunction with a service to which item 13200 or 13206 applies <strong>(Anaes.).</strong> <strong>(See paragraph T1.3 of explanatory notes to this category)</strong></td>
</tr>
<tr>
<td>Fee: $315.20 Benefit: 75% = $236.40 85% = $267.95</td>
<td>Fee: $98.90 Benefit: 75% = $74.20 85% = $84.10</td>
</tr>
<tr>
<td><strong>PREPARATION AND TRANSFER</strong> of frozen or donated embryos or both ova and sperm, to the female reproductive system, by any means and including quantitative estimation of hormones and all treatment counselling but excluding artificial insemination services rendered in 1 treatment cycle and excluding a service to which item 13200, 13203, 13206, 13212 or 13215 applies <strong>(Anaes.).</strong> <strong>(See paragraph T1.3 of explanatory notes to this category)</strong></td>
<td><strong>PREPARATION OF SEMEN</strong> for the purposes of assisted reproductive technologies or for artificial insemination. <strong>(See paragraph T1.3 of explanatory notes to this category)</strong></td>
</tr>
<tr>
<td>Fee: $741.50 Benefit: 75% = $556.15 85% = $680.00</td>
<td>Fee: $45.15 Benefit: 75% = $33.90 85% = $38.40</td>
</tr>
<tr>
<td>**SEmen, collection of, from a patient with spinal injuries or medically induced impotence, for the purposes of analysis, storage or assisted reproduction, by a medical practitioner using a vibrator or elect-ejaculation device including catheterisation and drainage of bladder where required. **(Fee: $196.80 Benefit: 75% = $147.60 85% = $167.70)</td>
<td>**SEmen, collection of, from a patient with spinal injuries or medically induced impotence, for the purposes of analysis, storage or assisted reproduction, by a medical practitioner using a vibrator or elect-ejaculation device including catheterisation and drainage of bladder where required, under general anesthetic, in a hospital or approved day-hospital facility <strong>(Anaes.).</strong> **(Fee: $353.70 Benefit: 75% = $265.30 85% = $300.65)</td>
</tr>
</tbody>
</table>

5 ART items and explanatory notes – as appears in the 1 November 2005 Medicare Benefits Schedule. Please note: further explanatory notes appears with the items, but are not included here.
Prior to 1 November 2000, patients were limited to a maximum of six stimulated interventions using item 13200. The six-cycle limit for item 13200 was introduced at that time in response to evidence that about 90% of women who become pregnant by ART do so within four stimulated cycles. Currently, a limit is not applicable to ART services as provided under Medicare.

Following the lifting of the six-intervention limit, the impact on growth of services has been minimal. Tables 2 and 3 provide details of the number of women claiming item 13200 up to six, and more than six, times in the 2002 calendar. Table 2 provides an age breakdown and indicates that women aged 35 years or more are far more likely to claim item 13200 more than six times in a lifetime.

Table 2. Frequency of treatment cycles undertaken (including current cycle) for fresh non-donor ART treatment cycles, Australia 2002

<table>
<thead>
<tr>
<th>Number of treatment cycles undertaken</th>
<th>Frequency</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-6</td>
<td>17,068</td>
<td>94.7%</td>
</tr>
<tr>
<td>7+</td>
<td>833</td>
<td>4.6%</td>
</tr>
<tr>
<td>Missing</td>
<td>114</td>
<td>0.6%</td>
</tr>
<tr>
<td>Total</td>
<td>18,015</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 3. Frequency of treatment cycles undertaken (including current cycle) for fresh non-donor ART treatment cycles by maternal age group, Australia 2002

<table>
<thead>
<tr>
<th>Number of treatment cycles undertaken</th>
<th>&lt;35 years</th>
<th>Per cent</th>
<th>35-39 years</th>
<th>Per cent</th>
<th>40+ years</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td></td>
<td>Frequency</td>
<td></td>
<td>Frequency</td>
<td></td>
</tr>
<tr>
<td>1-6</td>
<td>7,563</td>
<td>97.3%</td>
<td>5,780</td>
<td>94%</td>
<td>3,704</td>
<td>91%</td>
</tr>
<tr>
<td>7+</td>
<td>145</td>
<td>1.9%</td>
<td>342</td>
<td>5.6%</td>
<td>345</td>
<td>8.5%</td>
</tr>
<tr>
<td>Missing</td>
<td>65</td>
<td>0.8%</td>
<td>29</td>
<td>0.5%</td>
<td>20</td>
<td>0.5%</td>
</tr>
<tr>
<td>Total</td>
<td>7,773</td>
<td>100%</td>
<td>6,151</td>
<td>100%</td>
<td>4,069</td>
<td>100%</td>
</tr>
</tbody>
</table>

In the four-year period between 1 January 2000 and 31 December 2003, 50,440 women had at least one type of intervention. The average number of interventions per woman during this period was 3, with an average of 1.9 interventions per annum.

ART can involve many different medical interventions and each woman may undergo different interventions to achieve conception and live birth. Although the range and number of items claimed for one intervention differ, a Medicare benefit is eligible for the planning of every intervention, indicated by Item 13209. A claim for this item is used as a reliable indicator that a woman has commenced an ART intervention. Item 13209 can also be used in combination with the other ART items to monitor the number of interventions commenced and to measure the success of ART treatment.

Data on the number of treatment cycles reported to ANZARD for ART treatment undertaken in 2002; based on the data element n_13200 cycle of stimulate treatment: the number of billed Australian Medicare item 13200 (excludes transfer of frozen embryo and donor embryos).
ART and the Pharmaceutical Benefits Scheme (PBS)

Depending on whether an intervention is stimulated or not, and the individual’s clinical circumstances, the costs associated with pharmaceuticals will vary. At July 2005, estimated PBS expenditure for an average intervention is approximately $1,620\(^7\). These costs are indicative, as different combinations and dosages of drugs will be selected according to individual patient ART treatment regimes.

Costs associated with ART under Medicare

Medicare data can only reliably show what rebates were received by the women during this period and their out-of-pocket costs for the doctors’ charges, where a Medicare item was claimed. Under Medicare, the Australian Government subsidises 75% of the MBS fee for services provided to private patients admitted to hospitals and day-hospital facilities, with private health insurance funds being required to pay the ‘gap’ between the benefit and the MBS fee for insured patients. For private services provided outside of hospital, Medicare subsidises 85% of the MBS fee.

A government-funded safety net to cover all Australians against high out-of-pocket medical costs outside the hospital system was introduced on 12 March 2004. The Medicare safety net arrangements cover all out-of-hospital Medicare eligible services. Out-of-hospital services are defined as those services provided to non-admitted patients, such as services conducted in doctors’ rooms, private clinics and private hospital emergency departments.

Government expenditure for ART services under Medicare

Australian Government expenditure on ART almost doubled from $25.6 million in calendar year 1991, to $50 million in calendar year 2003.

Prior to the introduction of the EMSN in March 2004, patients were required to pay a significant percentage of costs for ART services covered by Medicare. The EMSN has not impacted on patient payments for non-MBS rebated items, e.g. Cryostorage or ICSI. Under the EMSN, the Australian Government now meets 80% of out-of-pocket costs for ART services provided out of hospital once a set annual threshold is reached.

From calendar year 2003 to 2004, Medicare expenditure for ART treatment increased by 57%, from $50 million to $78.6 million; from 2004 to 2005, Medicare expenditure increased by 38% to $108.4 million, a 117% increase over two years.

For calendar year 2003 to 2004, PBS expenditure for ART treatment increased by 18% from $37.1 million to $43.9 million; and from 2004 to 2005, PBS expenditure increased by 9% to $47.7 million, a 29% increase over two years.

For the six-year period, from 1 January 2000 to 31 December 2005, the Australian Government spent, via Medicare, $584.6 million on ART, as follows in Table 4:

---

\(^7\) Pharmaceutical Benefits Branch, Department of Health and Ageing 2006
Table 4. Australian Government expenditure on assisted reproductive services 2000-2005

<table>
<thead>
<tr>
<th>Calendar Year</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>Total (2000-05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBS</td>
<td>$39.3</td>
<td>$43.3</td>
<td>$46.0</td>
<td>$50.0</td>
<td>$78.6</td>
<td>$108.4</td>
<td>$365.6</td>
</tr>
<tr>
<td>PBS</td>
<td>$27.0</td>
<td>$31.6</td>
<td>$31.7</td>
<td>$37.1</td>
<td>$43.9</td>
<td>$47.7</td>
<td>$219.0</td>
</tr>
<tr>
<td>Annual total</td>
<td>$66.3</td>
<td>$74.9</td>
<td>$77.7</td>
<td>$87.1</td>
<td>$122.5</td>
<td>$156.1</td>
<td>$584.6</td>
</tr>
</tbody>
</table>

All figures in millions

The original Medicare safety net covers the difference between the Medicare benefit paid and the schedule fee for out-of-hospital services. Under this safety net, only the gap between the Medicare benefit and the schedule fee count towards reaching the original Medicare benefits safety net threshold. Under the extended Medicare safety net, Medicare meets 80% of out-of-pocket costs for Medicare-claimable services provided outside hospital, once annual thresholds are reached.

Out-of-pocket costs are defined as the difference between the fees charged by the doctor and the Medicare benefits paid. It should be noted that the safety net covers out-of-pocket expenses for the specific Medicare service, but does not cover other fees or charges levied by the doctor that are not directly associated with the service provided or are not claimable through Medicare.

Previously, high costs associated with ART services meant that some patients could not afford ART or were limited in the services they could access. Since the introduction of the extended Medicare Safety Net, patients are now covered for 80% of out-of-pocket expenses for ART services. Many couples become eligible for the safety net in the first cycle and then 80% of out-of-hospital expenses are reimbursed for the remainder of the calendar year. It could be that the EMSN is assisting patients to access ART who in the past could not afford these services.

Yet, the increase in the number of patients accessing services by no means accounts for the 117% increase in costs in the period 2003-2005. Over the same period, there were 21% more patients and 26% more services (see Tables 5 and 6).

Table 5. ART services provided under Medicare by patient and service number 2000-2005

<table>
<thead>
<tr>
<th>Calendar Year</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>Total (2000-05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>19,678</td>
<td>20,665</td>
<td>21,421</td>
<td>22,869</td>
<td>24,818</td>
<td>27,663</td>
<td>77,675</td>
</tr>
<tr>
<td>No. services</td>
<td>131,004</td>
<td>135,187</td>
<td>139,086</td>
<td>145,517</td>
<td>159,181</td>
<td>182,834</td>
<td>892,809</td>
</tr>
</tbody>
</table>

Date of processing data
Table 6. Increases in numbers of patients and number of services of each year compared with preceding year

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>5%</td>
<td>3.7%</td>
<td>6.8%</td>
<td>8.5%</td>
<td>11.5%</td>
</tr>
<tr>
<td>No. Services</td>
<td>3.2%</td>
<td>2.9%</td>
<td>4.6%</td>
<td>9.4%</td>
<td>14.9%</td>
</tr>
</tbody>
</table>

It is clear much of the increase in expenditure must be due mainly to some combination of an increase in total charges and transfer of out-of-pocket gaps to MBS items numbers, as well as lesser factors such as service growth, indexation and the introduction of new technologies.

While it is impossible to determine the precise impact of the introduction of the EMSN with regards to the shift relating to the out-of-pocket costs from the patient to the Australian Government, the net effect would appear to be a profound increase in government expenditure in this area.

**Key findings of the ART Review Committee:**

- *Data show that women aged 35 years and over access more ART treatment cycles.*
- *Australian Government expenditure on ART has doubled since the introduction of the extended Medicare Safety Net.*
- *Current MBS items do not reflect current ART practice.*

**International funding models**

Unlike other countries, Australia currently provides public funding for an unlimited number of ART cycles for women eligible to receive benefits under Medicare and appears to be one of the only countries in the world to do so. A comparison of international ART funding models is at Appendix B.

Most developed countries have recognised infertility as a medical condition and have made provisions for infertility treatment within national health policies, with Australia, Austria, Denmark, Finland, France, Germany, Iceland, the Netherlands, Norway and Sweden providing public funding for IVF as of June 2000 (Katz et al., 2002). However, the regulation of practice, policies and access to ART varies internationally, reflecting differences in socio-cultural values and health service resources.

Legislation governing practice and access to ART has been implemented and developed in countries such as Australia, New Zealand, the United Kingdom, Canada, Sweden and Germany, to regulate activities associated with ART in clinical practice and research (WHO, 2001). In particular countries, this has led to the establishment of specialist committees and agencies which are responsible for licensing, inspecting and enforcing activities controlled under the Act (HFEA 2005/2006, Health Canada 2004).
Key variations in policies in developed countries include: restrictions to ART funding according to the women’s age or prior number of failed cycles; and the maximum number of embryos transferred at one time.

Many countries place restrictions on public funding for ART based on women’s age. In the United Kingdom (UK) and Germany, women must be under 40 years of age to be eligible for reimbursement. In the UK, women must also be clinically assessed as having a reasonable chance of responding to treatment (i.e. not approaching menopause) and priority may be given to couples without children living with them, while in New Zealand funding for infertility services is provided to couples assessed as meeting the agreed eligibility criteria under referral and assessment guidelines (HFEA 2005/2006, New Zealand Ministry of Health, 2005). In Canada, IVF is only provided for women with bi-tubal obstruction in the province of Ontario (Health Canada, 2004).

From October 2004 in New Zealand, additional public funding has been provided for a second treatment cycle to those eligible patients whose first treatment cycle does not result in a live birth (New Zealand Ministry of Health, 2005). From April 2005 in the UK, all women aged between 23 and 39 years are eligible to receive one free IVF cycle on the National Health System (HFEA 2005/2006). As a result of health care reform in Germany, from January 2004 only three rather than four ART cycles have been partially covered by health insurance.

Medical, social and economic concerns associated with twins and higher order pregnancies have resulted in guidelines to limit the number of embryos transferred in ART treatments. Many ART centres in Australia and internationally limit the number of embryos transferred to two as a standard of care, and some countries are introducing legislation regarding the number of embryos to be transferred. In Australia, it is recommended that no more than two embryos or oocytes be transferred in one treatment in women less than 40 years of age (FSA RTAC, 2005).

In the UK, the HFEA restrict embryo transfer to two embryos. In contrast, in Sweden, public reimbursement is provided for an unlimited number of SET cycles, but only up to four cycles if more than one embryo is transferred.

In the United States of America, the high national rate of multiple births has been attributed to the limited availability of insurance coverage for ART (ASRM, 2004). The high cost of the procedure is suggested to serve as an incentive to the transfer of a higher number of embryos to maximise pregnancy rates (Reynolds et al., 2003). The Society for Assisted Reproductive Medicine (SART) and the ASRM have produced guidelines on the number of embryos to be transferred in ART cycles (SART & ASRM, 2004b). These guidelines recommend that no more than two embryos be transferred in women under 35 years or age.

In Australia, the NHMRC and the FSA are funding the Australian Study of Single Embryo Transfer (ASSET). This is a multicentre double-blind randomised controlled trial to compare the outcomes of pregnancy following the transfer of either a single embryo or two embryos in an optimal group of patients undergoing IVF with or without ICSI. Subjects in the trial are women less than 35 years of age with at least three high quality embryos. Other policies regarding the use of donor oocytes and sperm, surrogacy, embryo selection, cryopreservation and preimplantation genetic diagnosis also vary among countries.
Key findings of the Review Committee:

- Most countries limit access to publicly funded ART services.
- Australia appears to be unique in not limiting access to funding for ART services.
- The cost of providing ART in Australia is broadly comparable with those overseas, including countries such as the United Kingdom, where the predominant service provision model is through the public sector.
Regulation of ART

In Australia, there is currently no national legislation covering the regulation of ART clinical practice. Legislation regarding ART is determined individually by each state and territory and the use of MBS ART items are subject to individual state or territory legislation\(^8\). Therefore, laws and practices regarding ART services, including in relation to access, differ by region.

State and territory legislation relating to the provision of ART services is underpinned by a national system of accreditation of individual fertility units by the RTAC of the FSA. This is consistent with the *Ethical Guidelines on Assisted Reproductive Technology 2004*, produced by the National Health and Medical Research Council (NHMRC).

The NHMRC has a policy to review its guidelines and advisory publications every five years. In September 2001, the Australian Health Ethics Committee (AHEC) – a principal committee of the NHMRC – undertook to revise the NHMRC’s *Ethical Guidelines on Assisted Reproductive Technology* that were issued in 1996 and were re-issued in 2004. The NHMRC act enables NHMRC to issue guidelines, however it does not give NHMRC the mandate to oversee compliance with its guidelines.

While RTAC accreditation is not a mandatory requirement for facilities that provide ART services in Australia, those facilities using embryos are required to be RTAC-accredited under the *Research Involving Human Embryos Act, 2002*. Where no legislation exists in a state or territory to regulate the provision of ART services, the default position for regulation is voluntary accreditation with RTAC. RTAC is funded by, and draws its membership from, relevant health care providers.

ART services are subject to any provisions in the following:

- *Health Insurance Act, 1973*
- *Research Involving Human Embryos Act, 2002*
- *Infertility Treatment Act, 1995 (Victoria)*
- *Reproductive Technology Act, 1988 (South Australia)*
- *Human Reproductive Technology Act, 1991 (Western Australia)*

If ART facilities are not RTAC accredited, they may still provide ART services – other than IVF – in accordance with the various acts as listed above. There is no mechanism in place to monitor the practices of non RTAC accredited facilities providing non IVF services such IUI. The quality of service provision in these facilities is thus unknown. The introduction of national, mandatory accreditation would ensure that IUI is practised to measurable and safe standards, reducing the risk of adverse health outcomes.

---

\(^8\) *Health Insurance Regulations 2004*, Part 2.2: ‘An item … does not apply to a service provided in contravention of a law of the Commonwealth or of a state or territory’.
Victoria, South Australia and Western Australia have legislation that regulates access to ART services. Victorian and South Australian laws restrict access to IVF treatment to women who are married or in a de facto relationship with a man. Western Australia recently amended its act to remove these restrictions. In July 2000, the Federal Court ruled that the *Victorian Fertility Treatment Act, 1995* was inconsistent with Section 22 of the *Sex Discrimination Act, 1975*, which prohibits discrimination in the provision of goods and services on the grounds of sex or marital status. The ruling was in response to a challenge to the Victorian act lodged in the Federal Court by a clinician practising in Victoria on behalf of a single woman who wished to access IVF treatment. The Federal Court decision rendered invalid the restrictions in the Victorian act and effectively any such restrictions in the legislation of other jurisdictions.

There is little available information/statistics on same sex couples and single women accessing reproductive services. Reimbursement through Medicare is dependent upon the presence of a medical condition determining a clinical need and not dependent upon partner status.

**Accreditation of ART**

The Code of Practice for ART Units has been developed by the RTAC of the FSA. The purpose of the RTAC Code of Practice is to set and maintain minimum standards for clinics or centres offering ART services, and to encourage continuous improvement in the quality of care offered to people accessing fertility treatment in Australia and New Zealand.

The code was first introduced in 1986, when the FSA produced a series of standards as a guide for ART units. In 1987, RTAC was established and added explanatory notes to many of the original standards drawn up by the FSA. This initial code was revised in 1992, 1997 and 2001, and has been further developed and extensively revised in 2004.

The RTAC Code of Practice is to be observed in units involved in the treatment of patients with artificial insemination, surrogacy, IVF and related techniques, and in all procedures involving donated gametes or embryos. This is a very detailed Code of Practice that demands a high standard of adherence by ART units.

**Key findings of the Art Review Committee:**

- *While, under national legislation, accreditation of ART practices is required for treatments involving the use of human embryos, there is no requirement for accreditation for IUI services.*
- *States and territories vary in the requirement of accreditation of ART services.*
ART and the Therapeutic Goods Administration (TGA)

The Therapeutic Goods Administration (TGA) is responsible for administering the Therapeutic Goods Act 1989 with the overall objective of ensuring the quality, safety, efficacy and timely availability of therapeutic goods, including complementary medicines. The TGA maintains the Australian Register of Therapeutic Goods (ARTG) which includes details of all therapeutic goods that are imported into, supplied in, or exported from, Australia.

It is a legal requirement that unless specifically exempt or excluded, all therapeutic goods must be included in the ARTG before their importation, exportation, manufacture, or supply. In general, only therapeutic goods that have been assessed or evaluated by the TGA are included in the ARTG. None of the complementary medicines currently included in the ARTG are classified as an ‘Assisted Reproductive Technology’. The use of complementary medicines by individual practitioners for ART is unknown to the TGA as the practices of healthcare practitioners is currently governed and controlled by state and territory governments.

Australia has codes of good manufacturing process and quality system requirements for the manufacture of medicinal products, sunscreen products, human blood and tissues, active pharmaceutical ingredients and medical devices – for example, culture media used in ART treatment. Each code/quality system sets out requirements relating to quality management, personnel, premises and equipment, documentation, production, quality control, contract manufacture and analysis, complaints and product recall and self-inspection.

Complementary Medicine and ART

Complementary and alternative medicine is a group of diverse medical and healthcare systems, practices, and products that are not presently considered to be part of conventional medicine (National Center for Complementary and Alternative Medicine). Some evidence exists that patients are increasingly using complementary medicine for many medical conditions including the treatment of infertility. In the UK this was found to be as high as 40% of women and 13% of men using ART services (Coulson and Jenkins, 2005).

Commonly used complementary medical therapies include herbal remedies such as traditional Chinese therapies, acupuncture, reflexology, vitamin and selenium supplementation, aromatherapy, homeopathy and massage.

Overall, reviews of the use of complementary medicine in the treatment of couples with infertility (NICE Clinical Guidelines, 2004; Coulson and Jenkins, 2005) have found little high quality evidence supporting its use. As the use of complementary medicine appears reasonably high in couples undertaking ART there is a need to inform people that the effectiveness and safety of complementary medicine is unknown and that further research is required before such interventions should be recommended.
Outcomes of ART

Data collection

The Australian Institute of Health and Welfare (AIHW) National Perinatal Statistics Unit (NPSU) is the data custodian for the Australian and New Zealand Assisted Reproduction Database (ANZARD). ANZARD was jointly set up by the FSA and the NPSU, implemented in 2002, and the data are held in accordance with the AIHW act. Data for ANZARD are provided by the individual ART clinics in Australia and New Zealand.

The NPSU is primarily funded by the AIHW, with additional funding from the University of New South Wales and the Sydney Children’s Hospital. The core funding is supplemented by external research grants and contract work. The ANZARD is also funded through a block grant from the Fertility Society of Australia. NPSU is responsible for annual reporting of ART treatment and pregnancy outcomes, for providing national and clinic data for use by RTAC and for developing and maintaining the ANZARD collection.

The ANZARD is based upon treatment cycles as reported by all IVF and GIFT centres in Australia to NPSU on an annual basis. ANZARD is not a register of individual women undergoing ART and does not contain named data. Treatment cycle data are not linked and therefore if a woman undergoes three cycles in one year she will be included in the data collection three times as independent records, rather than once as one woman having three treatment cycles.

As the population is treatment cycles rather than women, the design of the database precludes reporting on patient-based statistics. There is potential to improve the scope of the ANZARD to monitor the number of stimulated cycles by reorienting ANZARD to be a data set of women undergoing ART rather than a data collection of treatment cycles.

A further limitation of the ANZARD is that recording of perinatal outcomes is sometimes based on personal recall by the women themselves. The lack of a systematic approach to linking ART treatment data with perinatal outcome data leads to an incomplete data set with, potentially serious, under-reporting of adverse perinatal events.

Aggregated Medicare data on a range of services are frequently provided to the AIHW and there is potential for the department to liaise with the AIHW to simplify and confirm arrangements and ownership issues between the organisations, particularly with the implementation of the 2005 Memorandum of Understanding between the department and the AIHW for the provision of information services.

Key findings of the ART Review Committee:

- Data as currently collected, while allowing cycle success to be recorded, do not allow success per woman to be collected.
- Data on perinatal outcomes following treatment with ART are incomplete and are subject to collection errors.
Methodological issues

This section discusses issues relevant to the interpretation of evidence about the safety, effectiveness and cost-effectiveness of ART to clinical practice and includes factors that have been shown to predict ART success, treatment discontinuation rates and spontaneous pregnancy rates in couples who have been classified as infertile and received ART treatment.

Predictors of ART success

ART success rates fall with increasing maternal age (Bryant et al., 2004). Observational studies have also indicated that success rates may vary according to the primary diagnosis, past reproductive history, duration of infertility and number of previous ART cycles (Kupka et al., 2003a; NCCWCH, 2004; Templeton et al., 1996a).

ART success also varies according to the underlying diagnosis (Bryant et al., 2004), although estimates of relative effectiveness in different patient groups is not established. In couples with severe male factor infertility, IVF success rates may be so low that ICSI may be the only viable means for conception.

In studies comparing the outcomes of different ARTs where the distribution of the underlying predictive factors are not equivalent in the groups compared, results will be confounded by these differences.

Discontinuation rate

Observational studies have estimated that around 50% of women discontinue ART treatment after an unsuccessful cycle with higher discontinuation rates observed in older women (NCCWCH, 2004; Olivius et al., 2004). A prospective cohort study of 450 Swedish couples who started IVF treatment and did not achieve a live birth reported that 54% discontinued the treatment before receiving the three cycles offered under subsidy. The investigators reported that a majority of these discontinuations were due to the psychological burden of treatment (26%) or a poor prognosis (25%). Other reasons for discontinuation included spontaneous pregnancy (19%), physical burden (6%) and serious disease (2%) (Olivius et al., 2004).

Spontaneous pregnancies

In the UK, 84% of couples in the general population will conceive within one year if they do not use contraception and have regular sexual intercourse. Of those who do not conceive in the first year, about half will do so in the second year, giving a cumulative pregnancy rate of 92% (NICE). While these are UK data it is expected that Australian couples would have similar levels of fertility.

It is clear that ART is assisting couples to conceive when they would never do so naturally, or conceive more quickly than they would do naturally. It is usually not possible to predict which couples will fall into which category. Undoubtedly, some couples would conceive spontaneously without ART if they continued trying for a prolonged period of time.
Despite a diagnosis of infertility, spontaneous pregnancies may still occur with rates of between 7 and 21% observed in couples who are being or are being treated with ART (Hennelly et al., 2000a; Kupka et al., 2003b). Spontaneous pregnancies are more likely in younger women (Hennelly et al., 2000b) and may vary according to the criteria used to select couples for ART and the underlying cause of infertility. Many of those couples who fail to achieve pregnancy after a year of unprotected intercourse are not absolutely infertile or sterile, but relatively infertile; many will eventually become pregnant.

Therefore, consideration needs to be given to what is an acceptable time limit of natural attempts at conception before proceeding to ART, with obvious need to take the age of the female partner into consideration.

**Comparison of Australian and international ART outcomes**

There are inherent problems involved in analysing ART outcomes. These difficulties can largely be attributed to initial difficulty in accurately measuring an outcome. The issue has been addressed to different extents internationally. In the United States, the SART has worked together with the Centres for Disease Control and Prevention (CDC) to identify variables and outcomes to be collected, and definitions of these variables and outcomes. While progress has been made in reporting outcomes, outstanding issues remain, including variance in patient population and selection from program to program, delays in reporting clinic-specific results, programs using varying first line treatment protocols and combinations of treatments, individual patient values and preferences, and programs transferring varying numbers of embryos (Advanced Reproductive Care Inc, 2005).

Multiple and varying definitions for, and terminology associated with, ART result in variances in reporting a measurable outcome, such as a live birth. For example, in Australia the ANZARD does not include data for live births resulting from ovulation induction using gonadotrophins and artificial insemination using partner’s sperm, as a large proportion of this treatment is conducted outside identifiable IVF units.

Further difficulty associated with outcomes measurements includes accounting for unwanted outcomes such as spontaneous miscarriage, multiple births, congenital abnormalities, and other long-term disabilities (Advanced Reproductive Care Inc, 2005). In Australia, national registry data on treatments and pregnancy report outcomes and success rates of all ART treatment cycles carried out in Australia. However, data on outcomes such as complications and neonatal morbidity and mortality is limited as ongoing patient care is generally provided by non-ART practitioners. For pregnancies where follow up is successful, data are reliant on self-reporting by patients which may result in unknown inaccuracies (Bryant et al., 2004).

In light of variances in national and international outcome measures and reporting, and associated health policies, current practice and guidelines, key biases must be recognised and appropriate adjustments made.
Key findings of the ART Review Committee:

- ART outcomes in Australia are as good as, if not better, than outcomes overseas.
- Use of inconsistent terminology by healthcare providers including significant variation in the presenting ART treatment outcomes, causes significant difficulties in interpretation for the consumer.
Evaluation of ART

A systematic literature review was undertaken by the NHMRC Clinical Trials Centre (NHMRC CTC); this report in its entirety is at Appendix A.

The clinical questions considered by the ART Review Committee are outlined below. These were considered to be the main clinical questions of relevance when considering ART. The following section of the report considers the published evidence for each of the clinical questions. The literature findings are summarised and the ART Review Committee’s discussion of the findings are outlined.

The ART Review Committee formulated five clinical questions to be addressed in this review *a priori* by describing the relevant population, intervention, comparator and outcomes. The questions were addressed by reviewing international Health Technology Assessment (HTA) reports published since 1997; conducting a systematic literature search and undertaking a cost-effectiveness analysis.

The research questions of the ART Review Committee were as follows:

**Primary question**

1. What is the safety, effectiveness and cost-effectiveness of 4 stimulated treatment cycles with *in vitro* fertilisation compared with 3 stimulated treatment cycles in women aged <35 years, 35-39 years and ≥40 years, or by duration of infertility, assuming all fresh cycles (OR 1 fresh, 2 frozen embryo transfers per stimulated treatment cycle if rates available)?
   - 3 versus 2 cycles
   - 2 versus 1 cycle
   - 6 versus 5 cycles
   - 5 versus 4 cycles

**Secondary questions**

2. What is the safety, effectiveness and cost-effectiveness of 4 stimulated treatment cycles with intrauterine insemination compared with 3 stimulated treatment cycles in women aged <35 years, 35-39 years and ≥40 years?
   - 3 versus 2 cycles
   - 2 versus 1 cycle
   - 6 versus 5 cycles
   - 5 versus 4 cycles

3. What is the safety, effectiveness and cost-effectiveness of low-dose stimulated treatment cycles with intrauterine insemination compared with *in vitro* fertilisation with a single fresh embryo transfer in women aged <35 years, 35-39 years and ≥40 years?

4. What is the safety, effectiveness and cost-effectiveness of a stimulated treatment cycle with intracytoplasmic sperm injection compared with *in vitro* fertilisation in couples by severity of male factor infertility?

5. What is the safety and effectiveness of a health management system recommending the transfer of frozen embryos (when available) compared with a system recommending the use of fresh embryo transfer only?
Clinical effectiveness of ART

IVF

IVF by maternal age

The NHMRC CTC systematic review found the following:

An AIHW NPSU report on ART in Australia comprehensively captures the success rates of more than 99% of all ART cycles in Australia and New Zealand for 2002 (Bryant et al., 2004). These data from the ANZARD provide the highest quality of observational epidemiological data (Tyldesley et al., 2001). Limitations in the accuracy of the data are related to patient self-reporting of pregnancy complications and neonatal morbidity and mortality. Key biases in interpreting the data on the effectiveness of IVF by maternal age are likely to be due to differences in characteristics of the women due to factors other than age.

Different proportions of causes of infertility, duration of infertility or practices in different age categories may confound the results. For example, the proportion of cycles with three embryos transferred increases by maternal age from 1.7% for women aged 25-29 years to 12.7% for women aged 40-44. Information on the comparability of age groups for other characteristics is not available.

The clinical pregnancy and live birth rates of fresh non-donor ART cycles by maternal age are shown in Tables 7 and 8. The outcome rates for all ART procedures combined are provided in Appendix A. The latter data include outcomes for donor oocytes/embryos and frozen cycles.

ART success rates are highest in the maternal age group 25-29 years, with a live birth rate of approximately 26% for fresh, non-donor cycles (Appendix A). Live birth rates decline significantly in the age categories over 35 years, to approximately 6% in women aged 40-44 years. This is a 76% reduction in the chance of a live birth from fresh, non-donor cycles, by comparison with women aged 25-29 (Rate Ratio Reduction = 0.76, 95% CI 0.73 – 0.79).

Across all ART procedures, miscarriage rates per cycle increased in women aged 30-34, 35-39 and 40-44, by comparison with women 25-29 (Appendix A). Miscarriages for women aged 25-59 occurred in 3% of cycles started, and 4% of cycles in women aged 40-44. This equated to miscarriage rates per pregnancy of approximately 12% and 35%, respectively. Ectopic pregnancy rates per cycle and stillbirths per delivery did not significantly differ across the age groups. Neonatal death rates per delivery did not significantly differ across the age categories between 25 and 40 years of age. However, a significantly higher neonatal death rate was observed in the age group ≤ 25 years than women aged 25-29. The cause of this association cannot be determined as differences in the populations for factors other than age are not known.
Importantly, multiple birth rates, when expressed per live birth, also decreased in women 35-39 and 40-44 years of age, by comparison with women 25-59 (Appendix A.). This effect was observed despite a tendency to transfer more embryos in older women (P<0.0001, χ² test for interaction between age and the transfer of ≥3 embryos). Three embryos were transferred in 1.7% of (fresh and frozen) transfer cycles in women aged 25-29, and 2.4%, 5.6% and 12.7% of cycles in women in the age ranges 30-34, 35-39 and 40-44, respectively. The multiple birth rate per live birth was similar in women aged 45 years or older, by comparison with women aged 25-29 (Appendix A). However, the smaller number of cycles in this age group limits the power of this analysis to detect and estimate a true effect should one exist.

Figure 4. Live birth per cycle started by woman’s age for fresh, non-donor ART treatment, 2002
Source: (Bryant et al., 2004)
Note: values for women aged ≥45 years were combined due to small numbers
Table 7. Success rates of fresh, non-donor ART by maternal age, ANZARD data
Source: (Bryant et al., 2004) a versus 25-29 year age group. Note: data not published by ANZARD due to small sell size.

<table>
<thead>
<tr>
<th>Maternal age (years)</th>
<th>Cycles Started (N)</th>
<th>LBR % per cycle started</th>
<th>Clinical Pregnancy Rate % per cycle started</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rate</td>
<td>RR</td>
</tr>
<tr>
<td>≤ 24</td>
<td>266</td>
<td>22.6</td>
<td>0.87</td>
</tr>
<tr>
<td>25-29</td>
<td>2213</td>
<td>25.9</td>
<td>1.00</td>
</tr>
<tr>
<td>30-34</td>
<td>6131</td>
<td>24.7</td>
<td>0.95</td>
</tr>
<tr>
<td>35-39</td>
<td>6935</td>
<td>17.9</td>
<td>0.69</td>
</tr>
<tr>
<td>40-44</td>
<td>3971</td>
<td>6.1</td>
<td>0.24</td>
</tr>
<tr>
<td>&gt;45</td>
<td>344</td>
<td>np</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval, LBR = live birth rate, RR = rate ratio
*P<0.0001
Note: The few data available for cycles in women less than 25 years of age and over 45 years of age make estimates of success rates in these age groups unreliable.

HTA reports

The authors of the NICE report presented data from the UK HFEA database from 1995 to 1999 to conclude that an increase in maternal age reduces IVF success (NCCWCH, 2004). Data were presented per year of age but no statistical analysis, or measures of variance, were reported. The overall live birth rate for fresh treatment cycles in this data set was 17.6%. The rates were greater than 20% between the ages of 23 and 33 years. Above 33 years the live birth rates declined to less than 10% by the age of 40. Women older than 40 years of age had a further decrease in the chance of a live birth. Live births rates were below 5% for women 42 years or older, reducing to 1% at the age of 45. The report guidelines recommend that the optimal female age for IVF is 23 to 39 years. The live birth rates per treatment cycle started for fresh non-donor IVF cycles in women aged over 33 years of age are shown in Table 8.
Table 8. Live birth rates by maternal age for fresh, non-donor IVF cycle started, UK HFEA data 1995-1999
Source: (National Collaborating Centre for Women's and Children's Health, 2004)

<table>
<thead>
<tr>
<th>Maternal age (years)</th>
<th>Treatment cycles (N)</th>
<th>Live birth rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>9435</td>
<td>20.4</td>
</tr>
<tr>
<td>34</td>
<td>9850</td>
<td>19.8</td>
</tr>
<tr>
<td>35</td>
<td>9301</td>
<td>18.6</td>
</tr>
<tr>
<td>36</td>
<td>8337</td>
<td>17.0</td>
</tr>
<tr>
<td>37</td>
<td>7623</td>
<td>15.0</td>
</tr>
<tr>
<td>38</td>
<td>6597</td>
<td>13.2</td>
</tr>
<tr>
<td>39</td>
<td>5602</td>
<td>10.7</td>
</tr>
<tr>
<td>40</td>
<td>4021</td>
<td>9.2</td>
</tr>
<tr>
<td>41</td>
<td>2780</td>
<td>6.6</td>
</tr>
<tr>
<td>42</td>
<td>1818</td>
<td>4.0</td>
</tr>
<tr>
<td>43</td>
<td>1238</td>
<td>3.6</td>
</tr>
<tr>
<td>44</td>
<td>730</td>
<td>2.1</td>
</tr>
<tr>
<td>45</td>
<td>390</td>
<td>1.0</td>
</tr>
</tbody>
</table>

The HFEA data reviewed in the NICE report also showed a decline in pregnancy rates by maternal age with a distribution similar to that of the live birth rates. Ectopic pregnancy rates per treatment cycle were 0.9% for women aged 18 to 25 years and less than 0.3% in women aged more than 35 years. However the authors pointed out that another study showed no significant difference in ectopic pregnancy rates following IVF in women over 35 compared with younger women. Miscarriage rates per pregnancy were 10.5% at 30 years of age, 13.1% at 35 years, 22.7% at 40 years and 40.7% at 43 years. No tests for statistical significance or confidence intervals were provided for the ectopic pregnancy or miscarriage rate data.

The NICE report also indicated that the effectiveness of IVF in women aged less than 23 years is uncertain as very few women in this age range undergo IVF treatment.
Primary studies (2003–2005)

Twenty-four studies were identified in the period 2003-2005 that reported on outcomes of IVF by maternal age. Due to the large number of studies identified, systematic reviews, RCTs, prospective cohort studies, and retrospective cohort studies which were based on national registry data or were multi-centre were included for full review. Of these, four studies reported data from the annual USA CDC SART report (Jain et al., 2004; Kissin et al., 2005; SART & ASRM, 2004a; Vahratian et al., 2003). Three of these studies were excluded from review (Jain et al., 2004; Kissin et al., 2005; SART & ASRM, 2004a), instead updated data from the most recent published report was included for review (Centers for Disease Control and Prevention et al., 2004). This report provided IVF success rates for all cycles conducted in the USA in 2002. The fourth study was retained for review as it provided novel information in the form of adjusted odds ratios for live birth by maternal age (Vahratian et al., 2003). One single centre retrospective study conducted in a Sydney IVF clinic was included for review (Jansen, 2003). The remaining 13 single centre studies were excluded from review.

Characteristics of the seven studies reporting the prognostic value of maternal age on IVF outcome – which were reviewed in full – are summarised in Appendix A.

Three reviewed studies were prospective cohort studies, providing high-level evidence for prognosis (level II by NHMRC criteria). Two of these were multi-centre studies conducted in the USA (Keye, Jr. et al., 2004; Klonoff-Cohen & Natarajan, 2004b), one of which was considered a high quality study (Klonoff-Cohen et al., 2004b). The applicability of the US studies to the Australian setting may be limited as practice differs between the countries. The third study was a single centre study conducted in Japan, which reported success rates expressed per embryo transfer and thus may overestimate the true effects of IVF.

A further three reviewed studies were registry or multi-centre retrospective cohort studies, providing a lower level of evidence (NHMRC level III-3 evidence for prognosis). Two of these were reports using ART data from the USA national registry. The SART report provided success rates of both fresh and frozen-thawed non-donor cycles in 2002 by maternal age (Centers for Disease Control and Prevention et al., 2004). A second USA registry study reported outcomes from frozen-thawed embryos in 1999-2000, and statistically adjusted for differences in characteristics of the women other than age (adjusted odds ratios Vahratian et al., 2003). The evidence from this study was therefore considered high quality. One further retrospective study reported outcomes by maternal age from first IVF cycles from all IVF clinics in the Netherlands.

The final study reviewed was a retrospective study conducted in a single Sydney private IVF clinic. The results from these studies are summarised in Appendix A.

Three studies provided high-level evidence of the influence of maternal age on success of ART.

Two of these studies were conducted in the USA. Both of these studies demonstrated a significant decrease in live birth rates in older women. One study was conducted over the period 1993-1998 in seven centres with high reported success rates (Klonoff-Cohen & Natarajan, 2004b). This study provided high quality evidence of the impact of maternal age on ART success rates by adjusting for many factors other than age that may influence the outcome. The range of the number of embryos transferred (average 4), as well as the time period of the study limited the applicability of the findings to current practice in Australia.
In this study, each additional year of maternal age was associated with a 19% increased odds of not achieving a live birth (OR 1.19, 95% CI 1.06 – 1.34, P=0.003), after adjustment for the number of embryos transferred, parity, number of previous IVF attempts, number of years of smoking, cause of infertility, type of procedure and clinic site. Duration of infertility was not adjusted for in the analysis. In an analysis of different age ranges of women, the odds of women not achieving a pregnancy or a live birth was significantly higher for women over 40 than for women under 35 (OR for no pregnancy = 4.74, 95% CI 1.53 – 14.69, P=0.01, OR for no live birth = 20.31, 95% CI 2.43 – 169.7, P=0.01). This study also stated that no significant association was found between maternal age and miscarriage (however, rates or odds ratios were not reported, n=71). Similarly, when analysed per live birth (n=41) multiple birth rates were not significantly associated with maternal age. The absolute rates of these outcomes were not reported and the findings are limited by the small sample size.

The second study, conducted in 21 US centres, provided fair quality evidence on IVF outcomes in women aged <34 years by comparison with women 34-40 years of age (Keye, Jr. et al., 2004). The inclusion criteria for this study were quite strict (eg, excluded smokers, see Appendix A) so the generalisability of the findings may be limited. The women in the two age groups did not significantly differ in their mean body mass index (BMI) or the proportion of women with tubal factor infertility. However, there were significantly more women with endometriosis (18.3% vs 9.2%, P=0.04, respectively) and significantly fewer women with unexplained infertility (28.8% vs 42.4%, P=0.03, respectively) in the <34 years group. Day 1 serum LH was significantly lower and E2 levels significantly higher in the women in the older age group. This may be as a result of aging in the women, or may be a sign of other underlying differences between the two groups. This study demonstrated a lower live birth rate, but a similar ectopic pregnancy and clinical pregnancy rate between women 34-40 years (34.2%, 44.2% and 0.8%, respectively) compared to women <34 years of age (41.7%, 45.2% and 0.9%, respectively), overall. No variability measures or statistical testing of these overall event rates in the two age groups of women were reported. Statistical adjustment for the imbalance in the infertility diagnoses in the two groups of women to the different success rates of IVF was not performed.

The prospective study based on data from a single Japanese centre reported lower clinical pregnancy and multiple pregnancy rates and a higher miscarriage rate in women greater than or equal to 35 years of age (31.3%, 20.0% and 12.5% per ET respectively) by comparison with women under 35 (46.9%, 26.7% and 6.3% per ET, respectively), although these differences were not statistically significant (variability estimates not reported). The authors reported that women in the two age groups had the same number of embryos at the same stage of development transferred. The similarity of the groups for the cause or duration of infertility, or other factors predictive of IVF success rates is unknown.

Four additional studies provided lower level (level III-3) evidence for the association between maternal age and success of ARTs.

Two studies reported success rates of ART by maternal age from USA registry data. Variations in practice between the USA and Australia may limit the generalisability of the findings in these studies. For example, approximately 62% of fresh, non-donor ART cycles in the USA in 2002 involved the transfer of three or more embryos (Centers for Disease Control and Prevention et al., 2004). Unadjusted live births and clinical pregnancy rates from fresh ART cycles in 2002 declined with increasing maternal age, however statistical testing was not reported (Centers for Disease Control and Prevention et al., 2004, see Figure 5 & Table 8).
Live birth rates decreased sharply between the ages of 40 and 43, from approximately 16% at age 40 to 2% for women aged over 43 (Appendix A). The data also indicated decreasing rates of multiple pregnancy and multiple births with increasing maternal age. These findings were supported by a high quality study of ART success rates from frozen embryo transfers in 1999-2000 (Vahratian et al., 2003). This study found that other patient and procedure characteristics (including the number of embryos transferred) varied according to age. Nevertheless, a significant trend of declining live birth and multiple birth rates was demonstrated with increasing age, after adjustment for the number of embryos transferred, prior births, prior ART cycles, and use of assisted hatching. This data are likely to underestimate the true effect, as the rates are reported per embryo transfer. The number of embryos transferred was shown to be significantly associated success rates. The comparability of the age groups for the cause of infertility was not reported. No data or adjustment for the duration of infertility were reported.

Figure 5. Success rates for ART by maternal age (US CDC data, 2002)

Extracted from CDC report (Centers for Disease Control and Prevention et al., 2004)

Success rates of fresh IVF cycles in the Netherlands between 1983 and 1995 were reported by Linsten et al (2005). ART practices in the Netherlands are similar to current Australian practice, however the technology or practices used in this study may be outdated. The odds of a live birth in women aged 35 years or over was significantly reduced by comparison with women under 35 (OR 0.80, 95% CI 0.67 – 0.96), after adjustment for differences in cause of infertility, smoking, BMI, time period of IVF and duration of infertility.
A limitation to the design of this study is that the study population may not be representative of all patients receiving IVF as only subjects who completed a questionnaire were included. These women comprised only 52% of all women approached. This study therefore provides evidence of limited quality and generalisability for a reduction of IVF effectiveness in older women.

One Australian single centre study was also included for review, due to the high applicability of this study to current practice in Australia (Jansen, 2003). Limitations to this study are that success rates are expressed per oocyte pick-up, which will tend to overestimate the true success rate per cycle started. Approximately 8% of cycles were excluded from the data. Nevertheless, this study indicates that ART success rates decrease noticeably as maternal age increases, although statistical analysis or variability measures were not reported. Rates were noticeably lower in women aged over 40 years than in younger women. Miscarriage rates also appeared higher in women aged over 40 years.

Summary

Australian registry data, a high quality HTA report, three studies providing high level evidence and four providing a lower level of evidence for the prognostic value of maternal age on the success rates of ARTs were reviewed. The reviewed evidence provided a large quantity of data which consistently demonstrated declining success rates with increasing maternal age. Although four studies provided no information on possible confounding factors, three studies provided odds ratios for live birth rates adjusted for several known confounders. The effect of decreasing ART success rates with increasing maternal age persisted after adjustment for known confounders. One study of limited quality and generalisability on ART cycles in the Netherlands between 1983 and 1995 adjusted for the duration of infertility. This study demonstrated a significant decrease in the odds of a live birth in women aged over 35 by comparison with women aged under 35 (Lintsen et al., 2005). The decrease in the success rates of ART for women over 40 years of age was marked.

Only two sets of registry data provided data by individual year of age for women over the age of 40. UK data from 1995-1999 demonstrated live birth rates of less than 10% for women 40 years of age of older, and less than 5% for women 42 years or older (NCCWCH, 2004). US data from 2002 demonstrated live birth rates of less than 10% for women 42 or 43 years of age, and of 2% for women over 43 (Centers for Disease Control and Prevention et al., 2004). This equated to an average live birth rate of 4% for US women in the age range of 43 or older. US practice differs from Australian practice in terms of a tendency to transfer more embryos per cycle. These two studies did not provide any information on the comparability of the underlying characteristics of the women. Four studies and Australian registry data also indicated that after taking account of the decrease in live birth rates, rates of multiple births also decrease in older women.
Key findings of the ART Review Committee:

- Australian data provide strong evidence that maternal age impacts on success rates of ART, with a large quantity of data consistently demonstrating declining success rates with increasing maternal age.
- There is undisputed evidence that age is the single most important factor in determining the success of ART.
- Evidence demonstrates that the effect of decreasing ART success rates with increasing maternal age persists even after adjustment for known confounders.
- There is a significant decrease in the number of live births in women aged over 35 by comparison with women aged under 35, with a further marked decrease in the success rates of ART for women over 40 years of age.
- The success of ART begins to decline after the age of 33 and shows a significant decline after the age of 37.
- The evidence examined in this review demonstrate that there is a definite association between maternal age and success of ART, with a marked decrease in the success rate of ART for women over the age of 40 years.

IVF by cycle number

The NHMRC CTC systematic review found the following:

The most applicable evidence available regarding the safety and effectiveness of IVF by cycle number is that provided for the purposes of this review by the AIHW NPSU.

These are national registry data for IVF outcomes from fresh, non-donor stimulated cycles in Australia and New Zealand in 2002. It should be noted that the identification of cycle number is based on subject self-reporting and therefore may contain inaccuracies. The data are expressed per successful oocyte pick-up (OPU). The data may therefore overestimate the true success rates and underestimate the differences between age categories and cycle numbers. Key biases in interpreting the data on the effectiveness of IVF by cycle number are likely to be due to differences in characteristics of the women due to factors other than cycle effects. Different proportions of women in different age ranges, causes of infertility, duration of infertility, or IVF practices in different cycle numbers may confound the results. For example, older women make up a larger proportion of women undergoing higher cycle numbers (women aged 30-33 account for 33.4% of women undergoing cycle 1, as opposed to 17.9% of women undergoing cycle 4; women aged 38-41 comprise 25.1% of women in cycle 1, but 38.9% of women undergoing cycle 4).
Table 9. Success rates of fresh, non-donor IVF by maternal age and cycle number, ANZARD data
Source: (Bryant et al., 2004) a versus 25-29 year age group. np data not provided by ANZARD due to small sell size (<5).

<table>
<thead>
<tr>
<th>Cycle</th>
<th>OPU (N)</th>
<th>Age 30-33</th>
<th>Age 34-37</th>
<th>Age 38-41</th>
<th>Age 42-45</th>
<th>Total</th>
<th>RR vs cycle 1</th>
<th>(95% CI)a</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2502</td>
<td>2524</td>
<td>708</td>
<td>352</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle 1</td>
<td></td>
<td>28.4</td>
<td>26.7</td>
<td>14.5</td>
<td>5.8</td>
<td>22.3</td>
<td>1.00</td>
<td>0</td>
<td>0.750 - 0.967</td>
</tr>
<tr>
<td>Cycle 2</td>
<td></td>
<td>23.5</td>
<td>21.4</td>
<td>17.3</td>
<td>3.3</td>
<td>19.0</td>
<td>0.85</td>
<td>(0.652 - 0.928)</td>
<td>0.0043</td>
</tr>
<tr>
<td>Cycle 3</td>
<td></td>
<td>20.8</td>
<td>23.6</td>
<td>14.3</td>
<td>np</td>
<td>17.4</td>
<td>0.78 –</td>
<td>(0.675 - 0.955)</td>
<td>0.0116</td>
</tr>
<tr>
<td>Cycle 4</td>
<td></td>
<td>np</td>
<td>np</td>
<td>np</td>
<td>np</td>
<td>17.9</td>
<td>0.80</td>
<td>0.633 - 1.014</td>
<td>0.0586</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval, LBR = liver birth rate, OPU = oocyte pick-up, RR = rate ratio
Note: cycle data are determined by subject self-reporting and therefore may contain inaccuracies. Data may overestimate success rates by comparison with rates expressed per cycle started.

For the total of women in all age ranges, the effectiveness of IVF in terms of live birth per OPU was significantly decreased in cycle 2 and cycle 3, by comparison with the first cycle (RR = 0.85, 95% CI 0.75 – 0.97, P=0.01; RR= 0.78-0.81, P <0.05). The chance of a live birth in the second IVF cycle was reduced by 15% by comparison with the first cycle (RRR = 0.15, 95% CI 0.033 – 0.25). The fourth cycle demonstrated a reduction in effectiveness by comparison with cycle 1 of a similar magnitude to that of cycles 2 and 3, with a non-statistically significant effect (P=0.059). However, the smaller number of women undergoing a fourth cycle limits the power of this analysis to detect and estimate a true effect should one exist. The cause of the relationship between overall cycle number and success rates is not known, it may be due to other factors. The magnitude of the reduction in effectiveness occurring in the third cycle compared to the first was less than the reduction seen with increasing maternal age from 25-29 to 35-39 (RRR (cycle 3 vs cycle 1) = 0.20 – 0.22, 95% CI (0.05 – 0.33) – (0.07 – 0.35), P = 0.004 – 0.012; RRR (age 35-39 vs 25-29) = 0.31, 95% CI 0.19 – 0.42, P<0.001). The difference between cycle numbers may be underestimated due to expression of success rates per successful OPU.

HTA reports

The NICE report cited the systematic review conducted by Allgood (2003) for the Wessex Institute for Health Research and Development to assess the influence of treatment cycle number on IVF effectiveness. This review was also identified in the literature search for the current review (see below). Allgood identified one study of 33,701 cycles started in the UK between 1991 and 1994 that reported live birth rates per cycle started. The results indicated that the probability of IVF success decreases with each treatment cycle from 14.0% (95% CI 13.5-14.5%) for first cycle to 13% (95% CI 12.2-13.7%) at the second attempt, 11.4% (95% CI 10.4-12.5%) at the third attempt and 10.2% (95% CI 7.7-13.7%) for the 6th to 9th cycles.
However, the NICE authors reported that these findings have not been confirmed by three smaller registry studies. Analyses of 5,028 cycles started in the UK between 1995-2001 (Oxford Fertility Unit) and 2,247 cycles started between 1995-1999 (HFEA) did not show a trend of decreasing live birth rates over the first three and four treatment cycles (respectively). A registry study from the United States (4,043 cycles, 1994) observed a significant decrease in live birth rates per treatment cycle after the third treatment cycle independent of maternal age.

The NICE authors used the more recent HFEA data (2,247 cycles, 1995 – 1999) in their economic analysis. The small number of patients undergoing more than four treatment cycles in this dataset did not allow estimates of the success rate per cycle after the fourth cycle.

**Systematic reviews and primary studies (2003–2005)**

One systematic review (Allgood, 2003) and two retrospective cohort studies based on national registry data were identified that reported on ART outcomes by cycle number (Centers for Disease Control and Prevention et al., 2004; Vahratian et al., 2003). Three single centre retrospective cohort studies were also included for review due to the limited amount of evidence identified. One single centre study was excluded from review as it presented live birth rates over the first three cycles by comparison with the average live birth rate over all cycles (Klipstein et al., 2004). Characteristics of the studies reviewed in full are summarised in Appendix A. If of these studies provided low level (level III-3 evidence) for the prognostic value of cycle number on ART success rates.

The systematic review conducted by Allgood (2003) was considered to provide fair quality evidence, due to limitations in the literature search. One included study was considered high quality as it reported outcomes from the US registry adjusted for predictors of ART success other than cycle number (Vahratian et al., 2003). One single centre study was considered poor quality. This study reported success rates per embryo transfer cycle, including fresh or frozen transfers (Check et al., 2005). Therefore the cycle numbers in this study do not relate the number of ovarian stimulation treatment cycles. The results are considered uninformative and are not discussed further. All other studies were rated as providing fair quality evidence.

The results of the included studies are summarised in Appendix A.

As described above (under HTA report, previous), the Allgood systematic review (2003) identified a study of UK data from the early 1990s which demonstrated a decrease in live birth rates per cycle started from 14% for first cycle to 10% for the 6th to 9th cycles. This review identified four additional observational studies of more than 500 couples reporting birth rates in successive IVF cycles. One large study demonstrated that delivery rates using oocyte retrieval as the denominator were slightly higher. Delivery rates per oocyte pick up declined with successive cycles from 15.6% for the first cycle to 13.4% at the second attempt, 12.3% at the third attempt, 10.3% at the fourth attempt, and 10.4% at the fifth attempt. This study may have included cycles with donations, frozen embryo transfers or ICSI. The author of this review concluded that too few couples were included in the other three studies to assess success rates for third and fourth attempts reliably. These studies did not demonstrate a decrease in birth rates between the first and second cycle. Nevertheless, these studies also indicated a general trend for decreasing success of IVF in terms of delivery rate (1 study) or live birth rate (2 studies) over increasing numbers of cycles.
Two studies provided information on ART success rates by cycle number from US registry data. One report indicated higher live birth rates for women undergoing their first ART cycle than for women who had previously undergone ART cycles in all age groups other than women over 42 years of age (Appendix A.) (Centers for Disease Control and Prevention et al., 2004). Statistical testing was not reported in this study of 2002 data. The decline in success across later cycles represented approximately 16 per cent of the first cycle success rate for women aged <35 or 35-37 years (16.1% and 16.6 percent, respectively). The magnitude of this reduction in success rates with more than one cycle gradually decreased as maternal age increased beyond the 35-37 age group. Overall, 55.5% of women were undergoing their first ART cycle, 20.8% of women were undergoing their second ART cycle, and 11.3%, 5.7% and 6.7% were undergoing their third, fourth and fifth or more cycles, respectively. However, the similarity of the different age groups for the breakdown of cycle number, the cause or duration of infertility, or other factors predictive of IVF success rates is unknown. Therefore the cause of any observed interaction of age and cycle number for ART success rates cannot be determined. A higher quality study by Vahration et al (2003) demonstrated a significantly decreased odds for live birth in later cycles by comparison with the first cycle for frozen embryo transfers in 1999-2000, after adjusting for maternal age, the number of embryos transferred, prior births, and use of assisted hatching. Adjustment for differences in the groups of women in the cause or duration of infertility was not performed.

Two single centre studies from The Netherlands reported ART success rates for each COH cycle inclusive of fresh and frozen embryo transfers (Appendix A). Neither of these studies reported statistical testing for the comparison of interest for this review. Practices in The Netherlands are more similar to those in Australia than in the US studies described above. Both described high drop-out rates.

In the study by Witsenberg et al (2005) data were reported for live birth rates per cycle started, which is the most patient relevant outcome for treatment success. The cumulative live birth rate per patient and cumulative singleton live birth rate per patient increased with successive cycles (Appendix A). However, the magnitude of this increase diminished with successive cycles, with a decrease in live birth rates per cycle for cycles beyond the second cycle. However, as the Netherlands funds only up to 3 cycles of IVF, the success rates of later cycles may have limited generalisability due to selection bias (van Montfoort et al., 2005). Only 5.2% of patients continued treatment up to the sixth cycle and 39.5% of patients discontinued treatment without achieving a live birth.

Van Montfoort et al (2005) reported pregnancy rates and multiple pregnancy rates during a trial of elective SET. The findings of this study may not be generalisable to the whole population as only patients <38 years were included in the study. The differences in pregnancy rate between the first, second and third elective single embryo transfer (eSET) cycle and the first, second and third double embryo transfer (DET) cycles were not statistically significant. The overall data indicated a decline in pregnancy rate between the first and second cycle, although statistical testing was not performed for this comparison (Appendix A). Expression of the data per successful oocyte pick-up may overestimate the true rates and underestimate a difference in between cycle comparisons. The also study indicated that overall twin on-going pregnancy rates did not differ greatly between the first and third treatment cycle.
Summary

In summary, one fair quality systematic review and five studies providing low level evidence of the success rates of ARTs by cycle number were reviewed. Two studies were based on USA national registry data and three studies were conducted in single centres. In general, the comparability of women undergoing successive numbers of cycles for other factors predictive of ART success rates was not reported. The studies demonstrated a general trend for decreasing birth rates with increasing numbers of successive cycles. One study demonstrated significantly decreased odds for live birth in non-first frozen embryo transfer cycles versus first frozen embryo transfer cycles, after adjustment for several known confounding factors, but not the cause or duration of infertility. Australian registry data on cycles one to four of IVF fresh, non-donor treatment indicated that the effectiveness of IVF significantly decreased in cycles 2 and 3 by comparison with the first cycle. The cause of this relationship cannot be determined as no adjustment was made for maternal age or other possible confounding factors. The cycle number at which success rates decreased was inconsistent between studies and the quality and quantity of the data available was limited.

Key findings of the ART Review Committee:

- There is a general trend for decreasing birth rates with an increasing number of successive treatment cycles.
- To a lesser extent, the number of previous unsuccessful treatment cycles also affects the success of ART but, while statistically significant, has less impact than maternal age.

IVF by duration of infertility

The NHMRC CTC systematic review found:

HTA reports

The NICE report cites an analysis of HFEA data by Templeton et al (1996) to conclude that the duration of infertility is also associated with a reduction in IVF success. The data were for 26,389 women undergoing 36,961 fresh, non-donor, conventional IVF cycles in 1991-1994. This study showed a significant decrease (P<0.001) in the IVF live birth rate with increasing duration of infertility from 1-12 years, which persisted after adjusting for the woman’s age. The live birth rate for women with infertility of 1-3 years duration was 15.3% (95% CI 14.6, 16.1) by comparison with 12.4% (95% CI 11.4, 13.6) for women with infertility of 10-12 years duration. This effect was observed whether live birth rates were expressed per treatment cycle, oocyte pick-up, or embryo transfer.

No other HTA reports addressed the issue of the effectiveness of IVF by increasing duration of infertility.
Primary studies (2003–2005)

The literature review identified a single study that reported effectiveness of IVF by duration of infertility, providing low level (level III-3) evidence of the predictive value of duration of infertility. The characteristics and results of this study are summarised in Appendix A.

This national study reported outcomes of IVF in first, non-donor, fresh cycles. In this study the odds of women with a duration of infertility of 8 years or more having a live birth was 0.79 (95% CI, 0.62 - 1.00) compared to women with a duration of infertility less than 8 years. The broad range of duration of infertility in the group used for comparison (ie, 1 to 8 years infertility) may reduce the relevance of this result. This finding may underestimate an effect of increasing duration of infertility on ART success rates for a comparison of women with infertility of 8 years of more to those with infertility of 1-2 years. The study used multivariate logistic regression to adjust for differences in cause of subfertility, smoking, BMI, time period of IVF and age. However, the study population may not be representative of all patients receiving IVF as only subjects who completed a questionnaire were included in the study. These women comprised only 52% of all women initially approached. This single study provides some limited evidence for a reduction of IVF effectiveness in women with a long duration of infertility.

Summary

In summary, two studies providing low level evidence indicate that duration of infertility is associated with a reduction in the success rate of IVF. The magnitude of this effect appears to be smaller than that associated with increasing maternal age. However, the quantity and quality of data on which this conclusion is based is limited.

Key finding of the ART Review Committee:

- The duration of infertility also affects the success of ART but to a less significant extent, and has less impact than maternal age.
The NHMRC CTC systematic review found:

**Primary studies identified (2003–2005)**

The literature search identified three primary studies in the period 2003-2005 that reported on outcomes of low-dose IUI. Studies or systematic review not reporting the use of low-dose stimulated IUI were excluded (11 studies). Low-dose IUI was defined as studies reporting insemination following maturation of a maximum of three follicles. A major registry study reporting outcomes from IUI in 15 European countries was identified and excluded as the ovarian stimulation protocol used was not known (Andersen et al., 2005). Two systematic reviews were also excluded as adequate information on the ovarian stimulation protocol of the included trials was not provided (Duran et al., 2002; Pandian et al., 2005). The characteristics of the three included studies are summarised in Appendix A.

One retrospective cohort study reported the effect of maternal age on IUI effectiveness. Two single centre retrospective cohort studies reported comparative outcomes for IUI versus IVF.

**HTA reports**

Existing HTA reports have not reported on the effectiveness of IUI by maternal age. Evidence in the original 1998 AHTAC report cited observational evidence that maternal age and normal sperm parameters predict IUI success. This evidence indicated a significant decrease in success rates for IUI in women greater than 35 years with few deliveries reported in women less than 42 years. The AHTAC report did not state whether or not COH was used during IUI in these studies.

**Primary studies (2003–2005)**

The results of the retrospective cohort study reporting on the effectiveness of low-dose IUI by maternal age are summarised in Appendix A (Papageorgiou et al., 2004). This study of limited quality provides low level evidence that the effectiveness of IUI declines with maternal age. Women aged over 40 years of age had significantly lower live birth, singleton live birth and clinical pregnancy rates by comparison with the other age groups. These outcomes were, respectively, 4%, 4% and 6% for women aged over 40 in comparison with 10%, 9% and 12% for women aged <30 years (P<0.05 χ² test, variability measures not reported). The protocol for COH used in this study is representative of that used in current practice in Australia. However, the comparability of the age groups in terms of other predictors of success of fertility treatments (such as diagnosis or duration of infertility) were not reported. This study provides evidence of an association between IUI effectiveness and maternal age, but does not provide adequate information to determine the cause of this relationship.

The success rates reported in this study exclude cycles cancelled due to more than 2 dominant follicles developing or due to the risk of OHSS.
Summary

In summary, a single study provided low level evidence that increasing maternal age is associated with decreased success of low-dose IUI. This reduction was statistically significant for women aged over 40 years, compared to younger age groups. The contribution of other possible confounding factors to this finding was not investigated.

IUI by cycle number

The NHMRC CTC systematic review found the following:

HTA reports

Existing HTA reports have not reported on the effectiveness of IUI by number of treatment cycles. Evidence cited in the original Australian Health Technology Advisory Committee report produced in 1998 indicated that success rates decrease after 3 to 7 cycles. The report stated that different studies suggest that IUI should not be continued after three cycles, four cycles, or seven cycles. It was not discussed whether or not these studies used controlled ovarian hyperstimulation, or the dose regimen used.

Primary studies (2003–2005)

No studies reporting on the safety or effectiveness of low-dose IUI by cycle number were identified in the literature search.

Summary

In summary, no primary or secondary research providing evidence on the success rates of low-dose IUI by cycle number, as indicated by live birth rates, were identified.

IUI vs IVF

The NHMRC CTC systematic review found:

HTA reports

The NICE report concluded that there is no evidence to demonstrate a difference in live birth rates between IVF and stimulated or unstimulated IUI. A systematic review included one small RCT that showed no difference in the multiple pregnancy rate or live birth rate (live birth rate OR 1.2, 95% CI 0.55 to 2.4, n =118) between stimulated IUI and IVF. No details of the controlled ovarian hyperstimulation protocol used were provided. This conclusion is limited by the small sample size of the studies.
Primary studies (2003–2005)

Two single centre retrospective cohort studies were identified that reported success rates of low-dose IUI versus IVF. These studies provide low level (III-2) evidence for the comparative effectiveness of these interventions. In both studies up to 2 embryos were transferred in the IVF protocol. No studies comparing low-dose IUI to IVF with the transfer of a single embryo were identified. Results of these studies are summarised in Appendix A.

The single centre study by Bungum et al (2004) provided delivery and pregnancy rates for IUI and IVF. Live birth rates were not reported but are assumed to approximate the delivery rates. This study indicated higher success rates for IVF (delivery rate 28.4%, clinical pregnancy rate 31.2% for IVF versus 15.3% and 17.6% respectively for IUI). However statistical comparisons for the patient groups as a whole were not reported. The couples receiving IUI and IVF are likely to differ in their fertility characteristics. The couples receiving IUI were those with unexplained fertility, at least one patent tube and a sperm concentration of \( \geq 2.5 \times 10^6 \text{sperm/ml} \). Baseline characteristics of the IVF population regarding infertility diagnosis were not provided, however inclusion criteria were for a sperm concentration of greater than or equal to \( 1 \times 10^6 \text{ml} \). The contribution of underlying differences in the fertility of the populations to the results cannot be determined. In this study, despite likely lower male factor fertility in the IVF group, success rates for IVF were higher than that of IUI.

The second study reviewed provided information on the effectiveness of IUI and IVF in a cohort of couples with unexplained infertility or mild male factor infertility (Olufowobi et al., 2005). This study was not designed for direct comparisons of effectiveness of the treatments. The study reported outcomes for women with a high response to controlled ovarian stimulation (>3 follicles of >15mm diameter) who converted to IVF, by comparison with those who went on to receive IUI. Twenty-three of these women converted to IVF, while 17 declined and cancelled the treatment. Results in the women converting to IVF are compared with those of 283 women received IUI. The average age and duration of infertility was similar in the two groups. One case of OHSS occurred in the group with a high response to ovarian stimulation. Due to the design of the study, success rates for IVF are expressed per embryo transfer cycle, rather than per ovarian stimulation cycle started. In this study, the groups of women receiving each treatment have clear differences in their clinical characteristics and direct comparison of IVF and IUI success rates in these groups is uninformative. Nevertheless, the study demonstrates a high success rate of IVF in a group converted from IUI treatment and proposes an interesting model of service delivery.

Summary

In summary, a single study designed to investigate the comparative effectiveness of low-dose IUI and IVF was identified. This study indicated a higher success rate for IVF than IUI, despite inclusion criteria specifying higher male factor fertility in the IUI group. This study provided low level evidence for this comparison.
**Key findings of the ART Review Committee:**

- There was limited evidence that increasing maternal age is associated with decreased success of low-dose IUI.
- IUI is less effective than IVF and is associated with a higher multiple birth rate.
- The effect of maternal age, cycle number and the duration of infertility on the success of IUI is likely to be the same as for IVF.

**ICSI**

The NHMRC CTC systematic review found:

**ICSI vs IVF effectiveness – by male factor infertility**

**HTA reports**

Three HTA reports classified as high quality systematic reviews assessed the relative effectiveness of IVF versus ICSI by male factor infertility (Corabian, 1998; Medical Services Advisory Committee, 2003; NCCWCH, 2004).

The NICE report did not identify any RCTs comparing ICSI with IVF in patients eligible for both treatments that reported on live birth rates. The authors presented trial evidence to conclude that there is no difference in pregnancy rates for ICSI versus IVF for the treatment of non-male infertility (3 RCTs). Evidence regarding the relative efficacy of ICSI versus IVF in couples where the male partner is sub-fertile was not consistent across the systematic reviews and RCTs identified. The results of these studies are also difficult to interpret without corresponding data on live birth rates. Comparisons of ICSI versus IVF where semen quality is too low to achieve fertilisation without micromanipulation are not appropriate; however the NICE report identified trial evidence that ICSI achieves higher fertilisation rates than alternative techniques in this patient group (subzonal sperm injection or additional IVF).

The NICE report did find that ICSI is beneficial in couples with failed IVF, although efficacy appeared to be dependent on underlying diagnosis.

The authors also cited observational evidence that ICSI is more effective for cases with obstructive azoospermia than non-obstructive azoospermia. Another study observed that female age, number of oocytes retrieved and number of oocytes injected were predictive of pregnancy success per embryo transfer, whereas sperm origin (epididymal, testicular), sperm status (fresh or thawed), paternal age and serum FSH level were not predictive.
An older Canadian HTA report also reviewed the effectiveness of IVF and ICSI for male factor infertility (Corabian, 1998). This report stated that 'ICSI seems to offer a significant benefit over IVF-ET in terms of fertilisation, cleavage and implantation rates in severe male factor infertility cases’. However, no studies providing comparative effectiveness for the outcomes of this review were identified. Expert opinion was that in cases of severe male factor infertility, ICSI should be considered as the best possible option for assisted reproduction.

An Australian report produced for MSAC in 2003 that reviewed the effectiveness of ICSI is awaiting further information before ministerial endorsement and release. An Australian report produced for MSAC in 2003 that is not yet published drew similar conclusions with one study confirming benefits of ICSI in couples unsuited for IVF who failed at least one cycle of high concentration insemination; and favourable fertilisation or clinical pregnancy rates in couples where the male partner has moderate to severe sperm abnormalities (2 systematic reviews, 10 primary studies); patients with failed IVF (3 studies). The results were not consistent for couples with mixed indications for IVF.

**Systematic reviews and primary studies (2003–2005)**

Eleven studies were identified in the period 2003-2005 that reported on effectiveness outcomes of ICSI vs IVF. Seven of these did not report the comparison by severity of male factor infertility and were excluded from review. Exclusions on this basis include an Australian, European and US registry studies (Andersen et al., 2005; Andersen et al., 2004; SART & ASRM, 2004a; Wang et al., 2005). Four studies remained for review. The characteristics of these studies are summarised in Appendix A.

Two of the remaining studies were systematic reviews. Both of these reviewed success rates of IVF versus ICSI in infertile couples with no male factor infertility. One was considered high quality (van Rumste et al., 2003a), the other poor (Van Steirteghem & Collins, 2003). Both systematic reviews identified only one study. This study did not report on live birth rates, or any other eligible outcomes for the current review.

Two cohort studies, which provide low level evidence for effectiveness (level III-2) were included for review (Appendix A). The results of these studies are shown in. A report of USA registry data from the CDC and SART provided a comparison of IVF to that of ICSI for couples not diagnosed with male factor infertility for the period 2003-2005 (SART & ASRM, 2004a) (Appendix A). The outcomes presented for ICSI are for couples without male factor infertility. The success rate for IVF is for all couples receiving IVF, with an assumption that this does not include large numbers of couples with diagnosed male factor infertility. Biases in this comparison are likely to occur as a result of differences in subject characteristics between the IVF and ICSI groups. Live birth rates for ICSI are lower than that of IVF for all maternal age ranges. However, this result should be interpreted with caution as the subjects receiving each intervention are unlikely to be comparable. No adjustment for possible confounding factors has been made.
A single centre study by Bungum et al (2004) also provided delivery and pregnancy rates for IVF and ICSI. Inclusion criteria for the study included a sperm concentration of ≥1 x 10^6 per ml, however the comparability of sperm motility or density in the two groups at baseline was not provided. This study indicated a higher success rate for ICSI than IVF (delivery rates of 37.9% and 28.4% respectively). Statistical comparisons for the patient groups as a whole were not reported. A greater proportion of the couples in the ICSI group had a high index of sperm DNA damage (sperm DNA fragmentation index (DFI) of >27%, ICSI 25.8%, IVF 16.5%, P=0.014). In couples with a DFI of greater than 27%, a higher delivery rate was observed with ICSI than IVF, however the adjusted ORs did not exclude 1 (ICSI 47.1% versus IVF 22.2%; adjusted OR = 7.0, 95% CI 0.75 – 65). The OR was adjusted for sperm concentration, percentage progressively motile sperm, female age and cycle number. It is possible that this study may lack the power to show a statistically significant difference, should one exist.

Summary

The evidence of the relative effectiveness of IVF and ICSI identified in this review comprised two studies providing low level evidence of limited quality. The results of the studies were conflicting. Interpretation of the findings of the studies is difficult in the absence of information on the similarity of the populations receiving ICSI and IVF, in particular with regard to male factor infertility. Differences in success rates between the technologies may be related to differences in subject characteristics, rather than to the use of the microinjection technique. High quality evidence from randomised trials is required to inform the comparative effectiveness of ICSI and IVF in a population with equivalent mild male factor infertility. In populations with severe male factor infertility where fertilisation without micromanipulation is not possible a comparison of ICSI with IVF is not appropriate.

Key findings of the ART Review Committee:

- Limited evidence of the relative effectiveness of IVF and ICSI was identified due to the lack of information on the similarity of populations receiving ICSI and IVF.
- In severe male factor infertility ICSI remains the only viable treatment in conceiving a genetically related child to both parents.
- In unexplained infertility ICSI has not been shown to be any more effective than IVF.
- ICSI is successful at achieving fertilisation where fertilisation has failed using conventional IVF.
**ICSI vs IVF safety – congenital malformation rate**

The NHMRC CTC systematic review found the following:

**HTA reports**

Four HTA reports assessed the adverse effects of ART for infants conceived by ICSI versus IVF. Each of these three reports were classified as high quality systematic reviews according to the criteria listed in Appendix A.

In a systematic review conducted for the Norwegian Knowledge Centre for the Health Services, Tanbo et al (2002) assessed 30 cohort and case series studies that compared ICSI, IVF and spontaneous conceptions and reported on one or more of the following outcomes: congenital malformations, growth disturbances, neurological development disturbances, chromosomal abnormalities and transmission of subfertility to male offspring (Tanbo et al., 2002). Conclusions about the relative safety of ICSI in the NICE report were based on the findings of this review (NCCWCH, 2004). Of the 30 studies included in the review, 13 were rated as acceptable quality cohort studies with well-defined control groups and 17 were cohort or case studies of weaker design. The outcome most reported was congenital malformations. Overall, no increased risk of major birth defects, including chromosomal abnormalities, was found in offspring resulting from treatment of severe male infertility with ICSI compared with offspring conceived by standard IVF treatment or naturally conceived (OR 1.13, 95% CI 1.00 to 1.29, \( p = 0.06 \); test for heterogeneity \( p = 0.35 \), based on seven cohort studies and two reports). Furthermore separate meta-analyses on specific categories of malformations did not show any increased risk after ICSI.

An Australian report for the MSAC in 2003 conducted a systematic review of the safety of ICSI is awaiting further information before ministerial endorsement and release. A systematic review conducted by the MSAC in 2003 assessed evidence from 16 registry studies and case series drew similar conclusions (unpublished).

An older Canadian HTA report concluded that at the time there was no reported increase in congenital malformation rates or paediatric follow-up in children born after ICSI by comparison with IVF (Corabian, 1998). It was also stated that relatively few live births had occurred from ICSI at the time and its safety needed to be substantiated.

**Systematic reviews and primary studies (2003–2005)**

Seventeen studies were identified in the period 2003-2005 that reported on congenital malformation or perinatal mortality rates of ICSI versus IVF offspring. Studies examining developmental outcomes were excluded. Two systematic reviews (Lie et al., 2005; Rimm et al., 2004), two prospective cohort studies (Bonduelle et al., 2003; Place & Englert, 2003) and six large registry or multicentre studies (Bonduelle et al., 2005; Kallen et al., 2005; Mansour, 2004; 2003; Ombelet et al., 2005; Pinborg et al., 2004a; Pinborg et al., 2004c) were included. Five single centre retrospective studies reporting congenital malformation rates were excluded from review (Elizur et al., 2005; Frydman et al., 2004; Kuwata et al., 2004; Martikainen et al., 2004; Merlob et al., 2005). The characteristics of the included studies are summarised in Appendix A.
Since congenital malformations are rare events, reliable data on this outcome will not be captured by RCTs. Therefore, the highest quality data will come from large scale observational studies. National multicentre registry studies are considered to provide the most accurate estimation of the rates of congenital malformations (Tyldesley et al., 2001). However, large prospective cohort studies are likely to provide the most reliable information on the comparability of two different patient groups and a higher level of evidence for the comparative effects of the two interventions. Information on the characteristics of the groups being compared can be accurately collected enabling analysis controlling for possible confounding factors. The power of these studies to detect differences in rates may be limited, depending on the study size.

**Systematic reviews**

Lie et al (2005) conducted a meta-analysis of peer-reviewed prospective studies reporting IVF and ICSI malformation rates in the same population. Only studies reporting malformation rates inclusive of stillbirths and elective terminations were included. These comprised four non-overlapping prospective cohort studies including 5395 ICSI and 13086 IVF children. No significant differences in the odds of overall major malformations, cardiovascular, musculoskeletal, hypospadias, neural tube defects or cleft lip or palate malformations were identified (see Appendix A). Heterogeneity between the risks of hypospadias in different studies was found. A sensitivity analysis of major malformations incorporated additional data from 6 reports from 3 national registries. This analysis estimated an increased risk of 1.2 fold for ICSI children (OR = 1.20, 95% CI 1.09 – 1.31). The risk significantly differed between the studies, indicating a level of uncertainty in this finding (heterogeneity P<0.001). The authors indicated that the increase in risk was only noted in the three reports from the UK registry, but the effect of excluding these studies from the meta-analysis was not reported. Data from the prospective studies provide a higher quality of evidence and indicates that there is no large increase in risk of malformations in ICSI children; however the power to detect small increases in risk is limited, particularly for subtypes of malformations.

Rimm et al (2004) assessed 19 studies designed to compare congenital malformation rates for ICSI, IVF and spontaneous conception. Malformation rates ranged from 0 to 9.5% for IVF (total infants 28,524), from 1.1% to 9.7% for ICSI (total infants 7234) and from 0 to 6.9% for spontaneous pregnancies (total infants 2,520,988). There was statistically significant heterogeneity across studies and the authors combined the data using a random effects model to conclude that risk of malformation was similar following ICSI versus IVF (ICSI 7 studies, OR=1.23, 95% CI 0.80-1.88; IVF 16 studies, OR=1.28, 95% CI 0.93-1.75). Four studies directly compared outcomes following IVF versus ICSI, including two studies not included in the earlier HTA reports. None of these studies showed a difference between the malformation rates following IVF and ICSI.
Primary studies

All of the primary studies identified reporting congenital malformation rates in IVF versus ICSI offspring provided low level (III-2) evidence for this comparison. Limitations in interpreting the findings from these studies will relate to dissimilarities of the populations receiving the two interventions. In particular, the indications for IVF and ICSI differ, so the clinical characteristics of the parents in observational studies are likely to differ between the study groups. The cause of any differences in outcomes observed generally cannot be determined from this study design, ie, differences observed may be due to factors other than the effect of the ICSI microinjection technique (and the associated non-natural sperm selection). Statistical adjustment for likely confounding factors will increase the quality of the studies. Several of the studies conducted multiple statistical comparisons without adjustment of the significance level for repeated testing.

Two small prospective cohort studies were identified. Bonduelle et al (2003) followed a cohort of 12% of infants born from IVF or ICSI at two centres between 1995 and 2002. The indications for IVF and ICSI differed (see Appendix A). Forty four per cent of children in this cohort attended a follow-up consultation at 2 years of age. Perinatal, birth and neonatal characteristics differed between those who participated and those who did not (see Appendix A). In particular, compared to the complete cohort, there were significantly more neonatal malformations in the children from 1985 pregnancies seen at 2 years of age than in those that were not seen (malformations 10.1%, n=1985 pregnancies in those participating; versus malformations = 6.1%, n= 2406 pregnancies; P<0.001, Fischer’s exact test). Therefore, the generalisability of the findings from the study population (children seen and completing full developmental assessment) to the whole population is uncertain. This study found no difference in malformation rates of 2 year old children born from ICSI or IVF.

Place & Englert (2003) reported findings from a single centre prospective cohort study of singleton children born from fresh IVF or ICSI cycles. Follow-up was of 60-70% of the full cohort. There were no significant differences in several parental, birth or obstetric characteristics of the IVF and ICSI children. The study found no significant differences in major, or combined major plus minor congenital malformation rates.

The remaining studies were all retrospective cohort studies. Two reports by Mansour et al (2003 & 2004) reported congenital malformation rates from the first Middle East registry, for Egypt and the Middle East. In both studies it was reported that data on malformations and follow-up of children were incomplete. These results are therefore not discussed as they are considered poor quality and uninformative for the purposes of this review.

One study reported congenital malformation rates in a Swedish national cohort (registry data from 1982 - 2001, Kallen et al., 2005). This study found no significant differences in the total or major congenital malformation rate in IVF and ICSI infants, after adjustment for year of birth, maternal age & number of infants in birth (Appendix A). This study also compared total malformation rates between infants from ICSI using sperm from different sources (ejaculated, epididymal, testicular, frozen ejaculated, or frozen unspecified sperm) and infants from standard IVF. No significant differences were observed. No significant differences were observed in the rates of 11 specific types of malformations in IVF versus ICSI infants (after adjustment for year of birth only, see Appendix A.)
However, the odds of infants with hypospadias having been conceived by ICSI were almost twice that of having been conceived by IVF (OR 1.94, 95% CI 1.09 – 3.44, adjusted for year of birth). Hypospadias is a congenital defect where the urethra opening is on the bottom of the penis, rather than on the glans. As this comparison was not adjusted for many potential confounding factors, the cause of this difference cannot be determined.

A Danish registry study reported data on singletons and twins aged 2-7 years who were born in Denmark between 1995 and 2000 (Pinborg et al., 2004c). The study reported odds ratios for neurological sequelae, adjusted for maternal age, sex, year of birth, low birth weight and low gestational age. This large study found no differences in the odds of neurological disorders in ICSI versus IVF children overall, or twins or singletons, analysed separately. The odds of having cerebral palsy also did not differ between ICSI or IVF children.

Ombelet et al (2005) reported outcomes for IVF and ICSI births in Flanders, Belgium, for the period 1997 to 2003. For singletons, gestational age, parity, birth weight and maternal age significantly differed between the IVF and ICSI groups. The odds of neonatal mortality, stillbirths and congenital malformations were not found to differ between IVF and ICSI singletons. Within the twins in this cohort study, parity significantly differed between the IVF and ICSI groups (1.4 ± 0.6 versus 1.5 ± 0.8, respectively, P=0.008). The odds of neonatal mortality and congenital malformations did not differ between the twin groups, however the odds of stillbirth was significantly great in the ICSI group, after adjustment for maternal age and parity (OR =1.99, 95% CI 1.15-3.44, P=0.01). The proportion of infants transferred to intensive care units did not differ between IVF and ICSI infants, for either singletons or twins.

The International Collaborative Study of ICSI - Child and Family Outcomes (ICSI-CFO) study by Bonduelle et al (2005) reported congenital malformation rates in IVF and ICSI children, as well as a cohort of matched naturally conceived children (1515 children in total). There will be some duplication of subjects included in this study and the study by Ombelet et al (2005). The study was designed to compare the outcomes of the children conceived by ART to naturally conceived children, therefore statistical comparisons of malformation rates in IVF and ICSI children were not performed. Malformation rates were presented as those detected in the neonatal period and those detected after the neonatal period up to 5 years. For the purposes of this review, only total malformations are presented. Major malformations were also presented by organ type (cardiac; eyes, ears, face; urogenital; gastrointestinal; musculoskeletal and skin). The rates of these malformations by organ type were between 0 and 1 per cent for both IVF and ICSI for all outcomes except urogenital malformations. The urogenital malformation rates are presented in Appendix A. Rates of many components of medical history and parental and perinatal characteristics were also presented in the study but are not discussed in this review, although these items will be relevant to resource use. All of these reported characteristics appeared similar between IVF and ICSI groups, although statistical testing was not performed for this comparison. The study stated that oligozoospermia did not influence the presence of major or minor malformations, when comparing ICSI to naturally conceived children. The authors of this review performed statistical analyses comparing the odds for major, minor, overall and urogenital malformations in IVF and ICSI children and found no significant differences.
Summary

In summary, one HTA report, two systematic reviews, two prospective cohort studies and six large retrospective cohort studies were reviewed for evidence on comparative malformation rates in ICSI versus IVF offspring. All of these studies provide low level (III-2) evidence for the comparative safety of the ICSI microinjection technique versus conventional IVF. Higher quality prospective studies did not indicate any significant differences in the congenital malformation rates in ICSI versus IVF children. However, evidence from prospective studies was limited. Two retrospective cohort studies were considered poor quality and their results are not considered in the conclusions made. All other studies did not consider the contribution of differences in indication (male factor infertility) between the study populations. Six studies, a HTA report and a meta-analysis of 19 studies did not demonstrate any difference in the overall chance of malformations in IVF or ICSI offspring. However, one Swedish registry study demonstrated a significantly higher rate of hypospadias (a urogenital malformation) in ICSI children, after adjustment for year of birth. Another study based on infants born over a seven year period in all hospitals in Flanders, Belgium, demonstrated a significantly higher rate of stillbirths in ICSI twins, by comparison with IVF twins (after adjustment for maternal age and parity). A meta-analysis of four prospective studies and six registry reports from three countries also indicated a possible increased risk of major malformations in ICSI children. The differences observed in the safety of ICSI and IVF appeared when large, lower quality retrospective studies were considered. These studies do not adequately control for factors other than the intervention technique that may bias the findings. Whether the evidence from limited higher quality prospective studies or from larger lower quality retrospective studies is indicative of the true effect cannot be determined. Clear evidence for whether or not the use of ICSI results in detrimental outcomes in the offspring requires a larger quantity of higher quality research.

Randomised studies of IVF versus ICSI for patients with equivalent male factor infertility would provide evidence with the least amount of bias in assessing the comparative safety of the two interventions. However, due to the rarity of congenital malformations this outcome is unlikely to be appropriately captured in studies of this design. Large prospective or retrospective cohort studies adjusting for many differences in study populations (eg. male factor infertility), or comparing outcomes for IVF versus ICSI in patients with equivalent mild male factor infertility are likely to most accurately assess the relative safety of IVF versus ICSI. A future review examining congenital malformation rates within ICSI infants, by the severity of male factor infertility is likely to be informative. This would provide information on the value of this characteristic as a prognostic factor for congenital malformation rates following ICSI treatment.
**Key findings of the ART Review Committee:**

- **All forms of ART involving embryo transfer are associated with a small but statistically significant increase in congenital malformations.**
- **There is no significant difference in the congenital malformation rate between ICSI and IVF.**
- **While the number of reported cases is not statistically significant, where ICSI is offered as the appropriate ART treatment, couples should be informed of the relevant issues.**

**Other**

The NHMRC CTC systematic review found:

**Frozen embryo transfer**

**HTA reports**

None of the six existing HTA reports directly assessed the relative effectiveness of the routine use of cryopreservation to allow frozen-thawed embryo transfer cycles following unsuccessful fresh embryo transfer compared to fresh embryo transfer alone. Although, the NICE report cited observational studies to support the relative safety of cryopreservation and frozen-thawed embryo transfer versus fresh embryo transfers. These studies showed that frozen-thawed embryo transfer did not have a negative impact on perinatal outcomes, early infant development or congenital malformation rates.

The NICE report cited an analysis of live birth rates with frozen IVF cycles obtained from the HFEA (22,546 IVF treatment cycles registered between 1995 and 1999, non-donor eggs and frozen embryo transfer). The overall live birth rate per treatment cycle was 11.5%, ranging from 10% to 16% in women between the ages of 23 years and 38 years and less than 7% for women aged more than 38 years. Although these rates are lower than those achieved by treatment cycles with fresh embryo transfers, the authors cited early observational studies (pre-1992) that have indicated that the use of cryopreservation and frozen-thawed embryo transfer increases the cumulative pregnancy rate versus fresh IVF alone by up to 11%. The authors suggested that these benefits may be even greater given the current practice of only selecting good quality embryos for cryopreservation. However, they found no recent studies addressing this issue.

**Systematic reviews and primary studies identified (2003–2005)**

The literature review identified two systematic reviews and four primary studies published between January 2003 and September 2005 that compared ART outcomes when standard practice included cryopreservation and frozen embryo transfer versus the practice of only transferring fresh embryos.
Two recent systematic reviews have attempted to assess the approach of using frozen embryos (Bergh, 2005; Pandian et al., 2004). Pandian et al (2005) conducted a high quality systematic review but did not identify any relevant randomised controlled trials published between 1970 and 2003. Bergh (2005) searched the literature for randomised controlled trials and observational studies published between 1995 and 2004. The article provided insufficient information for a quality assessment of the review methods. One relevant randomised controlled trial was identified and is reviewed below (Thurin et al 2004). Preliminary results from a second trial were also identified but did not report on live birth rates and are not included in the current review. Bergh (2005) also cited delivery rates from Sweden following the introduction of a SET policy in 2003 to discuss the safety and effectiveness of this approach.

One high quality randomised controlled trial (level II evidence) compared the eSET followed by a single frozen embryo (if needed) versus the transfer of DET (Thurin et al., 2004). The other three studies included a single centre Australian prospective cohort study (level III-2 evidence) (Catt et al., 2003) and two case series with historical controls (level III-3 evidence): a national study from Italy (Ragni et al., 2005a); and a single centre study from Finland (Soderstrom-Anttila et al., 2003). All three studies investigated the impact of a change in policy regarding cryopreservation; and two compared outcomes following a policy recommending eSET versus DET (Catt et al., 2003; Soderstrom-Anttila et al., 2003).

The characteristics of included studies are summarised in Appendix A.

**Systematic reviews**

The results of the randomised trial identified by Bergh (2005) are described below (Thurin et al 2004). The authors also reported national Swedish data for delivery rates and multiple birth rates over the period 2000 to 2004 to investigate the impact of a policy of routine SET introduced in 2003. SET rates rose from approximately 10% to 60% over this period, live birth rates per embryo transfer were described as ‘fairly constant’ while the multiple birth rates dropped from over to 20% to less than 10%.

**Primary studies (2003–2005)**

The results of the four primary studies are summarised in Appendix A. The high quality randomised controlled trial by Thurin et al (2004) provides strong evidence that a policy of routine cryopreservation with transfer of a single fresh embryo followed by a single frozen embryo when required will decrease the relative risk of multiple pregnancies by 98% compared to a policy of double fresh embryo transfer (p<0.0001). The cumulative live birth rate using fresh +/-frozen SET was 4% lower than double fresh embryo transfer, however this difference was not statistically significant (absolute reduction in cumulative live birth rate of 4%; 95% CI -3 – 12%). These results indicate that the ‘true’ effect a combination of one elective fresh SET and one frozen-thawed SET versus a fresh DET may lie between a 12% reduction and a 3% increase in the cumulative live birth rate. Larger studies would be required to produce a more accurate estimate of the relative effect size of these two approaches. A cost-effectiveness analysis of this study, incorporating maternal and paediatric complications is soon to be published (Kjellberg et al., 2006).
The three observational studies provide weaker evidence about the impact of ART policies that incorporate frozen embryo transfer. The largest study reported on the impact of banning frozen embryo transfer and limiting the number of embryos transferred to a maximum of three (Ragni et al., 2005a). The authors reported a statistically significant difference in cumulative clinical pregnancy rates favouring a policy of cryopreservation (cumulative pregnancy rate pre-legislation = 34%, post-legislation = 26%, p=0.009). The multiple birth rate appeared to be lower after legislation banning cryopreservation (multiple birth rate pre-legislation=26%, post-legislation=21%, p=0.11). This difference is likely to reflect the impact of introducing legislation to limit the maximum number of embryos to three and was not statistically significant. The other two studies reported on single centre experiences following policies to offer eSET with cryopreservation and subsequent frozen-thawed embryo transfer if needed. Neither of these studies observed a statistically significant difference in cumulative pregnancy or live birth rates, however both reported a drop in multiple birth rates. It is likely that the characteristics of couples receiving eSET differed from those electing to receive DET. Thus these results provide weaker evidence about the safety and effectiveness of cryopreservation and eSET policies in couples eligible for both procedures. Even so they provide some general support that policies of eSET and cryopreservation may result in improved safety without severely compromising success rates.

Summary

In reviewing policies of using fresh plus frozen embryo transfer, a high quality study indicated that a policy of elective SET, with transfer of a frozen embryo when necessary, significantly reduces multiple pregnancy rates. Limited evidence generally indicated that this may occur without severely compromising success rates.

Key findings of the ART Review Committee:

- **In general single embryo transfer (SET) is the preferable approach.**
- **There is no evidence to suggest any difference in the rate of congenital abnormalities between fresh and frozen embryo transfers.**
- **Frozen embryo transfers have a lower success rate than fresh embryo transfer.**
- **Frozen embryo transfer can increase the number of pregnancies that can be achieved per stimulated cycle.**
- **The practice of transferring frozen embryos can support a policy of SET and assist in reducing the rate of multiple pregnancies.**
- **High quality evidence indicated that a policy of elective SET significantly reduces multiple pregnancy rates, and limited evidence generally indicated that this may occur without severely compromising success rates.**
Blastocyst transfer

Keeping embryos in in vitro culture for a longer period of time before uterine transfer is now possible due to improvements in laboratory techniques. The transfer of embryos to the uterus at a later stage of development may mimic natural physiology more closely and also allow better selection of embryos for transfer. Much research on this approach has been conducted in the last decade, but with conflicting results.

Although the effectiveness of blastocyst transfer was not a clinical question addressed in the current systematic review, a high quality systematic review was published at the time of the preparation of this report. A recently updated Cochrane review has investigated the relative success of cleavage stage (day 2-3) versus blastocyst stage (day 5-6) embryo transfer (Blake et al., 2005). This review searched literature to May 2005 for high quality trials (randomised controlled trials, RCTs) reporting live birth, clinical pregnancy or multiple pregnancy rates.

The review identified 16 included trials published over the period 1998 to 2004 comparing cleavage to blastocyst stage transfer. Quasi-randomised studies were excluded in addition to a single study from 1993 using outdated culture techniques. Across seven RCTs, the live birth rates resulting from day 2/3 or day 5/6 embryo transfer did not differ (Odds Ratio (OR) 1.16, 95% CI 0.74 – 1.44). Data from 15 RCTs did not demonstrate a difference in clinical pregnancy rates (OR 1.05, 95% CI 0.88 – 1.26). Multiple pregnancy rates did not differ between cleavage stage and blastocyst stage embryo transfer (12 RCTs, OR 0.85, 95% CI 0.63 – 1.13). No differences were demonstrated for higher order multiple pregnancy rates or miscarriage rates (across 5 RCTs and 9 RCTs, respectively). No differences in any outcome were observed in subgroups of couples with good, poor or unselected prognosis.

There were also no differences in outcomes observed in subgroups of studies with equal numbers of embryos transferred or in those with more cleavage stage than blastocyst embryos transferred. These results were unchanged in a sensitivity analysis excluding studies where different media were used for the two study arms. The authors of this review concluded that ‘There is no difference in live birth or pregnancy outcomes between day 2 to 3 and day 5 to 6 transfer of embryos. Blastocyst transfer was associated with an increase in failure to transfer any embryos in a cycle and a decrease in embryo freezing rates. In the absence of data on cumulative live birth rates resulting from fresh and thawed cycles, it is not possible to determine if this represents an advantage or disadvantage.’

In this review, many of the studies identified were transferring two to three embryos. The only study which transferred a single blastocyst transferred two cleavage stage embryos. Further research comparing the outcomes from transfer of a single cleavage stage or blastocyst stage embryo is required. In addition, research into the best patient selection criteria for blastocyst culture is continuing as media composition and culture techniques improve.
Cost-effectiveness of ART

Summary of findings

The NHMRC CTC systematic review found the following:

The purpose of the economic evaluation was to estimate the incremental costs and outcomes of IVF therapy in Australia, specifically the effect of maternal age and the number of previous attempts of IVF therapy (IVF treatment programs\(^9\)). The economic analysis aimed to estimate the expected incremental cost and effects on Australian cohorts of women aged 30-33, 34-37, 38-41 and 42-45 from:

- 3 IVF treatment programs compared with 2;
- 2 IVF treatment programs compared with 1; and,
- 1 IVF treatment program compared with no treatment programs.

The economic analysis was based on 2002 data from the AIHW NPSU on the effects of fresh and frozen embryo treatment by age and treatment program number. As IVF treatment consists of using both fresh embryos (a fresh cycle) plus IVF treatment using frozen embryos (where frozen embryos are available), this model was used and generally reflects the model used in the UK NICE review (2003). The number of frozen cycles is dependent on the number of embryos successfully frozen, the expected number of embryos successfully transferred and whether a live birth occurs. Each treatment program therefore consists of a fresh cycle followed by a variable number of frozen cycles. The model also includes the costs associated with miscarriage, ectopic pregnancy, still and live birth.

The available data on the effectiveness of low-dose IUI by maternal age, treatment cycle or versus IVF, or of ICSI versus IVF in a population with equivalent male factor infertility were considered inadequate to inform cost-effectiveness analyses.

---

\(^9\) A treatment program is modelled to include attempts at IVF with fresh and frozen embryos (where frozen embryos are available).
Existing literature

A scoping search for economic studies investigating the research questions for this review did not identify any studies published since the NICE review (NCCWCH, 2004, Appendix A). The study of Chambers, Ho and Sullivan (2005) became available at the time of writing this report.

NICE Review

NICE economic modelling was predominantly based on data from the UK HFEA database. Age specific and cycle specific models were developed to estimate cost per live birth. In each case resource use and costs were modelled to include the expected treatment patterns for IVF outcomes; live birth, ectopic pregnancy, miscarriage and no pregnancy.

The NICE age specific model assumed couples underwent 1 round of fresh IVF treatment with up to two attempts at frozen treatment. Results from this model suggest the cost per live birth were similar for ages up to 33 then increase for older age groups. The cost per live birth was £11,917 (GBPs) at 24 years, £12,931 at 35 years and £20,056 at 39 years.

Two NICE cycle specific models assumed couples only underwent fresh IVF treatment, with no attempts at frozen embryo transfer. The first cycle specific model was based on HFEA data up to 4 treatment cycles, and was not age specific. This model estimated costs per live birth for one, two, three and four rounds of treatment as £15,281, £16,169, £14,793 and £14,336 respectively.

A second cycle specific NICE model was based on data from Oxford Fertility Unit and included estimates of up to three treatment cycles for maternal age groups less than 39 and 39 years and over. The cost per live birth for first, second and third rounds of treatment was estimated as £11,694, £11,548 and £12,758 (women less than 39 years) and £27,611, £28,938, £12,835 (women 39 years and over). The estimates for older women were noted as unreliable due to small sample size.

The study of Chambers, Ho and Sullivan (2005) considers the average costs of ART treatment delivery and live birth rate per fresh (and frozen) cycle, by age of women treated (30-34, 35-39, 40+, 42+) from Australian 2002 AIHW NPSU data. The study reports the average cost of ART treatment per live birth event as $24,905 for women aged 30-34, $33,636 for women aged 35-39, $97,884 for women aged 40 and over and $182,794 for women aged 42 and over.

This review though maybe considered to have some limitations to modelling and economic interpretation of cost-effectiveness ratios and their relativities across age groups reported by Chambers Ho and Sullivan (2005):

- first, while including costs to government and individuals of ART treatment delivery, costs of events and effects resulting from ART treatment, particularly those associated with pregnancy and pregnancy outcomes, were not included;
- second, estimates of cost, effect and cost effectiveness are based on a cross sectional sample of women, rather than modelling cohorts of women as they transit between cycles of ART treatment; and,
- third, costs, live birth rates and the cost effectiveness ratio are not reported incremental to a comparator (for example, the first treatment program or reference age range).
The NHMRC CTC analysis sought to address these limitations by:

- estimating expected costs to the health care system beyond IVF treatment delivery, in particular those associated with IVF pregnancies (consistent with the NICE study);
- modelling costs and effects for cohorts of women as they transit though treatment programs (consistent with the approach of the NICE study); and
- modelling costs and effects incrementally by the number of IVF attempts (treatment programs).

It is important to consider the additional treatment costs, as well as benefits, associated with additional pregnancies when modelling the resource and cost impacts of IVF therapy (from a government or societal perspective). All other things being equal the inclusion of costs associated with pregnancies from IVF treatment will increase expected costs and cost-effectiveness ratios for each age group. The increase in costs will however be greater in the younger age groups, due to higher pregnancy rates. However it should be noted that the inclusion of resource use and costs from pregnancy outcomes narrows the difference between cost per live birth for the young and old reported by Chambers, Ho and Sullivan (2005).

It should also be noted that the current cost-effectiveness analysis is limited to conventional IVF treatment only, where the study by Chambers et al (2005) is concerned with an average of all non-donor ART treatments (IVF, ICSI and GIFT) recorded in the ANZARD database (excludes IUI).

**Results**

The expected cumulative cost and live births per 1000 women commencing IVF treatment by treatment program (number of attempts at IVF therapy) are reported by maternal age group and modelled on available ANZARD data for 1, 2 and 3 attempts at IVF for women aged 30-33, 34-37 and 38-41 and for 1 and 2 attempts for women aged 42-45. The expected incremental cost, effects and incremental cost effectiveness (incremental cost per additional live birth) are reported by additional IVF attempt (3 vs 2, 2 vs 1 and 1 vs 0) by age group from a government perspective in (MBS plus Medicare safety net costs) and a societal perspective and presented graphically on the incremental cost effectiveness plane in Figures 6 and 7.
Figure 6. Cumulative live births and costs by number of IVF treatment programs per couples commencing IVF treatment – Government perspective (MBS plus Medicare Safety Net Costs)

Figure 7. Cumulative live births and costs by number of IVF treatment programs per couples commencing IVF treatment – Societal perspective (Total Costs)
The 2002 ANZARD data used suggested a significant reduction in live birth rate by treatment program (using fresh embryos) from a rate of 22.3% for first treatment program to 19.0% in second treatment program (p=.0124) and 17.4% in third treatment program (p=.0045). When considering the impact of number of cycles this maybe partly explained by the higher proportion of older women (with lower live birth rates) in later treatment programs. It should be noted that while the IVF outcomes and costs in 30-33 and 42-45 year old women have been modelled dependent on number of IVF attempts (treatment programs) to reflect these findings. IVF outcomes and costs in 34-37 and 38-41 year old women have been modelled with live birth rates independent of the number of IVF attempts.

The cost-effectiveness modelling undertaken showed that for women aged 30-33 years the incremental cost per live birth from a Societal perspective increased from $27,373 (1 vs 0 treatment programs) to $30,098 (2 vs 1) and $31,836 (3 vs 2). For women aged 34-37 and 38-41 years the incremental cost per additional treatment program was independent of the number of treatment programs at $32,604 and $51,680 respectively. For women aged 42-45 years the incremental cost per live birth from a societal perspective increased from $130,951 (1 vs 0 treatment programs) to $187,516 (2 vs 1 treatment programs).

The equivalent incremental costs per live birth from the Government perspective were $16,208, $17,428 and $18,308 for 1 vs 0, 2 vs 1 and 3 vs 2 treatment programs in women aged 30-33 years. For women aged 34-37 and 38-41 the incremental costs per treatment program was $18,953 and $29,531, respectively. In women 42-25 years of age, the incremental costs per live birth were $73,401 and $105,109 for 1 vs 0 and 2 vs 1 treatment programs.

The modelled incremental cost per live birth increases across age groups and in 30-33 and 42-45 age cohorts by the number of treatment programs. This is the case whether a Government perspective or societal perspective is taken. The incremental cost per additional birth appears to be sensitive to variations in pregnancy rates associated with each maternal age group.

In all modelled sensitivity analyses undertaken the estimated incremental cost per live birth followed the base case trend and increased across age groups and in 30-33 and 42-45 age cohorts by the number of treatment programs. As previously noted, the economic modeling did not examine the cost-effectiveness of ICSI. Previous reviews have shown that, depending on the cause of male infertility that compared to the option of vasectomy reversal and repeat reversal, cost per delivery with ICSI are higher by as much as a factor of three. ICSI also costs nearly twice as much per birth as donor insemination.

A review of the economic implications of ART (Garceau 2002) found that although the quality of the economic benefit studies were mixed, they consistently showed that initiating treatment with IU1 appeared to be more cost-effective than IVF, and that vasectomy reversal appeared to be more cost-effective than ICSI. Factors associated with poor prognosis decreased the cost effectiveness of all interventions. For men with severe infertility, ICSI remains the only viable treatment in conceiving a child genetically related to both parents.
Key findings of the ART Review Committee:

- While the exact dollar amount varies across models used both in Australia and overseas, all show that the cost to achieve a live birth significantly increases with maternal age.
- Within younger (30-33 year) and older (42-45 year) age groups the cost per live birth increases with a greater number of treatment cycles.
- There is a higher pregnancy rate from IVF treatment in the younger age groups.
- An increase in public information on the consequences of delaying having children coupled with the known reduced effectiveness with increasing maternal age may help to reduce the need for ART in older women.
Conclusions

The evidence examined supported the continuation of funding for ART under the Medicare Benefits Scheme to clinically appropriate cases of medical infertility; the clinical appropriateness of ART for individual patients is best determined by the treating physician/s, having regard to evidence-based clinical research, expected treatment outcomes and the relevant national clinical practice guidelines.

To support good clinical practices, such as elective single embryo transfer (SET), and to ensure that appropriate standards of practice are available to all Australian couples seeking ART, mandatory accreditation should be introduced for all facilities providing any form of ART treatment, with public funding of ART services under the MBS and PBS linked to valid accreditation status.

Moreover, since the introduction of ART under the MBS the description of services under items has not been revised. A revision of the arrangement of the ART items is obviously warranted particularly in an area of such rapid technological change.

While the current data collection methods have provided useful information on the utilisation and success of ART in Australia there is some room for improvement in the type of data that are collected and reported that would aid both clinicians and patients in treatment decisions. Specifically, the introduction of a patient identifier would increase the utility and quantity of information available to review clinical effectiveness. Further development of the national data collection and reporting structures is, therefore, recommended to facilitate measurement of outcomes such as access to ART, clinical outcomes of ART treatment, and the costs for different treatment regimes. The development of a minimum data set in relation to ART services may be useful, as well as regular revision of the ART items as listed in the MBS to accurately reflect clinical practice.

There exists the possibility, in all disciplines, that previously unidentified clinical incidents can sporadically occur across the country. There is considerable merit in implementing mechanisms such as a carefully designed national reporting system to disseminate information about serious clinical incidents. Such a mechanism has great potential for improving the systems of care provision.

Although high quality evidence to support ICSI is limited, the treatment has gained widespread acceptance and use by clinicians and appears to be a clinically effective treatment for specific cases of severe male factor infertility where IVF is not suitable. There is also very limited evidence that it may improve the success of ART in couples who have not been successful in achieving a pregnancy using standard IVF techniques. There is an obvious need for further objective research to strengthen the evidence base for the development of safe and efficacious ART treatments, and to increase public awareness of the factors which affect fertility.

The evidence examined in this review demonstrates that there is a definite association between maternal age and success of ART, with a marked decrease in the success rate of ART for women over the age of 40 years. There is also a correlation between the length of infertility and the success of ART. These two factors, combined with the noted delay in childbearing in Australian women, may not be fully appreciated by couples and medical practitioners. There is an obvious
need to increase public awareness of the factors affecting fertility which may then encourage women to seek ART treatment when it has the highest chance of success.

It is also apparent that there are significant gaps in the current evidence for some aspects of ART, particularly new techniques such as blastocyst culture. It is also apparent that there are significant gaps in the current evidence for some aspects of ART, for example the success of SET with blastocyst stage embryos.

The cost-effectiveness analyses of ART, with regard to different age groups, support previous findings that the cost of a live birth increases with maternal age, and the number of treatment programs undertaken, indicating that due consideration should be given to maternal age and previous ART exposure when formulating clinical practice guidelines to assist evidence-based decision making by treatment providers.

Efforts to ensure quality and continuously improve the national provision of ART services should be approached in a collaborative manner sourcing appropriate expertise from all governments, relevant health care providers and consumer advocate groups.