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In Vitro Fertilization and Multiple Pregnancies

An Evidence-Based Analysis

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The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

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Executive Summary

Objective

The objective of this health technology policy assessment was to determine the clinical effectiveness and cost-effectiveness of IVF for infertility treatment, as well as the role of IVF in reducing the rate of multiple pregnancies.

Clinical Need: Target Population and Condition

Typically defined as a failure to conceive after a year of regular unprotected intercourse, infertility affects 8% to 16% of reproductive age couples. The condition can be caused by disruptions at various steps of the reproductive process. Major causes of infertility include abnormalities of sperm, tubal obstruction, endometriosis, ovulatory disorder, and idiopathic infertility. Depending on the cause and patient characteristics, management options range from pharmacologic treatment to more advanced techniques referred to as assisted reproductive technologies (ART). ART include IVF and IVF-related procedures such as intra-cytoplasmic sperm injection (ICSI) and, according to some definitions, intra-uterine insemination (IUI), also known as artificial insemination. Almost invariably, an initial step in ART is controlled ovarian stimulation (COS), which leads to a significantly higher rate of multiple pregnancies after ART compared with that following natural conception. Multiple pregnancies are associated with a broad range of negative consequences for both mother and fetuses. Maternal complications include increased risk of pregnancy-induced hypertension, pre-eclampsia, polyhydramnios, gestational diabetes, fetal malpresentation requiring Caesarean section, postpartum haemorrhage, and postpartum depression. Babies from multiple pregnancies are at a significantly higher risk of early death, prematurity, and low birth weight, as well as mental and physical disabilities related to prematurity. Increased maternal and fetal morbidity leads to higher perinatal and neonatal costs of multiple pregnancies, as well as subsequent lifelong costs due to disabilities and an increased need for medical and social support.

The Technology Being Reviewed

IVF was first developed as a method to overcome bilateral Fallopian tube obstruction. The procedure includes several steps: (1) the woman's egg is retrieved from the ovaries; (2) exposed to sperm outside the body and fertilized; (3) the embryo(s) is cultured for 3 to 5 days; and (4) is transferred back to the uterus. IFV is considered to be one of the most effective treatments for infertility today. According to data from the Canadian Assisted Reproductive Technology Registry, the average live birth rate after IVF in Canada is around 30%, but there is considerable variation in the age of the mother and primary cause of infertility.

An important advantage of IVF is that it allows for the control of the number of embryos transferred. An elective single embryo transfer in IVF cycles adopted in many European countries was shown to significantly reduce the risk of multiple pregnancies while maintaining acceptable birth rates. However, when number of embryos transferred is not limited, the rate of IVF-associated multiple pregnancies is similar to that of other treatments involving ovarian stimulation. The practice of multiple embryo transfer in IVF is often the result of pressures to increase success rates due to the high costs of the procedure. The average rate of multiple pregnancies resulting from IVF in Canada is currently around 30%.

An alternative to IVF is IUI. In spite of reported lower success rates of IUI (pregnancy rates per cycle range from 8.7% to 17.1%) it is generally attempted before IVF due to its lower invasiveness and cost.

Two major drawbacks of IUI are that it cannot be used in cases of bilateral tubal obstruction and it does not allow much control over the risk of multiple pregnancies compared with IVF. The rate of multiple pregnancies after IUI with COS is estimated to be about 21% to 29%.

Ontario Health Insurance Plan Coverage

Currently, the Ontario Health Insurance Plan covers the cost of IVF for women with bilaterally blocked Fallopian tubes only, in which case it is funded for 3 cycles, excluding the cost of drugs. The cost of IUI is covered except for preparation of the sperm and drugs used for COS.

Diffusion of Technology

According to Canadian Assisted Reproductive Technology Registry data, in 2004 there were 25 infertility clinics across Canada offering IVF and 7,619 IVF cycles performed. In Ontario, there are 13 infertility clinics with about 4,300 IVF cycles performed annually.

Literature Review

Royal Commission Report on Reproductive Technologies

The 1993 release of the Royal Commission report on reproductive technologies, *Proceed With Care*, resulted in the withdrawal of most IVF funding in Ontario, where prior to 1994 IVF was fully funded. Recommendations of the Commission to withdraw IVF funding were largely based on findings of the systematic review of randomized controlled trials (RCTs) published before 1990. The review showed IVF effectiveness only in cases of bilateral tubal obstruction. As for nontubal causes of infertility, there was not enough evidence to establish whether IVF was effective or not.

Since the field of reproductive technology is constantly evolving, there have been several changes since the publication of the Royal Commission report. These changes include: increased success rates of IVF; introduction of ICSI in the early 1990's as a treatment for male factor infertility; and improved embryo implantation rates allowing for the transfer of a single embryo to avoid multiple pregnancies after IVF.

Studies After the Royal Commission Report: Review Strategy

Three separate literature reviews were conducted in the following areas: clinical effectiveness of IVF, cost-effectiveness of IVF, and outcomes of single embryo transfer (SET) in IVF cycles.

1. Clinical effectiveness of IVF: RCTs or meta-analyses of RCTs that compared live birth rates after IVF versus alternative treatments, where the cause of infertility was clearly stated or it was possible to stratify the outcome by the cause of infertility.
2. Cost effectiveness of IVF: All relevant economic studies comparing IVF to alternative methods of treatment were reviewed
3. Outcomes of IVF with SET: RCTs or meta-analyses of RCTs that compared live birth rates and multiple birth rates associated with transfer of single versus double embryos.

OVID MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Cochrane Library, the International Agency for Health Technology Assessment database, and websites of other health technology assessment agencies were searched using specific subject headings and keywords to identify relevant studies.

Summary of Findings

Comparative Clinical Effectiveness of IVF

Overall, there is a lack of well composed RCTs in this area and considerable diversity in both definition and measurement of outcomes exists between trials. Many studies used fertility or pregnancy rates instead of live birth rates. Moreover, the denominator for rate calculation varied from study to study (e.g. rates were calculated per cycle started, per cycle completed, per couple, etc…).

Nevertheless, few studies of sufficient quality were identified and categorized by the cause of infertility and existing alternatives to IVF. The following are the key findings:

- A 2005 meta-analysis demonstrated that, in patients with idiopathic infertility, IVF was clearly superior to expectant management, but there were no statistically significant differences in live birth rates between IVF and IUI, nor between IVF and gamete-intra-Fallopian transfer.
- A subset of data from a 2000 study showed no significant differences in pregnancy rates between IVF and IUI for moderate male factor infertility.
- In patients with moderate male factor infertility, standard IVF was also compared with ICSI in a 2002 meta-analysis. All studies included in the meta-analysis showed superior fertilization rates with ICSI, and the pooled risk ratio for oocyte fertilization was 1.9 (95% Confidence Interval 1.4-2.5) in favour of ICSI. Two other RCTs in this area published after the 2002 meta-analysis had similar results and further confirmed these findings. There were no RCTs comparing IVF with ICSI in patients with severe male factor infertility, mainly because based on the expert opinion, ICSI might only be an effective treatment for severe male factor infertility.

Cost-Effectiveness of IVF

Five economic evaluations of IVF were found, including one comprehensive systematic review of 57 health economic studies. The studies compared cost-effectiveness of IVF with a number of alternatives such as observation, ovarian stimulation, IUI, tubal surgery, varicocelectomy, etc… The cost-effectiveness of IVF was analyzed separately for different types of infertility. Most of the reviewed studies concluded that due to the high cost, IVF has a less favourable cost-effectiveness profile compared with alternative treatment options. Therefore, IVF was not recommended as the first line of treatment in the majority of cases. The only two exceptions were bilateral tubal obstruction and severe male factor infertility, where an immediate offer of IVF/ICSI might the most cost-effective option.

Clinical Outcomes After Single Versus Double Embryo Transfer Strategies of IVF

Since the SET strategy has been more widely adopted in Europe, all RCT outcomes of SET were conducted in European countries. The major study in this area was a large 2005 meta-analysis, followed by two other published RCTs.

All of these studies reached similar conclusions:

- Although a single SET cycle results in lower birth rates than a single double embryo transfer (DET) cycle, the cumulative birth rate after 2 cycles of SET (fresh + frozen-thawed embryos) was comparable to the birth rate after a single DET cycle (~40%).
- SET was associated with a significant reduction in multiple births compared with DET (0.8% vs. 33.1% respectively in the largest RCT).

Most trials on SET included women younger than 36 years old with a sufficient number of embryos available for transfer that allowed for selection of the top quality embryo(s). A 2006 RCT, however, compared SET and DET strategies in an unselected group of patients without restrictions on the woman's age or embryo quality. This study demonstrated that SET could be applied to older women.

Estimate of the Target Population

Based on results of the literature review and consultations with experts, four categories of infertile patients who may benefit from increased access to IVF/ICSI were identified:

1. Patients with severe male factor infertility, where IVF should be offered in conjunction with ICSI;
2. Infertile women with serious medical contraindications to multiple pregnancy, who should be offered IVF-SET;
3. Infertile patients who want to avoid the risk of multiple pregnancy and thus opt for IVF-SET; and
4. Patients who failed treatment with IUI and wish to try IVF.

Since, however, the latter indication does not reflect any new advances in IVF technology that would alter existing policy, it was not considered in this analysis.

Economic Analysis

Economic Review: Cost–Effectiveness of SET Versus DET

Conclusions of published studies on cost-effectiveness of SET versus DET were not consistent. While some studies found that SET strategy is more cost-effective due to avoidance of multiple pregnancies, other studies either did not find any significant differences in cost per birth between SET and DET, or favoured DET as a more cost-effective option.

Ontario-Based Economic Analysis

An Ontario-based economic analysis compared cost per birth using three treatment strategies: IUI, IVF-SET, and IVF-DET. A decision-tree model assumed three cycles for each treatment option. Two separate models were considered; the first included only fresh cycles of IVF, while the second had a combination of fresh and frozen cycles. Even after accounting for cost-savings due to avoidance of multiple pregnancies (only short-term complications), IVF-SET was still associated with a highest cost per birth. The approximate budget impact to cover the first three indications for IVF listed above (severe male factor infertility, women with medical contraindications to multiple pregnancy, and couples who wish to avoid the risk of multiple pregnancy) is estimated at $9.8 to $12.8 million (Cdn). Coverage of only first two indications, namely, ICSI in patients with severe male factor infertility and infertile women with serious medical contraindications to multiple pregnancy, is estimated at $3.8 to $5.5 million Cdn.

Other Considerations

- International data shows that both IVF utilization and the average number of embryos transferred in IVF cycles are influenced by IVF funding policy. The success of the SET strategy in European countries is largely due to the fact that IVF treatment is subsidized by governments.
- Surveys of patients with infertility demonstrated that a significant proportion (~40%) of patients not only do not mind having multiple babies, but consider twins being an ideal outcome of infertility treatment.
- A women's age may impose some restrictions on the implementation of a SET strategy.

Conclusions and Recommendations

- A review of published studies has demonstrated that IVF-SET is an effective treatment for infertility that avoids multiple pregnancies.
- However, results of an Ontario-based economic analysis shows that cost savings associated with a reduction in multiple pregnancies after IVF-SET does not justify the cost of universal IVF-SET coverage by the province. Moreover, the province currently funds IUI, which has been shown to be as effective as IVF for certain types of infertility and is significantly less expensive.
- In patients with severe male factor infertility, IVF in conjunction with ICSI may be the only effective treatment.

Thus, 2 indications where additional IVF access should be considered include:

- IVF/ICSI for patients with severe male factor infertility
- IVF-SET in infertile women with serious medical contraindications to multiple pregnancy

Abbreviations

ART	Assisted Reproductive Technologies
CARTR	Canadian Assisted Reproductive Technology Registry
CDC	Center for Disease Control
CI	Confidence Interval
CIHI	Canadian Institute for Health Information
COS	Controlled Ovarian Stimulation
DET	Double Embryo Transfer
ESHRE	European Society for Human Reproduction and Embryology
eSET	Elective Single Embryo Transfer
FZET	Frozen Embryo Transfer
GIFT	Gamete Intra-Fallopian Transfer
IAAC	Infertility Awareness Association of Canada
ICSI	Intracytoplasmic Sperm Injection
IUI	Intrauterine Insemination
IVF	In Vitro Fertilization
OCCI	Ontario Case Costing Initiative
OHIP	Ontario Health Insurance Plan
OHSS	Ovarian Hyperstimulation Syndrome
RCNRT	Royal Commission on New Reproductive Technologies
RCT	Randomized Clinical Trial
SET	Single Embryo Transfer
SOGC	Society of Obstetricians and Gynaecologists of Canada
ZIFT	Zygote Intra-Fallopian transfer

Objective

The objective of this health technology policy assessment was to determine the clinical effectiveness and cost-effectiveness of IVF for infertility treatment, as well as the role of IVF in reducing the rate of multiple pregnancies.

Background

Multi-fetal pregnancy is considered to be an adverse effect of infertility treatment due to its association with a number of maternal and neonatal complications. Among the available infertility treatment options, only in vitro fertilization (IVF) permits control of the risk of multiple pregnancy through limitation of the number of embryos transferred. The Infertility Awareness Association of Canada (IAAC), therefore, advocates a broader use of IVF and requested an inquiry into expansion of IVF coverage. The inquiry was approved for further investigation by the Provider's Services Branch, Ministry of Health and Long-Term Care and the Ontario Health Technology Advisory Committee.

Clinical Need: Target Population and Condition

Infertility is typically defined as the failure to conceive after a year of regular unprotected sexual intercourse. (1)

Prevalence of Infertility

The most commonly cited estimate of the prevalence of infertility among North American couples is 15%. This number is based on a 1995 Center for Disease Control (CDC) estimate of the percentage of women between 15 and 44 years old who had ever received infertility services. (2) Studies from the United Kingdom report similar rates of prevalence ranging from 14% (3) to 16% (4). Similar studies from conducted in the Netherlands (5) and India (6) report a somewhat lower prevalence of around 10%.

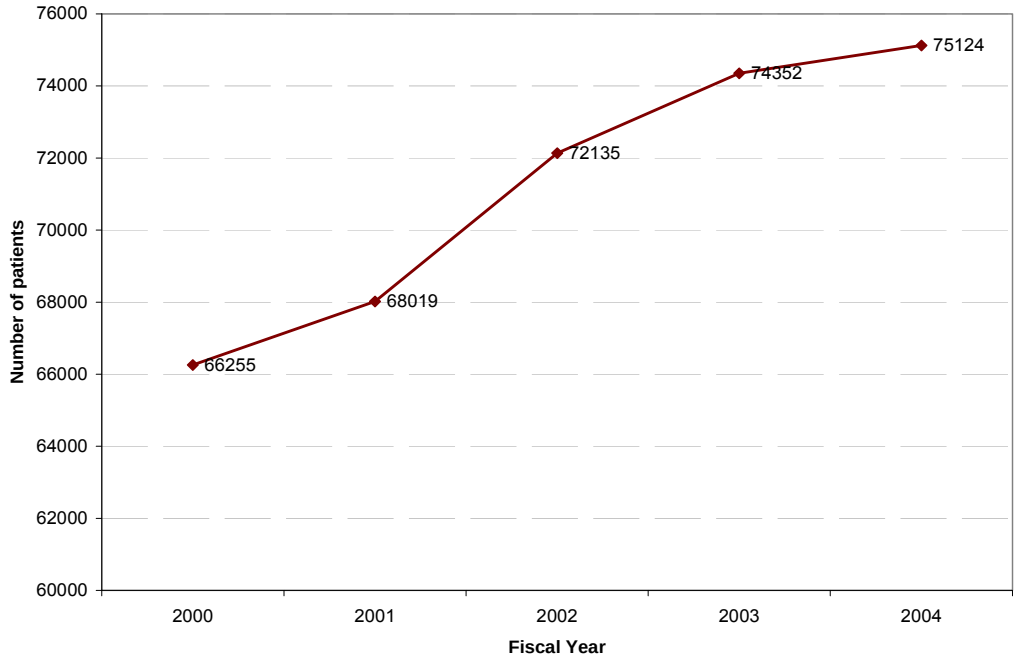
The only official Canadian estimate of prevalence of infertility was based on three telephone surveys conducted across Canada in the early nineties which included a total of 1,412 respondents. (7) All three surveys yielded similar results showing that about 8.5% (95% Confidence Interval [CI] 7.0%-9.9%) of couples were experiencing infertility at the time of the survey. It may, however, be that the prevalence of infertility in Canada has since risen due to factors such as increasing age for having a first child (8;9), an increase in the incidence of sexually transmitted diseases (10) and the rising prevalence of obesity (11).

The growing prevalence of infertility, along with an increasing awareness and willingness to seek medical care for infertility, may explain an increase in the number of infertility-related doctor's visits in Ontario (Figure 1). These numbers are likely an underestimation as patients with infertility often seek medical treatment in private clinics, which are not covered by the Provincial Health Planning Database. (12)

Causes of Infertility

The causes of infertility can be broadly divided into female and male factor infertility. Female factors include blocked or damaged Fallopian tubes, endometriosis, ovulation failure, fibroids, and hostile cervical mucus. Male factor infertility can be due to failure of sperm production, low sperm motility, and/or the production of antibodies to spermatozoids. Table 1 gives the approximate distribution of infertility causes as reported by a population study from the United Kingdom. (13)

Figure 1: Number of Patients with Ontario Health Insurance Plan Billing for Diagnosis or Treatment of Infertility by Year



Source: Canadian Institute for Health Information, Provincial Health Planning Database, Ontario Ministry of Health, 2006

Table 1: Annual Causes of Fertility by Final Diagnostic Classification and Related to Parity (From a Population Study in the United Kingdom)

Cause of infertility	No of couples with each cause	% Of couples (n=472)	Previous pregnancy (%)		
			Any	Termination of pregnancy	Child*
Ovulatory failure†	97	21	39	6	30
Tubal damage‡	68	14	70	20	44
Endometriosis	27	6	21	6	15
Mucus defect/dysfunction	16	3	6	0	6
Sperm defect/dysfunction	111	24	27	11	18
Other male infertility	9	2	12	0	12
Coital/suspected coital failure	26	6	57	22	20
Unexplained§	133	28	47	10	41
Others	50	11			
Total No of causes‖	537				
Total % of couples			41	11	29

*Child = gestation at least 28 weeks, not necessarily successful.
†Includes three women with primary ovarian failure, which is untreatable to induce ovulation.
‡Includes three women with endometriosis.
§Defined by exclusion of all preceding causes, but includes some patients with minor abnormalities of doubtful importance—namely, tubal adhesions (2), endometriosis (11), and oligospermia with normal postcoital penetration of mucus (7).
‖Total causes reduced compared with table I by 14 cases of oligospermia with normal penetration of mucus, now treated as normal. 13% Of couples have two or more causes of infertility.

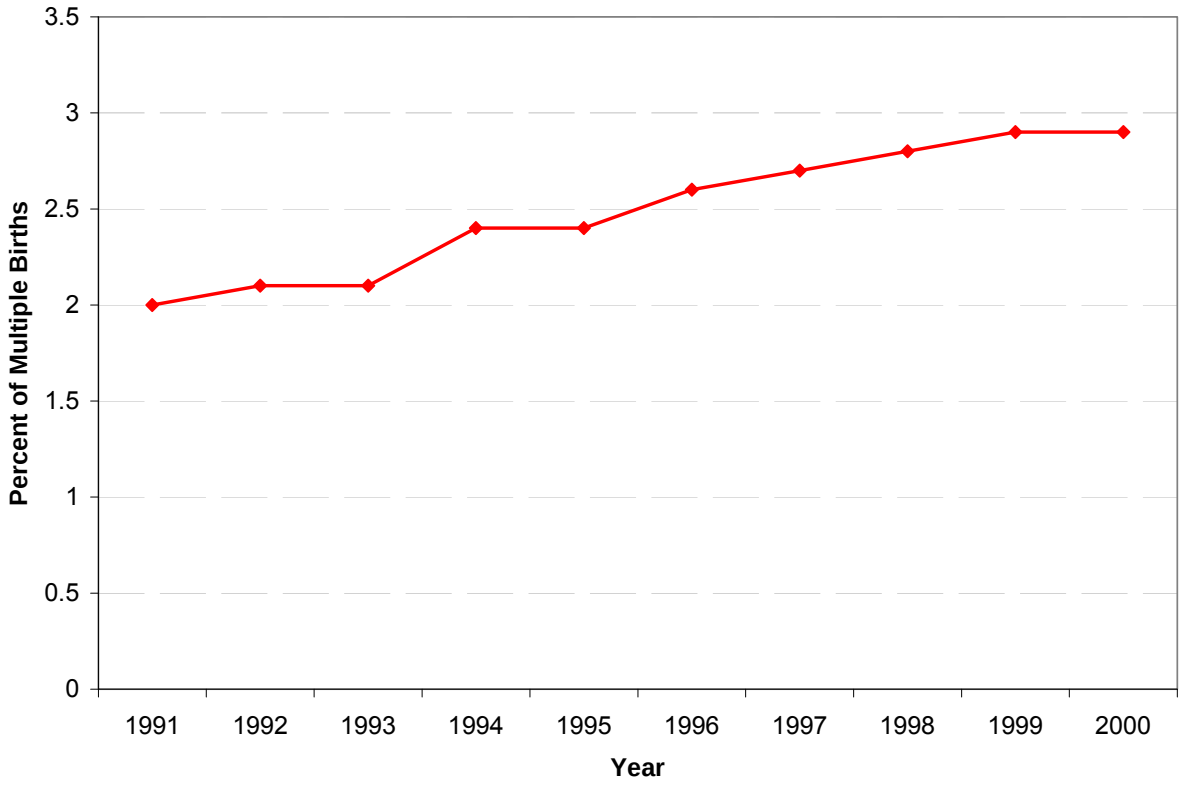
Source: Hull MG, Glazener CM, Kelly NJ, Conway DI, Foster PA, Hinton RA et al. Population study of causes, treatment, and outcome of infertility. Br Med J (Clin Res Ed) 1985; 291(6510): 1693-1697

The distribution presented in Table 1 reflects the situation observed in the United Kingdom more than 2 decades ago, which may have since changed. For example, an increase in the incidence of pelvic inflammatory disease might have led to the increased prevalence of tubal infertility.

Infertility Treatment and Multiple Pregnancy

The rate of natural twinning is relatively stable worldwide at under 2 %. (14) Over the last few decades, however, there has been an increase in the rate of twin births and higher order multiple births in developed countries including Canada (Figure 2). This phenomenon can be attributed to two changes in human reproduction that have taken place over this time period: an increasing delay in the age of childbearing and the use of assisted reproduction. It has been shown that the delay in childbearing accounts for less than 30% of the recorded increase in multiple births. (15) The main contributing factor to the rise in multiple pregnancies is, therefore, believed to be the rise of infertility treatments. It has been estimated that births resulting from infertility treatments account for about 1% to 3% of all single live births, 30% to 50% of twin births, and for more than 75% of higher order multiple births. (16)

Figure 2: Rate of Multiple Births in Ontario, 1991-2000



Source: Health Canada. Canadian Perinatal Health Report, 2003. Ottawa: Minister of Public Works and Government Services Canada, 2003.

Difficulties Related to Multiple Pregnancies

Multiple pregnancies and births are associated with a wide range of negative consequences for both mother and a baby. The major consequences and difficulties of this are: (16)

Maternal Obstetric

- Miscarriage
- Fetal reduction
- Pregnancy complications: anaemia, pre-eclampsia, gestational diabetes, intra-uterine growth retardation
- Caesarean section
- Post-partum haemorrhage
- Mortality

Maternal Postnatal

- Infection
- Bleeding
- Isolation, stress, depression
- Bonding with child or children

Child Perinatal

- Prematurity
- Low birthweight
- Mortality, morbidity
- Malformations

Child Long-term

- Cerebral palsy
- Disability
- Learning difficulties
- Infant mortality
- Adult health risks (Barker hypothesis)

Family Single-survivor

- Guilt
- Blamed by parents

Sibling

- Attention deficit
- Delayed development

Parents

- Stress
- Isolation, depression
- Divorce

Source: Fauser BC, Devroey P, Macklon NS. Multiple birth resulting from ovarian stimulation for subfertility treatment. Lancet 2005; 365(9473): 1807-1816, modified from original source: Ombelet W, De Sutter P, Van der EJ, Martens G. Multiple gestation and infertility treatment: registration, reflection and reaction--the Belgian project. Hum Reprod Update 2005; 11(1): 3-14

Use of Assisted Reproduction in Infertility Treatment

The choice of a specific option for infertility treatment is determined by the cause of infertility and patient characteristics. Treatment could be relatively simple, such as pharmacological stimulation of the ovaries using drugs such as clomiphene citrate and gonadotropins, or it may require more advanced techniques, which, as a group, are referred to as assisted reproductive technologies (ART).
ART is defined as either:

1. Treatment of infertility, in which both eggs and sperm are manipulated. (17) According to this definition used by CDC, ART includes only IVF and IVF-related procedures, but not intra-uterine insemination (IUI), in which only sperm is handled.

Or

2. Treatment of infertility that involves handling eggs, sperm, or both outside the human body. (18) According to this definition used by the Society of Obstetricians and Gynaecologists of Canada (SOGC), IUI is also considered to be ART.

Regardless of the definition used, ART (IVF and IUI) almost always employs controlled ovarian (hyper)stimulation (COS) as an initial step, which leads to an increased risk of multiple pregnancy.

While the IVF procedure is the main focus of this report, in the economic analysis IVF will be compared with the most common non-IVF alternatives, namely, IUS with COS, also known as IUI-COS.

Non-IVF alternative: Intra-Uterine Insemination (IUI)

IUI can be described simply as the deposition of sperm into the uterine cavity using a fine plastic catheter (Appendix 2a). The timing of an IUI procedure is critical: it should be done at the time of ovulation or shortly thereafter. Onset of ovulation is determined through careful monitoring of a patient's serum hormone levels and ultrasound of the ovaries.

IUI increases the chances of pregnancy by increasing the number of sperm entering the uterine cavity. Although IUI can be performed using the natural ovulatory cycle, COS before IUI significantly enhances its effectiveness.

The clinical effectiveness of IUI has been well established. (19;20) Compared with timed intercourse, IUI increases the chances of pregnancy by 2- to 3-fold. When combined with COS, IUI further increases the odds of pregnancy 6-fold compared with timed intercourse. (20) The increased pregnancy rate after IUI-COS is related to the larger number of eggs available for fertilization after ovarian stimulation. Reported clinical pregnancy rates associated with IUI-COS range between 8.7% (21) and 17.1% (22). While increasing the success rate of the procedure, COS before IUI is associated with an increased risk of multiple pregnancies. Ideally the goal of COS before IUI is to have 2 to 3 preovulatory follicles. When more than 3 follicles are seen, which is observed in up to 40% of cycles, the chances of multiple pregnancy are substantial. (23) These cycles should be either cancelled or converted to IVF. (14)

One of the disadvantages of IUI is that it cannot be used for the treatment of tubal infertility because an ovum has to reach the uterine cavity for IUI to work. But apart from cases of tubal obstruction, IUI is a widely used method of assisted reproduction due to its relative simplicity, lower invasiveness and cost compared with IVF. In majority of cases it is tried first before proceeding to IVF.

In-Vitro Fertilization

History

IVF derived its name from the fact that fertilization occurs outside of the woman's body in a "glass tube". The procedure was first introduced for the treatment of bilateral tubal obstruction when other treatments failed. In July 1978, Louise Brown, the world's first baby conceived outside the human body, was born in Britain as a result of the work of IVF pioneers, Dr. Edwards and Dr. Steptoe. Since then, the technology has been refined and developed by physicians and embryologists, with over 20,000 babies born worldwide. Currently, IVF is performed not only for tubal infertility, but also for unexplained male factor infertility, endometriosis, and ovulatory disorders. In Canada, almost half of all IVF cycles performed in 2001 were for nontubal indications. (24).

The IVF Procedure

IVF involves four principal steps:

1. First, under ultrasound guidance, the eggs are retrieved from the ovaries by placing a needle into the ovarian follicle and removing the fluid containing the egg (Appendix2b)
2. Second, the ovum is exposed to spermatozoa for fertilization outside the woman's body
3. After fertilization, the eggs are cultured for 3 to 5 days. After 5 days, an embryo is called a blastocyst. Although it's generally believed that blastocysts have a greater chance for implantation, a recent systematic review failed to show any significant differences in live birth rates between either Day 2 to 3 or Day 5 to 6 transfer of embryos. (25)
4. The final step involves transferring the embryos back into the woman's uterus through the cervix using a small, soft catheter.

Typically IVF cycles are done after COS. A more aggressive regimen of COS is used compared with COS before IUI as in this case the goal of ovarian stimulation is to yield a large number of oocytes (9-10 on average, see Appendix 4). The large number of eggs compensates for the inefficiency of the laboratory procedures that limit fertilization and subsequent embryo development *in vitro*. (16) This also allows for the choice of top quality embryos for transfer, termed 'elective embryo transfer'.

IVF enhancements and other ART procedures

'Spare' embryos that are remain unused in the current IVF cycle can be frozen for use in future cycles. Frozen embryo transfer (FZET) is a procedure in which such frozen embryos are thawed and placed in the womb. Since FZET can be attempted without the need for a new cycle of ovarian stimulation and egg retrieval, it increases the efficiency and cost-effectiveness of a single IVF cycle.

Other IVF-related procedures include:

Intracytoplasmic Sperm Injection (ICSI) – a procedure in which a single sperm cell is selected and injected directly into each egg to fertilize it (Appendix 5). ICSI is mainly indicated for severe male factor infertility and in cases of previous IVF failure.

In Gamete Intra-Fallopian Transfer (GIFT) – a procedure in which mature eggs and sperm are placed directly into the woman's Fallopian tubes where natural fertilization takes place.

Zygote Intra-Fallopian Transfer (ZIFT) – a combination of IVF and GIFT: eggs are fertilized *in vitro* and the embryos then placed in the Fallopian tubes.

National registries data on success rates of IVF

Data on success rates and complications associated with IVF/ICSI are routinely collected in many countries by national ART registries. Success rates of IVF can be defined in several ways: on-going clinical pregnancy rates (the presence of an intrauterine gestational sac with a fetal heartbeat on ultrasound), delivery rates, or live birth rates per IVF cycle or per embryo transfer. According to international registries data, overall pregnancy rates associated with IVF cycle are approaching and sometimes exceed 30% depending on the treatment centre and country. Success rates are also largely determined by patient characteristics, mainly the woman's age. There is an almost exponential decline in the success of ART after the age of 35 due to the natural age-related decline in fertility.

Data from European ART registries (26) showed that the mean clinical pregnancy rates after IVF across 25 European countries was 29.5% in 2002, ranging from 23.5% (Croatia) to 40.5% (Belgium). The live birth rate per embryo transfer was somewhat lower and ranged from 10.6% (Bulgaria) to 28.5% (Norway). On the other hand, the mean clinical pregnancy rates resulting from IUI-COS (reported by the same source) were considerably lower compared with pregnancy rates after IVF: in women under the age of 40, the IUI-associated pregnancy rate was 11.6% and ranged from 6.4% (Slovenia) to 21.2% (Greece).

In North America, the average success rates for IVF are higher due to a more aggressive approach in the transfer of a larger number of embryos than in Europe. In 2003, the IVF-associated live birth rates after the transfer of fresh and frozen-thawed nondonor embryos in the United States were 34.7% and 27%, respectively. (17)

In Canada, data on outcomes of IVF cycles has been routinely collected by the Canadian Assisted Reproductive Technologies Registry (CARTR) since 1999. Table 2 displays a summary of the last 2 years of available data.

Table 2: Outcomes of IVF/ICSI Cycles in Canada in 2003-2004*

	Year 2003	Year 2004
Number of reporting IVF centres	24	25
Number of IVF/ICSI cycles performed in Canada	7415	7619
Average live birth rate per cycle started	24%	31%
Average live birth rates by age of the mother		
<35 years old	31%	38%
35-39 years old	22%	30%
40+ years old	9%	16%
Plurality of births		
Singletons	69%	70%
Percent of twins among multiple births	95%	92%

*ICSI refers to Intracytoplasmic Sperm Injection; IVF, in vitro fertilization
Source: Canadian Fertility and Andrology Society. Human assisted reproduction live birth rates for Canada. CFAS Press Release [Web page]. November 17, 2005. [cited 2006 Aug. 11]. Available at: http://www.cfas.ca/english/news/Nov17-2005.asp

The success rates of IUI in Canada are not systematically collected. Statistics reported by a few infertility clinics (reported IUI pregnancy rates range from 13% to 22%) are not reliable as they are based on a small number of observations and not standardized across centres.

Characteristics of Patients Undergoing IVF/ICSI in Canada

According to CARTR data, the majority of women undergoing IVF/ICSI cycles in Canada in 2001 were under age of 35(except for cycles using donor eggs where the majority of women were older than 40 years). Tubal and male factor infertility were the main primary diagnoses; half of the patients undergoing IVF had tubal infertility and more than a half of those undergoing ICSI had male factor infertility.

Table 3: Number of ART Cycles in Canada (2001) by Female Age*

Female age (years)	IVF/ICSI	IVF/ICSI-DO	FZET
Mean (range)	35 (21-49)	40 (23-54)	35 (19-48)
Count (percent) of cycles by age group			
<35	2, 394 (44.4)	59 (19.7)	868(44.9)
35-39	2,148 (39.8)	79 (26.3)	819 (42.3)
≥40	851 (15.8)	162 (54.0)	247 (12.8)

* IVF/ICSI-DO refers to *in vitro* fertilization/ intracytoplasmic sperm injection using donor oocyte; FZET, frozen embryo transfer

Adapted from Gunby J, Daya S. Assisted reproductive technologies (ART) in Canada: 2001 results from the Canadian ART Register. Fertil Steril 2005; 84(3): 590-599

Table 4: Distribution of ART Cycles in Canada (2001) by the Cause of Infertility

Primary diagnosis	IVF		ICSI	
	Number (%) of cycles	PR*	Number (%) of cycles	PR*
Male factor	98 (4.6)	26 (26.5)	1,489 (56.0)	543 (36.5)
Tubal factor	1,057 (50.1)	300 (28.4)	359 (13.5)	98 (27.3)
Idiopathic	477 (22.6)	153 (32.1)	349 (13.1)	114 (32.7)
Endometriosis	204 (9.7)	81 (39.7)	177 (6.7)	39 (22.0)
Ovulatory disorder	124 (5.9)	46 (37.1)	145 (5.5)	44 (30.3)
Other	148 (7.0)	45 (30.4)	140 (5.3)	33 (23.6)

* PR –pregnancy rate per oocytes retrieval

Adapted from Gunby J, Daya S. Assisted reproductive technologies (ART) in Canada: 2001 results from the Canadian ART Register. Fertil Steril 2005; 84(3): 590-599

Side effects of IVF

Aside from multiple pregnancy, other side effects of IVF include ovarian hyperstimulation syndrome (OHSS) and increased risk of birth defects. Ovarian hyperstimulation syndrome is a rare complication of assisted reproduction with a reported incidence of between 1% and 10% of IVF cycles. (27) It can be defined as an exaggerated response to ovulation induction therapy. The syndrome has a broad spectrum of clinical manifestations, from mild symptoms to severe disease conditions requiring hospitalization and intensive care. (28) Severe forms of OHSS occur in 0.5% to 2% of women undergoing COS for IVF. Several patient factors such as younger age, lean appearance, polycystic ovarian syndrome, and high serum estradiol might be associated with a higher incidence of OHSS.(27)

There appears to be a higher risk of birth defects associated with IVF/ICSI. (29;(30) Results of a recent systematic review (25 studies) and a meta-analysis (7 studies) (30) demonstrated a 30% to 40% increased risk of birth defects associated with IVF/ICSI. It still unclear though, whether this risk is due to the technique itself or just a reflection of the elevated background risk associated with infertility.

Rates of Multiple Pregnancy After ART

The most common side effect of ART is multiple pregnancies. According to various estimates, the rate of multiple births after IUI ranges from 21% (31) to 29% (21). The rate of multiple births resulting from IVF is comparable. In Canada, the average rate of multiple deliveries associated with IFV/ICSI was 33% (24) in 2001, dropping slightly to 30% in 2004 (32). However, the relative contribution of IVF to the number of multiple births resulting from infertility treatment might be higher than that of IUI due to higher the success rates of IVF. (14)

The risk of multiple births associated with IVF is directly related to the number of embryos transferred in each cycle. The practice of transferring more than 1 embryo goes back to the early days of IVF when embryo quality and implantation rates were quite low and placing multiple embryos was performed to compensate for low implantation potential. Recent estimates of the average implantation rate is around 50% (16), but this varies considerably according to the woman's age.

Improvements in implantation rates removed the pressure to transfer multiple embryos. This possibility, as well as recognition of complications associated with multiple pregnancies, has led to the promotion of an elective single embryo transfer (eSET) policy (33) that became widely adopted in many European countries. Table 5 shows the percent of multiple deliveries resulting from ARTs in the United States, Europe, and Canada. Note that stricter rules on the number of embryos transferred explains the lower rate of multiple births in Europe compared to North America.

Table 5: Percentage of Deliveries in the United States, Europe, and Canada Following ART by Plurality* (18)

Country/ Year	Number of deliveries following ART	Singleton %	Twin %	Triplet and higher order pregnancy %
United States 2002	25,641	58	29	7†
Europe 2000	34,392	74	24	2
Canada 2002	2201‡	68	29	3

*ART refers to assisted reproductive technology.
†United States figures do not total 100% since 6% of pregnancies ended in miscarriage in which the number of fetuses could not be accurately determined.
‡Number of ongoing pregnancies (pregnancy rate minus miscarriage rate).
Source: Allen VM, Wilson RD, Cheung A. Pregnancy outcomes after assisted reproductive technology. J Obstet Gynaecol Can 2006; 28(3): 220-250

Regulatory Status

Before 1994, the Ontario Health Insurance Plan (OHIP) covered IVF services for all clinically qualified recipients. (34) However, after the release of the final report of the Royal Commission on Reproductive Technologies *Proceed With Care* in 1993 (7), most of the IVF coverage was removed. Currently, only women with bilaterally blocked Fallopian tubes are eligible for OHIP coverage, in which case it is funded for three cycles only and excludes the cost of drugs. In contrast, the cost of IUI is covered by OHIP except for the preparation of sperm and the cost of drugs used for ovarian stimulation.

Literature Review on Effectiveness & Cost-Effectiveness of IVF and its Role in Reduction of Multiple Pregnancy

The Royal Commission Report on Reproductive Technologies

The final report of the Royal Commission on Reproductive Technologies *Proceed With Care* (7) released in 1993 brought about significant changes in the funding policy of IVF in Ontario. The report's recommendations were based on a comprehensive (for the time) review of evidence on the clinical effectiveness of IVF. In order to be considered an effective treatment, IVF was expected to meet 2 criteria set by the Commission:

1. *IVF would have to be shown to be effective for a specific indication through appropriately designed RCTs that allowed meta-analysis of combined studies with a total of at least 200 couples in both the control and the treatment group; or*

2. *If a specific mechanism is known to be causing the infertility, IVF would have to be shown to correct it in a way that is biologically convincing.*

Among the 501 RCTs conducted before 1990, only five were judged by the Commission to be of sufficient quality to be included in systematic review. Based on results of these five, the Commission concluded that standard IVF was effective only in cases of bilateral Fallopian tube blockage resulting from tubal disease or defect, severe endometriosis, or surgical sterilization. As for nontubal indications, there was not enough evidence to categorize IVF as either effective or non-effective. The Report emphasized that *"…this is not the same as saying that IVF does not work; rather, additional and better data are required before firm conclusions can be drawn about the appropriateness of IVF as a treatment for most types of infertility"* (7)

Research Questions for the Present Literature Review

Over the greater than a decade period since the release of the Royal Commission report, several significant changes have occurred in the field of reproductive technology. Constant improvements in IVF methods and techniques have resulted in higher success rates. While the Royal Commission report cited live birth rates after IVF of around 10% per cycle, the CARTR data for 2004 reported an overall live birth rate of 31%. The technique of ICSI was also introduced in early 1990, specifically as a method to overcome severe male factor infertility. Finally, better knowledge of embryo physiology and improved techniques of transfer have led to higher embryo implantation rates and made it possible to adapt a single embryo transfer strategy as a way of eliminating the risk of IVF-associated multiple pregnancy.

In light of the current situation, the following questions were posed for the literature review:

1. Is IVF/ICSI superior to other non-IVF modalities for the treatment of infertility conditions other than tubal?
2. Is IVF a cost-effective treatment for infertility?
3. How do live birth rates and multiple birth rates after eSET compare with those after DET?

Methods

Literature Review Strategy

Three separate literature reviews were conducted to answer the three questions of the analysis.

1. The first review focused on the evidence of clinical effectiveness of IVF as compared to non-IVF methods of infertility treatment. Clinical effectiveness was defined in terms of live birth rates. In order to be considered in the analysis, the study had to be either an RCT or a meta-analysis of RCTs, with a clearly stated cause of infertility (male factor or idiopathic). If a study included patients with multiple types of infertility, it would have to allow for stratification of outcomes by the cause of infertility.
2. The second review analyzed the cost-effectiveness of IVF in comparison to other methods of treatment. All types of health economic studies were included in the economic reviews as long as the study was relevant to the study question.
3. The third review analyzed two major clinical outcomes, namely live birth rates and multiple pregnancy rates associated with SET versus DET. Only RCTs and meta-analyses of RCTs were considered.

OVID MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, The Cochrane Library, the International Agency for Health Technology Assessment database, and websites of other health technology assessment agencies were searched using specific key words to identify relevant studies. Appendix 1 describes details of each of the three review strategies.

Results of Literature Review

Comparative Effectiveness of IVF

Issues with studies on comparative effectiveness of IVF

Two main issues encountered during the literature review were: an apparent lack of good quality trials on the comparative effectiveness of IVF, and significant methodological diversity between existing studies that precluded them from being directly compared. Except for variations in treatment protocols, studies often have different definitions and methods of reporting outcomes. A substantial portion of reviewed studies reported fertility or pregnancy rates instead of live birth rates. The denominator used for the rate calculation was also not consistent across studies. Rates were reported per oocyte retrieval, per cycle initiated, per cycle completed, per embryo replacement, per couple, etc… In addition, many published studies were limited by small sample size and insufficient follow-up periods, which could be explained by challenges in recruiting, randomizing, and following this population of patients.

IVF for Idiopathic Infertility

A meta-analysis by Pandian et al. (2005) (35) explored the use of IVF for idiopathic infertility. The authors searched for RCTs published between 1970 and 2004 that compared live births rates after IVF with live birth rates following several non-IVF methods of treatment. Ten RCTs that met the criteria for methodological quality were selected for their meta-analysis. The results of this analysis by comparison group and outcome measure are displayed in the Table 6.

Table 6: Outcomes of IVF Versus. Alternative Treatment (Results of a Meta-Analysis)*

Comparison and outcomes	Number of RCTs (patients in each arm)	Pooled OR (95% CI)	Conclusion	Quality Grade
IVF vs. expectant management –PR per woman	2 (45 vs. 41)	3.24 (1.07-9.80)	Favours IVF	Moderate (inconsistency in direction of effect)
IVF vs. expectant management – LBR per woman	1 (24 vs. 27)	22.00 (2.65-189.37)	Favours IVF	High
IVF vs. IUI, LBR per woman	1 (59 vs. 54)	1.96 (0.88-4.36)	No difference	High
IVF vs. IUI-COS, LBR per woman	1 (59 vs. 59)	1.15 (0.55-2.42)	No difference	High
IVF vs. IUI-COS, MPR per woman	1 (59 vs. 59)	0.63 (0.27-1.47)	No difference	High
IVF vs. IUI-COS, incidence of OHSS per woman	1 (59 vs. 59)	1.53 (0.25-9.49)	No difference	High
IVF vs. GIFT, PR per woman	2 (69 vs. 77)	2.14 (1.08-4.22)	Favours IVF	Moderate (individual studies below statistical significance)
IVF vs. GIFT, LBR per woman	1 (34 vs. 35)	2.57 (0.93-7.08)	No difference	High
IVF vs. GIFT, MPR per woman	2 (69 vs. 77)	6.25 (1.70-23.00)	IVF has higher risk of multiple pregnancy than GIFT	High
IVF vs. GIFT, incidence of OHSS per woman	1 (35 vs. 42)	0.39 (0.02-9.87)	No difference	High

*CI refers to confidence interval; GIFT, gamete intra-Fallopian transfer; IVF, in vitro fertilization; IUI-COS, intra-uterine insemination-controlled ovarian stimulation; LBR, live birth rate ; MPR, multiple pregnancy rate; OHSS, ovarian hyperstimulation syndrome; OR, odds ratio; PR, pregnancy rate.
Source: Pandian Z, Bhattacharya S, Vale L, Templeton A. In vitro fertilisation for unexplained subfertility (Cochrane Review). The Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD003357. DOI:10.1002/14651858.CD003357

Results of this meta-analysis demonstrated that for unexplained infertility:

- IVF is superior to expectant management;
- Although there was a trend towards higher live-births rates per women associated with IVF compared to IUI, IUI-COS and GIFT, the superiority of IVF did not reach statistical significance.

Authors' recommendation was that *"until more evidence is available IVF may not be the preferred first line of treatment for couples with unexplained infertility and it might be appropriate to continue with less invasive options".(35)*

IVF vs. IUI for Male Factor Infertility

Only one RCT was found comparing the effectiveness of IVF versus IUI in couples with male factor infertility. In this trial by Goverde et al. (21) a total of 258 couples were randomized to six cycles of either IUI (86), IUI-COS (85) or IVF (87). The majority of participants (181 couples) had idiopathic infertility (and thus were included in the above described Pandian et al. meta-analysis), while only 77 couples had male factor infertility. Although the overall pregnancy rate per cycle was higher in the IVF group than in the IUI or IUI-COS groups (12.2% vs. 8.7% and 7.4%, respectively), the cumulative delivery rate in the IVF group was not significantly greater than in either IUI group, probably due to higher drop-outs in the IVF group (42% vs. 15% vs. 16% drop-out rates in IFV, IUI alone and IUI-COS respectively).

Table 7 displays the results of the study for the subset of patients with male factor infertility.

Table 7: IVF Versus IUI for Couples With Male Factor Infertility*

Outcome (pregnancy rate per woman)	Number of patients	Pooled OR (95% CI)	Conclusion
IVF vs. IUI	26 vs. 27	0.77 (0.25-2.35)	No difference
IVF vs. IUI-COS,	26 vs. 24	0.88 (0.28-2.80)	No difference

*Based on Data From an RCT by Goverde et al.
CI refers to confidence interval; IVF, in-vitro fertilization; IUI-COS, intra-uterine insemination-controlled ovarian stimulation; OR, odds ratio.
Source: Goverde AJ, McDonnell J, Vermeiden JP, Schats R, Rutten FF, Schoemaker J. Intrauterine insemination or in vitro fertilisation in idiopathic subfertility and male subfertility: a randomised trial and cost-effectiveness analysis. Lancet 2000; 355(9197): 13-18

These results show no apparent statistically significant difference between IVF and IUI (with or without COS) in patients with mild to moderate male factor infertility.

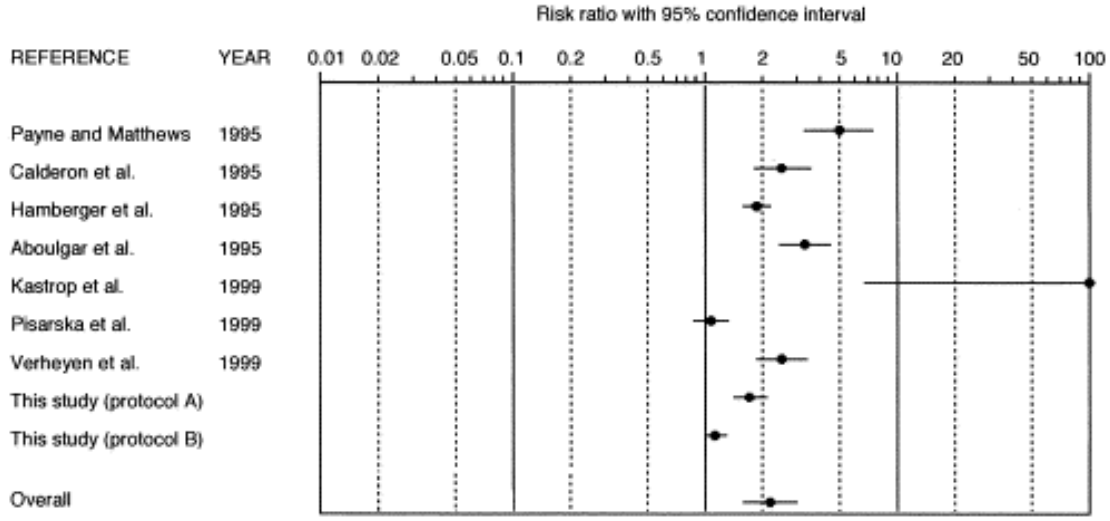
ICSI Versus Standard IVF for Male Factor Infertility

Since its introduction in early nineties (36;37), ICSI has been accepted worldwide as an efficient technique for the treatment of male factor infertility. Although the effectiveness of ICSI for male factor infertility is highly supported by biological credibility and expert opinion (38-40), good quality RCTs in this area are sparse. All existing studies compare ICSI with standard IVF in patients with mild to moderate male factor infertility.

The most comprehensive study in this field is a meta-analysis by Tournaye et al. (41), which was based on 8 trials in couples with moderate male factor infertility that compared ICSI versus either 1) standard IVF, or 2) IVF with high insemination concentration. Included studies had the same design: sibling oocytes (retrieved from the same woman) were randomized between IVF and ICSI and then fertilization rates were compared. The results of the meta-analysis are shown in a forest plot in Figure 3. All eight studies showed improved fertilization rates after ICSI: the pooled risk ratio (RR) for an oocyte becoming fertilized was 1.9 (95% CI 1.4-2.5) in favour of ICSI.

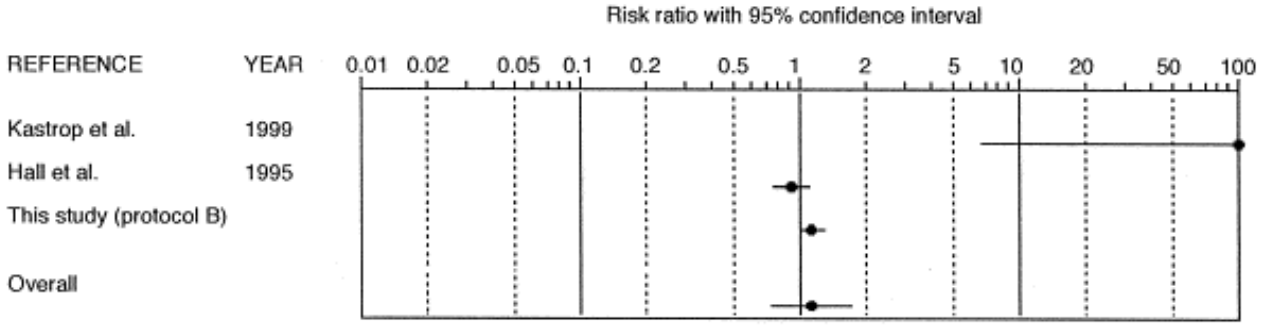
The authors also conducted a subgroup analysis restricting the comparison of ICSI to modified IVF with a high insemination concentration. In this subgroup, the pooled odds ratio (OR) did not reach statistical significance (see Figure 4).

Figure 3: Results of a Meta-Analysis of Nine Randomized Controlled Trials Comparing Fertilization *In Vitro* After Conventional IVF and ICSI in Patients With Moderate Male Subfertility* †.



*Results are expressed as risk ratios (RR) with 95% confidence intervals (CI). RRs >1 are in favour of ICSI. When the CI crosses the vertical line with RR = 1, there is no significant difference between conventional IVF and ICSI.
†"This study" refers to Tournaye et al. (2002), in protocol A ICSI was compared with IVF with a standard insemination concentration of 0.2 x 10^6/mL, whereas in protocol B ICSI was compared with IVF with high insemination concentration of 0.8 x 10^6/mL
Source: Tournaye H, Verheyen G, Albano C, Camus M, Van Landuyt L, Devroey P et al. Intracytoplasmic sperm injection versus in vitro fertilization: a randomized controlled trial and a meta-analysis of the literature. Fertil Steril 2002; 78(5): 1030-1037

Figure 4: Results of a Meta-Analysis of Three Randomized Controlled Trials Comparing Fertilization *In Vitro* After Conventional IVF and ICSI in Cycles in Which [3]0.8 × 106/mL Motile Spermatozoa are Used to Inseminate the Oocyte*†



*Results are expressed as risk ratios (RR) with their 95% confidence intervals (CI). RRs of >1 are in favour of ICSI. When the CI crosses the vertical line with RR = 1, there is no significant difference between conventional IVF and ICSI.
I† This study (protocol B) refers to where ICSI was compared with IVF with high insemination concentration of 0.8 x 10^6/mL
Source: Tournaye H, Verheyen G, Albano C, Camus M, Van Landuyt L, Devroey P et al. Intracytoplasmic sperm injection versus in vitro fertilization: a randomized controlled trial and a meta-analysis of the literature. Fertil Steril 2002; 78(5): 1030-1037

Overall, results of this meta-analysis demonstrated that ICSI significantly improves the probability of fertilization in couples suffering from moderate male infertility. The odds of fertilization were about twice as high with ICSI than with conventional IVF and 3.1 ICSI cycles may be needed to avoid a complete fertilization failure after conventional IVF (95% CI 1.7-12.4). However, as the subgroup comparison of ICSI with high insemination concentration IVF did not reach statistical significance, the authors were reluctant to promote ICSI as the first-choice approach for moderate male factor infertility.

Since the release of this meta-analysis, two more RCTs have been published in this area. A study by Plachot et al. (2002) compared standard IVF with ICSI in 58 couples with moderate male factor infertility. (42) The fertilization rate in the first cycle was almost twice as high in oocytes allocated to ICSI, 61% compared with those allocated to standard IVF, 36%. Use of ICSI enabled the avoidance of complete fertilization failure after IVF in 19 of 58 couples (32.8%).
In the second study by van der Westerlaken et al. (2006) 106 couples with borderline semen values were undergoing IVF and ICSI on sibling oocytes. (43) The overall fertilization rate was higher in oocytes treated by ICSI (56%) than in oocytes treated with standard IVF (40%). Among couples who reached fertilization through both ICSI and IVF, however, fertilization rates through each of these techniques were comparable. Based on these results, the authors suggested that in the case of borderline semen values, ICSI should be applied only when the number of oocytes is too small for a fair chance of fertilization through either IVF or ICSI.

At the time of writing, no formal comparative study of ICSI versus IVF for severe male factor infertility has been published. Nevertheless, large case series (44;45) and expert opinion (40) strongly suggest that ICSI may be the only option available for patients with severe male factor infertility (i.e. $< 0.5 \times 10^6$/ml of progressively motile spermatozoa) and should be the first-line treatment. This fact in itself may explain the absence of RCTs in patients with severe male factor infertility.

Cost-Effectiveness of IVF

The literature search for cost-effectiveness studies yielded 288 citations in total. After reviewing titles and abstracts, five studies remained; a summary of these is displayed in Table 8.

Guzick et al. analyzed the cost-effectiveness of different treatments for unexplained infertility. (22) Data on clinical pregnancy rates after various infertility treatments (derived from a retrospective analysis of 45 reports) were combined with the average cost in the United States for each treatment to calculate the cost per pregnancy. The authors reported the following findings:

- IUI does not appear to be efficacious without some form of ovarian stimulation.
- Clomiphene citrate + IUI is more cost-effective than human menopausal gonadotropin + IUI, and should be tried for several cycles as the initial treatment after expectant management.
- IVF and GIFT are the next choices for couples who have not conceived from COS and IUI.
- Cost-effectiveness may vary depending on patient characteristics (woman's age), and is likely to change with time as success rates of IVF continue to increase.

Van Voorhis et al. conducted a nonsystematic review of existing literature on the cost-effectiveness of various approaches to infertility treatment. (46) This review compared the cost-effectiveness of IVF versus 1) tubal surgery, 2) IUI, and 3) IUI-COS. It was shown that, in the absence of tubal blockage and severe male factor infertility, IUI is more cost-effective than IVF, while in cases of tubal infertility, IVF is at least as cost-effective as tubal surgery.

A large systematic review by Garceau et al. (2002) included 57 health-economic studies of infertility treatment published between January 1990 and March 2001 (it did not include the 2 above mentioned studies). (47) Among the papers included in the review were 30 economic evaluations, 22 cost studies and five economic benefit studies. The methodological quality of these studies was diverse. The most common study limitations reported by the authors were: the failure to provide detailed and disaggregated information on reported costs, failure to incorporate data on long-term costs (e.g. long-term consequences of multiple births) and benefits, and lack of sensitivity analysis. In spite of these limitations, there was a similar trend in key findings across the studies, such as:

- Natural-cycle IVF (without ovarian stimulation) may be more cost-effective than stimulated cycle IVF.
- Initiating treatment with IUI or IUI-COS appears to be a more cost-effective option than immediate IVF for all couples, except those with severe male factor or tubal factor infertility.
- For male factor infertility resulting from vasectomy, vasectomy reversal was found to be a more cost-effective treatment than ICSI.
- Donor insemination is more cost-effective than ICSI.
- For women with mild or moderate tubal disease, surgery may be a more cost-effective option than IVF. However, for women with severe tubal disease or severe endometriosis, immediate IVF is more cost-effective.
- Patient characteristics such as increased maternal age (>37 years old), decreased semen concentration, and increased severity of infertility were associated with decreased cost-effectiveness of selected interventions.

There were two other cost-effectiveness studies published after Garceau's systematic review. A study by Penson et al. (2002) looked at the cost-effectiveness of treatments for varicocele-related male factor infertility. (48) The authors demonstrated that IVF should not be the first therapeutic choice and should be tried only after failure of surgical correction or IUI.

The latest study by Pashayan et al. (2006) compared the clinical and cost-effectiveness of a single immediate IVF cycle versus up to six cycles of IUI followed by IVF if IUI fails, for treatment of unexplained and male factor infertility. (49) The analysis used a mathematical model emulating the clinical experience of a hypothetical cohort of 100 couples. Results of this exercise demonstrated that the cost per live birth was higher for IUI followed by IVF than for immediate IVF. The authors thus concluded that the offer of full IVF cycle might be more cost-effective than IUI followed by IVF.

Overall, the majority of the health-economic studies (except that by Pashayan et al.) agreed that due to high costs, IVF has a less favourable cost-effectiveness profile compared to other treatment options and should, therefore, not be considered as a first-line therapy. Notable exceptions were tubal and severe male factor infertility where IVF /ICSI were the only effective treatments.

IVF With Single Versus Double Embryo Transfers

The largest study in this field, a meta-analysis by Pandian et al. (2005) was based on the results of 4 RCTs. (51) While three of these trials compared fresh cycles of eSET versus eDET, the most recent multicentre trial (52) compared two strategies: 1) the transfer of a single fresh embryo followed by a single frozen-and-thawed embryo (FZET); versus 2) the transfer of two fresh embryos. The total number of patients in all four studies was 456 in the SET group and 453 in the DET group, with the majority of patients coming from the last trial. (53) The results of the pooled analysis are displayed in Table 9.

Table 8: Summary of Literature on Cost-effectiveness of IVF Compared to Other Treatments for Infertility*

Authors /Year of publication/Country	Type and focus of study	Methods	Conclusions
Guzick et al. 1998, USA (22)	Clinical and cost-effectiveness of various treatments for unexplained infertility.	Published data from 45 reports on clinical pregnancy rates after various infertility treatments was combined with average cost of these treatments in the United States.	1. IUI is not efficacious without COS 2. Clomiphene citrate + IUI is more cost-effective than hMG + IUI. 3. IVF and GIFT the next choice after IUI.
Van Voorhis et al. 1998, USA (46)	Nonsystematic review of the published literature on the cost-effectiveness approach to infertility treatment.	Comparison of cost-effectiveness of IVF, tubal surgery, IUI, and COS-IUI.	1. In the absence of tubal blockage and severe male factor, use of IUI and COS-IUI is more cost-effective than IVF. 2. IVF is at least as cost-effective as tubal surgery.
Garceau et al. 2002, UK (50)	Systematic review of health-economic studies of ARTs.	The review included 30 economic evaluations, 22 cost studies and 5 economic benefit studies that compared a variety of infertility treatment methods.	IUI, COS-IUI is a more cost-effective than immediate IVF/ICSI except for severe male factor and tubal infertility.
Penson et al. 2002, USA (48)	Cost effectiveness study of treatments for varicocele- related male factor infertility.	Compared strategies: 1. observation ; 2. surgical varicocelectomy followed by IVF if surgery is unsuccessful; 3. IUI-COS followed by IVF if IUI is unsuccessful; and 4. immediate IVF.	Immediate IVF is less cost-effective than varicocelectomy/IVF or IUI/IVF.
Pashayan et al. 2006, UK (49)	Mathematical model of cost-effectiveness (treatment for unexplained and male factor infertility).	Comparison: 1 IVF vs. 6 IUI + IVF.	Primary offer of IVF cycle is more cost-effective than IUI followed by IVF

*ART refers to assisted reproductive technologies; COS, controlled ovarian stimulation; hMG, human menopausal gonadotropin; ICSI intracytoplasmic sperm injection; IUI, intra-uterine insemination; IVF, in vitro fertilization.

Table 9: Results of the Meta-analysis by Pandian et al.: Single versus Double Embryo Transfer*

Outcome	Number of RCTs (number of patients)	Pooled OR (95% CI)	Conclusion
eDET versus eSET			
Pregnancy rate per woman	4 (453 vs. 456)	2.16 (1.65 - 2.82)	Favours eDET
Live birth rate per woman	4 (453 vs. 456)	1.94 (1.47 - 2.55)	Favours eDET
Multiple pregnancy rate per woman	4 (264 vs. 254)	23.55 (8.00 - 69.29)	Favours eSET
eDET versus eSET + 1FZET			
Pregnancy rate per woman	1 (331 vs. 330)	1.21 (0.89 - 1.64)	No difference
Live birth rate per woman	1 (331 vs. 330)	1.19 (0.87 - 1.62)	No difference
Multiple pregnancy rate per woman	1 (142 vs. 128)	62.83 (8.52 - 463.57)	Favours eSET

*CI refers to confidence interval; eDET, elective double embryo transfer; eSET, elective single embryo transfer; FZET, frozen-thawed embryo transfer; OR, odds ratio, RCT, randomized controlled trial.
Source: Pandian Z, Templeton A, Serour G, Bhattacharya S. Number of embryos for transfer after IVF and ICSI: a Cochrane review. Hum Reprod 2005; 20(10): 2681-2687

It is evident from these results that although in fresh cycles, eDET leads to higher pregnancy and live birth rates, two cycles of eSET - one fresh and one frozen - give success rates comparable to eDET. In both situations SET permits the avoidance of multiple pregnancies (the rate of twinning after SET was under 2%, which is similar to that of naturally occurring twinning).

There were 2 RCTs published after the Pandian et al. meta-analysis. One of these, an RCT by Lukassen et al. (2005) was not completed by the time the Pandian's meta-analysis was published, but part of the results were still included in the meta-analysis. (54) In this trial, women were randomized to either the two fresh-cycle eSET (n = 54) or single fresh-cycle eDET (n = 53) groups. There was no significant difference between these groups in live birth rates: 41% (95% CI 27-54%) and 36% (95% CI 27-49%), respectively. However, the multiple pregnancy rate was 37% (95% CI 15-49) in eDET group while there were no multiple pregnancies in the two eSET group.

The latest RCT by van Montfoort et al. (2006) compared eSET (154 patients) and DET (154 patients) in an unselected group of women, without restrictions on age or embryo quality. (55) Note, that all trials discussed above included women with relatively good prognoses: younger than 36 years old and with a relatively high number of embryos available for transfer. In van Montfoort et al., about 5% of randomized women were 38 years and older (8 women in the eSET group and 6 in the DET group). Although the pregnancy rate after eSET was significantly lower compared with DET (21.4% versus 40.3%), the twin pregnancy rate was reduced from 21.0% after DET to 0% after eSET. Women who refused randomization received standard transfer policy (SP) according to their prognostic factors: 100 of them had SP-eSET and 122 SP-DET. The ongoing pregnancy rate after SP-eSET and SP-DET did not differ significantly (33.0% versus 30.3%), with an overall twin rate of 12.9%. The study demonstrated that the eSET strategy could be successfully applied to older patients.

Overall, the published studies highly support the policy of eSET as means for reducing multiple pregnancy rates while achieving satisfactory pregnancy rates in groups of patients with good prognoses. The cost-effectiveness of eSET could be further increased by the addition of a second frozen-thawed cycle.

Summary of Medical Advisory Secretariat Review

Table 10 displays the summary of literature review with grading of the level of evidence.

Table 10: Summary of the Medical Advisory Secretariat Literature Review*

Outcome of interest	Level of evidence	Conclusion	Quality grade**
IVF vs. IUI for unexplained infertility	Meta-analysis of RCTs (10 RCTs)	There is no statistically significant difference in live birth rates between IVF and IUI.	High
IVF vs. IUI for mild to moderate male factor infertility	Subset of data from a single RCT	There is no statistically significant difference in pregnancy rates between IVF and IUI.	Moderate (small subset of data from a single RCT)
ICSI vs. standard IVF for moderate to severe male factor infertility	Meta-analysis of RCTs (8 RCTs) + 2 later RCTs	ICSI is superior to standard IVF in terms of fertilization rates.	Moderate (Studies reported fertilization rates instead of live birth rates)
Cost-effectiveness of IVF	5 health –economic studies including a large systematic review of health economic studies	IVF is not a preferred first-line treatment except for tubal and severe male factor infertility.	N/A
IVF-eSET as a way to avoid multiple pregnancies	Meta-analysis of RCT (4 RCTs) + 2 additional RCTs	IVF-SET allows almost complete elimination of the risk of multiple pregnancy while giving a cumulative live birth rate after 1 fresh + 1 FZET comparable to 1 cycle of DET	High

eSET refers to elective single embryo transfer; ICSI, intra-cytoplasmic sperm injection; IUI, intra-uterine insemination; IVF, in vitro fertilization; RCT, randomized controlled trial; FZET, frozen embryo transfer.

**Based on the Grade Evaluation system that is used for grading quality of evidence and strength of recommendations for clinical guidelines (for details see Appendix 6 in the end of the review). (56)

Economic Analysis

Notes & Disclaimer

The Medical Advisory Secretariat (MAS) uses a standardized costing methodology for all of its economic analyses of technologies. The main cost categories and the associated methodology from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative (OCCI) cost data is used for all program costs when there are 10 or more hospital separations, or one-third or more of hospital separations in the ministry's data warehouse are for the designated International Classification of Diseases-10 diagnosis codes and Canadian Classification of Health Interventions procedure codes. Where appropriate, costs are adjusted for hospital-specific or peer-specific effects. In cases where the technology under review falls outside the hospitals that report to the OCCI, PAC-10 weights converted into monetary units are used. Adjustments may need to be made to ensure the relevant case mix group is reflective of the diagnosis and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, MAS normally defaults to considering direct treatment costs only. Historical costs have been adjusted upward by 3% per annum, representing a 5% inflation rate assumption less a 2% implicit expectation of efficiency gains by hospitals.

Non-Hospital: These include physician services costs obtained from the Provider Services Branch of the Ontario Ministry of Health and Long-Term Care, device costs from the perspective of local health care institutions, and drug costs from the Ontario Drug Benefit formulary list price.

Discounting: For all cost-effective analyses, discount rates of 5% and 3% are used as per the Canadian Coordinating Office for Health Technology Assessment and the Washington Panel of Cost-Effectiveness, respectively.

Downstream cost savings: All cost avoidance and cost savings are based on assumptions of utilization, care patterns, funding, and other factors. These may or may not be realized by the system or individual institutions.

In cases where a deviation from this standard is used, an explanation has been given as to the reasons, the assumptions, and the revised approach.

The economic analysis represents an estimate only, based on assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied for the purpose of developing implementation plans for the technology.

Literature Review

Kjellberg et al., (2006) in a Swedish-based study, found that SET was superior to the DET strategy, when the number of deliveries with at least one live-born child, the incremental cost-effectiveness ratio, and maternal and pediatric complications are taken into consideration. (57) The incremental cost per extra delivery in the DET alternative compared with SET was estimated at €73,307 (~ $104,500 Cdn) per extra delivery with a live-born child. They also concluded that the rates of prematurely born and low birth weight complications were significantly lower in the SET option. The authors expressed caution that the calculated incremental cost-effectiveness ratio might not be comparable to traditional cut-offs for the incremental cost-effectiveness ratio, and in fact might be considered low given that the expected life years gained might be 75 years per new born baby. Gerris et al. (2004) showed that the transfer of a single top quality embryo is equally effective as, but substantially cheaper than, DET in women less than 38 years of age during their first IVF/ICSI cycle. (58) However, Sutter et al. (2002) in their Belgium-based study showed contradictory results; that the SET cost per child born was in all instances the same as with DET. (59) They concluded that the real advantage of SET is the avoidance of very high long-term costs resulting from the increase of complications associated with twin births.

Ontario-Based Economic Analysis/Budget Impact Analysis

All costs are in Canadian dollars unless specified otherwise

Assessing the need for IVF

In 2004, there were approximately 4,300 IVF cycles performed in the province (personal communication with CARTR expert, July 2006). Of these, approximately 860 (20%) were IVFs performed for tubal-related complications and were covered by OHIP. On the other hand, the accurate number of IUI cycles performed in the province is unknown but could be estimated at around 5,700 cycles annually. (60)

The real demand for IVF in Ontario could be higher than the current utilization level. In order to estimate the potential utilization rate of IVF if the procedure were funded, expert opinion was sought and health economic studies that attempted to estimate the need for IVF in population were reviewed.

According to expert opinion and the Infertility Awareness Association of Canada Advisory Board, the real need for IVF treatment is approximately triple the current number of cycles (personal communication, July 31, 2006). This estimate is supported by international economic analysis of correlation between average costs of IVF to a patient and IVF national utilization rate conducted by Collins. (61) Based on experiences in 25 countries, this survey estimated the *price elasticity* for IVF (defined as the change in volume of services in response to a change in prices to the consumer) according to the formula:

$$\text{Elasticity} = \frac{\%\text{change in quantity of services}}{\%\text{change in price to consumer}}$$

It was estimated that a 10% reduction in cost per IVF cycle would be associated with a 32% increase in utilization of IVF cycles. Thus, the complete coverage of IVF (100% reduction in price) would result in a 3-fold increase in IVF utilization, equating to a total of 13,000 cycles annually in Ontario.

The European Society for Human Reproduction and Embryology (ESHRE) Capri Workshop Group offered an alternative estimate of the need for IVF services. According to their estimate, the annual need for IVF services is approximately 1,500 couples per million population (see Appendix 7). (9) Although the average couple would undergo more than one cycle in a given year, it was considered appropriate to accept 1,500 cycles per annum as a conservative underestimate. The Ontario population for July 1, 2004 was 12,416,700 based on a Statistics Canada report. (12) Thus, according to the ESHRE estimate, about 18,600 cycles of IVF are needed in Ontario – more than four times higher than the number of IVF actually performed.

These two independent estimates give us a range of annual need for IVF in Ontario under "ideal" circumstances of 13,000 to 18,600 IVF cycles per year.

Costs

Physician Costs

The costs of physician services for deliveries in a hospital were estimated from the Ontario Physician Schedule of Benefits (2005). The following were costs estimated for different methods of delivery:

- Vaginal delivery = $396
- Caesarean section = $704
- Multiple births = additional $145 for each additional birth

Hospital Costs (Average Costs)

Due to a lack of data from the Ontario Case Costing Initiative (OCCI), all hospital cost estimates were obtained from the 2006 Canadian Institute for Health Information (CIHI) annual report on birthing costs in Canada. (62) The following were estimates for average costs of delivery procedures (which included the cost of care for the baby):

- Vaginal delivery = $3,600/baby
- Caesarean section = $6,000/baby
- Neonatal intensive care unit (NICU) = $9,700/baby

The cost of the NICU was an average cost calculated per baby for a range of different lengths of stay. Using these costs, the hospital costs were estimated for singleton, twin and high order births[1] both in the case that the birth was normal and in the case that the baby was admitted into NICU due to complications. The following table shows the average costs associated with each of these procedures as well as the cost of care.

Table 11: Average Hospital Costs

	Vaginal Delivery		*Caesarean Section*	
	Normal Birth	**Baby admitted to NICU**	**Normal Birth**	**Baby admitted to NICU**
Singleton	$3,996	$13,696	$6,704	$16,404
Twin	$4,941	$24,341	$8,249	$27,649
Triplet	$5,886	$34,041	$9,794	$37,349

[1] For this analysis, it was assumed that all high ordered births resulted in triplets

Average Infertility Treatment Costs

Due to a lack of data from the OCCI, all hospital cost estimates were obtained from the 2006 CIHI annual report on birthing costs in Canada (62), except the cost of an IUI, which was estimated from a study by Collins et al. (60) and was adjusted to a 2006 value using an annual discount rate of 3%. An estimate for the cost of an IVF procedure was difficult to obtain. The CIHI report estimated this cost as being approximately $5,000. However, this was based on an average from private infertility clinics from across Canada. Communication with experts in the field, as well as, estimates from the Provider Services Branch (personal communication, September 2006) yielded this cost as being approximately $2,500. Therefore, a range from $2,500 to $5,000 was used for the cost estimate of an IVF procedure. The following are estimates of average costs associated with assisted reproductive procedures:

- Cycle of Intra-Uterine Insemination (IUI) = $282
- Cycle of IVF = $2,500 - $5,000
- Cost of ICSI = $1,172
- Cycle of IVF for male factor infertility (includes the cost of ICSI) = $3,600 - $6,100
- IVF cycle with FZET = $1,000
- Annual storage fee = $225

Decision Analysis

A Markov decision analysis was conducted to compare different procedures in various different scenarios to determine the most cost-effective option and scenario. The three main options considered were:

- *Option 1:* **IUI**
- *Option 2:* **IVF-eSET**
- *Option 3:* **IVF-eDET**

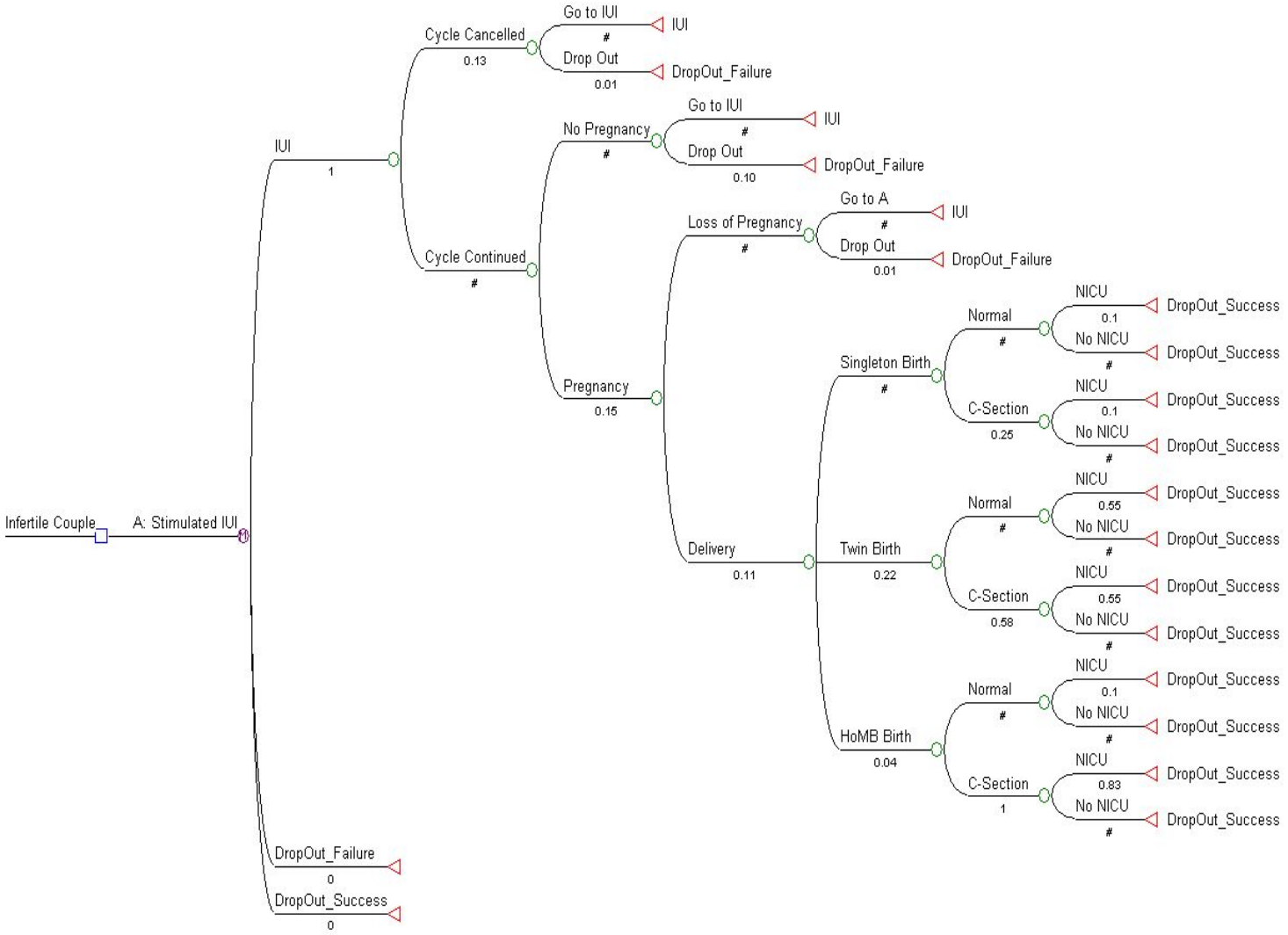
Three separate decision tree models were constructed using TreeAge Pro 2006 software to represent three different scenarios (illustrated in Figures 5 and 6). These were:

- ***Model I*** – Three cycles each of Option 1, 2 and 3 (each with a fresh embryo)
- ***Model II*** – For Option 2 and 3, only a first cycle with fresh embryo and each cycle thereafter with FZET. In the case of IVF-eSET the 2nd and 3rd cycle were simulated assuming all eggs used were frozen. In the IVF-eDET scenario, in each of the 2nd and 3rd scenario, half the eggs used were frozen while half were fresh. The rationale behind the 50-50 split was that in the case of DET, a greater number of high quality eggs are needed for implantation. Therefore, to increase the chances that all eggs were of good quality, half of the eggs transferred were fresh.
- ***Model III*** – Patient undergoes 3 cycles of Option 1 (IUI) followed by 2 cycles of Option 2 (IVF-eSET)

Each of the three separate models assumed that all patients were women less than 36 years old, with nontubal infertility and no previous IVF treatment history. Only short-term costs were considered, while the cost of drugs was not included in the analysis.

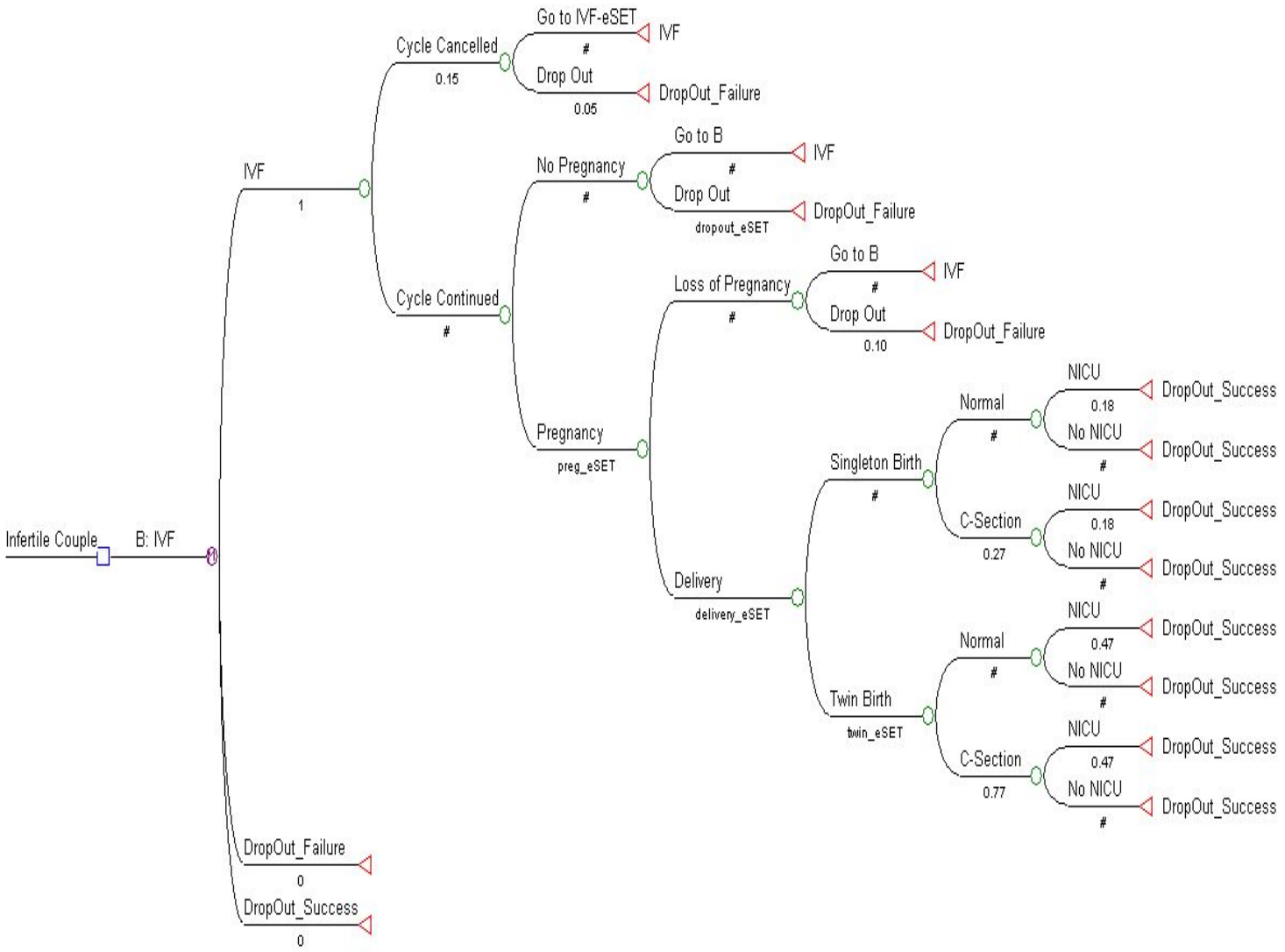
Table 12 illustrates the probabilities that were used in the Markov decision model in each of the three different cycles for each of the treatment options (IUI, IVF-eSET and IVF-eDET). See Appendix 8 in the end of the review for the full list of probabilities.

Figure 5: Decision Node Representing Option 1 (Intra-Uterine Insemination)



C-Section refers to Caesarean section; HoMB birth, higher order multiple births (triplets and higher), IVF, *in vitro* fertilization, IUI, Intra-Uterine Insemination**,** NICU, neonatal intensive care unit.

Figure 6: Decision Node Representing Options 2 and 3 (*In Vitro* Fertilization via Single or Double Embryo Transfer)



C-Section refers to Caesarean section; HoMB birth, higher order multiple births (triplets and higher), IVF, *in vitro* fertilization, IUI, Intra-Uterine Insemination, NICU, neonatal intensive care unit.

Table 12: Decision Analysis Transition Probabilities*

	IUI	IVF-eSET			IVF-eDET		
	All Cycles	1st Cycle	2nd Cycle	3rd Cycle	1st Cycle	2nd Cycle	3rd Cycle
Cycle cancelled	0.13	0.15	0.15	0.15	0.15	0.15	0.15
Drop after cycle cancelled	0.01	0.05	0.05	0.05	0.05	0.05	0.05
Pregnancy	0.15	0.34	0.24	0.24	0.53	0.36	0.36
Drop out after no pregnancy	0.10	0.18	0.23	0.23	0.18	0.23	0.23
Delivery	0.11	0.28	0.16	0.16	0.43	0.29	0.29
Drop out after loss of pregnancy	0.01	0.10	0.10	0.10	0.10	0.10	0.10
Singleton birth	0.74	0.98	1.00	1.00	0.78	0.82	0.82
Normal birth after singleton	0.75	0.73	0.73	0.73	0.73	0.73	0.73
C-Section after singleton	0.25	0.27	0.27	0.27	0.27	0.27	0.27
Twin birth	0.22	0.02	0	0	0.22	0.18	0.18
Normal birth after twin	0.42	0.23	0.23	0.23	0.23	0.23	0.23
C-Section after twin	0.58	0.77	0.77	0.77	0.77	0.77	0.77
Higher ordered multiple birth (HOMB)	0.04	-	-	-	-	-	-
Normal birth after HOMB	0	-	-	-	-	-	-
C-Section after HOMB	1.00	-	-	-	-	-	-

eDET refers to elective double embryo transfer; eSET, elective single embryo transfer; IUI, intra-uterine insemination; IVF, in vitro fertilization; HOMB birth, higher order multiple births (triplets and higher).

Each of the three separate models was simulated using births as the measure for effectiveness. The cost-effectiveness is thus estimated as cost per birth. In each of the 3 models, the 2nd and 3rd cycle were identical to the first, except that the probabilities estimated were different (results summarized in Tables 13 to 15).

Table 13: Results of the decision tree analysis for Model 1*

	Model I (3 Cycles; B or C: fresh embryos)	
Strategy	**Cost-Effectiveness (Cost of IVF = $5,000) per birth ($Cdn)**	**Cost-Effectiveness (Cost of IVF = $2,500) per birth ($Cdn)**
Option 1: Simulated IUI	21,000	21,000
Option 2: IVF-eSET	85,000	46,000
Option 3: IVF-eDET	33,000	20,000

*eDET refers to elective double embryo transfer; eSET, elective single embryo transfer; IUI, intra-uterine insemination; IVF, in vitro fertilization.

Table 14: Results of the decision tree analysis for Model 2*

	Model II (3 Cycles; B or C: frozen embryos in the 2nd and 3rd cycles)	
Strategy	**Cost-Effectiveness (Cost of IVF = $5,000) per birth ($Cdn)**	**Cost-Effectiveness (Cost of IVF = $2,500) per birth ($Cdn)**
Option 1: Simulated IUI	21,000	21,000
Option 2: IVF-eSET	50,000	34,000
Option 3: IVF-eDET	28,000	18,000

*eDET refers to elective double embryo transfer; eSET, elective single embryo transfer; IUI, intra-uterine insemination; IVF, in vitro fertilization.

Table 15: Results of the decision tree analysis for Model 3

	Model III (3 Cycles; B or C: fresh embryos)	
Strategy	**Cost-Effectiveness (Cost of IVF = $5,000) per birth ($Cdn)**	**Cost-Effectiveness (Cost of IVF = $2,500) per birth ($Cdn)**
Option 4: 3 cycles of IUI followed by 2 cycles of IVF-eSET	38,000	25,000

*eDET refers to elective double embryo transfer; eSET, elective single embryo transfer; IUI, intra-uterine insemination; IVF, in vitro fertilization.

As is evident from the tables above, the Model 2 (with FZET in the 2nd and 3rd cycles) is a more cost-effective strategy for adaptation. The effectiveness of Model 2 remains the same as Model 1 while the cost is significantly less. Therefore, its overall cost-effectiveness estimate is lower that of Model 1. The cost-effectiveness estimate for a strategy to adopt IVF-eSET after three failed cycles of IUI is estimated to be in the range of $25,000 to $38,000 per birth.

Budget Impact Analysis

Patients could be eligible for additional IVF coverage above that currently offered in several situations. Table 16 lists four potential indications for IVF, which were used for the budget impact analysis. Note, that in the case of IVF following failed IUI (indication #4) there have been no significant changes in the technology in recent years that would alter existing provincial policy. Therefore, although budget impact is estimated for this scenario, this indication will not be considered in policy development.

Table 16: Indications for additional coverage of IVF/ICSI cycles

	Indication for IVF/ICSI coverage	Estimated percent of infertile couples	Source of evidence	Grade of evidence
1.	ICSI for severe male factor infertility	~ 10%	Meta-analysis, RCTs, large case-series, biological plausibility, published treatment guidelines, expert-opinion	High
2.	IVF-SET for women who cannot sustain multiple pregnancy for medical reasons	~ 5%	Meta-analysis, expert opinion	High
3.	IVF-SET for any infertile couples who do not want to assume the risk of multiple pregnancy	~ 60%	Meta-analysis, Surveys of infertile couples	High
4.	IVF for patients with failure of standard medical treatment (includes at least 3 IUI cycles)	~ 75%	Case-series, published treatment guidelines, expert opinion	Low-Moderate

ICSI refers to intracytoplasmic sperm injection; IVF, in vitro fertilization; RCT, randomized controlled trial; SET, single embryo transfer.

In real world circumstances, couples undergo an average of two to three treatment cycles for infertility. The budget impact for IVF (both SET and DET) was estimated using an average cost of cycle of IVF with a fresh embryo transfer and a cycle of IVF with FZET. The cost of ICSI was included in the calculation of the budget impact for severe male factor infertility. The range of costs for a regular IVF procedure was estimated as $1,750 to $3,000, while that for male factor infertility was estimated at $2,900 to $4,100 for the budget impact estimates (see Table 17).

Table 17: Results of the Budget Impact Analysis*

Population	Predicted Budget Impact (Assuming shifts within current Ontario case load) ($ millions)
Severe male factor infertility	2.8 to 4
Medically proven high risk women	1 to 1.5
Those who do not want to assume the risk of MBs	6 to 7.3
IVF for couples after failed IUI	7 to 12

*IUI refers to intrauterine insemination; IVF, in vitro fertilization; MB, multiple births

The budget impact was calculated with the underlying assumption that the entire population of couples utilizing IVF treatment is already seeking treatment. The international estimates for the increase in IVF utilization under a publicly funded system could not be used to calculate the budget impact for any of the above scenarios. For example, it is not possible to identify how many of the 13,000 to 18,600 cycles of IVF, as estimated based on international data, included those couples who previously chose IUI as infertility treatment.

Unmeasured Costs

The analysis did not include costs of miscarriages or maternal complications. It also did not include downstream costs of complications such as cerebral palsy and/or other developmental complications associated with the newborn. In addition, societal costs such as loss in productivity, absence from work and decreased quality of life for the mother were not considered. Data on complications in both SET and DET were not available and could not be factored into the analysis. Finally, one could assume that due to public coverage of IVF in any of the different scenarios considered above, overall utilization would increase due to absence of cost-barriers. As mentioned previously, this could not be included in the analysis due an inability to estimate the actual increase in utilization of IVF procedures for this reason.

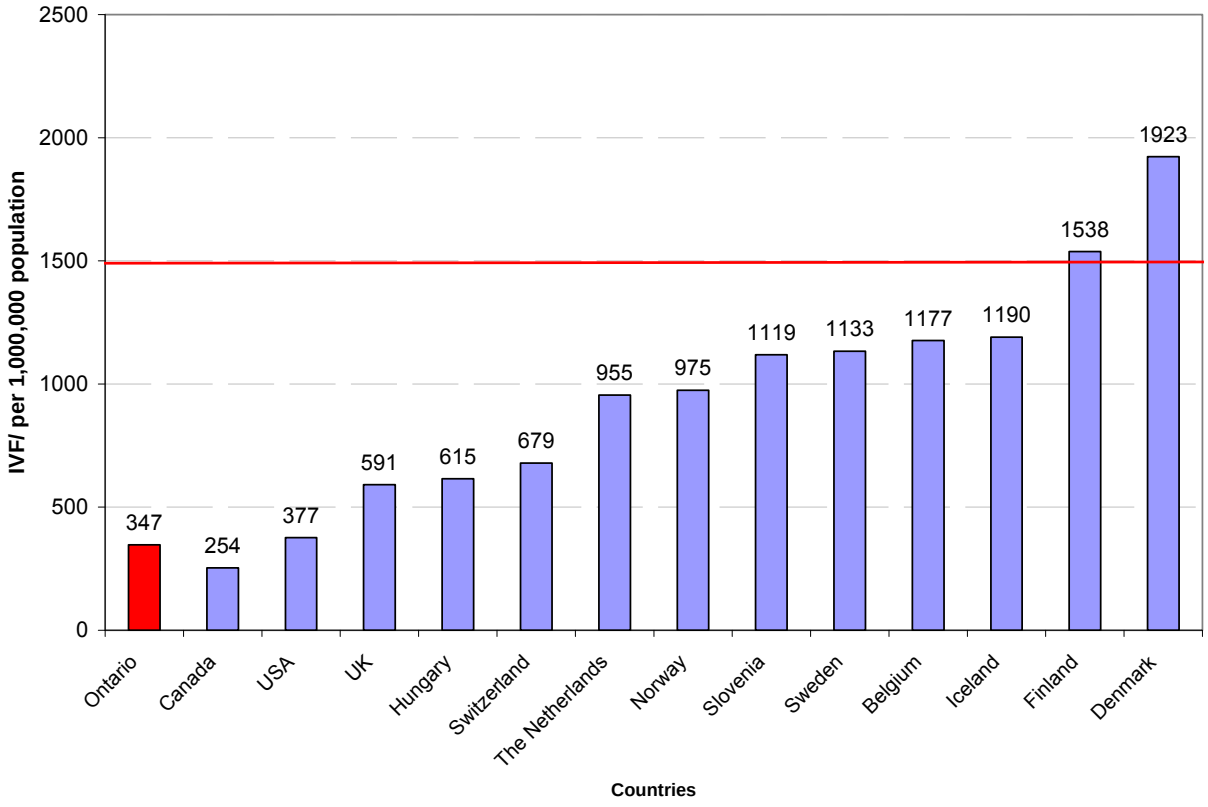
Other Policy Considerations

International Comparisons of IVF Diffusion

The diffusion of ART is typically measured by the number of ART cycles per million population. Figure 7 shows the IVF/ICSI utilization in different countries based on 2001 data. Among the countries represented, Canada has the lowest utilization rate (254/million) while Denmark has the highest (1,923/million). The red line corresponds to the ESHRE "ideal" estimate of the annual need for IVF/ICSI of 1,500 per million population. (9)

Note that the utilization rate of IVF in Ontario in 2004 was 347 IVF cycles per million population, slightly higher than overall Canadian rate (238 in 2004).

Figure 7: Number of IVF Cycles Per Million Population, 2001*†



* Except for Ontario estimate which is based on 2004 data
†Sources: European data are from ESHRE registries (63), U.S. data are from CDC (17) and the U.S. Census, Canadian data are from CARTR (24) and Statistics Canada.

Existing Guidelines for Number of Embryos Transferred in IVF cycles

International

Globally, there is considerable variation between countries in the regulation of the number of embryos transferred in IVF/ICSI cycles, but, in general, the average number transferred is lower in Europe than in North America. This is largely due to the fact that many European countries publicly subsidize IVF treatment. (34) Yet even among European countries there is significant diversity in standards. In 2002, the highest percent of IVF/ICSI cycles with SET was performed in Finland (38.7%), followed by Sweden (30.6%). Not surprisingly, these two countries also report the lowest rate of IVF-associated multiple births; 15.4% and 19.4% respectively (data for 2002). (26) Currently, among European countries only Finland, Sweden, Belgium and the Netherlands have a policy of routine eSET.

Finland pioneered implementation of eSET. In the country's largest infertility clinic at the Helsinki University Central Hospital, the eSET program started in 1997 and in 2000 eSET became a primary option. Two embryos are transferred only when the couple has a history of unsuccessful IVF-cycles, embryo quality is poor, or the women is older than 37 years with a long history of infertility and no top quality embryos. This policy resulted in an increase in the number of eSET procedures from 11% in 1997 to 60% in 2003. Over the same period, multiple birth rates dropped from 25% to 7%, while the delivery rates remained relatively stable at around 34%. (64)

In Sweden, a revision of the guidelines from the National Board of Health and Welfare on ART passed in December 2002, made SET the predominant policy in all of the country's reproductive centres. (65) The only exceptions are patients with a low risk of twin pregnancy, in which case two embryos may be transferred, but only after informing the couple about the risk of multiple pregnancy and consultation with a pediatrician. Based on preliminary data from 2004 this policy resulted in a drop in the IVF multiple birth rate below 10% while keeping the same overall delivery rate. (65)

In Belgium, the government has reimbursed IVF/ICSI costs since 2003 for couples among whom the woman's age is below 43 years, for a maximum of six treatment cycles in a lifetime. A single embryo is routinely transferred in women younger than 35 years old; in women between 35 and 39 years old typically two embryos are transferred (three only in case of several previous unsuccessful attempts), and after the age of 39 there is no restriction on number of embryos transferred. (33)

Denmark has the highest availability of IVF services in Europe with 2,178 IVF/ICSI cycles performed per million population in 2002. This has resulted in the highest percent of infants born through ART across Europe (4.2% of all infants). (26) Typically, three IVF cycles are funded for couples, who have no other children and if the woman is younger than 40 years old (66) but there is no strict policy for SET in the country. Based on results of the cost-effectiveness study conducted by the Danish National Health Board, transfer of two embryos appears to be more cost-effective than SET (67). Still, the rate of IVF-associated multiple pregnancies in Denmark is relatively low (23.1% in 2002). (26)

In the United States, there is no public funding for IVF, and insurance coverage is limited and varies by state. Guidelines on the number of embryos transferred are provided by the American Society of Reproductive Medicine. (68) According to these, only patients with the most favourable prognoses should be considered for SET. This group is defined as those who are undergoing their first IVF cycle, have good quality embryos (judged by morphologic criteria), and have an excess of embryos to warrant cryopreservation. In 2002, among all IVF cycles performed in the United States, the percent of those in which a single embryo was transferred ranged from 5% to 15% in fresh cycles and from 9% to 12% in frozen-thawed cycles. (69) The multiple birth rate associated with IVF remains fairly high in the US: 34.2% after fresh cycles and 25.3% after frozen cycles. (17)

Canada

Currently, there are no guidelines regulating the number of embryos to transfer in Canada. In 2004, among all IVF/ICSI cycles performed in Canada, one or two embryos were transferred in 66% of IVF/ICSI cycles. The rate of multiple pregnancy after IVF/ICSI treatment is around 30%. (70)

Effect of IVF Funding on Number of Embryos Transferred

It is evident from international data that the number of embryos transferred is influenced by IVF funding policy. The success of the SET policy in European countries is, to a large degree, due to public subsidizing of IVF treatment. In contrast, in countries where IVF is available only in the private sector, patients might prefer multiple embryo transfer in order to maximize the chances of live birth during their first attempt. Studies conducted in the United States have shown that insurance coverage increases the utilization of IVF services, and decreases the number of embryos transferred per cycle, pregnancy rate per cycle, and the rate of multiple deliveries. (71;72)

Patients' Perspective on Multiple Pregnancy

Although from a medical perspective any multiple pregnancy is always considered to be high-risk, patients may have different personal opinions. Several studies have shown that a significant proportion of infertile couples not only do not object to having a multiple birth, but consider twins as being an ideal outcome of infertility treatment.

Table 18: Proportion of Infertility Patients Desiring Multiple Births Reported by Different Studies

Study Author/Year/Country	Design (N)	Percent of couples desiring multiple (twin) pregnancy	Characteristics associated with the desire for multiple pregnancy
Gleicher et al., 1995, United States (73)	Survey (582)	67% - 90%	The wish for multiple births was positively correlated with woman's age and the duration of infertility
Ryan et al., 2004, United States (74)	Survey (449)	20.3%	Nulliparity and lower family income were associated with woman's desire to have multiple pregnancy
Ingerslev et al., 2005, Denmark (75)	Personal interview with infertile couples (18 couples)	59%	N/A
Child et al., 2004, Canada (76)	Survey (801)	41%	Desire for multiple births was positively associated with duration of infertility and history of assisted conception treatment, and negatively associated with having previous children and recognition of associated risks

Thus it cannot be denied that a certain proportion of infertile couples do wish to have a multiple birth, more specifically, twins. The opinion of the couple has to be considered in the decision-making process for the number of embryos to be transferred. This raises the question of whether the funding body (i.e. government, insurance company) has an exclusive right to regulate the number of embryos transferred. Secondly, the results of these studies also suggest that more emphasis should be given to educating infertile couples and the general public about the risks involved with multiple births. It has been shown that increased knowledge and awareness of risks associated with multiple gestation can change the patients' attitudes towards multiple pregnancy (77).

Fetal Reduction: Is it a Viable Alternative to Single Embryo Transfer?

Fetal reduction is another way to control multiple pregnancy rates. It is normally carried out between 10 and 14 weeks of gestation by means of ultrasound-guided potassium chloride injection into the heart of a fetus selected for reduction. In spite of major ethical issues surrounding this intervention, it is considered to be a safe and effective method to improve outcomes in multiple pregnancies, particularly in quadruplet and higher order pregnancies. (14;78) It has been estimated that embryo reduction from triplet to twins increases gestation by 2-3 weeks (78) and may reduce the handicap rate from 1.5% to 0.6%. (79) Lately, this intervention has even been advocated for reduction of twins to singletons. (80)

Due to major ethical issues with the acceptability of this option, no RCT has been reported in this area. (81) The only published meta-analysis (2006) was based on 6 observational studies that compared expectant management of triplet pregnancies (n = 411) with selective embryo reduction to twins (n = 482). (82) The meta-analysis demonstrated that although reduction to twins is associated with an almost 3-fold decrease in risk of early preterm birth, it nearly doubles the risk of subsequent miscarriage.

In Ontario, selective embryo reduction is covered by OHIP and costs approximately $241, excluding the fee for ultrasound. Currently, there are two centres in the province that carry out fetal reduction – Mount Sinai and Women's College hospitals, where approximately 50 to 60 cases of fetal reduction are performed annually (personal communication with clinical expert, October 3, 2006). While the procedure is routinely done for triplets and higher order multiple pregnancies, reduction from twins to singleton is an exception and is carried out only in case of severe malformations in one of the twins.

Since the majority of multifetal pregnancies after assisted reproduction are twin pregnancies, only a small fraction of patients (2.4% after IVF and about 4.0% after IUI) will be eligible for fetal reduction in the province. Moreover, even among women with higher order multiple pregnancies, not all would agree to undergo fetal reduction due to the significant emotional burden of the procedure. Therefore, fetal reduction does not seem be a viable alternative to IVF with SET.

Woman's Age and Single Embryo Transfer

As was earlier mentioned, the majority of RCTs on outcomes of SET were conducted in women younger than 36 years of age. Typically, a higher number of embryos is transferred in women older than 35 to 36 years in order to compensate for a decline in implantation rates with age. However, two Finnish studies demonstrated that SET could be safely applied to older women. In addition to the already discussed RCT by van Montfoort et al. (55), the newly released prospective study (83) demonstrated that eSET policy is quite successful in women aged 36 to 39. The clinical pregnancy rate achieved in this group of women (33%) was similar to that in younger women after eSET. Results of this study suggest that embryo morphology, rather than the woman's age, determines the chance of pregnancy, and therefore selection for eSET should be based on embryo quality rather than age. (83)

Conclusions

1. Advances in IVF technology since the publication of the Royal Commission Report have brought three new indications for IVF (refer to Table 19 for the GRADE analysis of these):
    1) Patients with severe male factor infertility, where IVF should be offered in conjunction with ICSI;
    2) Infertile women with serious medical contraindications to multiple pregnancy, who should be offered IVF-SET; and
    3) Infertile patients who want to avoid the risk of multiple pregnancy and therefore may opt for IVF-SET.

2. An Ontario-based budget impact analysis estimated that coverage of all three of these new indications would cost approximately $9.8 to $12.8 million (Cdn). Coverage of only first two indications, namely, ICSI in patients with severe male factor infertility and infertile women with serious medical contraindications to multiple pregnancy, is forecast to be $3.8 to $5.5 million (Cdn).

Table 19: GRADE Analysis*

Indication for IVF/ICSI	Benefits	Risks	Burdens	Trade-Off	Quality of evidence (for benefits)	Grade of recommendation to adopt
ICSI for severe male factor infertility	Higher success rates with ICSI in male factor infertility. ICSI might be the only effective treatment for severe male factor infertility	The purported higher risk of congenital malformations after ICSI compared with standard IVF has not been proven.	Cost of IVF + ICSI	Benefits > risks, burdens	Moderate-High	High
IVF-SET for women who cannot sustain multiple pregnancy for medical reasons	Avoidance of multiple pregnancy	Risk of standard IVF (OHSS, increased risk of congenital malformations)	Cost of IVF	Benefits > risks, burdens	High	High
IVF-SET for any infertile couples who do not want to assume the risk of multiple pregnancy	Avoidance of multiple pregnancy	Risk of standard IVF (OHSS, increased risk of congenital malformations)	Cost of IVF	Benefits > risks, burdens are considerable	High	Moderate

*ICSI refers to intra-cytoplasmic sperm injection; IVF refers to in vitro fertilization; OHSS, ovarian hyperstimulation syndrome; SET, single embryo transfer.

** Based on the Grade Evaluation system (56) that is used for grading quality of evidence and strength of recommendations for clinical guidelines (for details see Appendix 6 at the end of the review).

Appendices

Appendix 1: Literature Search Strategies

A. Clinical effectiveness of IVF- Final Search

Search date: June 30, 2006
Databases searched: OVID MEDLNE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, International Agency for Health Technology Assessment (INAHTA), and The Cochrane Library

Database: Ovid MEDLINE(R) <1996 to June Week 3 2006>
Search Strategy:
---

1 exp Fertilization in Vitro/ (10463)
2 (vitro adj1 fertil$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (5447)
3 1 or 2 (11828)
4 exp Ovulation Induction/ or controlled ovarian stimulation.mp. (3229)
5 controlled ovarian hyperstimulation.mp. (528)
6 exp Artificial Insemination/ or insemination.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (4016)
7 or/4-6 (6934)
8 3 and 7 (2456)
9 exp Treatment Outcome/ (232833)
10 exp Treatment Failure/ (11293)
11 exp pregnancy rate/ or exp birth rate/ (3838)
12 exp Pregnancy Outcome/ (15069)
13 exp Pregnancy/ (159990)
14 (rate adj4 (birth or pregnanc$ or fertili$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (8588)
15 or/9-14 (389666)
16 8 and 15 (1613)
17 limit 16 to (humans and english language) (1324)
18 limit 17 to (case reports or comment or editorial or letter) (157)
19 17 not 18 (1167)
20 limit 19 to (controlled clinical trial or meta analysis or randomized controlled trial) (227)
21 exp Double-Blind Method/ (41978)
22 exp Random Allocation/ (20516)
23 exp single-blind method/ (7447)
24 (random$ or metaanalysis or meta-analysis or systematic$ review$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (289311)
25 or/20-24 (295400)
26 19 and 25 (282)
27 (metaanalysis or meta-analysis or systematic$ review$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (24317)
28 26 (282)
29 limit 28 to "review" (30)
30 28 not 29 (252)
31 26 and 27 (25)
32 30 or 31 (266)

Database: EMBASE <1980 to 2006 Week 25>
Search Strategy:

---

1 exp Fertilization in Vitro/ (17249)
2 (vitro adj1 fertil$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (19131)
3 1 or 2 (19131)
4 exp artificial insemination/ or exp intrauterine insemination/ or exp ovulation induction/ (9807)
5 (controlled ovarian stimulation or controlled ovarian hyperstimulation).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (935)
6 insemination.mp. (6332)
7 or/4-6 (12053)
8 3 and 7 (4673)
9 exp pregnancy/ (155988)
10 exp birth rate/ or exp fetus outcome/ or exp pregnancy rate/ (12437)
11 exp treatment outcome/ or exp treatment failure/ (321582)
12 (rate adj4 (birth or pregnanc$ or fertili$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (16660)
13 or/9-12 (484139)
14 8 and 13 (2544)
15 limit 14 to (human and english language and yr="1996 - 2006") (1490)
16 limit 15 to (editorial or letter or note) (106)
17 Case Report/ (890125)
18 15 not (16 or 17) (1278)
19 Randomized Controlled Trial/ (106609)
20 Double Blind Procedure/ (60108)
21 Single Blind Procedure/ (5943)
22 exp randomization/ (19380)
23 (random$ or metaanalysis or meta-analysis or systematic$ review$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (364776)
24 or/19-23 (379340)
25 18 and 24 (264)
26 (metaanalysis or meta-analysis or systematic$ review$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (39667)
27 25 and 26 (60)
28 25 (264)
29 limit 28 to "review" (53)
30 28 not 29 (211)
31 27 or 30 (245)

B. IVF – Costs - Literature Search Strategy

Search date: July 7, 2006
Databases searched: OVID MEDLNE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, International Agency for Health Technology Assessment (INAHTA), and The Cochrane Library

Database: Ovid MEDLINE(R) <1996 to June Week 4 2006>
Search Strategy:
---
1 exp Fertilization in Vitro/ (10506)
2 (vitro adj1 fertilization).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (4922)
3 ivf.mp. (5837)
4 exp Economics/ (156155)
5 or/1-3 (12627)
6 4 and 5 (314)
7 limit 6 to (humans and english language and yr="2000 - 2006") (167)
8 from 7 keep 1-167 (167)

Database: EMBASE <1980 to 2006 Week 26>
Search Strategy:
---
1 exp Fertilization in Vitro/ or ivf.mp. (18606)
2 (fertilization adj1 vitro).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (18860)
3 1 or 2 (19812)
4 exp economic evaluation/ (79110)
5 3 and 4 (355)
6 limit 5 to (human and english language and yr="2000 - 2006") (208)
7 limit 6 to (editorial or letter or note) (38)
8 6 not 7 (170)
9 Case Report/ (891419)
10 8 not 9 (166)

C. Single-Embryo Transfer Search Strategy

Search date: July 18, 2006
Databases searched: OVID MEDLNE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, International Agency for Health Technology Assessment (INAHTA), and The Cochrane Library

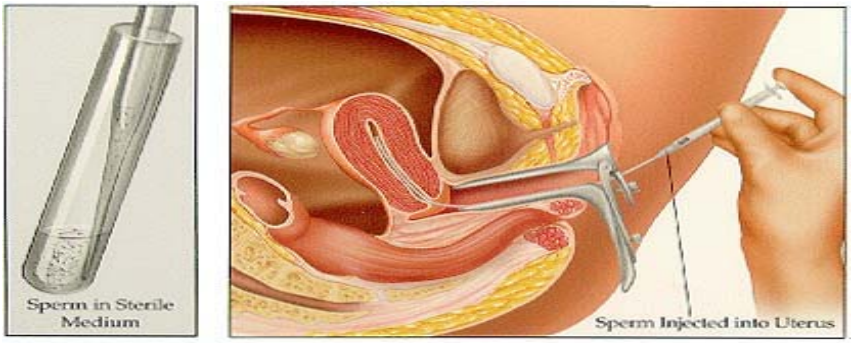
Database: Ovid MEDLINE(R) <1996 to July Week 1 2006>
Search Strategy:
---
1 exp Embryo Transfer/ (4428)
2 single embryo transfer.mp. (118)
3 exp Multiple Birth Offspring/ (6386)
4 exp Pregnancy, Multiple/ (7485)
5 (1 or 2) and (3 or 4) (502)
6 limit 5 to (humans and english language) (445)

7 (systematic$ review$ or meta-analysis or metaanalysis or random$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (290686)
8 6 and 7 (44)
9 6 (445)
10 limit 9 to (case reports or comment or editorial or letter or "review") (173)
11 9 not 10 (272)
12 8 or 11 (287)
13 (systematic$ review$ or meta-analysis or metaanalysis or random$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (290686)
14 12 and 13 (44)

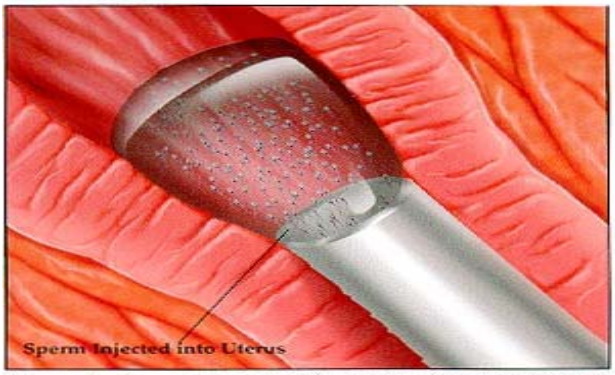
Database: EMBASE <1980 to 2006 Week 28>
Search Strategy:
---
1 exp embryo transfer/ (7352)
2 single embryo transfer.mp. (133)
3 exp Multiple Pregnancy/ (7058)
4 exp twins/ (9957)
5 (1 or 2) and (3 or 4) (920)
6 limit 5 to (human and english language and yr="1996 - 2006") (677)
7 (systematic$ review$ or meta-analysis or metaanalysis or random$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (367281)
8 6 and 7 (66)
9 6 (677)
10 limit 9 to (editorial or letter or note or "review") (181)
11 Case Report/ (893610)
12 9 not (10 or 11) (387)
13 12 or 6 (677)
14 (systematic$ review$ or meta-analysis or metaanalysis or random$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (367281)
15 13 and 14 (66)

Appendix 2: IVF Procedures

a) IUI Procedure



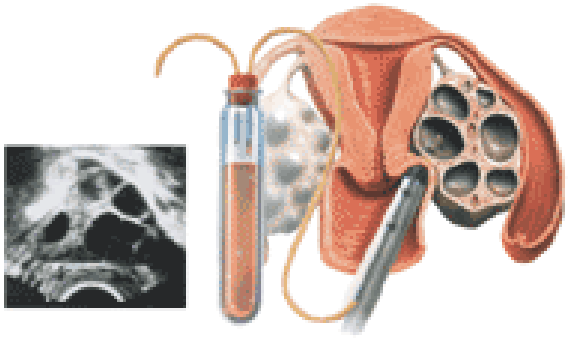
For IUI, sperm are first washed and placed into a sterile medium. The sperm are then concentrated in a small volume of medium and are injected directly into the uterus.



Through the process of IUI, sperm are placed high in the female reproductive tract to enhance the chance of successful fertilization.

Source: The Fertility Institutes: http://www.fertility-docs.com/images/graphic_iui.jpg

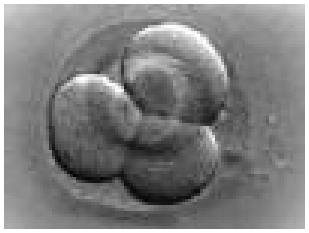
b) IVF Procedure (egg retrieval)



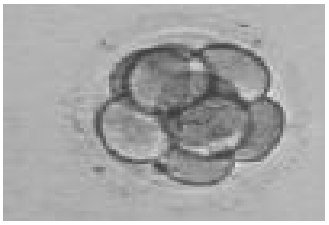
Source:.IVF Australia: http://www.ivf.com.au/pages/ivf_egg.php

Appendix 3: Embryos in Different Stage of Development

Day 2 Embryo



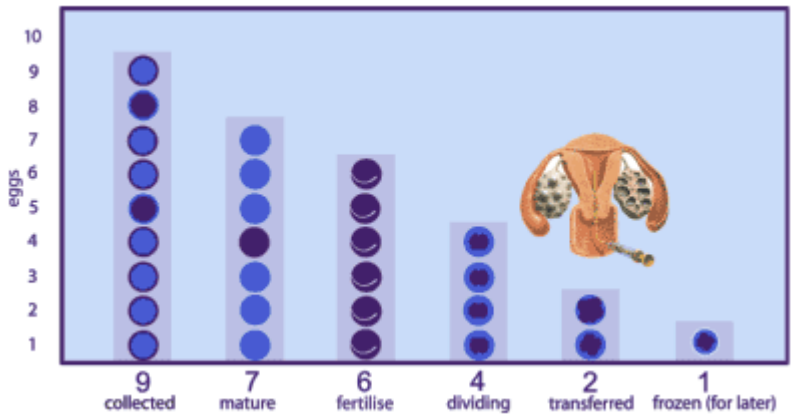
Day 3 Embryo



Day 5 Embryo – Blastocyst

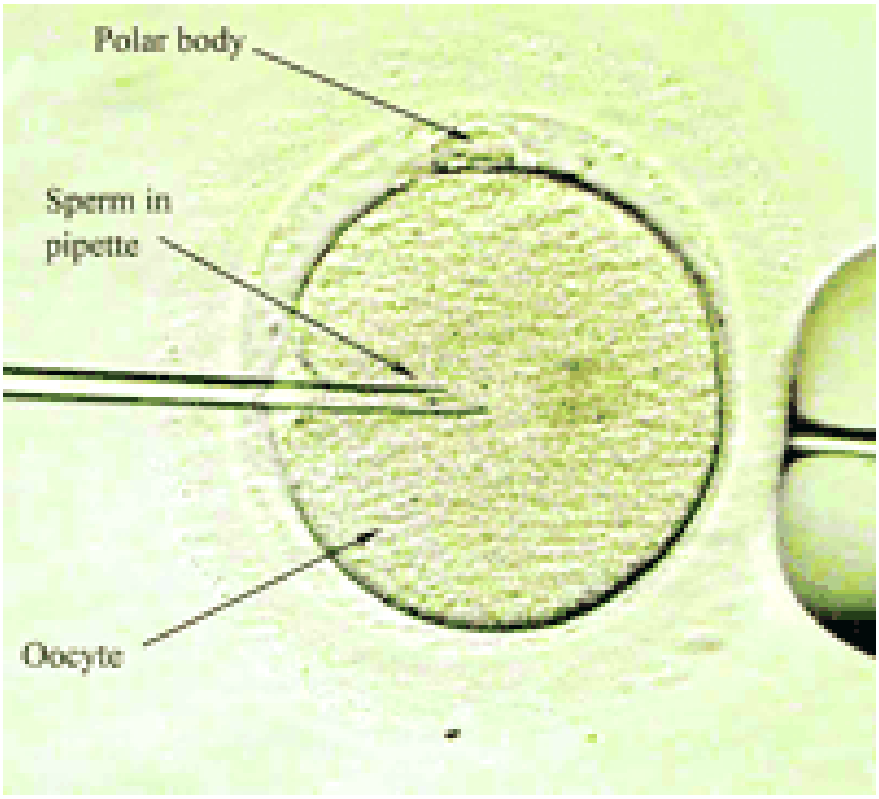
Source: Nashville Fertility Center: http://www.nashvillefertility.com/embryo_development_photo_gallery.htm

Appendix 4: Number of Eggs in IVF Procedure



*Source: IVF Australia: **http://www.ivf.com.au/pages/ivf_hormone.php***

Appendix 5: Intra-Cytoplasmic Sperm Injection



Source: Braude P, Rowell P. Assisted conception. II--in vitro fertilization and intracytoplasmic sperm injection. BMJ. 2003 Oct 11;327(7419):852-5.

Appendix 6: The Grade Evaluation System

The quality of the trials was examined according to the GRADE Working Group criteria. (56)

Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.

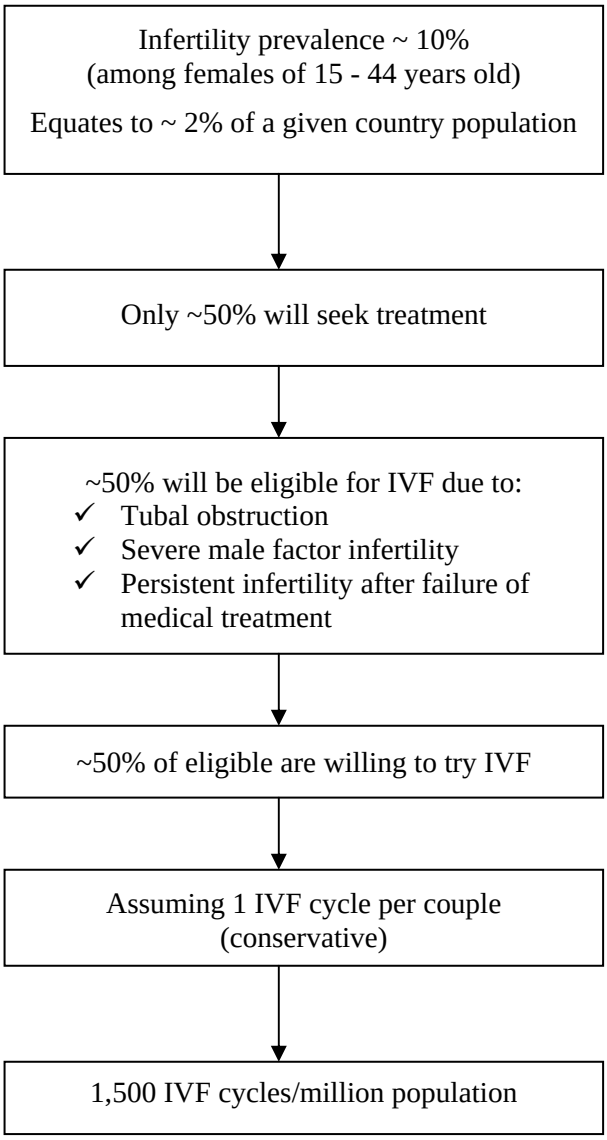
Consistency refers to the similarity of estimates of effect across studies. If there is important unexplained inconsistency in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the size of the differences in effect and the significance of the differences guide the decision about whether important inconsistency exists.

Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions were used in grading the quality of the evidence.

High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain

Appendix 7: Estimating the Need for IVF in a Population (from the ESHRE Group Workshop)



Source: Social determinants of human reproduction. Hum Reprod 2001; 16(7): 1518-1526

Appendixes 8: Probability Matrix for Economic Model

Probability matrices used for economic models. Probabilities were derived from literature and consultations with experts. The full list of references used for these probabilities is available upon request.

Table 1: Probability Matrix for Decision-Analysis Tree per Cycle, Assuming Only Fresh Cycles of IVF (Model 1)*

Clinical Outcomes	IUI-COS	IVF	
Cycle cancelled	15%	15%	
Dropout rate after cancelled cycle	1%	5%	
Dropout rate if not pregnant	10%	30%	
Dropout rate after loss of pregnancy	1%	10%	
	IUI-COS	**IVF-SET**	**IVF-DET**
Clinical pregnancy	13%	34%	53%
Delivery/Live birth	11%	28%	43%
Rate of multiple birth	**All multiple births after IUI-COS**	**Twins after SET**	**Twins after DET**
	26%	2%	22%
	% of Twins among all multiples	**% Triplets and higher order multiple births among all multiples**	
	84%	16%	

Maternal and neonatal outcomes					
	IUI-COS			IVF	
	Singleton	Twins	Triplets and higher order multiple births	Singleton	Twins
C-section rate	25%	58%	100%	27%	77%
NICU admissions	10%	55%	83%	18%	47%

*COS refers to controlled ovarian stimulation; DET, double embryo transfer; IUI, intrauterine insemination; IVF, in vitro fertilization; NICU, neonatal intensive care unit; SET, single embryo transfer.

Table 2: Pregnancy, Delivery and Multiple Delivery Rates After Second and Third Frozen-Thawed IVF Cycles for Model 2. *†‡

Outcomes	SET	DET
Clinical pregnancy	24%	36%
Delivery/Live birth	16%	29%
Multiple pregnancy	0%	18%
Dropout rate if not pregnant	18% after 1st cycle, 23% after 2nd cycle	

*****All other probabilities are assumed to be similar to Table 1.
†In SET, all 2nd and 3d cycles were frozen-thawed, while in DET only 50% of the 2nd and 50% of the 3d cycles were frozen-thawed). ‡DET refers to double embryo transfer; SET refers to single embryo transfer.

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