**Alberta Heritage Foundation
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In vitro fertilization and embryo transfer as a treatment for infertility

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This Health Technology Assessment Report has been prepared on the basis of available information of which the Foundation is aware from public literature and expert opinion, and attempts to be current to the date of publication. It has been externally reviewed. Additional information and comments relative to the Report are welcome, and should be sent to:

Acknowledgments

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Summary

- *In vitro* fertilization and embryo transfer (IVF-ET) was the earliest of the assisted reproductive technologies. In Canada, it remains the most commonly practiced technique of assisted reproduction.

- IVF-ET is a technology which continues to evolve. It was developed as a treatment for infertility caused by absent or irreparably damaged Fallopian tubes. In the last 15 years, indications for its use have broadened to include unexplained infertility, male factor infertility, infertility related to endometriosis, infertility caused by ovulation defects and immunological infertility. In 1992, over half of the IVF procedures undertaken in Canada were for non-tubal indications.

- IVF-ET has diffused widely without comprehensive assessment of its efficacy and safety. No adequate prospective randomized controlled trials or other prospective comparative studies of sufficient power on the use of IVF-ET for specific infertility diagnoses have been reported to date. There is limited information on IVF-ET outcomes derived from prospective controlled or comparative studies.

- Most of the published reports concerning results with IVF-ET as a treatment of infertility have been based upon small, uncontrolled studies. Investigators have used different designs, treatment protocols, patient populations, sample sizes, definitions of outcome measures and types of outcome.

- The success rates after IVF-ET are expressed in a variety of ways. There are few follow-up data on outcomes after pregnancy is established or on long-term health consequences of the use of IVF-ET on mothers and their babies.

- Reliable conclusions cannot be drawn on the effectiveness of IVF-ET for most indications.

    - The available evidence supports the use of IVF-ET as a treatment of infertility related to damaged, occluded or absent Fallopian tubes.

    - For other indications, the present evidence does not establish whether IVF-ET is more effective than receiving conventional treatment or no treatment at all.

- In the last five years, several assisted fertilization techniques have been developed in an attempt to improve fertilization in couples with severe male factor infertility who could not be helped by standard IVF-ET. Of these techniques, intra-cytoplasmic sperm injection (ICSI) appears to be the most promising. However, its efficacy and safety need to be substantiated further.

- The use of IVF-ET is associated with a wide range of obstetric and pediatric complications. Both mothers and their babies appear to be at increased risk of having multiple morbidities following IVF-ET.

- The risk of having congenital malformations does not seem to be increased in babies conceived by IVF-ET or by ICSI and IVF-ET.

- The present findings are consistent with those on standard IVF from the earlier report of the Canadian Royal Commission on New Reproductive Technologies.

- Long-term, well-designed, prospective controlled clinical trials are required to determine when and for what indications IVF-ET is effective and what its long-term health effects are on both mothers and their babies.

- It would be desirable for the Canadian IVF registry to collect cycle-specific data and information on outcomes (both immediate and longer term) from all IVF programs in Canada.

- Those offering or considering the use of IVF-ET should be aware that:

    - IVF-ET has been shown to be effective only for severe bilateral tubal disease

    - for other infertility diagnoses the present evidence is limited and does not establish whether IVF-ET is effective or not

    - obstetric and pediatric complications following IVF-ET may be significant

Introduction

The intent of this report is to inform medical practitioners and the public on the current status of *in vitro* fertilization and embryo transfer (IVF-ET) as a treatment for various types of infertility, and on its use and coverage in Canada. The report has been prepared because of the interest and debate regarding funding of IVF services in Alberta.

The inability to conceive leads many couples to use infertility treatments, but only half the women who have such treatment eventually conceive and an even smaller proportion take babies home. The infertility treatment success rate is affected, among other factors, by the duration and cause of the infertility and by the age of the female partner. Conventional treatments for infertility may include induction of ovulation, artificial insemination and surgical therapy. Infertile couples failing to conceive through conventional treatment may be referred for assisted reproductive techniques.

IVF-ET, the earliest technique of assisted reproduction, is the extracorporeal fertilization of human oocytes and the subsequent transfer of the resulting embryo(s) back into the uterus. It was initially used to produce pregnancy in women suffering from loss of or irreversible damage to their Fallopian tubes. Today, it is used for many other indications including unexplained infertility, male factor infertility, immunological infertility, infertility caused by ovulation disorders, infertility related to endometriosis and failed tuboplasty. While a number of other approaches have been developed, IVF-ET remains the most commonly performed assisted reproductive technique.

Scope of the report

This report considers specific aspects of IVF-ET and is not intended as a comprehensive review of all issues related to this technology. The aim has been to provide an up-to-date review of the studies conducted to examine the efficacy and safety of IVF-ET as a treatment of the various types of infertility and to present the available information on its use and coverage in Canada. Some discussion is included on the use and value of different types of outcome measure.

A number of other important issues relating to this technology are not addressed here. Economic aspects of IVF-ET as a treatment of infertility have not been considered. Nor does the review include discussion on the psychological and

social impact of the procedure, ethical and access issues, or overall efficacy/effectiveness of IVF programs. These matters require separate review.

The final report of the Royal Commission on New Reproductive Technologies has been used as background material for this assessment. The Commission was established by the Canadian Government in October 1989 to study the impact of assisted reproduction on Canadian society. It assessed the effectiveness of IVF-ET and its variations for specific indications from the "Canadian Infertility Therapy Evaluation Study" and from review and analysis of 501 randomized controlled trials conducted in Canada and elsewhere between 1966 and 1990 (59). The focus of the present review has been on studies published since the completion of the study by the Royal Commission.

The report consists of two main sections. The first summarizes the Royal Commission's findings regarding standard IVF and then presents a review of more recent literature which has provided evidence on the efficacy and safety of IVF-ET for different indications as compared to conventional infertility treatment or no treatment. Discussion on the efficacy and safety of intra-cytoplasmic sperm injection (ICSI) as a variation in the IVF-ET treatment for severe male factor infertility is included.

The other section presents data on the use and coverage of IVF-ET services in Canada.

Methodology

A literature search of English-language articles was conducted. Databases searched were: EMBASE, Medline, Cochrane Pregnancy and Childbirth Database, Cochrane Database of Systematic Reviews, ACP Journal Club, HSTAT, CMA, CPGs, Current Contents, and HSTAR. The term 'fertilization *in vitro*' was applied as a MeSH heading. Other key words used (alone or in combination) included: 'infertility', 'subfertility', 'effectiveness', 'efficacy', 'risks', 'pregnancy outcome', 'guidelines', 'controlled clinical trials', 'follow-up studies' and 'review'.

For the purpose of this review, the search was limited to studies on human subjects published in the last five-year period (1992 to January 1997).

The search focused on studies that have examined the efficacy and safety of IVF-ET and of ICSI and IVF-ET. Other variations of IVF-ET such as gamete intra-Fallopian transfer (GIFT) and zygote intra-Fallopian transfer (ZIFT) were excluded.

From the references identified, a selection was made that included all publications reporting the results of prospective controlled clinical trials (randomized and non-randomized), cohort studies and retrospective comparative studies with large series (more than 80 subjects in each arm) which had been conducted to evaluate the efficacy and safety of IVF-ET as compared with conventional treatment or no treatment for the various infertility diagnoses. Also selected were review articles presenting risks and complications associated with IVF-ET and ICSI and follow-up studies reporting health consequences of the treatment on mothers and their babies. Editorials, letters and comments were excluded. The bibliography of each retrieved article was examined to identify references that might have eluded the computer-based search.

The review of the literature was supplemented by expert opinion from specialists in obstetrics and gynecology with expertise in assisted reproductive technologies.

The Canadian Fertility and Andrology Society (CFAS), and the Society of Obstetricians and Gynecologists of Canada (SOGC) were contacted for guidelines, position papers, consensus statements, or minimum standards for IVF in Canada.

The Medical Directors of the provincial and territorial medical insurance plans in Canada were contacted by telephone to determine whether IVF services were publicly funded, with a follow-up contact by mail.

The IVF-ET procedure

The IVF-ET procedure has become fairly standardized. After diagnostic evaluation, before the typical IVF-ET treatment cycle begins, the referred couple is counseled regarding the likely outcomes of the treatment, the financial and emotional stress involved, and alternative options.

The IVF-ET treatment cycle begins with the maturation of one or more fertilizable oocytes, usually accomplished with ovarian stimulation (OS) procedures. IVF-ET may also begin with spontaneous oocyte maturation in a natural menstrual cycle. The second step is the retrieval of the mature oocytes from the ovaries, either by ultrasound-guided aspiration or laparoscopy. The retrieved oocytes are incubated *in vitro* and the prepared sperm added. After incubation, the dividing embryos are transferred back into the woman's uterus. In order to increase the chances of pregnancy, multiple embryos are transferred during one embryo transfer procedure (27, 59, 83).

There are variations between the IVF programs in the OS protocols, the techniques used for detection and retrieval of the mature oocytes, the laboratory protocols for fertilization and culture of the retrieved oocytes, the number of implanted embryos, and the outcome measures used to report the pregnancy success rates after IVF.

In the years since the first child conceived by IVF-ET was born, the technology has evolved and the number of indications has increased. IVF is still subject to refinement and modification. The standard technique of IVF-ET may be varied by freezing embryos (excess embryos can be cryopreserved and transferred in later treatment cycles; this allows for more than one embryo transfer from the same ovarian stimulation). Other variations include donation of oocytes, embryos or sperm. Also, in order to improve the relatively low IVF-ET pregnancy rates, other modifications of the treatment cycle have been introduced. These include GIFT (when fertilization of the retrieved oocytes takes place within the Fallopian tubes) and ZIFT (when the embryos resulting from fertilization *in vitro* are placed in the Fallopian tubes).

Recently, new variations of IVF-ET, called assisted fertilization techniques, have been developed to bypass the barrier of the zona pellucida in order to improve human gamete interaction, particularly in cases of severe sperm abnormalities (63, 74, 76). Fertilization is assisted by insemination after opening the zona pellucida with glass microneedle by partial zona dissection (PZD), by introducing a small number of sperms with micropipette into the perivitelline space by sub-zonal insemination (SUZI), or by microinjection of a single sperm directly into the oocyte by ICSI.

Efficacy/effectiveness of IVF-ET

Findings of the Royal Commission on New Reproductive Technologies

The Commission defined standard IVF as being effective when couples who received the treatment had a greater likelihood of having a healthy baby than those in a similar group who did not receive the IVF procedure. Because most of the studies used clinical pregnancy rates, not live-birth rates, the Commission decided that IVF should satisfy one of two specific criteria in order to be categorized as effective:

1. IVF for specific clinical indications would have to be proven effective in well designed RCTs that allowed meta-analysis of combined studies with a total of 200 couples in both the control and experimental group; and

2. IVF would have to be shown to correct a specific mechanism known to be causing infertility, in a way that is biologically convincing (59).

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. Since standard IVF bypassed the Fallopian tubes by allowing fertilization to take place outside of the woman's body, it satisfied one of the Commission's criteria as an effective treatment for that indication.

The Commission also concluded that there was not enough evidence to determine whether standard IVF was effective or not for non-tubal indications and that the available evidence did not suggest that it overcomes a specific mechanism known to cause infertility for indications other than complete tubal blockage.

Based on these findings, the Commission recommended that standard IVF be provided as treatment for bilateral Fallopian tube blockage. The Commission also recommended that the other non-tubal indications, for which standard IVF has not been proven effective, should be considered for research.

General points from the present review

Some general points can be made concerning the evidence obtained during the present assessment.

There are no published practice guidelines, position papers, consensus statements or minimum standards for IVF-ET and related techniques in Canada. However, CFAS and SOGC have established a joint committee to develop both practice guidelines and guidelines for accreditation of centres using IVF-ET and related techniques. These are expected in 1997.

There are no adequate prospective randomized controlled trials (RCTs) or other comparative studies of sufficient power on the efficacy and safety of IVF-ET for specific types of infertility. The literature search revealed little information on IVF-ET derived from planned prospective controlled or comparative studies. Most published reports on IVF-ET have been based either on non-randomized studies or on retrospective analyses with no controls or with historical controls. Only two RCTs comparing IVF-ET with conventional treatment or no treatment in couples suffering from different infertility diagnoses have been published to date (39, 65).

The reported results on efficacy and safety of IVF-ET are not directly comparable (Table 1) as the studies used different designs, treatment protocols, patient populations, sample sizes, definitions for outcome measures and methods of reporting outcomes. Methodological quality of the studies was limited in several aspects. There was little or no information on the selection of patients, inappropriate use of cross-over design, lack of appropriate control groups and lack of definitions for outcome measures. Because of these limitations, it is not possible to draw reliable conclusions from these results.

It is also difficult to determine whether the results of studies refer to efficacy of the technology (performance under optimum conditions) or its effectiveness (performance under routine conditions). Given the nature of the institutions in which most of the larger studies have been undertaken, the impression is that reported results tend to reflect efficacy rather than effectiveness.

In IVF-ET practice, efficacy/effectiveness is usually expressed in terms of "success rates". The definition of IVF-ET success rate includes a measure of the number of pregnancies obtained after IVF-ET as the numerator and an indicator of the number of IVF-ET events that occur for each pregnancy as the denominator. The success rates may appear optimistic or discouraging depending on the definitions used for the different numerators and denominators (59, 83).

IVF-ET success rates vary widely among different programs, due in part to the lack of standardization of the definitions of outcome measures and of the methods of reporting. Most programs define success of IVF-ET as achieving clinical pregnancy, but different definitions for clinical pregnancy have been used. Some clinics define success as achieving delivery (of live-births only, or including stillbirths). The denominator most frequently used to calculate the success rate is the IVF-ET treatment cycle, which is also defined in different ways ranging from started cycle and oocytes retrieval cycle to embryo transfer cycle (23, 59, 83).

Since the main goal of the infertile couple undergoing IVF-ET is to have a normal and healthy child following the treatment, an appropriate measure of the success would be the number of live deliveries related to the number of treatment cycles initiated to achieve those deliveries, the "take-home baby" rate. Another appropriate measure of success with IVF-ET would be the health status of the children at subsequent long-term follow-up.

However, most published reports express the IVF-ET success rate as number of clinical pregnancies obtained per total number of started, oocyte retrieval, or

completed (embryo transfer) treatment cycles and/or as the total number of deliveries related to the same denominators. Few programs reported success rates as the number of live-births obtained per total number of started, oocyte retrieval, or completed cycles. More recently, success rates have been expressed as cumulative pregnancy and live-birth rates for a given number of treatment cycles, using life-table calculation. However, it has been argued that cumulative results may give a "totally unrealistic impression" (80).

Few follow-up data exist on the potential risks and complications associated with IVF-ET procedure after pregnancy is established (Table 1). There are also few follow-up studies on long-term health consequences of the use of IVF-ET therapy on mothers and their babies.

Available data on efficacy/effectiveness of IVF-ET

Details of studies on outcomes of IVF-ET which met the selection criteria used for the literature review are summarized in Table 1. These studies took a variety of approaches and comparison between them is not straightforward. Main conclusions from reviews of IVF-ET and related techniques are given in Table 2. The following commentary outlines the most important points which emerged from the literature review.

Probability of live-birth

The reviewed literature suggests that the probability that IVF-ET will result in a live-birth depends on many factors. These include the couple's characteristics (e.g., female partner's age, the duration and cause of infertility); the clinic's characteristics (e.g., size of the clinic, experience of the medical team, the criteria used to select couples for treatment); and variations in the IVF-ET protocol (e.g., treatment used for OS, techniques used for fertilization and culture of the retrieved oocytes, number of embryos transferred) (23, 44, 59, 68). The significant influence of the female partner's age and cause of infertility has been retrospectively analyzed by several investigators who reported that the couples with the female older than 40 years and those suffering from male factor infertility or multiple infertility factors had the lowest chances to conceive through IVF-ET (4, 18, 29, 36, 40, 64, 71).

Accepted indications for treatment

According to the published literature, IVF-ET is accepted as standard treatment for women with bilaterally damaged, occluded, or absent Fallopian tubes. In terms of pregnancy rates, IVF-ET treatment has been reported to be statistically significantly better than conventional treatment or no treatment at all in patients

with severe bilateral tubal disease (sub-group analyses for diagnosis category conducted by Soliman et al. (65)). Jarrell et al. (39) has reported improved pregnancy rates associated with IVF among women with tubal damage. Spontaneous pregnancies are reported occasionally in these patients, with a live-birth rate of 1.4% (20) while chances of live-birth with IVF-ET are, on average, 8% to 12% per treatment cycle (42). Soliman et al. (65) reported that IVF-ET increases the likelihood of pregnancy by 40% in patients with severe tubal disease.

IVF-ET has been advocated as an alternative to tubal surgery for infertility caused by tubal factors (62, 63). Benadiva et al. (9) reported a cumulative pregnancy rate, after four cycles of IVF-ET, of 77% in patients with pure tubal factor infertility and of 75% in patients with tubal factor and other infertility factors. They found that these rates compare favorably with the best outcomes reported after tubal surgery in patients with tubal factors. However, it has been suggested that these rates are not realistic and a more appropriate figure would be in the 50% range (Daya, personal communication).

According to the reviewed studies, both tubal surgery and IVF-ET should be offered and the choice should be governed by the severity of the tubal disease. IVF-ET appears to be a preferable treatment for some causes of tubal infertility (e.g., bilateral salpingectomy, bilateral multi-site tubal obstruction and complete tubal obstruction). In others (e.g., tubal sterilization) tubal surgery appears to be the preferred choice (24).

The length of time between treatment and conception is longer following tubal surgery than after IVF-ET (35, 37, 62). The potential advantage of tubal surgery over IVF-ET is that women who give birth after tubal surgery may not need further intervention if another pregnancy is desired (62). It has been reported that women who have achieved a pregnancy through IVF-ET have a high probability of success if they wish to try for another IVF-ET baby (70). However, it has been suggested that IVF-ET is associated with more adverse effects than tubal surgery and the pregnancies obtained by IVF-ET are at higher risk of obstetrical complications (24).

Other indications

In recent years, indications for IVF-ET treatment have expanded beyond bilateral Fallopian tube blockage, and currently the procedure is used for a wide range of non-tubal infertility diagnoses. It has been suggested that in non-tubal infertility the age of the female partner and the duration of infertility are the most important prognostic factors and these two variables may be used to select IVF as a possible therapeutic option (Wood, personal communication). However, the

efficacy of IVF-ET in these cases is debatable in the view of the frequency of spontaneous pregnancies that may occur (54, 59, 65). It has been reported that treatment-independent pregnancies occur more frequently in women with patent Fallopian tubes awaiting IVF-ET. The cumulative live-birth rate at 36 months ranges from 16.1% for those with infertility related to endometriosis to 33.3% for women with unexplained infertility (20). This range compares with a rate of 15.7% for women with tubal defects and with a rate of 8.0% for women with bilateral obstruction of Fallopian tubes (20).

On the basis of information obtained from the literature review, the efficacy of IVF-ET for treatment of infertility for causes other than those related to tubal defects is not established. The superiority of IVF-ET to conventional therapy or no treatment at all has not been clearly demonstrated to date for infertility related to endometriosis or ovulation defects, immunological infertility, unexplained infertility and male factor infertility (Tables 1 and 2). Further, there is no evidence to suggest that IVF-ET can overcome factors known to cause infertility in any of these indications.

It has been suggested that the results from an RCT (39) established the overall effectiveness of IVF for women with different infertility diagnoses, but predominantly through benefit to patients with blocked Fallopian tubes (Jarrell, personal communication). From the study findings, IVF appeared to be effective in increasing the pregnancy, parturition and live-birth rates from the perspective of intention to treat. However, the study had insufficient power for sub-group analysis. When patients in the control group were compared to those actually receiving IVF, IVF treatment was associated with a non-significant higher rate of viable pregnancy and parturition.

Male factor infertility

Within the major categories of non-tubal infertility diagnoses, the most important developments have occurred in the male factor infertility group. Spontaneous pregnancy rates in cases of male factor infertility (when sperm are defective in quality and quantity) may be as low as 1 to 2% (22, 63, 65) since the sperm must have the capacity to fertilize whether *in vivo* or *in vitro*. IVF-ET has been used widely to treat couples with male factor infertility but with relatively disappointing results (8, 64) due mainly to poor fertilization rates and hence fewer available embryos for transfer. Limited success rates have been reported, especially in couples with severe male factor infertility (2, 10, 40).

In an attempt to overcome the infertility associated with sperm disorders, modifications of the standard IVF-ET have been developed, including assisted fertilization techniques, also called micromanipulative techniques, such as PZD,

SUZI and ICSI. Reports published in the last five years suggest that ICSI is the most beneficial approach for severe male factor infertility, which is associated with a variety of sperm abnormalities. Of all assisted fertilization techniques only ICSI seems to offer a significant benefit over IVF-ET in terms of fertilization, cleavage and implantation rates (10, 52, 53) in severe male factor infertility cases. Studies on outcomes achieved with ICSI are summarized in Table 3.

Studies on infertile couples who did not benefit from IVF-ET (failed to achieve fertilization) or who had too few spermatozoa to be accepted for IVF-ET, reported pregnancy rates per oocyte retrieval cycle ranging from 32% to 37% (Table 3). However, pregnancies obtained by ICSI and IVF-ET seem to carry a higher risk of obstetric and pediatric complications than spontaneous pregnancies (75, 84). Other drawbacks are its complexity and cost (75). Of all assisted fertilization techniques developed so far ICSI is also the most invasive approach, requiring micromanipulation of the gametes at different and delicate stages of their development (53, 75, 82).

Unstimulated IVF-ET

The concerns raised about the increased risk of having multiple pregnancies and severe ovarian hyperstimulation syndrome (OHSS) with the use of OS as an adjunct for IVF-ET procedure, renewed the interest in unstimulated IVF-ET treatment (25, 55, 74). Reported pregnancy rates per cycle range from 2.7 to 21% (28). The expected live-birth rates per started cycle range from 2.7% to 18 % (25). All pregnancies obtained after unstimulated IVF-ET treatment have been reported to be singletons (25, 28, 55). Although the procedure is associated with high drop-out rates at each stage, it has been suggested that this approach is a low-cost alternative that may be more accessible and offers many advantages to patients as compared to stimulated IVF-ET (25). However, in current practice the unstimulated IVF-ET treatment is not completely natural, minimal stimulation regimens being administered (25, 28, 55) (Table 1).

Expert opinion

Opinion from gynecologists and obstetricians in Canada who are experts in assisted reproduction is that IVF-ET treatment is the only option for infertile couples suffering from absent or irreparably damaged Fallopian tubes. For other indications, it should be offered as the last resort, after all other options have failed. In case of severe male factor infertility, couples should consider ICSI in combination with IVF-ET as the best possible option.

Risks and complications associated with IVF-ET

There is evidence that pregnancies conceived after IVF-ET have associated risks and complications related to ovarian stimulation, the extracorporeal methods used during the treatment and to the surgical and other procedures used for oocyte retrieval and embryo transfer (25,59, 61). Some information from recent studies is included in Tables 1 and 2.

According to the published literature, pregnancies achieved by IVF-ET tend to be more complicated than normally conceived pregnancies. Recent reports from individual centres and national registries have drawn attention to the high rates of ectopic pregnancies (ranging from 2.1% to 8.8%), spontaneous abortions (ranging from 10.6% to 25%) and premature deliveries (ranging from 20% to 37%) after IVF-ET (7, 27, 46, 50, 67).

Published results also suggest that during IVF-ET pregnancies there is a higher incidence of pregnancy-induced hypertension and vaginal bleeding requiring hospitalization, and a greater likelihood of delivery by Caesarean section, which involves small but real additional risks (26, 45, 67, 69, 79). Higher rates of maternal diseases in IVF-ET pregnancies contribute to fetal intra-uterine growth retardation (61).

The major problem of pregnancies resulting from IVF-ET is the increased rate of multiple pregnancies which are associated with the use of ovarian stimulation drugs during the IVF -ET treatment cycle (17, 59, 61). Attempts to increase the probability of successful pregnancy by increasing the number of embryos transferred also increase the probability of multiple pregnancies (23, 34, 59). The multiple pregnancy rate varies (between 17.3% and 38 %) and is significantly higher than that for spontaneous pregnancies (about 1%) (6, 26, 32, 46, 50, 61, 69). Published evidence suggests that multiple pregnancies are associated with increased rates of stillbirths, pre-term deliveries (with attendant maternal and pediatric complications), deliveries by Caesarean section, and congenital malformations (3, 27, 29, 45, 61).

IVF-ET has also been associated with an increased rate of heterotopic pregnancies (multiple pregnancies that occur in the uterus and are also associated with ectopic locations). However, in the review of the complications of ovulation induction published in the Royal Commission Report, ovulation induction with or without IVF was identified as responsible for the increased rate of heterotopic pregnancies.

Increased rates of perinatal mortality and morbidity following IVF-ET have been related to prematurity (27, 61). Different studies on births resulting from IVF-ET reported a high incidence of pre-term (40 to 60% in twin pregnancies, and 80 to 95% for triplet pregnancies) and low birth-weight babies (30, 41, 45, 67). The incidence remains high even when the analysis is restricted to singletons (23, 32, 56, 69, 79). It has been reported that both singletons and multiples conceived by IVF-ET and related techniques have an increased risk of obstetric and pediatric complications, need more neonatal intensive care and stay longer in hospital as compared to the general population (21, 33, 45, 50, 67).

There is some evidence to suggest that poor perinatal outcomes after IVF-ET and related techniques are not entirely due to multiple and pre-term births. It has been reported that full-term singletons conceived by IVF-ET have a lower birth-weight than naturally conceived singletons (62).

OHSS, a frequent complication of ovarian stimulation (especially in women with polycystic ovaries (16)), is also recognized as a relatively common complication of IVF-ET and related techniques (29, 59, 61). There are few conclusive data on its long-term effects on women, although studies have pointed to a rise in ovarian, breast and endometrial cancers (50).

Recently, Bristow and Karlan (15) critically reviewed the published data regarding the association between ovarian cancer and the use of fertility drugs. They concluded that "an association between ovarian stimulation and ovarian cancer does not indicate necessarily a causal effect" and that infertility alone is an independent risk factor for ovarian cancer. Venn et al. (78) examined the incidence of breast and ovarian cancers in a cohort of 10,358 women referred for IVF. They found that ovarian stimulation with IVF is not associated with an increased risk of breast or ovarian cancer.

The reviewed literature suggests that the overall congenital malformation (major and minor) rate is not increased after IVF-ET and related techniques. This incidence was studied in the last five years (Table 2) and it was found that the reported rates (ranging from 1.5% to 3.3%) are comparable to those reported for the general population (5, 7, 44, 61, 69, 74).

To date, studies on children born after ICSI combined with IVF-ET reported no increase in the congenital malformation rate (up to 3.9%) and no differences in the pediatric follow-up as compared with children born after conventional IVF-ET (12, 52, 73). However, Tummon et al. (75) reviewed the English language papers on the use of ICSI and found that the available data are inadequate to assess the risks of congenital malformations and long-term health effects after

this procedure. Another concern is that the use of ICSI may increase the risk of sex chromosomal abnormalities (75, Daya, personal communication).

It has been suggested that children conceived by IVF-ET do not have increased risk of psychosocial or developmental problems as compared with children conceived naturally(43). However, only a few studies relate to the state of health of babies conceived by IVF-ET, when they are over a month old.

Brandes et al. (14) assessed the physical and mental development at the age of 12 to 45 months of 116 children conceived by IVF-ET and born at the same centre. They found that, overall, infants were within the normal range of physical and mental indices and did not differ when compared with matched controls (n=116). Twins and triplets in both groups had significantly lower physical and mental indices as compared to singletons.

Saunders et al. (60) evaluated the growth and physical outcome at 2 years of age for children born after IVF and related techniques (n=314) as compared with controls matched for plurality and gestation (n=150). The results suggested that there was no independent IVF effect on the growth and physical outcome of children at 2 years of age. Twins in both groups had significantly poorer physical outcomes than singletons on some measures.

Several investigators found that couples undergoing IVF-ET represent a specific group of people and may differ from the general population because of their infertility history, higher female age, low parity, and possibly their socio-economic and psychosocial status. Hence, poor obstetric outcomes and an increased incidence of obstetric complications would be expected from this population, even if the women would or could become pregnant spontaneously or as a result of another infertility treatment (30, 45, 61, 69, 79, 81). It has also been suggested that characteristics such as a higher female age at conception, an infertility history or a higher frequency of poor obstetric history, may not explain all the differences with spontaneous pregnancies (41, 69).

IVF-ET in Canada

Utilization and outcomes of IVF-ET in Canada

In a response to calls for better data on IVF-ET and related techniques, national registries have been organized in several countries. These registries represent the main sources of data on a national scale related to treatment effectiveness and risks associated with the technology. Reports that summarize treatments by IVF-

ET and related techniques are published annually in France, the United Kingdom, Australia/New Zealand, the United States of America and Belgium.

In Canada , a national registry of assisted reproduction by IVF-ET and GIFT/ZIFT was established in 1988 (47). Sixteen Canadian IVF centres have reported their outcomes manually since 1989 using the form that has been developed by the International Working Group of IVF Registers (IWG). IWG is a voluntary association that has standardized the reporting of all IVF and GIFT information for the collection of national data in 55 countries.

Data available from the Canadian IVF registry are cumulative and by centre. They are not cycle-specific and do not allow for either life-table analysis or cross-sectional analysis (47). The registry monitors the incidence and prevalence of various indications for IVF and GIFT/ZIFT, stimulation protocols, treatment outcomes and reports on factors associated with pregnancy. Data on outcome of pregnancy following these procedures are least effectively monitored.

According to the Canadian registry, assisted reproductive technologies have been used by a very small proportion of the infertile couples in Canada and the annual rate of increase is small (from 86 to 90 cycles per 100,000 women aged 25 to 44 years, between 1991 and 1992). In Australia, between 1990 and 1991, the comparable rate of increase was from 428 to 549 cycles per 100,000 women.

GIFT or ZIFT accounted for less than 1% of all treatment cycles reported between 1989 and 1992 in the Canadian IVF registry. In 1992, more than 50% of all IVF procedures were used for non-tubal infertility diagnoses. Of all women who underwent IVF in 1992, 63% were over the age of 34. That year, pregnancy rate/ oocyte retrieval for IVF-ET was 17%and the rate of births/oocyte retrieval was 14.2%. The corresponding pregnancy rate for Germany in 1992 was 11.7%.

In Canada, the average number of embryos transferred per IVF-cycle is higher than for most IWG member countries and the multiple pregnancy rate is higher than in most countries (47). The multiple pregnancy rate increased from 24.4% in 1991 to 27.9% in 1992. In 1992, the twin rate increased to 21.3%, the triplet rate declined to 6.4% and 2 quadruplet births were reported.

The outcomes of 13.4% of all IVF and GIFT/ZIFT pregnancies reported from 1989 to 1992 in Canada (resulting from a total of 12,111 transfer cycles) are not known. For the remaining 86.6% of pregnancies, the spontaneous abortion rate was 22.5% of intra-uterine pregnancies and the ectopic pregnancy rate was 5.1%. Comparative data from France (collected between 1987 and 1991) for over 60,000

transfer cycles showed a spontaneous abortion rate of 18.3% of intra-uterine pregnancies and ectopic pregnancy rate of 5.6% (47).

The perinatal mortality rate for all treatments in 1992 was 53.1 per 1,000 total births in singletons, 31.9 per 1,000 total births in twins, and 6.4 per 1,000 total births in triplets (47). The overall incidence of low birth-weight (<2,500 g) was 31.5% in 1992 (47). The Australian and New Zealand incidence of low birth-weight in 1991 was 32.6%. The congenital malformation rate in IVF infants is about 1% higher in Canada as compared to the world average (47). There are no follow-up data on long-term effects.

Coverage of IVF-ET in Canada

The Medical Directors of the provincial and territorial medical insurance plans in Canada were surveyed to determine whether IVF services were publicly funded. Responses are summarised in Table 4. All provincial plans pay for the parental diagnosis of infertility and the usual treatments for infertility.

Ontario pays for three courses of IVF treatment for patients with complete bilateral tubal blockage. Patients who have been sterilized surgically do not qualify under this policy. IVF treatment is available in public hospitals and private clinics for other indications, but at cost to the patient. Prince Edward Island pays for a portion of the physician charges for patients receiving ovum transfer and embryo transfer at the private clinic in Halifax. In Saskatchewan and Québec some services such as laparoscopies, ultrasound examinations and office visits, which are provided as part of a course of IVF treatment, are probably billed to the medical plans under other indications.

In Canada, IVF-ET is offered in 18 centres (public hospitals and private clinics) (38). Private IVF services are offered in six provinces. Only Ontario has publicly funded IVF clinics. Most private clinics are located within public facilities. The Medical Directors did not have information about the number of clinics in their provinces.

Discussion

IVF-ET, the earliest and most commonly performed assisted reproductive technique, is a technology which continues to evolve. Initially developed to treat infertility caused by irreparably damaged, occluded or absent Fallopian tubes, IVF-ET is currently used for the treatment of many other types of infertility. In Canada, in 1992, more than 50% of all IVF procedures were used for non-tubal indications.

IVF-ET has become a widely used treatment for infertility without a comprehensive assessment of its efficacy and safety. Consistent collection and analysis of data on specific outcomes have not taken place. There are no adequate comparative studies of sufficient power on the efficacy and safety of IVF-ET for specific infertility diagnoses. Most of the published reports which provide results of IVF-ET as a treatment of infertility are based upon small uncontrolled studies, or retrospective analyses, and have various methodological weaknesses.

The success rates with IVF-ET vary widely due to a number of factors including couples' characteristics, characteristics of the centres using the technology and variations in the application of the IVF-ET procedure. The differences in success rates are also due to the lack of standardization of definitions for outcome measures and of calculation methods.

Given the paucity of data on the efficacy and safety of IVF-ET for specific infertility diagnoses, the question of whether this technology is more beneficial than conventional treatment or no treatment at all remains unanswered for most indications.

From the available evidence, the effectiveness of IVF-ET is established only for the treatment of infertility caused by severely damaged, blocked or absent Fallopian tubes.

For other conditions, there is not enough evidence to determine whether IVF-ET is effective or not. Women suffering from these other types of infertility who undergo IVF-ET are subject to risk from the potential complications of this treatment without certainty that they are more likely to deliver a normal, healthy baby than if they receive no treatment or conventional treatment (which may be less aggressive). Treatment-independent pregnancies continue to occur while women are waiting for IVF-ET or in the months following failure to conceive with IVF-ET.

In the last five years, various assisted fertilization techniques have been developed and explored in an attempt to increase the chance of fertilization in couples suffering from severe sperm disorders, who cannot benefit from standard IVF-ET. Of these techniques, ICSI appears to be the most beneficial approach. In Canada, ICSI has been adopted rapidly and currently it is offered in most of the Canadian IVF programs (38, 75). However, its efficacy and safety have yet to be determined, since relatively few live-births have been documented to date. Also, the female partner is still subjected to the rigours of IVF-ET and undertakes almost all of its medical risks.

Women who undergo IVF-ET appear to be at increased risk of having spontaneous abortions, ectopic pregnancies or multiple pregnancies, pre-term labors, deliveries by Caesarean section, babies with low birth-weight and higher perinatal morbidity and mortality. The risk of congenital malformations does not seem to be increased after IVF-ET or ICSI combined with IVF-ET as compared with the general population.

According to the data reported from 1989 to 1992, in Canada the multiple pregnancy rate is higher than in most countries and the malformation rate is higher than the world average. There are no published Canadian data on long-term outcomes.

It would be desirable for the Canadian IVF registry to report cycle-specific data and information on short- and long-term outcomes from all IVF programs in the country. Such an approach would provide more realistic measures of pregnancy rates obtained by IVF and related techniques and of the outcomes for women and their children. These data would allow comparisons with data reported by other members of IWG which have large national registries.

The findings of the present review are consistent with those of the Canadian Royal Commission on New Reproductive Technologies. More comprehensive data, derived from long-term, well-designed, prospective investigations, are required to determine when and for what indications IVF-ET is effective and what its long-term health effects are on mothers and their babies. The available information is incomplete and often controversial.

Practitioners offering IVF-ET and infertile couples considering treatment by IVF-ET should take into consideration that:

- the available evidence supports the use of IVF-ET as a treatment of infertility due to severely damaged, occluded or absent Fallopian tubes.

- for other indications the present evidence is limited and does not establish whether IVF-ET is effective or not.

- risks of having multiple complications after IVF-ET may be significant for both mothers and their babies.

Table 1 : Studies on IVF-ET outcomes

Study	Study design	Patients' characteristics	Treatment	Pregnancy outcome	Complications and adverse effects
Mills 1992 (49)	*prospective controlled study to compare results of IVF, GIFT, and OS with IUI (1988-1990) in infertile patients (with normal uterus and ovulatory cycles)	*n_1=60 couples (IVF): tubal infertility; mean age: 32.5 years *n_2= 47 couples (GIFT); endometriosis (healthy tubes) or unexplained infertility; mean age: 34.2 years *n_3=44 couples (IUI): endometriosis (healthy tubes) or unexplained infertility, ovaries free of adhesions; mean age 33.7 years *overall, median infertility duration 5 years	*all couples had a previous IVF cycle *2 stimulation protocols *up to 4 embryos transferred (IVF) *2 to 4 eggs transferred (GIFT) *only 1 treatment cycle	*IVF group: implantation rate 11%; 17 clinical pregnancies (PR/cycle 28%; PR/ET 29%); 14 births (birth rate /cycle 23%; birth rate/ET 24%) *GIFT group: implantation rate 21%; 19 clinical pregnancies (PR/cycle 40%); 15 births (birth rate/cycle 32%) *IUI group: implantation rate 13%; 9 clinical pregnancies (PR/cycle 20%); 7 births (birth rate/cycle 16%)	*IVF group: 3 twins *GIFT group: 6 twins; 2 triplets *IUI group: 1 twin; 1 triplet *overall, 2 stillbirths and 2 neonatal deaths
Tan 1992 (71)	*retrospective study (1984-1989) to assess the results of IVF in infertile patients at one centre	*n=2735 couples (1161 tubal; 168 endometriosis; 196 male factor infertility; 134 other causes; 332 multiple causes); 744 unexplained infertility; age: 20 -45 years	*up to 8 cycles (3 women had 9 or more cycles)	*5055 consecutive IVF cycles; 773 clinical pregnancies; 518 live-births; after 5 cycles, CPR 48.7% and CLR 37.9% *both CPR and CLR were significantly different between causal groups (p<0.001 and p=0.02), declined with age (p<0.001), and were lowest in patients with male infertility or multiple infertility factors *there was a significant decline in the chance of pregnancy and live-birth per cycle with successive treatment cycles	
Jarrell 1993 (39)	*RCT, to evaluate the effectiveness of an IVF program compared with standard management with respect to correction of infertility (almost 3 years)	*n=399 couples (tubal disease, endometriosis, semen deficiency, idiopathic infertility) *n_1=194 (control): mean age: 32.5 years; infertility duration: 5.5 years *n_2=205 (IVF): mean age: 32.3 years; infertility duration: 5.9 years	*control patients allocated to a delay of 6 months prior to IVF-ET (allowed to have other infertility treatments); *IVF patients allocated to 1 to 4 cycles of IVF-ET;	Control group: 31 drop outs; 13/163 clinical pregnancies (8%); 3/13 EPs (23%); 2/13 abortions (15.3%); 8/163 deliveries (4.9%) (singletons); Experimental group: 15 drop outs; 190/205 included in the analysis *n_1= 139 started IVF-ET; 286 started cycles; 29/139 cancellations (20.9%); 20/139 clinical pregnancies (14.3%); 5/20 abortions (25%); 2/20 EPs (10%); 13/139 deliveries (9.35%); crude PR/started cycle 6.7%; crude PR/completed cycle 9.7% *n_2= 51 did not start IVF-ET; 13/51 conceived before IVF (13/190 treatment-independent pregnancies, 6.84%); 9 deliveries (singletons), 1 abortion, 3 EPs Subgroup analysis: higher IVF PRs (p=0.009) in endometriosis or tubal groups as compared with other diagnostic categories	Experimental group: 1 twin and 1 quadruplet *no stillbirths in either group *all babies were healthy at birth

Table 1 (continued)

Study	Study design	Patients' characteristics	Treatment	Pregnancy outcome	Complications and adverse effects
Soliman 1993 (65)	*RCT to evaluate the effectiveness of IVF in infertile couples (6 month trial period, 13 month follow-up period)	*n=245 couples enrolled; 199 couples completed study (77 tubal, 60 male, 21 endometriosis, 35 unexplained infertility, 6 ovulation defect; mean age: 32 years; infertility duration: 65 months); 46 drop outs (28 IVF patients; 18 controls)	*n₁=99 couples allocated to one IVF-ET cycle (treatment group); *n₂=100 couples allocated to late IVF, after 6 months (control group); 73% had other infertility treatment, and 27% no treatment	Treatment: 16/99 cancellations (16.2%); 65/99 ETs (65.6%); 17/99 pregnancies (17.4%); 4/17 chemical pregnancies; 1/17 EPs; PR (excluding chemical pregnancies): 13.1% (13/99);12 live-births (live-birth rate/started cycle 12.1%); PR in endometriosis significantly higher than in tubal (p=0.03) and in unexplained infertility (p=0.05) Control : 8/100 pregnancies (8%); 2/8 abortions; 6/8 live-births (live-birth rate/started cycle 6%); PR/cycle 1% * IVF PR/cycle (12%) significantly higher (p=0.0042) *significant difference in favor of IVF in patients with bilateral tubal obstruction (p=0.04); for other infertility diagnoses, differences in PRs (excluding chemical pregnancies) did not reach statistical significance	
Kahn 1993 (40)	*prospective cohort study to determine the efficacy and efficiency of an IVF program (Jan 1898 to Feb1991, followed till June 1992)	*n=485 couples (293 tubal; 59 endometriosis; 69 reduced sperm quality ; 17 unexplained infertility; 47 multiple factors); mean age: 31.9 years	* 3 completed IVF-ET cycles; 4 different stimulation protocols *up to 3 embryos transferred *additional embryos cryopreserved	*1086 started cycles; 235 canceled cycles (21.8%); 851 ETs; 244 clinical pregnancies; 35 abortions (14.3%);20 EPs (8.2%);after 3 cycles: CPR/started cycle 22.5%; CPR/ET 27.3%; 189 ongoing pregnancies/deliveries; cumulative THBR /started cycle 17.4%; cumulative THBR /ET 22.2% *patients with reduced sperm quality had DR significantly lower (p<0.01) compared to tubal group *18/485 awaiting further treatment (3.7%) *cryopreservation gave a 5.2% (25/485) increase in baby take-home rate and a 13.2% (25/189) increase in number of ongoing pregnancies/deliveries	*131/189 singletons (69.3%); 47/189 twins (24.9%); 11/189 triplets (5.8%) *5 women experienced complications : 3 moderate to severe OHSS, 1 PID, 1 anesthetic complication
Claman 1993 (19)	*prospective non randomized controlled clinical trial to compare natural IVF with stimulated IVF-ET (same period of time, at one centre)	*both groups: normal ovulatory function; tubal factor infertility; age <38 years (natural IVF), <41years (stimulated IVF); ovaries accessible to transvaginal US-guided egg retrieval	*natural IVF-ET: hCG administered 34-36 hours before oocyte retrieval; *stimulated IVF-ET: 1 to 4 embryos transferred *in all, fertilization with Percoll-treated sperm	*natural IVF-ET: 75 started cycles; 35/75 canceled cycles (47%); 18 ETs; 2 clinical pregnancies; PR/started cycle 2.7% (2/75); PR/oocyte retrieval 5% (2/40); PR/ET 11% (2/18); 2/2 ongoing pregnancies (100%) (singletons) *stimulated IVF-ET: 450 started cycles; 112/450 canceled cycles (25%); 298 ETs; 65 clinical pregnancies; 17/65 miscarriages or EPs (26% early pregnancy loss); PR/started cycle 14.4% (65/450); PR/oocyte retrieval 19% (65/338); PR/ET 22% (65/298); 48/65 ongoing pregnancies (74%)	*stimulated IVF-ET: 13/65 (20%) multiple pregnancies (8 twins, 4 triplets, 1 quadruplet)
Peterson 1994 (57)	*prospective, non randomized, cohort study, at one centre (1990 to 1991) to compare 1 to 4 cycles of OS and IUI with one cycle of standard IVF and no treatment	*all: mean age:32.4-33.4 years, tubal disease, anovulation, unexplained infertility, endometriosis; n₁=47 (OS+IUI), infertility duration18-92 mo; n₂=19 (IVF), infertility duration 18-144 mo; n₃=21 (observational), infertility duration18-96 mo	*OS+IUI: hCG and IUI up to 4 cycles *IVF: 1 cycle of standard IVF-ET (using hCG for OS), with 4 to 6 embryos transferred	*OS+IUI: 99 cycles initiated and completed; PR 15% (15/99); 13% (2/15) SAs; THBR/cycle 13% (13/99); CLR 28% (13/47) *IVF: 19 cycles initiated; PR/cycle 26% (5/19); 20% SAs; THBR/cycle 21% (4/19) *observational: 210 cycles (over 1 year); chance of pregnancy/cycle 1.4%; CPR 14%	*OS and IUI: 23% (3/13) multiple pregnancies *IVF: 50% (2/4) multiple pregnancies *observational: no SAs or multiple pregnancies

Table 1 (continued)

Study	Study design	Patients' characteristics	Treatment	Pregnancy outcome	Complications and adverse effects
Crosignani 1994 (22)	*prospective randomized multicentre trial to compare 5 treatments	*n=346 patients (primary infertility due to male factor; women's age: 32 .4 - 32.7 years)	*15 centres participated in a balanced incomplete block arrangement (2 treatments at each centre)	*499 treatment cycles (156 IUI, 70 IPI, 24 GIFT, 154 IVF, 95 OS) *IUI: 20 pregnancies (PR/cycle 12.8%); IPI: 2 pregnancies (PR/cycle 2.9%); GIFT:7 pregnancies (PR/cycle 29.2%); IVF: 28 pregnancies (PR/cycle 18.2%); OS: 7 pregnancies (PR/cycle 7.4%) *results of OS alone and IPI were inferior to IUI, IVF and GIFT (p<0.01)	
Fahy 1995 (28)	*prospective study to assess the efficacy of natural cycles IVF in tubal and unexplained infertility	*n=39 couples (26 tubal infertility, mean age 32.5 years, infertility duration 4.5 years;13unexplained infertility, mean age 34 years, infertility duration 6 years); all males with normal semen	* with spontaneous ovarian cycles (no stimulation at all) *fertilization with Percoll-treated sperm	*overall: 79 started cycles; 14/79 (17%) canceled cycles; 65 attempted oocyte retrievals yielded 54 oocytes; 43 ETs: fertilization rate 80% (43/54); implantation rate 14% (6/43 embryos); 6 clinical pregnancies (PR/ started cycle 7.6%; PR/ET 14%) *a trend was observed for higher success in women with tubal disease.	
Bergh 1995 (11)	*prospective cohort study to evaluate the cumulative childbirth rate after IVF (Jan 1990 to Dec 1992)	*n=39couples(75%tubal, 11%endometriosis, 10.5% unexplained infertility, 2%anovulation, 1.5%sperm defects); mean age: 32.2 years; infertility duration:4years	* completed IVF course included 3 to 4 cycles (2 stimulation protocols) *2 -3 embryos replaced; additional embryos cryopreserved	*826 started cycles; 793 ETs (fresh); 228 ETs (frozen) *204/398 deliveries (51%) (includes transfer of frozen embryos from the same cycle; after 4 cycles, cumulative no. of deliveries/started cycle 51.3%; cumulative no. of women with deliveries/completed cycle 52.2% *cumulative childbirth rate/completed cycle: 51.7% (tubal disease); 57.1% (unexplained infertility); 48.8% (endometriosis); 67% (anovulation); 33% (sperm defects); no statistically significant differences	
Alsalili 1995 (2)	*retrospective analysis (Feb 1984 to Dec 1993, followed till Jan 1994) to evaluate IVF outcomes at one centre	*n=2391 couples (from all cycles, 45.8% tubal, 13.8 endometriosis, 11.4 idiopathic infertility, 6.3% male factor, 22.7% multifactorial infertility)	*up to 6 completed IVF cycles *up to 5 embryos transferred	*5209 started cycles; 824 canceled cycles (16%); 4385 oocyte retrievals; 3351 ETs (64%); 644 intrauterine pregnancies; 24 EPs; 7 heterotopic pregnancies; 68 SAs (10.6%); 3 induced abortions; PR/oocyte retrieval 15%; PR/ET 20%; PR/couple 28%; 496 deliveries and 68 ongoing pregnancies; no information on 9pregnancies; LBR/oocyte retrieval 13% ; LBR/ET 17%; LBR/couple 23% *significant differences in CPRs (after 6 cycles) among diagnostic categories (p=0.04): tubal 55%; idiopathic 65%; endometriosis 60%; multifactorial 63%; male infertility couples had the lowest CPR (p=0.001) as compared with other diagnostic categories; *success rates did not decline with successive IVF cycles *better PRs associated with younger age of the woman (p<0.003)	*multiple pregnancies 22% *pre-term birth rate: 20% (higher in multiples than in singletons; p<0.001) *Caesarean section rate: 35% (higher in multiples than in singletons; p<0.001); *15 stillbirths and/or neonatal deaths (12 in multiples); *18 (3.3%) congenital malformations (9 in multiples)
Ben-Chetrit 1995 (10)	*retrospective analysis(Aug '92-Dec '93): IVF-ET for severe male factor infertility	*n=672 couples (38 severe male factor, 74 moderate male factor, 47 mild male factor, 513 female factor)	*up to 3 embryos transferred *1stimulation protocol	*overall, 672 oocyte retrieval cycles; *increase in fertilization rate: 21.5% (severe male factor); 63.5% (female factor) *PR/retrieval: 3/38 (7.8%) severe male; 11/74 (14.8%) moderate male; 10/47 (21.2%) mild male; 115/513 (22.4%) female factor *PR/ET: 3/20 (15%) severe male; 11/51 (21.5%) moderate male; 10/39 (25.6%) mild male; 115/461 (24.9%) female factor	
Gurgan 1995 (31)	*retrospective case control study	*n_1=117 unexplained infertility(after failure of	*up to 4 embryos transferred	*unexplained infertility: 157 IVF-ET cycles; fertilization rate 57.8%; clinical pregnancy/cycle: 21%; clinical pregnancy/ET: 31.1%; abortion rate/clinical	

Table 1 (continued)

Study	Study design	Patients' characteristics	Treatment	Pregnancy outcome	Complications and adverse effects
	to determine results of IVF-ET in unexplained infertility as compared with those in tubal infertility	4-6 cycles of OS+IUI); infertility duration: 11.4 years; *n$_2$=194 tubal factor(after failure of conventional treatments); infertility duration: 10.2 years *mean age: 33.8 years	*3 stimulation protocols	pregnancy: 21.6%; after 3 cycles, CPR 44.9% *tubal factor: 250 IVF-ET cycles; fertilization rate 60.9%; clinical pregnancy/cycle 21.6%; clinical pregnancy/ET 25.1%; abortion rate/clinical pregnancy 20.8%; after 3 cycles, CPR 44%	
Tanbo 1995 (72)	*retrospective analysis (1986-1994):results of IVF-ET in minimal peritoneal endometriosis and unexplained infertility	*n$_1$=215 unexplained infertility (mean age 32 years); n$_3$=180 tubal (mean age 31.9 years); n$_2$=143 endometriosis (mean age: 31.7 years)	*up to 5 embryos transferred (reduced to two during the study period)	*unexplained infertility: 385 started cycles; 359 oocyte retrievals; implantation rate 13.8%; 84 pregnancies (PR/retrieval 23.4%; PR/transfer 29%) *endometriosis: 285 started cycles; 265 oocyte retrievals; implantation rate11.6%; 54 pregnancies (PR/retrieval 20.4%; PR/transfer 23.8%) *tubal infertility: 353 started cycles; 331 oocyte retrievals; implantation rate 9.8%; 74 pregnancies (PR/Retrieval 22.4%; PR/transfer 23.2%)	
Abu-Heija 1995 (1)	*retrospective study to compare IVF with OS and IUI in unexplained infertility	*n$_1$=77 (IVF); mean age: 34.7 years; infertility duration: 4.7 years; *n$_2$=54 (IUI); mean age: 32.4 years; infertility duration: 5.2 years *all males:normal semen	*one stimulation protocol in all patients	*IVF group: 125 started cycles; 12 canceled cycles (9.6%); PR/started cycle: 17.6% *IUI group: 131 started cycles; 9 canceled cycles (6.9%); PR/started cycles: 19%	

RCT- randomized controlled trial
ET - embryo transfer
PR - pregnancy rate; CPR - cumulative pregnancy rate
DR - delivery rate; CDR - cumulative delivery rate
LBR - live-birth rate; CLR - cumulative live-birth rate
EP - ectopic pregnancy
SA - spontaneous abortion
GIFT - gamete intra-Fallopian transfer
IUI - intrauterine insemination
OS - ovarian stimulation
IPI - intra-peritoneal insemination
PID - pelvic inflammatory disease
OHSS - ovarian hyperstimulation syndrome
THBR - take-home baby rate

Table 2 : Reviews on IVF-ET and related techniques

Study	Subject	Main conclusions
Lancaster 1992 (44) 27 references (published: 1978-1990)	Reviews data provided by national registries or published by individual centres	• there is a lack of agreement on definitions and on the methods of reporting the results • there is a lack of consensus on what information is desirable and how it should be collected • perinatal mortality after ARTs was about 3 times higher than the national rates for all births • preterm birth occur frequently after ARTs because of the high incidence of multiple pregnancy(20-25% twins, 2-5% triplets, up to 2.8% quadruplets), but it is also higher in singleton births than in natural conceptions • ectopic pregnancy occurs more frequently after ARTs (from 2.1% to 8.8%; more likely if the treatment is used for tubal factors) • the reported incidence of major congenital malformations is usually in the range of 2-3%, similar to that in the general population
Lenton 1992 (48) 18 references (published: 1980-1991)	Presents history of IVF in natural cycles and describes the experience of one centre	• patients with pure tubal occlusion are ideal candidates for IVF in natural cycles • initial success in patients with tubal lesions was not translated to patients with other infertility indications; the greater the proportion of infertility factors present, the lower will be the pregnancy rates after IVF in natural cycle
Paulson 1993 (54) 43 references (published: 1972-1992)	Reviews and describes various ARTs (presenting the experience at one centre)	• patients without Fallopian tubes or with damaged Fallopian tubes who are poor candidates for tubal surgery, are appropriate candidates for IVF as primary therapy, since IVF replaces and functions as the Fallopian tube; for infertile patients with patent Fallopian tubes, alternative treatment options must be considered, since they have substantial treatment-independent pregnancy rates • IVF pregnancy rates are highly variable, due in part to selection bias, small sample sizes, and lack of standardization of criteria for reporting the outcomes; on a per-cycle basis, IVF appear to be not very efficient; therefore, IVF may be attempted repeatedly to achieve a higher chance of pregnancy
Trounson 1993 (74) 43 references (published: 1987-1992)	Presents the current status of IVF and related techniques (with the description of the clinical experience and research at one centre).	• IVF and related techniques (ARTs) have been developed to treat infertile couples when conventional treatments or no treatment have failed • the incidence of congenital malformation after ARTs is not increased (1.5%) as compared with natural conception (around 2%) • problems related to multiple pregnancy and the use of stimulated cycles are being reduced and new techniques for severe male infertility are being introduced
Amso 1993 (4) 52 references (published: 1970-1992)	Presents a critical appraisal of the effectiveness of assisted reproductive techniques	• for bilaterally occluded and irreparable Fallopian tubes, the choice of treatment is clearly IVF-ET • there is conflicting evidence on the efficacy of simpler methods such as ovarian stimulation with or without artificial insemination and the available data suggest that IVF or GIFT are more effective for the treatment of unexplained infertility • there is no conclusive evidence that pregnancy rates with any of the ARTs are superior to any others
Hull 1994 (35) 37 references (published: 1968-1993)	Assesses the relative effectiveness of both conventional and assisted conception methods .	• the only treatments that can achieve a normal chance of pregnancy are ovarian stimulation methods in cases of oligomenorrhea / amenorrhea, and the ARTs for other female causes and unexplained infertility; • tubal/pelvic infective damage and endometriosis require new severity classifications which are sensitive to functional potential before and after surgery and IVF would often be indicated as primary choice • duration of unexplained infertility determines the need and therefore benefit of any treatments used, of which the assisted conception methods are by far the most effective • in cases of well-defined sperm dysfunction there is little or no therapeutic benefit to the chance of natural conception, nor by intrauterine insemination; there is moderate success by IVF, but no proven benefit over standard IVF by any micromanipulative technique, exempt probably ICSI.
Schenker 1994 (61) 158 references (published: 1960-1992)	Reviews the relevant data on ARTs and their potential complications	• the main problem of ARTs is not the cost but the complications, which may endanger the patients who otherwise are healthy

Table 2 (continued)

Study	Subject	Main conclusions
Van Steirteghem 1994 (76) 55 references (published: 1988-1994)	Reviews the current status of standard IVF and the most used assisted fertilization techniques for the treatment of male factor infertility	• a number of couples with severe male factor infertility cannot be helped by standard IVF even when sperm preparation and sperm selection procedures are used • from the different procedures of assisted fertilization , it is clearly established that ICSI yields the best results in terms of fertilization, embryo development, and pregnancy rates • the safety and efficiency of ICSI need to be substantiated further
ECRI's Exec. Briefings 1994 (27) 44 references (published: 1978-1994)	Presents the ARTs now in use, laboratory standards for ARTs, costs, outcomes, and coverage perspectives.	• IVF-ET is indicated especially for women with severely compromised (occluded) or absent Fallopian tubes. It has also been offered successfully to treat male factor infertility and somewhat less successfully to treat unexplained infertility after other treatments have failed. • most practitioners believe that IVF and GIFT are the standard of care in an appropriate clinical setting • IVF protocols are called into question because of the higher incidence of multiple-gestation pregnancies and deliveries and the extremely high costs that go with these conceptions.
Feichtinger 1994 (29) 49 references (published: 1985-1993)	Discusses the current efficacy of IVF-ET, factors influencing the success rates, and complications associated with this technology	• IVF-ET is not an empirical treatment anymore; it is a relatively safe procedure • Success rates depend on patient's specific data • IVF-ET is the treatment of choice for infertility caused by severe tubal damage; also, male factor infertility and unexplained infertility are increasingly accepted indications for IVF-ET • The costs and complexity of treatment and stress and social inconvenience of therapy have to be reduced
Paulson 1995 (55) 25 references (published: 1978-1994)	Focuses on the current practice of unstimulated IVF, its indications, relative advantages and disadvantages as compared with stimulated IVF	• available data suggest that per-cycle pregnancy rate favors stimulated IVF cycles • all potential candidates for stimulated IVF may be considered for unstimulated IVF as the first choice; couples with severe male factor infertility and those in which the female partner is over 40 may benefit from additional follicular stimulation • there are not sufficient data to conclude that patients with pure tubal factor have the best pregnancy rates with unstimulated IVF • in the current practice of unstimulated IVF, minimal stimulation regimens are administered • all unstimulated IVF pregnancies reported to date have been singletons
Hull 1995 (37) 43 references (published: 1986-1995)	Assesses the role of tubal surgery and IVF-ET in infertility therapy for patients with tubal/pelvic infective damage	• there are no RCTs for strictly valid comparison of tubal surgery with IVF-ET in women with tubal/pelvic damage caused by infection • women with tubal infertility benefit little from tubal surgery • majority of women with tubal/pelvic infective damage have a poor prognosis for natural conception, and IVF-ET would be a better primary choice
Hull 1995 (34) 49 references (published: 1968-1994)	Reviews complications of pregnancy after infertility treatment	• the biggest fetal loss after infertility treatment is due to miscarriage, often related to past obstetric performance and cause of infertility • the advancing age of the female partner has a great impact on the success of the treatment • multiple pregnancy increases the risks for both mother and babies and the risks increase exponentially with every additional fetus; most twin pregnancies still occur spontaneously, but two-thirds of triplets and higher-order multiple pregnancies are due to gonadotropin therapy • Caesarean section rate is much higher after infertility treatments
Shushan 1995 (63) 92 references (published: 1977-1995)	Describes the changes that have occurred in the practice of ARTs and discusses the efficacy of ARTs as treatment of various conditions that cause infertility	• although IVF and related techniques are currently used for a wide range of infertility diagnoses and have become acceptable tools in infertility practice, there is an ongoing debate regarding the effectiveness of IVF vs. conventional infertility treatments for the various conditions that cause infertility • the effectiveness of IVF in terms of pregnancy rates has been demonstrated only in patients with severe bilateral tubal disease and male subfertility (using assisted fertilization); for other causes of infertility, the differences in pregnancy rates do not reach statistical significance and the efficacy of IVF has not been demonstrated clearly to date • in women with unexplained infertility, menotropin treatment appears to be as successful, less expensive and carries a smaller risk than IVF and related techniques • the exact role of IVF and related techniques in the management of PCOS, immunological infertility, and endometriosis still is to be determined
Buyalos 1996 (16) 63 references (published: 1962-1994)	Assesses the efficacy of IVF-ET in infertile women with polycystic ovary syndrome (PCOS)	• IVF-ET is an effective therapy for PCOS patients who are refractory to conventional ovarian stimulation techniques or who have coexisting infertility factors. • several reports (of relatively small patients series, with poor statistical power) suggest that pregnancy rates for PCOS patients undergoing IVF-ET are comparable with those for women with tubal factor infertility

Table 2 (continued)

Study	Subject	Main conclusions
Dawood 1996 (23) 26 references (published: 1987-1995)	Reviews the efficacy and potential risks and complications of IVF, GIFT and superovulation with intrauterine insemination	• IVF is effective in infertile women with bilaterally damaged, occluded, or absent Fallopian tubes • there are no adequate prospective, randomized controlled trials, or comparative studies of sufficient power on the efficacy of IVF, GIFT and ovarian stimulation with intrauterine insemination in well-defined infertile couples • the efficacy or relative superiority of IVF, GIFT, or superovulation with intrauterine insemination in non-tubal subfertility remains to be demonstrated ; therefore, less invasive and less expensive methods should be used before IVF or GIFT • further studies on the outcome of babies after IVF and related techniques are required
Palermo 1996 (52) 80 references (published: 1962-1995)	Reviews the history of ICSI and presents the current experience in humans	• the consistently high success rate resulting from the application of ICSI to treat couples with male factor infertility is comparable with the results obtained using standard IVF for nonmale factor infertility • it has been demonstrated convincingly that ICSI can be used successfully to treat severe male factor infertility

RCT - randomized controlled trial
GIFT - gamete intra-Fallopian transfer
ART - assisted reproductive technology
ICSI - intra-cytoplasmic sperm injection
IVF-ET - *in vitro* **fertilization and embryo transfer**

Table 3 : Studies on ICSI outcomes

Study	Patients' Characteristics	Findings	Reported Risks and Complications
Van Steirteghem et al, 1994 (77) Retrospective study (28 months)	• couples selected suffered from long-standing infertility and failed at least one IVF attempt or could not be selected for IVF because of severe impairment of semen parameters	• n=750 consecutive treatment cycles by SUZI or ICSI performed at one centre; ET rate: 74% (556/750) • SUZI: 3283 injected oocytes; 3008 intact oocytes (92%); 17% normally fertilized oocytes; 156 ETs (up to 3 SUZI embryos); 23 pregnancies (PR/ET 15%); 15 deliveries of 21 children • ICSI: 3944 injected oocytes; 3401 intact oocytes (86%); 55% normally fertilized oocytes; 350 ETs (up to 3 ICSI embryos); 130 pregnancies (PR/ET 37%); 98 ongoing pregnancies; 20 children born after ICSI • SUZI and ICSI: 50 ETs of a mixture of SUZI and ICSI embryos; 10 pregnancies (PR/ET 20%); 8 deliveries of 10 children	• ICSI: 14 preclinical abortions; 18 clinical abortions • The pediatric follow-up of the 51 children born after SUZI, ICSI, or mixed SUZI and ICSI, revealed 1 major congenital malformation.
Van Steirteghem 1994 (76) Review (including the description of the experience at one centre).	• ICSI as routine procedure of assisted fertilization (as of 1992) at one centre in couples who could not be treated by IVF	• n=801 cycles • 7907 injected oocytes; 6994 intact oocytes (88.5%); 3465 transferable embryos (76.2%); 3139 embryos transferred or frozen (69.0%); 728 ETs (up to 4 ICSI embryos) (90.8%); 277 pregnancies, PR/cycle 35%; 211 deliveries DR/cycle 26%	• Data on 130 children born after ICSI revealed 4 major malformations (3.1%).
Palermo et al 1995 (51) Controlled clinical study (6 months)	• n=227 couples (male factor or idiopathic infertility who repeatedly failed previous IVF attempts or who were not accepted for IVF because of severe impairment of semen parameters) • female partners' mean age: 35 years	• ICSI: 227 oocyte retrieval cycles; 1923 injected oocytes; 1787 survived oocytes (92.9%); 1142 normally fertilized (59.4%); 653 quality embryos (fresh or frozen) transferred in 217 ETs; 94 pregnancies with fetal heartbeats; 84 ongoing pregnancies PR/retrieval 37% (84/227) ; PR/ET 38.7% (84/217)) • IVF (no sperm abnormalities): 179 retrieval cycles; 1719 inseminated oocytes; 1086 fertilized oocytes (63.2%); 530 embryos transferred in 173 Ets; 59 ongoing pregnancies (PR/retrieval 32.9%)	• of 124 clinical pregnancies: 19 biochemical pregnancies;10 pregnancies with blighted ovum; 1 EP • of 94 pregnancies with fetal heartbeats: 10 miscarriages • of 84 births: 47 singles; 30 twins; 6 triplets; 1 quadruplet
Bourne et al 1995 (13) Cohort observational study (12 months)	• n=263 pregnancies with severe male factor infertility	• 296 consecutive oocyte retrievals (3636 oocytes) • ICSI: 2858 injected oocytes (79%); 2561 intact oocytes (90%); 1774 normally fertilized embryos (69%); 1613 embryos transferred (582 fresh embryos in 269 ETs; 511 thawed embryos in 268 ETs) ; overall 76 clinical pregnancies, PR/retrieval 35%; overall 57 ongoing or delivered pregnancies (19% per retrieval) • IVF :175 oocytes inseminated in 20 patients; 6/20 (33%) achieved normal fertility with IVF.; 20/20 achieved normal fertility with ICSI	• of 76 clinical pregnancies: 2 EPs; 5 blighted ovum pregnancies; 12 SAs • of 69 intrauterine pregnancies: 8 twins
Palermo et al 1996 (53)	• n=751 couples (males presumed to be the cause of repeated failed IVF attempts or	• 987 ICSI cycles; 3021 embryos transferred in 943 ETs; 437 clinical pregnancies (with fetal heartbeats) (44.3% clinical	• 44 miscarriages; 4 Eps, 7 pregnancies terminated (chromosomal abnormalities);

Table 3 (continued)

Study	Patients' Characteristics	Findings	Reported Risks and Complications
Retrospective study (24 months)	whose semen parameters were unacceptable for IVF) • female partners' mean age: 35.1 years	PR/oocyte retrieval); 382 deliveries (38.7%DR/ICSI cycle) resulted in 578 neonates	• multiple pregnancy: 42.4% (128 twins, 34 triplets) • 15 congenital malformations (2.6%)

ICSI - intra-cytoplasmic sperm injection
SUZI - sub-zonal insemination
IVF - *in vitro* fertilization
PR - pregnancy rate
DR - Delivery rate
ET - embryo transfer
EP - ectopic pregnancy
SA - spontaneous abortion

Table 3 (continued)

Table 4 : Coverage of IVF-ET in Canada

Province	Funded Diagnosis of Infertility	Some IVF Funding	Private Clinic
British Columbia	Yes		Yes
Alberta	Yes		Yes
Saskatchewan	Yes		
Manitoba	Yes		Yes
Ontario	Yes	Yes	Yes
Québec	Yes		Yes
New Brunswick	Yes		
Nova Scotia	Yes		Yes
Prince Edward Island	Yes	Yes	
Newfoundland	Yes		
Northwest Territories	Yes		
Yukon	Yes		

Source: Provincial and Territorial medical insurance plans

Table 3 (continued)

References

1. Abu-Heija A, Yates R. Comparison of intrauterine insemination and in vitro fertilization for the treatment of unexplained infertility. *Annals of Saudi Medicine*, 1995;15(5):462-3.

2. Alsalili M, Yuzpe A, Tummon I, Parker J, Martin J, Daniel S, et al. Cumulative pregnancy rates and pregnancy outcome after in-vitro fertilization: >5000 cycles at one centre. *Human Reproduction*, 1995;10(2):470-4.

3. Alsalili M, Yuzpe AA, Tummon IS, Parker J, Martin JSB, Nisker JA, et al. Confounding variables affecting in vitro fertilization success: a decade of experience. *Journal of Assisted Reproduction and Genetics*, 1995;12(2):88-92.

4. Amso NN, Shaw RW. A critical appraisal of assisted reproduction techniques. *Human Reproduction Update*, 1993;8(1):168-74.

5. Anonymous. French in vitro fertilization registry. 1994 report [Abstract]. *Contraception, Fertilite, Sexualite*, 1995;23(7-8)490-3.

6. Anonymous. FIVNAT (French *In Vitro* National) Multiple pregnancies. [Abstract]. *Contraception, Fertilite, Sexualite*, 1995;23(7-8):494-7.

7. Anonymous. FIVNAT (French In Vitro National) Pregnancies and births resulting from in vitro fertilization: French national registry, analysis of data 1986 to 1990. [Abstract]. *Fertility and Sterility*, 1995;64(4):746-56.

8. Anonymous. FIVNAT (French *In Vitro* National) The results of classical in vitro fertilization in male infertility. [Abstract]. *Contraception, Fertilite, Sexualite*, 1995;23(7-8):498-501.

9. Benadiva CA, Kligman I, Davis O, Rosenwaks Z. In vitro fertilization versus tubal surgery: is pelvic reconstructive surgery obsolete? *Fertility and Sterility*,1995;64(6):1051-61.

10. Ben-Chetrit A, Senoz S, Greenblatt EM, Casper RF. In vitro fertilization outcome in the presence of severe male factor infertility. *Fertility and Sterility*, 1995;63(5):1032-7.

11. Bergh C, Josefsson B, Nilsson L, Hamberger L. The success rate in a Swedish in-vitro fertilization unit: a cohort study. *Acta Obstetricia et Gynecologica Scandinavica*, 1995;74:446-50.

12. Bonduelle M, Legein J, Derde M-P, Buysse A, Schietecatte J, Wisanto A, et al. Comparative follow-up study of 130 children born after intracytoplasmic sperm injection and 130 children born after in-vitro fertilization. *Human Reproduction*, 1995;10(12):3327-31.

Table 3 (continued)

13. Bourne H, Richings N, Harari O, Watkins W, Speirs AL, Johnston WIH, et al. The use of intracytoplasmic sperm injection for the treatment of severe and extreme male infertility. *Reproduction. Fertility, and Development*, 1995;7:237-45

14. Brandes JM, Scher A, Itzkovits J, Thaler I, Sarid M, Gershoni-Baruch R. Growth and development of children conceived by in vitro fertilization [Abstract]. *Pediatrics*, 1992;90(3):424-9.

15. Bristow RE, Karlan BY. Ovulation induction, infertility, and ovarian cancer risk. *Fertility and Sterility*, 1996;66(4):499-507.

16. Buyalos RP, Lee CT. Polycystic ovary syndrome: pathophysiology and outcome with in vitro fertilization. *Fertility and Sterility*, 1996;65(1):1-10.

17. Callahan TL, Hall JE, Ettner SL, Christiansen CL, Greene MF, Crowley WF Jr. The economic impact of multiple-gestation pregnancies and the contribution of assisted-techniques to their incidence [Abstract]. *New England Journal of Medicine*, 1994;331(4):244-9.

18. Check JH, Lurie D, Callan C, Baker A, Benfer K. Comparison of the cumulative probability of pregnancy after in vitro fertilization-embryo transfer by infertility factor and age [Abstract]. *Fertility and Sterility*, 1994;61(2):257-61.

19. Claman P, Domingo M, Garner P, Leader A, Spence JEH. Natural cycle in vitro fertilization-embryo transfer at the University of Ottawa: an inefficient therapy for tubal infertility. *Fertility and Sterility*, 1993;60(2):298-302.

20. Collins JA, Burrows EA, Willan AR. The prognosis for live-birth among untreated infertile couples. *Fertility and Sterility*, 1995;64(1):22-8.

21. Congress, Office of Technology Assessment. *Health care technology and its assessment in eight countries*. Washington, DC: U.S. Government Printing Office, February 1995.

22. Crosignani PG, Walters DE. Clinical pregnancy and male subfertility; the ESHRE multicentre trial on the treatment of male subfertility. *Human Reproduction*, 1994;9(6):1112-8.

23. Dawood MY. In vitro fertilization, gamete intrafollopian transfer, and superovulation with intrauterine insemination: efficacy and potential health hazards on babies delivered. *American Journal of Obstetrics and Gynecology*, 1996;174(1):1208-17.

24. Daya S. Comparison of in vitro fertilization with conventional treatment for tubal infertility. *References en gynecologie obstetrique: N° Special Congres Vichy - IFFS, Paris 1995*;pp. 206-14.

Table 3 (continued)

25. Daya S, Gunby J, Hughes EG, et al. Natural cycles for in-vitro fertilization: cost-effectiveness analysis and factors influencing outcome. *Human Reproduction,* 1995;10(7):1719-24.

26. Diedrich K, Bauer O. Indications and outcomes of assisted reproduction. *Baillière's Clinical Obstetrics and Gynaecology*, 1992;6(2):373-88.

27. ECRI. *Female infertility technologies part II: assisted reproductive technology*. Executive Briefings, Plymouth Meeting, 1994.

28. Fahy UM, Cahill DJ, Wardle PG, Hull MGR. In-vitro fertilization in completely natural cycles. *Human Reproduction* 1995;10(3):572-5.

29. Feichtinger W. Results and complications of IVF therapy. *Current Opinion in Obstetrics and Gynecology*, 1994;6:190-7.

30. Gissler M, Silverio MM, Hemminki E. In-vitro fertilization pregnancies and perinatal health in Finland 1991-1993. *Human Reproduction*, 1995;10(7):1856-61.

31. Gürgan T, Urman B, Yarali H, Kisnisci HA. The results of in vitro fertilization-embryo transfer in couples with unexplained infertility failing to conceive with superovulation and intrauterine insemination. *Fertility and Sterility*, 1995;64(1):93-7.

32. Harrison RF, Hennelly B, Woods T, Lowry K, Kondaveeti U, Barry-Kinsella C, et al. Course and outcome of IVF pregnancies and spontaneous conceptions within an IVF setting. *European Journal of Obstetrics and Gynecology and Reproductive Biology*, 1995;(59):175-82.

33. Hemminki E, Gissler M, Silverio MM. *Choice of outcomes and assessment – in vitro fertilization as an example* [Abstract]. International Society for Technology Assessment in Health Care Eleventh Annual Meeting, Stockholm, Sweden, June 4-7, 1995.

34. Hull M. Complications of pregnancy after infertility treatment: awareness and prevention. *British Journal of Obstetrics and Gynaecology*, 1995;102:520-4.

35. Hull MGR. Effectiveness of infertility treatments: choice and comparative analysis. *International Journal of Gynecology & Obstetrics*, 1994;47:99-108.

36. Hull MG, Armatage RJ, McDermott A. Use of follicle-stimulating hormone alone (urofollitropin) to stimulate the ovaries for assisted conception after pituitary desensitization [Abstract]. *Fertility and Sterility*, 1994;62(5):997-1003.

37. Hull MGR, Fleming CF. Tubal surgery versus assisted reproduction: assessing their role in infertility therapy. *Current Opinion in Obstetrics and Gynecology*, 1995;7:160-7.

Table 3 (continued)

38. Infertility Awareness Association of Canada. A report on in vitro fertilization services in Canada. *Infertility Awareness,* September 1996.

39. Jarrell JF, Labell R, Goeree R, Milner R, Collins J. In vitro fertilization and embryo transfer: A randomized controlled trial. *The Online Journal of Current Clinical Trials*, Document No. 73, 1993 July.

40. Kahn JA, von During V, Sunde A, Sordal T, Molne K. The efficacy and efficiency of an in-vitro fertilization programme including embryo cryopreservation: a cohort study. *Human Reproduction*, 1993;8(2):247-52.

41. Keirse MJNC, Helmerhorst FM. The impact of assisted reproduction on perinatal health care. *Soz Praventivmed,* 1995;40:343-51.

42. Kenny DT. In vitro fertilisation and gamete intrafallopian transfer: an integrative analysis of research, 1987-1992. *British Journal of Obstetrics and Gynaecology*, 1995;102:317-25.

43. Kovacs GT. Assisted reproduction: a reassuring picture. *Medical Journal of Australia,* 1996;164:628-630.

44. Lancaster PAL. International comparisons of assisted reproduction. *Assisted Reproduction Reviews (REP)*, 1992;2(4):212-21.

45. Lancaster P, Huang J, Lin M. Australia's mothers and babies 1993. *Perinatal Statistics Series Number 3*, Sydney: Australian Institute of Health and Welfare National Perinatal Statistics Unit, 1996.

46. Lancaster P, Shafir E, Huang J. Assisted conception Australia and New Zealand 1992 and 1993. *Assisted Conception Series Number 1*. Sydney: Australian Institute of Health and Welfare National Perinatal Statistics Unit, 1995.

47. Leader A. The Canadian IVF registry experience – how are we doing?. *Journal of the Society of Obstetricians and gynaecologists of Canada*, 1995;17:272-8.

48. Lenton EA, Cooke ID, Hooper M, King H, Kumar A, Monks N, et al. In vitro fertilization in the natural cycle. *Baillière's Clinical Obstetrics and Gynaecology*, 1992;6(2):229-45.

49. Mills MS, Eddowes HA, Cahill DJ, Fahy UM, Abuzeid MIM, McDermott A, et al. A prospective controlled study of in-vitro ferilization, gamete intra-Fallopian transfer and intrauterine insemination combined with superovulation. *Human Reproduction* 1992;7(4):490-4.

50. National Health and Medical Research Council. *Long-term effects on women from assisted conception*. Canberra: Australian Government Publishing Service, 1995.

Table 3 (continued)

51. Palermo GD, Cohen J, Alikani M, Adler A, Rosenwaks Z. Intracytoplasmic sperm injection: a novel treatment for all forms of male factor infertility. *Fertility and Sterility*, 1995;63(6):1231-40.

52. Palermo GD, Cohen J, Rosenwaks Z. Intracytoplasmic sperm injection: a powerful tool to overcome fertilization failure. *Fertility and Sterility*, 1996;65(5):899-908.

53. Palermo GD, Colombero LT, Schattman GL, Davis OK, Rosenwaks Z. Evolution of pregnancies and initial follow-up of newborns delivered after intracytoplasmic sperm injection. *Journal of the American Medical Association,* 1996;276(23):1893-97.

54. Paulson RJ. In vitro fertilization and other assisted reproductive techniques. *Journal of Reproductive Medicine*, 1993;38(4):261-8.

55. Paulson RJ. IVF in unstimulated cycles. *Seminars in Reproductive Endocrinology*, 1995;13(1):16-21.

56. Petersen K, Hornnes PJ, Ellingsen S, Jensen F, Brocks V, Starup J, et al. Perinatal outcome after in vitro fertilisation. *Acta Obstetricia et Gynecologica Scandinavica*, 1995;74:129-31.

57. Peterson CM, Hatasaka HH, Parker Jones K, Poulson AM Jr, Carrell DT, Urry RL. Ovulation induction with gonadotropins and intrauterine insemination compared with in vitro fertilization and no therapy: a prospective, nonrandomized, cohort study and meta-analysis. *Fertility and Sterility*, 1994;62(3):535-44.

58. Ron-El R. Complications of ovulation induction. *Baillière's Clinical Obstetrics and Gynaecology*, 1993;7(2):435-53.

59. Royal Commission on New Reproductive Technologies. *Proceed with care: final report of the Royal Commission on new reproductive technologies*. Ottawa: The Commission, 1993.

60. Saunders K, Spensley J, Munro J, Halasz G. Growth and physical outcome of children conceived by in vitro fertilization. *Pediatrics,* 1996;97(5):688-92.

61. Schenker JG, Ezra Y. Complications of assissted reproductive techniques. *Fertility and Sterility*, 1994;61(3):411-22.

62. School of Public Health, University of Leeds. The management of subfertility. *Effective Health Care*, 1992 Aug;No. 3.

63. Shushan A, Eisenberg VH, Schenker JG. Subfertility in the era of assisted reproduction: changes and consequences. *Fertility and Sterility*, 1995;64(3):459-69.

64. Society for Assisted Reproductive Technology, American Society for Reproductive Medicine. Assisted reproductive technology in the United States and Canada: 1993

Table 3 (continued)

results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. *Fertility and Sterility*, 1995;64(1):13-21.

65. Soliman S, Daya S, Collins J, Jarrell J. A randomized trial of in vitro fertilization versus conventional treatment for infertility. *Fertility and Sterility*, 1993;59(6):1239-44.

66. Stephens T and Associates. *Highlights from survey of Canadian fertility programs*. Royal Commission on New Reproductive Technologies, Ottawa. 1993 Apr.

67. Tallo CP, Vohr B, Oh W, Rubin LP, Seifer DB, Haning RV Jr. Maternal and neonatal morbidity associated with in vitro fertilization. *Journal of Pediatrics*, 1995;127(5):794-800.

68. Tan SL, Prognosis for successful outcome with in vitro fertilization treatment. *Journal of the Society of Obstetricians and Gynaecologists of Canada*, 1995;17:421-9.

69. Tan SL, Doyle P, Campbell S, Beral V, Rizk B, Brinsden P, et al. Obstetric outcome of in vitro fertilization pregnancies compared with normally conceived pregnancies. *American Journal of Obstetrics and Gynecology*, 1992;167(3):778-84.

70. Tan SL, Doyle P, Maconochie N, Edwards RG, Balen A, Bekir J, Brinsden P, et al. Pregnancy and birth rates of live infants after in vitro fertilization in women with and without previous in vitro fertilization pregnancies: a study of eight thousand cycles at one center. *American Journal of Obstetrics and Gynecology,* 1994;170(1 Pt 1):34-40.

71. Tan SL, Royston P, Campbell S, Jacobs HS, Betts J, Mason B, et al. Cumulative conception and livebirth rates after in-vitro fertilisation. *Lancet*, 1992;339:1390-4.

72. Tanbo T, Omland A, Dale PO, Abyholm T. In vitro fertilization/embryo transfer in unexplained infertility and minimal peritoneal endometriosis. *Acta Obstetricia et Gynecologica Scandinavica*, 1995;74:539-43.

73. Tournaye H, Liu J, Nagy Z, Joris H, Wisanto A, Bonduelle M, et al. Intracytoplasmic sperm injection (ICSI): the Brussels experience. *Reproduction, Fertility, & Development*, 1995;7(2):269-78.

74. Trounson AO, Wood C. IVF and related technology: the present and the future. *Medical Journal of Australia*, 1993;158:853-7.

75. Tummon IS, Skinner KA, Sharma A, Tekpetey FR, Bany BM, Martin JSB. Success, safety, single sperm: Intracytoplasmic sperm injection today. *Journal of the Society of Obstetricians and Gynaecologists of Canada,* 1997;19:19-26.

76. Van Steirteghem A. IVF and micromanipulation techniques for male-factor infertility. *Current Opinion in Obstetrics and Gynecology*, 1994;6:173-7.

Table 3 (continued)

77. Van Steirteghem A, Nagy Z, Liu J, Joris H, Verheyen G, Smitz J, et al. Intracytoplasmic sperm injection. *Baillière's Clinical Obstetrics and Gynaecology*, 1994;8(1):85-93.

78. Venn A, Watson L, Lumley J, Giles G, King C, Healy D. Breast and ovarian cancer incidence after infertility and in vitro fertilisation. *Lancet,* 1995;346:995-1000.

79. Verlaenen H, Cammu H, Derde MP, Amy JJ. Singleton pregnancy after in vitro fertilization: expectations and outcome. *Obstetrics & Gynecology*, 1995;86(6):906-10.

80. Walters DE. Clinical assisted reproduction: A plea for a more fastidious and objective use of statistics. *Journal of Assisted Reproduction and Genetics,* 1994;11(2):63-73.

81. Wang JX, Clark AM, Kirby CA, Philipson G, Petrucco O, Anderson G, et al. The obstetric outcome of singleton pregnancies following in-vitro fertilization/gamete intra-Fallopian transfer. *Human Reproduction*, 1994;9(1):141-6.

82. Wennerholm UB, Bergh C, Hamberger L, Nilsson L, Reismer E, Wennergren M et al. Obstetric and perinatal outcome of pregnancies following intracytoplasmic sperm injection. *Human Reproduction,* 1996;11(5):1113-19.

83. Wilcox LS, Peterson HB, Haseltine FP, Martin MC. Defining and interpreting pregnancy success rates for in vitro fertilization. *Fertility and Sterility*, 1993;60(1):18-25.

84. Wisanto A, Magnus M, Bonduelle M, Liu J, Camus M, Tournaye H, et al. Obstetric outcome of 424 pregnancies after intracytoplasmic sperm injection. *Human Reproduction*, 1995;10(10):2713-18.