

Assisted Reproductive Technologies

A Report Prepared for the Laboratory Centre for Disease Control (Health Canada)

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The following writing sample is an **excerpt** from a larger document. The general introduction, references and additional chapters have been excluded.

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1.0 An Introduction to ART

Cryopreservation of human sperm achieved credibility in 1953 when Bunge and Sherman showed that frozen sperm could be thawed and used to produce a normal human child (Benshusan *et al*, 1998). The panoply of sciences now called New Reproductive Technologies or Assisted Reproductive Technologies (ARTs) was thus born, and has since grown to include techniques in intrauterine insemination (IUI) and *in vitro* fertilization (IVF). These technologies have arisen to service a basic human need, that of reproduction.

IUI is the simplest modern form of ART, involving the manual introduction of sperm to a woman's uterus. Its use usually implies a reasonably healthy female reproductive system, and is thus often obviated by a male-factor etiology. In the present era, IVF –the “test tube baby” procedure-- is the flagship ART technologically, legally, medically and ethically. The recent inclusion of intracytoplasmic sperm injection (“ICSI”, discussed in greater detail below) as an enhancement to IVF has further revolutionized the field.

Since the 1978 birth of Louise Brown, the first "test-tube baby", over 100,000 children have been born worldwide via IVF (FIVNAT, 1995). Once a scientific miracle, the procedure is now commonplace. In the USA, IVF accounts for about 2% of all fertility services used by women (Wilcox & Mosher, 1993) and it is possible that the demand in that country for fertility services of all types, including IVF, may increase by as much as 25% each year (Mosher & Pratt, 1991). In Australia, the proportion of such assisted births is only 1%, but the number of procedures performed is increasing by hundreds every year (Kovacs, 1996). While estimates in Canada are difficult to compile, across the globe, IVF is an intervention gaining popularity and technological refinement.

IVF is an infertility treatment in which gametes are combined *ex utero* and returned *in utero* as viable embryos. Though the technology has been in use in humans for over 20 years, it is still growing in refinement. There is a great deal of publication activity with respect to consolidating and understanding elements of IVF therapy.

According to at least one source (Tallo *et al*, 1995), IVF Mothers have more perinatal complications than the so-called “spontaneously conceiving” population. Tallo also points out that mortality and morbidity rates are higher in IVF infants. Determining characteristics that might be predictive of either the aforementioned complications or a desirable obstetric outcome is a goal worthy of epidemiologic study. Beyond further demographic factors and criteria specific to the clinical application of the IVF procedure, several elements have been investigated as possible risk factors for either adverse or desirable IVF outcomes, and summarized by such researchers as Heitlinger (1989).

This document comprises a brief overview of the major issues surrounding IVF and its affiliated technologies, and proposes several questions to be included in Health Canada's survey of maternal perceptions.

2.0 ICSI

One of the most technologically advanced of the IVF technologies, ICSI (pronounced *ik-see*) involves the direct injection of sperm (and hence genetic material) into an egg. Since ICSI in essence bypasses natural selection by allowing sperm of inferior motility to fertilize an egg that would have otherwise been unreachable, there is concern that the resulting embryos may exhibit genetic abnormalities. The technique cannot therefore be ignored as a risk factor for various adverse outcomes, and as a source of consternation for ethicists.

Govaerts *et al* (1996) summarize ICSI concerns into three categories:

- (1) severely infertile men are known to suffer from an increased incidence of genetic abnormalities which are further conferred upon their sperm;
- (2) conventionally used methods of assessing semen quality do not provide information about DNA quality;
- (3) direct injection of spermatozoa bypasses the natural selection process mediated by the ovum's envelope.

Though the ICSI technique has only been in regular use since 1993, it has in many ways already revolutionized IVF and thus all ARTs. It is now the preferred treatment method of severe male infertility, resulting in pregnancy rates of 25%-35% per cycle (Coulam *et al*, 1996). It is possible that any noticeable increase in North American IVF success rates over the past few years may be largely attributable to the advent of ICSI. Since ICSI is primarily a treatment for male factor infertility, which is the underlying problem of up to 50% of infertile couples (Gil-Salom, 1996), it can be expected that women receiving ICSI-fertilized embryos are otherwise healthy. Their rates of successful pregnancies may then be expected to be greater than those of women who pursue IVF for reasons of personal reproductive dysfunction.

Under the assumption that abnormalities resulting from ICSI's bypassing of natural selection might manifest as spontaneous abortion, Coulam *et al* (1996) examined the rates of pregnancy loss for ICSI (136 pregnancies out of 405 women initiated) versus those of conventional IVF (35 pregnancies out of 69 women treated) at one American clinic. They concluded that there was no difference in rates, but failed to control for patient age. Coulam's small sample size is worthy of concern, however, since their findings are likely statistically insignificant.

The Coulam study reported that the frequency of karyotypic anomalies was not increased by ICSI, but that the incidence was high for pre-implantation embryos which were, presumably, not used. In a prospective follow-up study of 55 Belgian children born via ICSI, Bonduelle *et al* (1994) made a similar conclusion: the incidence of major malformations was not different from the incidence in the general population. Low birth weight and neonatal morbidity of the children were all within the expected range. It is unclear, however, whether chromosomally problematic parents were discouraged from continuing with the treatment during the study's genetic counselling sessions: 13 of the 136 couples were found to be at increased risk of parenting a genetically abnormal child due to malformations such as chromosomal inversions and a family

history of spina bifida. The authors do not report if these couples were removed from the programme. Furthermore, they say nothing of the expected prevalence and association of the measured conditions, so the statistical strength of their small sample is in serious question.

Veld *et al* (1995) suggest that the specific male fertility problems that led to ICSI may in some cases be accompanied by an increased incidence of sex chromosomal abnormalities in sperm cells. They report a frequency of chromosomal disorder an order of magnitude higher than what would have been expected from the general population (Hoegerman *et al*, 1995). A suggestion is made that their method of selection of ICSI sperm from the ejaculate (e.g. by motility or morphology) may influence the rate of abnormalities. Within the academic literature, reports of genetic abnormalities via ICSI are few.

An exception is a recent study by Wennerholm (2000) who suggest that ICSI is responsible for a variety of genetic abnormalities. A flaw in this study is the author's choice to have compared the ICSI findings to the natural population, and not to the non-ICS IVF population. A result of this oversight is that it fails to measure whether the adverse contribution is from the technique of ICSI, or from the genetically disadvantaged nature of the patient population.

IVF and ICSI developmental pathways do seem to differ considerably. Dumoulin *et al* (2000) found, in a retrospective analysis of 1628 consecutive cycles, that embryos obtained after ICSI were significantly further developed, in terms of mean cell count, than those obtained after plain IVF. This difference disappeared after 63-66 hours. What this means for eventual fetal health is unknown. Unfortunately, the protocol was not a matched study, so many differences were not controlled.

At least one lay journalist has commented on the lack of epidemiological studies to establish the long term safety of IVF techniques, especially ICSI (Vines, 1993). This is of concern since cases of male infertility often involve a greater than normal risk of congenital abnormality. In the words of Wagner (1996), no randomized controlled clinical trial has been performed on ICSI, "and the largest published study [is] of 150 cases... with no control group. This is not a sufficiently large sample for determining efficacy or risk."

3.0 Gamete Donation

Sperm donation has been an important part of infertility treatments for decades, and is obviously employed to bypass elements of male-factor infertility in cases in which the female is otherwise of acceptable fecundity. Ever since the first successful pregnancy following oocyte donation in 1984, however, oocyte donation has become an increasingly established part of ART programs (Kan *et al*, 1998). Recently, public attention has been focussed on this practice as more commercial services are offering couples the option of purchasing oocytes from such supposedly high-demand donors as fashion models.

Since oocyte donation is more invasive and costly a procedure than sperm donation, oocyte donors taking the commercial route can expect remuneration in the thousands of dollars. A study by Kan *et al* (1998) showed that donors are not unlike other women in terms of marital

or employment status. Those who initially inquired about donation, but who eventually chose not to donate, cited distance and concern over the required drug regime as their primary reasons for declining. Sauer *et al* (1994) noted that American oocyte donors tend to be generally well educated, "gainfully employed," and that their primary motivation for having donated an oocyte was "altruism."

Recent commercial developments, primarily in the United States, have seen the establishment of a high-profile market for gametes of supposed high quality: semen from Nobel prize-winners, and ova from fashion models (Wilson, 1999). These developments have brought the ethical and legal aspects of gamete donation to the public forefront.

4.0 Defining Success Rates

Success rates reported by ART clinics vary with regard to the indices and patient populations used to compute them. The phenomenon is most notable in the IVF realm. Selection bias and misunderstood statistics are major factors contributing to the inappropriateness of certain rates. The influence of privatization and market forces may also contribute to the need to oversimplify IVF statistics (Deonandan *et al*, in press).

Accusations have been made of clinics having distorted their outcome rates (Soules, 1985; Hershlag *et al*, 1992) in an attempt, unconscious or otherwise, to artificially inflate estimates of their programs' success. Since the success rate continues to be regarded as the primary criterion of a clinic's proficiency (Hershlag *et al*, 1992), it can be expected that the need to compete for patients in an open-market system may lead to a certain bias, subtle and perhaps unconscious, in the publishing of IVF outcomes. Women's perception of prevailing ART success rates is therefore an important factor to measure.

5.0 The ART Patient Population

Data on ART patient demographics, especially those relating to IVF, tend to be almost anecdotal, and are confounded by advances in technology, such as ICSI, which broaden the acceptable age and health status ranges, and by changes in health insurance policy which affect the socio-economic profile of the patient population. A link between demographic characteristics and obstetric outcomes of IVF interventions has not been attempted, however, but only discussed peripherally as side topics of more clinical papers.

A study of patient profiles of both IVF recipients and oocyte donors was conducted by Sauer *et al* (1994) on patients of the fertility clinic of the University of Southern California. As would be expected, younger recipients were less likely to have been previously pregnant, remarried or have undergone reparative surgical procedures. Where the patient age cut-off ten years ago was typically 35 years, it is not uncommon to find women in their 50's undergoing IVF treatment today.

Sauer *et al* concluded that "women of a variety of ages and with a wide range of clinical diagnoses for infertility may successfully conceive and deliver following oocyte donation." No mention was made of the socio-economic stratum of IVF recipients, though one would expect it to be relatively high since, in California, the procedure requires either personal wealth or extensive private medical insurance.

While certain objective demographic criteria, such as SES (socioeconomic status) and ethnicity, may be assumed to be identical for both the parents and the eventual offspring, concern for the latter has taken a somewhat ominous turn in the policies of at least one government. Heitlinger (1989) reported that it was desirable in Czechoslovakia to encourage reproduction via IVF, even for fully fecund couples. This was motivated by a triple desire to curb the decline in population, to elevate that nation's scientific world standing and to improve the socioeconomic status and civil behaviour of their population. The argument behind the latter goal is that children born via IVF are "wanted" children and will therefore receive better care, and therefore be better socialized. The nation of Czechoslovakia dissolved before this policy could be implemented, but the potential for IVF to influence the profile of a population is demonstrated by the policy's very conceptualization.

In New Zealand, a survey of IVF couples found 41% to be from professional, technical, administrative or managerial occupations; 25% from agriculture and production; and 15% from the sales and service industries (Daniels, 1989). Many respondents --43%-- were described as having "technical qualification." However, since the survey was applied to couples and not to individuals, it is unclear whether these characteristics apply to both partners or to just one spouse. Their data nevertheless suggest an equal distribution of high and low SES patients: surprising since the procedure is privatized in that country.

Like in the American study, most (93%) were married, and had been so for an average of 7 years, and 84% were childless. The investigators were careful to note that almost all of their respondents were of European extraction, though it is conceivable that SES in New Zealand may not follow the racial patterns we have come to expect in North America. Despite these intriguing suggestions, the connection between demographics and clinical IVF behaviour has not been explicitly studied or indeed postulated. What is more suggestive is that SES probably influences which infertile people will seek IVF treatment.

6.0 Access

Socioeconomic status is but one element affecting an infertile individual's decision to pursue treatment. In this sense, SES is a component of access, an umbrella term informed by geography, wealth, education, personal morality and even jurisprudence. As IVF grows in ubiquitousness, understanding the issues related to its access gains importance.

Often, we find it difficult to separate issues of equity, legality, cost and ethics, as all are manifestations of the greater question: "Is this the appropriate thing to do, given my circumstance?" It is, of course, accepted as a truism that the best guarantors of healthy children are access to health care and an absence of poverty. What role do ARTs play in this milieu? Parents' access to ART does not guarantee healthy offspring, after all, but does affect the resulting

health profile of the offspring population.

Reproductive technologies essentially offer treatments for infertility and avenues for avoiding genetic traits and disabilities considered undesirable. The advent of these technologies holds out promise for the greater health of conceived children, by virtue of close monitoring of the pregnancies and by the greater knowledge gleaned of the fertilization process, yet threaten child health on a subtler scope.

Aral & Cates (1983) report that infertility is highest in those groups that have the least access to reproductive technologies: poor, undereducated and minority communities who also suffer the highest rates of child morbidity and mortality. Furthermore, new reproductive technologies, by encouraging the quest by the infertile for genetically related children, decrease the number of potential adoptive and foster parents (Henifin, 1993), and delay the eventual policy determinations regarding trans-racial adoption and other socially divisive issues relating to adoption.

The scope of any research on reproductive technology cannot be limited to clinical aspects of the ART procedures in isolation. The issues of surrogacy and ovum donation, skirted in this protocol, have broader implications for future access to this technology. Since for older women, donor oocytes have a higher chance of success than native ones (editors, 1991), will it be possible, then, for a woman to sell some of her valuable ova to pay for her own *in vitro* therapy? Or is the mediation of assisted reproduction tantamount to baby-selling? And as legal issues of custody eventually resort to scrutiny of the economic disparity between competing interests --surrogate mother, legal mother, ovum and sperm donors-- once more our attention is turned to the demographic profile of ART seekers.

There is no question, then, that the power of the technology, under the influence of market forces, has created an environment from which are emerging very serious issues regarding class distinction and access to health care.

7.0 Cost

Discussion of ethical and legal considerations of ARTs has been fuelled by the added dimension of cost. If IVF in particular were an inexpensive procedure, it is likely that its stature in the agendas of ethicists and law-makers might not be as great, and its effect on the population's demographic profile would be enhanced by its greater ease of access.

Few direct studies of IVF cost are available. One of the most comprehensive is Page's (1989) assessment of the patterns of British IVF expenditure. One must differentiate, however, between costs borne by society (including dilute and difficult to trace externalities), direct costs borne by the government or taxpayer, and costs absorbed by the patient herself. While Page is concerned primarily with the first type of cost, she does offer the following bit of insight: costs of attending a private clinic will tend to exceed those at a public clinic. This is because patients referred to a private clinic may not have had the investigation and treatment which, in a public clinic, would have normally preceded IVF. The private clinic would then include these costs in its bill.

In Ontario, the situation may be reversed. A couple may receive pre-IVF treatment under

OHIP (Ontario Health Insurance Plan), then defer with their records and results to a private clinic, the initial costs already having been borne by the state.

Seibel & Bernstein (1994) report an average American expenditure of US\$8000 per cycle, though this number is reduced by US\$2000 for naturally stimulated cycles. They further estimate a "cost to society" of US\$66,667 per cycle! A more comprehensive analysis is provided by Neumann *et al* (1994) who agree with the estimate given by Seibel & Bernstein for the first treatment cycle, but insist that a sixth cycle escalates to US\$114, 286. This is because with each cycle, the probability that a subsequent effort will be successful declines. This of course has bearing on the patients' profiles from cycle to cycle, especially in clinics that are not funded by a medical insurance system.

The more high-tech procedure of ICSI has fallen under recent economic scrutiny. One cost analysis (Schlegel, 1997) shows that as an infertility treatment for men, ICSI is less cost efficient than a comparable surgical procedure, varicocelectomy (assuming a fully fertile female partner). The inappropriate application of ICSI may then unnecessarily raise the cost of an IVF intervention for a given couple.

As an example of IVF patient expense in Ontario, Ottawa Civic Hospital charges patients CDN\$4,500 for a single cycle of treatment (Civic Hospital, 1996). Cryopreservation starts at CDN\$600, donor semen at CDN\$400 and an ICSI procedure at CDN\$1,200. When considering the *total* cost of a procedure, however, more indirect costs should be factored. These costs include expenses arising from lost wages and unanticipated illness to the mother or child. Of the latter, post-natal IVF medical care usually arises from the multiple births common to IVF families. One estimate is that efforts to reduce the number of multiple pregnancies resulting from assisted reproduction would save the American health system US\$3 million per year (Callahan *et al*, 1994).

While these numbers are impressive, they take on greater relevance when examined in the light of Ontario's health insurance plan, OHIP. Ontario provides an excellent case analysis for the future bifurcation of public/private ART services in other provinces. In the earliest days of IVF treatment in Ontario, the services of medical staff tended not to appear in the formal accounting procedure (possibly because their services were donated). OHIP covered most other costs, and the couple was required to provide approximately CDN\$1000, exclusive of medication (Ontario Law Reform Commission, 1985). The OHIP Schedule of Benefits of 1992 listed greater coverage for IVF therapy, but this was to last only two years.

On April 1, 1994, IVF became an insurable benefit only for complete bilateral anatomical fallopian tube blockage (Ontario Ministry of Health, 1995). The term "blocked tube" refers to:

- # tubes blocked bilaterally or removed because of disease (e.g. endometriosis, tubal pregnancy);
- # congenital absence of tubes.

Patients having had their tubes removed or occluded via elective surgery for the purposes of sterilization do not qualify for funding.

Several additional caveats are necessary to fully appreciate these guidelines:

- # Patients who were in active IVF treatment between April 1, 1993, and April 1, 1994, were "grandfathered" into the insured programme until the completion of three cycles. "Completion" requires that embryo transfer occurs, but says nothing about pregnancy or length of time to complete a cycle.
- # Qualifying patients are insured for only three completed cycles. Patients failing to achieve egg fertilization *must* proceed to donor insemination, absorb the costs of ICSI or abandon the treatment; ICSI costs are *not* insured. This may tend to guide patients toward using donated sperm.
- # No service associated with *uninsured* IVF may be billed to OHIP (e.g. assessments, ultrasounds, serum hormone monitoring and counseling from a private clinic.)

The analysis of cost leads one to greater questions: who should have the procedure and who should pay for it? Such cost analyses are an exercise for the diligent economist.

ART is undeniably a lucrative business. It is estimated that a private clinic can "break even" after only 50 procedures (Miller *et al*, 1992), leaving the rest as pure profit. As IVF is rapidly moving out of the realm of socialized medicine, it comes further under the influence of permeating market forces. What makes such technology different from other medical concerns is the way they fragment human eggs and embryos themselves into factors of mass production and commodity. By being made into "discrete, laboratory-friendly entities with economic value" (editors, 1994), human eggs and embryos are being enclosed and transformed into scarce resources circulating in a claustrophobic market system.

The latter is undoubtedly an extreme alarmist perspective, but does have value in its call for an ethical examination of this collusion of science and health with commerce.

8.0 Ethical Implications

Fertility technology, given its cost and its venture into the holy realm of human reproduction, is rife with serious implications both ethical and theological, and any researcher would be remiss in not acknowledging this fact. The scope of this document is, however, such that the broad realm of ethics cannot be tackled here in its entirety. However, the major ethical issues associated with ART can be summarized in the following points:

- # *The purpose of medicine and the allocation of resources.* If a nation's medical system is intended to treat the unhealthy, then is infertility truly a state of ill health? This question speaks to the heart of the government billing issue: how to justify enormous ART expenditures when truly life-threatening illnesses go underfunded. The "solution" of privatization has spawned its own concerns, notably that marketing may supercede medical concern when such a procedure becomes a profit-motivated operation. At least one American IVF clinic is offering a questionable "guarantee" of success given a

sufficiently large monetary payment (Hamilton, 1996).

- # *Who benefits?* This is a question of social justice to be partially addressed by further demographic studies. American data would suggest that ART patients are upper middle class and white. Given the expenditures involved, and even societal externalities incurred by so-called "private" clinics, the pursuit of ART as a viable consumer option may prove distasteful.

- # *The risks associated with the procedure.* As discussed, ART involves medical and psychological risks to the parents and to the child. As the desired outcome is a live birth, given the number of children available for adoption, is the risk justifiable? Furthermore, IVF in particular extends fertility beyond the "natural" cessation of these processes within an aging woman. In response, the Health Minister of France announced a new legislation that would allow prosecution of doctors who permitted IVF for women beyond child-bearing age (Chalmers, 1994).

- # *Informed consent.* The purpose of informed consent is to ensure that patients freely grant permission for the recommended medical procedure; the provision of information does not necessarily mean the patient has been informed (Macklin, 1995), only that the practitioner may be free of some degree of official liability. "The population seeking IVF is a vulnerable one" (Shannon, 1987) who have exhausted all other avenues of reproduction. Addressing this concern is a task for psychologists, and fortunately most ART clinics insist upon a degree of counselling before couples are admitted to the programme.

- # *Implications of controlling human gametes.* Since IVF and ICSI remove the previously hidden process of fertilization from the protection of the mother's womb, and from the forces of chance and natural selection implicit in all couplings, the question becomes: who controls what is done to the fertilized egg? The issues of propriety, most naturally belonging to the parents, are confused by anonymous gamete donors and the techniques of cryopreservation.

- # *Social standards of parent acceptability.* There are subtle social filters surrounding many specialty medical procedures. For example, some clinics may require heterosexual marriage as a criterion for acceptance to an IVF programme (Shannon, 1987). The broader question is then asked, and it relates to the issue of public funding: who is allowed to reproduce? Reproductive technology is ostensibly meant to make reproduction accessible to more people, yet it may prove to be an instrument of demographic control and socialization, hence a compelling argument for making IVF a publicly funded procedure immediately available to all citizens regardless of race, sexual preference and socio-economic status.

The Council of The Society of Obstetricians and Gynaecologists of Canada issued a "Statement on In-Vitro Fertilization and Embryo-Transfer" to attempt to address some ethical issues, as has

the American Fertility Society. The difficult questions are still left to the individual practitioners to resolve for themselves.

Some attempts have been made, however, to provide an ethical framework in which some of these questions could be resolved. Howard Jones (1985) reminds us the most pertinent ethical constraints to overcoming a medical handicap are that: (1) the potential risk to the patient must not be disproportionate to the benefit and (2) there be little or no harm to any other individual. In classical medical ethics, Jansen (1985) applied formal ethical principles to conclude, as did Edwards (1985), that the evolution of new reproductive technologies should be taken out of the hands of physicians and left to administrators and law-makers to deal with.

9.0 Legal Considerations

As with most examples of advanced technology, its practice has exceeded the legal machinery's ability to legislate it. Most legal concerns are related to the ethical and access concerns listed above, and one cannot be resolved without considering the others. By many international laws, including the European Convention (1978), every woman is "entitled to have children."

A debate once raged over whether the provision of artificial conception services constitute the "practice of medicine." Ontario law holds that it does, under the rationale that such designation precludes unqualified individuals from undertaking the procedure under their own advisement (Ontario Law Reform Commission, 1985). It is possible that in the distant future this designation will have to be re-thought if technology progresses to the stage where IVF is a commonplace procedure in even the smallest venues.

While interesting, these legal considerations must remain peripheral to the intent of this document. However, it is useful to remember the uncertain state of legality where reproductive technology is concerned, especially as it relates to a government's ability to dictate policy concerning the procedure, and to the patient population's anxiety regarding the procedure's physical efficacy and ethical foundation.

Related to this debate is the larger legal issue brought to the forefront by the abortion laws: what is the legal status of the embryo or the gamete? Large governmental commissions have been established to explore these questions: the 1985 Warnock Commission in the U.K., for example, allowed for some level of protection of the embryo under various statutes. And Canada's Royal Commission on New Reproductive Technologies (1989) attempted to provide guidelines for research and therapy, but has not yet resulted in actual amendments to law. In the United States, the legal status of the fetus was established by the landmark *Roe vs. Wade* legal decision of 1973 as being less than that of a "legal person," yet sufficient to inherit property. With regard to ART, this has relevance since legalistic battles have been more concerned with the rights of the parents and of society, and less so of the zygote and resulting embryo. Public concern with this concern was recently voiced via the USA's Human Embryo Research Panel of 1996 which finally declared that all research done on embryos *ex utero* would not receive federal funding (Annas *et al*, 1996).

Janet Gallagher (1987) raised the point that legal considerations of IVF should concern

the invasiveness of the procedure: whether it is appropriate to use a woman's body for experimental purposes. Not surprisingly, feminist writing has been unmitigatedly hostile toward reproductive technologies. The argument is often that "women's choice to participate in infertility treatments is so conditioned by the socially constructed stigma of infertility and a societally imposed norm of maternity as to be no real 'choice' at all" (Gallagher, 1987).

Britain's Warnock Commission is an example of legal-ethical discourse that was conspicuously devoid of any consideration of women's reproductive rights. The administration of powerful drugs to induce superovulation, for example, was considered objectionable by Warnock, not for the risks posed to the women being treated, but because of the moral problem of creating "spare" embryos (Spallone, 1986).

In popular culture, this fear that male appropriation of female power will extend into the realm of reproduction is expressed through such avenues as the Canadian novel and subsequent film *The Handmaid's Tale* (Atwood, 1985) in which women are kept as fertility slaves. Under this feminist paradigm, it is impossible to separate legal from ethical and psychological concerns. The balance of legal rights can only be shaped in an ethical framework that allows women to define their identities through their function as child-bearers.

10.0 Long-term Undesirable Outcomes for Children Produced fro ARTs

10.1 Sleep Apnoea

As the eldest "test tube baby" has entered adulthood, more data becomes available on the health states of the population of children born via this process. One such study found that IVF babies have more "periodic breathing episodes", or apnoea, indicating an immature respiratory pattern, than normally conceived babies (Audiens *et al*, 1995). The 50 children in each of the test and control groups were matched for their personal demographic characteristics (gestational age, sex, season, etc.), but not for those of their parents (e.g. mother's age).

Morin *et al* (1989) matched 83 IVF babies with 93 non-IVF babies to test for differences in rates of congenital malformations between the two groups. They found no such differences, but did find that IVF children were more psychosocially developed, probably because of the greater motivation of their parents (a phenomenon called "wantedness").

10.2 Genetic Abnormalities

Genetic adversities resulting from artificial reproduction are a popular lay concern. Valid scientific concerns are more attributed to the underlying methodology of ICSI which, as discussed, bypasses natural selection. Interestingly, Morin *et al* (1989) reported a tendency for IVF children to score higher on standard intelligence tests, supposedly attributable to greater parental intervention by virtue of the children being more "wanted."

In the literature, “wantedness” appears to be a universally positive condition conferring the developmental advantages of parental investment. In the abstract, it is conceivable that “wantedness” may lead to overprotection and the psychosocial negatives that that condition implies. However, the findings of Wennerholm (2000), discussed above, may change clinicians’ attitudes about the long-term genetic safety of certain ART techniques.

10.3 Cancer

Only one notable study, that of Bruinsma *et al* (2000), has comprehensively considered the potential association between IVF and neonatal cancer. While there is evidence of neuroblastoma in children conceived using fertility drugs (e.g., Kramer *et al*, 1987), longitudinal data of this nature have been hard to come by. Bruinsma examined the records of 5349 Australian assisted reproduction births, over 16 years with an average follow-up of 3 years per child, and found no significant association between child cancer and IVF, compared to the general population. While it is conceivable that such neoplasms will manifest after the 3 year follow-up period, there is no evidence to suggest this.

10.4 Sex Selection

A fascinating unexpected outcome of an IVF intervention may be the inadvertent selection of offspring sex. This is clearly not a policy of North American fertility clinics, nor is such a voluntary service widely offered (and may indeed prove unethical). However, there is some evidence (Tarin *et al*, 1995) that the process of embryo selection favours male offspring for younger women, and female offspring for older women.

If borne out, this trend may indicate a need to re-evaluate the accepted criteria for selecting good embryos for transfer, or for selecting which sperm are forwarded for ICSI. Current policy proposals by the government of Canada are rumoured to see all reproductive therapies conferring a sex selection effect either tightly controlled or banned outright. If IVF is, however unintentionally, one such therapy, the extent of this effect needs to be evaluated.

10.5 Miscellaneous Maternal and Neonate Morbidity Risks

Tallo’s *et al* (1995) study of maternal and neonatal IVF morbidity found that a significant number of IVF mothers suffered from pregnancy-induced hypertension, premature labour, labour induction and preterm delivery than did comparable non-IVF women. Their children had longer hospitalizations, more days of oxygen therapy, more days of continuous positive airway pressure, and an increased prevalence of respiratory distress syndrome, patent ductus arteriosus and sepsis. Since most of these neonatal problems are a result of the multiple pregnancy scenario so common in IVF, it is difficult to say whether the procedure itself is conferring a greater extent of maternal and child suffering.

Shelley *et al* (1999) provide a list of potential morbidities resulting from IVF and related ARTs, including maternal bone loss, mood swings, ovarian bleeding and complications related to the increased risk of preterm delivery. The risk of pelvic and circulatory infection is identical to that posed by sexual intercourse: the transmission of infection (viral, mycoplasmal and bacterial) through semen (Royal Commission, 1989). Routine screens are performed on all donors of gametes to minimize this risk.

11.0 Short-Term Undesirable Outcomes for ART

11.1 Multifetal Pregnancy

A controversial approach to maximizing outcome potential is to consider the risk factor posed by multiple pregnancies. It is commonly held that multiple gestations are at risk for premature birth, supposedly caused by the increased concentration of serum relaxin, and “the risk resulting from [IVF] treatment appears to be greater than that of age and fetal number matched pregnancies without IVF” (Haning *et al*, 1996).

Multifetal reduction (selective abortion of some of the embryos) early in the pregnancy may then be a viable option for improving the chances of a live birth. Haning *et al* (1996) found that, indeed, multifetal reduction of pregnancies with three or more fetuses was "beneficial" in that it increased the duration of gestation. One might expect future developments in IVF to see greater multiple embryo transfers, followed by a multifetal reduction later in the pregnancy. The ethical considerations spawned by such an approach may prove prohibitive.

A further attempt to reduce this risk is to limit the number of embryos transferred *in utero*. At present, most North American clinics transfer a standard 3 embryos, thus presenting a fair chance of a multiple gestation. While IVF technology and success rates improve, a movement exists (e.g. Staessen *et al*, 1993) to reduce this number to 2 while maintaining an acceptable pregnancy rate.

IVF pregnancies, even singleton ones, may have an increased risk of preterm delivery and fetal growth restriction (Verlaenen *et al*, 1995). But by far the adverse obstetric outcome of greatest likelihood is that of multiple gestations. Up to 25% of IVF pregnancies are multiple pregnancies (Feichtinger, 1994). Given that women undergoing an IVF procedure are typically older and therefore more prone to a variety of health complications, this is a serious consideration.

Several further complications may arise from an IVF pregnancy, most notably ectopic pregnancies of which a cervical pregnancy is one of the most potentially catastrophic (Qasim *et al*, 1996). Such pregnancies are often linked to the diagnosis of the underlying cause of infertility. In such cases, prompt intervention is often necessary, not only to save the pregnancy, but to preserve the patient's future fecundity.

Furthermore, reports on assisted-reproduction pregnancy outcomes, of which IVF pregnancies are a subset, show that the rates of preterm delivery, low birth weight and perinatal death are all greater than those of the rest of the birthing population (Tanbo *et al*, 1995). For this reason, according to some, even a singleton pregnancy is considered a case of greater obstetric

risk. Hull's *et al* (1996) recommendation of multifetal reduction still does not remove the burden of "risk" from the pregnancy.

12.0 Major Traditional Risk Factors for Poor ART Outcome

12.1 Age

By far the most commonly mentioned risk factor in both the literature and anecdotally is a demographic one: age. After correcting for confounding factors such as the partner's age, duration of the partnership, coital frequency and parity, it has been estimated that fecundity declines gradually from 30 years of age onward, in both women and men (Hull *et al*, 1996). The ability to implant an embryo via IVF drops dramatically after a maternal age of 40 (Hull *et al*, 1996). Indeed, in an unusual attempt to create a regression model for determinants of IVF, notably uterine receptivity and embryo viability, Baeten *et al* (1993) found that age was the only variable to influence uterine receptivity significantly.

On the other hand, recent refinements have indicated a lessening influence of age upon IVF outcome. Widra *et al* (1996) found that women over 40 will respond well enough to ovarian stimulation to result in four or more embryos ready to transfer, hence conferring upon them a probability of pregnancy comparable to that for much younger women. Similarly, Sen *et al* (1997) concluded that it is a fallacy that the risk of multiple pregnancy, an adverse outcome, is greater for older women.

Age in an IVF population is related to other demographic factors. Van-Balen *et al* (1997) claimed to measure an association between the desire to reproduce at a later age with a high level of education, a high "professional" level and a high level of family income. It goes without saying that advanced age is related to a host of common factors which may contribute adversely to pregnancy attempts, e.g., obesity and type II diabetes. As a result, the measurement of a direct relationship between age and potential IVF success is confused by many intermediate modifiers.

An important issue for policy makers is to consider if age limitations need to be placed upon an ART patient population, in order to maximize the positive outcomes of publicly-funded ART programmes, and to address ethical concerns related to post-menopausal conception.

12.2 Smoking

There are conflicting reports regarding the influence of maternal smoking on ART outcome. Maximovich & Beyler (1995) retrospectively analysed patient questionnaires to correlate with a trichotomous outcome: not pregnant, spontaneous abortion or live birth. They suggest that cigarette smoking has an adverse effect on potential pregnancy outcome by increasing the rate of spontaneous abortion. An admitted gap in the study was that there was no indication of whether an external influence, such as an ART counsellor, may have encouraged some patients to reduce their smoking before commencing the treatment cycle.

Sterzik *et al* (1996), however, report that there is no impairment of fertility potential caused by smoking, and that other ART risk factors should take precedence. This study measured cotinine, a metabolite of tobacco, in the follicular fluid to determine smoking status, rather than relying on a questionnaire.

The Sterzik study cannot distinguish between non-smokers and passive smokers, and no mention of such a distinction was made by Maximovich & Beyler. This is an important consideration since IVF mothers are almost always part of a two adult household; the smoking behaviour of both persons must be considered.

12.3 Psychosocial Stress

Psychosocial factors certainly play a role in the administration of ART therapy. A vulnerability to stress may be an indicator for a decreased likelihood of treatment success. Patients in North America are characterized as older, professional women who are supposedly exposed to more daily stress than their domestic counterparts.

Reproductive science has long been a field well explored by psychologists. The motivations that compel a patient to pursue a reproductive intervention can be characterized as purely psychological, i.e. the desire to procreate, and contributory to overall health only to the extent that procreation garners a greater sense of well-being. Psychosocial factors associated with IVF have therefore been extensively studied, as have patients' attitudes toward certain aspects of childbirth. Wilcox & Mosher (1993), for example, found that the association between a history of endometriosis and use of a fertility service was twice as strong among American women who reported not wanting a child.

Due to the newness of the technology, there are few if any studies on the psychosocial implications for the children resulting from IVF anonymous gamete-donation therapies. Psychosocial investigations of IVF have typically been of five issues: anxiety associated with the intervention, cultural considerations, fear of adverse outcomes, propriety, and psychological screening.

12.3.1 ANXIETY

Feichtinger (1994) suggests that patients with high anticipatory anxiety tend to have lower pregnancy rates, and that endocrinological responses during oocyte retrieval and embryo transfer may prove the avenue of that relationship. The findings of a survey by Visser *et al* (1994) suggest that IVF women feel more anxious than a normal population, but do not express more emotional complaints. Unfortunately, their instrument was unable to measure any influence exerted by psychosocial factors on actual fertility or ART success.

The anxiety associated with treatment has been attributed by Daniels (1989) to the "marvel and concern" surrounding both the seemingly magical qualities of the technology and its serious moral and ethical implications. Couples pursuing IVF were "united and determined to exhaust all opportunities to achieve pregnancy." There is also some evidence that the stress of

IVF imparts a degree of psychoneuroendocrine dysfunction upon the patients (Kemeter *et al* 1985). It is theorized that this dysfunction can affect gonadal hormone levels, and therefore the outcome of the IVF procedure itself.

12.3.2 CULTURE

Macer (1994) published a comparison of attitudes toward biotechnology across different cultures. He found that opinions about whether ART was worthwhile and positive differed between peoples of different countries and cultures. In relation, Silverio & Hemminki (1996) implied that North American doctors were more resentful toward government interference in the implementation of reproductive technology than were European doctors. Clearly, attitudes toward ART stress and acceptability are strongly influenced by cultural considerations.

12.3.3 FEAR OF ADVERSE OUTCOME

Baluch's *et al* study (1992) indicated that the IVF psychological stress among patients, rather than fear and pain of the actual procedures, was more associated with the outcome of different stages of treatment. Similarly, Goldfarb *et al* (1996) found that patients feel that a high-order pregnancy --a common IVF outcome-- is not an optimal outcome. It is blindly assumed that the infertile will gratefully accept any proposed therapy, but there has been little investigation into their true desires and into the extent of risk they are willing to assume to alleviate their problem.

12.3.4 PROPRIETY

Since many IVF procedures involve gamete donation, the issue of *biological* versus *social* parenthood (Royal Commission, 1989) arises, particularly for the father who does not "benefit" from the bonding process of live birth. This is rapidly becoming more of a legal issue than a psychosocial one.

12.3.5 SELECTION OF PATIENTS

Psychological appraisal is an important method for selecting patients into an IVF programme. It is obvious that an individual seeking medical help is different from one who does not seek help, but who suffers from the same ailment. Furthermore, a patient who is admitted to such a unique procedure --one that affects one's offspring as intimately and as dangerously (to potential offspring) as do ART therapies-- would tend to be different from individuals who are not admitted. These differences may play a role in determining the profile of IVF patients in a given population.

Attitudes toward high technology, or toward the assumption of doctors' moral authority regarding decisions associated with ethically-laden ART protocols, tend not to be captured by psychological assessments described in the literature. Yet these attitudes may be correlated to

both the seeking and the admittance into an IVF programme.

As a result of the importance of psychological assessment in programme screening, such studies have usually focussed on the needs of the clinician. Little measurement has been performed on the attitudes of patients toward the morbidity and mortality risks they are assuming.

12.4 Cause of Infertility

Other possible risk factors include a variety of patient illnesses or disorders that may or may not be related to the underlying cause of their infertility. Congenital uterine malformation, for example, has been shown to increase the rate of preterm delivery and cesarean section (Marcus *et al*, 1996). In addition, hormonal signs of ovarian insufficiency are related to IVF treatment failure (Csemiczky *et al*, 1995).

Similarly, the poor success of couples with male infertility undergoing IVF is well recognized, although some authors claim that pregnancy rates for male factor infertility are similar to those of female bilateral blockage (Feichtinger, 1994). The reason for infertility is therefore predictive of a patient's performance in the programme.

A frustration to IVF meta-analysis attempts is an inability of clinics (and hence published researchers) to agree upon definitions for specific causes of infertility. For example, Bruinsma *et al* (2000) reduced types to "male factor", "tubal", "ovulation disorder" and "unexplained", while Hughes *et al* (1989) used a completely different set of prognostic groups which are not quite etiologies, but which included "advanced age", "poor stimulation", "low sperm motility" and "poor embryos".

13.0 Cryopreservation

One of the major technological advancements of the late 1980's and early 1990's is the ability to put into deep freeze successfully formed embryos not chosen for implantation. Such embryos may then be thawed at a later date for implantation into the uterus of its mother or that of a surrogate mother. The first large survey of cryopreservation practice was conducted between 1985 and 1993 by the French Federation of IVF Biologists (Anonymous, 1996). That study showed that approximately 94% of the 102,812 frozen embryos in France were eventually transferred *in utero* to the parental couple, 6% were thawed and destroyed, while 0.2% were donated to non-parental couples.

The prevalence of cryopreservation is dependent upon: the availability of the service, the desires of the parents, and the viability of the embryos as suitable for freezing. As IVF costs soar, storage of unused embryos becomes an economically attractive option. Issues to be discussed by policy makers include definitions of ownership of cryopreserved embryos, and whether such embryos should be made saleable or available for experimentation.

14.0 Conclusion

ARTs are growing in popularity, accessibility and in media profile. Increasingly, headlines centred on infertility treatments grace Canadian newspapers. From seemingly seasonal stories about sextuplet births, to more dire reports of women receiving the wrong embryos (Egan, 1999) and the threat of contaminated donor sperm (Associated Press, 1999), this medical realm has carved out a niche in the public vocabulary. The legal, theological and academic institutions scurry to catch up.