# The Epidemic of Multiple Gestations and Neonatal Intensive Care Unit Use: The Cost of Irresponsibility

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**Objectives** To determine the proportion of infants admitted to our neonatal intensive care unit (NICU) from multiple gestations resulting from artificial reproductive technology (ART), the complications experienced and interventions required by these infants, and the estimated effect of a mandatory policy of single embryo transfer on admissions and complication rates in our hospital and across Canada.

**Study design** We conducted a review of a prospectively maintained database and of hospital records and calculated excess complications compared with either universal single embryo transfer or a policy allowing transfer of two embryos in as many as 33% of women.

**Results** Of our NICU admissions, 17% are infants from multiple gestations after ART, a significant increase in 10 years. In a 2-year period, the excess NICU use that would have been saved by mandatory single embryo transfer included 3082 patient days and 270 patient ventilator days. Extrapolated across Canada, a policy of single embryo transfer would prevent 30 to 40 deaths, 34 to 46 severe intracranial haemorrhages, and 13 to 19 retinal surgeries annually. Savings in NICU resources would be 5424 to 7299 patient-days of assisted ventilation and 35 219 to 42 488 patient-days of NICU care.

**Conclusions** A mandatory policy of single embryo transfer would be of substantial benefit to the health of Canadian babies while still benefiting infertile couples. *(J Pediatr 2011; ■: ■-■).*

Maternal age and the prevalence of infertility are increasing in the developed world.[1] Artificial reproductive technologies (ARTs) have become very successful; however, this success has been accompanied by an epidemic of multiple births.[1,2] Multiple gestations may occur after ovarian stimulation or when more than one embryo is transferred during in vitro techniques. In vitro fertilization (IVF) refers to all in vitro techniques, after which a known number of embryos are transferred to the uterus (ie, including intra-cytoplasmic sperm injection and in vitro maturation, in which immature oocytes are retrieved and matured in vitro before insemination, regardless of whether maternal or donor eggs or fresh or frozen embryos are used). IVF accounts for 1% of all births in the United States, but 16.2% of twin deliveries and 38.3% of triplet deliveries.[3]

The frequency of prematurity is also increasing,[4] some of which is caused by the increase in multiple gestations.[1] Infertile women are already at a substantially increased risk of preterm delivery with singleton pregnancy (17.3%[5] compared with 7.6%[6]). This risk increases considerably for multiple pregnancies.

The frequency of multiple pregnancies from ovarian stimulation is uncertain. In contrast, all 26 IVF centers accredited by the Canadian Andrology and Fertility Society submit data to the Canadian Assisted Reproduction Technologies Register.[5] The 2005 report notes that 28.5% of IVF deliveries were twins and 1.4% were triplets (total deliveries n = 2663). Canada thus has one of the highest rates of multiple deliveries after IVF in the world, similar to that in the United States, where in 2005 31.7% of IVF deliveries were multiple[3] (n = 38 910). In Canada, the number of embryos transferred during IVF is not subject to federal or provincial restriction. In addition, no province in Canada currently reimburses IVF. Partial tax relief is available in some provinces, such as in Quebec, and plans to reimburse IVF more completely are being developed in Quebec.

The Canadian Assisted Reproduction Technologies Register annual report defines a live birth as the delivery of at least one living infant at >19 weeks gestation. Although preterm delivery (<37 weeks) and very preterm delivery (<34 weeks) are recorded, neonatal complication rates and extreme prematurity (<29 weeks) are not recorded.

The objectives of this study were to determine: (1) the proportion of the multiple gestation infants admitted to our NICU from IVF or other ART and whether this has changed in the last 15 years; (2) the complications experienced and interventions required by these infants; and (3) the estimated impact of a mandatory policy of single embryo transfer on admissions and complication rates for our hospital and across the country.

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|---|---|
| ART | Artificial reproductive technologies |
| IVF | In vitro fertilization |
| NICU | Neonatal intensive care unit |
| RVH | Royal Victoria Hospital |

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## Methods

After consent from the Royal Victoria Hospital (RVH) was obtained, we searched our prospectively maintained database for infants who were a product of multiple gestation after ART and the type of ART. We compared 1-year epochs at a 10-year interval: 1996 and 2005. We then reviewed the hospital charts for NICU admissions of multiples, irrespective of mode of conception, between July 2005 and July 2007.

We determined from the mother's charts the mode of conception, the number of embryos transferred, the mode of delivery and complications. From the infant charts, we determined the frequency of significant complications (Table I).

We estimated the additional adverse outcomes incurred by IVF multiples compared with the expected frequencies with universal single embryo transfer. Because there is an increase in prematurity in mothers delivering singletons after treatment for infertility, we assumed that 4% of mothers carrying singletons would deliver very preterm (<34 weeks) and another 8% late preterm (34-37 weeks). There is a minor increase in monozygotic twinning after infertility treatment; therefore, we estimated that 3% of mothers would have twins after single embryo transfer (and no triplets).[3] Of the mothers who would give birth to twins, 23% would deliver very preterm, and a further 49% would deliver late preterm (these figures are from the 2005 Canadian Assisted Reproduction Technologies Register annual report[5]). Therefore, for every 1000 mothers pregnant after single embryo transfer, there would be 30 pairs of twins, 14 pairs of whom would be delivered late preterm and 7 pairs of whom would be delivered very preterm. Of the remaining 970 singletons, 40 would be delivered very preterm and 80 would be delivered late preterm. At RVH, approximately 60% of late preterm infants[7] and all very preterm infants are admitted to the NICU; therefore, 30 of the twins and 88 of the singletons would be admitted to the NICU (ie, 118 or 11% of the total number of infants).

We then reviewed the database for average duration of hospital stay and incidence of each adverse outcome for infants delivered after each completed week of gestation. From this, we estimated the numbers of days of interventions required for infants who would still have needed NICU care even when universal single embryo transfer had been used. We also made a second estimate for a policy of selective single embryo transfer, which would allow for double embryo transfer in exceptional circumstances. (Similar to the Swedish policy in which 67% of 8135 procedures were single embryo transfer, 32.5% were double embryo transfer, and 0.1% were 3-embryo transfer, resulting in a 6% twin pregnancy rate).[8] In the second estimate, for each 1000 women, there would be 60 pairs of twins, or 120 twin infants, 26 of whom would be very preterm and would all require NICU admission, and 50 late preterm infants, 30 of whom would require NICU admission. Of the remaining 944 singletons, there would be 86 NICU admissions. Therefore in this second estimate, 142 infants or 13.4% would need NICU admission.

We then used the Canadian Assisted Reproduction Technologies Register 2005 results to extrapolate our findings to the entire country. We assumed that all infants <34 weeks and 60% of late preterm infants would be admitted to a level 2 or 3 NICU. We assumed that the adverse outcomes in infants conceived with ART admitted to NICUs across the country would be equivalent to our local results.[9]

Extremely preterm infants, <29 weeks gestation, have increased complications of prematurity and usually make up approximately one-third of very preterm infants; however, in our sample, closer to 50% of the very preterm infants were extremely preterm. We are not the only ones to have shown this skewed distribution of gestational ages after ART,[10,11] but we wished to be conservative in our estimates. We therefore made a second Canada-wide estimate by further adjusting our estimates to a distribution similar to the large Australian registry, assuming 41% of the very preterm ART multiples would be extremely preterm.[10] We then used these distributions to estimate the proportion of infants in whom various complications of prematurity would develop by using the incidence of those complications from the Canadian Neonatal Network annual report.

## Results

In 1996, there were 3713 births at RVH. Of these births, 108 infants were from multiple gestations; the average age of the mothers of the multiples was 31.4 years, and 11 of these infants were multiples from an IVF pregnancy. In 2005, there were 3751 mothers who delivered at the RVH. A total of 220 infants were delivered from multiple gestations, and the average age of their mothers was 33.4 years; 46 infants were from IVF multiple pregnancies. The proportion of multiple births and the proportion of multiple births from IVF were significantly different in the 2 periods (both $P < .01$, $\chi^2$).

In the recent 2-year period, there were 82 infants admitted to NICU from 44 ART multiple gestations, representing 17% of all NICU admissions. The total included 4 sets of triplets, all of whom were admitted to the NICU, 30 pairs of twins of whom both were admitted, and 10 twin gestations in which only one infant was admitted to the NICU. Of these 82 infants, there were 75 from IVF pregnancies, including 3 sets of triplets; the remaining infants were the result of ovarian stimulation. None of the IVF multiples originated from single embryo transfer; the number of embryos transferred ranged from 2 to 6 (mean, 3.2).

Of the mothers who gave birth to IVF multiple infants at RVH, 7 had a fetal reduction during the pregnancy and 5 others had spontaneously lost at least 1 fetus. Four of the 44 mothers had previously experienced the death of a preterm baby after NICU admission after an ART pregnancy.

Of the 75 babies admitted after a multiple pregnancy from IVF, 20 were extremely preterm (<29 weeks). There were 6 deaths and 5 severe intraventricular hemorrhages; bronchopulmonary dysplasia developed in 5 infants, and 4 infants

with severe retinopathy of prematurity required retinal surgery.

If a policy of universal single embryo transfer had been followed for these 44 mothers, with a 3% twin frequency we would have admitted 4 preterm twins (and no triplets); we would have had an additional 4 admissions of singletons from IVF mothers, half of whom would have been very preterm. The estimated differences between the interventions actually required by our 75 infants who were IVF multiples and the 8 infants who we would have admitted with a policy of universal single embryo transfer are shown in Table I. With a selective single embryo transfer policy, we would have admitted 8 preterm twins and 4 singletons. Thus, the reduction in morbidities would have been less and are shown in Table I.

Of the mothers, 7% had pre-eclampsia, 9.8% had gestational diabetes, and 72% delivered via cesarean section. Four mothers required a blood transfusion, 3 mothers had a deep vein thrombosis, 3 mother developed cholestasis of pregnancy, and 2 mothers had pulmonary edema associated with magnesium tocolysis.

The Canadian Assisted Reproduction Technologies Register 2005 report[5] notes that there were 1516 liveborn twins, 72% delivered preterm, 665 were late preterm and 312 very preterm. In addition, there were 110 liveborn triplets, 100% were preterm, 23 of whom were late preterm and 87 very preterm. With selective single embryo transfer policy, the twin rate would have been 6%, and the triplet rate would have been 0, thus the current unregulated approach led to an excess of 1200 twins and 110 triplets, and a consequent excess of 730 NICU admissions. We estimate that 182 of the excess preterm deliveries were extremely preterm. The excess adverse outcomes resulting are shown in Table II We also calculated the adverse outcomes avoided with a universal single embryo transfer regimen, allowing no exceptions. For both a selective single embryo transfer and a universal single embryo transfer approach, we calculated the figures assuming that 41%, or alternatively 50%, of the very preterm infants would be extremely preterm (Table II).

**Table I. Estimates of the reduction in morbidities that would be achieved in 2 years at one regional neonatal intensive care unit if universal or greatly increased single embryo transfer were instituted**

| Morbidities Saved | With universal single embryo transfer | Selective single embryo transfer |
|---|---|---|
| NICU admissions | 67 | 63 |
| Retinal examinations | 270 | 253 |
| Patient-days of assisted ventilation | 260 | 244 |
| Patient-days of CPAP | 171 | 160 |
| Patient-days of oxygen | 643 | 604 |
| Patient-days of TPN | 950 | 893 |
| Patient-days of gavage feeding | 2001 | 1881 |
| Patient-days of hospitaliaation | 3082 | 2897 |

*CPAP*, continuous positive airway pressure; *TPN*, total parenteral nutrition.

## Discussion

For the local data, the use of ART was retrieved from the hospital record; it is possible, therefore, that this list is incomplete. In a comparison of our local figures with the database of one local ART center, only one case initially recorded as IVF was actually intra-uterine insemination after ovarian stimulation, and a few other cases of IVF not recorded in the charts were discovered, thus these figures may be an underestimate.

Twins are more likely to be growth restricted and therefore more likely to be admitted to NICU. At extremely low gestational age, twins have an odds of death of 1.29 compared with singletons,[12] and other complications are also significantly increased. We have probably underestimated adverse outcomes for twins by applying the Canadian Neonatal Network data, which are from a mixture of singletons and multiples. The estimates are sensitive to the proportions of infants born at extremely preterm gestational ages; a few infants born at 23 to 25 weeks have a big effect on the results. That is why our second estimate of the Canada-wide effects used a more conservative estimate of this proportion. We also assumed that late preterm infants not admitted to the NICU did not incur additional costs. This is clearly untrue, but was beyond the scope of this study.

Despite all the potential limitations and assumptions inherent in these sorts of calculations, our estimate of the excess neonatal mortality is remarkably similar to an analysis from the United Kingdom that used entirely different methods.[13] From that analysis, when the prevalence of births from ART is 1% and the proportion of ART births that are multiple is 30%, the excess neonatal mortality for the United Kingdom (594 000 annual births) would be 48 infant deaths per year. Applying the same calculations to Canada (350 000 births per year) leads to an estimate of 28 excess deaths as a result of ART multiple embryo transfers, a finding very similar to our estimates.

It is clear that the physicians performing IVF are aware of these risks,[14] but remain willing to perform procedures that increase risks to mothers and babies. We think that there are a number of reasons for this ethically unusual situation. In a society in which the patient pays directly for IVF, there is a perverse economic incentive—for both patients and providers—to increase complications for mothers and their babies. Couples, who spend an average of 25% of the annual family income on a procedure,[15] want to pay for the fewest cycles. The clinics also are pressured to have the highest "success" rates to attract patients. Infertile patients are also often emotionally drained and ready to accept higher risks. Thus to have "two babies for the price of one" is attractive. Even after being adequately informed, as many as 85% of childless women in fertility clinics still want twins.[16] Is it acceptable to continue to transfer multiple embryos because mothers want to have twins? We consider that the medical system sometimes has the responsibility to refuse to offer interventions that increase morbidity when there are equally effective alternatives available, which lead to lower morbidity; especially when the large part of the morbidity is suffered by another individual, in this case, the baby.

**Table II. Estimates of the interventions required and complications experienced for one year across Canada that would be eliminated if we instituted either universal or greatly increased single embryo transfer**

| | Universal selective embryo transfer | | Selective single embryo transfer in 67% (Swedish approach) | |
|---|---|---|---|---|
| Morbidity | Assuming GA distribution and morbidities similar to the RVH results | Assuming 41% extremely preterm among the very preterm and morbidities extrapolated from CNN | Assuming GA distribution and morbidities similar to the RVH results | Assuming 41% extremely preterm among the very preterm and morbidities extrapolated from CNN |
| NICU admissions | 840 | 840 | 729 | 729 |
| Extremely preterm infants (<29 wk) | 209 | 168 | 182 | 148 |
| Very preterm infants (29-31 wk) | 201 | 332 | 180 | 204 |
| Deaths | 40 | 34 | 35 | 30 |
| Serious IVH | 46 | 39 | 40 | 34 |
| NEC | 23 | 21 | 20 | 19 |
| ROP | 24 | 20 | 21 | 17 |
| ROP surgery | 19 | 15 | 16 | 13 |
| BPD | 113 | 103 | 99 | 91 |
| Home O2 | 12 | 10 | 10 | 9 |
| Ventilator patient-days | 7299 | 6161 | 6349 | 5423 |
| CPAP days | 4796 | 4217 | 4187 | 3716 |
| Oxygen days | 6912 | 5919 | 6015 | 5207 |
| Retinal exams | 3022 | N/A | 2626 | N/A |
| TPN days | 10634 | N/A | 9240 | N/A |
| Gavage days | 22398 | N/A | 19462 | N/A |
| NICU days | 42488 | 40253 | 37037 | 35220 |

*GA*, gestational age; *CNN*, Canadian National Network; *IVH*, intraventricular hemorrhage; *NEC*, neonatal necrotizing entereocolitis; *ROP*, retinopathy of prematurity; *BPD*, brochopulmonary dysplasia; *CPAP*, continuous positive airway pressure; *N/A*, data not available from the Canadian Neonatal Network report; *TPN*, total parenteral nutrition.

If reduction in twin pregnancy rates after IVF is to be achieved, concerns about reduced pregnancy rates must be addressed. It is often assumed that pregnancy rates will fall if single embryo transfer is practiced. Recent improvements in technologies have decreased the differential between single and double embryo transfer; nevertheless, universal single embryo transfer would likely lead to some decrease in pregnancy rates. Preparation of a woman for a cycle of IVF is also not without medical impacts and potential complications. Administration of potentially toxic medications to stimulate ovulation, egg retrieval, and implantation of fertilized embryos are all procedures that can have substantial negative impacts on the life of a woman undergoing infertility treatment; affects including pain, discomfort, potential complications, time off work, travel, and disruption to life-style. Therefore most jurisdictions that have restricted multiple embryo transfers do allow double embryo transfers in controlled circumstances; this can lead to acceptable pregnancy rates with very low rates of multiple births, and almost eliminates higher order multiple births. Also, advances in ART[17] mean that a single oocyte retrieval cycle can now produce embryos that can be successfully used for several cycles of single embryo transfer. An individual patient data meta-analysis of the randomized trials comparing single with double embryo transfer confirms that single embryo transfer results in a higher chance of delivering a term singleton live birth compared with double embryo transfer,[18] and further states that "although this strategy yields a lower pregnancy rate than a double embryo transfer in a fresh IVF cycle, this difference is almost completely overcome by an additional frozen single embryo transfer cycle."

Infertility is a serious health problem for which ARTs are proven effective. They therefore should be included in insurance coverage, such as in Canada the coverage mandated by the Canada Health Act. The reimbursement of IVF could then be contingent on strictly enforced and regulated single embryo transfer for most women. The goal should be to reduce the frequency of multiple gestation after ART to be similar to that in the general population, which is approximately 2%. At the very least, it should be reduced to <6%, a rate shown to be achievable in Sweden, which has a legally enforced single embryo transfer protocol, allowing for strictly defined exceptions. The exceptions are generally for the age of the mother for whom a double embryo transfer can be considered and the quality of the embryos. The proportion of older mothers undergoing IVF in Sweden (14.4% are >40 years)[8] is very similar to the proportion in Canada (16%), so the Swedish success in limiting multiple IVF gestations could certainly be extrapolated to our population, without compromising overall success. They achieve an overall proportion of deliveries per cycle of 21.9% compared with a Canadian total of 23.9%. A discussion of the impact of embryo quality is beyond the scope of this article, but better, more objective, techniques for assessing the viability of embryos are developing, and evaluation of the quality of the embryos is clearly important in decision-making about regulations for single embryo transfer.

The consequences of reimbursing and at the same time regulating IVF may be a temporary increase in the numbers of women who desire IVF, among those for whom it is currently too expensive. In addition, IVF would probably be commenced at an earlier age. This would have two advantages: it would bypass procedures of limited efficacy such as tubal surgery resulting in savings and would improve IVF success rates. Finally, a mandatory policy on single embryo

transfer would dramatically reduce NICU use; at an estimated daily cost of NICU of roughly $1000,[19] we can estimate annual Canada-wide cost savings of approximately $40 million.

This cost offsetting is not just theoretical, 2 randomized trials of single embryo transfer have compared a protocol of 2 successive attempts at single with one double embryo transfer.[20,21] Both demonstrated that live birth rate was identical, but that twins and prematurity were substantially greater in the double embryo transfer arms. A cost benefit analysis of one of those trials confirmed that costs were increased by €4000 per woman by double embryo transfer. [21] Another "real world" study comparing single with double embryo transfer showed no difference in the live birth rate (37.4% and 36.6%, respectively) but a substantial reduction in twins (0% versus 30.8%) and an additional cost of each double embryo transfer of about 4000 Euros. [22]

Many complications of pregnancy are more common with multiple gestation. Because we only reviewed data for mothers who had at least one infant in the NICU, we cannot make an overall estimate for women who had multiple gestations and delivered at the RVH or extrapolate the figures across Canada.

In conclusion, we have demonstrated that the impact of multiple births from unregulated ART is substantial, causing 17% of our NICU admissions and leading to enormous unacceptable human, emotional and financial costs.[23] The estimated costs across Canada and other countries in the developed world are of such magnitude that our governments must take a responsible approach to stop the ongoing epidemic of iatrogenic multiple pregnancies.

Since July 2010 the government of Quebec has reimbursed IVF procedures with restrictions of the numbers of embryos transferred. Preliminary results from this program show a frequency of twin gestations of only 3.8%. ■

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# Virtual Mentor
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**POLICY FORUM 2**
**Jumping to Premature Conclusions**
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In the United States, one in eight babies is born prematurely, accounting for more than 500,000 births each year. Before the 1970s, babies that were even mildly premature often died, but recent scientific developments have led to a decrease in their mortality. Contemporary with the birth of the neonatology field was the birth of modern bioethics. Ethical questions posed as a result of improved treatment of prematurity have been numerous—one prominent concern being the tiny baby at the "limits of viability." To assume that extreme prematurity is the main ethical problem in neonatology, however, is to jump to premature conclusions. The large majority of preterm infants are between 32 and 36 weeks' gestation, and these "late preterm" births impose the largest emotional and financial burdens on families and society.

This article will discuss prematurity, the recent technological advances that led to increased neonatal survival, and the complexity of decision making for treatment of these infants. I will focus on a neglected ethical issue of great importance: the rising number of premature births. As a consequence of lax governmental investment in the prevention of preterm birth, society, babies, and families continue to pay more every year—financially, physically and emotionally—for avoidable burdens of prematurity.

Neonatology is a recent subspecialty of pediatrics that focuses on the medical care of newborn infants who require intensive monitoring and treatment. The majority of patients in neonatal intensive care units (NICUs) are born prematurely. A normal gestation lasts 40 weeks after the mother's last menstrual period, and prematurity is defined as a gestation lasting fewer than 37 weeks. In 1963, Patrick Bouvier Kennedy, son of the late President John F. Kennedy, was born at a gestational age of 35 weeks and died 2 days later. At that time, to be born 5 weeks early was a substantial risk. Three recent developments in neonatology—respirators, antenatal corticosteroids, and surfactant replacement therapy—have given babies born at 35 weeks' gestation mortality rates only slightly higher than those of full-term infants.

Babies born in the last 20 years are more likely to survive and less apt to develop a disability than those at the same gestational age born before 1980. Even so, the number of premature babies with disabilities or significant morbidity as a result of prematurity has remained relatively unchanged because, even though a lower percentage of survivors have impairments, more babies survive. And prematurity rates are continuing to rise. Although all developed countries have rising rates of preterm births, the United States retains the highest rate among industrialized countries with 12.5 percent in 2004 [1], and most of these preterm babies in NICUs are late preterm, with gestational ages

between 32 and 36 weeks. Babies that are extremely preterm, with a gestation of fewer than 28 weeks or a weight of less than 1,000 grams (also called extremely low-birth-weight babies), comprise 0.8 percent of all deliveries and about 10 percent of NICU admissions. Currently, infants weighing 1,000 grams or born at 27 weeks' gestation have an approximately 90 percent chance of survival, with the majority having normal neurological development [2].

The earlier in its gestation that a baby is delivered, the greater the risks of complications, mainly developmental delay, cerebral palsy, chronic pulmonary disease, learning disability, hyperactivity, and, much less frequently, deafness and blindness. Babies of less than 26 weeks' gestation, as noted, form a minority of babies in the NICU. Of the survivors, about half are without disability at 3 years of age, and 25 percent have a major impairment such as cerebral palsy (10 percent), blindness (2 to 5 percent), deafness (2 to 5 percent), and developmental delay. These are the babies that make the headlines in newspapers and receive much attention from bioethicists regarding the decision-making dilemmas they pose.

The questions are of three main types: (1) whether to intervene medically, (2) whether a medical intervention should be stopped once it has started, and (3) who should be primarily responsible for these decisions and how. The decisions are critical; failure to provide the medical care in question often leads to death, whereas intervening often brings a chance of survival, either with or without serious impairments. Dilemmas arise on a case-by-case basis, raising one of the most profound questions regarding human life: which life with disability is worse than death?

Thankfully decision making for the majority of preterm infants is much simpler; more than 80 percent of NICU preterm admissions are babies born after 30 weeks' gestational age. Mortality in these babies is extremely low, and individual outcomes are generally excellent. On a population basis, however, the implications of the large numbers of late preterm infants are more important. About 10 percent of babies are born late preterm in the United States, and the frequency of long-term disabilities such as cerebral palsy, although low, is higher in these babies than in those born at term. More babies with disabilities originate each year from this group of patients than from extremely preterm or full-term infants. Half the patients in cerebral palsy registries were not admitted to a NICU at birth. For the remaining half, most were of a gestation greater than 28 weeks at birth. In general, there would be no ethical question about whether to admit these babies to the NICU. In order to substantially decrease disability rates from late prematurity in the population and the NICU costs, one would have to let patients of 28 to 36 weeks' gestation die, which would of course be morally unacceptable.

**Preventing Prematurity**

A major issue in neonatal ethics is how to prevent babies from being born preterm in the first place. Because of advances in obstetric surveillance, the number of medically induced preterm births for fetal or maternal reasons has grown,

accompanied by a decrease in the stillbirth rate. About 25 percent of preterm deliveries are medically induced because of risk to the fetus or mother [3]. Limiting this source of prematurity may be neither feasible nor desirable.

Today, multiple pregnancies (twins, triplets, or more) and delayed childbearing account for a significant, and potentially reducible portion in the rate of prematurity. The substantial increase in multiple births over the last 2 decades [1, 4, 5, 6] is attributable, in large part, to artificial reproductive technologies (ART). Multiple gestations can occur following ovarian stimulation or when more than one embryo is transferred during in vitro fertilization (IVF). In the United States, 32 percent of live births following IVF are multiple pregnancies. Multiple births increase the risks of fetal, maternal, and neonatal morbidities. Fifty percent of twins and more than 90 percent of triplets are born preterm and admitted to the NICU.

Also contributing to growing numbers of preterm babies is the fact that the average maternal age is increasing; women who deliver after 40 years of age have a greater than 16 percent risk of delivering preterm [1]. As women age, their fertility declines and more employ ART to get pregnant, which places them at even greater risk for premature delivery because now they may have twins or triplets.

Given these biological realities and their consequences for newborns, our society should inform women about the risks of delayed child bearing and encourage them to have children earlier. On average, women in their early twenties have fewer financial resources than those over 35. When a woman decides to have children in early adulthood, does the government provide generous maternity leave, social and economic support for their education, and subsidized, universal childcare services when the child is young? The answer, unfortunately, is no. Society rewards performance, work, and wealth, creating an incentive to delay childbearing. The same women who would receive very limited financial incentives were they to become pregnant at an earlier age when the risks of prematurity were lower end up paying for expensive ART services years later and increasing their risks.

**Conflicts between Goals of ART and Best Interest of Newborns**

Infertility is a health problem that ART can help treat. There are some alternatives to ART, mainly adoption (local and international) and surrogacy, but these alternatives can be complicated and costly, and are unacceptable to some. ART services are neither reimbursed nor regulated by the Canadian and U.S. governments, which creates discrimination in access to treatment due to the cost of services. Physicians who provide ART are vulnerable to conflicts of interest. ARTs are effective—the rate of conception for fertile couples trying to conceive a baby naturally is about 25 percent per cycle. Some IVF providers, on the other hand, state a success rate per cycle as high as 60 percent [7]. This efficacy comes with a cost: an epidemic of multiple births created by physicians and governments that oftentimes produces complications for babies, their families, and society.

Infertile couples are emotionally vulnerable, which can mean they are willing to take greater health risks to acquire a baby. Because patients pay per cycle of IVF, a "two- or three-for-one" deal is an appealing alternative. But having twins is a lottery; 50 percent of IVF twins are preterm, some extremely preterm. It is also a gamble for women, inasmuch as every risk associated with pregnancy increases when a woman carries more than one fetus. In one study, despite being adequately informed of the risks, patients in fertility clinics still wanted twins: 85 percent of childless women in one study had the goal of getting pregnant with twins [8]. In fertility literature, success of a cycle of infertility treatment is counted as a live birth after 20 weeks' gestation. By implanting more than one embryo and impregnating patients with fewer treatment cycles, the success rate of a fertility clinic improves, which attracts more clients and improves financial competitiveness: multiple pregnancies can therefore also be seen as beneficial for the fertility physician. These conflicts of interest are largely responsible for the tremendous increase in multiple pregnancies in the United States and Canada. Hence, in a society where the patient pays for IVF, there is a perverse economic incentive for both patients and physicians to increase the risk of complications for mothers and disabilities in babies.

While the ethics hot topics in the reproductive world are pre-implantation genetic diagnosis, selection of various performance genes, and pregnancy in woman over 60, the numbers involved in those endeavors are very small, or even theoretical. In contrast, we calculated that 17 percent of NICU admissions were multiple gestations following ART [9]. Most of these could have been avoided by rigorously controlling the clinical practices relating to the treatment of infertility. It's easy to envision a public policy to decrease multiple births. Unlike Canada and the United States, some countries—Sweden, Belgium, Finland, and Denmark, for example—regulate and reimburse ART services. In these countries, single-embryo transfer during IVF is the norm. Where financial conflicts of interest related to ART are avoided, patients and physicians seem far less willing to take the unnecessary risk of multiple births in order to become pregnant as quickly as possible. Having children with the least risk for the mother and infant seems to be the morally responsible position.

The cost of IVF treatment goes beyond fees for the procedure itself; it includes the cost of health care to women and their children born from such techniques. Reimbursement for ART should be contingent upon regulating IVF and ovarian stimulation. Exceptions to single-embryo transfer could be considered only for mothers over 38, where the transfer of two embryos can be acceptable to achieve a singleton pregnancy. Medical societies and health-system regulations in the United States and Canada have a moral responsibility to reduce the frequency of multiple gestations following IVF to a level similar to that found in countries where single-embryo transfer is the norm, for example to 6 percent in Sweden (compared to about 32 percent in the United States). Restricting embryo transfers without including reimbursement will likely lead to "reproductive tourism"—women traveling abroad to find unregulated fertility centers where they can continue to have multiple-embryo transfers and hope for multiple gestations with the attendant risks and costs.

Do U.S. hospitals want to decrease NICU stay? While in most areas of pediatrics, frequency and duration of hospitalization have decreased over several years, NICU admissions have gone up mainly because of the increase in prematurity. According to pediatrician and ethicist John Lantos, "NICUs have become the economic engine that keeps children's hospitals running [10]." Lantos adds, "It almost seems as if society, by some mechanism, is working against health to produce more and more low-birth-weight babies, and that medicine is then working against society, desperately trying to patch the wounds caused by some nameless thing that is forcing our babies from the womb too soon [11]." Countries that have made single-embryo transfer the norm have drastically reduced the rate of multiple births without affecting the pregnancy rate. These countries have lower prematurity rates. Why do we see the epidemic of multiple births as an immutable social and political phenomenon when so many countries have demonstrated that this epidemic is controllable? Do our institutions also have conflicts of interest?

Canada and the United States are successful in developing specialists who have the skills to make preterm babies survive with a good prognosis. NICUs are the most efficient and cost-effective ICUs in modern medicine, but they should not be seen as the only solution to prematurity. In my NICU, physicians and our government are responsible for a preventable 17 percent of the admissions and for significant avoidable mortality and morbidity, which produce unacceptable financial and emotional costs [9]..Medical developments have changed the way physicians and society respond to diseases of neonates, to their illnesses, and to the pain and suffering of their parents. We have to question whether we are responding adequately to these new challenges. Rising prematurity rates and the continued unchecked epidemic of multiple births are a sign of political and moral failure.

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# The pediatric consequences of Assisted Reproductive Technologies, with special emphasis on multiple pregnancies

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***Key Words: Neonatology, Assisted reproduction, Prematurity, Congenital Anomalies***

*Abbreviations used. ART: Assisted Reproductive Technologies. IVF: In Vitro Fertilisation. IVM: In Vitro Maturation. ICSI: Intra-Cytoplasmic Sperm Injection. GIFT: Gamete IntraFallopian Transfer. IUI: Intra-Uterine Insemination. NICU: Neonatal Intensive Care Unit. USA: United States of America. UK: United Kingdom.*

## Abstract

Paediatricians will encounter many babies and children who are the result of assisted reproductive technologies. Although in most cases there are no adverse health consequences, ART is associated with some risks which are reviewed in this article.

**Conclusion**: ART has had a major impact on multiple gestation and the incidence of prematurity in many countries. Among singletons there are also increases in prematurity, small for gestational age, congenital anomalies and perinatal mortality.

## Key Notes

- Singleton pregnancies which result from ART have increased risks of prematurity and small for gestational age, largely associated with increased maternal age and a history of infertility, as well as congenital heart disease and other anomalies,
- The major risk of ART is multiple pregnancy and consequent prematurity, which can be dramatically reduced by policies of Single Embryo Transfer with little effect on pregnancy rates, but enormous benefit for the health of the babies that result.

## *Introduction*

The first baby conceived from a fertilisation in vitro, the first "test-tube baby", was born in 1978 in the UK. Since that time techniques have advanced remarkably. Average maternal age has also been increasing in much of the developed world; infertility is much more prevalent as maternal age increases, therefore the demand for ART is increasing in many countries. In Canada, more than 3 percent of births now result from ART, and in Denmark as many as 6%. This demonstrates the high prevalence of infertility; a health problem which distresses many women and couples as well as remarkable success of the techniques. At times pregnancy success rates from ART may even be greater than the success rate of normal sexual relations; current early pregnancy rates for in vitro fertilisation (IVF), for example, range between 25 and 40% per attempt.

However, the manipulation of human gametes and embryos carries risks. Risks of pregnancy and childbirth are increased in women who present to infertility clinics, even if they become pregnant spontaneously; advanced maternal age, and reduced fertility being risk factors for several pregnancy complications, congenital anomalies, and neonatal complications. Prematurity and multiple gestation have been increasing over the developed world in recent years, much of the increase being due to ART. This combination of increased prevalence of infertility, increased risks among subfertile women, increased success of ART and increased prematurity and multiple birth leads to an increasing proportion of the infants seen by pediatricians and neonatologists having been conceived after ART. This article will review the techniques used, the complications of those techniques, and discuss strategies to reduce the adverse impacts of ART, while retaining the enormous benefits to infertile couples.

## *Techniques Used.*

### Ovarian stimulation

Gonadotropin medications, or clomiphene which increases endogenous gonadotropin production, are used to stimulate the maturation of ova. The medications used may lead to the development of more than one ovarian follicle, leading to multiple pregnancies, the frequency of which is 6 to 13% with clomiphene and up to 30% with gonadotropins(1). In most jurisdictions there are no restrictions on who is allowed to prescribe these medications. Appropriate use of ovarian stimulation requires monitoring the response in terms of the number of follicles that develop and counselling a couple against attempting pregnancy if the number is elevated, However, as shown by the occasional occurrence of extreme multiple pregnancy, quintuplets and more, (usually due to ovarian stimulation, but not always) it is clear that sometimes these procedures are not followed, and/or couples seeking pregnancy do not always follow this advice. Ovarian stimulation may be accompanied by intrauterine insemination (IUI) where ejaculated or aspirated semen is directly injected across the cervix into the uterine cavity.

The other services we discuss are in contrast offered uniquely in fertility clinics and are not reimbursed by any of the Canadian provincial health care plans except for Quebec; most American insurers also do not reimburse advanced ART, although in a few states legislation requires some coverage. The situation varies greatly around the world, with Belgium, for example, recently covering advanced ART under its national health plan, while Denmark, which previously covered much ART, cut the funding severely in 2010. Many other countries have partial or limited funding of ART, and some provide no coverage. This situation is somewhat paradoxical as techniques such as fallopian tube surgery, which has a much lower

success rate than advanced ART, are commonly reimbursed by both private and public health care systems/insurers.

A cycle of in vitro fertilisation (IVF), therefore, is expensive to the patient. An international evaluation of costs in 2002(2) showed that costs per live birth after IVF were on average $US54,000 in the US and $US22000 in non-US countries with a range from $15,617 to $30,618. When expressed as a proportion of family income IVF cost from around 10% of mean annual family income in some lower-cost European countries to as much as 25% in the USA and Canada. An article from Holland based on 2004 costs(3) reported somewhat lower costs of around 2500 Euros per cycle, and 10,500 Euros per ongoing pregnancy, which although less expensive remains a substantial burden for many. Some private clinics may have "special offers" such as $5,000 for one cycle but $12,000 for three cycles, with no refund if success is achieved on the first cycle.

## In Vitro Fertilisation (IVF)

Ovulation is induced by medication, usually gonadotropins, and follicles are needle-aspirated using ultrasound guidance. In the laboratory the ova are prepared for fertilisation and incubated with ejaculated or aspirated spermatozoa in a culture medium. Successfully fertilised ova undergo 1 to 3 days of incubation in vitro after which they are examined to determine 'quality' and evidence of obvious abnormal development prior to being transferred to the uterine cavity. Most commonly the embryo is transferred back to the mother at the 6 to 8 cell stage (a 'cleavage' embryo). Often multiple embryos are created, and decisions must be taken afterwards on the number of embryos to be transferred as opposed to being destroyed or frozen. Clearly the transfer of more than one embryo increases the risk of multiple pregnancy. Embryos which are of 'poor quality' are less likely to successfully develop, the fertility specialist may transfer more embryos if they are of poor quality.

## Blastocyst transfer

In this method of performing IVF, embryos are transferred a little later, after 5-6 days of incubation, at the blastocyst stage; the likelihood of a successful pregnancy is increased if embryos are transferred at the blastocyst stage.

## Intra-cytoplasmic sperm injection, ICSI

ICSI is performed in cases of low spermatozoid motility or numbers as an add-on to IVF. Sperm are obtained by needle aspiration from the epidydimis. In-vitro a spermatozoid is injected directly into the ovum, followed by incubation and then transfer of the embryo (or embryos).

## Assisted Hatching

Assisted hatching involves artificially breaching or thinning of the Zona Pellucida and may improve implantation and pregnancy rates following in vitro fertilization (IVF).

## IVM

In vitro maturation is a newer technique, not available in all centers, where follicles are harvested at a specific stage of their development, without ovarian stimulation, and matured in vitro until a mature oocyte develops, the oocyte is then fertilised. This avoidance of ovarian stimulation is particularly useful in patients at high risk of ovarian hyperstimulation syndrome such as women with polycystic ovary syndrome(4). It may also avoid the expense of gonadotropin medication, which is a substantial part of the costs of IVF. However, the follicular environment is important for the production of a normally developed oocyte, as illustrated by the frequent occurrence of errors during meiosis. Thus further evaluation of the clinical outcomes of IVM is critical prior to more widespread application.

## GIFT

Gamete intra-fallopian transfer is a technique where harvested ova are introduced into the fallopian tubes along with semen. It has become uncommon with the improved success of IVF.

Following IVF, ICSI, and IVM embryo transfer and after GIFT, ultrasound is performed to determine whether the embryos have implanted and are starting to develop.

## Donor gametes.

The use of donor sperm or ova can be combined with most of the above techniques. If donated ova are used, usually the age of the donor will be less than the woman who is undergoing the technique, as donor ova are more often used for older women. Using ova from a younger donor substantially improves success rates for women over 35, and success rates similar to those of younger women can be achieved even into the woman's 40's. The risk of aneuploidy is obviously related to the age of the woman who supplies the ovum, not the age of the woman whose uterus receives the embryo; the technique may also be used when there is a risk of other genetic diseases, or in cases where harvesting of maternal ova is unsuccessful. The uncertainty about the genetic heritage of a patient may have clinical pediatric implications.

## Embryo freezing.

Embryos which are created in vitro but not transferred can be frozen for later transfer in future cycles. Newer techniques such as vitrification have substantially increased the viability of frozen embryos,(5) allowing an increase in pregnancy success with embryos created from a single episode of ova harvesting. In some countries (such as Italy) embryo freezing is not permitted, disposal of the embryos may also not

be permitted and all the embryos created must be transferred.(6) In other countries there are time limits to how long embryos can be retained, after which they are disposed of.

### Surrogacy.

An embryo created in vitro is transferred into the uterus of another woman, usually unrelated. In some situations the embryo may also be the result of gamete donation, leading to situations where none of the individuals initiating the procedure, nor the mother carrying the fetus, are genetically related to the fetus.

### Ovarian transplantation.

Recent advances mean that autologous or even donor ovarian tissue can be successfully transplanted. Autologous transplantation may be especially useful if ovarian tissue is harvested prior to potentially sterilizing forms of chemotherapy, for example. Donor transplantation may become a technique to be considered for early ovarian failure, (premature menopause).

## *Complications of ART*

### Multiple pregnancy

Ovarian stimulation and in vitro techniques carry a risk of multiple pregnancy. Frequently, more than one embryo is transferred in either IVF/ICSI or IVM; although this should only occur after informed consent with regard to the risks of multiple pregnancy and the consequent prematurity risk. It is in fact not rare that three or more embryos may be implanted, the latest report from the European Registry (ESHRE) of data from 2008 shows that in 22% of cycles there were 3 embryos transferred, and, in 2%, 4 or more(7); although this varies between countries with many reporting no cases of transfer of 4 or more; some also limit the transfer of 3 embryos, Sweden reported 0 transfers of 3 embryos and Norway

and Finland reported less than 1%. Other countries with a high volume of procedures (more than 5000 transfers per year) had between 5% (UK) or 6% (Denmark) of procedures being 3 embryo transfers of more, to as high as 20% (Germany and Russia). Turkey and Italy were outliers among high volume countries, both have about 50% of transfers being 3 embryos, Turkey also having the largest proportion among high volume countries of 4 or more embryos being transferred (10%); in contrast in Italy, as noted above the law regulating IVF mandates that all embryos created are transferred(6), but limits the creation of embryos to 3, therefore there are no transfers of 4 embryos. Not surprisingly Italy and Turkey had the highest proportions of triplets for high volume countries, 5% of deliveries being triplets in Turkey. In Australia in 2010(8) only 0.8% of transfers were 3 or more, and 30% were 2 embryos. In the US in contrast the latest report from the Centers for Disease Control (CDC)/Society for Assisted Reproduction Technologies showed that in 23.4% of IVF cycles there was transfer of 3, 7.8% transfer of 4, 2.5% transfer of 5 and 1.2% transfer of 6 or more embryos. Only 5% of procedures were elective single embryo transfer (that is transferring just 1 embryo when more than 1 embryo is available).

The frequency of multiple deliveries closely follows the numbers of embryos transferred, In Australia, the incidence of multiple deliveries in 2010 was 7.9%, only 0.1% being triplets or more; whereas in the USA the incidence remains at about 30%. Figure 1.

The only way to avoid multiple pregnancy with in vitro techniques is to transfer a single embryo. However, this does not prevent 100% of twins, as infrequently mono-zygotic twinning can occur after single embryo transfer (SET) with an incidence of 2 to3%, about double the frequency of mono-zygotic twinning in spontaneous pregnancies.

The lack of regulation of multiple embryo transfer in many parts of the world has led to an epidemic of multiple pregnancies and consequent prematurity over the past several years(9). The report of the 2005

data from the Canadian ART registry(10) noted that 30% of deliveries resulting from IVF/ICSI were twins and 2.7% were triplets or quadruplets a dramatic increase over the natural frequency of twinning of about 1:60 pregnancies. The most recent published report, of 2007 data, shows a reduction in triplets or more, to about 1%, but a twinning frequency which has not changed at 29%. This is very similar to the lack of improvement in the USA; in 2009 about 29% of all IVF cycles which resulted in live births were twins and 1.6% were triplets(11).

The increase in multiple pregnancies is a major risk factor for prematurity; and a consequent increased risk for mothers and for babies. Over the last decades, the incidence of twins has increased by 30 to 40 percent, and triplets and higher order pregnancies by 300 to 400 percent; these increases appear to be almost entirely due to ART(12). This is one of the factors leading to an overall increase in the rate of premature delivery in the USA, Canada, and around the developed world. Seventy percent of perinatal mortality and morbidity are directly tied to premature birth(13).

Among twin pregnancies, the gestational age at birth is lower for those conceived by IVF than for spontaneous twins.(14, 15) This may be in part because of a higher proportion of IVF mothers being primigravid, as primigravidae carrying twins deliver earlier in gestation than multigravidae, even among spontaneous pregnancies.

## Maternal Complications

Maternal complications are increased during multiple pregnancies. The elevated maternal risk for mothers with multiple pregnancy is probably the same in IVF multiple pregnancies compared to spontaneous multiple pregnancies when maternal age and history of subfertility are taken into account. The relevant risks include an increased frequency of antepartum and postpartum hemorrhage leading to a requirement for transfusion; and increases in gestational diabetes, the frequency of instrumented delivery, pre-eclampsia and eclampsia, caesarean section, maternal mental ill health such as depression,

and even of divorce and maternal mortality. In addition, among mothers who deliver prematurely in association with a multiple pregnancy, having chosen to implant more than one embryo, many experience acute guilt feelings.

## Selective Fetal Reduction

The successful achievement of a pregnancy that is complicated by multiple delivery may lead to a consideration of selective fetal reduction by the family in order to reduce the fetal numbers to two or three (or sometimes to one), to improve the likelihood of delivery closer to term(16). Fetal reduction entails a risk of approximately five percent of losing the entire pregnancy, and therefore the parents have to decide whether or not to eliminate one of the fetuses that they have conceived, sometimes after many years of attempted fertility treatments, and by doing so, put the entire pregnancy at risk(17). This is an intolerable decision for many families, many of whom, even having considered the statistical increase and the likelihood of having a healthy baby after selective reduction, choose not to undergo this procedure with the hope that their pregnancy is going to be one of those that goes near to term. More than seventy percent of women have significant grieving after fetal reduction, and more than sixty-five percent experience feelings of guilt and depression(18), which may well last beyond the delivery of the remaining healthy child, or children. Performance of fetal reduction is extremely variable around the world, overall about 2% of pregnancies from IVF in Europe underwent a fetal reduction, with many countries reporting zero procedures(7), in Canada it is about 0.5%(19), in the USA the CDC do not obtain data for fetal reductions.

## Fetal Complications

Fetal complications from multiple pregnancy are numerous. Although, as mentioned, there is an augmentation of monozygotic twinning after IVF, the large majority of twins and triplets after assisted

reproduction are dizygotic and trizygotic, therefore complications which usually occur in mono-zygotic twins, such as twin-to-twin transfusion, are quite uncommon. Overall, monozygotic twins have a higher perinatal mortality than dizygotic twins. This explains the apparent paradox that for the same gestational age in twins born after in-vitro fertilization there appears to be a slightly lower mortality and some lower morbidities, than twins born after spontaneous pregnancy. However, if only dizygotic twins are considered the mortality and morbidities are similar and as there is overall a dramatically higher incidence of multiple gestation there is increased perinatal mortality among infants from IVF compared to those from spontaneous pregnancy. Other twin complications, such as intrauterine growth restriction of one of the twins, occur in both di- and mono-zygotic twins and are present among twins from assisted reproduction(20). Congenital malformations are more frequent among dizygotic twins than singletons, but rather more so in mono-zygotic twins. This explains another paradox of the literature on complications after advanced ART, that congenital anomalies are significantly increased among singletons after advanced ART but not among twins(21). Correcting for zygosity is very difficult in large database or epidemiologic studies, but it is probable that congenital anomalies are increased among dizygotic twins after ART if compared to dizygotic spontaneously conceived twins.

## Neonatal and Pediatric Complications

Multiple pregnancies significantly increase the risk of prematurity. Seven percent of women carrying a singleton fetus deliver prematurely before 37 weeks; for twins the frequency is 50 percent, and for triplets 90 percent. The incidence of more serious prematurity, that is, being born before 32 weeks is 1.1 percent for singletons in general, 8 to 14 percent amongst twins and 28 to 41 percent amongst triplets(22). As well as gestation, birth weight is obviously also lower amongst twins and triplets. Two percent of singletons weigh less than 2.5 kilograms at delivery, in contrast, 30 to 50 percent of twins and

92 percent of triplets weigh less than 2.5 kilos and 24 to 31 percent of triplets weigh less than 1.5 kilos at birth(23).

Although the majority of infants admitted to neonatal units survive and have good long-term outcomes, the frequency of mortality and long-term sequelae are much greater than among infants born at term. The incidence of cerebral palsy for example is approximately four percent amongst ex-premature infants who were born at < 28 weeks, compared to 0.2 percent among full term infants. Cerebral palsy is four times more frequent amongst twins and 40 times more frequent amongst triplets than among singletons, an increase which is almost entirely due to prematurity. In fact, at least one impaired child occurs amongst 7.5 percent of twin pairs, 21.6 percent of triplets and 50 percent of quadruplets. Caring for one impaired child is difficult enough, but caring for one impaired child with one or more siblings of the same age, who may also be impaired, is extremely stressful for any family.

## Quantifying the epidemic of prematurity and the associated costs

Obstetrical costs are 2.1, 4.5 and 7 times higher for twins, triplets and quadruplets compared to singletons. Premature delivery has a significant impact upon total societal costs: during the first five years of life, low birth weight infants in general cost 17 times more in medical costs than an infant of normal birth weight. We estimate the costs to the health care systems of Canada have been greater than sixty million dollars per year solely in increased NICU costs because of the increase in prematurity among assisted reproductive technologies.(22) Currently, as many as twenty percent of the babies admitted to neonatal intensive care units in some countries are there because of prematurity and its complications related to assisted reproductive technologies.(22)

## Adverse Pregnancy Outcomes among Singletons

After ART, the risks for singletons are increased for the following outcomes, prematurity, low birth weight, very low birth weight, neonatal and perinatal mortality, and small for gestational age, with Odds Ratios between 1.6 and 2.2.(24) The increased risk for prematurity occurs after IVF and also after ovarian stimulation.(25) Some of these risks may be related to maternal age and a past history of subfertility, but there is some debate as to whether a residual increase in risk remains after correcting for these factors, i.e. due to some effect of the procedures themselves. Several meta-analyses have confirmed that the increase in preterm delivery and being small for gestational age persists after correcting for maternal age and parity(26) one study, that further correcting for a history of subfertility ,showed that the differences disappeared, while another has shown persistent differences with increased risks in the ART group(26).

Whatever the causes, it is clear that singelton infants conceived after ART are more likely to be low birthweight, very low birth weight, to be admitted to NICU, and that perinatal mortality is increased, compared to population frequencies of these outcomes.

## Congenital malformations

Systematic reviews have shown an increased risk of congenital malformations among infants conceived after IVF. The Odds ratio varies depending on definitions, on how malformations are divided into minor and major malformations, and which articles are included in the meta-analysis. The most complete systematic review showed an Odds Ratio of 2.0 for major birth defects and an Odds Ratio of 1.30 for all birth defects combined, compared to control groups that were either matched for baseline characteristics or statistically adjusted for them(27). A recent large database study from Australia, published after that systematic review(21), found that adjusted Odds Ratios for all congenital anomalies was 1.25 compared to spontaneous conceptions, and documented that the overall incidence increased

from 5.2% to 7.4%. That study showed the most consistent effect on cardiovascular abnormalities, the incidence increasing from 1.2% to 1.8% with assisted conception, and also suggested that the majority of the increase in risk was associated with ICSI. Another large recent case-control study(28) confirmed a significant association of IVF with cardiac defects, and also specifically identified trachea-esophageal fistula (adjusted OR 4.5), anorectal atresia (adjusted OR 3.7) and cleft lip with or without cleft palate (adjusted OR 2.4) as being increased among infants conceived with advanced ART. ICSI also appears to carry a specific significantly increased risk for genitourinary malformation among male offspring, most commonly hypospadias(29), and possibly also, in both sexes, of chromosomal rearrangements.(30)

## Paternity and Maternity

Among infants conceived by ART with gamete donation the genetic heritage of the infant is uncertain. The situation may be complicated because couples often continue unprotected intercourse after IUI with donor sperm or after the transfer of embryos with donor gametes. Spontaneous pregnancy during such procedures is possible, making evaluation of genetic risks even more complicated. In the past many jurisdictions allowed donors to be anonymous, although this practice is changing, tracing donors is often a long and somewhat complex process, and investigating their genetic background may be impossible.

## Long-term Outcomes

A few studies of long term development, intellectual and motor outcomes among infants conceived by ART have been performed. Many have either excluded preterm infants(31), or corrected the analysis for the GA of the infants. Such studies are useful for investigating whether ART has a direct effect on these outcomes which is independent of prematurity, but can not determine the overall impact of ART on the family or on the community. In general, there do not appear to be major direct independent effects of ART on neurodevelopmental outcomes(32), however, as the number of preterm, and extremely preterm

infants is increased (particularly, as we have mentioned, among twins) the developmental outcome of the entire cohort of ART infants is less optimal than spontaneously conceived babies(33).

One recent study has shown an increase in cerebral palsy among singletons from advanced ART compared to spontaneously conceived infants (21). That study did not correct for gestational age at birth, so it may be that the OR of 2.22 after adjustment for several other risk factors was due to the increase in prematurity among singleton preterm infants (the increase in CP is well demonstrated even among the late preterm). This interpretation is confirmed by a high quality recent population based cohort study which found that the increased risk of cerebral palsy disappeared after adjusting for multiplicity and prematurity(34). Similarly epilepsy is more common among children conceived by ART, this also appears to be partly due to increased preterm delivery, but there was a persistent significant increase in risk among IVF infants delivered at term.(35)

In summary, neurological and developmental outcomes of singleton infants are more frequently problematic that infants conceived naturally, most, but not all of this effect is due to increased prematurity, and most of the remaining effect is due to other maternal characteristics which differ between groups. Whatever the cause of these findings, the population incidence of neuro-developmental disorders is increased by ART, even though the majority of infants do well.

## Reproductive tourism

Health law varies around the world. In Canada for example it is no longer permitted to pay an individual for their gametes, nor is payment for surrogacy allowed (although in both cases re-imbursement of expenses is possible). On occasion this will lead to a couple travelling to another jurisdiction, which may be another state, another country or even another continent, to find the services that they wish to have. In the UK where the number of embryos that can be transferred is controlled, there are physicians who

have an IVF clinic in the UK and also a subsidiary in another country with different regulations; couples may be referred to those subsidiaries if they wish to avoid the UK restrictions.

Surrogate mothers are allowed to receive compensation in some countries, the travel to India to find a paid surrogate mother, when the search for a volunteer in the home country has failed, is not unknown.

Such reproductive tourism allows couples to avoid the restrictions placed on embryo transfers for example, but they will often return home to deliver, and their home country is then faced with the increased medical and societal costs of their multiple deliveries.

## *Discussion*

This review of the most common techniques of assisted reproductive technologies has demonstrated that they are effective and largely safe. By far the greatest proportion of complications is due to multiple pregnancies, but other pediatric impacts are significant. Many techniques have been introduced and become widespread years before adequate evaluation of the clinical outcomes, in terms of congenital anomalies and neurological or developmental progress. For some techniques only a tiny number of babies have been adequately evaluated(36).

Currently in many countries the financial benefits accrued from advanced ART are earned by private enterprise, however the costs incurred from the implantation of multiple embryos and the epidemic of prematurity (and the comparatively lesser costs of increased congenital anomalies) are borne by the greater public in terms of increased health care costs, lifelong disability, and emotional and financial stress on individual families.

It seems to us that there are two possible solutions: strict regulation of advanced assisted reproductive technologies to prevent the implantation of more than one embryo, with perhaps exceptions under exceptional circumstances as practiced in Sweden, to allow the occasional implantation of two embryos. The only reasonable alternative would be to require all assisted reproductive technology centre practitioners to carry insurance that would cover the excess health care costs associated with preterm delivery of iatrogenic multiple gestations. This would relieve the financial burden on the state of the unfettered practice of advanced assisted reproductive technologies, but would not reduce the emotional hardship of lifelong disability faced by many infants with iatrogenic prematurity. The current laissez-faire approach in most of North America, and in many other places in the world is harming families and children. Has this happened partly because pediatricians have not had a voice in the debate?

## Ethical considerations

Why has this problem reached these epidemic proportions? The majority of women and couples presenting for ART express a desire to have twins. These vulnerable patients have an optimistic view of life after ART; with two healthy twin infants, and a family which matches their dreams. Although the reality may often match this dream, the major increases in risk with multiple pregnancies are not considered realistically, and even when well counselled, and when there is clear understanding of the statistical chances of poor outcomes, there is often a form of magical thinking, that after such difficulty getting pregnant, the "bad outcomes could not happen to us".

There is no ethical compulsion to comply with a request to put our patients' health at risk, nor that of their hoped-for offspring. Just because a woman/couple request a multiple pregnancy, that does not mean that they, and their children to be, should be exposed to the risks. Indeed the implantation of more than one embryo is in conflict with the principle of "Primum Non Nocere". The first principle here

should be the principle of caution, to avoid increasing the health care burden of the patient and her family (and of society as a whole).

## Solutions

The way to prevent almost all multiple pregnancies in IVF and related techniques is the transfer of only a single embryo. Restrictions on multiple-embryo transfers have been instituted in many countries with dramatic benefits for children and families (figure 1). In Finland in 2001, the fertility clinics came to an agreement to adopt the practice of transfer of a single embryo as the practical standard. As a consequence, multiple pregnancies decreased from 24 percent to 8 percent after 2001. In Belgium, the state health care program generally covered assisted reproduction at 75 percent before 2002. From 2002 onwards, the Belgian Society of Physicians in Reproductive Medicine decided that their mission was to reduce the birth of twins by half and to abolish triplets. The strategy adopted was to reimburse six cycles of IVF to infertile women of 42 years of age and less, and two cycles to women of 35 years and less, on the condition that only a single embryo was implanted. This strategy has drastically diminished the frequency of multiple gestations, from 19 percent to 3 percent, without reducing the frequency of successful pregnancy. In Sweden in 2003, legislation was adopted which made obligatory single embryo transfer during IVF. Under exceptional circumstances two embryos may be transferred when rigorously established criteria are met. In one year, SET increased from 25 percent to 71% of IVF procedures, the frequency of successful pregnancy was unchanged and the rate of twin pregnancy decreased from 23 to 6 %.(37) One of the most recent changes is in Turkey, where legislation in 2010 enforces SET for women under 35 with some exceptions for older mothers after 3 cycles of SET. This appears to already have had a measurable effect on NICU admission(38).

Do such regulations not reduce pregnancy rates and unfairly impact on infertile couples? There are two randomized controlled trials comparing the frequency of successful pregnancy and healthy live birth

when a policy of two attempted cycles of single embryo transfer were compared to a single cycle of two embryo transfers(39, 40). These two studies showed no significant difference in the rates of live births, but dramatic decreases in twin pregnancies. A cost analysis of one of these showed that the total cost up to six weeks after birth was identical for the two policies, because of the increased costs associated with twin pregnancies with DET. When lifetime costs of handicaps were added to this analysis, a saving of 7,000 Euros per live birth was calculated(41). An individual patient data meta-analysis of the 8 RCTs comparing SET to DET confirmed the near-total avoidance of multiple delivery, and that very preterm delivery decreased from 6% to less than 1%.(42) Comparing success rates between countries (figure 2) there is no correlation between the proportion of SET and the percentage of transfer cycles that result in delivery of a baby.

## Defining Success

Many ART program advertise their products, in press or on the internet. Such advertisements often cite the program's success rates; such rates may be derived from locally kept data, or from public registries. Unfortunately a 'successful IVF cycle' is defined by confirmation of a viable pregnancy, even if the pregnancy is lost the subsequent week. Even the definition of a live birth usually is determined by delivery of a live born infant after 20 weeks gestation; thus delivery of twins at 23 weeks who subsequently die is counted as a successful live birth. Indeed from publications of the CDC or the Canadian registry, it is not possible to determine how many infants were born at term in good health.

We (and others) propose that the definition of a successful cycle of ART should be the delivery at term of a healthy single infant(43).

## Reimbursement

In Quebec recently (August 2010), the provincial government introduced regulations enforcing SET in a large proportion of pregnancies, and allowing DET in a few others. This occurred simultaneously with re-imbursement of IVF via the provincial health insurance system. This combination has markedly and instantly reduced the numbers of twins resulting from IVF from a frequency which was typical of North America at about 30%(44) to below 5%(45). The reimbursement inhibits reproductive tourism as the costs are covered in Quebec, but would be substantial elsewhere. This illustrates that interventions to control these procedures and improve outcomes need to be co-ordinated, with regulations, funding and collaboration with other jurisdictions all being important.

The benefits of ART to infertile women and their partners could be further increased by research to reduce the adverse consequences among singleton pregnancies. The universal introduction of SET as the default approach to in vitro methods, with transfer of 2 embryos in a strictly limited, small proportion, of cases, would further increase the benefits of ART to the infertile and to their babies.

## *Legends for Figures*

### Figure 1.

Relationship between percentage of IVF/ICSI cycles with fresh non-donor embryos which had 2 or more embryos transferred and the proportion of deliveries that were multiple births

The area of each bubble is proportional to the number of procedures performed. The filled circles are the individual countries within Europe, the countries with the highest and lowest proportions of multiple deliveries are labelled. Overall European, Canadian, USA, Australian and Quebec figures are shown by open circles. European data are from 2008 (7), Canadian data including Quebec are from 2009(44), USA data are from 2009(11), Australian data are from 2010(8). Quebec data are from the 1$^{st}$ 6 months of the provincial program 2010-2011(45).

## Figure 2

Relationship between percentage of IVF/ICSI cycles with fresh non-donor embryos which had 2 or more embryos transferred and the proportion of procedures that resulted in the delivery of at least 1 baby.

The area of each bubble is proportional to the number of procedures performed. The filled circles are the individual countries within Europe, the countries with the highest and lowest proportions of multiple deliveries are labelled. Overall European, Canadian, USA, Australian and Quebec figures are shown by open circles. European data are from 2008 (7), Canadian data including Quebec are from 2009(44), USA data are from 2009(11), Australian data are from 2010(8). Quebec data from the 1st 6 months of the provincial program 2010-2011(45).

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