

## 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.<sup>1</sup> Artificial reproductive technologies (ARTs) have become very successful; however, this success has been accompanied by an epidemic of multiple births.<sup>1,2</sup> 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.<sup>3</sup>

The frequency of prematurity is also increasing,<sup>4</sup> some of which is caused by the increase in multiple gestations.<sup>1</sup> Infertile women are already at a substantially increased risk of preterm delivery with singleton pregnancy (17.3%<sup>5</sup> compared with 7.6%<sup>6</sup>). 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.<sup>5</sup> 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<sup>3</sup> (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.

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

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The authors declare no conflicts of interest

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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).<sup>3</sup> 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<sup>5</sup>). 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<sup>7</sup> 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).<sup>8</sup> 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.<sup>9</sup>

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,<sup>10,11</sup> 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.<sup>10</sup> 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<sup>5</sup> 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**).

## 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,<sup>12</sup> 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.

**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.

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.<sup>13</sup> 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,<sup>14</sup> 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,<sup>15</sup> 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.<sup>16</sup> 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

Morbidity	Universal selective embryo transfer		Selective single embryo transfer in 67% (Swedish approach)	
	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 enterocolitis; ROP, retinopathy of prematurity; BPD, bronchopulmonary 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<sup>17</sup> 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,<sup>18</sup> 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 insur-

ance 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)<sup>8</sup> 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,<sup>19</sup> 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.<sup>20,21</sup> 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.<sup>21</sup> 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.<sup>22</sup>

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.<sup>23</sup> 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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