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

Annie Janvier, MD, PhD, Bridget Spelke, BSc, and Keith J. Barrington, MB, ChB

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;159:409-13)*.

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.

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

From the Department of Pediatrics, University of Montreal, Montreal, Quebec, Canada

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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 $P < .01$, χ^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