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Working to eliminate multiple pregnancies: a success story in Québec

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Abstract In August 2010, the provincial government of Québec, Canada introduced funding of assisted reproduction treatment through the provincial health programme. Alongside this benefit, legislation was introduced to control assisted reproduction treatment activities in the province, including restrictions on the number of embryos that could be transferred in any one cycle. The aim of the programme was to transfer a single embryo in every cycle; multiple embryos could be transferred under suboptimal conditions but required physician justification. In the first 3 months of this programme, 1353 cycles of IVF were performed in five Québec assisted reproduction centres, with an overall clinical pregnancy rate of 32% per embryo transfer and 50% of transfers used elective single-embryo transfer (eSET). The multiple-pregnancy rate was only 3.7% per clinical pregnancy. In 2009, prior to the introduction of the programme, eSET was used in only 1.6% of embryo transfers, resulting in a multiple-pregnancy rate of 25.6%. These data demonstrate that providing provincially funded assisted reproduction treatment created an environment in which the aggressive use of eSET was not only possible, but also rapidly implemented. The result was a dramatic drop in multiple-pregnancy rates, approaching those for natural pregnancies. 

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KEYWORDS: cumulative pregnancy rate, eSET, funding, IVF, multiple pregnancies

Introduction

Huge advances have been seen in IVF success rates over the more-than 30 years that this treatment has been applied

clinically. Improvements in laboratory practices, ovarian stimulation protocols, cryopreservation techniques and genetic aspects of treatment have all served to increase implantation and live-birth rates. However, despite these

advances, one major drawback of IVF has remained constant: the disproportionately high rates of multiple pregnancies, including high-order multiple pregnancies, and the associated risks seen with such outcomes.

In Canada, professionals working in the field of assisted human reproduction meet under the auspices of the Canadian Fertility and Andrology Society (CFAS). For the last 11 years, the CFAS has managed a registry of assisted reproduction cycles performed across the country. Participation in the Canadian ART Register (CARTR) is not mandatory but all Canadian assisted reproduction clinics participate and provide funding for this initiative. The registry allows Canadian clinics to monitor the outcome measures associated with treatment in the country. Although only aggregate data are released to participants and the general public, the CARTR outcome-improvement committee has confidential access to clinic-specific data, permitting them to identify and offer help to clinics whose results fall below the national standard.

Looking at published data from 2005, it is clear that North America has the greatest problem with multiple births from assisted reproduction treatment; Canada and the USA topped the statistics with >30% multiple-birth rates, whereas the lowest rates were seen in countries with state coverage for assisted reproduction treatment, such as Sweden (6%), Australia/New Zealand (14%) and Belgium (13%) ([Assisted Human Reproduction Canada, 2011](#)).

Data from CARTR shows the progression of the multiple-birth rate compared with the live-birth rate in Canada from 2001 to 2008 ([Figure 1](#)) ([Gunby et al., 2010](#)). The live-birth rate has improved gradually over the years, but the multiple-pregnancy rate fluctuates consistently around the 30% rate. Although the use of elective single-embryo transfer (eSET) for assisted reproduction in Canada has been slowly increasing, by 2009 it remained at a very low rate ([Figure 2](#)). The low use of eSET can be attributed to the fact that, when patients are paying for their treatment, the pressure to achieve a pregnancy with as few attempts as possible becomes a driving force for both the patient and treating physician. In the absence of strict guidelines, a

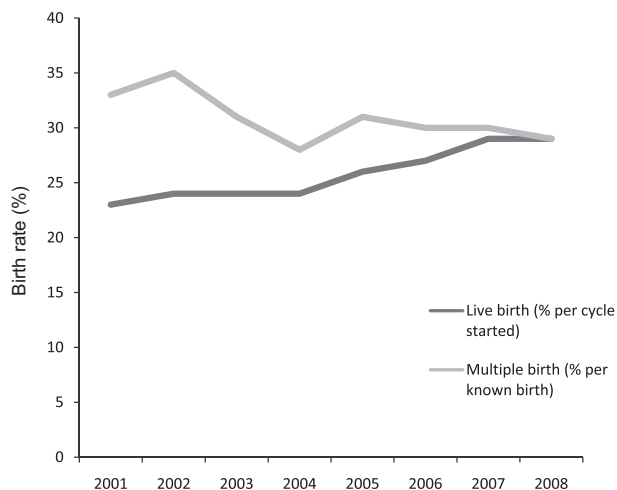


Figure 1 Change in multiple-birth rate compared with live-birth rate in Canada between 2001 and 2008 (data from the Canadian ART Register).

clinic may be tempted to transfer more embryos to improve its pregnancy rate.

Table 1 shows comparative data for 2009 between Québec and the rest of Canada, according to CARTR. It is clear that, although the multiple-pregnancy rate in Québec was slightly lower than the rest of Canada (25.6% versus 29.3%), the use of eSET was more popular in the rest of Canada (6.5% of embryo transfers) than in Québec (1.6%).

A large number of studies have discussed the potential benefits of eSET and the financial issues, comparing ongoing costs associated with multiple pregnancies and repeated IVF cycles due to reduced pregnancy rate when using eSET ([Bromer et al., 2011](#); [Fauque et al., 2010](#); [Gerris, 2009](#); [McLernon et al., 2010](#); [Moustafa et al., 2008](#); [Van Peperstraten et al., 2008](#)).

In Canada, health care is the responsibility of the individual provinces; thus, each province determines healthcare coverage. In Québec, the provincial government decided to include assisted reproduction treatment for infertility under the provincial health plan starting on 5 August 2010. The policy provides for any woman of reproductive age to have to up to three cycles of IVF with ovarian stimulation or up to six cycles of natural or modified natural cycle IVF at no charge; this applies whether the cycles are performed within a hospital unit or a privately owned facility. A cycle counts once an embryo transfer has been performed. Patients who have excess embryos cryopreserved following an IVF cycle are obliged to have those embryos thawed for transfer before embarking on another ovarian stimulation cycle, but frozen–thawed embryo transfers do not count against their three attempts.

In exchange for this coverage, the government imposed a limit on the number of embryos that could be transferred in any one cycle. In effect, the law states that only one embryo should be transferred in either a fresh or frozen IVF cycle. However, an option to transfer up to two embryos in a woman aged 36 years or younger and up to three embryos (including no more than two blastocysts) in a woman aged 37 years or older is available, but the physician must justify his decision ([An Act Respecting Clinical and Research Activities related to Assisted Procreation, 2010](#)).

The purpose of this study is to report on the outcomes (pregnancy rates and multiple-pregnancy rates) of IVF

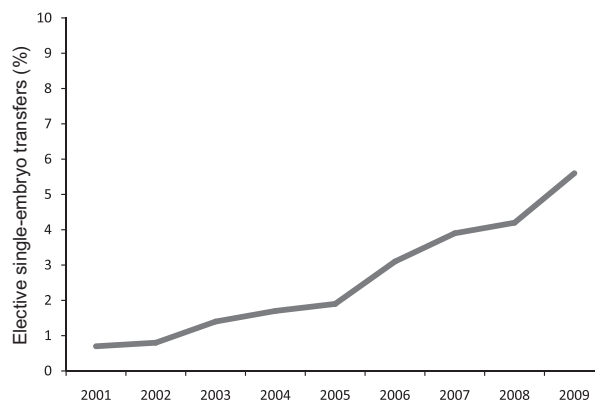


Figure 2 Change in percentage of embryo transfers using elective single-embryo transfer in Canada between 2001 and 2009 (data from the Canadian ART Register).

Table 1 IVF cycle data for Québec and Canada 2009 (from the Canadian ART Register).

Variable	Québec	Canada except Québec	Canada
IVF cycles	1831	8524	10,355
Embryo transfers	1618	7417	9035
Clinical pregnancies (rate per ET)	692 (42.8)	3164 (42.7)	3856 (42.7)
eSET (rate per ET)	26 (1.6)	484 (6.5)	510 (5.6)
Multiple pregnancies (rate per pregnancy)	177 (25.6)	927 (29.3)	1104 (28.6)

Values are *n* or *n* (%). eSET = elective single-embryo transfer; ET = embryo transfer.

cycles in Québec from the first 3 months of provincially funded assisted reproduction treatment.

Materials and methods

All IVF cycles started in Québec assisted reproduction centres from 5 August to 5 November 2010 were recorded. The average patient age was 37 years, with patients ranging from 22 to 46 years old. Each of the five centres applied its own standard protocols for ovarian stimulation and laboratory procedures. Ovarian-stimulation protocols, including long gonadotrophin-releasing hormone (GnRH) agonist, short GnRH agonist and GnRH antagonist, were selected based on physician preference and patient characteristics. Egg retrieval was performed 34.5–36 h after the administration of human chorionic gonadotrophin, based on individual clinic policy. Insemination was performed using standard IVF or intracytoplasmic sperm injection. Embryo culture was performed using Cook Sydney IVF media (Cook, Canada) in all centres.

Embryo transfer was performed in all centres under ultrasound guidance on either day 2, day 3 or at the blastocyst stage depending on cycle-specific characteristics. Two clinics performed the majority of their embryo transfers at the blastocyst stage, one clinic transferred equally on day 2, day 3 and at the blastocyst stage, one clinic performed the majority of their transfers on day 3 and one clinic performed transfers on both day 3 and at the blastocyst stage.

Each clinic applied their own internal policies for embryo quality and selection as well as when it was judged pertinent to transfer more than one embryo. In general, the patient's age and quality of the embryos were primary factors in any decision to transfer multiple embryos as well as previous IVF history. Embryo-quality characteristics were applied when selecting suitable embryos for cryopreservation based on individual clinic protocols. Oocyte and embryo development parameters were strictly applied in order to eliminate embryos with very low potential.

Pregnancy was assessed by serum human chorionic gonadotrophin concentration 15 days after egg retrieval and clinical pregnancy was determined by ultrasonographic evidence of intrauterine fetal heartbeat at 8 weeks' gestation.

Results

From 5 August to 5 November 2010, a total of 1353 IVF cycles were started in Québec centres, 1276 cycles had

egg retrieval and 1103 cycles resulted in embryo transfer. For comparison, only 517 IVF cycles were started in the same time period in 2009.

Overall, the clinical pregnancy rate was 32% and eSET was used in 50% of embryo transfers (Table 2). In the younger patient group (<35 years old), eSET was used in 79% of embryo transfers and resulted in a clinical pregnancy rate of 40%. There were a total of only 13 twin pregnancies and no triplet pregnancies. All twin pregnancies resulted from the transfer of two embryos, either elective double-embryo transfer (eDET) where two embryos were selected from more than two available embryos or non-elective DET where only two embryos were available for transfer. This equates to a multiple-pregnancy rate of 3.7%.

Table 3 describes the outcomes based on the number of embryos transferred, grouped by female age. For all age groups combined, pregnancy rates per embryo transfer were highest with eSET (38%), compared with non-elective SET (21%), eDET (32%), non-elective DET (21%) and transfer of more than two embryos (25%). Twin pregnancy rates were 0% for eSET and non-elective SET, 13% for eDET, 17% for non-elective DET and 0% for transfer of more than two embryos.

Overall, 42% of patients had supplementary embryos cryopreserved following their IVF cycle, with an average of 3.4 embryos per patient. For patients <35 years of age, 60% of patients had cryopreservation, with an average of 3.7 embryos per patient (Table 4).

A summary of the results seen in Québec prior to and after the implementation of the programme can be seen in Table 5.

Discussion

Multiple pregnancies are, undoubtedly, the major negative side effect of assisted reproductive therapies and, in countries where patients are responsible for the total cost of treatment, the multiple-pregnancy rate is often higher. An assumption that the transfer of multiple embryos will substantially increase the chance of pregnancy and, therefore, reduce the number of expensive attempts to achieve the desired live birth, places pressure on patients who, in turn, transfer this pressure to healthcare professionals charged with their reproductive care.

In Québec, the government decided that provincially funded assisted reproduction was the correct direction to take. This policy provides access to treatment for all members of society, regardless of income and resources. In addition, by imposing limitations on the number of embryos that

Table 2 Results from IVF cycles started in the first 3 months of assisted reproduction treatment funding in Québec.

Variable	<35 Years	35–39 Years	≥40 Years	Overall
Cycles started	522	491	340	1353
Egg retrievals	500	458	318	1276
Embryo transfers	443	388	272	1103
Clinical pregnancies (rate per ET)	177 (40)	124 (32)	47 (17)	348 (32)
eSET (rate per ET)	348 (79)	175 (45)	33 (12)	556 (50)
Multiple pregnancies (rate per pregnancy)	2 (1.1)	7 (5.6)	4 (8.5)	13 (3.7)

Values are *n* or *n* (%). eSET = elective single-embryo transfer; ET = embryo transfer.

Table 3 Results from elective and non-elective single- and double-embryo transfers in IVF cycles started in the first 3 months of assisted reproduction treatment funding in Québec.

Variable	<35 Years	35–39 Years	≥40 Years	Overall
eSET	348	175	33	556
eSET clinical pregnancies (rate per ET) ^a	144 (41)	61 (35)	8 (24)	213 (38)
Non-elective SET	48	54	49	151
Non-elective SET clinical pregnancies* (rate per ET) ^a	15 (31)	13 (24)	3 (6)	31 (21)
eDET	17	74	81	172
eDET clinical pregnancies (rate per ET)	9 (53)	27 (36)	19 (23)	55 (32)
eDET twin pregnancies (rate per ET)	1 (11)	4 (15)	2 (11)	7 (13)
Non-elective DET	30	72	70	172
Non-elective DET clinical pregnancies (rate per ET)	9 (30)	18 (25)	9 (13)	36 (21)
Non-elective DET twin pregnancies (rate per ET)	1 (11)	3 (17)	2 (22)	6 (17)
>Two embryos transferred	0	13	39	52
Clinical pregnancies > Two embryos ^a	0	5 (38)	8 (21)	13 (25)

Values are *n* or *n* (%). DET = double-embryo transfer; cDET = elective double-embryo transfer; eSET = elective single-embryo transfer; ET = embryo transfer; SET = single-embryo transfer.

^aAll singleton pregnancies.

Table 4 Proportion of patients having embryo cryopreservation.

Variable	<35 years	35–39 years	≥40 years	Overall
Patients with embryo cryopreservation (<i>n</i> (%))	286 (60)	144 (37)	57 (21)	487 (43)
Embryos cryopreserved per patient (mean)	3.7	3.2	2.7	3.4

can be transferred in any one cycle, a reduction in multiple-pregnancy rates should occur. Although the policy has the implicit aim of single-embryo transfer in as many cases as possible, the Québec government had been listening to clinicians who stated that there are situations that justify the transfer of more than one embryo. The costs associated with the ongoing care of multiple pregnancies, both during the pregnancy itself and for the care of premature infants, possibly with life-time increased health costs, can be exorbitant. By reducing the number of multiple pregnancies and multiple births, the subsequent reduction in associated health costs can be used to pay for the assisted reproduction treatment. This appears to be a more positive use of provincial health funds since it is aimed at producing healthy babies rather than needing to support babies with health issues.

Although other countries have introduced similar policies, the authors believe that this case demonstrates the quickest realization of the aim of almost eliminating multiple pregnancies in response to state-sponsored IVF. Québec fertility specialists are very motivated to make this programme work and have adopted stricter criteria than those imposed by government. In Québec, the multiple-pregnancy rate was reduced from 25.6% to only 3.7% by using 50% eSET, compared with only 1.6% eSET previously, in only 3 months. The correct application of the law can be demonstrated by the fact that in those cycles where two embryos were transferred the twin rate is very low and that there are no triplets from cycles where three embryos were transferred. This indicates that the appropriate selection of patients needing more than eSET can be achieved if clinicians apply careful criteria in patient selection. If this is

Table 5 Summary of impact of the state coverage of IVF cycles in Québec.

	<i>Before programme (2009)</i>	<i>After programme (August–November 2010)</i>
Embryo transfers performed using eSET	1.6	50.4
Clinical pregnancy rate	42.8	31.6
Multiple-pregnancy rate	25.6	3.7

Values are %. eSET = elective single-embryo transfer.

done it means that legislative terms such as those created in Québec, whereby the clinician has some flexibility to transfer multiple embryos if deemed truly necessary, can be successfully applied. It is clear that buy-in by the clinics is necessary with a programme such as this where the option to transfer more than one embryo is permitted. Whilst this option is important to allow for those cases where multiple embryo transfer is required to maintain pregnancy potential for the patient, it opens the door to potential abuse; if only one clinic in the state continues to unnecessarily transfer multiple embryos, the aim of the programme to reduce multiple pregnancies will not be achieved.

Furthermore it is noted that there is a higher-than-usual rate of cycles with no embryo transfer. This may be explained by the fact that all the centres applied their own internal policies on embryo selection criteria but that the criteria were strictly applied, so that the elimination of suboptimal embryos led to a higher cancellation rate. This was carried out in an attempt to maintain clinical pregnancy rates with eSET and ensure that only suitable embryos were considered for cryopreservation.

The major concern when using eSET liberally is that the pregnancy rate will be negatively affected. The implementation of this programme saw the overall clinical pregnancy rate fall from 42.8% to 31.6%; however, it is important to remember that nearly 50% (48.7%) of patients under 40 years of age had at least one embryo cryopreserved following their fresh IVF cycle, with an average of 3.5 embryos each. Although this may seem a high proportion of patients having a high number of embryos cryopreserved, it is believed that this relates to the fact that when transferring only one embryo the chance that at least one other embryo will be available for cryopreservation increases.

With the improvement of outcomes in cryopreserved embryos, especially with the introduction of vitrification, it is logical to use the cumulative pregnancy rate or cumulative live-birth rate per initiated cycle, combining results from transfer of fresh and frozen embryos, as the standard measure of a patient's chances for a baby. Certainly, in this programme, where the use of cryopreserved embryos is included and does not reduce the patient's number of funded cycles, it is clear that the cumulative pregnancy rate and cumulative live-birth rate must be considered.

Further analysis will need to be performed as more data becomes available to ensure that the patterns demonstrated by the initial analysis remain constant and also to assess the cumulative pregnancy rate once sufficient frozen–thawed embryo transfers have been performed. It is believed that once this data is included the cumulative pregnancy rate for patients under 40 years of age will dem-

onstrate that the policy of 'one embryo at a time' can be successfully implemented in the right environment.

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References

- An act respecting clinical and research activities related to assisted procreation, 2010. (2009, c.30) – Coming into force of certain provisions of the Act. O.C. 643-2010, 7 July 2010. Gazette Officielle du Québec, July 21, 2010, vol. 142, No. 29.
- Assisted Human Reproduction Canada, 2011. Prevention of multiple births associated with infertility treatments: building a Canadian framework. Available from: <<http://www.ahrc-pac.gc.ca/v2/pubs/births-multiple-naissances-eng.php#a212>> (accessed 15 Jan 2011).
- Bromer, J.G., Ata, B., Seli, M., Lockwood, C.J., Seli, E., 2011. Preterm deliveries that result from multiple pregnancies associated with assisted reproductive technologies in the USA: a cost analysis. *Curr. Opin. Obstet. Gynecol.* (Epub ahead of print).
- Fauque, P., Jouannet, P., et al., 2010. Cumulative results including obstetrical and neonatal outcome of fresh and frozen–thawed cycles in elective single versus double fresh embryo transfers. *Fertil. Steril.* 94 (3), 927–935.
- Gerris, J., 2009. Single-embryo transfer versus multiple-embryo transfer. *Reprod. Biomed. Online* 18 (Suppl. 2), 63–70.
- Gunby, J., Bissonnette, F., Librach, C., Cowan, L., 2010. IVF Directors Group of the Canadian Fertility and Andrology Society. Assisted reproductive technologies (ART) in Canada: 2007 results from the Canadian ART Register. *Fertil. Steril.* (Epub ahead of print).
- McLernon, D.J., Harrild, K., et al., 2010. Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials. *BMJ* 341, c6945. doi:10.1136/bmj.c6945.
- Moustafa, M.K., Sheded, S.A., El Aziz Moustafa, M.A., 2008. Elective single embryo transfer versus double embryo transfer in assisted reproduction. *Reprod. Biomed. Online* 17 (1), 82–87.
- van Peperstraten, A.M., Nelen, W.L., et al., 2008. Why don't we perform elective single embryo transfer? A qualitative study among IVF patients and professionals. *Hum. Reprod.* 23 (9), 2036–2042 (Epub 2008 Jun 18).

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