

Assisted reproductive technologies (ART) in Canada: 2008 results from the Canadian ART Register

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Abstract

All 28 Canadian assisted reproductive technology (ART) clinics participated in the Canadian ART Register (CARTR) for 2008. A total of 15,000 cycles was reported to CARTR, resulting in 5034 clinical pregnancies and at least 3976 deliveries, 3932 live births, 1089 multiple births (including 38 high-order multiple births), and 5104 infants, 43% of whom were from multiple gestations. Birth outcomes were unknown for 140 ongoing pregnancies (3.4%).

In 9904 IVF/ICSI cycles using the woman's own oocytes, per cycle started, the clinical pregnancy rate was 36.5% (42.1% per ET), the live birth rate was 29.1%, the singleton live birth rate was 20.7%, and the healthy term singleton rate was 15.9%; the multiple birth rate per delivery was 28.9%, with a high-order multiple birth rate of 1.0%. ICSI was performed in 71% of cycles. One or two embryos were transferred in 69% of cycles. In 431 IVF/ICSI cycles using donor oocytes, per cycle started, the clinical pregnancy rate was 49.7%, the live birth rate was 39.8%, the singleton live birth rate was 24.7%, and the healthy term singleton rate was 18.4%; the multiple birth rate was 37.4%, with a high-order multiple birth rate of 1.1%. In 3738 FET cycles using the woman's own oocytes, per cycle started, the clinical pregnancy rate was 26.0%, the live birth rate was 19.8%, the singleton live birth rate was 15.7%, and the healthy term singleton rate was 12.2%; the multiple birth rate was 20.3%, with a high-order multiple birth rate of 0.9%.

Clinical pregnancy and live birth rates and number of ART cycles performed continued to increase in 2008 compared with previous years. In IVF/ICSI and FET cycles, multiple birth rates decreased and the high-order multiple birth rate was 1% or less.

INTRODUCTION

The Canadian Assisted Reproductive Technologies Register (CARTR) was first established in 1999 for the collection of treatment cycle data from Canadian fertility centres that were using assisted reproductive technologies (ART), including in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), and frozen embryo transfer (FET). The IVF Directors Group of the Canadian Fertility and Andrology Society (CFAS) directs the CARTR programme, which is financially supported by participating ART centres. Participation of ART centres in CARTR is voluntary.

The first report from the Canadian ART Register, describing ART cycles performed in 2001, was published in 2005 (1). Subsequent publications reported on CARTR data from 2002 to 2007 (2-7). This is the eighth annual report of Canadian ART outcomes.

The purpose of this paper is to report on ART cycles performed in Canadian centres in the 2008 calendar year and submitted to CARTR. Trends in outcomes over four years will also be examined.

MATERIALS & METHODS

Data Collection

For 2008, 13 centres submitted data to CARTR using the CARTR Treatment Outcome Reporting System (CARTR-TORS; CompuArt Technology, Richmond Hill, Ontario) and 15 centres exported data to CARTR from their own clinic database.

Staff at each centre entered information about patient demographics, diagnosis, and obstetrical history; details of treatment; complications; and pregnancy and birth outcomes for each ART treatment cycle initiated. The completed anonymous case records were sent electronically from each ART centre to the CARTR coordinating centre, where they were

manually checked for accuracy and completeness. Corrections or clarifications were requested from the centres as necessary. No on-site data validation from source documents was performed. The records from each centre were then aggregated for data analysis using the computer programme Statistical Package for the Social Sciences (SPSS), version 17 (SPSS Inc., Chicago).

Definitions of Outcomes

The definitions established by the International Committee for Monitoring Assisted Reproductive Technology (ICMART) are followed by CARTR (8). A treatment cycle is considered to have “started” when a woman undergoing ovarian stimulation receives the first dose of gonadotropins or, in a non-stimulated cycle (e.g., for FET), when monitoring is begun. A canceled cycle is one that is stopped before the oocyte retrieval procedure or thawing of embryos.

Clinical pregnancy includes intrauterine gestation (presence of a gestational sac on ultrasonography), ectopic pregnancy, and miscarriage diagnosed by histology. Cycles with only a positive pregnancy test (biochemical pregnancy) are not considered to have a clinical pregnancy. Implantation rate is the number of gestational sacs observed on ultrasonography divided by the number of embryos transferred.

Pregnancy loss includes miscarriage and therapeutic abortion of a clinical intrauterine pregnancy occurring at ≤ 20 weeks' gestation. Any pregnancy termination, either spontaneous or therapeutic, occurring after 20 weeks' gestation with no liveborn infant is considered a stillbirth. A delivery is the birth of one or more infants, either living or not, after 20 weeks' gestation. A live birth is a delivery that results in at least one living infant (but, if a multiple birth, may include one or more stillborn infants). A singleton live birth is the delivery of one baby, born alive. A new outcome this year, healthy term singleton birth is defined as one baby born alive at

term from a singleton pregnancy, with birth weight >2500 g, no birth defect reported, and no neonatal death. A neonatal death is the death of a liveborn infant in the first 28 days of life. A multiple birth is the delivery of more than one infant, either liveborn or stillborn, including deliveries with all infants stillborn. High-order multiple births (triplets or more) are reported separately. A preterm birth is a delivery at <37 weeks of gestation and a very preterm birth is a delivery at <32 weeks.

Statistical Analysis

The statistics used in this report are mainly descriptive, i.e., rates, proportions, means, and medians. The χ^2 test was used occasionally to compare proportions.

Unless otherwise noted, the clinical pregnancy rate is reported per cycle started. Cycle cancellation, ectopic pregnancy, and other complications are reported per cycle started. The miscarriage or pregnancy loss rate is reported per intrauterine pregnancy. Birth rates are reported per cycle started, excluding from both the numerator and the denominator cycles in which the outcome of the clinical pregnancy has not been reported. Because of these missing data, the birth rates reported may underestimate the true birth rates. The multiple birth rate, which includes stillbirths, is reported per delivery.

These data from CARTR for 2008 were presented at the annual IVF Directors' Meetings in November 2009 (pregnancy outcomes) and September 2010 (birth outcomes). A brief summary of the national clinical pregnancy and live birth rates was provided to the media immediately after each meeting. As agreed among all IVF Directors, clinic-specific data are not presented to the public or published.

RESULTS

Participating Centres

All 28 Canadian ART centres operating in 2008 voluntarily contributed to CARTR for that year (listed in the Appendix). Three of the 28 centres performed more than 1000 ART cycles (of all types) in 2008, 11 centres performed between 500 and 1000 cycles, nine centres performed between 200 and 500 cycles, and five centres performed fewer than 200 cycles.

Overall Outcomes

In total, 15,000 treatment cycles involving ART were reported to CARTR for 2008. Overall, 5034 ART cycles (34.0% of cycles started, excluding 193 embryo and oocyte banking cycles) resulted in a clinical pregnancy, at least 3976 cycles resulted in a delivery (27.1% per cycle started), and at least 3932 cycles resulted in a live birth (26.8% per cycle started). There were 140 cycles with ongoing pregnancies (3.4% of ongoing pregnancies) for which the birth outcome was not reported. Overall, there were at least 1089 multiple births (27.4% of known births): 1051 twin births (26.4% per birth), 37 triplet births (0.9% per birth), and 1 quadruplet birth.

The various procedures and their success and adverse outcome rates are described in the following sections. The cycle outcomes of the four most common procedures are summarized in Table 1.

Table 1. 2008 cycle outcomes for the four most common types of ART procedures.

Outcome	IVF/ICSI	IVF/ICSI-DO	FET	FET-DO
Cycles started	9904	431	3738	261
Cancelled cycles (% of cycles started)	764 (7.7)	13 (3.0)	108 (2.9)	5 (1.9)
Oocyte retrievals (% of cycles started)	9098 (91.9)	414 (96.1)	3630 (97.1) ^a	256 (98.1) ^a
Embryo transfers (% of cycles started)	8545 (86.3)	403 (93.5)	3489 (93.3)	250 (95.8)
Clinical pregnancy (% per cycle started)	3611 (36.5)	214 (49.7)	972 (26.0)	79 (30.3)
Ectopic pregnancy (% per cycle started)	81 (0.8)	1 (0.2)	18 (0.5)	0
Miscarriage (% per IU pregnancy)	537 (15.2)	38 (17.8)	171 (17.9)	15 (19.0)
Therapeutic abortion (% per IU pregnancy)	17 (0.5)	0	8 (0.8)	0
Delivery ^b (% per cycle started)	2879 (29.4)	174 (40.5)	744 (20.1)	63 (24.2)
Live birth ^b (% per cycle started)	2851 (29.1)	171 (39.8)	732 (19.8)	62 (23.8)
Singleton live birth ^b (% per cycle started)	2028 (20.7)	106 (24.7)	582 (15.7)	53 (20.4)
Healthy term singleton ^b (% per cycle started)	1555 (15.9)	79 (18.4)	453 (12.2)	33 (12.7)
Singleton delivery ^b (% of deliveries)	2047 (71.1)	109 (62.6)	593 (79.7)	54 (85.7)
Twin delivery ^b (% of deliveries)	804 (27.9)	63 (36.2)	144 (19.4)	9 (14.3)
Triplet or more delivery ^b (% of deliveries)	28 (1.0)	2 (1.1)	7 (0.9)	0

^a Cycles with embryos thawed.

^b Cycles with unknown delivery status omitted: 101 IVF/ICSI, 1 IVF/ICSI-DO, 33 FET, 1 FET-DO

IVF/ICSI with Own Oocytes

IVF, including ICSI, using the woman's own oocytes, was the most common procedure performed, with 9904 cycles reported. Per IVF/ICSI cycle started, the clinical pregnancy rate was 36.5%, the live birth rate was 29.1%, the singleton live birth rate was 20.7%, and the healthy term singleton rate was 15.9%. Donated sperm was used in 4.1% of cycles with oocytes retrieved. There were 81 ectopic pregnancies (0.8% per cycle started), including four heterotopic pregnancies, three of which ended in miscarriage and one of which resulted in a singleton live birth. The pregnancy loss rate was 15.7% of clinical intrauterine pregnancies (miscarriage 15.2%, therapeutic abortion 0.5%). Of the 2879 known births (97% of ongoing pregnancies), 28.9% were multiple births (27.9% twins and 1.0% triplets). Included in these figures are 10 pregnancies, one miscarriage, eight singleton live births, and one twin live birth that resulted from intrauterine insemination performed after the IVF/ICSI cycle was cancelled.

Rates for IVF and ICSI separately can only be provided per successful retrieval (i.e., one or more oocytes retrieved) because the decision to use ICSI might not be made until the sperm and oocytes are assessed in the embryology laboratory (Table 2). Of 9098 IVF/ICSI cycles with a successful retrieval, 29.0% had insemination by standard IVF (including 30 cycles with failed fertilization that had ICSI performed the next day [rescue ICSI]), 66.3% by ICSI, and 4.4% by IVF/ICSI split (some oocytes inseminated by each method). The clinical pregnancy rates per successful retrieval were 39.2% for standard IVF (23.3% for the rescue ICSI cycles), 39.4% for ICSI, and 48.0% for IVF/ICSI split. Including the IVF/ICSI split cycles in the ICSI group, the clinical pregnancy rates per retrieval were 39.2% for IVF and 39.9% for ICSI, and the live birth rates per retrieval were 31.1% and 32.0%, respectively. The ectopic pregnancy rate per retrieval was 0.9% with IVF and 0.9% with ICSI, and the pregnancy loss rates per intrauterine pregnancy were 16.5% (miscarriage 16.0%, therapeutic abortion 0.5%) and 15.4% (miscarriage 14.9%,

therapeutic abortion 0.5%), respectively. Of 822 known births after IVF, 28.5% were multiple births (28.0% twins and 0.5% triplets); of 2048 known births after ICSI, 29.2% were multiple births (28.0% twins and 1.2% triplets).

Table 2. 2008 clinical pregnancy and birth outcomes by type of insemination method in IVF/ICSI cycles with successful retrieval.

Insemination method	No. of cycles (% of all retrieval cycles)^a	No. of pregnancies (% per retrieval)	No. of singleton live births (% per retrieval)^b	No. of multiple births (% per birth)^b	No. of triplet births (% per birth)^b
IVF	2642 (29.0)	1035 (39.2)	581 (22.2)	234 (28.5)	4 (0.5)
IVF/ICSI split	398 (4.4)	191 (48.0)	117 (29.6)	43 (26.7)	1 (0.6)
ICSI	6028 (66.3)	2375 (39.4)	1322 (22.2)	554 (29.4)	23 (1.2)

^a 30 cycles with oocytes retrieved did not have insemination.

^b 101 cycles with unknown delivery status omitted.

IVF/ICSI with Oocyte Donation

IVF/ICSI using donor oocytes (IVF/ICSI–DO) was reported in 431 cycles in 2008. In IVF/ICSI-DO cycles, per cycle started, the clinical pregnancy rate was 49.7%, the live birth rate was 39.8%, the singleton live birth rate was 24.7%, and the healthy term singleton rate was 18.4%. Donated sperm was used in 8.0% of cycles with oocytes donated. There was one ectopic pregnancy (0.2% per cycle started). The pregnancy loss rate was 17.8% per intrauterine pregnancy (all miscarriages). Of 174 known births (99% of ongoing pregnancies), 37.4% were multiple births (36.2% twins, 1.1% triplets).

Of 414 cycles with a successful retrieval, 30.9% had insemination by standard IVF (including 3 cycles that used rescue ICSI), 61.8% by ICSI, and 7.0% by IVF/ICSI split. The clinical pregnancy rates per successful retrieval were 49.2% (0% for the rescue ICSI cycles),

52.3%, and 58.6%, respectively.

Information about the oocyte donor's age was available for all cycles. Donor age was <30 years in 57% of cycles, 30-34 years in 28%, 35-39 years in 15%, and ≥40 years in 1%. The clinical pregnancy rates per cycle started were 49.6%, 55.4%, 41.3%, and 0%, respectively.

FET with Own Oocytes

In 2008, 3738 cycles of FET, using cryopreserved embryos created from the woman's own oocytes, were reported. Per cycle started, the clinical pregnancy rate was 26.0%, the live birth rate was 19.8%, the singleton live birth rate was 15.7%, and the healthy term singleton rate was 12.2%. There were 18 ectopic pregnancies (0.5% per cycle started), including 2 heterotopic pregnancies that both resulted in a singleton live birth. The pregnancy loss rate was 18.7% per intrauterine pregnancy (miscarriage 17.9%, therapeutic abortion 0.8%). Of 744 known births (96% of ongoing pregnancies), 20.3% were multiple births (19.4% twins, 0.9% high-order multiples including 1 set of quadruplets).

FET with Oocyte or Embryo Donation

The category FET-DO includes transfer of cryopreserved embryos created from donor oocytes in a previous IVF/ICSI-DO cycle (229 cycles) and cryopreserved donated embryos (32 cycles). In this category, per cycle started, the clinical pregnancy rate was 30.3%, the live birth rate was 23.8%, the singleton live birth rate was 20.4%, and the healthy term singleton rate was 12.7%. There was no ectopic pregnancy. The miscarriage rate per intrauterine pregnancy was 19.0%. Of 63 known births (99% of ongoing pregnancies), 14.3% were multiple births (all twins).

Information about the oocyte donor's age was available for 95% of cycles. Donor age

was <30 years in 59% of cycles, 30-34 years in 31%, 35-39 years in 9%, and ≥40 years in 1%.

The clinical pregnancy rates per cycle started were 34.7%, 28.6%, 22.7%, and 33.3%, respectively.

Gestational Carrier Cycles

There were 190 cycles in which embryos were transferred into the uterus of a woman other than the one who intended to raise the child. Gestational carriers were used in 80 IVF/ICSI and 51 FET cycles with the parenting woman's own oocytes, 30 IVF/ICSI and 27 FET cycles with donated oocytes, one cycle using natural IVF, and one cycle using in vitro maturation. Use of donated sperm was reported for six cycles.

In fresh embryo cycles using a gestational carrier, per cycle started, the clinical pregnancy rate was 53.6%, the live birth rate was 36.6%, the singleton live birth rate was 25.0%, and the healthy term singleton rate was 17.9%; in frozen embryo cycles, the rates were 34.6%, 23.7%, 17.1%, and 13.2%, respectively. Of the 87 clinical intrauterine pregnancies in gestational carriers, 29.9% ended in miscarriage; there was no ectopic pregnancy. Of 59 known births (97% of ongoing pregnancies), 30.5% were multiple births (all twins).

Other Cycle Types

Several other types of ART procedures that did not fit into the categories previously described were reported to CARTR for 2008. Natural (unstimulated) IVF was performed in 136 cycles, with clinical pregnancy rates of 16.2% per cycle started and 31.4% per ET, and live birth rates of 12.7% and 25.0%, respectively; there was one twin birth (5.9%). One hundred and seven cycles were reported in which oocyte retrieval was performed for the sole purpose of freezing oocytes. In 26 cycles, previously frozen oocytes were thawed and inseminated, with a clinical

pregnancy rate per cycle started of 19.2% and a live birth rate per cycle started of 11.5%, all singletons. Sixty-seven cycles of in vitro oocyte maturation were reported, with a clinical pregnancy rate per cycle started of 35.8% and a live birth rate per cycle started of 26.9%; of 18 live births, five were multiple births (27.8%), including one set of triplets. Eighty-six cycles were performed for the purpose of embryo banking, with oocyte freezing also done in six cycles.

Preimplantation genetic diagnosis (PGD) was performed in 47 cycles using fresh embryos, 4 cycles using frozen embryos, and 3 cycles using both, resulting in 20 pregnancies and 19 live births (11 singleton and 8 twin births). In addition, preimplantation genetic screening (PGS) for aneuploidy was reported for 55 IVF/ICSI cycles, four FET cycles, three IVF/ICSI-DO cycles, two in vitro maturation cycles, one cycle using frozen oocytes, and one gestational carrier cycle, resulting in 20 pregnancies and 17 live births (10 singleton and 7 twin births).

Birth Outcomes for All ART Procedures

At least 3976 deliveries resulted in at least 5104 infants born from all types of ART cycles started in 2008 in Canada: 2887 infants from 2887 singleton births (56.6% of infants), 2102 infants from 1051 twin births (41.2%), 111 infants from 37 triplet births (2.2%), and 4 infants from 1 quadruplet birth (0.1%). Thus, 43% of infants were born from multiple gestations. An additional 140 pregnancies had no delivery information reported. Of these pregnancies, 94 had one viable fetus, 38 had two viable fetuses, and two had three viable fetuses at last report; thus, as many as 176 additional babies may have been born.

Of the 2887 infants born as singletons, there were 34 stillbirths and 14 neonatal deaths, a total perinatal mortality rate of 1.7% per infant. The median gestational age at birth was 39 weeks (range, 21-42 wk) for liveborn infants and 24 weeks (range, 21-38 wk) for stillborn infants. Preterm delivery (<37 weeks) occurred in 15.2% of births and very preterm delivery

(<32 weeks) in 3.5% of births. Birth weight was normal (>2500 g) for 91.6% of liveborn singletons, low (1500-2500 g) for 7.3%, and very low (<1500 g) for 1.2%. Some type of birth defect was reported for 68 infants (2.4% of infants).

Of the 2102 infants born as twins, there were 24 stillbirths and 18 neonatal deaths, a total perinatal mortality rate of 2.0% per infant. The median gestational age at birth was 36 weeks (range, 21-42 wk) for live births and 21 weeks (range, 21-25 wk) for stillbirths. Preterm delivery occurred in 71.0% of births and very preterm delivery in 11.5% of births. Birth weight was >2500 g for 47.7% of liveborn twins, 1500-2500 g for 44.0%, and <1500 g for 8.3%. Some type of birth defect was reported for 46 infants (2.2% of infants).

Of the 115 infants born as triplets or quadruplets, there were six stillbirths and two neonatal deaths, a total perinatal mortality rate of 7.0% per infant. The gestational age at birth was median 32 weeks (range, 24-37 wk) for triplet live births, 32 weeks for the one quadruplet live birth, and 21 weeks for the two triplet stillbirths. Preterm delivery occurred in 97.3% of births and very preterm delivery in 40.5% of births. Birth weight was >2500 g for 4.9% of liveborn infants, 1500-2500 g for 53.4%, and <1500 g for 41.7%. Some type of birth defect was reported for four infants (3.5% of infants).

Results for deliveries by multiplicity are summarized in Table 3 and for infants by multiplicity in Table 4.

Table 3. Birth outcomes per delivery by multiplicity.

Multiplicity	Deliveries, n (%)	Live birth, n (%)	Median gestational age at live birth (wks) ^a	Preterm birth, n (%) ^a	
				<37 weeks	<32 weeks
Singleton	2887 (72.6)	2853 (98.8)	38.9	436 (15.2)	101 (3.5)
Twins	1051 (26.4)	1043 (99.2)	36.1	742 (71.0)	120 (11.5)
Triplets	37 (0.9)	35 (94.6)	32.4	35 (97.2)	15 (41.7)
Quads	1 (0.03)	1 (100)	32.4	1 (100)	0

^a Gestational age missing for 24 births.

Table 4. Infant outcomes by multiplicity.

Multiplicity	Infants, n (%)	Stillborn/neonatal death, n/n (% perinatal death)	Birth weight, live births, n (%) ^a			Birth defect, n (%)
			>2500 g	1500-2500 g	<1500 g	
Singleton	2887 (56.6)	34/14 (1.7)	2525 (91.6)	201 (7.3)	32 (1.2)	68 (2.4)
Twins	2102 (41.2)	24/18 (2.0)	955 (47.7)	881 (44.0)	166 (8.3)	46 (2.2)
Triplets	111 (2.2)	6/2 (5.4)	5 (5.1)	51 (51.5)	43 (43.4)	4 (3.6)
Quads	4 (0.08)	0/0	0	4 (100)	0	0

^a Birth weight missing for 177 live born infants.

Information on sex of the infant was available for 97% of babies: 50.7% were male and 49.3% were female.

The information provided on birth defects was limited. Overall, some type of birth defect was reported for 118 infants (2.3 of infants): 30 cases of cardiac defect (two stillbirths and four neonatal deaths), four cases of chromosome aneuploidy (one stillbirth), eight cases of gastrointestinal defect, three cases of limb defect, three cases of urogenital defect, eight cases of cleft lip or palate (2 stillbirths), three cases of metabolic disorder (one stillbirth), two cases of neural tube defect, and 57 cases of other unspecified defects (four stillbirths and four neonatal deaths).

The risk of a couple experiencing perinatal death was related to multiple birth. Perinatal death of one or more infants occurred in 1.7% of singleton deliveries, 2.9% of twin deliveries, and 10.5% of triplet or quadruplet deliveries (risk ratio, 1.9; 95% confidence interval, 1.2 to 2.9; $P=0.004$, multiple vs. singleton). The risk of perinatal death of all infants was 1.7%, 1.1%, and 5.3%, respectively ($P=0.39$, multiple vs. singleton). By type of ART procedure, perinatal death of one or more infants occurred in 2.1% of deliveries resulting from IVF/ICSI cycles (2.4% in IVF cycles and 2.1% in ICSI cycles), 3.4% from DO cycles, and 2.0% from FET cycles.

Effect of Female Age

The clinical pregnancy and birth outcomes for women categorized into three age groups are given in Table 5. The mean female age was 35 years in IVF/ICSI and FET cycles and 41 years in DO cycles. The proportion of cycles in women aged 40 years and older was 19% in IVF/ICSI cycles, 14% in FET cycles, and 62% in DO cycles. In IVF/ICSI and FET cycles, the clinical pregnancy and live birth rates declined with female age, especially after age 40 years. In DO cycles, clinical pregnancy and live birth rates were highest in the oldest age group, and similar in the two younger age groups. The multiple birth rates declined with age in IVF/ICSI cycles; in FET and DO cycles, age had no clear effect on multiple births.

In IVF/ICSI cycles using the woman's own oocytes, the age-related decline in ART success can be attributed to suboptimal outcomes at several steps in the process. The proportion of started cycles with successful retrieval decreased with age (94.4% for women aged <35 years, 91.8% for those aged 35-39 years, and 86.1% for those aged \geq 40 years), as did the mean number of oocytes retrieved (13.5, 11.2, and 9.1, respectively). In women who had one or more embryos replaced, the mean implantation rate per embryo transferred declined with increasing female age (35.7%, 23.8%, and 10.5%), as did the clinical pregnancy rate per ET (50.4%, 40.7%, and 24.5%), even though older women had more embryos transferred (mean, 2.0, 2.4, and 3.0). The proportion of women having ET who had surplus embryos available for cryopreservation gradually decreased from the younger to older women (59.4%, 41.7%, and 20.7%). In women who achieved clinical intrauterine pregnancy, the pregnancy loss rate per intrauterine pregnancy became higher as women aged (10.3%, 18.3%, and 34.1%). However, adverse birth outcomes were not found to be related to advanced female age: the risks of preterm birth, very preterm birth, and perinatal death were similar across age groups after adjusting for multiple births.

Table 5. 2008 clinical pregnancy and birth outcomes by female age for the three most common ART procedures.

Outcome/female age group	IVF/ICSI	IVF/ICSI -DO	FET
Mean female age, years (range)	35 (20-48)	41 (22-53)	35 (20-51)
Cycles started, n (% of cycles within procedure)			
<35	4185 (42.3)	73 (16.9)	1738 (46.5)
35-39	3864 (39.0)	90 (20.9)	1488 (39.8)
≥40	1855 (18.7)	268 (62.2)	512 (13.7)
Clinical pregnancy, n (% per cycle started)			
<35	1876 (44.8)	32 (43.8)	496 (28.5)
35-39	1374 (35.6)	41 (45.6)	377 (25.3)
≥40	361 (19.5)	141 (52.6)	99 (19.3)
Pregnancy loss, n (% per intrauterine pregnancy)			
<35	190 (10.3)	6 (19.4)	78 (16.0)
35-39	245 (18.3)	10 (24.4)	74 (20.1)
≥40	119 (34.1)	22 (15.6)	27 (27.6)
Live birth, n (% per cycle started) ^a			
<35	1586 (38.4)	24 (32.9)	392 (22.7)
35-39	1055 (27.5)	30 (33.7)	272 (18.5)
≥40	210 (11.4)	117 (43.7)	68 (13.4)
Singleton live birth, n (% per cycle started) ^a			
<35	1045 (25.3)	16 (21.9)	302 (17.5)
35-39	802 (20.9)	18 (20.2)	225 (15.3)
≥40	181 (9.8)	72 (26.9)	55 (10.8)
Healthy term singleton, n (% per cycle started) ^a			
<35	810 (19.6)	13 (17.8)	236 (13.7)
35-39	611 (16.0)	11 (12.4)	174 (11.8)
≥40	134 (7.3)	55 (20.5)	43 (8.4)
Multiple birth, n (% per delivery) ^a			
<35	547 (34.1)	8 (32.0)	90 (22.7)
35-39	255 (24.0)	12 (40.0)	48 (17.2)
≥40	30 (14.0)	45 (37.8)	13 (19.1)

^a135 cycles with unknown delivery status omitted.

Effect of Infertility Diagnosis

In IVF/ICSI cycles, the reason for ART treatment was most commonly male factor infertility (32% of cycles) or a single female infertility factor (29%). Idiopathic or unexplained infertility was the diagnosis in 21% of cycles. Both female and male infertility factors were diagnosed in 14% of cycles and more than one female factor in 4%. Mean female age, use of ICSI, and the clinical pregnancy rate per cycle started varied across diagnostic categories (Table 6).

Table 6. 2008 clinical pregnancy and birth outcomes by infertility diagnosis category in IVF/ICSI cycles.^a

Diagnostic Category	No. of cycles (% of all IVF/ICSI cycles)	Mean female age (years)	Proportion of cycles^c using ICSI (%)	No. of pregnancies (% per cycle started)	No. of live births (% per cycle started)^d
Idiopathic	2060 (20.9)	35.8	56	802 (38.9)	639 (31.3)
Male factor only	3142 (31.9)	34.3	95	1310 (41.7)	1066 (34.3)
Male + female factor	1404 (14.3)	35.8	90	457 (32.5)	357 (25.7)
Tubal factor only	1026 (10.4)	35.4	36	334 (32.6)	240 (23.7)
Endometriosis only	540 (5.5)	34.7	46	196 (36.3)	170 (31.8)
Ovulatory disorder only ^b	471 (4.8)	34.4	54	193 (41.0)	147 (31.5)
Other female factor only	480 (4.9)	37.3	63	133 (27.7)	102 (21.4)
Diminished ovarian reserve only	298 (3.0)	38.9	74	58 (19.5)	38 (13.0)
>1 female factor	425 (4.3)	35.9	39	109 (25.6)	80 (18.8)

^a 58 cycles with unknown diagnosis omitted. Categories are mutually exclusive.

^b Including polycystic ovarian syndrome.

^c Cycles with insemination done.

^d 99 cycles with unknown delivery status omitted.

Pregnancy rate per cycle started was highest when male factor infertility was the only diagnosis (41.7%). Couples with idiopathic infertility had a clinical pregnancy rate of 38.9%. In couples with a single female infertility factor, the clinical pregnancy rate varied from 41.0% with ovulatory disorder to 19.5% with diminished ovarian reserve. Pregnancy rate was reduced in the presence of both female and male infertility factors (32.5%) or multiple female infertility factors without male factor (25.6%). These differences across diagnostic groups were statistically significant ($P < 0.001$).

Effect of Number of Embryos Transferred

The number of embryos transferred in IVF/ICSI cycles ranged from one to eight with a mean of 2.3. A single embryo was transferred in 12% of transfer cycles. More commonly, either two (58% of cycles) or three (22% of cycles) embryos were transferred. More embryos were transferred in older women: the mean age of women receiving four or more embryos (9% of cycles) was 39 years, compared with 37 years for those receiving three embryos and 34 years for those receiving two embryos.

Overall, the clinical pregnancy rate was 42.1% per ET. Clinical pregnancy and birth outcomes by number of embryos transferred are shown in Table 7. The clinical pregnancy rate per ET was low when only one embryo was transferred (29.4%). Transferring three or more embryos did not increase the clinical pregnancy rate beyond the high level observed with two embryos (46.9% per ET); indeed, the clinical pregnancy rate declined when more than two embryos were transferred (37.9% per ET). The mean implantation rates per embryo transferred followed a similar pattern: 28.9% with one embryo, 31.6% with two embryos, 18.8% with three embryos, and 11.1% with four or more embryos.

Table 7. 2008 clinical pregnancy and birth outcomes by number of embryos transferred in IVF/ICSI cycles.

No. of embryos transferred	No. of cycles (% of all ET cycles)	No. of pregnancies (% per ET)	No. of singleton live births (% per ET) ^a	No. of multiple births (% per birth) ^a	No. of triplet births (% per birth) ^a
1	993 (11.6)	292 (29.4)	230 (23.4)	3 (1.3)	0
2	4942 (57.8)	2319 (46.9)	1288 (26.5)	601 (31.6)	8 (0.4)
3	1838 (21.5)	714 (38.8)	364 (19.9)	185 (33.6)	17 (3.1)
4 or more	772 (9.0)	276 (35.8)	138 (18.0)	42 (23.1)	3 (1.6)

^a 101 cycles with unknown delivery status omitted.

Thirty per cent of two-embryo transfers were performed on day 5 after oocyte retrieval and 67% on day 3, with similar clinical pregnancy rates per ET: 48.0% on day 5 and 47.4% on day 3. In contrast, only 10% of three-embryo transfers and 5% of \geq four-embryo transfers were performed on day 5.

Although cycles with only one embryo transferred had a clinical pregnancy rate per ET much lower than that of cycles with two embryos transferred, the singleton live birth rate per ET was almost as high with one embryo as with two (23.4% vs 26.5%). Of IVF/ICSI cycles with more than one embryo transferred, the multiple birth rate per known birth was similar whether two embryos (31.6%) or three or more embryos (31.0%) were transferred (Table 7). The triplet birth rate per birth was 2.7% when three or more embryos were transferred. Of note, 29% of triplets in IVF/ICSI cycles resulted from cycles with only two embryos transferred.

When the effect of number of embryos transferred was examined by female age group, different patterns emerged, for both the distribution of number of embryos transferred and the resulting clinical pregnancy and singleton live birth rates (Table 8). Within each age group, multiple birth rates were higher when three embryos or four or more embryos were transferred than when two embryos were transferred. However, 72% of multiple births resulted from cycles with only two embryos transferred, and most of these in women aged <35 years.

Table 8. 2008 clinical pregnancy and birth outcomes by female age and number of embryos transferred in IVF/ICSI cycles.

Female age group (years)	No. of embryos transferred	No. of cycles (% within age group)	No. of pregnancies (% per ET)	No. of singleton live births (% per ET) ^a	No. of multiple births (% per birth) ^a
<35	1	466 (12.6)	181 (38.8)	146 (31.8)	3 (2.0)
	2	2779 (75.0)	1485 (53.4)	800 (29.2)	464 (36.4)
	3	414 (11.2)	181 (43.7)	85 (20.7)	71 (45.5)
	4 or more	48 (1.3)	23 (47.9)	10 (21.3)	8 (44.4)
35-39	1	346 (10.3)	89 (25.7)	70 (20.3)	0
	2	1764 (52.4)	757 (42.9)	452 (26.0)	135 (22.8)
	3	980 (29.1)	415 (42.3)	220 (22.5)	99 (31.0)
	4 or more	276 (8.2)	109 (39.5)	56 (20.4)	21 (27.3)
≥40	1	181 (12.3)	22 (12.2)	14 (7.8)	0
	2	399 (27.1)	77 (19.3)	36 (9.2)	2 (5.3)
	3	444 (30.2)	118 (26.6)	59 (13.4)	15 (20.0)
	4 or more	448 (30.4)	144 (32.1)	72 (16.2)	13 (14.9)

^a 101 cycles with unknown delivery status omitted.

The number of thawed embryos transferred in FET cycles ranged from one to 15, with a mean of 2.2. A single embryo was transferred in 21% of cycles, two embryos in 48%, three embryos in 24%, and four or more embryos in 7%. Overall, the clinical pregnancy rate was 27.9% per ET. Clinical pregnancy and birth outcomes by number of embryos transferred are shown in Table 9. In FET cycles, clinical pregnancy rate per ET was lowest when one embryo was transferred (17.0%) and highest when two or three embryos were transferred (31.2%). Mean implantation rate per embryo transferred was highest when two embryos were transferred (19.5%), compared with 16.8% with one embryo, 14.3% with three embryos, and 8.3% with four or more embryos. The multiple birth rate per known birth increased with number of thawed embryos transferred: 3.1% with one embryo, 20.6% with two embryos, and 26.4% with three or more embryos. The high-order multiple birth rate was 1.6% when three or more embryos were transferred. Three high-order multiple births (including one set of quadruplets) occurred when

only two embryos were transferred, representing 43% of high-order multiple births in FET cycles.

Table 9. 2008 clinical pregnancy and birth outcomes by number of embryos transferred in FET cycles.

No. of embryos transferred	No. of cycles (% of all FET cycles)	No. of pregnancies (% per ET)	No. of singleton live births (% per ET) ^a	No. of multiple births (% per birth) ^a	No. of triplet or more births (% per birth) ^a
1	746 (21.4)	127 (17.0)	92 (12.4)	3 (3.1)	0
2	1672 (47.9)	522 (31.2)	312 (18.9)	83 (20.6)	3 (0.7)
3	824 (23.6)	257 (31.2)	144 (17.6)	54 (27.0)	4 (2.0)
4 or more	247 (7.1)	66 (26.7)	34 (13.9)	11 (23.9)	0

^a 33 cycles with unknown delivery status omitted.

Effect of Day of Embryo Transfer

In IVF/ICSI cycles, ET was performed on day 2 (after oocyte retrieval) in 6% of transfers, day 3 in 70%, day 4 in 0.7%, day 5 in 24%, and day 6 in 0.3%. More embryos were transferred to each woman on day 2 and day 3 (mean, 2.7 and 2.4) than on day 5 (mean, 2.0). The proportion of cycles with one or two embryos transferred was 46% on day 2, 65% on day 3, and 89% on day 5.

The clinical pregnancy rates per ET were 33.0% on day 2, 41.5% on day 3, 31.6% on day 4, 46.9% on day 5, and 12.0% on day 6. The mean implantation rates per embryo transferred were 17.3%, 25.0%, 17.5%, 34.3%, and 8.0%, respectively. The multiple birth rates per known birth were 18.9% on day 2, 29.4% on day 3, 18.8% on day 4, 29.5% on day 5, and 0% on day 6. Triplet birth rates were 0%, 1.1%, 6.3%, 0.8%, and 0% , respectively.

Table 10 shows clinical pregnancy rates and birth outcomes for ET days 2, 3, and 5 by number of embryos transferred. These rates are confounded by both female age and the availability of surplus embryos, which allows the best embryos to be selected for transfer.

Table 10. 2008 clinical pregnancy and birth outcomes by ET day and number of embryos transferred in IVF/ICSI cycles.

ET day	No. of embryos transferred	Mean female age (years)	Surplus embryos available (% of ETs)	No. of cycles (% within ET day)	No. of pregnancies (% per ET)	No. of singleton live births (% per ET) ^a	No. of multiple births (% per birth) ^a
2	1	36.1	3	76 (15.9)	17 (22.4)	12 (16.0)	0
	2	36.3	6	143 (29.9)	45 (31.5)	22 (15.6)	7 (23.3)
	3	37.5	5	152 (31.7)	55 (36.2)	33 (22.0)	7 (17.5)
	4 or more	39.3	5	108 (22.5)	41 (38.0)	18 (16.7)	6 (25.0)
3	1	36.1	15	559 (9.4)	103 (18.4)	82 (14.8)	1 (1.2)
	2	33.5	58	3298 (55.4)	1562 (47.4)	884 (27.2)	390 (30.4)
	3	36.8	37	1481 (24.9)	582 (39.3)	300 (20.4)	154 (33.8)
	4 or more	39.5	24	615 (10.3)	222 (36.1)	112 (18.4)	34 (23.0)
5	1	32.9	76	344 (16.9)	171 (49.7)	135 (39.7)	2 (1.4)
	2	34.4	58	1461 (71.9)	701 (48.0)	373 (25.9)	203 (34.9)
	3	38.0	31	187 (9.2)	70 (37.4)	26 (14.0)	22 (45.8)
	4 or more	39.7	13	39 (1.9)	11 (28.2)	7 (17.9)	2 (22.2)

^a 101 cycles with unknown delivery status omitted.

Effect of Surplus Embryos

The clinical pregnancy rate per ET was 32.8% when all available embryos were transferred (54% of transfers, mean female age 36.3 years) and 53.2% when surplus embryos were available (46% of transfers, mean female age 33.8 years). The mean implantation rates per embryo transferred were 18.6% and 36.2%, respectively. Surplus embryos were available in 59% of transfer cycles in women aged <35 years, 42% of cycles in women 35-39 years, and 21% of cycles in women ≥40 years.

In Canada in 2008, a single embryo was transferred by choice (elective SET) in 351

IVF/ICSI cycles (35% of single ETs and 4.1% of all transfer cycles). The clinical pregnancy rate per ET was 51.0% in elective SETs, compared with 17.6% when only one embryo was available. Some of this difference can be explained by female age, as 75% of elective SETs were performed in women <35 years and only 2% in women ≥40 years. Looking at it another way, when a single embryo was transferred, it was elective SET in 56% of women <35 years and 23% of women 35-39 years, but only 4% of women ≥40 years. The clinical pregnancy rate per ET was 42.2% when elective SET was done on day 3 (24% of transfers) and 55.0% when it was done on day 5 (74% of transfers).

Two embryos were transferred by choice (elective DET) in 2783 IVF/ICSI cycles (56% of double ETs and 33% of all transfer cycles). In these cycles, the clinical pregnancy rate per ET was 55.1%, compared with 36.4% when only two embryos were available. Again, female age was a factor in this result: 64% of elective DETs were performed in women <35 years and only 4% in women ≥40 years. When two embryos were transferred, it was elective DET in 64% of women <35 years and 51% of women 35-39 years, but only 26% of women ≥40 years. The clinical pregnancy rate per ET was 55.3% when elective DET was done on day 3 (69% of transfers) and 55.2% when it was done on day 5 (30% of transfers). The multiple birth rate per known birth was 35.6% with elective DET and 23.2% when only two embryos were available.

Results for elective and non-elective SET and DET by female age group are shown in Table 11. In women aged <35 years, the clinical pregnancy rate per ET was lower with eSET (49.8%) than with eDET (59.2%), but the singleton live birth rate per ET was higher (40.5% vs 31.0%) because of a multiple birth rate of 39.7% in the eDET group. Pregnancy rates with eSET were high in the two older age groups (55.6% for 35-39 years and 42.9% for ≥40 years), but these figures represent only a few, carefully selected cases.

Table 11. 2008 clinical pregnancy and birth outcomes by female age in elective and non-elective single and double embryo transfer IVF/ICSI cycles.

Female age group (years)	Type of embryo transfer ^a	No. of cycles (% within age group)	No. of pregnancies (% per ET)	No. of singleton live births (% per ET) ^b	No. of multiple births (% per birth) ^b
<35	eSET	263 (7.1)	131 (49.8)	104 (40.5)	2 (1.9)
	SET	203 (5.5)	50 (24.6)	42 (20.8)	1 (2.3)
	eDET	1784 (48.1)	1057 (59.2)	544 (31.0)	363 (39.7)
	DET	993 (26.8)	427 (43.0)	256 (26.0)	101 (28.1)
35-39	eSET	81 (2.4)	45 (55.6)	32 (39.5)	0
	SET	265 (7.9)	44 (16.6)	38 (14.4)	0
	eDET	895 (26.6)	447 (49.9)	265 (30.0)	93 (25.8)
	DET	867 (25.8)	310 (35.8)	187 (21.9)	42 (18.1)
≥40	eSET	7 (0.5)	3 (42.9)	3 (42.9)	0
	SET	174 (11.8)	19 (10.9)	11 (6.4)	0
	eDET	104 (7.1)	29 (27.9)	11 (10.9)	2 (15.4)
	DET	295 (20.0)	48 (16.3)	25 (8.6)	0

^a eSET, eDET = elective single or double embryo transfer (surplus embryos available); SET, DET = non-elective single or double embryo transfer (all available embryos were transferred).

^b 79 cycles with unknown delivery status omitted.

Complications and Fetal Reduction

Complications were reported in 212 IVF/ICSI cycles (2.1% per cycle started). There were 108 cases of moderate ovarian hyperstimulation syndrome (1.1% per cycle started), 13 of which (12%) required hospitalization, and 50 cases of severe ovarian hyperstimulation syndrome (0.5% per cycle started), 33 of which (66%) required hospitalization. Also reported were 28 complications related to medications, four complications related to procedures (one hospitalization), two cases of infection, and 20 other unspecified complications (one hospitalization). No maternal death was reported.

Of 1381 multiple pregnancies from all types of ART cycles, outcomes were known for 1341 multiple pregnancies. Of these, 242 (18.0%) had fetal reduction (loss of one or more, but not all fetuses) following ultrasonographic confirmation of fetal viability at 6-8 weeks' gestation;

the reduction was spontaneous in 211 cases (87%) and therapeutic in 31 cases (13%). Of 1240 pregnancies that were originally twins, reduction to one fetus occurred spontaneously in 14.3% and therapeutically in 0.9%, and loss of the whole pregnancy occurred in 5.2%, including one loss after therapeutic reduction was attempted; 80% of viable twin gestations resulted in a twin birth. Of 93 pregnancies that were originally triplets, reduction to two fetuses occurred spontaneously in 25.8% and therapeutically in 10.8%; reduction to one fetus occurred spontaneously in 9.7% and therapeutically in 4.3%; and loss of the whole pregnancy occurred in 9.7%. Thus, only 40% of viable triplet pregnancies resulted in a triplet birth. Of eight pregnancies that originally had four or five viable fetuses, two were therapeutically reduced to one fetus, three were therapeutically reduced to two fetuses, one was spontaneously reduced to two fetuses, one had early spontaneous loss of the whole pregnancy, and one resulted in a quadruplet birth.

Trends over Time

Table 12 compares the major outcomes from CARTR over a 4-year period (2005-2008) for IVF/ICSI, FET, and IVF/ICSI-DO cycles. Continuing increases were seen in the number of cycles submitted to CARTR, the proportion of IVF/ICSI cycles using ICSI, and the clinical pregnancy, live birth, and singleton live birth rates for IVF/ICSI cycles. FET cycles showed increases in success rates in 2008, after dropping slightly in 2007. In IVF/ICSI-DO cycles, clinical pregnancy and live birth rates were higher in 2008 than in previous years, but the singleton live birth rate was lower than in 2007 because of a higher multiple birth rate. Multiple birth rates were lower in 2008 than in previous years for IVF/ICSI and FET cycles. The lower high-order multiple birth rate for IVF/ICSI cycles seen in 2007 was maintained in 2008.

Table 12. Comparison of cycle outcomes from CARTR for the years 2005 to 2008

Outcome	CARTR 2005 (5)	CARTR 2006 (6)	CARTR 2007 (7)	CARTR 2008
No. of clinics participating (%)	25 (100)	25 (100)	26 (100)	28 (100)
Total no. of ART cycles reported	11,414	12,052	13,482	15,000
IVF/ICSI cycles				
No. of cycles reported	8195	8278	8972	9904
Cycles with ICSI (%)	60	64	68	71
Cycles in women aged ≥ 40 y (%)	18	17	17	19
Cycles with ≤ 2 embryos transferred (%)	68	67	69	69
Clinical pregnancy rate per cycle (%)	32.1	33.7	35.6	36.5
Live birth rate per cycle (%)	25.6	27.1	28.6	29.1
Singleton live birth rate per cycle (%)	17.7	18.9	20.0	20.7
Multiple delivery rate per delivery (%)	30.8	30.3	30.2	28.9
Triplet or more rate per delivery (%)	1.4	1.5	1.1	1.0
FET cycles				
No. of cycles reported	2498	2838	3224	3738
Clinical pregnancy rate per cycle (%)	22.8	24.3	23.7	26.0
Live birth rate per cycle (%)	17.4	18.6	17.8	19.8
Singleton live birth rate per cycle (%)	13.1	14.4	13.5	15.7
Multiple delivery rate per delivery (%)	24.5	22.5	24.1	20.3
Triplet or more rate per delivery (%)	1.6	0.6	0.2	0.9
IVF/ICSI-DO cycles				
No. of cycles reported	301	350	404	431
Clinical pregnancy rate per cycle (%)	46.5	42.3	44.6	49.7
Live birth rate per cycle (%)	35.2	33.6	36.1	39.8
Singleton live birth rate per cycle (%)	23.4	20.9	26.4	24.7
Multiple delivery rate per delivery (%)	33.3	37.3	26.5	37.4
Triplet or more rate per delivery (%)	0	0	0	1.1

Acknowledgments: The authors thank the personnel from each centre responsible for data entry for CARTR for their hard work and devotion to detail.

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Appendix – Canadian ART Centres Reporting Data to CARTR for 2008

Victoria Fertility Centre, Victoria, British Columbia

University of British Columbia Centre for Reproductive Health, Vancouver, British Columbia

Genesis Fertility Centre, Vancouver, British Columbia

Pacific Centre for Reproductive Medicine, Burnaby, British Columbia

Regional Fertility Program, Calgary, Alberta

Assisted Reproductive Technology at University of Saskatchewan (ARTUS), Saskatoon,
Saskatchewan

Heartland Fertility Clinic, Winnipeg, Manitoba

London Health Sciences Centre, London, Ontario

Hamilton Health Sciences Centre for Reproductive Care, Hamilton, Ontario

ISIS Regional Fertility Centre, Mississauga, Ontario

Astra Fertility Centre, Mississauga, Ontario

NewLife Fertility Centre, Mississauga, Ontario

CRaTe IVF Program, Toronto, Ontario

LifeQuest Centre for Reproductive Medicine, Toronto, Ontario

Mt. Sinai Reproductive Biology Unit, Toronto, Ontario

Toronto Centre for Advanced Reproductive Technology (TCART), Toronto, Ontario

Toronto Institute for Reproductive Medicine, Toronto, Ontario

IVF Canada & LIFE Programme, Scarborough, Ontario

Markham Fertility Centre, Markham, Ontario

Ottawa Fertility Centre, Ottawa, Ontario

McGill University Reproductive Centre, Montreal, Quebec

Montreal Fertility Clinic, Montreal, Quebec

OVO Fertility Clinic, Montreal, Quebec

Procrea, Montreal and Quebec, Quebec

Conceptia Clinic, Moncton, New Brunswick

Atlantic Assisted Reproductive Therapies (AART), Halifax, Nova Scotia