Assisted Reproductive Technologies and Pregnancy Outcomes in Alberta 2009-2014: A Population-based Study

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Abstract:	Objectives: The purpose of this study is to describe the trends in assisted reproductive technologies (ART) in Alberta and evaluate the impact of ART on perinatal outcomes in a large population-based cohort. Methods: Maternal and child administrative data for all live-births occurring July 1, 2009-December 31, 2014 in Alberta, Canada, were linked and included in this retrospective study. ART pregnancies were identified from pharmaceutical claims or ICD-10 codes. Main outcome measures: Incidence and temporal trends of live-births in ART pregnancies. Maternal characteristics and perinatal outcomes were evaluated as ART vs non-ART pregnancies and categorised by maternal age group. Results: Of the 277,847 live-births between 1 July 2009 and 31 December 2014, 11,258 (4.1%) were conceived with ART therapies. The incidence of ART pregnancies increased from 28.4 to 43.8 per 1000 pregnancies. The number of women aged 30-35 and >35 years delivering following ART increased over time (30-35 years: 33.4 to 48.7 per 1000 pregnancies; >35 years: 76.5 to 97.5 per 1000 pregnancies). Women who underwent ART were older with higher rates of pre-existing and pregnancy-related conditions. Newborns of ART pregnancies were more likely delivered via C-section (49.1 vs 27.6%, $p<0.001$) and smaller than non-ART newborns (low birth weight: 14.8 vs 5.1%, $p<0.001$). Notably, there was no increased risk of adverse anomalies in the newborns. Conclusion: The incidence of live-births following ART pregnancies in Alberta, Canada, is 4.1% and is increasing by approximately 0.31% per year. Newborns following ART appear smaller at birth but show no signs of poor health.

Assisted Reproductive Technologies and Pregnancy Outcomes in Alberta 2009-2014: A Population-based Study

Running title: ART in Alberta

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Abstract

Objectives: The purpose of this study is to describe the trends in assisted reproductive technologies (ART) in Alberta and evaluate the impact of ART on perinatal outcomes in a large population-based cohort.

Methods: Maternal and child administrative data for all live-births occurring July 1, 2009-December 31, 2014 in Alberta, Canada, were linked and included in this retrospective study. ART pregnancies were identified from pharmaceutical claims or ICD-10 codes. Main outcome measures: Incidence and temporal trends of live-births in ART pregnancies. Maternal characteristics and perinatal outcomes were evaluated as ART vs non-ART pregnancies and categorised by maternal age group.

Results: Of the 277,847 live-births between 1 July 2009 and 31 December 2014, 11,258 (4.1%) were conceived with ART therapies. The incidence of ART pregnancies increased from 28.4 to 43.8 per 1000 pregnancies. The number of women aged 30-35 and >35 years delivering following ART increased over time (30-35 years: 33.4 to 48.7 per 1000 pregnancies; >35 years: 76.5 to 97.5 per 1000 pregnancies). Women who underwent ART were older with higher rates of pre-existing and pregnancy-related conditions. Newborns of ART pregnancies were more likely delivered via C-section (49.1 vs 27.6%, $p<0.001$) and smaller than non-ART newborns (low birth weight: 14.8 vs 5.1%, $p<0.001$). Notably, there was no increased risk of adverse anomalies in the newborns.

Conclusion: The incidence of live-births following ART pregnancies in Alberta, Canada, is 4.1% and is increasing by approximately 0.31% per year. Newborns following ART appear smaller at birth but show no signs of poor health.

Key words: reproductive assisted technologies, ART, infertility, pregnancy

Introduction

Infertility, defined as failure to conceive despite frequent sexual intercourse without the use of contraceptive measures for twelve months, affects up to 1 in 6 Canadian couples.[1] The risk of infertility increases with advancing maternal age, and while infertility is sometimes unexplained, it often stems from underlying medical conditions. Assisted reproductive technologies (ART) is an umbrella term for medical interventions aiming to improve fertility and includes techniques where eggs or sperm are manipulated outside of the body such as in vitro fertilization (IVF). In Canada, ART also includes ovulation induction and intrauterine insemination.[1] Previous studies have found that ART pregnancies are associated with a higher risk of unfavorable outcomes including high rates of multiple births[2,3], low birth weights[2,4,5], premature births[2,4,5], and increased maternal morbidity and mortality[2,6].

In Canada, pregnant women have access to universal healthcare, and despite ART not being publicly funded in all provinces, the number of ART cycles resulting in live births are comparatively high.[7] With increasing success rates, large population-based studies evaluating the health outcomes in ART pregnancies in Canada are needed. In this retrospective study, we evaluated temporal trends, socio-demographic, and clinical characteristics of all women with live births following ART and non-ART in the province of Alberta, Canada over the last decade. We also compared obstetric and neonatal outcomes between ART pregnancies and naturally conceived pregnancies, overall and across maternal age groups.

Materials and methods

Ethical approval was received from the University of Alberta Research Ethics Board (Pro00056999). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki. Due to the retrospective and unidentifiable nature of the data, informed consent from individuals was not required.

Data linkage and population

This is a retrospective, population-level study using data received from the Province of Alberta Ministry of Health (Alberta Health). The study is based on data from the longitudinal Alberta Pregnancy-Birth cohort, which has been previously described.[8,9] Briefly, maternal inpatient data, ambulatory records, physician claims, pharmaceutical claims data, and laboratory data, were linked to the offspring records via the birth registry. Women giving birth to a live offspring following ART treatment[1] were identified as either those with prescriptions filled with pharmaceutical agents known to increase fertility (Supplementary Table S1) or as those who had an International Classification of Disease (ICD) 9th or 10th revision (Supplementary Table S2) code for ART treatment in any diagnostic field of their inpatient, outpatient clinic, or physician office visit records within six-months prior to or during the pregnancy. All other women were classified as non-ART. Pharmaceutical data became available for research as of April 1, 2008, allowing for adequate capture prior to conception. The current cohort was restricted to women giving birth between July 1, 2009 to December 31, 2014. Women residing outside of Alberta at the time of delivery, under the age of 14 or over the age of 54, and with missing or incorrect dates were excluded from the study.

Clinical and demographical data

Maternal age at delivery was obtained from the population registry. Previously validated naming algorithms were used to identify women of South-Asian or Chinese ethnicity.[10,11] All other women were categorized as general population, which in Alberta at the time of the study was compromised largely of Caucasians. The vital statistics birth registry provided information on maternal marital status (married or not married). Annual household income was obtained at the neighbourhood level by linking residential postal codes of the mother to Statistics Canada 2006 census data. Pre-existing conditions of the mother, such as diabetes, cardiovascular disease, chronic obstructive pulmonary disease, asthma, renal failure, liver disease, epilepsy, and lupus, were identified using ICD codes (Supplementary Table S3) from the delivery hospitalization, any previous hospitalization, or ambulatory records as of April 1, 1997.

Gestational diabetes and hypertensive disorders of pregnancy (including preeclampsia and eclampsia) were identified using ICD codes from the delivery hospitalization records (Supplementary Table S3).

Obstetrical delivery was classified as spontaneous vaginal birth, induction of labour, and/or Caesarean section from the delivery hospitalization records. The Vital Status Birth records were used to access information on birth weights and the delivery hospitalization records for length of neonatal intensive care unit (NICU) stay, when applicable. Congenital anomalies were identified according to ICD9 and ICD10 codes (Supplementary Table S4) from the delivery hospitalization.

Statistical analysis

The incidence of ART pregnancies was calculated by dividing the number of ART pregnancies by the total number of pregnancies for each birth year and reported ART pregnancies per 1000 pregnancies. Frequency tables were created for each maternal age category. Distribution of maternal characteristics and obstetrical/neonatal outcomes were compared between women with and without ART pregnancies using Pearson chi-square test and independent t-test for categorical and continuous variables, respectively. The unit of analysis for maternal characteristics was the pregnancy and the unit of analysis for obstetrical and neonatal outcomes was the live birth events. All analyses were performed using R version 3.5.0.

Results

There were 286,183 live births in Alberta between July 1, 2009 and December 31, 2014. After excluding 8268 (2.9%) live births of women not residing in Alberta at the time of delivery, 17 (0.00006%) live births to mothers at the age of less than 14 years or over 54 years, and 50 (0.0002%) births with missing or incorrect dates, a total of 277,847 live births remained. Of these 11,258 (4.1%) pregnancies were classified as the ART cohort and the remaining 266,589 (95.9%) live births constituted the non-ART cohort (Figure 1). The incidence of live births with ART increased from 28.4 per 1000 pregnancies in 2009 to 43.8 per 1000 pregnancies in 2014 (Figure 2), resulting in a 0.31% (95%CI: 0.28%, 0.34%, $p<0.001$) increase per year in newborns following ART pregnancies. When stratified by maternal age

group, the temporal trends in live births following ART showed an increase across all groups. The highest proportion of newborns following ART were in women aged 30-35 years or in women 35 years and older (Figure 3).

Compared to women giving birth following pregnancies without ART treatment, women undergoing ART treatment were older (33.4 vs 29.2 years, p<0.001), more likely to be married (79.2 vs 69.3%, p <0.001), more often primiparous (62.8 vs 53.3%, p<0.001), delivered more twins (11.0 vs 1.3%) and triplets (0.4 vs 0.02, p<0.001), and lived in urban areas (89.8 vs 83.5%, p<0.001, Table 1). There were no differences in median household income or large differences in ethnic backgrounds between ART and non-ART cohorts. Women who underwent ART treatment had higher rates of pregnancy disorders such as gestational diabetes (11.0 vs 7.2%, p<0.001) and hypertensive disorders of pregnancy (9.4 vs 6.4%, p<0.001) and pre-existing conditions including diabetes (1.7 vs 1.0, p<0.001) and cardiovascular disease (1.4% vs 1.1%, p=0.003). Rates of composite pre-existing conditions, including chronic obstructive pulmonary disease, asthma, renal failure, liver disease, epilepsy, and lupus were similar between ART and non-ART cohorts.

C-section rates were higher in ART pregnancies than non-ART pregnancies (41.9 vs 27.6%, p<0.001) and a there was a higher incidence of ART conceived newborns with a body weight of less than 2500 grams (14.8 vs 5.1%, p<0.001, Table 2). Admission to NICU immediately following birth was about twice as frequent among neonates conceived following ART compared to non-ART pregnancies (27.8 vs 15.8%, p<0.001). Crucially, there were no differences in the rate of congenital anomalies between newborns in the ART and non-ART cohorts (0.49 vs 0.43%, p=0.466).

The highest incidence of twin pregnancies was among women who had undergone ART treatment and were over 30 years of age (Table 3). These groups also showed the highest rates of C-section (Table 4). Conversely, younger women (<25 years) with ART had the proportionally highest rates of pre-term delivery (ART vs non-ART: 21.8 vs 6.0%) and newborns at low birth weights (ART vs non-ART: 17.0 vs 5.0% of babies born at <2.5kg) (Table 4).

Discussion

This retrospective population-based study of all live-birth deliveries in Alberta, Canada, between July 2009 and December 2014 found that 4.1% of live-births were following ART, while the incidence of ART pregnancies resulting in live-births increased by 0.31% per year over the study period. Women in the ART cohort were on average older and had higher rates of pre-existing and pregnancy-related conditions compared to the non-ART cohort. Newborns following ART conceptions were more likely to be multiples, have low birth weight, and born preterm, while the presence of congenital anomalies were similar between ART and non-ART cohorts.

Reports to date on the outcomes of ART treatments leading to live births in Canada have shown varied results. At the time of the current study, the annual CARTR report from 2012 recorded 5971 live births in Canada following ART that year.[12] Based on data from Statistics Canada from 2012[13], this would have constituted only 1.5% of all live births. In contrast to this low number, a 2013 prospective study from Calgary, Alberta containing data on 1564 pregnant women, reported that 5.9% were conceived following ART.[14] These large differences in rates of live births following ART may be in part due to incomplete reporting, reporting bias, or differences in the definition of ART. Similarly, in the United States, reports of the number of procedures performed, techniques used, and outcomes disclosed to the National ART Surveillance System (NASS), only includes procedures where one or more embryos are transferred but does not include ovulation induction or artificial insemination.[15]. As such, the overall rate from the most recent NASS report with data from 2015/2016 indicates that only 1.8% of babies born in the United States are from ART pregnancies[15], which is lower than what has been reported in other contemporary American studies.[16] Our population-based study used data from all live births from a defined geographical area with universal healthcare between July 2009 and December 2014. Our finding of an overall rate of 4.1% of newborns following ART likely reflects a more accurate incidence of ART births in a North American population.

Similar to previous studies[2-5], we found that women undergoing ART had increased rates of pregnancy complications, multiple births, and obstetric interventions. Newborns following ART were more often premature and had lower birth weights than non-ART conceptions. However, contrary to what has been reported previously[17], we did not see increased rates of congenital anomalies in the neonates following ART. It has been suggested that the increased risk of birth defects following ART may be more strongly linked to the etiology of infertility rather than the ART medications.[17-19] As such, subfertility, which is when couples conceive without the use of ART after more than a year of not being able to conceive, could be a confounding factor that could not be adjusted for in the current analysis. It may partly explain why we did not find increased rates of congenital anomalies in our ART cohort. The current study only assessed outcomes reported during the delivery hospitalization. Any anomalies reported beyond the delivery hospitalization were not captured in the current analysis.

An unexpected finding in the current study was the comparatively high rates of preterm births and low birth weight newborns among young mothers (<25 years) with ART. While numerous studies have assessed the impact of advanced maternal age on perinatal outcomes both after conceiving spontaneously and following ART[20, 21], little is known about why newborns of younger women with ART may be at increased risk of adverse perinatal outcomes when compared to mothers of advanced age. It can be speculated that the etiology of infertility among women under the age of 25 undergoing ART is different to that of older women undergoing ART because of delayed childbearing. For example, polycystic ovarian syndrome (PCOS) is a cause of infertility among young women[22] and has been associated with poorer obstetric and perinatal outcomes.[23] While the underlying infertility diagnosis was beyond the scope of the current study, aetiologies such as PCOS in younger women may explain why this group had poorer perinatal outcomes compared to those of higher ages or non-ART women. Further studies are needed to confirm these findings and the reasons behind them. The incidence of live births amongst women 30 years and older increased over the span of the study, but increasing maternal age was not associated with increased maternal or perinatal health risks beyond what would be expected for non-ART women in the

same age-groups. This finding supports previous population-level research from Sweden looking specifically at pregnancy outcomes among women of advanced age with and without ART treatment.[20]

Although the current study utilized data from a large population-based cohort, it is limited by the lack of some key data, such as maternal weight and paternal fertility. As the data linkage in the current study was via the birth registry, only live births were included with no information on ART success rates or trends in overall use of ART could be evaluated.

Conclusions

In summary, the incidence of live births following ART in Alberta, Canada is 4.1% and is increasing over time. Women who had ART have higher rates of pregnancy complications, while newborns following ART are more often preterm and have a low birth weight. In this population-level contemporary study, we did not see signs of increased risk of congenital anomalies following ART.

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Authors' contributions: All authors contributed to the study conception and design. Data analysis were performed by MH and results were discussed and interpreted by all authors. The first draft of the manuscript was written by LM and all authors commented on previous versions of the manuscript. TM

provided content expertise. PK provided methodological expertise. All authors read and approved the final manuscript.

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Table 1. Maternal characteristics according to ART group

Characteristics	Without ART	With ART	p
Pregnancy, N	263,169	10,072	--
Women, N	203,391	9168	--
Children, N	266,589	11,258	--
Primiparous N (%)	140,307(53.31%)	6325(62.8%)	<0.001
Multiple Birth N (%)	3362(1.28%)	1144(11.36%)	<0.001
Multiple Birth N (%), categories			
Twins	3304(1.26%)	1103 (10.95%)	<0.001
Triplets	58(0.02%)	40 (0.4%)	
Quadruplets	0(0%)	1(0.01%)	
Age at delivery, mean (SD), years	29.21 (5.3)	33.44 (4.9)	<0.001
Age at delivery, years			
<25 N (%)	51,053(19.4%)	312(3.1%)	<0.001
25-30 N (%)	84,715(32.19%)	1802(17.89%)	
30-35 N (%)	84,433(32.08%)	3790(37.63%)	
>35 N (%)	42,968(16.33%)	4168(41.38%)	
Ethnicity			
General Population N (%)	168,120(93.02%)	7478(91.78%)	<0.001
Chinese N (%)	6667(3.69%)	354(4.34%)	
South Asian N (%)	5944(3.29%)	316(3.88%)	
Rural Residence at delivery N (%)	43,559(16.55%)	1026(10.19%)	<0.001
Married N (%)	126,697(62.29%)	7265(79.24%)	<0.001
Annual household income CAD, median (IQR)	58,618 (47,685-73,284)	58,637	0.280

		(48,039-72,765)	
Pre-existing diabetes N (%)	2031(1%)	153(1.67%)	<0.001
Pre-existing cardiovascular disease N (%)	2209(1.09%)	130(1.42%)	0.003
Other pre-existing medical conditions * N (%)	6629 (3.26%)	328 (3.58%)	0.099
Gestational diabetes N (%)	18,906(7.18%)	1110(11.02%)	<0.001
Hypertensive disorders of pregnancy N (%)	16,794(6.38%)	945(9.38%)	<0.001

*Including chronic obstructive pulmonary disease, asthma, renal failure, liver disease, epilepsy, and lupus

Table 2. Obstetric and neonatal outcomes according to ART group

Characteristics	Without ART	With ART	p
Spontaneous vaginal births, n (%)	146,112 (54.8%)	4383 (38.9%)	<0.001
Induced labor, n (%)	95,734 (35.9%)	4174 (37.1%)	0.012
C-section, n (%)	73,474 (27.6%)	4713 (41.9%)	<0.001
Pre-term delivery (<37 weeks), n (%)	16,494(6.27%)	1691(16.79%)	<0.001
Prolonged pregnancy (>41 weeks), n (%)	687(0.26%)	13(0.13%)	<0.001
Birth weight, g (SD)	3330.63 (579.68)	3039.72 (778.14)	<0.001
Birth weight <2.5 kg, n (%)	13,353(5.07%)	1491(14.8%)	<0.001
Birth weight 2.5-4.0 kg, n (%)	177,416(67.42%)	6436(63.9%)	<0.001
Birth weight >4.0 kg, n (%)	22,160(8.42%)	629(6.25%)	<0.001
Neonatal ICU stay			
Yes, n (%)	42,156 (15.8%)	3128 (27.8%)	<0.001
Congenital anomalies	1139 (0.43%)	49 (0.49%)	0.466

Table 3. Maternal characteristics according to ART group and maternal age at delivery

Characteristics	Without ART					With ART				
	<25	25-30	30-35	>35	**Total**	<25	25-30	30-35	>35	**Total**
Pregnancy, N	51,053 (99.4%)	84,715 (97.9%)	84,433 (95.7%)	42,968 (91.2%)	**263,169**	312 (0.61%)	1802 (2.1%)	3790 (4.3%)	4168 (8.8%)	**10,072**
Children, N	51,522 (99.4%)	85,745 (97.7%)	85,661 (95.3%)	43,661 (90.3%)	**266,589**	329 (0.6%)	1993 (2.3%)	4254 (4.7%)	4682 (9.7%)	**11,258**
Primiparous N (%)	33,695 (66.0%)	46,473 (54.9%)	39,898 (47.3%)	20,241 (47.1%)	**140,307 (53.3%)**	224 (71.8%)	1216 (67.5%)	2366 (62.4%)	519 (60.4%)	**6325 (62.8%)**
Multiple Birth N (%)	460 (0.9%)	1014 (1.2%)	1204 (1.43%)	684 (1.59%)	**3362 (1.28%)**	16 (5.13%)	181 (10.04%)	449 (11.85%)	498 (11.95%)	**1144 (11.36%)**
Multiple Birth N (%), categories										
Twins	451 (0.88%)	998 (1.18%)	1180 (1.4%)	675 (1.57%)	**3304 (1.26%)**	15 (4.81%)	172 (9.54%)	434 (11.45%)	482 (11.56%)	**1103 (10.95%)**
Triplets	9 (0.02%)	16 (0.02%)	24 (0.03%)	9 (0.02%)	**58 (0.02%)**	1 (0.32%)	8 (0.44%)	15 (0.4%)	16 (0.38%)	**40 (0.4%)**

Quadruplets	0 (0%)	0 (0%)	0 (0%)	0 (0%)	**0 (0%)**	0 (0%)	1 (0.06%)	0 (0%)	0 (0%)	**1 (0.01%)**
Age at delivery, mean (SD), years	21.48 (2.2)	27.20 (1.4)	31.79 (1.4)	37.25 (2.2)	**29.21 (5.3)**	22.36 (1.8)	27.52 (1.3)	32.10 (1.4)	38.10 (2.8)	**33.44 (4.9)**
Rural Residence at delivery N (%)	13,908 (27.24%)	14,743 (17.4%)	10,264 (12.16%)	4644 (10.81%)	**43,559 (16.55%)**	71 (22.76%)	281 (15.59%)	368 (9.71%)	306 (7.34%)	**1026 (10.19%)**
Gestational diabetes N (%)	1660 (3.25%)	4648 (5.49%)	6958 (8.24%)	5640 (13.13%)	**18,906 (7.18%)**	22 (7.05%)	129 (7.16%)	396 (10.45%)	563 (13.51%)	**1110 (11.02%)**
Hypertensive disorders of pregnancy N (%)	3013 (5.9%)	5225 (6.17%)	5401 (6.4%)	3155 (7.34%)	**16,794 (6.38%)**	13 (4.17%)	162 (8.99%)	311 (8.21%)	459 (11.01%)	**945 (9.38%)**

*Including chronic obstructive pulmonary disease, asthma, renal failure, liver disease, epilepsy, and lupus

Table 4. Obstetric and neonatal outcomes by ART group and maternal age at delivery

Characteristics	Without ART					With ART				
	<25	25-30	30-35	>35	**Total**	<25	25-30	30-35	>35	**Total**
Spontaneous vaginal births, n (%)	30,364 (58.9%)	48,873 (57.0%)	46,382 (54.1%)	20,493 (46.9%)	**146,112 (54.8%)**	181 (55.0%)	942 (47.3%)	1734 (40.8%)	1526 (32.6%)	**4383 (38.9%)**
Induced labor, n (%)	17,957 (34.9%)	31,202 (36.4%)	30,708 (35.8%)	15,867 (36.3%)	**95,734 (35.9%)**	96 (29.2%)	742 (37.2%)	1518 (35.7%)	1818 (38.8%)	**4174 (37.1%)**
C-section, n (%)	10,814 (21.0%)	21,700 (25.3%)	25,488 (29.8%)	15,472 (35.4%)	**73,474 (27.6%)**	84 (25.5%)	667 (33.5%)	1712 (40.2%)	2250 (48.1%)	**4713 (41.9%)**
Pre-term delivery (<37 weeks), n (%)	3084 (6.04%)	4996 (5.9%)	5201 (6.16%)	3213 (7.48%)	**16,494 (6.27%)**	68 (21.79%)	307 (17.04%)	620 (16.36%)	696 (16.7%)	**1691 (16.79%)**
Prolonged pregnancy (>41 weeks), n (%)	147 (0.29%)	184 (0.22%)	223 (0.26%)	133 (0.31%)	**687 (0.26%)**	0 (0%)	1 (0.06%)	5 (0.13%)	7 (0.17%)	**13 (0.13%)**

Birth weight, g (SD)	3343 (574.39)	3351.63 (566.91)	3339.77 (572.65)	3306.47 (600.13)	**3330.63 (579.68)**	2916.47 (840.13)	3070.63 (783.37)	3062.4 (776.36)	3040.7 (770.35)	**3039.72 (778.14)**
Birth weight <2.5 kg, n (%)	2515 (4.93%)	3887 (4.59%)	4262 (5.05%)	2689 (6.26%)	**13,353 (5.07%)**	53 (16.99%)	264 (14.65%)	554 (14.62%)	620 (14.88%)	**1491 (14.8%)**
Birth weight 2.5-4.0 kg, n (%)	32,914 (64.47%)	55,929 (66.02%)	57,962 (68.65%)	30,611 (71.24%)	**177,416 (67.42%)**	179 (57.37%)	1084 (60.16%)	2386 (62.96%)	2787 (66.87%)	**6436 (63.9%)**
Birth weight >4.0 kg, n (%)	4202 (8.23%)	7118 (8.4%)	7229 (8.56%)	3611 (8.4%)	**22,160 (8.42%)**	13 (4.17%)	107 (5.94%)	251 (6.62%)	258 (6.19%)	**629 (6.25%)**
Neonatal ICU stay, n (%)	7870 (15.3%)	13,191 (15.4%)	13,657 (15.9%)	7438 (17.0%)	**42,156 (15.8%)**	99 (30.1%)	579 (29.1%)	1182 (27.8%)	1268 (27.1%)	**3128 (27.8%)**
Congenital anomalies	276 (0.54%)	390 (0.46%)	310 (0.37%)	163 (0.38%)	**1139 (0.43%)**	1 (0.32%)	6 (0.33%)	20 (0.53%)	22 (0.53%)	**49 (0.49%)**

Figure Legends

Figure 1. Flow diagram of cohort selection.

Figure 2. Number of mothers giving birth to a live offspring following ART treatment and incidence of ART pregnancies leading to live births per 1000 pregnancies in Alberta July 1, 2009 – December 31, 2014. The increase in ART live births per year was 3.12 per 1000 pregnancies (0.31%, 95%CI: 0.28%-0.24%, p<0.001).

Figure 3. Number of mothers giving birth to live offspring following ART treatment according to maternal age groups at the time of delivery July 1, 2009 – December 31, 2014 in Alberta. The annual increase in babies born following ART was 1.27 (0.13%; 95%CI: 0.08%, 0.17%; p=0.005), 1.72 (0.17%; 95%CI: 0.11%, 0.23%; p=0.004), 2.96 (0.30%; 95% CI: 0.24%, 0.35%; p<0.001) and 4.44 (0.34%; 95%CI: 0.34%, 0.55%; p=0.001) per 1000 pregnancies for mothers <25, 25-30, 30-35, and >35 years of age, respectively.

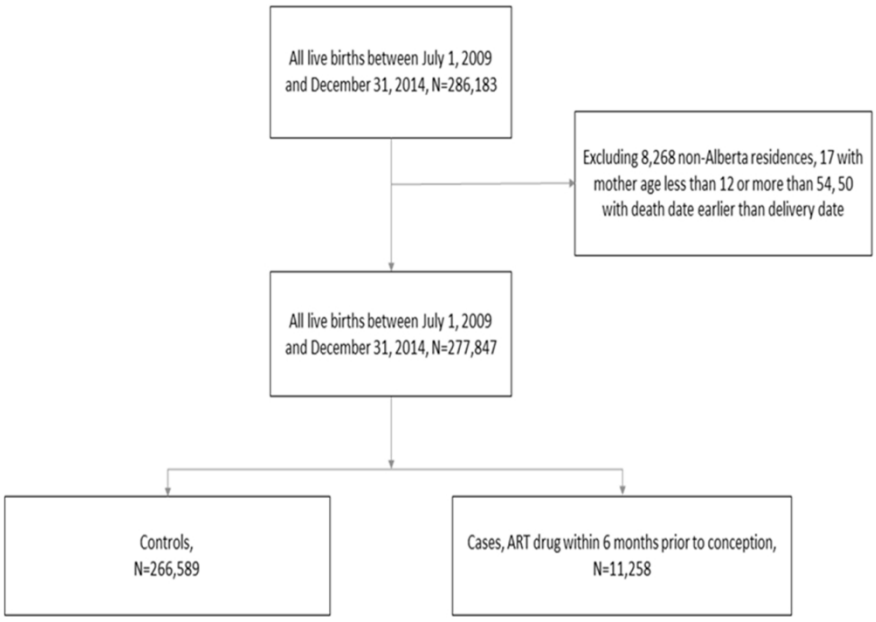
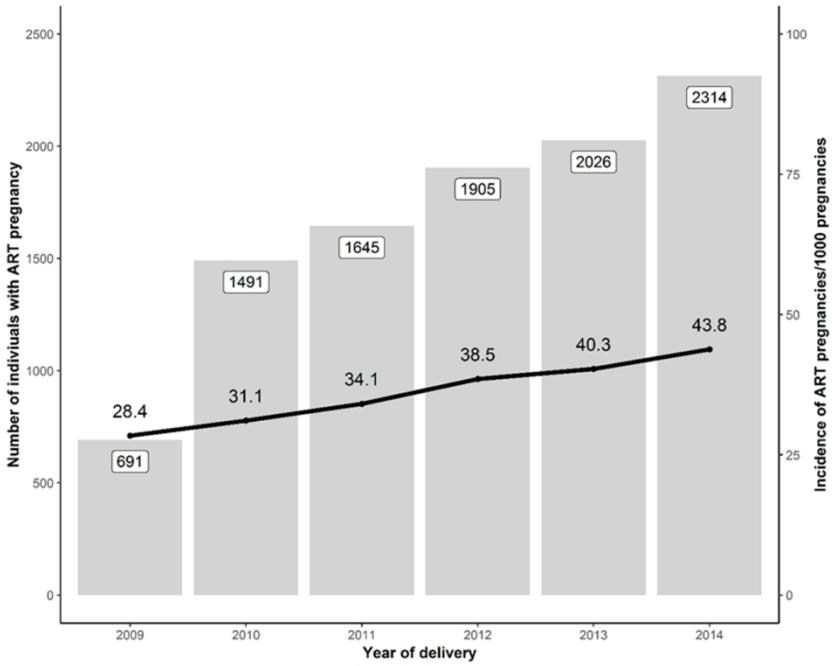


Figure 1. Flow diagram of cohort selection.

254x190mm (300 x 300 DPI)



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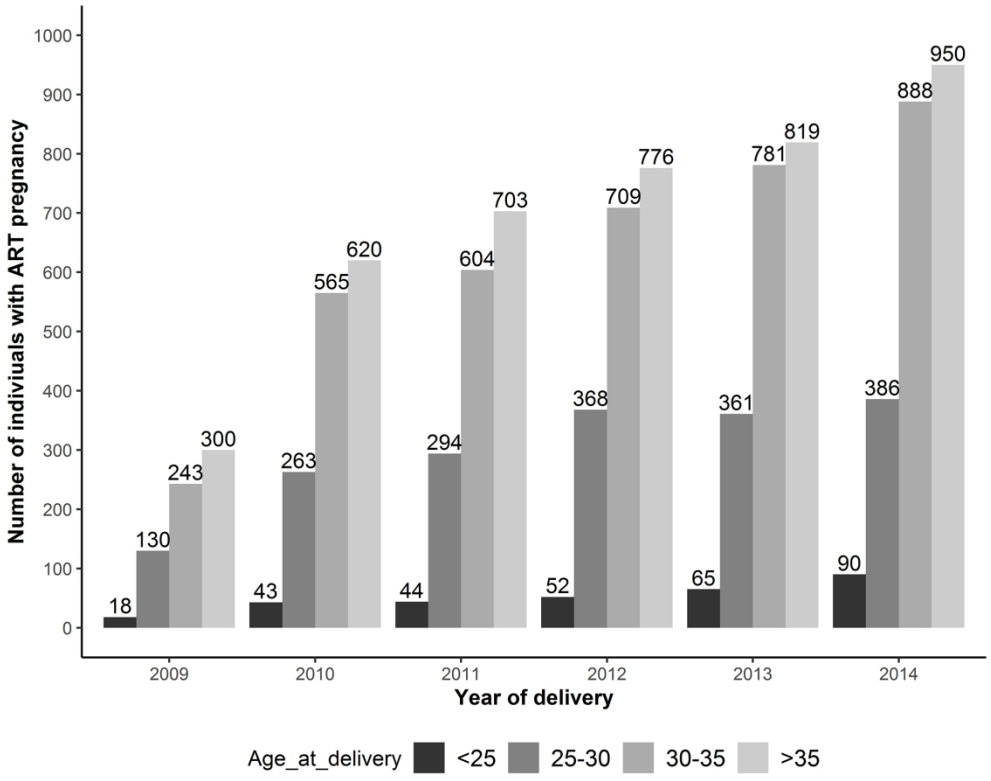

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181x145mm (300 x 300 DPI)

Supplementary Table S1. Drugs used to find ART cases in PIN dataset

Drug Name	DIN	ATC
Clomid/ Clomifene	02091879	G03GB02
	00018031	
Repronex/ Menopur	02247790	G03GA02
	02283093	
Ovidrel/ choriogonadotropin alpha	02262088	G03GA08
	02371588	
Bravelle/ Urofollitropin	02268140	G03GA04
Gonal-F/ follitropin alfa	02231464	G03GA05
	02231465	
	02243004	
	02244787	
	02248154	
Puregon/ Follitropin beta	02242439	G03GA06
	02242441	
	02243948	
	02243949	
	02231656	
	02231655	
Oregalutran/ Ganirelix	02245641	H01CC01
Cetrotide/ Cetrorelix	02247766	H01CC02
	02247767	
Crinone/ Progesterone	02241013	G03DA04
Endometrin/ Progesterone	02334992	G03DA04
Femara/ Letrozole	02231384	L02BG04

Supplementary Table S2. ICD-9 and ICD-10 codes used to identify ART cases in ambulatory care, inpatient hospital separations, and practitioner claims databases.

ICD 10	ICD 9
Z31.1: Artificial insemination	**V26.1:** Artificial insemination
Z31.2: In vitro fertilization	**V23.85:** Pregnancy resulting from assisted reproductive technology
Z31.3: Other assisted fertilization methods	

Supplementary Table S3. ICD codes for medical conditions in the mother (pre-existing and gestational)

Conditions	**ICD 10 codes**	**ICD 9 codes**	**Procedure**
CHD	745-747	Q20-Q28	
Preeclampsia	O14	642.4, 642.5	
HELLP syndrome	O14.2	642.53	
Eclampsia	O15	642.6	
Preeclampsia/eclampsia superimposed on pre-existing hypertension	O11 (superimposed preeclampsia)	642.7	
Hypertension	I10-I15	401-405	
Pre-existing hypertension complicating pregnancy, childbirth and the puerperium	O10	642.0, 642.1, 642.2	
Unspecified maternal hypertension	O16	642.9	
Gestational hypertension	O13	642.3	
Postpartum hemorrhage	O72	666	
Placental abruption	O45	641.2	
Nutritional anemia	D50-D53	280, 281	
Cardiac arrest	I46	427.5	
following C/S or other obstetric surgery or procedures, including delivery NOS	O75.4		
Following abortion or ectopic or molar pregnancy	O08.8		
Heart failure	I50	428	
following C/S or other obstetric surgery or procedures, including delivery NOS	O75.4		
Following abortion or ectopic or molar pregnancy	O08.8		
Cardiomyopathy in puerperium	O90.3		

Diseases of the circulatory system complicating pregnancy, childbirth and puerperium	O99.4	648.6	
Acute pulmonary oedema	J81	518.4	
Heart Failure/ Peripartum cardiomyopathy	I50, J81, O08.8, O75.4, O90.3, O99.4		
Cerebrovascular disease	G45, G46, H34, I60-I69	430-438	1.JE.xx, 1.JJ.xx, 1.JK.xx, 1.JW.xx, 1.JX.xx
Peripheral artery disease	I70, I71, I72, I73, I74, I77, I79, K55, Z95	440, 441, 442, 443, 444, 447, 557, 785.4, V34.4	1.KG.xx, 1.KA.xx 1.KE.xx, 1.KT.xx, 1.xx.93
Coronary artery disease	I20, I21, I22, I23, I24	410, 411, 412, 413, 429.6	1.IJ.50, 1.IJ.76, 1.IJ.55, 1.IJ.57, 1.IJ.26, 3.IP.10
Anemia	D50, D53.9, D64.9, D62.0	280-289	
Anemia complicating pregnancy, childbirth and the puerperium	O99.0	648.2	
Diabetes	E10-E14	250	

Pre-existing diabetes in pregnancy	O24.0-O24.3, O24.5-O24.7, O24.9	648.0	
Gestational diabetes	O24.4, O24.8	648.8	
Lupus	M32	7100	
Renal disease	I210, I131, N03.2-N03.7, N05.2-N05.7, N18, N19, N25.0, Z49.0-Z49.2, Z94.0, Z99.2	582, 583, 585, 586, 588	

Supplementary Table S4. ICD codes for congenital abnormalities in the child

Conditions	ICD 10 codes	ICD 9 codes
Congenital anomalies in child		
Congenital heart disease	Q20-Q28	745-747
Anencephaly/Acrania	Q00.0	740.0
Transposition of great vessels	Q20.1, Q20.3, Q20.5, Q20.8	745.1X
Hypoplastic left heart syndrome:	Q23.04	746.7
Renal agenesis and dysgenesis	Q60.2, Q60.5	753.0
Anomalies of diaphragm: Absence of diaphragm, Congenital hernia: diaphragmatic, foramen of Mrgagni, Eventration of diaphragm	Q79.0, Q79.1	756.6
Patau's syndrome	Q91.7	758.1
Edward's syndrome	Q91.3	758.2
Tetralogy of Fallot	Q21.3	745.2
Common ventricle	Q20.4	745.3
Endocardial cushion defects	Q21.2	745.6X
Anomalies of pulmonary valve congenital	Q22.0-3	746.0X
Other specified congenital anomalies of heart	Q24.0-6, Q24.8	746.8X
Patent ductus arteriosus	Q25.0	747.0
Coarctation of aorta (preductal) (postductal)	Q25.1	747.10
Anomalies of pulmonary artery	Q25.5, Q25.6, Q25.71, Q25.72, Q25.79	747.3
Agenesis, hypoplasia, and dysplasia of lung	Q33.2, Q33.3, Q33.6	748.5

Tracheosophageal fistula, esophageal atresia and stenosis	Q39.0-4	750.3
Atresia and stenosis of small intestine	Q41.9	751.1
Atresia and stenosis of large intestine, rectum, and anal canal	Q42.9	751.2
Congenital single renal cyst	Q61.01	753.11
Polycystic kidney	Q61.2, Q61.3, Q61.19	753.12-14
Renal dysplasia	Q61.4	753.15
Other specified cystic kidney disease	Q61.8	753.19
Anomalies of abdominal wall	Q79.2-4, Q79.51, Q79.59	756.7
Other conditions due to autosomal anomalies: Accessory autosomes NEC, Triploidy	Q92.7	758.5

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6

Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5-6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5-6
Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	5
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	6
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	6

Statistical methods	#12c	Explain how missing data were addressed	6
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	6
Statistical methods	#12e	Describe any sensitivity analyses	6
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	6
Participants	#13b	Give reasons for non-participation at each stage	6
Participants	#13c	Consider use of a flow diagram	6
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	7
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	6

Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
Main results	#16b	Report category boundaries when continuous variables were categorized	7
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	#18	Summarise key results with reference to study objectives	8

Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	10
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	10
Generalisability	#21	Discuss the generalisability (external validity) of the study results	10
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2