

Assisted human reproduction and pregnancy outcomes in Alberta, 2009–2018: a population-based study

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Abstract

Background: Assisted human reproduction (AHR) can be used to help individuals and couples overcome infertility issues. We sought to describe trends in pregnancies using AHR and to evaluate the impact of AHR on perinatal outcomes in a large population-based cohort in Alberta, Canada.

Methods: We linked maternal and child administrative data for all live births occurring July 1, 2009, to Dec. 31, 2018, in Alberta, Canada, for this retrospective study. We identified AHR pregnancies from pharmaceutical claims or codes from the *International Classification of Diseases and Related Health Problems* (9th or 10th revision). Our main outcome measures were the incidence and temporal trends of live births in AHR pregnancies. We also compared maternal characteristics and perinatal outcomes of AHR and non-AHR pregnancies, and by maternal age group.

Results: Of 518 293 live births during the study period, 26 270 (5.1%) were conceived with AHR. The incidence of AHR pregnancies increased from 30.8 per 1000 pregnancies in 2009 to 54.7 per 1000 pregnancies in 2018. Females who used AHR were older (33.9 yr v. 30.1 yr, $p < 0.001$) and the number of females aged 30–35 years and older than 35 years who delivered following AHR increased over the study period (30–35 yr: 36.9 to 55.3 per 1000 pregnancies; > 35 yr: 79.1 to 95.2 per 1000 pregnancies). The proportion of live births with cesarean delivery (40.5% v. 23.3%, $p < 0.001$), low birth weight (26.9% v. 7.6%, $p < 0.001$), congenital malformation (0.5% v. 0.3%, $p = 0.002$) and admission to the neonatal intensive care unit (25.3% v. 9.7%, $p < 0.001$) was higher in the AHR group than the non-AHR group.

Interpretation: The incidence of live births following AHR pregnancies in Alberta was 5.1% between 2009 and 2018, and increased by 0.26% per year; newborns in the AHR group appeared smaller and showed signs of poorer health. This study provides insights on potential perinatal complications following AHR that may be important when caring for the newborn child.

Infertility, defined as failure to conceive despite frequent sexual intercourse without the use of contraceptive measures for at least 12 months, affects up to 1 in 6 couples in Canada.¹ The risk of infertility increases with advancing maternal age, and although infertility is often unexplained, it may also stem from underlying medical conditions.¹ Assisted human reproduction (AHR) is an umbrella term for medical interventions that aim to improve fertility, and includes techniques where eggs or sperm are manipulated outside of the body, such as in vitro fertilization (IVF). In Canada, AHR also includes ovulation induction and intrauterine insemination.¹ Previous studies have found that AHR pregnancies are associated with a higher risk of unfavourable outcomes including high rates of multiple births,^{2,3} low birth weights,^{3–5} premature births^{3–5} and increased maternal morbidity and mortality.^{3,6}

In the Canadian province of Alberta, pregnant people have access to publicly funded health care. Although AHR is not being publicly funded in Alberta, the number of AHR

cycles resulting in live births is relatively high compared with contemporary reports from other countries.^{7,8} With increasing success rates, large population-based studies that evaluate the health outcomes in AHR pregnancies in Canada are needed. In this retrospective study, we sought to evaluate temporal trends, and sociodemographic and clinical characteristics of all women with live births following AHR and non-AHR pregnancies in Alberta, Canada, between 2009 and 2018. We also sought to compare obstetric and neonatal outcomes between AHR pregnancies and naturally conceived pregnancies, overall and across maternal age groups.

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Methods

Study setting

Alberta is one of the most populous provinces of western Canada and, at the time of the study, had a population of 4 million people.⁹ The population increased by about 400 000 people over the study period of 2009 to 2018.¹⁰ Around the same time, the general population in Alberta comprised predominantly people of European descent (70%), and people of South Asian (5.8%) and Chinese (4%) descent were the most common visible minority groups.¹¹ Around 6.5% of the population identified as First Nations, Métis or Inuit.¹¹ The number of people from visible minority groups increased from 500 588 in 2009 to 565 808 in 2018 (overall growth rate 1.4%).¹⁰ The Alberta Health Care Insurance Plan offers health care coverage to all residents of Alberta and is administered through the Alberta Health Services. As of 2009, through to 2018, medical consultations and laboratory diagnostic work to confirm infertility were covered through public funding in Alberta; however, AHR procedures were not publicly funded.¹²

Data linkage and population

This is a retrospective, population-level study using data received from the Alberta Ministry of Health (Alberta Health). The study is based on data from the longitudinal Alberta Pregnancy–Birth cohort, which has been previously described.^{13,14} Briefly, maternal inpatient data, ambulatory records, physician claims, pharmaceutical claims data and laboratory data were linked to the records of the children born following each index pregnancy via the birth registry. Pre-pregnancy health data were available as of Apr. 1, 1997.

We identified people with live births following AHR treatment as either those with prescriptions filled with pharmaceutical agents known to increase fertility (Appendix 1, Supplementary Table S1, available at www.cmajopen.ca/content/11/2/E372/suppl/DC1) or as those who had an *International Classification of Diseases and Related Health Problems* (ICD, 9th or 10th revision) code for AHR treatment (Appendix 1, Supplementary Table S2) in any diagnostic field of their inpatient records, AHR treatment in outpatient clinic records or AHR treatment in records of physician office visits within 6 months before or during the pregnancy. The 6-month period was chosen based on the experience and advice of the clinical content expert on the study team (T.M.), who advised that any pregnancy exposed to AHR treatment could be identified during this time period. We classified all other live births as non-AHR. Pharmaceutical data became available for research as of Apr. 1, 2008, allowing for adequate capture before conception. We restricted the current cohort to children born from July 1, 2009, to Dec. 31, 2018, and their mothers. We excluded child–mother dyads where the mother resided outside of Alberta at the time of delivery, and those aged younger than 14 years or older than 54 years, as well as dyads with missing or incorrect dates. We did not exclude children born with extreme low birth weight (< 500 g) or those born extremely premature

(< 20 weeks' gestation). All information used in this study was based on routinely collected administrative health data. Data were extracted and linked by the Analytics, Performance and Reporting Health Standards, Quality and Performance group within Alberta Health; a biostatistician (M.H.) checked for errors.

Clinical and demographic data

We obtained maternal age at delivery from the population registry. We used previously validated naming algorithms to identify patients of South Asian or Chinese ethnicity.^{15,16} We categorized all others as general population. The vital statistics birth registry provided information on maternal marital status (married or not married). We obtained annual household income at the neighbourhood level by linking residential postal codes of the mother to Statistics Canada 2016 Census data. We identified pre-existing conditions of the mother, such as diabetes, cardiovascular disease and renal failure, via validated algorithms using ICD codes from the delivery hospital admission, any previous hospital admission or ambulatory records as of Apr. 1, 1997.^{17–19} We identified gestational diabetes and hypertensive disorders of pregnancy (including preeclampsia and eclampsia) via validated algorithms using ICD codes from records of the delivery hospital admission.^{20,21}

We classified type of obstetric delivery as spontaneous vaginal birth, induction of labour or cesarean delivery from records of the delivery hospital admission. We used vital status birth records to access information on birth weights, and records of the delivery hospital admission for length of neonatal intensive care unit (NICU) stay, when applicable. We identified congenital malformations according to ICD-9 and ICD-10 codes from the delivery hospital admission.

Statistical analysis

We calculated the incidence of AHR pregnancies by dividing the number of AHR pregnancies by the total number of pregnancies for each birth year, and reported AHR pregnancies per 1000 pregnancies. We evaluated the trend in AHR pregnancies per year using linear regression. We used generalized estimating equation (GEE) models with binary (for binary outcomes), Poisson (for count outcomes) and multinomial (for outcomes with multiple categories) link functions, using exchangeable correlation structure and robust standard errors to calculate *p* values (where applicable) to account for multiple live births over time from the same mother (as a cluster) and higher statistical power. We created frequency tables for each maternal age category. We compared the distribution of maternal characteristics and of obstetric and neonatal outcomes between patients with and without AHR pregnancies using GEE models. To ensure maternal characteristics were included only once per pregnancy but more than once if the mother gave birth more than once during the study period, the unit of analysis for maternal characteristics was the pregnancy. The unit of analysis for obstetric and neonatal outcomes was the child. We performed all analyses using R version 3.5.0.

Ethics approval

Ethics 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. Given the retrospective and unidentifiable nature of the data, informed consent from individuals was not required.

Results

There were 527 251 live births in Alberta between July 1, 2009, and Dec. 31, 2018. After excluding 8865 (1.7%) live births to patients who did not reside in Alberta at the time of delivery, 62 (0.00001%) live births to patients younger than 14 years or older than 54 years, and 31 (0.000006%) births with missing or incorrect dates, a total of 518 293 live births remained. Of these, 26 270 (5.1%) live births constituted the

AHR cohort and the remaining 492 023 (94.9%) live births constituted the non-AHR cohort (Appendix 1, Supplementary Figure S1). Characteristics and outcomes by AHR treatment, and additional results related to birth weight and prematurity are available in Appendix 1 (Supplementary Tables S3–S6).

The incidence of live births with AHR increased from 30.8 per 1000 pregnancies in 2009 to 54.7 per 1000 pregnancies in 2018 (Figure 1), resulting in a 0.26% (95% confidence interval 0.24%–0.29%) increase per year in newborns following AHR pregnancies. When stratified by maternal age group, the temporal trends in live births following AHR showed an increase across all groups (Figure 2). The highest relative proportion of newborns following AHR were among patients aged 30–35 years (37.1%) and among those aged 35 years and older (44.4%) compared with those younger than 25 years (2.7%) and those aged 25–30 years (15.8%, Table 1).

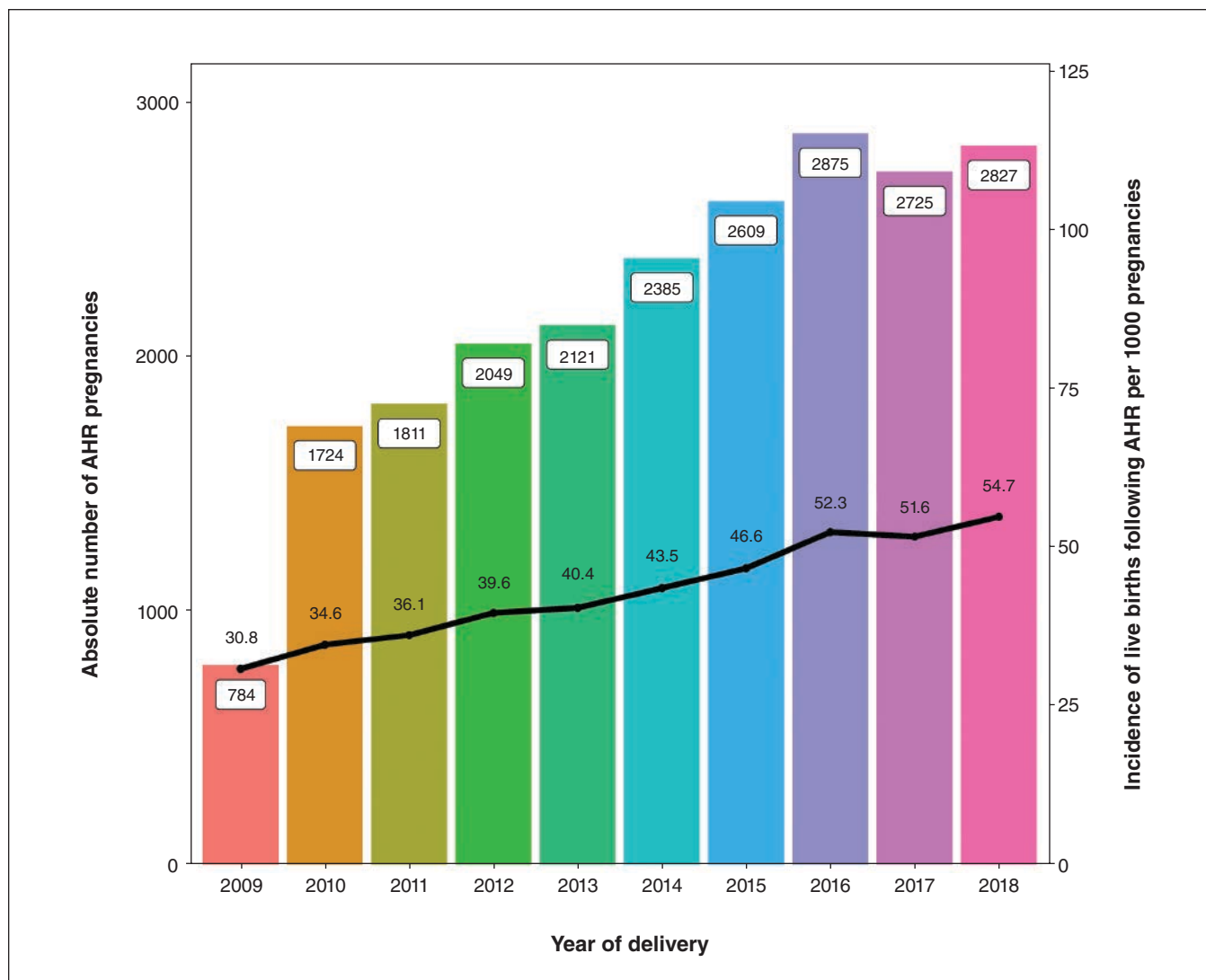


Figure 1: Absolute number of pregnancies resulting in live births following assisted human reproduction (AHR) treatment and incidence of AHR pregnancies leading to live births per 1000 pregnancies in Alberta from July 1, 2009, to Dec. 31, 2018. The absolute increase in AHR live births per year was 2.66 per 1000 pregnancies (0.26%, 95% confidence interval 0.24%–0.29%). For the year 2009, data were available only for July–December.

Compared with women giving birth following pregnancies without AHR treatment, those who underwent AHR treatment were older (33.9 yr v. 30.1 yr, $p < 0.001$), were more likely to be married (86.8% v. 69.7%, $p < 0.001$), were less often primiparous (54.7% v. 41.1%, $p < 0.001$), had higher rates of multiple births (18.8% v. 2.8%, $p < 0.001$) and were more likely to live in urban areas (85.3% v. 78.6%, $p < 0.001$) (Table 1). Women who underwent AHR treatment had lower median household incomes (\$76374 v. \$83039). There was an overall difference in the ethnic backgrounds of AHR and non-AHR cohorts, with higher rates of people who identified as being of South Asian (3.6% v. 2.8%) or Chinese (3.9% v. 3.2%) descent in the AHR group compared with the non-AHR group (Table 1). There was no difference in the rates of pre-existing conditions (including pre-existing diabetes and cardiovascular disease) or pregnancy-related conditions (gestational diabetes and hypertensive disorders of pregnancy). Women who underwent AHR treatment had lower rates of renal disease than those without AHR (2.5% v. 3.7%, $p < 0.001$).

Rates of cesarean delivery were higher among AHR pregnancies than non-AHR pregnancies (40.5% v. 23.3%, $p < 0.001$) and there was a higher incidence of AHR-conceived

newborns with a body weight of less than 2500 g (26.9% v. 7.6%, $p < 0.001$; Table 2). Admission to the NICU immediately after birth was more than twice as frequent among neonates conceived following AHR than among non-AHR pregnancies (25.3% v. 9.7%, $p < 0.001$). We observed a small but statistically significant difference in the rate of congenital malformations between newborns in the AHR and non-AHR groups (0.5% v. 0.3%, $p < 0.001$).

The highest incidence of twin pregnancies was among women who had undergone AHR treatment and were older than 30 years (Table 3). These groups also showed the highest rates of cesarean delivery (Table 4). Conversely, the youngest and the oldest AHR subgroups had the proportionally highest rates of preterm delivery (AHR v. non-AHR 32.2% v. 8.5% and 32.3% v. 10.3% for those aged < 25 yr and > 35 yr, respectively; Table 4).

Interpretation

In this retrospective population-based study of all live births in Alberta, Canada, between July 2009 and December 2018, we found that the incidence of live births following AHR was

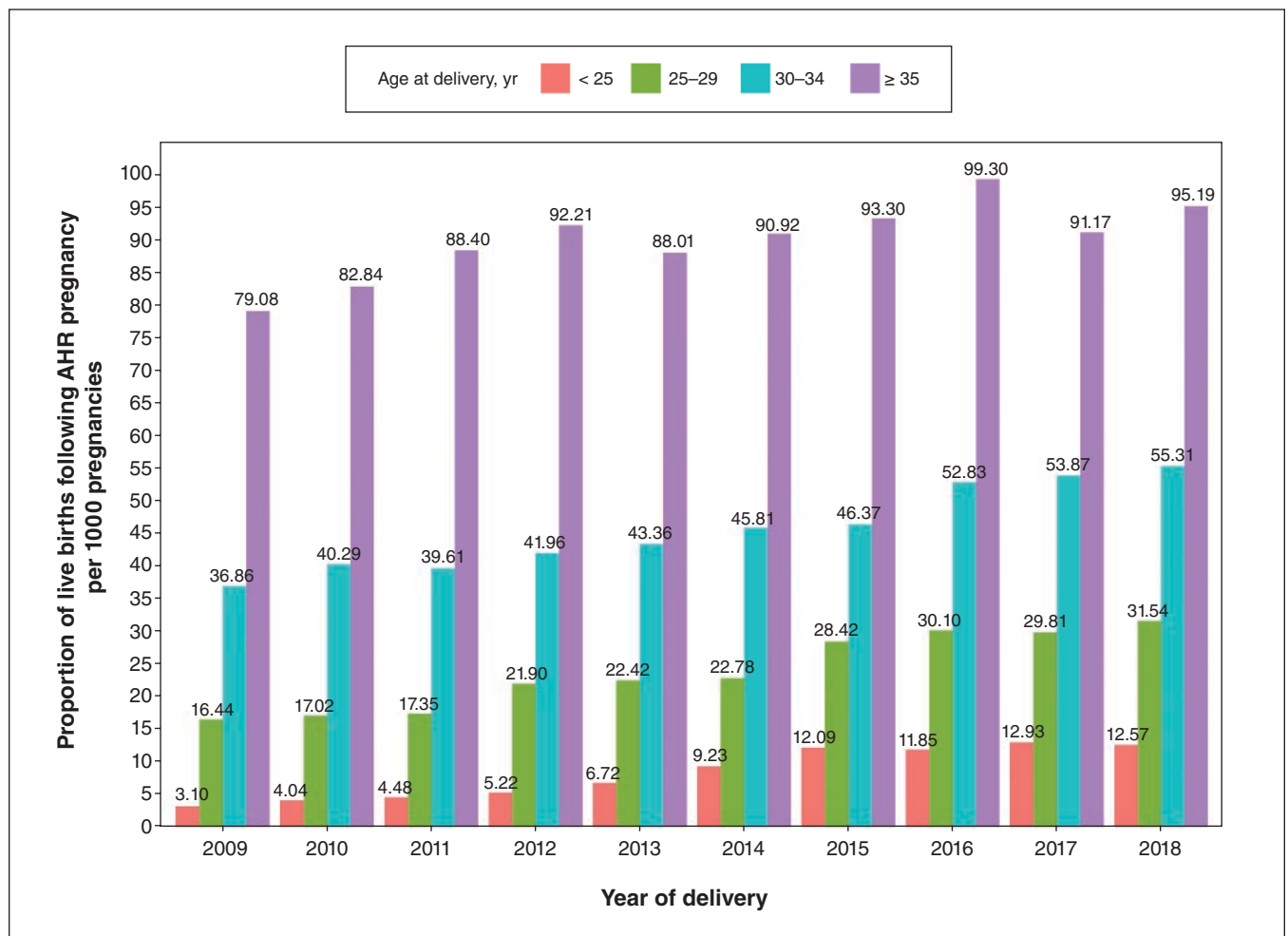


Figure 2: Proportion of pregnancies resulting in live births following assisted human reproduction (AHR) treatment according to maternal age group at the time of delivery in Alberta from July 1, 2009, to Dec. 31, 2018.

5.1%, and increased by 0.26% per year over the study period. Women who had undergone AHR treatment were, on average, older than those in the non-AHR group. In the AHR group, newborns were more likely to be multiples, have low birth weight, be born preterm and be admitted to the NICU; they also had higher rates of congenital malformations.

To date, reports on the outcomes of AHR treatments leading to live births in Canada have shown varied results. At the time of the current study, the annual report from the Canadian Assisted Reproductive Technology Register recorded 5971 live births following AHR in Canada in 2012.²² Based on

data from Statistics Canada from 2012,²³ this would have constituted only 1.5% of all live births. In contrast to this low number, a 2013 prospective community-based study from Calgary, Alberta, reported that 5.9% of 1564 pregnancies were conceived following AHR.^{24,25} These large differences in rates of live births following AHR may be in part owing to incomplete reporting, reporting bias, differences in the definition of AHR or reporting of conception rates versus live birth rates. Similarly, in the United States, reports of the number of procedures performed, techniques used and outcomes disclosed to the National AHR Surveillance System (NASS)

Table 1: Maternal characteristics among women who have or have not undergone assisted human reproduction (AHR) treatment

Characteristic	No. (%) of pregnancies*		p (GEE)
	Non-AHR n = 477 971	AHR n = 21 909	
No. of women	387 391	18 907	–
Primiparous	196 246 (41.1)	11 993 (54.7)	< 0.001
Singletons	464 472 (97.2)	17 790 (81.2)	< 0.001
Multiple births	13 539 (2.8)	4 119 (18.8)	
Twins	13 214 (97.6)	3 896 (94.6)	0.05
Triplets	311 (2.3)	205 (5.0)	
Quadruplets	14 (0.1)	18 (0.4)	
Age at delivery, yr, mean ± SD	30.1 ± 5.3	33.9 ± 4.9	< 0.001
Median (IQR)	30 (27–34)	34 (31–37)	
Age at delivery, yr			
< 25	73 840 (15.5)	594 (2.7)	< 0.001
25–29	140 553 (29.4)	3 455 (15.8)	
30–34	166 581 (34.9)	8 130 (37.1)	
≥ 35	96 997 (20.3)	9 730 (44.4)	
Missing data	0	0	
Ethnicity			
General population	321 015 (82.9)	15 378 (81.3)	< 0.001
Chinese	12 418 (3.2)	735 (3.9)	
South Asian	10 993 (2.8)	683 (3.6)	
Missing data	42 965 (11.1)	2 111 (11.2)	
Rural residence at delivery	102 084 (21.4)	3 215 (14.7)	< 0.001
Urban residence at delivery	375 927 (78.6)	18 694 (85.3)	
Married	333 098 (69.7)	19 008 (86.8)	< 0.001
Annual household income, \$, median (IQR)	83 039 (69 884–99 112)	76 374 (68 467–96 758)	< 0.001
Pre-existing diabetes at delivery	5 847 (1.2)	430 (2.0)	0.163
Pre-existing cardiovascular disease at delivery	5 753 (1.2)	304 (1.4)	0.153
Pre-existing renal disease at delivery	17 584 (3.7)	544 (2.5)	< 0.001
Gestational diabetes	38 646 (8.1)	2 264 (10.3)	0.651
Hypertensive disorders of pregnancy	43 537 (9.1)	2 586 (11.8)	0.314

Note: GEE = generalized estimating equation, IQR = interquartile range, SD = standard deviation.
*Unless indicated otherwise.

Table 2: Obstetric and neonatal outcomes among women who have or have not undergone assisted human reproduction (AHR) treatment

Characteristic	No. (%) of live births*		p (GEE)
	Non-AHR n = 492 023	AHR n = 26 270	
Mode of delivery			
Spontaneous vaginal birth	184 856 (37.6)	6221 (23.7)	0.327
Induced labour	91 355 (18.6)	4661 (17.7)	0.424
Cesarean delivery	114 581 (23.3)	10 643 (40.5)	< 0.001
Missing	101 231 (20.6)	4745 (18.1)	0.51
Preterm delivery (< 37 wk)	45 050 (9.2)	8156 (31.0)	< 0.001
Prolonged pregnancy (≥ 42 wk)	1252 (0.3)	26 (0.1)	–
Birth weight, g, mean ± SD	3320 ± 575	3020 ± 762	< 0.001
Median (IQR)	3350 (3010–3674)	3130 (2635–3520)	
Birth weight category, kg			
< 2.5	37 179 (7.6)	7058 (26.9)	< 0.001
2.5–4.0	405 333 (82.4)	17 767 (67.6)	0.171
> 4.0	43 707 (8.9)	1368 (5.2)	< 0.001
Missing	5804 (1.2)	77 (0.3)	–
Neonatal intensive care unit admission	47 936 (9.7)	6651 (25.3)	< 0.001
Congenital malformation	1410 (0.3)	134 (0.5)	0.002

Note: GEE = generalized estimating equation, IQR = interquartile range, SD = standard deviation.
*Unless indicated otherwise.

Table 3: Maternal characteristics according to assisted human reproduction (AHR) group and maternal age at delivery*

Characteristic	No. (%) of non-AHR pregnancies†				No. (%) of AHR pregnancies†			
	< 25 yr n = 73 840	25–29 yr n = 140 553	30–34 yr n = 166 581	≥ 35 yr n = 96 997	< 25 yr n = 594	25–29 yr n = 3455	30–34 yr n = 8130	≥ 35 yr n = 9730
Primiparous	46 087 (62.4)	66 254 (47.1)	60 109 (36.1)	23 796 (24.5)	352 (59.3)	2130 (61.6)	4519 (55.6)	4992 (51.3)
Singletons	72 329 (98.0)	136 851 (97.4)	161 570 (97.0)	93 722 (96.6)	544 (91.6)	2941 (85.1)	6637 (81.6)	7668 (78.8)
Multiple birth	1519 (2.1)	3714 (2.6)	5027 (3.0)	3279 (3.4)	50 (8.4)	514 (14.9)	1493 (18.4)	2062 (21.2)
Multiple birth categories								
Twins	1476 (2.0)	3621 (2.6)	4902 (2.9)	3215 (3.3)	44 (7.4)	487 (14.1)	1381 (17.0)	1984 (20.4)
Triplets	39 (0.1)	85 (0.1)	124 (0.1)	63 (0.1)	6 (1.0)	23 (0.7)	101 (1.2)	75 (0.8)
Quadruplets	4 (0)	8 (0)	1 (0)	1 (0)	0 (0)	4 (0.1)	11 (0.1)	3 (0)
Age at delivery, yr, mean ± SD	21.7 ± 2.0	27.2 ± 1.4	31.8 ± 1.4	37.3 ± 2.3	22.5 ± 1.6	27.5 ± 1.3	32.1 ± 1.3	38.3 ± 2.9
Median (IQR)	22 (20–23)	27 (26–28)	32 (31–33)	37 (36–39)	23 (22–24)	28 (27–29)	32 (31–33)	38 (36–40)
Rural residence at delivery	26 402 (35.8)	33 878 (24.1)	27 970 (16.8)	13 834 (14.3)	190 (32.0)	843 (24.4)	1224 (15.1)	958 (9.8)
Gestational diabetes	3170 (4.3)	8793 (6.3)	14 325 (8.6)	12 358 (12.7)	27 (4.6)	215 (6.2)	743 (9.1)	1279 (13.1)
Hypertensive disorders of pregnancy	6398 (8.7)	12 627 (9.0)	14 932 (9.0)	9580 (9.9)	49 (8.2)	334 (9.7)	859 (10.6)	1344 (13.8)

Note: IQR = interquartile range, SD = standard deviation.

*The interaction term of age (< 25 yr as reference) by group (non-AHR as reference) was significant at 0.05 in adjusted generalized estimating equation models (Wald Test) for primiparous, multiple v. singleton, rural residence at delivery, hypertensive disorders of pregnancy and age at delivery.

†Unless indicated otherwise.

include procedures where 1 or more embryos are transferred but do not include ovulation induction or intrauterine insemination.²⁶ As such, the overall rate from the most recent NASS report, with data from 2015 to 2016, indicates that only 1.8% of babies born in the US are from AHR pregnancies, which is lower than what has been reported in other contemporary American studies.²⁷ Our population-based study used data from all live births from a defined geographical area with publicly funded health care between July 2009 and December 2018. Our finding of an overall rate of 5.1% of newborns following AHR likely reflects a more accurate incidence of AHR births in a North American population.

Similar to previous studies, we found that women who underwent AHR treatment had increased rates of multiple births and obstetric interventions.²⁻⁵ Newborns from AHR pregnancies were more often premature and had lower birth

weights than those from non-AHR pregnancies. However, contrary to what has been reported previously,²⁸ we saw only a mildly increased rate (+0.2%) of congenital malformations among neonates in the AHR group. It has been suggested that the increased risk of birth defects following AHR may be more strongly linked to the cause of infertility rather than the AHR medications.²⁸⁻³⁰ As such, subfertility, when couples conceive without the use of AHR after more than a year of not being able to conceive, could be an effect modifier that we could not adjust for in the current analysis. The potential effect of subfertility thus remains as an unexplored factor in the current analysis and may partly explain why we did not find larger increases in the rates of congenital malformations in our AHR cohort. We assessed only outcomes reported during the hospital admission for delivery. Any malformations reported beyond this admission were not captured in the current analysis.

Table 4: Obstetric and neonatal outcomes by assisted human reproduction (AHR) group and maternal age at delivery*

Characteristic	No. (%) of non-AHR live births†				No. (%) of AHR live births†			
	< 25 yr n = 76 683	25–29 yr n = 140 553	30–34 yr n = 176 492	≥ 35 yr n = 104 125	< 25 yr n = 650	25–29 yr n = 4000	30–34 yr n = 9747	≥ 35 yr n = 11 873
Mode of delivery								
Spontaneous vaginal birth	32 520 (42.2)	57 423 (38.9)	63 641 (36.1)	31 272 (30.0)	239 (36.8)	1216 (30.4)	2550 (26.2)	2216 (18.7)
Induced labour	14 334 (18.7)	27 337 (18.5)	31 056 (17.6)	18 628 (17.9)	114 (17.5)	780 (19.5)	1722 (17.7)	2045 (17.2)
Cesarean delivery	12 969 (16.9)	29 857 (20.2)	41 551 (23.5)	30 204 (29.0)	163 (25.1)	1281 (32.0)	3648 (37.4)	5551 (46.8)
Missing	15 644 (20.4)	29 801 (20.2)	35 530 (20.1)	20 256 (19.5)	134 (20.6)	723 (18.1)	1827 (18.7)	2061 (17.4)
Preterm delivery (< 37 wk)	6483 (8.5)	12 426 (8.4)	15 430 (8.7)	10 711 (10.3)	209 (32.2)	1137 (28.4)	2973 (30.5)	3837 (32.3)
Prolonged pregnancy (≥ 42 wk)	210 (0.3)	327 (0.2)	423 (0.2)	292 (0.3)	0 (0.2)	6 (0.1)	9 (0.1)	11 (0.1)
Birth weight, g, mean ± SD	3329 ± 578	3333 ± 563	3327 ± 570	3285 ± 598	2979 ± 816	3047 ± 758	3036 ± 778	3000 ± 746
Median (IQR)	3352 (3020–3680)	3358 (3030–3680)	3350 (3020–3680)	3320 (2974–3653)	3110 (2571–3498)	3160 (2685–3540)	3150 (2658–3550)	3100 (2610–3500)
Birth weight category, kg								
< 2.5	5363 (7.0)	10 008 (6.8)	12 759 (7.2)	9049 (8.7)	172 (26.5)	1011 (25.3)	2613 (26.8)	3262 (27.5)
2.5–4.0	61 573 (80.3)	119 839 (81.3)	142 046 (80.5)	81 875 (78.6)	442 (68.0)	2744 (68.6)	6522 (66.9)	8059 (67.9)
> 4.0	6877 (9.0)	12 964 (8.8)	15 482 (8.8)	8384 (8.1)	36 (5.5)	233 (5.8)	573 (5.9)	526 (4.4)
Missing	1654 (2.2)	1607 (1.1)	1491 (0.8)	1052 (1.0)	0 (0)	12 (0)	39 (0.4)	26 (0.2)
Neonatal ICU stay	7436 (9.7)	13 578 (9.2)	16 116 (9.1)	10 806 (10.4)	146 (22.5)	965 (24.1)	2407 (24.7)	3133 (26.4)
Congenital malformation	300 (0.4)	355 (0.2)	437 (0.3)	318 (0.3)	11 (1.7)	13 (0.3)	37 (0.4)	73 (0.6)

Note: ICU = intensive care unit, IQR = interquartile range, SD = standard deviation.

*Interaction term of age (< 25 yr as reference) by group (non-AHR as reference) was significant at 0.05 in adjusted generalized estimating equation models (Wald Test) for cesarean delivery, preterm delivery (< 37 wk), birth weight < 2.5 kg, birth weight 2.5–4.0 kg and congenital malformations.

†Unless indicated otherwise.

An unexpected finding in the current study was the comparatively high rates of preterm birth and low birth weight newborns among young mothers (aged < 25 yr) who had undergone AHR treatment. Although numerous studies have assessed the impact of advanced maternal age on perinatal outcomes both after conceiving spontaneously and following AHR,^{31,32} little is known about why newborns of younger women with AHR may be at increased risk of adverse perinatal outcomes. It can be speculated that the cause of infertility among women younger than 25 years undergoing AHR is different to that of older women undergoing AHR because of delayed childbearing. For example, polycystic ovarian syndrome (PCOS) is a cause of infertility among young women,³³ and has been associated with poor obstetric and perinatal outcomes.³⁴ Although the underlying infertility diagnosis was beyond the scope of the current study, causes such as PCOS may explain why younger women had poorer perinatal outcomes than older women or those in the non-AHR group. Further studies are needed to confirm these findings and the reasons behind them. The incidence of live births among women aged 30 years and older increased over the span of the study, but increasing maternal age was not associated with increased maternal health risks among patients who underwent AHR beyond what would be expected for those who did not undergo AHR treatment in the same age groups. This finding supports previous population-level research from Sweden that looked specifically at pregnancy outcomes among women of advanced age with and without AHR treatment.³¹

Limitations

Although the use of routinely collected administrative health data allowed for the analysis of a large population-level sample, the data were not initially collected for research purposes and lack detail, which may compromise the accuracy of some of the study outcomes. For example, the current study does not contain information on maternal pre-pregnancy weight, paternal infertility or ethnicity (beyond what could be identified using validated naming algorithms), as these parameters were not recorded in the available data sets. Furthermore, as the data linkage in the current study was via the birth registry, only live births were included, with no information on AHR success rates or trends in overall use of AHR. Similarly, the comparison of pregnancy failure rates and rates of neonatal deaths between AHR and non-AHR pregnancies could not be evaluated using this data set.

We calculated trends in pregnancies resulting in live births following AHR treatment and extrapolated for the years 2019–2022 based on the assumption of linearity (Appendix 1, Supplementary Figure S2); however, it is likely that the COVID-19 pandemic affected access to AHR treatment. Therefore, these data should be interpreted with care. Of note, AHR is a medical specialty that has seen great development over the last decade. The increasing number of live births following AHR may thus be partly owing to improved ART treatments becoming available. Alberta also saw changing population demographics during the study period, with a large increase in

people from visible minorities (1.4% growth rate for visible minority groups, compared with the overall population growth rate of 1.2% from 2009 to 2019).¹⁰ The extent to which these changing demographics may have affected the rates and outcomes of AHR in Alberta requires further study.

The purpose of the current study was to give an overview of temporal trends and outcomes following any AHR treatment or procedure. However, different subtypes of AHR may be associated with different outcomes. Our inability to identify the different AHR subcategories (e.g., IVF, insemination, ovulation induction) remains a limitation of our study. As such, future studies are encouraged to build on our findings to examine outcomes according to the different types of AHR.

Conclusion

The incidence of live births following AHR in Alberta was 5.1% from 2009 to 2018, and increased over time. Women who had AHR were older, and newborns conceived following AHR were more often preterm and had a low birth weight. In this population-level study, we did not see signs of a clinically meaningful increased risk of congenital malformations following AHR, but more than twice as many of infants born following AHR were admitted to the NICU after birth, compared with infants without AHR. This study thus provides insights on potential perinatal complications following AHR that may be important when caring for the newborn child.

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