Article details: 2022-0073
Title: Assisted human reproduction and pregnancy outcomes in Alberta 2009–2018: a population-based study
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Reviewer 1: Matea Belan
Institution: Division of Endocrinology, University of Sherbrooke
General comments (author response in bold)

Very interesting article. Very good work form the authors.

How are reliable the ICD10 codes in your province? Are there any studies reporting their validity in selecting patients with the interested diseases/conditions? Because it is possible the condition/disease of interest is not the primary reason for consulting a physician.
The identifications of the conditions included were based on validated algorithms for administrative health data. The references for these algorithms have now been added to the revised version of the manuscript, as applicable.

Are there any information on BMI or weight for participants? At page 6, where you looked at the pre-existing conditions, would it be possible to check for obesity?
We agree with the reviewer that information on weight and BMI would be interesting to include in the analysis for this study; however, the administrative health data used for this study does not include details on these variables. The lack of these data is discussed in the limitation section of the revised manuscript (page 10, line 9-14).

Page 7 of 39, line 12, it is said that women with AHR had more often pre-existing conditions compared to non-AHR, but the contrary is said at page 8 of 39, lines 27 to 31. Are you referring to other conditions than those at p. 6 ?
The reviewer is correct in their observation that the two sentences referred to in the comment above are in regard to different pre-existing conditions reported (diabetes, heart disease, and others). In the updated analysis including data from an additional four years and with GEE modelling applied, some of these differences were diminished. In the updated analysis, the category for "other pre-existing condition" has been removed based on a previous comment (#26) and renal disease was added as a variable. Based on the output from the GEE model, only renal disease remained statistically different between the non-AHR and AHR groups. The manuscript has been updated to reflect this.

On page 8 of 39, lines 24 to 32, is it possible that the big differences in rates of live-births from AHR is to the fact that one study looked at the live-births from AHR and the other one the number of pregnancies (and not live-births) from AHR? Unfortunately, not all pregnancies conclude by a live-birth.
We agree with the reviewer that the reporting of live birth rates vs conception rates may help explain the big differences in rates reported between studies. Unfortunately, the study by Raguz 2014 does not report number of live births as a result of AHR, and as such, a direct comparison is not possible. To highlight this, the issue of comparing conception rates vs live birth rates has been added as a possible reason for the large differences seen across studies (page 8, line 20).

Would it be possible eventually to link with women's data pre-pregnancy?
Pre-pregnancy health data were available from April 1, 1997, for the women in this cohort. While this was only mentioned under the 'Clinical and demographical data'-section (page 5, line 16) of the previous version o the manuscript, it has now also been stated under 'Data linkage and population' in the revised version of the manuscript (page 4, line 14).

Why only Chinese and South Asian ethnicities are reported separately? Could indigenous people be reported separately?
Maternal ethnicity in our study is based on previously validated naming algorithms to identify Chinese and South Asians ethnicities, which are the largest ethnic groups in Alberta (outlined under Study setting, page 3-4, line 20-7). While indigenous people make up approximately 6.5% of the population in Alberta, identification of members of indigenous groups is not available for population level-research purposes unless the research question is directly and specifically evaluating indigenous health and disease. As such, we were not able to include this data in the current study.

Reviewer 2: Abdool Yasseen
Institution: Clinical Epidemiology, Ottawa Hospital Research Institute
General comments (author response in bold)

Dear authors,

Thank you for your thoughtful and informative analysis of the trends in AHR use and pregnancy outcomes in Alberta. It is always good to present population based data as this may be vital for public health planning and preventative care, and affords the power to enable a multitude of sub analyses and stratifications that would not be possible otherwise.

I enjoyed reading the manuscript and my main comments are that the data is a bit dated (8 years ago for the most recent records) and you should highlight the potential changing demographics (i.e., immigration into the region) and how this may potentially impact AHR use and subsequent adverse pregnancy/neonatal outcomes. I've also included some other comments regarding methodology and presentation of the results.

If these potential issues are fixed the article would make a nice addition to CMAJ-Open, however in its current form, I am recommending major revisions.

Please see below my comments/edits I hope these are helpful and can be addressed.

Overall
• Any idea about influx of migrant populations or other changing demographics over the time period? This is a plausible explanation that has not been discussed.
The overall population of Alberta increased with approximately 400,000 people over the span of the study period 2009-2018. During the same period, the number of people from visible minorities groups increased from 500,588 to 565,808 (overall growth rate: 1.4% (2009-2019)). This information has been added to the Study setting-section (pages 3-4) and is further discussed in the discussion section of the revised manuscript.

• Exclusion of extreme low birth weigh and extreme preterm births from these types of studies is advised, as these represent a fundamentally different group. At the least, a sub-analysis should be conducted to contrast the primary results (i.e., how much do these groups drive the current findings).

The purpose of this study was to give an overview at the population level; as such, we have not excluded cases due to extreme low birthweight or extreme premature birth. In response to the reviewer's comment, we did investigate the number of children born at a an extremely low birthweight or extremely premature, please see table below. The percentage of children with either extreme low birthweight or born extremely premature were very low in both groups. As such, we do not believe this would have significantly influenced the outcomes. This table has been added to the supplementary material in the revised submission (Table S6) and a comment added in the methods section of the revised paper (page 5, line 1-3).

	No-AHR	AHR
Extreme low birthweight	**492,023**	**26,270**
Yes	**803 (0.2%)**	**219 (0.8%)**
No	**485416 (98.7%)**	**25974 (98.9%)**
Missing	**5804 (1.2%)**	**77 (0.3%)**
Extremely premature births		
Yes	**142 (0.03%)**	**40 (0.2%)**
No	**485983 (98.8%)**	**26153 (99.6%)**
Missing	**5898 (1.2%)**	**77 (0.3%)**

• The data is a bit dated, since the most recent records are from 2014 (8 years ago). Not much can be done about this, but it should be more evident in the wright up that these data may not represent current practice. If the authors are comfortable extrapolating the stated trends, this might be useful and present a benchmark for further follow-up studies, once the data becomes available. The authors might also want to preface this with the caveats associated with the current pandemic and how this could potentially change the use of AHRs.

Based on the reviewers' previous suggestion, we have updated the cohort to include live-births until Dec 31, 2018 and have thus been able to show more up to date trends in the data (see updated figure 1). In addition, we have extrapolated the trend to include more recent years in Supplementary Figure S2. While this extrapolation of data is based on an assumption of linearity, the potential impact of the pandemic was not taken into consideration but we acknowledge that the pandemic likely affected people's ability to access AHR treatment. To highlight this, the following statement has been added to the limitation section of the revised manuscript (page 10, line 18-21):

"Trends in pregnancies resulting in live births following AHR treatment in the current studies were calculated and extrapolated for the years 2019-2022 based on the assumption of linearity (supplementary Figure S2); however, it is likely that the 2020 COVID-19 pandemic had significant impact on access to AHR treatment for many people. Therefore, these data should be interpreted with care."

Methods

• Ethics statement usually goes last in methods along with a general statement on what statistical software was used to conduct the analyses. Please re-arrange and include this information.

the ethics statement has been moved to the end of the manuscript in the revised version.

• The statement describing how AHR patients were identified includes the following phrase: "…, or physician office visit records within six-months prior to or during the pregnancy.", which is confusing. Do the authors mean that any woman visiting a physician's office (for any reason) 6 months prior to the date of conception/birth, are considered to be on AHRs? If so, there is a high likelihood for misclassifying AHR and non-AHR patients. If not, please rephrase this sentence to be more accurate.

To clarify that only cases with AHR treatment were considered, the sentence from which the line above is referring to has been changed as follows (updates in italic), on page 4, line 14-19 of the revised manuscript:

"Women giving birth to a live offspring following AHR treatment 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 AHR treatment in any diagnostic field of their inpatient *records*, *AHR treatment in* outpatient clinic *records*, or *AHR treatment in* physician office visit records within six-months prior to or during the pregnancy".

• Please add an inclusion/exclusion short paragraph, it is often useful to consolidate this information in one place. Also, you might want to exclude extremely low birth weight (<500g) and extremely preterm (<20 weeks), or at a minimum give a description of what portion of the study population these groups represent.

As this was a population-level study, we did not exclude any cases for reasons other than if the mother 1) did not live in Alberta (healthcare data not consistently available); 2) the mother was under the age of 14 or over the age of 54 (data deemed unreliable); or 3) there was incorrect information on dates in the dataset (if the mother had a death recorded prior to the birth date of the child). This has been stated in the methods section under Data linkage and population. Based on the reviewer's comment, we investigated the number of children born at an extremely low birthweight (<500g) or extremely prematurely (<20 week of gestation) and found that the rates were low across groups (see table in comment above). This information has been added in the supplementary material in the revised submission (Table S6) and a comment has been added to the methods section of the revised manuscript (page 5, line 1-3).

Please use a more updated census cycle, since the 2006 cycle is not even in the study period (i.e., 2009-2014).

With the updated data spanning from 2009 to 2018, we have used the census from 2016 for the analysis.

• Are the codes used to identify comorbidities (i.e., diabetes, cardiovascular disease, chronic obstructive pulmonary disease, asthma, renal failure, liver disease, epilepsy, and lupus) validated? If not, this should be stated in the manuscript, or at the least mention how these codes were identified.

Validated algorithms were used to identify cases with comorbidities. References for these have been added to the revised version of the manuscript, as applicable.

Results:
No need for figure 1, it's already described adequately in text. Please remove.
Figure 1 has been moved to the supplementary material in the revised submission.

• A statistical test for trend is required for figure 2. Please add. Also, see the previous comment on extrapolating these trends to the 2020-2022 period.
The test used to evaluate the trend in AHR rates has been added to the statistical analysis section of the manuscript (page 6, line 2-3). Based on the reviewer's suggestion, we have also added a figure included in the supplementary maternal (figure S2) showing the extrapolated trend for years 2019-2022.

• The method of estimating percentage change in incidence rate per year needs to be stated in the statistical analysis section. Please add.
This has been added to the revised version of the manuscript under the statistical analysis-section in methods (page 6, line 2-3).

• The y-axis of figure 3 shows absolute numbers, but would be more illustrative and accurate if you used proportions, please make this change.
Based on the reviewer's suggestion, figure 2 (former figure 3) has been updated to show proportions rather than count of pregnancies resulting in live births following AHR.

• Also, in text, figure 3 is described as: "The highest proportion of newborns following AHR were in women aged 30-35 years or in women 35 years and older (Figure 3)." are you representing the proportion of all live births following AHR? The sentence reads a bit ambiguous. Please revise. Also, please add a sentence describing the alternative (i.e., the highest proportion of neonatal deaths)
The difference in rates in AHR among different age groups have now been clarified in the revised version of the manuscript as follows (page 7, line 5-7):
"The highest relative proportion of newborns following AHR were in women aged 30-35 years (37.1%) and in women 35 years and older (44.4%) compared to mothers <25 years (2.7%) and 20-30 years old (15.8%, Table 1)."
The cohort was based on live births only, and data on neonatal deaths and were not available. Based on the reviewer's comment, this has been commented on in the limitation section of the revised manuscript.

• The p value for ethnicity in table 1 is statistically significant, but the authors make no mention of this important difference. Include this findings, as specific ethnic groups are known to have higher rates of SGA and other adverse obstetric and neonatal complications.
We agree with the reviewer that this is an important observation that needs to be highlighted and have added the following sentence to page 7, line 12-15 of the revised manuscript:
"…and there was an overall difference in ethnic backgrounds between AHR and non-AHR cohorts with less women with AHR being from the general population (81.3 vs 82.9%) and higher rates of South Asians (3.6 vs 2.8%) and Chinese (3.9 vs 3.2%) in the AHR than non-AHR group (Table 1).

• For birth weight in table 2, please report both mean and standard deviation, as well as the median and interquartile range. It is important to show how extreme values might have affected the overall distribution. Alternatively, birth weight categories could be reported and would illustrate this information better than a single scalar value. Please make this addition.
Based on the reviewer's suggestion, birth weight is now reported both as the mean (with SD) as well as the median, and IQR. We have also provided the distribution of birth weight categories in the revised version of the manuscript (table 2 and 4).

• An age by ethnicity table might be useful, more specifically a table on ethnicity by birthweight category might address the notion that the increase in AHR rate could be due to an influx of these communities. But much care is needed when making such inferences. Perhaps include these tables in an appendix.
A table showing counts and percentages for birthweight per AHR by ethnic groups has been added as an appendix to the revised manuscript (supplementary figure S5). While we saw high rates of children born at low birth weights (<2500g) in the AHR group, the overall differences between rates based on ethnicity within this group appear to be small (gen pop: 26.9%, South Asian: 27.5%, Chinese: 27.2%).

Discussion:
• 1.5% Canada-wide to 5.9% from Calgary, isn't considered a large difference in the rate. The statsCAN estimate is likely a population based sample, whereas the Calgary study is likely a specialist hospital institution and likely overestimates the rate of AHR. Please temper this sentiment and revise the opening part of the second paragraph of the discussion.
The study by Rahuz et al included a community-based sample of pregnant women receiving prenatal care in the Calgary-region for the "All Our Babies" study. This cohort was created to examine causes contributing to disease and is, as stated by the authors of the study referred to, population-based (not a specialist hospital institution), which is why comparisons with the current study cohort was deemed appropriate. Furthermore, Rahuz et al. excluded multiple gestation pregnancies, which are more commonly seen following AHR (18.8 vs 2.8%, p<0.001, in the current study [table 1]) and may have influenced the rates of AHR pregnancies reported to reflect lower rates than what would otherwise had been seen. The reference for the creation of the "All Our Babies"-cohort (McDonald et al., 2013) has been added to the revised manuscript and it has been clarified that it is a community-based study.

• In the following sentence: "As such, subfertility, which is when couples conceive without the use of AHR 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." subfertility is likely an effect modifier or interaction factor, rather than a confounder. Please revise, or add a sentence explaining why the authors believe it to be a confounder.
Upon reviewing this section, we agree with the reviewer that subfertility is more likely an effect modifier and have edited the sentence accordingly.

• Lastly, please add a few sentences towards the end of the discussion explaining the dynamic nature of the Alberta population across the study period. This may likely explain

changing trends in AHR use and is important to highlight. Otherwise, the reader may assume that the population is relatively static.

Information on population dynamics have been added to the methods section of the revised manuscript and a table S6 outlining rates in birthweight categories based on AHR and ethnicities have been added to the supplementary material. In addition, to highlight the impacts of the changing aspects of the population composition, we have also included the following text to the discussion (page 10-11, line 24-2):

"The province of Alberta also saw a large increase in people from visible minorities during the period of the study (growth rate for visible minority groups was 1.4% compared to the overall population growth rate of 1.2 2009-2019). The extent to which these changing demographics may have impacted the rates and outcomes of AHR in Alberta requires further study."