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| Title | Suicide and suicide attempts among women in the Manitoba Mothers FASD cohort: a retrospective cohort analysis utilizing linked administrative data |
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| **Reviewer 1** | Dr. Sharon Burey MD |
| Institution | University Of Western Ontario, Windsor Program, Pediatrics, London, Ont. |
| General comments (author response in bold) | 1. footnote pp 22 line 35- please review (who women) seems to be a typo.<br>**Thank you for catching this typo. We have corrected it.** |
| **Reviewer 2** | Allison J. Bethune MSc BSc |
| Institution | Division of Neurosurgery, Sunnybrook Hospital, University of Toronto, Toronto, Ont. |
| General comments (author response in bold) | This is interesting work.<br>1. Although suicide is a timely topic and significant problem for Canadian populations, the authors could better justify why understanding early alcohol consumption is linked to suicide.<br>**Upon reflection of the editors comments we have decided to re-phrase our study group from "women with substantial alcohol use" to "women who have given birth to children with FASD" – this is a more accurate description of who our study cohort really is. Therefore, to clarify, the intention of this paper is to discuss the relationship between drinking during pregnancy and suicide, not early alcohol consumption. We have edited the introduction to focus on the linkages between alcohol abuse (such behavior occurs among women who drink during pregnancy and give birth to children who are ultimately diagnosed with FASD) and suicide, which is well documented in existing literature. We have included the following references that demonstrate this relationship: "Women who give birth to children with Fetal Alcohol Spectrum Disorder (FASD), a diagnostic term that includes several disorders related to prenatal alcohol use, may be at increased risk of suicide. These women have histories of frequent and heavy alcohol use and there is a strong association between alcohol use and dependence and suicide(1-7)." (page 4)**<br>2. It is unclear what 'substantial' alcohol abuse refers to. Was this quantified, or could it be objectively defined in some way?<br>**Thank you for this comment. We agree that the term "substantial alcohol" use is ambiguous and not clear. We have edited the names of our study groups to "women who have given birth to children with FASD" and removed "women with substantial alcohol use", as we were unable to exactly quantify what substantial alcohol use was. (throughout the paper)**<br>3. Please clarify from the introduction, if the alcohol consumption is considered during the child-bearing years or only pregnancy.<br>**Alcohol consumption is considered during the pregnancy when defining our cohort. We do not have population-level information about the use before and after pregnancy.**<br>4. The non-parametric statistics seem appropriate, despite the small sample size. If the analysis with control for Indigenous status is possible, as stated in the limitations, it would be a more impactful and timely study.<br>**We agree that the ability to control for, or describe Indigenous status would make this study very timely given the recent suicide epidemics occurring in First Nations populations. However, gaining the permissions for using the First Nations Identifier in the database is an extremely time intensive process (over a year) and is outside the scope of this project, which is a PhD dissertation. We are, however, working on getting these permissions for future work using this study population and plan to go back and stratify these study results using First Nations and Metis identity information (the Inuit population in Manitoba is very small).**<br>**We have discussed this issue in our limitations section.**<br>**"We also could not identify what proportions of women from our study population were from Indigenous communities. Given that suicide is a significant issue in First Nations, Metis and Inuit communities(37, 38) it would be important to conduct this analysis to describe the burden of suicide among women who give birth to children with FASD who are First Nations." (page 11)**<br>5. Some of this data does come as far back as 1970. A description of key social changes would be a useful consideration. It would also be of interest to comment on the decade of suicidal behavior documented. If there is a trend for improvement or worsening, it may better guide current resources and management.<br>**We agree that examining the trends of suicidal behavior would be interesting in this population, we have relatively low outcome numbers and feel that this is outside the original objectives of this paper, which is to quantify suicide rates of these women in order to identify a potentially high risk group that requires targeted interventions. We do agree that we should include that suicide as a public health problem has increased over the years and have a included statistic given by the World Health Organization "in the last 45 years, suicide rates have increased by 60% worldwide" to provide social context to our results.** |
| **Reviewer 3** | Dr. Astrid Guttmann MSc MDCM |
| Institution | Institute for Clinical Evaluative Sciences, Toronto, Ont. |
| General comments (author response in bold) | Overall, this is a paper on an important topic that has not been well-investigated and makes a substantial contribution to the literature. It leverages multiple population-based and clinical datasets in Manitoba. However, a few modifications are needed.<br>The study design needs to be better articulated. Presumably this is a cohort study but it is unclear in the current version when the cohort begins since pre-pregnancy suicide attempts are listed as outcomes. However, given that women are "enrolled" in the study at the birth of the infants, these pre-pregnancy outcomes have to be considered as baseline characteristics of risk rather than outcomes, since women who successfully committed suicide prior to the birth of a child would be excluded and thus not present in the denominator, thus biasing the estimates that are calculated.<br>**Thank you for your important comments and thoughtful review.**<br>**The study design is a retrospective cohort study, we have added this to the title and methods section. We have also added a study setting and design section to the methods section. We have ensured that we have not described pre-suicide attempts as "outcomes' but as risks. (page 5)**<br>When covariates were measured and how those that were measured in the outcome period were handled analytically needs to be better described.<br>**We have added a covariate section as per your recommendation.**<br>**Covariates: The following variables, pre-specified on clinical relevance, were included as potential covariates in each of the models generating rates of suicide attempts and completions: age of mother at birth of child (18 or under, 19 to 24, 25 to 34, 35 and higher), and SES at the time of the birth of the index child. SES was defined according to area level data from census information. Area-level income quintiles were ranked from 1 (low) to 5** |

**(high) on the basis of ranges of mean household income from census information, and grouped into five categories, with approximately 20% of the population assigned to each quintile(36). (page 7)**

The other major issue is around the ascertainment of suicide. It is well-known that suicide is under-coded in vital statistics data. It would help contextualize the findings and highlight the high-risk nature of this cohort to also report all-cause mortality (which would have been measured in any case to censor the cohort).

**We have added more detail in our discussion regarding the problem of under-coding in suicide that may occur using vital statistics data.**

**"Suicide attempts are often under-coded in administrative databases as practitioners may list underlying mental illness as the diagnosis or not accurately chart the occurrence of suicidal behaviour. There is low sensitivity in the use of these data to track the prevalence of suicide outcomes; findings of a validation study comparing emergency department and patient coding for suicide and self-harm attempts versus clinical assessment data suggest that research using hospital and physician claims to identify suicidal outcomes in patients is missing one half to two thirds of outcomes. Furthermore, only women who received medical care owing to a suicide attempt or whose death has been classified as a suicide would be included in this study." (page 10)**

**We have also reported all cause-mortality statistics in our results section:**

**"Among the course of our study period a total of 101 women died, 75% of these women were from our study group; the most common cause of death was intentional self harm and assault; malignant neoplasms were the most common cause of death in our comparison group." (page 8)**

Abstract

1. Please add to the Methods 1) overall design , 2) the calendar years of observation

**We have added that this is a retrospective cohort study in our methods section of the abstract, as well as our study period (April 1st 1979 to November 30th, 2013). (pages 3, 5)**

2. Please add total number of women in the cohort and person/years to Results section

**We have added the total number of women in the cohort and person/years to the results section of our abstract. (page 3)**

**Background**

3. The writing of the study objectives could be sharpened: Objective 3 could be merged with 1 given that maternal suicide death is a subset of overall suicide and wording could be edited: ie."Compare rate of suicide by prenatal alcohol use in both the early postpartum period (maternal death) and longer term ". Again, specifying actual years encompassed by the study rather than just "study period" since the latter has not been defined at that point in the manuscript would be preferable.

4. Objective 2 needs to be re-written in light of the comments above.

**Thank you for your helpful suggestions. We have added the study period and we have edited the objectives to clarify them, make them more concise and more appropriate to what we are trying to achieve in this study: which is to quantify the suicidal burden in this population, and identify critical time periods of risk to aid the development of targeted interventions. We have changed the objectives to the following:**

**"The objective of this study is to compare rates of suicide among women who have given birth to children with FASD, relative to women who have not given birth to children with FASD during critical time periods in their live including: before pregnancy, during the prenatal period, during the postpartum period (to investigate rates of maternal death) and till the end of the study period (April 1, 1979 to November 11, 2013). The identification of suicide risk in critical time periods in these women's lives aids to the development of meaningful, targeted prevention and support programs." (page 6)**

**Methods**

5. An overall statement of design, inception of cohort, censoring (?outmigration from Manitoba, death from other causes) and calendar years of follow up would be helpful at the beginning of this section.

**We have added a study setting section and a statement of design that includes information about the development of our study cohort, and calendar years of follow-up.**

**The following section was added to the methods:**

**Study Setting & Design: This is a retrospective analysis of the Manitoba Mothers and FASD (MBMomsFASD) cohort, which consists of mothers of children born in Manitoba between April 1, 1984 and March 31, 2012 who had an FASD diagnosis between April 1st, 1999 to March 31st 2012, with follow-up till November 11th, 2013. The year 1995 was chosen as the first year to ascertain FASD diagnosis as this is when accurate FASD diagnosis data was attainable. Suicide attempts were investigated five years before and one year after the birth of the child, till the end of the study period, resulting in a total study period of April 1st 1979 to November 11th, 2013. (page 5)**

6. Data sources: If there are linkage statistics available (presumably the vital statistics data requires probabilistic linkage) please cite these here.

**Linkages are done at the Manitoba Health (provincial ministry of health) level using probabilistic and deterministic linkage, i.e. at a one to one PHIN. We do not have specific available probabilistic linkages for each of the databases used in this study but can go to some lengths to obtain them if this reviewer would like. MCHP is certain that we can link to 99% of the population in the majority of our databases. Details about linkages are avilable in the following papers:**

**Roos LL and Nichol, P. "A Research Registry: Uses, Development and Accurary" J Clini Epi Vod 53, No 1, 39-44, 1999**
**Roos LL, Gupta S, Sooden RA, Jebamani L. Data quality in an information-rich environment: Canada as an example Can J Aging, 2005**

7. Please add a covariate section rather than mentioning these in the analysis section. It was also not clear whether these were all measured at baseline (and please clearly define that this is at the birth of the infant) or whether any were calculated thereafter (ie time-dependent covariates). For instance in Table 2 there are postnatal psychological distress described as a baseline characteristic but no mention of it in the Methods section and no description of how this was handled analytically given that this was measured in the outcome period.

**We have added a covariate section to the methods section, and stated that these were measured at the birth of the index child or before the birth of the index child. We appreciate the confusion created by the inclusion of postnatal psychological distress, because it is a co-occurring disorder at the time our outcome is measured we have removed it. This was an oversight on our part.**

**We have left it in purely as a descriptive variable to provide context as to the mental health challenges of this cohort. (page 7)**

It was also not clear whether there had been any validation of the mental health definitions used (one or more diagnosis from an admission or one or more diagnosis from an outpatient visit). An older Ontario study which did chart reviews of primary care physician visits for mental health problems concluded that it was not possible to differentiate mental health diagnoses from a single outpatient encounter (Leah Steeleet al Med Care. 2004 Oct;42(10):960-5.)

**While the mental health definitions have not been formally validated, they have been used in countless projects and peer-review papers using the MCHP data repository. As with all data sources there are limitations inherent in**

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| | **the definitions used, however, numerous experts, including health researchers, epidemiologists, psychologists and psychiatrists have approved the use of these definitions in mental health research. We do appreciate your concenrs and we have included limitations inherent in ascertaining metnal health diagnoses in the limitations section:**<br>**"Moreover, in regards to the mental health outcomes investigated in this study, we are not reporting the true prevalence of psychiatric disorders in our cohort, but the prevalence of physician health service use for psychiatric illness; as MCHP data are dependent on women making contact with the health care system. Therefore, this study excludes women with undiagnosed psychiatric disorders and women who have not been assigned with relevant diagnostic codes. Mental disorders among women who have only sought care from a psychologist or support group would not be captured."**<br>**Our definitions also do not just involve a single patient encounter, most of them include at least two visits to either a hospital or physician, or the dispensing of a physiatrist medication. See appendix 1 for definitions of mental health outcomes. (page 11)**<br>8. Data Analysis: It wasn't clear whether the variables that were included in all the models were because of their frequency distribution and tests of significance (preceding sentence) or those were pre-specified based on clinical significance.<br>**The covariates included in the models were pre-specified based on clinical significance. The following line has been added to the manuscript:**<br>**"Covariates: The following variables, pre-specified on clinical relevance, were included as potential covariates in each of the models" (page 7)**<br>Results<br>9. As with abstract, please report total person-years of follow-up<br>**The following information has been added to the results: There were a total of 10103.40 person years for our study group, and 29331.55 person years for the comparison group when examining suicide attempts till the end of the study period.**<br>**There were a total of 10694.56 person years for our study group, and 29695.65 person years for the comparison group when examining suicide completions till the end of the study period (pages 8, 9)**<br>Discussion<br>10. Some additional limitations should be considered. Although the authors cite many of the papers around the MB Repository data in general, it would be worth discussing what is known about the validity of the specific outcome of this study. As mentioned above, it is well known that suicide is undercoded. It would also be worth discussing that the predictors may be measured well before any of the events (unless I have misunderstood when the covariates were measured) and as such that there may be many other unmeasured risk factors that develop or change in the time to event. This would be worth discussing in the implications/context of how public health programs can target or refine current programs.<br>**We have expanded our discussion to include information about the under-coding of suicide in administrative data and the possibility of unmeasured risk factors or those that have changed over time.**<br>**"In addition, as in all studies using administrative databases, this study is reliant on the accuracy of physician and hospital coding. Suicide attempts are often under-coded as physicians may list underlying mental illness as the diagnosis or not accurately chart the occurrence of suicidal behaviour. There is low sensitivity in the use of these data to track the prevalence of suicide outcomes; findings of a validation study comparing emergency department and patient coding for suicide and self-harm attempts versus clinical assessment data suggest that research using hospital and physician claims to identify suicidal outcomes in patients is missing up to one half to two thirds of outcomes. Furthermore, only women who received medical care owing to a suicide attempt or whose death has been classified as a suicide would be included in this study. These data also do not capture suicidal ideations, further underestimating the burden of suicidal behaviour in this population. Finally, these data are not collected for research purposes and there may be unmeasured risk factors that develop or change in the time to suicide that our analysis could not account for due to the limitations inherent in these data (page 10)**<br>11. The authors also talk about the limitation of not having indigenous status data. However, one could argue that this isn't something one would "control" for as much as one would want to better describe.<br>**Thank you for this comment, we agree with your assessment. Thus, we have changed the statement to read:**<br>**"it would be important to conduct this analysis to describe the burden of suicide among women who give birth to children with FASD who are Indigenous." (page 11)**<br>12. There is mention in the last paragraph of the Discussion of increased medical attention from paediatricians, this should also include mention of family physicians or just change to "primary care providers".<br>**Thank-you for your suggestion. We have changed the statement to "primary care physicians"**<br>Tables<br>13. Table 2 – please add "lowest" and/or " highest" to the labeling of income quintiles<br>**We have added lowest and highest to the labeling of the income quintiles**<br>14. Table 3 – you may want to delete the crude rate of # of women with suicide attempt that represents a small cell since one can calculate that if a rate of 1.67=6 women that the # representing a rate of 1.39 is 5 (first column of exposed cases)<br>**We have deleted the crude rate and this category out of the table so that no back calculations can be conducted**<br>15. Appendix 1 – these are not outcomes but are characteristics or covariates<br>**We have edited this appendix so that the suicide outcome definitions have been placed into a new table (Table 2) in the text and that the mental health characteristic definitions have been placed in appendix 1 (Tables 2, 3, 4)** |