Author's response to reviews

Title: Anti-diabetic Drug Utilization of Pregnant Diabetic Women in US Managed Care

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Version: 2 Date: 18 August 2013

Author's response to reviews: see over
August 19, 2013

Subject: Revision of Manuscript to BMC Pregnancy and Childbirth

Dear Dr. Robert Powers,

We wish to sincerely thank the reviewers for their insightful contributions. We have modified the manuscript to directly address all of the comments of the reviewers and believe they have greatly strengthened the paper. We appreciate the opportunity to address the concerns raised in a point-by-point manner below. We look forward to hearing from you.

Sincerely,

Caitlin A. Knox, MPH
Dear Ms Knox,

Your manuscript has now been peer reviewed and the comments are accessible in PDF format from the links below. Do let us know if you have any problems opening the files.

Referee 1: http://www.biomedcentral.com/imedia/4187723861010328_comment.pdf
Referee 2: http://www.biomedcentral.com/imedia/2050056064101516_comment.pdf

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

We look forward to receiving your revised manuscript by 30 August 2013. If you imagine that it will take longer to prepare please give us some estimate of when we can expect it.

You should upload your cover letter and revised manuscript through http://www.biomedcentral.com/manuscript/login/man.asp?txt_nav=man&txt_man_id=7052387196093820. You will find more detailed instructions at the base of this email.

Please don't hesitate to contact me if you have any problems or questions regarding your manuscript.

With best wishes,

Ms Janelyn Ann Cruz
on behalf of Dr Robert Powers

e-mail: editorial@biomedcentral.com
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Reviewer's report

Title: Anti-diabetic Drug Utilization of Pregnant Diabetic Women in US Managed Care

Version: 1 Date: 4 June 2013

Reviewer: Dharmintra Pasupathy

Reviewer's report:
Anti-diabetic drug utilization of pregnant diabetic women in US managed care

INTRODUCTION
1. Important area of study as the secular trends of prescription often results in widespread adoption of clinical practice with often limited evidence base. Trends in prescription will allow correlation and further study on the effects of medication use in pregnancy.

We would like to thank the reviewer for this assessment and concur with his assessment of the importance of this study, especially in regard to identifying important research questions for further study.

METHODS
2. It will be useful to have some further information / clarity on the IMS lifelink database due to the variation in the healthcare system in the US – for e.g. what % of the patients in the database are from the private vs state health care system. - Major Essential Revisions

Thank you for this comment. We have added further information about the payer type composition to the Methods section as follows:

We utilized the IMS LifeLink Database, which consists of commercial health plan information from more than 100 managed care plans throughout the US. The majority of the payer type within the database is commercially insured. The IMS LifeLink database also includes Medicaid, Medicare, self-insured and unknown payer types. The database records are generally representative of the commercially insured population in terms of gender and age. The IMS LifeLink database is comprised of eligibility and demographic information, as well as, inpatient and outpatient claims data with detail on diagnosis and procedures, and prescription drug claims.

3. In the first sentence of the second paragraph in the methods, the authors limit the entry criteria to only women seen in the preceding three months before conception. Is there a rationale to limit to only 3 months? - Minor Essential Revisions

We choose 3 months preceding conception in order to identify pre-existing diabetes and maintain equal exposure periods before, during, and after
pregnancy. Furthermore, as we required continuous eligibility and patients tend to change insurance plans and thus are lost for follow-up, it was necessary to restrict the eligibility period to the minimum necessary time frame needed for this study while retaining as many women as possible within the sample.

4. What is CPT-4? - Major Essential Revisions

CPT-4 is the Current Procedural Terminology code. It is a medical code set maintained by the American Medical Association. CPT-4 describes medical, surgical and diagnostic services. It is similar to ICD-9 coding, except that it identifies services rendered instead of the diagnosis on the claim. We have now spelled out the abbreviation of CPT-4 in the Methods section as follows:

We defined the delivery date as the date of the first Current Procedural Terminology (CPT-4) claim for live birth for each woman.

5. What is the basis of the calculation of the conception date? We know that the median gestational age of diabetic pregnancies are earlier than unselected population. There is also likely to be greater variation in the gestational age of delivery and consequently on the conception date by the proposed means of calculation. I see that the authors acknowledge this and attempt to address this. The estimation process may not be entirely clear for the general readership. - Minor Essential Revisions

We agree that the misclassification of the conception date as calculated is an important limitation to our descriptive analysis, which we have tried to address with sensitivity analyses. Since we did not have access to the gestational age of the infant through our claims data, we choose to use 270 days to identify the length of pregnancy. We chose this time-period based on the literature, Hardy et al. 2006 and Margulis et al 2012. We have attempted to clarify our reasoning for choosing the 270 days within the methods section as follows:

Because we relied on an imputed conception date, there was a potential for misclassification of the pre-pregnancy period and the following trimesters. The risk of misclassification of the pregnancy periods was particularly high in women with diabetes, because they are at higher risk for pre-term births (i.e. shorter gestation periods). In order to evaluate this effect we conducted a sensitivity analysis, where we utilized the first healthcare encounter with a pregnancy code (ICD-9-CM: V22, V23, V72.40, V72.42 and CPT-4:81025) to estimate conception date.[18] Using the first pregnancy claim as the conception date, the mean length of pregnancy for the cohort was 6.55 months with a standard deviation of 1.64 months. Five percent of the diabetes cohort had an ICD-9-CM claim for early delivery (644.2, 644.20, and 644.21). Therefore, we conducted another sensitivity analysis where we adjusted the gestation length to 245 days for women with an early delivery claim. [19] We saw that the drug class utilization in the sensitivity analysis did not differ significantly with the originally imputed pregnancy periods we calculated using 270 days subtracted from the delivery date.

RESULTS
6. In addition to the demographic trends presented over time, the general readership will also be interested in the trends of birthweight in these women. Although this is not the primary aim of the study. This data may not be available to the investigators. - Discretionary Revisions

Unfortunately, we only had access to the administrative claims of the IMS Lifelink Database. Since this database is de-identified, it was impossible to link to the infant’s claims or birth certificates, which are the traditional way to obtain information on gestational age and birth weight. Therefore, we are unable to report the trends in birth weight of infants born to mothers with pre-existing diabetes. We are currently working on creating a linked data set (claims data and birth certificates) which will greatly facilitate the suggested analysis and future research on pharmacotherapy effectiveness and safety. Of note, to our knowledge such a linkage has not been created in the US before.

DISCUSSION
7. The discussion is well written and addresses the strengths and limitations of the study. Further efforts in correlating drug utilization and pregnancy outcome are worthy of mention. - Discretionary Revisions

Thank you for your positive assessment. We have indeed used this study to develop an ongoing study analyzing the comparative safety of anti-diabetic agents in pregnancy. We have amended the discussion as follows:

The high rate of oral anti-diabetic drug use during pregnancy emphasizes the need for conclusive evidence regarding safety and efficacy in terms of glucose control as well as maternal outcomes. Further research is needed in order to evaluate the safety of oral anti-diabetic agent use in pregnant women with pre-existing diabetes in terms of pregnancy and neonatal outcomes.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: No

Reviewer's report

Title: Anti-diabetic Drug Utilization of Pregnant Diabetic Women in US Managed Care

Version: 1 Date: 10 June 2013

Reviewer: Anita Banerjee

Reviewer's report:
Major compulsory revisions
The subject is of interest however, more clinical evidence and information is required.
1) The data lacks all women who may have had a miscarriage, stillbirth or termination of the pregnancy due to congenital abnormalities. Collecting this data may provide an understanding of anti-diabetic utilization and glycaemic control.

This is indeed a very significant issue, but it is important to note that this study did not attempt to evaluate the safety and effectiveness of glycemic control, but rather to describe prescribing pattern by trimester. Inclusion of terminated pregnancies would not have allowed determination of trimesters, because the date of the termination relative to conception would be unknown. We understand that drug utilization pattern in women with unsuccessful pregnancies (i.e. miscarriage, stillbirth, or termination) may be different and now acknowledge this in the discussion section as follows:

*We limited this descriptive analysis to pregnant women with live births. Therefore, the drug utilization patterns that were seen within this descriptive analysis may be different from pre-existing diabetic women with unsuccessful pregnancies (i.e. miscarriage, stillbirth, or termination).*

2) The data was collected over ten years and no correlation made with glycaemic control and co-morbidities of the women. Can this be correlated?

Unfortunately, we only had access to the administrative claims of the IMS Lifelink Database. The administrative claims do not allow us to investigate glycemic control in this population because we do not see laboratory values within this database. Since this database is de-identified, it was also impossible to link the administrative claims to a medical record. We do report presence of comorbidities at baseline, but we have not made an attempt to formally analyze relationships with drug choice during pregnancy. As the reviewers correctly points out, drug choice during pregnancy is very likely influenced by glycemic control, which again is not available. Thus, any attempt to explain associations may be quite truncated with the data set at hand. We now note that further research might also focus on determinants of medication choice during pregnancy including presence or onset of co-morbidities and changes in glycemic control.

*Within this study, it we were unable to assess the impact of glycemic control and co-morbid conditions on the choice of anti-diabetic agents throughout pregnancy. Therefore, it will also be important for future research to focus on the determinates of medication choices during pregnancy including the presence or on-set of co-morbid conditions and changes in glycemic control.*

3) The data requires correlation with glycaemic control during pregnancy and outcome regarding birthweight, congenital defects and neonatal hypoglycaemia.

*Within this analysis, we aimed to describe anti-diabetic (AD) agent utilization among pre-existing diabetic pregnant women. This was done because little*
evidence is currently available regarding the use of oral anti-diabetic agents during pregnancy in women with pre-existing diabetes. The current literature tends to focus on utilization in gestational diabetic women or smaller samples of women with pre-existing diabetes. The study is informative into the real-world utilization of anti-diabetic agents in women with pre-existing diabetes and in our understanding has merit and informative value despite its purely descriptive nature. As stated, we are currently planning follow-up studies with different data sets to address some of the questions that the reviewer suggests and that we agree are critical for clinical care.

**Level of interest:** An article of limited interest

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I declare that I have no competing interests