PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Beta-blocker treatment during pregnancy and adverse pregnancy outcomes: a nationwide population based cohort study
AUTHORS	Meidahl Petersen, Kasper ; Jimenez-Solem, Espen; Andersen, Jon Traerup; Petersen, Morten; Brødbæk, Kasper; K&#65533;ber, Lars; Torp-Pedersen, Christian; Poulsen, Henrik

VERSION 1 - REVIEW

REVIEWER	Tiina Podymow Assistant Professor Nephrology McGill University Health Centre Montreal, Quebec Canada
REVIEW RETURNED	18-Jun-2012

THE STUDY	The authors are trying to answer the important question of safety of beta blocker use in pregnancy. My main comments are that this paper needs to be reviewed in detail by a statistician to vet the methods used. A major problem I have is that their population has a prevalence of preeclampsia that is far lower than the general popluation (table 1) and therefore their results are not generalizable. The gen pop has incidence of 5% and hyeprtensives 25% whereas their cohort has incidence of .83 and 4% (of women on beta blockers) respectively. The authors need to address this. Another major problem is that they don't state what percent of women have gestational or essential hypertension at the outset, and the fact that these conditions are known risk factors for the outcomes- are they controlled for adequately? Why aren't they in table 1 or 2? The concluding statement- the future treatment of pregnant women with beta blockers should therefore be based primarily on the individual needs of the mother and not the child- is very puzzling. Need to clearly state that this is an observational study and that it is hypothesis generating, need a trial to validate the hypothesis. Cannot make recommendations based on this study. Drug effect bblocker class effect vs. disease effect? This is not answered. Minor points Say filling prescription, not redeeming.

	No need to write icd10 codes Don't address women who are on 2 or 3 different antihypertensives, or on other meds as confounders. Results section- write out what the associations are on page 12 e.g. what was the rate of perinatal mortality?

REVIEWER	Anne Wallis, MHS, PhD Assistant Professor Department of Epidemiology College of Public Health University of Iowa USA I have no competing interests regarding this publication.
REVIEW RETURNED	30-May-2012

GENERAL COMMENTS	This is a clear, well-written paper. The design is replicable and the authors have access to an excellent source of data. They have controlled appropriately for potential confounders and their use of propensity scoring is innovative. The authors are clear about limitations.

VERSION 1 – AUTHOR RESPONSE

Response to reviewer 24-06-2012.
We would like to thank the reviewers for their detailed and constructive comments. In this reply we address their comments point-by-point and indicate where changes have been made. Reference to page (p.) and line (l.) numbers refer to the new main document.
Reviewer: Anne Wallis, MHS, PhD
Assistant Professor
Department of Epidemiology
College of Public Health
University of Iowa
USA
Comment: I have no competing interests regarding this publication.
This is a clear, well-written paper. The design is replicable and the authors have access to an excellent source of data. They have controlled appropriately for potential confounders and their use of propensity scoring is innovative. The authors are clear about limitations.
Response:
We thank the reviewer for these comments.
Reviewer: Tiina Podymow
Assistant Professor Nephrology
McGill University Health Centre
Montreal, Quebec
Canada

Comment:
A major problem I have is that their population has a prevalence of preeclampsia that is far lower than the general popluation (table 1) and therefore their results are not generalizable. The gen pop has incidence of 5% and hyeprtensives 25% whereas their cohort has incidence of .83 and 4% (of women

on beta blockers) respectively. The authors need to address this.
Response:
We appreciate this constructive comment. In the Method section, we explain that we removed 2836 records with pregnancy-induced hypertension from the cohort. We defined pregnancy-induced hypertension as having a first-time redemption of an antihypertensive drug prescription after the twentieth week of gestation, but never before. Assuming these women have gestational hypertension or pre-eclampsia, the prevalence increases to 1.2 % in the general population. An important reason for the low prevalence of pre-eclampsia in our study might be because we used primary discharge diagnoses from hospital admissions. Secondary diagnoses were not used, since these in general are not validated. Pre-eclampsia and eclampsia treated outside hospitals, e.g. in primary practice, were not included in our survey. Our cohort covers an entire nation, and we therefore believe that our primary results are generalizable. Our prevalence of pre-eclampsia was lower than expected due to the mentioned methods. We agree with the reviewer that this should be addressed. Accordingly, changes were made in the following sections of the article: we point out that we obtained primary diagnoses in the method section, p. 5, l 10-13. Changes are made on p. 10, table 1.

Comment
Another major problem is that they don't state what percent of women have gestational or essential hypertension at the outset, and the fact that these conditions are known risk factors for the outcomes- are they controlled for adequately? Why aren't they in table 1 or 2?
Response:
This is an important point. We agree that these are known risk factors for our primary outcomes. Unfortunately we could not adjust our analyses for these conditions, since we only had access to primary discharge diagnoses given at hospitals. We believe that many women receive treatment outside hospitals, e.g. in primary care. Our study focuses on the association between drug redemption and adverse pregnancy outcomes. We do not have access to valid data on maternal essential hypertension, which is regrettably an important limitation. Consequently we have not included rates and percentages on essential hypertension in tables 1 or 2. This limitation is addressed in the discussions section under limitations, p. 18, l. 19 with the sentence: “unfortunately information on diagnoses of essential hypertension was not available, since these are known risk factors for our primary outcomes.”

Comment:
The concluding statement- the future treatment of pregnant women with beta blockers should therefore be based primarily on the individual needs of the mother and not the child- is very puzzling. Need to clearly state that this is an observational study and that it is hypothesis generating, need a trial to validate the hypothesis. Cannot make recommendations based on this study.
Response:
We agree with the reviewer that recommendations should be based on a trial and not a study with an observational design. Therefore, changes were made in the following sentence: p3, l. 3-4 and p. 19, l. 9-11. On the basis of the reviewers comment we have changed the last section: “The increasing use and uncertainty of effects and possible side effects of treatment with beta-blockers during pregnancy call for further studies to validate our findings.”, p. 19, l. 11-13.

Comment:
Drug effect bblocker class effect vs. disease effect? This is not answered.
Response:
This is indeed a problem with the observational study design. We cannot adjust for treatment and severity of maternal disease, which is added in the Discussion section on p. 18. This section has been expanded with “Consequently we were unable to differentiate between a possible class effect of beta-blockers and the effect of the underlying maternal disease”, p. 18, l. 17.

Comment (minor):
No need to write icd10 codes
Response:
We chose to keep icd10 codes in our manuscript in order to ensure that our design is replicable. If reviewer disagrees, we will of course remove all icd10 codes.

Comment (minor):
Say filling prescription, not redeeming
Response:
We thank the reviewer for the comment. We have not replaced the word redeeming with filling, since, according to our understanding, their meaning is not quite the same. Our understanding is, the women redeem the prescription, whereas the pharmacy fills prescriptions. We are of course willing to change the formulation if we have misunderstood the meaning of the word redeeming.
Comment (minor):
Don't address women who are on 2 or 3 different antihypertensives, or on other meds as confounders.
Response:
Women redeeming prescriptions of multiple beta-blockers are mentioned in the results section. However, we did not adjust our analyses for redemption of 2 or 3 beta-blockers. This is not addressed as confounders. Redemption of prescriptions for insulins and analogues, statins and antiobesity preparations were used as a proxy for maternal disease other than hypertension. These are risk factors for the defined outcomes, and accordingly we believe that these adjustments are relevant.

Comment (minor):
Results section- write out what the associations are on page 12 e.g. what was the rate of perinatal mortality?
Response:
Associations and rates are only included in table 3. According to the BMJ open formatting instructions (http://group.bmj.com/products/journals/instructions-for-authors/formatting/), data contained in tables are not to be duplicated elsewhere in the text. Due to the large quantity of results we chose not to present all of them in the text. If editor or reviewer disagrees, we are of course willing to include a more detailed Results section.

Corrections made by authors:
In addition, we have rearranged the list of authors, and have made following corrections to table 2: redemption of an insulin or analogue in labetalol exposed: Yes 83 (5.72), No 1369 (94.28). Pre-eclampsia diagnosis in labetalol exposed: Yes 74 (5.10), No 1378 (94.90). Pre-eclampsia diagnosis in women exposed to other beta-blockers: Yes 21 (2.26), No 908 (97.84).