PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The effect of maternal age and planned place of birth on intrapartum outcomes in healthy women with straightforward pregnancies: secondary analysis of the Birthplace national prospective cohort study
AUTHORS	Hollowell, Jennifer; Li, Yangmei; Townend, John; Rowe, Rachel; Knight, Marian; Brocklehurst, Peter

VERSION 1 - REVIEW

REVIEWER	Dr Meredith McIntyre Monash University Australia
REVIEW RETURNED	25-Oct-2013

GENERAL COMMENTS	This is a carefully structured paper that describes in detail inclusion, exclusion criteria, sample sizes, management of data, size limitations of the sample being studied and findings. Tables used to illustrate findings are appropriate aiding the reader to comprehend the scope of the findings and the implications of the findings for the 40+ primigravid group. This is a well thought out report on a topic of interest to a range of maternity care providers and professional. The use of this prospective data from the Birthplace Cohort was well described and appropriate for the purposes of this study. A high quality article.

REVIEWER	Ank de Jonge VU university medical center, Amsterdam., Department of Midwifery Science
REVIEW RETURNED	14-Oct-2013

GENERAL COMMENTS	It is exciting to see another article being submitted on data from the Birthplace study – the best cohort study on planned place of birth in the Western world so far. The large numbers allowed the authors to explore the association between maternal age and intrapartum interventions and outcomes among low risk women and therefore this article makes very interesting and novel information available to the public domain. I have some major and minor comments that may improve the paper. - Major issues

	1. The aim and objectives of the paper are not entirely clear to me. The authors wrote that their aim was 'to evaluate the association between maternal age and intrapartum interventions and adverse maternal and perinatal outcomes that may influence the choice of place of birth….' From this, I take it that the authors want to provide information that can help women to make choices (together with their practitioner) about planned place of birth. In an earlier paragraph they report the findings of the main Birthplace study and state that (these are my own words:) they want to find out whether these outcomes are different for older women. I can think of two objectives that would provide important information to older pregnant women: a. To compare outcomes and interventions by planned place of birth in relation to age. This would provide information on which planned place of birth at a given age (or age range) is associated with the best outcomes/ lowest rates of interventions. b. To compare absolute rates of interventions in relation to age. This would provide information about the chance of being transferred during labour from a midwife-led to an obstetric setting. The first objective can be studied by comparing rates of outcomes and interventions by planned place of birth per 5-year age group. This would show that in every age category women have lower rates of adverse maternal and perinatal outcomes and interventions for non-OU settings than OU settings. In the discussion, the authors can comment, as they do, on the higher rate of adverse perinatal outcomes for planned home births, but the numbers are too small to compare these rates for different age groups. Relative risks should be given for planned non-OU versus OU setting (same as in the main study) in each age category. In the current article, the authors have given relative risks for the change in rates of outcomes and interventions within the OU group and within the non-OU group. I do not understand how this information is useful for making choices about planned place of birth. It is not surprising that relative risks within the OU group are lower than within the non-OU group as the rates at lower ages in the OU group are already high. In fact, the absolute increase in rates of outcomes and interventions is often higher in the OU group, but because their 'starting rate' is higher, the relative risk is lower. For example, the percentage of composite maternal outcomes for nulliparous women in OU units is 39.4% in the age group 16-19 and 65.5% in the age group 35-39. The absolute increase in risk is 26.1% and the percentage in the 35-39 group is 1.66 times higher than in the 16-19 group. In the non-OU group these percentages are 17.5% in the age group 16-19 and 39.9% in the age group 35-39. The absolute increase is 22.4% and the percentage in the 35-39 group is 2.28 times higher. The results for the second objective have already been beautifully displayed in tables 3-5. Nulliparous women between 35 -39 years can look at this information and choose to give birth in an OU if they are very worried about their chance of 39.9% of having an intervention for which they would need to be transferred if they would start in a non-OU unit. However, they should then also bear in mind that starting in an OU gives them a much higher chance of having an intervention (65.5%).

	In short, I think the authors should rephrase their objectives and conduct analyses in which the planned non-OU and planned OU groups are compared for different age groups. 2. The authors conclude that age 40 is an appropriate threshold for recommending individual assessment when planning place of birth. I do not think this statement is supported by the data. As the authors rightly state in the discussion, because of small numbers in the over 40 group, they had limited power to evaluate risks at older ages. They refer to graphical plots that suggest a possible upturn in neonatal admission/ perinatal death around the age of 40 for nulliparous women. I do not think these graphs can be used to suggest that individual assessment is needed when planning place of birth for women over 40. The rates of adverse perinatal outcomes are similar in the OU and non-OU group (2.1% versus 2.3%) and only in the planned home birth group the rate appears to increase sharply after 40. However the total number of adverse events in the three non-OU groups together is 20 versus 7 in the OU group and therefore the number in the planned home birth group is likely to be very small. In fact, the authors should consider truncating all figures at age 40 because the low number of women over 40 and very low number of events among this group result in very unreliable graphs. I agree with the authors that further research is neede to evaluate perinatal outcomes in low risk women over 40. All other outcomes are better in the non-OU than in the OU group. Therefore, which individual assessment should be made other than discussing the risk of transfer for needing interventions? And why should that discussion take place with women over 40 and not below 40? I think all women need to be informed about their chance of needing a transfer and this article can help greatly in individualising that chance for women in different age groups. 3. The study population for the analyses constituted of low risk women in the Birhtplace cohort. Sensitivity analyses were conducted for women without complicating conditions at the onset of labour. I would suggest to take the group without complicating conditions as the main study population and conduct sensitivity analyses for all low risk women. This would make the groups more comparable. In the current study, the OU group is at a disadvantage as it includes more women with complicating conditions. If the authors do not agree, please explain why the current study population was chosen. 4. The term ‘maternal composite outcome’ seems to be defined in two different ways: one comprises augmentation, instrumental delivery and intrapartum caesarean section and the other, in addition, general anaesthesia, maternal blood transfusion etcetera. Please indicate clearly in tables and figures which definition of maternal composite outcome was used. - Minor issues Page 5, line 28: current guidelines …. Only a reference to the NICE guideline is given. I would rephrase the sentence and state that the NICE guideline recommends… as this is not the recommendation in all Western countries. Page 11, first paragraph: The numbers do not seem to be consistent with those in the main study. In the main study, 64,538 women were

	low risk. In the current article 15,553 women with pre-existing medical and obstetric risk factors were exlcluded from the total of 79,774, resulting in a group of 64,221 low risk women. Please, explain the difference between both analyses. Page 15, first paragraph: the authors suggest that there may be some differences in characteristics of women opting for OU or non-OU settings. Actually, there is strong evidence for this as the authors know that women in planned OU settings had more complicating conditions at the onset of labour (see comment earlier). Page 15 and further: discussion needs to be rewritten if analyses have been repeated. The text addressing the steeper increase in augmentation should be left out. Page 16: 'The significant positive association between maternal age and epidural use… seen most strongly in nulliparous women planning a non-OU birth… the latter does not become clear from the figure in S2. Also, I think all material that is discussed in the paper should be shown in the main tables and figures, not in supplements. Page 16 and 17: Conclusion should be rewritten after redoing the analyses. I think the sentence: 'Younger nulliparous women appear to benefit more than older nulliparous women form planned birth in a non-OU setting' should be removed. - Textual Page 11, line 51: please write PPOB in full at the first occurrence. - Tables and figures Figure 1: the authors have not indicated where in the text this should be placed. Table 2: why were differences shown for OU and non-OU units for maternal composite outcome and augementation and not for instrumental delivery and caesarean section? No explanation has been given in the methods section. Please place tables with absolute numbers (3-5) before tables with associations (2). - References Reference 1: is this complete? Reference 23: please give year of publication

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Ank de Jonge
Institution and Country Department of Midwifery Science
VU university medical center, Amsterdam
Please state any competing interests or state 'None declared': None

It is exciting to see another article being submitted on data from the Birthplace study – the best cohort study on planned place of birth in the Western world so far. The large numbers allowed the authors to explore the association between maternal age and intrapartum interventions and outcomes among low risk women and therefore this article makes very interesting and novel information available to the public domain.

I have some major and minor comments that may improve the paper.

- Major issues

1. The aim and objectives of the paper are not entirely clear to me. The authors wrote that their aim was 'to evaluate the association between maternal age and intrapartum interventions and adverse maternal and perinatal outcomes that may influence the choice of place of birth….'
From this, I take it that the authors want to provide information that can help women to make choices (together with their practitioner) about planned place of birth. In an earlier paragraph they report the findings of the main Birthplace study and state that (these are my own words:) they want to find out whether these outcomes are different for older women.
I can think of two objectives that would provide important information to older pregnant women:
a. To compare outcomes and interventions by planned place of birth in relation to age.
This would provide information on which planned place of birth at a given age (or age range) is associated with the best outcomes/ lowest rates of interventions.
b. To compare absolute rates of interventions in relation to age.
This would provide information about the chance of being transferred during labour from a midwife-led to an obstetric setting.

The first objective can be studied by comparing rates of outcomes and interventions by planned place of birth per 5-year age group. This would show that in every age category women have lower rates of adverse maternal and perinatal outcomes and interventions for non-OU settings than OU settings. In the discussion, the authors can comment, as they do, on the higher rate of adverse perinatal outcomes for planned home births, but the numbers are too small to compare these rates for different age groups. Relative risks should be given for planned non-OU versus OU setting (same as in the main study) in each age category.

In the current article, the authors have given relative risks for the change in rates of outcomes and interventions within the OU group and within the non-OU group. I do not understand how this information is useful for making choices about planned place of birth. It is not surprising that relative risks within the OU group are lower than within the non-OU group as the rates at lower ages in the OU group are already high. In fact, the absolute increase in rates of outcomes and interventions is often higher in the OU group, but because their 'starting rate' is higher, the relative risk is lower. For example, the percentage of composite maternal outcomes for nulliparous women in OU units is 39.4% in the age group 16-19 and 65.5% in the age group 35-39. The absolute increase in risk is 26.1% and the percentage in the 35-39 group is 1.66 times higher than in the 16-19 group. In the non-OU group these percentages are 17.5% in the age group 16-19 and 39.9% in the age group 35-39. The absolute increase is 22.4% and the percentage in the 35-39 group is 2.28 times higher.

The results for the second objective have already been beautifully displayed in tables 3-5. Nulliparous

women between 35 -39 years can look at this information and choose to give birth in an OU if they are very worried about their chance of 39.9% of having an intervention for which they would need to be transferred if they would start in a non-OU unit. However, they should then also bear in mind that starting in an OU gives them a much higher chance of having an intervention (65.5%).

In short, I think the authors should rephrase their objectives and conduct analyses in which the planned non-OU and planned OU groups are compared for different age groups.

Response

The study aim (to evaluate the association between maternal age and intrapartum interventions and adverse maternal and perinatal outcomes that may influence the choice of place of birth….') was formulated in this way to indicate that the study would focus on the relationship between age and outcomes that would necessitate transfer to an OU if labour care started in another setting. The focus on outcomes that indicate a need for obstetric or neonatal care is made explicit in the paragraph that describes the study objectives.

The present study was designed to evaluate whether there was an interaction between age and planned place of birth for the outcomes under consideration. That is, to examine whether the risk reduction seen in non-OU births (as demonstrated in the primary Birthplace analysis 1) differed by age and, if so, to examine how age affected the risk reductions previously found in non-OU births. Our objectives overlap, to a considerable extent with those proposed by the reviewer – and we are pleased to note that she considered that "the results for the second objective have already been beautifully displayed in tables 3-5". We have now added an additional table showing the unadjusted and adjusted relative risk reductions associated with planned non-OU birth for the two outcomes where we found a significant interaction between age and PPOB.

To address the point raised below (point 3 relating to women with complicating conditions at the start of labour care) we have provided additional analyses in which we adjust for both maternal characteristics and complicating conditions. We have also re-ordered the results section so that the findings adjusted for complicating conditions at the start of labour care are given greater prominence. We hope that this re-ordering enables the two sets of results to be treated in a more balanced way.

2. The authors conclude that age 40 is an appropriate threshold for recommending individual assessment when planning place of birth. I do not think this statement is supported by the data. As the authors rightly state in the discussion, because of small numbers in the over 40 group, they had limited power to evaluate risks at older ages. They refer to graphical plots that suggest a possible upturn in neonatal admission/ perinatal death around the age of 40 for nulliparous women. I do not think these graphs can be used to suggest that individual assessment is needed when planning place of birth for women over 40.
The rates of adverse perinatal outcomes are similar in the OU and non-OU group (2.1% versus 2.3%) and only in the planned home birth group the rate appears to increase sharply after 40. However the total number of adverse events in the three non-OU groups together is 20 versus 7 in the OU group and therefore the number in the planned home birth group is likely to be very small. In fact, the authors should consider truncating all figures at age 40 because the low number of women over 40 and very low number of events among this group result in very unreliable graphs. I agree with the authors that further research is neede to evaluate perinatal outcomes in low risk women over 40. All other outcomes are better in the non-OU than in the OU group.
Therefore, which individual assessment should be made other than discussing the risk of transfer for needing interventions? And why should that discussion take place with women over 40 and not below 40? I think all women need to be informed about their chance of needing a transfer and this article

can help greatly in individualising that chance for women in different age groups.

Response
Current NICE guidelines recommend that women aged over 40 at booking should receive individual assessment when planning place of birth. We wholeheartedly agree with the reviewer that all women should be individually assessed, advised and informed. Our stated conclusion that our findings "support the current threshold" was intended to convey that we considered that our results did not (a) provide evidence suggesting that the threshold should be lowered or (b) provide evidence that might suggest raising the threshold. We feel, on reflection, that this is a judgement that may best be left to others and have removed this from the conclusion.

With regard to the number of women aged over 40, The sample includes 1681 women aged 40+ at the time of the birth, including 928 aged over 40. Given that few studies have large samples of outcomes in 'low risk' older mothers we feel that it is useful to report results for this group so have not truncated the graphs or excluded women aged 40+ from the tables. We clearly state on page 11 that the rates for the 40+ age group are based on small numbers, we report the sample size in detail in table S4 and all tables include confidence intervals.

3. The study population for the analyses constituted of low risk women in the Birhtplace cohort. Sensitivity analyses were conducted for women without complicating conditions at the onset of labour. I would suggest to take the group without complicating conditions as the main study population and conduct sensitivity analyses for all low risk women. This would make the groups more comparable. In the current study, the OU group is at a disadvantage as it includes more women with complicating conditions. If the authors do not agree, please explain why the current study population was chosen.

Response

We have added some additional analyses which we hope address the reviewer's concerns that our approach disadvantages the OUs (see response to point 1)

The reasons that we do not consider that it is appropriate for us to switch study populations are as follows:
• The absolute intervention rates in the main study population used by us have a clear 'real-life' meaning: they correspond to the predicted event rates for women who choose and start labour care in a given setting, whereas the intervention rates in 'women planning a non-OU birth without complicating conditions at the start of care in labour' have no obvious meaning at the time a woman is planning her birth setting. A woman cannot know in advance whether she will have complicating condition or not, so we do not think that it is informative or helpful to focus on the absolute event rates in this group by making this our main study population.
• We consider that we have used an appropriate study group for the investigation of whether the effect of PPOB varies by age (ie the stated study objective). We conducted our analyses with and without adjustment for complicating conditions and found that the additional adjustment for complicating conditions made no substantive change to our results. In terms of addressing our original objective there does not seem to be a strong justification for switching populations.
• We report the results of sensitivity analyses restricted to women without complicating conditions at the start of labour care so that the results for the population that the reviewer suggested that we might use as the main study population are already available to the reader, albeit in the supplementary material for some analyses.

We agree that the relative advantages of a non-OU birth should take account of the higher prevalence of complicating conditions in planned OU births so we have inserted a new table of adjusted relative risks showing the effect of adjusting for both maternal characteristics and' complicating conditions' for

the two outcomes where we found an interaction between maternal age and planned birth setting.

We have not re-calculated relative risks for outcomes where there was no age interaction because the odds of individual outcomes by planned place of birth have already been reported elsewhere, both for the main sample1 and for the restricted sample of women without complicating conditions.2
1. Birthplace in England Collaborative Group. Perinatal and maternal outcomes by planned place of birth for healthy women with low risk pregnancies: the Birthplace in England national prospective cohort study. BMJ. 2011;343:d7400. (Supplementay file, Appendix 8)
2. Hollowell J, Puddicombe D, Rowe R, Linsell L, Hardy P, Stewart M, et al. The Birthplace national prospective cohort study: perinatal and maternal outcomes by planned place of birth. Birthplace in England research programme. Final report part 4. London: NIHR Service Delivery and Organisation programme 2011. (Appendix 5)

4. The term ‘maternal composite outcome’ seems to be defined in two different ways: one comprises augmentation, instrumental delivery and intrapartum caesarean section and the other, in addition, general anaesthesia, maternal blood transfusion etcetera. Please indicate clearly in tables and figures which definition of maternal composite outcome was used.

Response
The same definition of the maternal composite was used throughout the study and we are uncertain why the reviewer thinks otherwise. We have amended one sentence on page 8 which may have erroneously given the impression that the maternal composite included only augmentation, instrumental delivery and intrapartum caesarean section.

- Minor issues

Page 5, line 28: current guidelines …. Only a reference to the NICE guideline is given. I would rephrase the sentence and state that the NICE guideline recommends… as this is not the recommendation in all Western countries.

Response - amended

Page 11, first paragraph: The numbers do not seem to be consistent with those in the main study. In the main study, 64,538 women were low risk. In the current article 15,553 women with pre-existing medical and obstetric risk factors were exlcluded from the total of 79,774, resulting in a group of 64,221 low risk women. Please, explain the difference between both analyses.

Response
The discrepancy is because we used study specific eligibility criteria (described on p7) that differ slightly from those used in the main study and we additionally excluded records where key variable were missing (e.g. age and parity). We have amended the sections describing the derivation of the study cohort to make this clearer.

Page 15, first paragraph: the authors suggest that there may be some differences in characteristics of women opting for OU or non-OU settings. Actually, there is strong evidence for this as the authors know that women in planned OU settings had more complicating conditions at the onset of labour (see comment earlier).

Response
Thank you for drawing our attention to this. The original wording did not convey the point that we were attempting to make. We have expanded the explanation so that we hope the meaning is now both

clear and correct.

Page 15 and further: discussion needs to be rewritten if analyses have been repeated. The text addressing the steeper increase in augmentation should be left out.

Response
The observation that we make about differences in the gradients observed for augmentation in the two setting is factually correct and we are uncertain why the reviewer does not think that it is relevant to discuss possible reasons for this.

Page 16: 'The significant positive association between maternal age and epidural use… seen most strongly in nulliparous women planning a non-OU birth… the latter does not become clear from the figure in S2. Also, I think all material that is discussed in the paper should be shown in the main tables and figures, not in supplements.

Response
We have conducted additional analyses that do clearly show this but we agree that this is not clear from figure S2. We have therefore removed the phrase "seen most clearly in nulliparous women planning a non-OU birth".

Page 16 and 17: Conclusion should be rewritten after redoing the analyses. I think the sentence: 'Younger nulliparous women appear to benefit more than older nulliparous women form planned birth in a non-OU setting' should be removed.

Response
We have amended this sentence to read "Amongst nulliparous women, younger women appear to benefit more from the reduction in interventions associated with planned birth in a non-OU setting."

We consider that this conclusion is justified. We have demonstrated that there is a significant interaction between age and PPOB and the new table now added to this report shows that the relative reduction in the risk of the maternal composite and of augmentation is greatest for younger nulliparous women and that this benefit decreases with increasing age:
• In nulliparous women the adjusted risk reduction for the maternal composite is 55% at age 16-19 decreasing steadily to 34% in women aged 40
• A strong age-related gradient is still evident after adjusting for complicating conditions. For example, the adjusted relative risk reduction for the maternal composite is 51% at age 16-19 decreasing to 32% at age 35-39.

- Textual

Page 11, line 51: please write PPOB in full at the first occurrence.

Response - amended

- Tables and figures

Figure 1: the authors have not indicated where in the text this should be placed.

Response – amended

Table 2: why were differences shown for OU and non-OU units for maternal composite outcome and augementation and not for instrumental delivery and caesarean section? No explanation has been

given in the methods section.

Response
An explanation is given on page 9 of the methods section:
“For each of the study outcomes, we tested for an interaction between age (as a continuous variable) and planned place of birth (OU vs. non-OU) using a Wald test, and where the interaction was significant at the 5% level, we modelled the effect of age on the outcome separately by planned place of birth.”

Please place tables with absolute numbers (3-5) before tables with associations (2).

Response
The tables are presented in this order (interaction analysis followed by event rates) for the following reasons. First, the analysis presented in table 2 corresponds to our first objective. Second, modelling age as a continuous variable has greater statistical power to detect an interaction between age and PPOB and provides a means of estimating the significance of the slope. We feel that this is better presented before the categorical analysis since the relative risks presented in table 2 and their associated p-values are fundamental to understanding whether the event rates presented in subsequent tables reflect statistically significant variations by age. Third, there will be a presentation issue if we move table 3-5 before table 2 as table 2 covers results for all outcomes whereas table 3-5 only cover results for the main outcomes.

- References

Reference 1: is this complete?
Reference 23: please give year of publication
Response – We have updated both references.

Reviewer Name Dr Meredith McIntyre
Institution and Country Monash University
Australia
Please state any competing interests or state ‘None declared’: None to declare

This is a carefully structured paper that describes in detail inclusion, exclusion criteria, sample sizes, management of data, size limitations of the sample being studied and findings. Tables used to illustrate findings are appropriate aiding the reader to comprehend the scope of the findings and the implications of the findings for the 40+ primigravid group.

This is a well thought out report on a topic of interest to a range of maternity care providers and professional. The use of this prospective data from the Birthplace Cohort was well described and appropriate for the purposes of this study.

A high quality article.

VERSION 2 – REVIEW

REVIEWER	Ank de Jonge Department of Midwifery Science, AVAG and the EMGO institute of health and care research, VU University Medical Center, Amsterdam, the Netherlands.
REVIEW RETURNED	12-Dec-2013

GENERAL COMMENTS	I only have some minor comments to make. 1. Key messages: it would be good to add the message: 'At all ages 'low risk' women who plan birth in a non-obstetric unit setting have lower intervention rates than comparable women who plan their birth in an obstetric unit'. The key message: 'Increased intervention rates at older ages may partly reflect women's expectations and preferences and possibly 'higher risk' labelling by clinicians' does not follow from the data. I would leave this one out, but this is optional. 2. Discussion: page 35, l. 48: 'across the age range 16-40' should read 'for all ages' as table 4 shows that women over 40 also experienced fewer interventions if they planned their birth in a non-obstetric unit. Congratulations on this interesting paper.