PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Parenteral Pethidine for labour pain relief and substance use disorder: 20 year follow-up cohort study in offspring
AUTHORS	Robert Rodrigues Pereira, Humphrey Kanhai, Frits Rosendaal, Paula van Dommelen, Dick Swaab, Erik Rodrigues Pereira, Ben van de Wetering and Bouman M

VERSION 1 - REVIEW

REVIEWER	Prof Em Dr M.F. Niermeijer, clinical geneticist[non-practising] Dept Human Genetics, Radboud University Medical Center, Nijmegen, the Netherlands[2002-2006]; Dept Clinical Genetics, Erasmus Medical Center, Rotterdam, the Netherlands[1968-2002]. No competing interests.
REVIEW RETURNED	13/12/2011

THE STUDY	=ref 17[Nejm] does only give neonatal and no long-term outcome data on children born under obstet analgesia;these are not immediately relevant in this study =ref 14 is extremely relevant, as it gives the outcome on learning disability before the 19th year 1500 obstet analgesia and 4500 unexposed children[Mayo Clinics], with equal rates in these groups;in the discussion, this references is not used as supporting the risk estimate of obstet analgesia. =ref23: a scale of a Dutch Mental Health Organisation was used, which categorises the substance use history of an individual. There is apparently no discrimination between presence/absence of SUD/addiction. Referral to an English documentation of this test might be relevant.The similarity of the substance use data in ObAnalg/control groups [table 3] suggest there is no difference in "substance use disorder", without availability of such a diagnosis in individuals in either group.
RESULTS & CONCLUSIONS	=This study is of great importance for the initiative and the endaveour of the group to perform a much needed follow up study without a centralised registry, necessitating a major record serach operation, etc. =There are very few data of good quality to establish the long term developmental risks of obstet analgesia. The older data, refs 5-8, are on Scandinavian and US women with various SUD histories and ob analg, while mothers in ref 14 and the present study were only known for ob analg. The data of the present study and ref 14 seem to support the strong impression, that obstet analg alone has a different postnatal risk

	profile for SUD and other brain disorders as compared with maternal SUD and obstet analg.This latter message might be more clearly expressed in the discussion. =The other message is, that record keeping and storage remains crucial for assessing longterm effects of medications with potential risks for the developing brain, and that replication of these data is very much indicated, also considering the increasing interest for obstetric analgesia and its more lenient indications recently.
REPORTING & ETHICS	=The data collection by record searching , analysis and extraction was done by E.D. Pereira, MD, and it is unexplainable and difficult to accept, that such a central activity for this work did not result in an authorship, but only in an acknowledgement.

REVIEWER	Roz Ullman Senior research Fellow and Clinical Lead (Midwifery) National Collaborating Centre for Women's and Children's Health UK
REVIEW RETURNED	22/01/2012

THE STUDY	Research question: The research question in the introduction (page 3) is described as an investigation of an association. However, the question as it appears in the summary is a bit different stating that the authors hypothesise no association. Study design: The restricted investigation of potential confounding factors means the study is very unlikely to be able to answer the research question. Particiapnts: The use of the term "analgesia" is confusing. It may be that the term "pethidine" shoudlhave been used. If so then this is appropriate and shoudl be stated. If participants were chosen on basis of use of intrapartum analgesia, covering all forms of analgesia, this would not be appropriate. Methods: The prevalence data used to perform the power calculation is not clear. It seems prevalence data from 1987 has been used, around the time the babies were born, rather than 2007 i.e. prevalence at the time the data were collected. Summary: The key message that "perinatal analgesia" (or "labour pain medication" as it is described int he abstract) seems to be safe is not appropriate. Firstly, this phrase covers all analgesia, not just pethidine. This confusion needs to be addressed throughout the paper. Secondly, there are a number of other reasons why there might be concerns about the safety of intrapartum opioid use which have not been investigated by this study e.g. other psychiatric disorders or autistic spectrum disorders. Thirdly, this study is an underpowered observational study with a large number of potential confounders not considered so any firm conclusions are inappropriate. Strengths and weaknesses: This study cannot really be described as a well-designed large cohort study. It has limitations (see above) and is underpowered. Abstract: Study groups are better described as intervnetion/experimental vs comparison. This is not strictly speaking a case-control study.

	Statistics: A multivariate logistic regression model is described, however it seems only odds ratios are presented rather than adjusted odds ratios. Standard of written English: Fair. The word "addiction" is usually avoided as it is considered judgemental - substance misuse is more commonly used. References: A recent Cochrane review has been published looking at the effectiveness and side-effects of intrapartum parenteral opioids - Ullman R, Smith LA et al 2011 "The use of opioid intramuscular and intravenous pain relieving drugs in labour". STROBE statement: The phrase used in objectives section raises some concern " The objective was to duplicate the alarming results from earlier studies published in the BMJ ....." This is at odds with the research question and hypothesis as stated in the summary.
RESULTS & CONCLUSIONS	The findings are not credible due to the high risk of confounding and low response rate. Because of the lack of trustworthiness of the findings the conclusions drawn are over-stated and limitations are not sufficiently taken account of. The discussion and conclusion need to be written in a more balanced way to take this into account. The message is clear, but cannot be stated so unequivocally given the limitations of the research. Further investigation of potential confounders would be very valuable if it were possible.
REPORTING & ETHICS	Reporting: More details about the content and validation of the data collection tools should be included, especially where the short questionnaire varied from the longer, original one.

VERSION 1 – AUTHOR RESPONSE

Dear professor Niermeijer, thank you for your valuable comments on our manuscript. My response to your comments is as follows.

• =ref 17[Nejm] does only give neonatal and no long-term outcome data on children born under obstet analgesia; these are not immediately relevant in this study.

• You are right that this reference is not immediately relevant to our study. Nevertheless as the other reviewer Roz Ullman indicated the recent Cochrane review on “Parenteral opioids for maternal pain management in labour” might be important for the manuscript. Both references show that the long term view on possible sequelae is underestimated as an important issue in the case of obstetrical medication.

• =ref 14 is extremely relevant, as it gives the outcome on learning disability before the 19th year in 1500 obstet analgesia and 4500 unexposed children[Mayo Clinics], with equal rates in these groups; in the discussion, this references is not used as supporting the risk estimate of obstet analgesia.

• This reference is indeed relevant and points in the same direction as our study. It is inserted in a more logical place in the text.

• ref23: a scale of a Dutch Mental Health Organisation was used, which categorises the substance use history of an individual. There is apparently no discrimination between presence/absence of SUD/addiction. Referral to an English documentation of this test might be relevant. The similarity of

the substance use data in ObAnalg/control groups [table 3] suggest there is no difference in "substance use disorder", without availability of such a diagnosis in individuals in either group.
• This reference is the Dutch equivalent of the ESPAD (The European School Survey Project on Alcohol and Other Drugs) project in Europe that collects data from older adolescents on drug and alcohol misuse, http://www.espad.org/espad-reports. The term substance use disorder is a umbrella term for all the addictive substances mentioned. To unravel these differences this term was not used in the figures. It is stated in the key results of ESPAD that: The overall impression of the Dutch results is that they are well in line with the ESPAD average, except as regards the use of cannabis. However, although the proportions reporting alcohol consumption (84%) and drunkenness (36%) during the past 12 months are both very close to average, the reported volume consumed on the latest drinking day (4.9 cl alc. 100%) is somewhat above average. The 30-days prevalence of smoking cigarettes (30%) is about the same as in many other countries.

• =This study is of great importance for the initiative and the endeavor of the group to perform a much needed follow up study without a centralized registry, necessitating a major record search operation, etc.
• We appreciate the comment of the reviewer and we agree that more elaborate and robust follow up studies are needed.

• =There are very few data of good quality to establish the long term developmental risks of obstet analgesia. The older data, refs 5-8, are on Scandinavian and US women with various SUD histories and ob analg, while mothers in ref 14 and the present study were only known for ob analg.
The data of the present study and ref 14 seem to support the strong impression, that obstet analg alone has a different postnatal risk profile for SUD and other brain disorders as compared with maternal SUD and obstet analg. This latter message might be more clearly expressed in the discussion.
• We do agree with the comment of the reviewer that there are only a few studies of good quality that have the same design. We hope new studies will be done to clarify the issue. We will adapt the text in the manuscript.

• =The other message is, that record keeping and storage remains crucial for assessing long term effects of medications with potential risks for the developing brain, and that replication of these data is very much indicated, also considering the increasing interest for obstetric analgesia and its more lenient indications recently.
• We thank the reviewer for this important warning to hospitals, authorities and individuals who sometimes carelessly keep research data or records of their patients for only 15 years.

• =The data collection by record searching , analysis and extraction was done by E.D. Pereira, MD, and it is unexplainable and difficult to accept, that such a central activity for this work did not result in an authorship, but only in an acknowledgement.
• The reviewer is right that mr ED Rodrigues Pereira MD did a lot of work in extraction of the data but he also actively participated in discussions on the study design, so we are glad to grant him an authorship.

Dr Roz Ullman

Senior research Fellow and Clinical Lead (Midwifery)
National Collaborating Centre for Women's and Children's Health
UK

Dear dr Roz Ullman, thank you for your valuable and critical comments on our manuscript. My response to your comments is as follows.

• Research question: The research question in the introduction (page 3) is described as an investigation of an association. However, the question as it appears in the summary is a bit different stating that the authors hypothesize no association.

• When we state we study an association this is meant in the most neutral way possible, and includes deleterious, beneficial or no effect. Hence, there is no conflict with the hypothesis.

• Study design: The restricted investigation of potential confounding factors means the study is very unlikely to be able to answer the research question.

• We agree that confounding is a potential source of bias in any observational study. We respectfully disagree, however, that the adjustments in our study were limited, and that therefore the study was uninformative. Firstly, we adjusted for age, education, religion, and find it difficult to think of other measurable factors that would have affected both perinatal exposure and substance use during later life (the definition of confounding). In fact, we doubt the existence of such factors. Secondly, if there were such factors, it seems likely that they would be both associated with perinatal exposure and later substance use. In that case, we would have found a spurious association (overestimation of the association). However, we found no association, and that finding, in the presence of a true, missed association, is difficult to explain by confounding.

• Participants: The use of the term "analgesia" is confusing. It may be that the term "pethidine" should have been used. If so then this is appropriate and should be stated. If participants were chosen on basis of use of intrapartum analgesia, covering all forms of analgesia, this would not be appropriate.

• Thank you for pointing at this confusion, you are right that we should have use “pethidine” uniquely; we made the corrections in the text.

• Methods: The prevalence data used to perform the power calculation is not clear. It seems prevalence data from 1987 has been used, around the time the babies were born, rather than 2007 i.e. prevalence at the time the data were collected.

• The referent is right: we used the prevalence data from the time of birth of the babies in 1987 and 1988. It is implausible that this makes a difference as we present results as effect estimates with confidence intervals. These are independent of whatever result from a power calculation.

• Summary: The key message that "perinatal analgesia" (or "labour pain medication" as it is described in the abstract) seems to be safe is not appropriate. Firstly, this phrase covers all analgesia, not just pethidine. This confusion needs to be addressed throughout the paper. Secondly, there are a number of other reasons why there might be concerns about the safety of intrapartum opioid use which have not been investigated by this study e.g. other psychiatric disorders or autistic spectrum disorders. Thirdly, this study is an underpowered observational study with a large number of potential confounders not considered so any firm conclusions are inappropriate. Strengths and weaknesses: This study cannot really be described as a well-designed large cohort study. It has limitations (see above) and is underpowered.

• Indeed, we only studied the focused hypothesis of substance abuse in later life, and not any other potential outcome. This aspect of the study, which is not a limitation, is mentioned on page 2. The issue of confounding has been discussed above: we would not know of other confounders to include,

not how they could explain our null result, although we readily admit confounding is always possible in observational studies. Since this is always possible, the burden of plausibility lies with the reviewer: which confounder is missing? As for the power: this is completely reflected in the confidence intervals. These range from 0.97 to 1.09. We know of few studies with smaller confidence limits, and cannot but conclude that the results are highly precise, and hence the study was more than adequately powered.

• Abstract: Study groups are better described as intervention/experimental vs comparison. This is not strictly speaking a case-control study.
• The reviewer is right that this is not a case-control study and this phrase has been omitted. We now call it a cohort study throughout the paper. However, we have not introduced the term 'experimental' in order to avoid confusion with a randomized study. So, we describe the groups as fully whenever possible, and when indicated in shorthand we speak of 'pethidine group' and 'non-pethidine group', or index and control group

• Statistics: A multivariate logistic regression model is described, however it seems only odds ratios are presented rather than adjusted odds ratios.
• The adjusted odds ratios are presented in table 3. We have now changed OR (95%-CI) in to Adj. OR (95%CI), adjusted for age, religion and parental education.

• Standard of written English: Fair. The word "addiction" is usually avoided as it is considered judgemental - substance misuse is more commonly used.
• We will change the wording from addiction to SUD as suggested by the referent.

• References: A recent Cochrane review has been published looking at the effectiveness and side-effects of intrapartum parenteral opioids - Ullman R, Smith LA et al 2011 "The use of opioid intramuscular and intravenous pain relieving drugs in labour" and Ullman R, Smith LA, Burns E, Mori R, Dowswell T. Parenteral opioids for maternal pain management in labour. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD007396. DOI: 10.1002/14651858.CD007396.pub2
• We are grateful that the referent draws our attention to the recent reviews about parenteral opioids for maternal pain management. We are glad to insert the articles in the references.
However the references are not immediately relevant to our study as the other reviewer also stated. Nevertheless it shows that the long term view on possible sequelae is underestimated as an important issue in the case of obstetrical medication.

• STROBE statement: The phrase used in objectives section raises some concern " The objective was to duplicate the alarming results from earlier studies published in the BMJ ....." This is at odds with the research question and hypothesis as stated in the summary.
The findings are not credible due to the high risk of confounding and low response rate.
• The answer is the same as stated in the bullet "study design".

• Because of the lack of trustworthiness of the findings the conclusions drawn are over-stated and limitations are not sufficiently taken account of. The discussion and conclusion need to be written in a more balanced way to take this into account.
The message is clear, but cannot be stated so unequivocally given the limitations of the research. Further investigation of potential confounders would be very valuable if it were possible.
• We adapted the wording in the conclusions concerning the limitations of the research. We agree

with the referent that further investigation, however difficult it may be, would be very valuable.

• Reporting: More details about the content and validation of the data collection tools should be included, especially where the short questionnaire varied from the longer, original one.

• We used three questionnaires for the study. The first is the validated questionnaire (questionnaire for young adults about life events, schooling and behaviour) that is described in ref 25. The second is the National Drugs Questionnaire as a part of the Permanent National Life Style Inquiry that is used from 1997 (with Computer Assisted Personal Interviewing or in case of drug questions with the Computer Assisted Self Interviewing method) in between 9-80.000 persons per year. The rules meet with the European Statistics Code of Practice. (http://epp.eurostat.ec.europa.eu). The third questionnaire consists of only a few questions: did you (lifetime or in the last month) smoke cigarettes or cannabis, drink alcohol or use (hard) drugs. We clarified the questionnaires in the text.

VERSION 2 – REVIEW

REVIEWER	Dr Roz Ullman Senior research fellow and clinical lead (midwifery) National Collaborating Centre for Women's and Children's Health UK I hereby confirm that I have no competing interests.
REVIEW RETURNED	13/03/2012

THE STUDY	Abstract/summary/key messages: Abstract should make clear only intrapartum medication under consideration is IM pethidine. Key message: I feel it is an overstatement to conclude intrapartum pethidine is safe - too broad. Should say appears not to be associated with substance misuse in later life or similar. The English needs some editing before the standard would be acceptable for publication e.g. a number of prepositions are wrong and tenses are mixed. This is particularly noted in the introduction. All supplemental documents satisfactory.
RESULTS & CONCLUSIONS	Presentation of findings: The text is inaccurate regarding reporting of adjusted odds ratios for lifetime prevalence of smoking, alcohol use and overall drug misuse. The text states that all the odds ratios are near unity ranging from 0.97 to 1.09. The revised table 3 reports these 3 odds ratios as being 0.84, 0.81 and 0.79 respectively. Conclusions: The sample size calculation is based on a large odds ratio derived from previous work. A possible conclusion could be that this is an overestimate of the effect size and that a smaller effect exists which would have required a larger study to detect. This should be mentioned, particularly if prevalence of misuse is going to be examined for different drugs. The overall conclusions should be couched in more tentative terms given the limitations of the study.

VERSION 2 – AUTHOR RESPONSE

Dear Dr Ullman, thank you for your constructive remarks. Our study shows that the odds ratios for all drugs are below 1.42. Although this number is not statistically significant and well below the expected number of 4.7 as described in the power analysis, one could argue that 1.42 is clinically relevant and

a larger study would have been needed to obtain statistical significance for smaller effects. We adapted this in the text.