PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Preterm infant outcomes in relation to the gestational age of onset and duration of prelabour rupture of membranes: A retrospective cohort study
AUTHORS	Pharande, Pramod; Mohamed, Abdel-Latif; Bajuk, Barbara; Lui, Kei; Bolisetty, Srinivas

VERSION 1 - REVIEW

REVIEWER	Richter, Jute University Hospitals Leuven Herestraat 49, 3000 Leuven BELGIUM Competing interests: none to declare
REVIEW RETURNED	24-Oct-2017

GENERAL COMMENTS	Large multicentric study, with limitations as mentioned by the authors (no information on termination,late miscarriage...) Several remarks - although no pregnancy information is included, the amount of residual amniotic fluid after PPROM seems crucial to the outcome of the neonates. We know that latency PPROM-delivery is often longer if amniotic fluid is normal. Also long duration of severe oligohydramnion can predispose to lung disease of the neonate. Can this information (amniotic fluid) be retrieved in the records? - can you explain why the late-PPROM group has better outcomes that no-PPROM group? - can you explain why latency >14d in late-PPROM group worsens outcome?

REVIEWER	Koutoumanou, Eirini UCL, UK Competing interests: None
REVIEW RETURNED	26-Oct-2017

GENERAL COMMENTS	This is a well written report. Appropriate statistical analysis has been used to address the questions of interest and the interpretation of the results has also been done carefully. Few suggestions are listed below, which I believe will improve the manuscript overall. Please correct multivariate to multivariable or multiple – see references below Could you please repeat your regression modelling and include variables that did not come out as univariately significantly associated with the outcome? Regression models allows us to do exactly that. See how numerous variables (that by default might be

associated with each other) influence the outcome together. A non-significant variable at univariate level, might turn out to be highly significant when other variables are accounted alongside it. You might find no different results when you repeat the analysis, but at least then you could remove the following phrase from you methods: "A univariate analysis was performed to identify the perinatal factors associated with the composite outcome. All the relevant significant variables were then entered into a multivariate logistic regression analysis"

I am a bit unclear of the significance level that was used. The authors mention that "Entry and removal from the model occurred if P<0.05 and p>0.1 respectively." So even though significance was defined as below 0.05, non-significance was 0.1? So p-values between 0.05 and 0.1 were treated as what?

Please accompany all * and NS notations with the actual mean/median differences and corresponding CI in table 1. It's fine to have a mixture of OR and mean differences presented. Just add an extra symbol to notate swapping between the two.

Emphasise on the magnitude of the differences, e.g. older mother in Late PPROM group, only by 1 year. Also, Antepartum haemorrhage was higher for No PPROM compared to Early – was that as expected?

Please correct: "the mortality rate in Early-PPROM group was nearly 4 times of No-PPROM group." The odds of mortality in the All GA weeks group were increased by 4, which is not the same as the mortality was 4 times as much, instead the odds were 4 times as much.

Finally, you might want to consider re-writing the results section of the abstract as it is too dense with numbers.

References:
Peters, T. J. (2008), Multifarious terminology: multivariable or multivariate? univariable or univariate?. Paediatric and Perinatal Epidemiology, 22: 506.
doi: 10.1111/j.1365-3016.2008.00966.x
B Hidalgo and M Goodman (2013), Multivariate or Multivariable Regression? American Journal of Public Health, Vol. 103, No. 1, pp. 39-40.
doi: 10.2105/AJPH.2012.300897

REVIEWER	Ekholm, Eeva Department of Obstetrics and Gynecology University of Turku and Turku University Hospital, Finland Competing interests: None
REVIEW RETURNED	08-Nov-2017

GENERAL COMMENTS	The article focuses on a clinically important subject and provides new, relevant data. The article is generally well written. In the results section, the effect of the latency of ROM in table 4 should be clarified. There are some points in the discussion that I like to address. The authors refer to Epipage 2 study. A recent study from the same cohort (Lorthe 2017) concluded that for a given gestational age at

birth, prolonged latency duration after PPROM does not worsen neonatal prognosis whereas in the present study the latency was associated with neonatal outcome. This should be discussed in the present manuscript.

The authors discuss that FIRS associated with PPROM may be a reason for the poor outcome in the PPROM group compared to no-Prom group. At these early weeks also spontaneous deliveries without PROM are known to associate with intrauterine infection/inflammatory response. This should be added to the discussion. Apart from FIRS the interrupted development of the lungs by various mechanisms in this early PPROM group may also contribute to the results.

The authors discuss the effects of different antibiotic regimens on neonatal outcome. What about anti-inflammatory drugs? The authors comment that FIRS is associated with CP and development delay. On the other hand , recent studies have found that clinical chorioamnionitis does not have a major independent role in neurodevelopmental problems in very preterm infants (Ylijoki et al 2016) and it seems that chorioamnionitis does not lead to increased risks for the brain of preterm infants compared to other pathologies behind preterm delivery (Ylijoki et al 2012).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1)Large multicentric study, with limitations as mentioned by the authors (no information on termination,late miscarriage...)

Response: Thank you for appreciative of our study. The limitations of the study are accepted.
2)Several remarks
-a) although no pregnancy information is included, the amount of residual amniotic fluid after PPROM seems crucial to the outcome of the neonates. We know that latency PPROM-delivery is often longer if amniotic fluid is normal. Also long duration of severe oligohydramnion can predispose to lung disease of the neonate. Can this information (amniotic fluid) be retrieved in the records?

Response: We agree with your comments about residual amniotic fluid after PPROM and neonatal outcomes. Although our database [Neonatal Intensive Care Units' (NICUS) Data Collection] prospectively collects the data; unfortunately, the information about amniotic fluid index is not collected which would have been valuable in this study.

-b) can you explain why the late-PPROM group has better outcomes than no-PPROM group?

Response: The better outcomes in Late-PPROM group can be explained by various factors as Late-PPROM group had higher antenatal steroid coverage (97 v 88%), was more mature [higher mean GA(29.1 vs 28.6wk) and birth weight(1367 vs 1247gm)] and had significantly less number of SGA infants(1.2 v 9%) as compared to No-PPROM group. This has been added to the discussion part of manuscript.

-c) can you explain why latency >14d in late-PPROM group worsens outcome?
Response: The worse neonatal outcomes in Late-PPROM group after latency>14days may be explained by higher chorioamnionitis (55.8% vs 39.8%, p 0.013) in that group. This is added in the discussion.

Reviewer: 2

1)This is a well written report. Appropriate statistical analysis has been used to address the questions of interest and the interpretation of the results has also been done carefully. Few suggestions are listed below, which I believe will improve the manuscript overall.

Response: Thank you for your supportive comments.

2) Please correct multivariate to multivariable or multiple – see references below

Response: We thank the reviewer for this important suggestion. We have amended our manuscript as suggested.

3) Could you please repeat your regression modelling and include variables that did not come out as univariately significantly associated with the outcome? Regression models allows us to do exactly that. See how numerous variables (that by default might be associated with each other) influence the outcome together. A non-significant variable at univariate level, might turn out to be highly significant when other variables are accounted alongside it. You might find no different results when you repeat the analysis, but at least then you could remove the following phrase from you methods: "A univariate analysis was performed to identify the perinatal factors associated with the composite outcome. All the relevant significant variables were then entered into a multivariate logistic regression analysis"

Response: We thank the reviewer for the insightful comments and agree that above sentence is unnecessary. We repeated the regression analysis including the variables at birth that might have influenced the outcomes such as chorioamnionitis, low Apgar scores and worst Base deficit and did not show any difference in the results. Also, these variables can be explained by gestational immaturity which is already a variable in the analysis. As statistician suggested, we have removed the sentence from the methods.

4) I am a bit unclear of the significance level that was used. The authors mention that "Entry and removal from the model occurred if P<0.05 and p>0.1 respectively." So even though significance was defined as below 0.05, non-significance was 0.1? So p-values between 0.05 and 0.1 were treated as what?

Response: We thank the reviewer for pointing out this important gap in significance level. We agree the sentence is misleading. The significance is defined as <0.05 for the study. The values ≥0.05 were not significant. We have added the sentence 'A two-tailed P-value <0.05 was considered to be statistically significant' and deleted "Entry and removal from the model occurred if P<0.05 and p>0.1 respectively. All p values were two sided."

5) Please accompany all * and NS notations with the actual mean/median differences and corresponding CI in table 1. It's fine to have a mixture of OR and mean differences presented. Just add an extra symbol to notate swapping between the two.

Response: Table 1 has been amended as per the suggestions. Mean differences have been added.

6) Emphasise on the magnitude of the differences, e.g. older mother in Late PPROM group, only by 1 year. Also, Antepartum haemorrhage was higher for No PPROM compared to Early – was that as expected?

Response: We have amended the magnitude of the difference for maternal age in manuscript. Actually the antepartum haemorrhage was higher for Early-PPROM group as compared to No-

PPROM group which is as expected from the literature and is already discussed in the manuscript.

7) Please correct: "the mortality rate in Early-PPROM group was nearly 4 times of No-PPROM group." The odds of mortality in the All GA weeks group were increased by 4, which is not the same as the mortality was 4 times as much, instead the odds were 4 times as much.

Response: We thank the reviewer for suggesting this important correction. We have rephrased the sentence as 'the odds of mortality in Early-PPROM group was nearly 4 times of No-PPROM group.'

8) Finally, you might want to consider re-writing the results section of the abstract as it is too dense with numbers.

Response: The results section of abstract has been amended as suggested with fewer numbers in it. Removed 95% CI word in all except the first one, percentages rounded off removing decimals.

Reviewer: 3

1)The article focuses on a clinically important subject and provides new, relevant data. The article is generally well written. In the results section, the effect of the latency of ROM in table 4 should be clarified.

Response: We have added one sentence in the manuscript clarifying the impact of latency as follows-'Latency>14days in Early and Late-PPROM groups increased the adjusted odds of CLD/mortality by 2 fold'.

2)There are some points in the discussion that I like to address.
The authors refer to Epipage 2 study. A recent study from the same cohort (Lorthe 2017) concluded that for a given gestational age at birth, prolonged latency duration after PPROM does not worsen neonatal prognosis whereas in the present study the latency was associated with neonatal outcome. This should be discussed in the present manuscript.

Response: We thank the reviewer for referring us to this important publication which has contradictory results to our study. We have included these findings in our discussion and have justified our study findings.

3)The authors discuss that FIRS associated with PPROM may be a reason for the poor outcome in the PPROM group compared to no-Prom group. At these early weeks also spontaneous deliveries without PROM are known to associate with intrauterine infection/inflammatory response. This should be added to the discussion. Apart from FIRS the interrupted development of the lungs by various mechanisms in this early PPROM group may also contribute to the results.

Response: We have amended manuscript to include both those points in discussion suggested by reviewer as follows- "Many of these morbidities can be explained by the earlier GA of Early-PPROM group, but these morbidities were significantly higher in the Early-PPROM group even after correcting for GA. The mechanism underlying these high morbidities and mortalities in this group can be explained by a combination of altered antenatal lung development, infection and the fetal inflammatory response syndrome (FIRS) induced by

PPROM and associated chorioamnionitis (Williams 2012). Hecht et al[16], demonstrated a strong inflammatory signal in the blood of preterm infants born before 28 weeks gestation whose placentas showed histological Chorioamnionitis. At these early weeks of gestation spontaneous preterm deliveries without PPROM are known to be associated with intrauterine infection/inflammatory response. FIRS is associated with high rates of long-term morbidities such as cerebral palsy and developmental delay"

4)The authors discuss the effects of different antibiotic regimens on neonatal outcome. What about anti-inflammatory drugs?

Response: The anti-inflammatory drugs were not used in our cohort.

5)The authors comment that FIRS is associated with CP and development delay. On the other hand , recent studies have found that clinical chorioamnionitis does not have a major independent role in neurodevelopmental problems in very preterm infants (Ylijoki et al 2016) and it seems that chorioamnionitis does not lead to increased risks for the brain of preterm infants compared to other pathologies behind preterm delivery (Ylijoki et al 2012).

Response: We thank the reviewer for referring us to the literature contradicting to our manuscript. We have accommodated those references to balance the discussion as follows- "FIRS is associated with high rates of long-term morbidities such as cerebral palsy and developmental delay[17-20]. But a recent report by PIPARI study collaborators (Ylijoki 2016) suggest that clinical chorioamnionitis does not have a major independent role in the pathogenesis of neurodevelopmental problems in very preterm infants. The authors (Ylijoki 2012) argue that rather than chorioamnionitis other underlying pathologies behind preterm delivery may be contributory to preterm brain injury."