## PEER REVIEW HISTORY

BMJ Medicine 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.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Medicine. The paper was subsequently accepted for publication at BMJ Medicine.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Preterm Prelabour Rupture Of Membranes (PPROM) before 23 weeks gestation: A prospective observational study |
| **AUTHORS** | Goodfellow, Laura; Care, Angharad; Curran, Ciara; Roberts, Devender; Turner, Mark; Knight, Marian; Zarko, Alfirevic |

## VERSION 1 - REVIEW

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| **REVIEWER 1** | Simpson, Nigel; University of Leeds/Leeds Teaching Hospitals. Competing Interest: None |
| **REVIEW RETURNED** | 13-Apr-2023 |

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| **GENERAL COMMENTS** | This is a welcome addition to the literature, providing reliable observational data on a rare complication of pregnancy, counselling regarding which has frequently been haphazard and ill-informed. The findings will be of immediate relevance and benefit.<br><br>I have no major concerns about the paper.<br><br>I would like the authors to consider whether 'infant' is the most apt word to describe the fetal-neonatal continuum they present - there are no longer-term data to be shared for that age range - would 'perinatal' be a reasonable alternative?<br><br>The other question relates to the presence of a cerclage in this context; did any of the mothers have one present? And if so, were they more likely to have had adverse maternal outcomes? From previous maternal mortality reports it would be surprising if this was not the case.<br><br>Other than this I would recommend publication - these findings require publication and will be of interest to the BMJ's wider readership. |

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| **REVIEWER 2** | Cumbers, Marion; Haberdashers School for Girls. Competing Interest: None |
| **REVIEW RETURNED** | 13-Apr-2023 |

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| **GENERAL COMMENTS** | PPROM under 23 weeks gestation is a serious pregnancy complication with high rates of morbidity for mothers and infants. Women are often advised to consider termination for medical |

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| | reasons .<br>Contemporary population based, pregnancy outcomes are not available, making counselling difficult. The study was carried out using the UK Obstetric Surveillance System (UKOSS), a research infrastructure that encompasses every consultant-led maternity department in the country. This has enabled the largest population-based study of PPROM prior to 23 weeks' gestation to provide UK population level data for pregnancies with PPROM stratified according to gestation when PPROM occurred.<br>It is reported in accordance with the "Strengthening the reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies". This has produced a report that is logically structured and clearly presented. I would recommend this format.<br>The tables of statistics produced are important to professionals and to further research. They "starkly illustrate the diverse infant and maternal outcomes possible with this condition".<br>Understanding these results is imperative to appropriate counselling and management of women facing this difficult complication The Infant outcomes were selected in order to allow compatibility<br>The tables are probably not useful to patients as such, but throughout this report there is consideration of how the information from this study can be used for counselling and advising them. Hopefully currently available guidelines will actually be updated accordingly.<br>Patient involvement was central to this study. "The patient support and advocacy group, Little Heartbeats, approached the author AC with concerns about inconsistency in counselling and management of cases of PPROM prior to 23 weeks gestation, stimulating this research. CC (the founder of Little Heartbeats) and the patient and public members of the UKOSS Steering Committee were then involved in the design of the study, the conduct of the study and interpretation of the results. CC met regularly with authors LG and AC to review the findings and plan the optimal presentation of the data. The completed analysis was also reviewed by patient and public representation within the UKOSS Steering Committee". The authors suggest that teams with expertise in management of very early PPROM, along with patient representatives, work together to develop guidelines for care. It us very heartening to see more PPI than usual.<br>This study identified significant maternal morbidity; 12% of women developed sepsis and 2 women (0.6%, 95%CI 0.17-2.2%) died. Conversely infant outcomes were relatively favourable; 26% of expectantly managed infants survived to hospital discharge and the potential worst-best case survival range including those that had termination for medical reasons (TFMR) was 16-54%. There was a wide difference between potential worst and best case survival, 16-54%, but the study figures took account of missing data. The rate of survival to discharge amongst liveborn infants was 55% (54/98). A further 20% (20/98) of liveborn infants had missing data about their discharge status. This missing data is disappointing.<br>The study was extended for six-months to investigate potential changes in outcomes secondary to the pandemic. There were no significant differences detected in infant or maternal pregnancy outcomes according to whether the PPROM occurred prior to or during the pandemic.<br>When facing making a decision about termination in these circumstances, parents are desperate to know what the future |

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| | might hold for their baby. Could further research follow to assess disability in a similar cohort as the children grow up if one cannot use the same children because of issues with anonymity? “The optimal way to communicate uncertainties within the data to a wider audience, and support families with such complex pregnancies, is yet to be determined”, but hopefully will also be the subject for further research. As professionals see so few of these cases, guidance will be very useful to them as well as to patients in such difficult circumstances. |

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| **REVIEWER 3** | Lorthe, Elsa; Geneva University Hospitals. Competing Interest: This review was conducted before I realized that I had published an article with one of the authors (A. Care) as part of the International Spontaneous Preterm birth Young investigators (I-SPY) group. We have not been in contact for some time, and I think I am perfectly qualified as a reviewer for this article because I have published an article on the same topic in the past. |
| **REVIEW RETURNED** | 13-Apr-2023 |

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| **GENERAL COMMENTS** | This article aims to describe maternal and neonatal outcomes after PPROM before 23 weeks of gestation, using data from a prospective population-based cohort study based on the UKOSS surveillance system covering all 194 obstetric units in the UK, over an 18-month period overlapping with the pandemic. I would like to congratulate the authors on a very interesting article that reports very important data for all clinicians, in the UK and worldwide. I would also like to highlight the close collaboration with patients, which is not so common but very relevant.<br><br>Major comments:<br>1. I would encourage the authors to report other outcomes such as BPD, neonatal sepsis, NEC and PVL, many of which are associated with later outcomes.<br>2. Table 3: Authors should also report all infant outcomes in relation to the total denominator (including expectant management and TFMR), in particular because cases of TFMR after expectant management are included in the TFMR group, and in order not to overestimate survival rates. This would be helpful in counselling patients immediately after PPROM, before a decision is made about TFMR or expectant management.<br>3. Routine medical practices after PPROM in the UK should be described, to give more context to these findings (antibiotics administration, home hospitalization, timing of antenatal steroids, indications for delivery, etc).<br><br>Minor comments:<br>4. I am not sure it is appropriate to make a value judgment about these perinatal outcome (for instance “relatively favourable” when reporting a 26% survival rate to discharge), I would leave to each reader (and ultimately to each couple facing this difficult situation) to decide whether this is a favourable outcome.<br>5. For foreign readers, I would briefly explain what a consultant-led maternity hospital is, and what % of all pregnant women give birth in such units in the UK.<br>6. Are data on pre-viable PPROM routinely collected in UKOSS? Are regular reminders a common practice or were they implemented specifically for this study?<br>7. How were previous medically-indicated preterm births |

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| | considered? In my experience, PPROM cases are often misclassified as medically-indicated when the classification is based on the mode of labour.<br>8. Data on intra-uterine infection would be very interesting and relevant in this setting.<br>9. Results: I would report the number of women excluded for duplication (n=), ineligibility (n=) and insufficient information to assess eligibility (n=). If a significant number of women fall into the latter category, I would provide more information to assess a potential selection bias.<br>10. Table 1: it is surprising to report only maternal BMI over 35, I would provide all the categories defined by WHO. Obstetric history: please make clear in the table which denominator was used for the category “at least one previous pregnancy affected by…”, I assume it is all multiparous women.<br>11. Tables 2, 3, 4 and 5 would read better if the exposure (Gestational age at PPROM) was presented as rows and outcomes (latency, infant outcomes …) as columns.<br>12. Results, page 8: I would not say that GA at PPROM is a confounder but a factor associated with all outcomes.<br>13. Table 3: there may be a typo in table 3 in the 20-21 column (21/74=28%, 13/74=59%).<br>14. When did the two maternal death occur? Before or after delivery? Did they receive antibiotics after PPROM? Were they discharged home before their condition deteriorated? What was the cause of death?<br>15. Do the authors plan to follow these children over time?<br>16. I don't know if this is British jargon, but several times the authors refer to “gestation” instead of “gestational age”.<br>17. Figure A1: Could the apparent decrease in the frequency in summer-fall 2020 be related to the non-initiation of pregnancy due to high uncertainty at the very beginning of the pandemic? |

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| **REVIEWER 4** | Reviewer 4. Competing Interests: None |
| **REVIEW RETURNED** | 13-Apr-2023 |

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| **GENERAL COMMENTS** | Thank you for allowing me to review this interesting paper. The most important aspect of this study, which distinguishes it from previous studies, is the inclusion of all cases in the population to provide reliable information regarding incidence and outcomes. However, I have some concerns about whether this was actually achieved:<br>• The paper notes that "one hundred and seventy-nine women were removed due to duplication, ineligibility, or insufficient information to assess eligibility." It is necessary to have more information about those with insufficient information to assess eligibility, as this may impact incidence and survival rates.<br>• The study relies on nominated reporting clinicians to notify UKOSS if women have PPROM. Therefore, the study depends on the availability and good will of the clinicians. This may not be a significant problem for rare and very serious maternal cases, but it can be problematic for PPROM between 16 and 22 weeks. The study of PPROM before 23 weeks gestation is challenging because cases may not be well identified at hospitalization by referring clinicians, particularly if hospitalization occurs during weekends or in emergency units rather than in high-risk pregnancy units. The impact of medical organization on the study results is suggested by the comparison of the two periods before and during |

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| | the pandemic. Therefore, it is important to understand how the investigators checked that all cases were actually included.<br>• Another potential bias is that the cases missed may be those with worse prognoses or shorter hospitalizations, which could directly impact survival rates. This should be discussed in the paper's discussion section.<br>Regarding survival rates, the authors provided a worst-case and best-case scenario for survival rates based on the hypothesized prognosis of medical interruption of pregnancy. However, this overlooks the fact that the rate of neonates who actually survived is not limited to the expectant management group, but includes the whole group, including those who underwent medical interruption. Therefore, the survival and prognosis should be provided for the entire group as the main analysis, as well as for those who underwent expectant management (including those who subsequently underwent medical termination of pregnancy). The current main analysis, which includes only those who did not undergo expectant management followed by medical termination, provides a very optimistic neonatal prognosis.<br>Minor comments:<br>• A flow chart should be provided to aid understanding of the various subgroups.<br>• The paper's description of the TFMR group is somewhat confusing. The medical reasons for TFMR should be described, particularly in cases where there is no sepsis.<br>• The definition of maternal sepsis should be provided.<br>• The number of women who had PPROM after amniocentesis or trophoblast biopsy should be stated.<br>• Survival without morbidity refers only to absence of IVH 3 and 4 or supplemental oxygen at 36 weeks, but does not necessarily indicate the absence of other morbidities (such as neurological, visual, neurodevelopmental, or intestinal). This is important information for counseling women.<br>• The multiple analyses with small numbers on multiple pregnancies with comparisons between MCDA and DCDA may not be very useful. |

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| **REVIEWER 5** | Joseph, KS; University of British Columbia. Competing Interest: None |
| **REVIEW RETURNED** | 13-Apr-2023 |

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| **GENERAL COMMENTS** | The authors provide a detailed description of maternal and fetal/neonatal outcomes of 330 women who were diagnosed with preterm pre-labour rupture of membranes between 16 and 22 weeks' gestation. The study involved data collection by 194 obstetric units in the United Kingdom. Analyses were stratified by plurality and addressed outcome assessment issues for pregnancies that were terminated using best/worst case scenarios in addition to analyses based on pregnancies that were expectantly managed.<br><br>Comments:<br>1. As mentioned by the authors, PPROM at a previable gestation can be an enormously stressful event for parents. The substantial morbidity and mortality risks to both mother and baby, combined with appreciable survival rates and rates of survival without severe morbidity for infants following expectant management mean that parents are faced with a serious and complex decision when |

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| | PPROM occurs.<br><br>2. The population-based nature of the study, the relative large study size and the detailed analyses are important strengths of the study.<br><br>3. The findings mostly corroborate findings from previous studies.<br><br>4. Some of the Tables provide live birth, survival and other rates by gestational week when PPROM occurred, and a P value is provided which shows whether rates differed significantly by gestational week. Since increasing gestational week at PPROM is expected to influence outcome rates, it may be more appropriate to test for an increasing/decreasing outcome rate by gestational week (using a chi-square test for linear trend in proportions). For instance, in Table 3, the rate of survival without severe morbidity after expectant management increases from 13% to 35% and the chi-square test yields a P value of 0.13, while a chi-square test for linear trend returns a P value of 0.05.<br><br>5. For the estimates of outcomes following expectant management, the authors have provided a range which incorporates the best case and worst case scenarios for the women who had a termination of pregnancy. However, it may be helpful if the authors could provide a 95% confidence interval on the outcome rates following expectant management.<br><br>6. A recent reference on this issue that the authors may wish to add is<br>Kraft et al. Pre-viable preterm premature rupture of membranes under 20 weeks of pregnancy: A retrospective cohort analysis for potential outcome predictors. Eur J Obstet Gynecol Reprod Biol 2022 Nov;278:177-182. |

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| **REVIEWER 6** | pierrat, Veronique; Inserm U1153 EPOPé team. Competing Interest: None |
| **REVIEW RETURNED** | 13-Apr-2023 |

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| **GENERAL COMMENTS** | This prospective national population-based cohort study, launched in UK, aims to describe infant and maternal outcomes of women with preterm prelabour rupture of membranes (PPROM) under 23 weeks of gestation. This situation is extremely rare and as mentioned by authors, is difficult for clinicians to experience and advice families. Data reported here were based on UK Obstetric Surveillance System allowing to have information for a large population and during a short period of time, as compared to the existing literature (Kibel, 2019 for example, whose data were collected during 10 years period). In addition, research questions were based on family complaints about variability of counselling. Results are thus of uttermost importance for professionals and families and may help to better care women/neonates facing PPROM. One of the main results is the prevalence of associated morbidity and mortality for women. Infants' outcomes were more expected (e.g. increase in percentages of livebirths as gestation with PPROM increases) but may benefit from a more detailed description, that could help neonatologists make better decisions in practice. |

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| | Methods:<br><br>Definitions: It could be helpful to have some more precise definitions for:<br><br>Maternal outcomes: Sepsis.<br>At the first reading, I was concerned by the definition of maternal sepsis. Fortunately, you referred to the form (ref 6) and this was very helpful. As far as I understand, the information is available in section 5c. “antenatal complications”. Could you give some more detail about the timing of maternal sepsis (before or after delivery) to better understand the complications faced by these women? Did you report maternal sepsis before delivery only? Did you have some more information in 6a.2 “Did any major maternal morbidity occur?”?<br><br>Infant outcomes: Severe lung disease.<br>Severe lung disease is defined in the form section 6b.7 and include high frequency oscillatory ventilation (HFOV), inhaled nitric oxide (NO) AND supplemental oxygen at 36 weeks PMA, which is also included in the definition of severe morbidity. I would suggest to report separately HFOV and NO on one side as “severe lung disease”, and supplemental oxygen at 36 weeks on the other side -which defines bronchopulmonary dysplasia and could be labeled as follows-. Indeed, for neonatologists, the problems are of different nature. HFOV and NO are usually required on the acute phase and associated with bronchopulmonary hypoplasia, a severe consequence of PPROM, when supplemental oxygen at 36 weeks is a marker of chronic lung disease and could develop in infants who do not have a severe lung disease -as defined above- in the acute phase.<br><br>Statistical analysis: 1) I assume that you have included TFMR and TFMR after a period of expectant management in the same group to increase the statistical power. However, the two groups are probably different in some ways and you may have information to describe these differences (see later). 2) I was concerned by the missing data and I would have like to have descriptive results of this population, in terms of characteristic but also medical organizations (for example, the proportion of transfers to another hospital). I agree with your strategy to account for the impact of termination of pregnancy for medical reasons (TFMR). I am more reluctant to use the same strategy for the missing data. For example, when the outcome is unknown, you may have neonates born before or after 22 weeks which was the lower limit in UK to consider resuscitation at that time. Consequently, the strategies 2 (considering that all died) or 3 (considering that all survived) could be more precise according to GA at birth. This remark is may be useless considering the number of missing data but I was not able to have an opinion reading the results.<br><br>Results:<br><br>Results answer the research question but may benefit from additional analyses. To my opinion, these results are very important and this group have unique data. That’s the main reason why I have tried to suggest additional descriptive results or analyses. A few variables are apparently available (although I have no idea what the percentage of missing data for these |

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| | variables is, and consequently how useful they might be). Using the variables proposed below may help to have a more in-depth picture of PPROM and their consequences.<br><br>Demographics: Comparison of women with expectant management and those with TFMR.<br>This comparison was very important and could help to give families an answer to the question about variability in staff attitudes. The only statistical difference between groups was gestational age at PPROM. It is reassuring that demographics characteristics were not associated with differences between groups. However, I suggest to also use data collected in section 3 (previous medical history) and section 5c (antenatal complications in pregnancy) to compare 3 groups of management: expectant / TFMR after expectant management/ TFMR. TFMR after expectant management could be associated with previous medical history or antenatal complications. This could help to better understand the strategies used by teams and to discuss the “wide uncertainties” mentioned several times in the manuscript. It could also allow to modulate the analysis strategy and the extreme presented for each outcome measure, at least in the discussion.<br><br>Pregnancy after PPROM: Numbers need to be checked. It is announced in the text that the latency between PPROM and birth was known for 223/227 women. In the Table (column “whole cohort”), the latency is not specified in 3 cases, with the sum of all cases being equal to 223. What is the real number? 223? 224?<br>Minor comment: I would speak of a risk of birth rather than a chance of birth.<br><br>Infant outcomes: It could be useful to have some more information about infant outcomes. In Table 3, considering livebirths only, I would add the mean gestational age at birth for each week of gestation at PPROM together with the number of women who received antenatal corticosteroids and magnesium sulfate. These two variables are available in the form. Their impact on outcome is well acknowledged but they are not always used at these extremely low gestational age. It could be useful to know if there is a potential for neonatal improvement at this step. I would also add a line with severe lung disease among livebirth infants. I would also present a Table with the different causes of antenatal death only, and then a Table with data for livebirths (the line TFMR is may be not necessary in the Table with data for livebirths). In this Table, you could add the number of neonatal deaths and the number of deaths with severe lung disease. Reading the form, I think that you cannot assume that this was the main cause of death, but it is a severe disease and the fear most neonatologists have for neonates born after PPROM.<br>I suggest to checked all your data for severe lung disease and bronchopulmonary dysplasia (as defined above), because reading the text I was wondering if there was a confusion between these two different clinical situations.<br>I also had difficulties to jump between Table 3 and Table 4, due to different denominators, that were not easy to understand. For example, in Table 3, the whole cohort is 330 but 310 in Table 4. This is in line with my previous comment about missing data. I suggest to report the same denominators (330 singleton pregnancies) in every table but with the number of missing data for the studied variable clearly included in the Tables. |

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| | Maternal outcomes: These are very important results of this paper. Don't you think that it could be useful to present factors associated with maternal and infant outcomes? In the paper of Kibel (ref 22), the increased duration of PPROM increased maternal morbidity but for infants, factors associated with survival and survival without morbidity were GA at PPROM > 22 weeks and a latency > 7 days. These results may suggest a conflict between maternal and fetal/neonate interest and I think that this is worth to document. This situation is unique in the field of perinatology. Unlike many other situations, where maternal risk is present, the risk for women in PPROM increased with the prolongation of pregnancy. This is different in pre-eclampsia for example where the risk for women is acute and the decision to prolong or stop the pregnancy must be taken in emergency. In PPROM, the decision-making process can be described as more complex, in subacute or chronic situations, requiring a closer collaboration between all members of a perinatal team. That's one of the reasons why I suggest to describe more precisely infants'outcome.<br><br>Discussion<br>The discussion is well-written, easy to follow, with clear messages in the light of previous evidence. I only have a few comments.<br><br>Statement of principal findings: "The additional complexity because of the uncertainty…" may again be highlighted if you could present some more data about TFMR (see above)<br><br>Page 14, paragraph about the definition of severe neonatal morbidity, line 12. I would be more cautious in the comparison with the results of Kibel as retinopathy of prematurity, unlike in the definition of Kibel, was not included in your definition of severe morbidity. This is however a huge concern, especially in infants born extremely preterm, and your results may underestimate long-term severe-moderate morbidity.<br><br>Page 14, line 20. The median length of stay was shorter in the UK cohort than in the Australian and Japanese cohort but the mean GA at birth was lower in these two cohorts and this could explain the difference. I agree that the length of stay is likely to have an impact upon the whole family, but like in every preterm birth. The specificity of PPROM is that mothers may have also been hospitalized a long period of time before birth and this add to the burden of hospitalization.<br><br>Page 15, line 20 to 30. You have explained why you did not consider fetal anomalies. However, you have data about the presence of "major congenital anomaly" (6b.7). I agree that with the form used, you were not able to say if fetal anomalies were diagnosed at PPROM or at birth. However, don't you think that it could be interesting to report the presence of such anomalies, both in TFMR group and in the livebirth group?<br><br>Minor comments:<br><br>Although all important results are reported, I did not always find a logical order in the organization of the paper and consequently I did not find that the lecture was fluid. For example, in the method section, the time for data collection was reported in the third paragraph, after having explain that a final reminder was fixed in |

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| | September 2021. I would also have appreciated to read the results with a chronological approach. For example, infant outcomes could have been reported first as intrauterine death including TFMR and then outcomes in livebirth, including neonatal deaths.<br><br>Singleton pregnancy losses. My first language is not English and my comment is may be unfounded but this sounds strange to me as you include neonatal deaths in this chapter. Can neonates be defined as pregnancy loss?<br><br>Table A3: You are presenting the NUMBER of surviving infants but not the percentage.<br><br>To conclude, I have read this paper with a great interest and I hope that all the proposals made will be helpful and read as demonstrating this interest. These data are very important for perinatal teams and unique. I may have suggested to report too much additional information but it appears that this information is available and I am convinced that it will reinforce the validity of these results for professionals but also for families. To my knowledge, the UK database is for the moment unique in Europe and it is a great opportunity to improve knowledge on rare diseases. PPROM is one of them in the field of perinatal medicine. |

**VERSION 1 – AUTHOR RESPONSE**

**Reviewer: 1**

Comments:
This is a welcome addition to the literature, providing reliable observational data on a rare complication of pregnancy, counselling regarding which has frequently been haphazard and ill-informed. The findings will be of immediate relevance and benefit.

I have no major concerns about the paper.

I would like the authors to consider whether 'infant' is the most apt word to describe the fetal-neonatal continuum they present - there are no longer-term data to be shared for that age range - would 'perinatal' be a reasonable alternative?

*We thank the reviewer for the comment and have altered the text to say 'perinatal' or 'baby' as appropriate*

The other question relates to the presence of a cerclage in this context; did any of the mothers have one present? And if so, were they more likely to have had adverse maternal outcomes? From previous maternal mortality reports it would be surprising if this was not the case.

*29 of these pregnancies had cervical cerclages present prior to PPROM, of whom 7 (24%) developed sepsis (none died) and 7 (24%) had a TFMR. We have added this to the manuscript.*

Other than this I would recommend publication - these findings require publication and will be of interest to the BMJ's wider readership.

**Reviewer: 2**

Comments:
PPROM under 23 weeks gestation is a serious pregnancy complication with high rates of morbidity for mothers and infants. Women are often advised to consider termination for medical reasons . Contemporary population based, pregnancy outcomes are not available, making counselling difficult. The study was carried out using the UK Obstetric Surveillance System (UKOSS), a research infrastructure that encompasses every consultant-led maternity department in the country. This has enabled the largest population-based study of PPROM prior to 23 weeks' gestation to provide UK population level data for pregnancies with PPROM stratified according to gestation when PPROM occurred.
It is reported in accordance with the "Strengthening the reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies". This has produced a report that is logically structured and clearly presented. I would recommend this format.
The tables of statistics produced are important to professionals and to further research. They "starkly illustrate the diverse infant and maternal outcomes possible with this condition". Understanding these results is imperative to appropriate counselling and management of women facing this difficult complication The Infant outcomes were selected in order to allow compatibility
The tables are probably not useful to patients as such, but throughout this report there is consideration of how the information from this study can be used for counselling and advising them. Hopefully currently available guidelines will actually be updated accordingly.
Patient involvement was central to this study. "The patient support and advocacy group, Little Heartbeats, approached the author AC with concerns about inconsistency in counselling and management of cases of PPROM prior to 23 weeks gestation, stimulating this research. CC (the founder of Little Heartbeats) and the patient and public members of the UKOSS Steering Committee were then involved in the design of the study, the conduct of the study and interpretation of the results. CC met regularly with authors LG and AC to review the findings and plan the optimal presentation of the data. The completed analysis was also reviewed by patient and public representation within the UKOSS Steering Committee". The authors suggest that teams with expertise in management of very early PPROM, along with patient representatives, work together to develop guidelines for care. It us very heartening to see more PPI than usual.
This study identified significant maternal morbidity; 12% of women developed sepsis and 2 women (0.6%, 95%CI 0.17-2.2%) died. Conversely infant outcomes were relatively favourable; 26% of expectantly managed infants survived to hospital discharge and the potential worst-best case survival range including those that had termination for medical reasons (TFMR) was 16-54%. There was a wide difference between potential worst and best case survival, 16-54%, but the study figures took account of missing data. The rate of survival to discharge amongst liveborn infants was 55% (54/98). A further 20% (20/98) of liveborn infants had missing data about their discharge status. This missing data is disappointing.
The study was extended for six-months to investigate potential changes in outcomes secondary to the pandemic. There were no significant differences detected in infant or maternal pregnancy outcomes according to whether the PPROM occurred prior to or during the pandemic.
When facing making a decision about termination in these circumstances, parents are desperate to know what the future might hold for their baby. Could further research follow to assess disability in a similar cohort as the children grow up if one cannot use the same children because of issues with anonymity? "The optimal way to communicate uncertainties within the data to a wider audience, and support families with such complex pregnancies, is yet to be determined", but hopefully will also be the subject for further research. As professionals see so few of these cases, guidance will be very useful to them as well as to patients in such difficult circumstances.
Marion Cumbers

*We thank the reviewer for her positive comments and recognition of the significant PPI involvement in this work. We agree that the inability to comment upon long term disability in the babies is a limitation and hope this will spark further research in this area.*

**Reviewer: 3**

Comments:
This article aims to describe maternal and neonatal outcomes after PPROM before 23 weeks of gestation, using data from a prospective population-based cohort study based on the UKOSS surveillance system covering all 194 obstetric units in the UK, over an 18-month period overlapping with the pandemic. I would like to congratulate the authors on a very interesting article that reports very important data for all clinicians, in the UK and worldwide. I would also like to highlight the close collaboration with patients, which is not so common but very relevant.

Major comments:
1. I would encourage the authors to report other outcomes such as BPD, neonatal sepsis, NEC and PVL, many of which are associated with later outcomes.

In order to make completion of data collection succinct for nominated reporting clinicians (midwives and obstetricians) we did not collect data on neonatal sepsis, PVL or NEC. We collected data on oxygen requirement at 36 weeks postmenstrual age, which is a commonly used definition of BPD and in order to report this clearly it is labelled as oxygen requirement at 36 weeks postmenstrual age. This is reported in table 2.

2. Table 3: Authors should also report all infant outcomes in relation to the total denominator (including expectant management and TFMR), in particular because cases of TFMR after expectant management are included in the TFMR group, and in order not to overestimate survival rates. This would be helpful in counselling patients immediately after PPROM, before a decision is made about TFMR or expectant management.

*Table 2 has been re-organised to now show the numerator and denominator for each item.*

3. Routine medical practices after PPROM in the UK should be described, to give more context to these findings (antibiotics administration, home hospitalization, timing of antenatal steroids, indications for delivery, etc).

*Data have been collected about administration of antibiotics, steroids, indication for delivery and whether the woman received outpatient care. However, we felt that adding these data to this manuscript detracted from the delivery of a simple message for clinicians, women and their families facing early PPROM. We have not therefore included them here.*

Minor comments:
4. I am not sure it is appropriate to make a value judgment about these perinatal outcome (for instance “relatively favourable” when reporting a 26% survival rate to discharge), I would leave to

each reader (and ultimately to each couple facing this difficult situation) to decide whether this is a favourable outcome.

*We agree, this language has been changed.*

5. For foreign readers, I would briefly explain what a consultant-led maternity hospital is, and what % of all pregnant women give birth in such units in the UK.

*Added to lines 115-117*

6. Are data on pre-viable PPROM routinely collected in UKOSS? Are regular reminders a common practice or were they implemented specifically for this study?

*UKOSS conducts national observational studies over a particular time period; PPROM under 23 weeks was one of the rolling programme of studies. Reference 6 has been added on line 118 of page 3 which links to the UKOSS website and methodology. Regular reminders are a standard practice of this methodology.*

7. How were previous medically-indicated preterm births considered? In my experience, PPROM cases are often misclassified as medically-indicated when the classification is based on the mode of labour.

We asked the *question "Has the woman had any of the following in a previous pregnancy?" With tick boxes for PPROM at $16^{+0}$-$22^{+6}$ weeks gestation, PPROM at $23^{+0}$-$33^{+6}$ weeks gestation, spontaneous midtrimester loss $16^{+0}$-$22^{+6}$ weeks gestation and spontaneous preterm birth $23^{+0}$-$36^{+6}$ weeks gestation. If the reporting clinician answered yes to any of these questions then the woman was classified as having "At least one previous pregnancy affected by any of: PPROM/midtrimester loss/preterm birth".*

8. Data on intra-uterine infection would be very interesting and relevant in this setting.

*Unfortunately we do not have definitive microbiological data on intrauterine infection.*

9. Results: I would report the number of women excluded for duplication (n=), ineligibility (n=) and insufficient information to assess eligibility (n=). If a significant number of women fall into the latter category, I would provide more information to assess a potential selection bias.

*Further detail about the reasons for exclusion has been added to the manuscript on lines 228-233. In addition Figure A1 has been added to the appendix to show participant flow though the study including further details on why women were excluded.*

10. Table 1: it is surprising to report only maternal BMI over 35, I would provide all the categories defined by WHO. Obstetric history: please make clear in the table which denominator was used for the category "at least one previous pregnancy affected by…", I assume it is all multiparous women.

*Table 1 has been edited to include all WHO BMI classifications and over 35. The difficulty in using multiparous women as the denominator for the previous obstetric history is that it is possible to be primiparous and have a history of midtrimester loss (parity being defined as birth over 24 weeks gestation or livebirth at any gestation in the UK). Therefore the denominator is all women.*

11. Tables 2, 3, 4 and 5 would read better if the exposure (Gestational age at PPROM) was presented as rows and outcomes (latency, infant outcomes …) as columns.

*These tables have been edited in light of this suggestion, and tables 3 and 4 amalgamated to accommodate the new table limit of BMJ Medicine (5 tables/figures total)*

12. Results, page 8: I would not say that GA at PPROM is a confounder but a factor associated with all outcomes.

*Thank you for the suggestion, edited in line with this.*

13. Table 3: there may be a typo in table 3 in the 20-21 column (21/74=28%, 13/74=59%).

*Thank you very much for informing us of this, you are right. Corrected in new table.*

14. When did the two maternal death occur? Before or after delivery? Did they receive antibiotics after PPROM? Were they discharged home before their condition deteriorated? What was the cause of death?

*Both women died from sepsis, this has been added into the results (page 10-11 lines 378-382). Further details are not allowed to be reported due to the reasonable risk of the women becoming identifiable, this has been explained on page 11 lines 314-317.*

15. Do the authors plan to follow these children over time?

*Due to the anonymous nature of reporting to UKOSS it is not possible to follow these children over time. This has been added to the limitations, page 19 lines 593-598*

16. I don't know if this is British jargon, but several times the authors refer to “gestation” instead of “gestational age”.

*Thank you for the comment, document edited in line with this suggestion.*

17. Figure A1: Could the apparent decrease in the frequency in summer-fall 2020 be related to the non-initiation of pregnancy due to high uncertainty at the very beginning of the pandemic?

*Whilst we agree this is possible, the UK national birth rate in 2020 was only 0.4% below the rate in 2019 (source: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/conceptionandfertilityrates/bulletins/conceptionstatistics/2020#:~:text=The%20conception%20rate%20for%20women,in%202021%20should%20also%20decrease.), so this seems unlikely to have made a material difference to the rate of early PPROM.*

**Reviewer: 4**

Comments:
Thank you for allowing me to review this interesting paper. The most important aspect of this study, which distinguishes it from previous studies, is the inclusion of all cases in the population to provide reliable information regarding incidence and outcomes. However, I have some concerns about whether this was actually achieved:
• The paper notes that "one hundred and seventy-nine women were removed due to duplication, ineligibility, or insufficient information to assess eligibility." It is necessary to have more information about those with insufficient information to assess eligibility, as this may impact incidence and survival rates.

*Further detail about the reasons for exclusion has been added to the manuscript on lines 228-233. In addition Figure A1 has been added to the appendix to show participant flow though the study including further details on why women were excluded.*

• The study relies on nominated reporting clinicians to notify UKOSS if women have PPROM. Therefore, the study depends on the availability and good will of the clinicians. This may not be a significant problem for rare and very serious maternal cases, but it can be problematic for PPROM between 16 and 22 weeks. The study of PPROM before 23 weeks gestation is challenging because cases may not be well identified at hospitalization by referring clinicians, particularly if hospitalization occurs during weekends or in emergency units rather than in high-risk pregnancy units. The impact of medical organization on the study results is suggested by the comparison of the two periods before and during the pandemic. Therefore, it is important to understand how the investigators checked that all cases were actually included.

*UKOSS is an established system which uses multiple methods to maximise case ascertainment, including multiple reporters in each hospital, cross checking with hospital electronic record systems, discussion of cases at monthly mortality and morbidity meetings, emails to all staff and active negative reporting. However, we cannot exclude the possibility of under-reporting and the wording of the limitations section has been edited to capture this. Importantly we did not detect a difference in pregnancy outcomes before or during the pandemic, giving no evidence of biased reporting which might influence the generalisability of the results.*

*Unfortunately, there is no mechanism for the central UKOSS team to check whether all cases are captured as the ethical approval relies on anonymous reporting.*

• Another potential bias is that the cases missed may be those with worse prognoses or shorter hospitalizations, which could directly impact survival rates. This should be discussed in the paper's discussion section.

*The latency between PPROM and birth has been calculated for expectantly managed singleton pregnancies and compared to contemporary literature within the discussion (page 20 lines 613-620) to address this point.*

Regarding survival rates, the authors provided a worst-case and best-case scenario for survival rates based on the hypothesized prognosis of medical interruption of pregnancy. However, this overlooks the fact that the rate of neonates who actually survived is not limited to the expectant management group, but includes the whole group, including those who underwent medical interruption. Therefore, the survival and prognosis should be provided for the entire group as the main analysis, as well as for those who underwent expectant management (including those who subsequently underwent medical termination of pregnancy). The current main analysis, which includes only those who did not undergo expectant management followed by medical termination, provides a very optimistic neonatal prognosis.

*Table 2 has been re-designed to show the numerator and denominators for both the expectantly managed pregnancies and the whole cohort including women who had termination of pregnancies, we hope this addresses this concern.*

Minor comments:
• A flow chart should be provided to aid understanding of the various subgroups.

*Thank you for the suggestion, this has been produced and forms figure A1*

• The paper's description of the TFMR group is somewhat confusing. The medical reasons for TFMR should be described, particularly in cases where there is no sepsis.

*This detail has been added to page 8, lines 249-277*

• The definition of maternal sepsis should be provided.

*A pragmatic decision was used to base the definition of sepsis upon that used by local clinicians. This is described on line 175-6 of page 4*

• The number of women who had PPROM after amniocentesis or trophoblast biopsy should be stated.

*This information has been added to the demographics table*

• Survival without morbidity refers only to absence of IVH 3 and 4 or supplemental oxygen at 36 weeks, but does not necessarily indicate the absence of other morbidities (such as neurological, visual, neurodevelopmental, or intestinal). This is important information for counseling women.

We agree, this has been added to the discussion, page 18 lines 549-522.

• The multiple analyses with small numbers on multiple pregnancies with comparisons between MCDA and DCDA may not be very useful.

*PPROM under 23 weeks gestation in twin pregnancies are a rare complication of an uncommon type of pregnancy. Six of the 10 MCDA pregnancies had either laser coagulation or amnioreduction for twin to twin transfusion syndrome. We wanted to report the multiple pregnancy outcomes in the most informative way possible, mindful that the case series is too small to justify detailed statistical analysis.*

**Reviewer: 5**

Comments:
The authors provide a detailed description of maternal and fetal/neonatal outcomes of 330 women who were diagnosed with preterm pre-labour rupture of membranes between 16 and 22 weeks' gestation. The study involved data collection by 194 obstetric units in the United Kingdom. Analyses were stratified by plurality and addressed outcome assessment issues for pregnancies that were terminated using best/worst case scenarios in addition to analyses based on pregnancies that were expectantly managed.

Comments:
1. As mentioned by the authors, PPROM at a previable gestation can be an enormously stressful event for parents. The substantial morbidity and mortality risks to both mother and baby, combined with appreciable survival rates and rates of survival without severe morbidity for infants following expectant management mean that parents are faced with a serious and complex decision when PPROM occurs.

*Thank you for your comment, we agree*

2. The population-based nature of the study, the relative large study size and the detailed analyses are important strengths of the study.

*Thank you for your comment, we agree*

3. The findings mostly corroborate findings from previous studies.

*Thank you for your comment, we agree*

4. Some of the Tables provide live birth, survival and other rates by gestational week when PPROM occurred, and a P value is provided which shows whether rates differed significantly by gestational week. Since increasing gestational week at PPROM is expected to influence outcome rates, it may be more appropriate to test for an increasing/decreasing outcome rate by gestational week (using a chi-square test for linear trend in proportions). For instance, in Table 3, the rate of survival without severe morbidity after expectant management increases from 13% to 35% and the chi-square test yields a P value of 0.13, while a chi-square test for linear trend returns a P value of 0.05.

*Thank you for this suggestion. In order to provide the most informative statistic for readers the relative rate ratio for each outcome in table 2 is now provided per additional week of gestational age at PPROM.*

5. For the estimates of outcomes following expectant management, the authors have provided a range which incorporates the best case and worst case scenarios for the women who had a termination of pregnancy. However, it may be helpful if the authors could provide a 95% confidence interval on the outcome rates following expectant management.

*The best-worst case range provides generally a wider confidence interval than the 95%CI which we feel is more appropriate to this data due to the inherent uncertainty introduced by 32% of women*

*having a TFMR. Table 2 has been re-organised and now includes the numerator and denominator for each outcome, hopefully this improves clarity and understanding of the level of (un)certainty.*

6. A recent reference on this issue that the authors may wish to add is
Kraft et al. Pre-viable preterm premature rupture of membranes under 20 weeks of pregnancy: A retrospective cohort analysis for potential outcome predictors. Eur J Obstet Gynecol Reprod Biol 2022 Nov;278:177-182.

*With thanks, this reference has been used*

**Reviewer: 6**

Comments:
This prospective national population-based cohort study, launched in UK, aims to describe infant and maternal outcomes of women with preterm prelabour rupture of membranes (PPROM) under 23 weeks of gestation. This situation is extremely rare and as mentioned by authors, is difficult for clinicians to experience and advice families. Data reported here were based on UK Obstetric Surveillance System allowing to have information for a large population and during a short period of time, as compared to the existing literature (Kibel, 2019 for example, whose data were collected during 10 years period). In addition, research questions were based on family complaints about variability of counselling. Results are thus of uttermost importance for professionals and families and may help to better care women/neonates facing PPROM. One of the main results is the prevalence of associated morbidity and mortality for women. Infants' outcomes were more expected (e.g. increase in percentages of livebirths as gestation with PPROM increases) but may benefit from a more detailed description, that could help neonatologists make better decisions in practice.

*We thank the reviewer for these positive comments. Unfortunately, due to small numbers and risk of deductive disclosure we are unable to report individual causes of infant deaths.*

Methods:

Definitions: It could be helpful to have some more precise definitions for:

Maternal outcomes: Sepsis.
At the first reading, I was concerned by the definition of maternal sepsis. Fortunately, you referred to the form (ref 6) and this was very helpful. As far as I understand, the information is available in section 5c. "antenatal complications". Could you give some more detail about the timing of maternal sepsis (before or after delivery) to better understand the complications faced by these women? Did you report maternal sepsis before delivery only? Did you have some more information in 6a.2 "Did any major maternal morbidity occur?"?

*As the reviewer describes the definition of maternal sepsis was defined by the reporting clinicians, as described on lines 216-217. The authors have reviewed the details of the dates of sepsis and birth. Amongst the 50 women that developed sepsis the date of diagnosis is available for 42 women, and*

*the diagnosis was either made before, or on the same day as birth for these 42 women. We feel this level of detail is unnecessary for readers but would be happy to add if desired by the editorial team.*

*Free text on complications was added for 12 women. In seven women the response related to sepsis (already captured in the sepsis box). In a further five women the response related to post partum haemorrhage and one woman had ovarian vein thrombosis with acute kidney injury. We do not feel this information materially improves that already presented within the main paper.*

Infant outcomes: Severe lung disease.
Severe lung disease is defined in the form section 6b.7 and include high frequency oscillatory ventilation (HFOV), inhaled nitric oxide (NO) AND supplemental oxygen at 36 weeks PMA, which is also included in the definition of severe morbidity. I would suggest to report separately HFOV and NO on one side as “severe lung disease”, and supplemental oxygen at 36 weeks on the other side -which defines bronchopulmonary dysplasia and could be 19abelled as follows-. Indeed, for neonatologists, the problems are of different nature. HFOV and NO are usually required on the acute phase and associated with bronchopulmonary hypoplasia, a severe consequence of PPROM, when supplemental oxygen at 36 weeks is a marker of chronic lung disease and could develop in infants who do not have a severe lung disease -as defined above- in the acute phase.

As discussed above we have limited the infant outcomes presented for clarity and to avoid the potential for deductive disclosure.

Statistical analysis: 1) I assume that you have included TFMR and TFMR after a period of expectant management in the same group to increase the statistical power. However, the two groups are probably different in some ways and you may have information to describe these differences (see later). 2) I was concerned by the missing data and I would have like to have descriptive results of this population, in terms of characteristic but also medical organizations (for example, the proportion of transfers to another hospital). I agree with your strategy to account for the impact of termination of pregnancy for medical reasons (TFMR). I am more reluctant to use the same strategy for the missing data. For example, when the outcome is unknown, you may have neonates born before or after 22 weeks which was the lower limit in UK to consider resuscitation at that time. Consequently, the strategies 2 (considering that all died) or 3 (considering that all survived) could be more precise according to GA at birth. This remark is may be useless considering the number of missing data but I was not able to have an opinion reading the results.

*The missing infant survival data only relates to the 16 infants that were liveborn at or after $22^{+0}$ weeks gestation. The authors considered imputing survival data for these infants, based on gestational age at PPROM, however given that only 38 neonates survived to discharge without severe morbidity this was felt to be inappropriate, and the worst-best case range was felt to give a more appropriate estimate of the certainty of the result, with the ability to consider pregnancies with TFMR too.*

Results:

Results answer the research question but may benefit from additional analyses. To my opinion, these results are very important and this group have unique data. That's the main reason why I have tried to suggest additional descriptive results or analyses. A few variables are apparently available (although I have no idea what the percentage of missing data for these variables is, and consequently how useful they might be). Using the variables proposed below may help to have a more in-depth picture of PPROM and their consequences.

Demographics: Comparison of women with expectant management and those with TFMR.
This comparison was very important and could help to give families an answer to the question about variability in staff attitudes. The only statistical difference between groups was gestational age at PPROM. It is reassuring that demographics characteristics were not associated with differences between groups. However, I suggest to also use data collected in section 3 (previous medical history) and section 5c (antenatal complications in pregnancy) to compare 3 groups of management: expectant / TFMR after expectant management/ TFMR. TFMR after expectant management could be associated with previous medical history or antenatal complications. This could help to better understand the strategies used by teams and to discuss the "wide uncertainties" mentioned several times in the manuscript. It could also allow to modulate the analysis strategy and the extreme presented for each outcome measure, at least in the discussion.

*The authors welcome the consideration that the reviewer has given to this analysis and agree that there are features within the captured demographic data that may relate to pregnancy outcome and aid counselling. However, this manuscript is aimed at conveying the main messages from this large study to the medical community and we have therefore limited the information presented.*

Pregnancy after PPROM: Numbers need to be checked. It is announced in the text that the latency between PPROM and birth was known for 223/227 women. In the Table (column "whole cohort"), the latency is not specified in 3 cases, with the sum of all cases being equal to 223. What is the real number? 223? 224?

*Thank you for this comment, this has now been addressed*

Minor comment: I would speak of a risk of birth rather than a chance of birth.

*The author team prefer to refer to chance of birth because risk implies a negative outcome and the outcome may not be perceived as negative by the woman. For example giving birth at 18 weeks gestation to a baby that is unable to survive may be preferable to giving birth at 24 weeks gestation to a baby that has a lot of suffering to some women.*

Infant outcomes: It could be useful to have some more information about infant outcomes. In Table 3, considering livebirths only, I would add the mean gestational age at birth for each week of gestation at PPROM together with the number of women who received antenatal corticosteroids and magnesium sulfate. These two variables are available in the form. Their impact on outcome is well acknowledged but they are not always used at these extremely low gestational age. It could be useful to know if there is a potential for neonatal improvement at this step.

*We believe that adding detail about corticosteroids and magnesium sulphate would detract from the main message of this paper for a general audience.*

I would also add a line with severe lung disease among livebirth infants. I would also present a Table with the different causes of antenatal death only, and then a Table with data for livebirths (the line TFMR is may be not necessary in the Table with data for livebirths). In this Table, you could add the number of neonatal deaths and the number of deaths with severe lung disease. Reading the form, I think that you cannot assume that this was the main cause of death, but it is a severe disease and the fear most neonatologists have for neonates born after PPROM.

Please see our earlier response.

I suggest to checked all your data for severe lung disease and bronchopulmonary dysplasia (as defined above), because reading the text I was wondering if there was a confusion between these two different clinical situations.

We have aimed to describe throughout the manuscript whether the neonatal respiratory morbidity was the requirement for oxygen at 36 weeks postmenstrual age (the often used definition of bronchopulmonary dysplasia) or 'severe lung disease' which is defined on page 4-5, lines 183-185 as "Severe lung disease was defined as requiring high frequency oscillatory ventilation during the neonatal admission, inhaled nitric oxide during the neonatal admission, or supplemental oxygen at 36 weeks postmenstrual age."

I also had difficulties to jump between Table 3 and Table 4, due to different denominators, that were not easy to understand. For example, in Table 3, the whole cohort is 330 but 310 in Table 4. This is in line with my previous comment about missing data. I suggest to report the same denominators (330 singleton pregnancies) in every table but with the number of missing data for the studied variable clearly included in the Tables.

*Thank you for your comment. We hope this is addressed with the next iteration/combinations of tables 3 and 4 into table 2 and new participant flow chart in figure A1.*

Maternal outcomes: These are very important results of this paper. Don't you think that it could be useful to present factors associated with maternal and infant outcomes? In the paper of Kibel (ref 22), the increased duration of PPROM increased maternal morbidity but for infants, factors associated with survival and survival without morbidity were GA at PPROM > 22 weeks and a latency > 7 days. These results may suggest a conflict between maternal and fetal/neonate interest and I think that this is worth to document. This situation is unique in the field of perinatology. Unlike many other situations, where maternal risk is present, the risk for women in PPROM increased with the prolongation of pregnancy. This is different in pre-eclampsia for example where the risk for women is acute and the decision to prolong or stop the pregnancy must be taken in emergency. In PPROM, the decision-making process can be described as more complex, in subacute or chronic situations, requiring a closer collaboration between all members of a perinatal team. That's one of the reasons why I suggest to describe more precisely infants'outcome.

*We thank the reviewer for these comments. Extra detail has been added to the maternal morbidity section to give information about duration between PPROM and sepsis and sepsis according to whether TFMR was performed.*

Discussion
The discussion is well-written, easy to follow, with clear messages in the light of previous evidence. I only have a few comments.

Statement of principal findings: “The additional complexity because of the uncertainty…” may again be highlighted if you could present some more data about TFMR (see above)

*We thank this reviewer for these comments and hope the added detail about TFMR and sepsis goes some way to addressing these concerns.*

Page 14, paragraph about the definition of severe neonatal morbidity, line 12. I would be more cautious in the comparison with the results of Kibel as retinopathy of prematurity, unlike in the definition of Kibel, was not included in your definition of severe morbidity. This is however a huge concern, especially in infants born extremely preterm, and your results may underestimate long-term severe-moderate morbidity.

*We agree with this comment and a cautionary note has been added to page 18 lines 549-522*

Page 14, line 20. The median length of stay was shorter in the UK cohort than in the Australian and Japanese cohort but the mean GA at birth was lower in these two cohorts and this could explain the difference. I agree that the length of stay is likely to have an impact upon the whole family, but like in every preterm birth. The specificity of PPROM is that mothers may have also been hospitalized a long period of time before birth and this add to the burden of hospitalization.

*We agree with this comment, however some women had outpatient management and so as to keep the length of the discussion manageable the current text has not been changed.*

Page 15, line 20 to 30. You have explained why you did not consider fetal anomalies. However, you have data about the presence of “major congenital anomaly” (6b.7). I agree that with the form used, you were not able to say if fetal anomalies were diagnosed at PPROM or at birth. However, don’t you think that it could be interesting to report the presence of such anomalies, both in TFMR group and in the livebirth group?

*Question 6b.7 was only answered for infants that were liveborn, therefore unfortunately we do not have this information for women who had TFMR.*

Minor comments:

Although all important results are reported, I did not always find a logical order in the organization of

the paper and consequently I did not find that the lecture was fluid. For example, in the method section, the time for data collection was reported in the third paragraph, after having explain that a final reminder was fixed in September 2021. I would also have appreciated to read the results with a chronological approach. For example, infant outcomes could have been reported first as intrauterine death including TFMR and then outcomes in livebirth, including neonatal deaths.

*The results section has been re-ordered to account for one less table in the main paper and in doing so we have attempted to address this concern*

Singleton pregnancy losses. My first language is not English and my comment is may be unfounded but this sounds strange to me as you include neonatal deaths in this chapter. Can neonates be defined as pregnancy loss?

*We hope this has been improved with the language of perinatal and baby loss*

Table A3: You are presenting the NUMBER of surviving infants but not the percentage.

*With thanks, legend edited*

To conclude, I have read this paper with a great interest and I hope that all the proposals made will be helpful and read as demonstrating this interest. These data are very important for perinatal teams and unique. I may have suggested to report too much additional information but it appears that this information is available and I am convinced that it will reinforce the validity of these results for professionals but also for families. To my knowledge, the UK database is for the moment unique in Europe and it is a great opportunity to improve knowledge on rare diseases. PPROM is one of them in the field of perinatal medicine.

**VERSION 2 – REVIEW**

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|---|---|
| **REVIEWER** | Perera, Rafael; University of Oxford, Primary Care Health Sciences. Competing Interest: None |
| **REVIEW RETURNED** | 13-Nov-2023 |

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|---|---|
| **GENERAL COMMENTS** | This manuscript describes a nationwide study of pregnant women who have a preterm prelabour rupture of membranes (PPROM) occurring before 23 weeks gestation. The authors characterise the maternal and child outcomes and provide estimates of these based on assumptions regarding potential outcomes for those pregnancies with termination for medical reasons (TFMR).<br><br>The manuscript is clearly written, and the results are presented in sufficient detail to help with decision-making in this challenging situation. The Conclusions are measured and follow from the main findings. The authors have replied adequately to the editors' and reviewers' comments, and I believe the current manuscript is suitable for publication in BMJ Medicine. |