PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort Profile: Prematurity Immunology in Mothers living with HIV and their infants Study (PIMS)
AUTHORS	Malaba, Thokozile R; Myer, Landon; Gray, Clive; Newell, Marie-Louise

VERSION 1 – REVIEW

REVIEWER	Theron, Gerhard University of Stellenbosch, Obstetrics and Gynaecology, Tygerberg Hospital
REVIEW RETURNED	10-Feb-2021

GENERAL COMMENTS	General Further research is necessary to understand the risks and to identify safest of maternal ART regimens for optimized pregnancy and infant outcomes. The present knowledge base is largely limited by studies that did not include ultrasound confirmation of gestational age in the first or second trimesters. Reporting results on preterm labour and appropriate for gestational age birth weight are thus limited. The authors are to be commended recruiting a large cohort of women that include a subset of women with gestational age confirmed by ultrasound. In addition, the authors used a standardised method that took account of the error margins of ultrasound. Gestational age was only adjusted when the date of the last normal menstrual period fell outside the ultrasound error margin. This is according to international accepted norms for gestational age determination. The main aim of the study is to study the reconstitution of cellular immune responses in women on ART from before pregnancy and ART commenced during pregnancy. The results will establish whether ART increases risks for PTD and small-for-gestational age (SGA) infants. The protocol for the immunology study is being submitted to be published and reference are made to sub-studies that were published relating to gestational age, obesity and placental histology emanating from the main study. The title of the submitted paper: “Cohort Profile: Prematurity Immunology in HIV-infected Mothers and their infants Study (PIMS)” correctly reflect the content of the paper. The paper is well written with hardly any errors and provided attention are given to the editing mentioned below can be accepted for publication. Editing required

	A proportion of the participants are mentioned to be “HIV infected”. People living with HIV resent this terminology and “women living with HIV” should be used. Mention in the “Cohort Description” section that only singleton pregnancies were included. Mention in the “Participant Baseline Characteristics” (sentences 5 and 6) that women referred from Basic Antenatal Care clinics were referred back to these clinics and not included in the study subsequent to screening complying with the provincial Department of Health’s health care model. Abstract, sentence 18 and 19: …, with data were collected …. Participant Baseline Characteristics, sentences 48 and 49: …. initiated ART during pregnancy …. Tables 1,2,3 and 5: Indicate with a footnote that percentages follow the numbers in brackets. Figure 1: Add the number of patients in the screened out blocks.

REVIEWER	Njom Nlend, Anne Esther National Insurance Fund Welfare Hospital
REVIEW RETURNED	01-Mar-2021

GENERAL COMMENTS	PTB has a lot kmown causes including genetics, immunology and inflammatory and infectious, endocrine and local causes. The authors attempted to analyze many of the factors than could induced PTB and SGA in regard to HIV infection and antiretroviral treatment, in concern of immunology This paper is truly hard to read with no clear study end points to the main objectives with 2 focus. Study design should be defined clearly Procedures of enrolment, follow-up and retention as well should be presented in a longitudinal flow chart on procedures according to the timing pre post and long post partum follow -up and not mixed with the results..... The flow chart would clearly show the design of the cohort and the case control.study Findings to date are quite limited not in line with the announced objectives In addition poor bibliography and references

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 (Prof. Gerhard Theron, University of Stellenbosch):

No	Comment	Amendment
Thank you for the positive comments; we address the minor editing required below		
1.	A proportion of the participants are mentioned to be “HIV infected”. People living with HIV resent this terminology and “women living with HIV” should be used.	Thank you for this comment, we agree and have amended this throughout the manuscript.

2.	Mention in the “Cohort Description” section that only singleton pregnancies were included.	All women were followed up regardless of their pregnancy status, however we only included singleton pregnancies in birth outcome analyses. We have included this information under the relevant sections in Findings to date, this now reads Gestational Age Assessment: “In the overall cohort, 1787 women with live singleton births were included in the analysis of the association between HIV status and timing of ART initiation and PTD by GA assessment method used (last menstrual period (LMP), measurement of symphysis fundal height (SFH) and ultrasound (US).” Obesity: “In the overall cohort, 2921 women with live singleton births were included in the analysis of the association between maternal body mass index and adverse birth outcomes.”
3.	Mention in the “Participant Baseline Characteristics” (sentences 5 and 6) that women referred from Basic Antenatal Care clinics were referred back to these clinics and not included in the study subsequent to screening complying with the provincial Department of Health’s health care model.	We agree with this and have added a sentence in the Recruitment section, this now reads “Following screening, ineligible women were referred back to their ANC clinics in line with the Western Cape Department of Health’s health care model.”
4.	Abstract, sentence 18 and 19: …, with data were collected ….	Thank you we have fixed this sentence to read “Women in the overall cohort were followed antenatally through to delivery using routine clinical records; further women in the nested cohort were actively followed up until 12 months postpartum, with data collected on maternal health (HIV care and ART use, clinical care and inter-current clinical history).”
5.	Participant Baseline Characteristics, sentences 48 and 49: …. initiated ART during pregnancy	We have now included the word ‘initiated’
6.	Tables 1,2,3 and 5: Indicate with a footnote that percentages follow the numbers in brackets.	Thank you, we have included “n (%)” to the footnotes of each of these tables as suggested.
7.	Figure 1: Add the number of patients in the screened out blocks	Thank you we have amended this in figure 1

Reviewer 2 (Dr. Anne Esther Njom Nlend, National Insurance Fund Welfare Hospital):

No	Comment	Amendment
2.	Study design should be defined clearly	We apologize for not being clear about the aim of this Cohort profile manuscript; we have clarified this to “This manuscript presents the details of the setting up of the cohort, including aims and objectives and a description of baseline findings along with other preliminary findings.” Additionally, to ensure a distinction between the aim and objectives of the manuscript and those of the PIMS study we have created a new separate section entitled “Aim and Objectives” which describes the overall aim and objectives of the PIMS study as well as the underlying hypotheses.
3.	Procedures of enrolment, follow-up and retention as well should be presented in a longitudinal flow chart on procedures according to the timing pre post and long post-partum follow -up and not mixed with the results.....	We have edited Figure 1 in line with reviewer 1 comments, and details re intended follow up of the Group 2 women are in the descriptive text for this Cohort profile manuscript
4.	The flow chart would clearly show the design of the cohort and the case control study?	Thank you, as suggested by the reviewer we have updated Figure 1 (cohort profile) to reflect the design of the cohort and case-control studies. We have also included more information in the Specimen collection section about the number of cases and control who contributed specimens for the case-control study.
5.	Findings to date are quite limited not in line with the announced objectives	As the Editor has mentioned, this comment is likely a result of the reviewer not fully understanding the aims of a Cohort Profile. We have now clarified the aim of the Cohort profile more explicitly, which we hope addresses this concern.
6.	In addition poor bibliography and references	Due to the nature of this manuscript we had to limit the number of references we cited