TITLE: CORRELATION OF PROCALCITONIN (PCT) LEVELS AND THE QUICK SEQUENTIAL ORGAN FAILURE ASSESSMENT (QSOFA) SCORE IN OBSTETRIC PATIENTS ADMITTED TO LABOUR WARD HIGH CARE AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL (CHBAH).

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This research reported is submitted to the University of the Witwatersrand Health Sciences Faculty in the submissible format in partial fulfilment of the degree of Master of Medicine in Obstetrics and Gynaecology in September 2022.

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Table of Contents

Abstract

Background:

Sepsis in the obstetric population is a significant problem in South Africa and around the world, accounting for 11% of maternal deaths annually. Early identification of sepsis in pregnancy is challenging and there is a need to validate early warning scores and biomarkers that could potentially be used to detect sepsis. The quick Sepsis Related Organ Failure Assessment (qSOFA) score has not yet been validated in the obstetric population and normal reference ranges for Procalcitonin (PCT) have yet to be determined for obstetric patients.

Aim:

We designed a prospective study to correlate PCT levels and the qSOFA score in 100 high risk obstetric patients admitted to labour ward high care at Chris Hani Baragwanath Academic Hospital (CHBAH).

Results:

A significant (p value <0.001), positive correlation was found between PCT and qSOFA scores, all patients in the study scored in the same category for PCT and the qSOFA score.

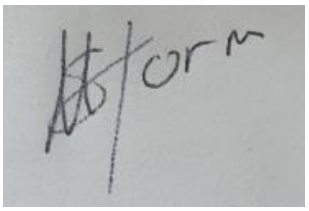
Discussion:

PCT levels below 0.5 ng/mL correlated significantly with a qSOFA score of 0 and these patients were unlikely to have bacterial sepsis.

Conclusion: Our data indicates the potential utility of the qSOFA score to predict PCT levels in the obstetric population studied. This may be especially useful outside of the ICU setting where PCT testing may not be available, as the qSOFA score can be easily and repeatedly calculated by clinicians, at the bedside. This simple scoring system can prompt the clinician to rapidly identify those patients who may need additional investigations like PCT levels and possible escalation to a higher level of care. This can help curb potential morbidity and mortality from sepsis.

Declaration

I, Michael Servaas Storm declare that this is my original work and is not copied entirely, or in part, from any other source unless indicated by quotation marks and accompanied by appropriate references. This research report has not been submitted to any other University for the purposes of obtaining a post-graduate degree.



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Dedication

I dedicate this work to my son, Logan Storm Mansour, who has been a happy distraction throughout this project.

Acknowledgements

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List of Abbreviations

CHBAH – Chris Hani Baragwanath Academic Hospital

COVID-19 – Coronavirus Disease 2019

CRP – C-reactive Protein

GCS – Glasgow Coma Scale

HIV – Human Immunodeficiency Virus

ICU – Intensive Care Unit

ID – Identification

IRIS – Immune Reconstitution Inflammatory Syndrome

LRTI – Lower Respiratory Tract Infection

NCCEMD – National Committee for Confidential Enquiries into Maternal Deaths

NVD – Normal Vaginal Delivery

PCT – Procalcitonin

qSOFA – quick Sepsis Related Organ Failure Assessment

SOFA – Sepsis Related Organ Failure Assessment

SOMANZ – Society of Obstetric Medicine of Australia and New Zealand

UNICEF – United Nations Children's Fund

Title

Correlation of Procalcitonin (PCT) levels and the quick Sequential Organ Failure Assessment (qSOFA) score in obstetrics patients admitted to labour ward high care at Chris Hani Baragwanath Academic Hospital (CHBAH).

Introduction

According to the World Health Organization, 303 000 females died from complications of childbirth and pregnancy in 2015.[1] Each year, sub-Saharan Africa accounts for 66% of all maternal deaths worldwide.[1] Women in sub-Saharan Africa face the highest lifetime risk of maternal death in the world.[1] A 15 year-old-girl living in sub-Saharan Africa has a 1 in 36 lifetime risk of dying from complications of pregnancy or childbirth.[1] According to the 2015 United Nations Children's Fund (UNICEF) report on trends in maternal mortality, 11% of maternal deaths globally are due to sepsis and these are mostly preventable.[1] The diagnosis of sepsis in pregnancy is challenging and there is a need to validate early warning scores and biomarkers that may be able to detect sepsis, to curb morbidity and mortality.

Sepsis

According to the 7th triennial report from the National Committee for Confidential Enquiries into Maternal Deaths (NCCEMD) of South Africa, there were 263 maternal deaths due to non-pregnancy-related infections in 2016. The final causes of death, in

decreasing order of frequency were: respiratory failure secondary to lower respiratory tract infection (LRTI), immune system failure, followed by septic shock.[2] Healthcare provider factors that were identified as being avoidable, were mainly due to problems of late recognition or delayed diagnosis of infection.[2] Recommendations from the NCCEMD include that the unwell pregnant woman needs appropriate investigation, especially for LRTI and that referral pathways need to be created for patients who warrant tertiary level expertise or admission to an Intensive Care Unit (ICU).[2] The recommendations from the NCCEMD also emphasised the need for creating obstetric critical care units in tertiary and referral hospitals in South Africa.[2] Pregnancy-related sepsis accounted for 71 cases of maternal deaths in South Africa in 2016.[2] A large majority of these deaths could have been prevented, as the severity of the infection is mostly unrecognized by healthcare providers, especially in ill post-partum women.[2] Early recognition, adequate resuscitation and administration of broad-spectrum antibiotics with source control, are crucial to improve the outcomes of patients with sepsis.[2] The NCCEMD has endorsed the Maternal Early Warning score since 2010, in an attempt to identify patients with abnormal vital signs timeously and prompt healthcare workers to respond appropriately.

qSOFA

The third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defines sepsis as “life-threatening organ dysfunction caused by a dysregulated host response to infection”.[3] The consensus describes significant organ dysfunction as a score of 2 or more points on the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) tool.[3] A score of 2 or more is associated with an in-hospital

mortality greater than 10%.[3] Application of the SOFA score requires invasive blood pressure monitoring and laboratory testing of multiple biomarkers including: platelet-, bilirubin- and creatinine levels, as well as an arterial blood gas.[3] This is usually done only in a high care setting or ICU. The full SOFA score has been shown to predict mortality from sepsis equally well in obstetric, as in non-obstetric populations.[4] Singer[3] et al. suggest using the bedside q(quick) SOFA score, outside of the ICU setting, to rapidly identify patients with suspected infection who are likely to have poor outcomes. The clinical parameters include alteration in mental status, systolic blood pressure of 100 mmHg or less and respiratory rate of 22 breaths per minute or greater.[3] Similarly to the SOFA, a score of 2 or more on the qSOFA should prompt additional investigation of organ dysfunction, initiation or escalation of intervention, referral to a higher level of care and more intensive monitoring.[3] The appeal of the qSOFA is that it can be applied quickly and repeatedly, although the test is less robust than the SOFA.[3] The qSOFA score is especially useful as a screening tool outside of ICU, in the emergency department, a regular ward or resource-poor settings, where laboratory testing may be limited. However, it is not meant to be used on its own to define sepsis.[3]

A qSOFA score of 2 or more has predictive validity for in-hospital morbidity and mortality. However, the guidelines recently published by the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ), stress that caution should be taken when extrapolating these data to post-partum and pregnant women.[5] Bowyer[5] et al. noted that the data from which the qSOFA score was derived, was retrospective and the population used to validate the data was a heterogenous

group, half of whom were male, with an average age of 61. No study using the qSOFA score in obstetric patients has as yet been published.[6]

The Society for Maternal-Foetal Medicine also published a consult series article on sepsis, in which they emphasized again that the qSOFA does not define sepsis.[6] Instead, it should be used as a rapid method to identify high risk patients who are more prone to develop severe complications.[6] The best early warning system in obstetric patients has yet to be defined, but what is important is that the implementation of an early warning system may decrease maternal risk.[6] The qSOFA score has not been evaluated in pregnancy and the physiological changes that occur during pregnancy may cause false positive results.[4] The lower limit of the normal range of systolic blood pressure at 15 weeks gestation extends to 92 mmHg and at 37 weeks it can be as low as 87 mmHg.[4] The upper limit of normal for respiratory rates in pregnant women range from 20 breaths per minute in the first trimester up to 22 breaths per minute in the third trimester and within the first 48 hours after delivery.[4]

Since the introduction of qSOFA, subsequent validation studies have raised concerns regarding its sensitivity, in that none of the criteria used for the qSOFA are specific for infection.[7] Biomarkers of infectious disease such as procalcitonin (PCT) and C-reactive protein (CRP), have been proven to detect infection and predict mortality accurately.[7] These biomarkers were included as part of the diagnostic criteria in Sepsis-2, however they were excluded in the Sepsis-3 definitions.[7] A large study from Asia confirmed that qSOFA has high specificity but low sensitivity in predicting mortality from sepsis.[7] This study attempted to incorporate an ordinal

scale of PCT into the qSOFA model and their results suggest enhanced sensitivity of the combined qSOFA-PCT screening tool.[7]

Procalcitonin

Procalcitonin is a pro-hormone in the serum, it is released by various tissues in response to pathogen associated molecular patterns including endotoxin and pro-inflammatory mediators.[8] PCT increases significantly in the presence of severe bacterial infection, particularly gram-negative infections.[8] The most common pathogen grown in blood cultures from patients with severe obstetric infections is the gram-negative organism *Escherichia-coli*, a member of the order Enterobaterales.[8] Tissue injury and systemic inflammation can also elevate PCT levels, although less so than with infectious insults.[8] A study from Finland concluded that although reference ranges for PCT have not yet been established in the pregnant population, it is likely to be a useful biomarker in obstetric patients to distinguish infection from inflammation.[8] PCT is more sensitive and specific than CRP for bacterial infection, with concentrations of PCT increasing rapidly within 2-4 hours of onset of severe bacterial infection.[8] CRP frequently rises post-partum from tissue injury and the leukocyte count is normally increased during pregnancy, which limits its use as a biomarker for infection in the obstetric population.[8] Quantitative estimation of PCT and particularly the change in PCT values over time is useful to diagnose infection and guide antibiotic management.[8] The Finnish study included 58 obstetric patients and suggested that a PCT level of less than 0.5 ng/mL indicates that systemic bacterial infection is unlikely.[8] Paccolat[9] et al. tried to establish “normal” PCT values in pregnant women during the third trimester, at delivery and up to ten days post-

partum. The authors included 60 women and proposed that a PCT level of less than 0.25 ng/mL could be used to rule out bacterial infection.[9] A recent study from India gathered data on PCT levels in 40 patients with Pregnancy-Associated Sepsis, they found a lower PCT cut-off value of 0.125 ng/mL should be used to diagnose bacterial infection.[10] The authors also suggested that PCT values can be used to differentiate between severe and non-severe Pregnancy-Associated Sepsis.[10] They cautioned that other pathologies such as pre-eclampsia/eclampsia, premature rupture of membranes and liver-, lung- and thyroid malignancies, can elevate PCT levels in pregnant patients.[10] Another study from Columbia measured PCT levels in 98 pregnant women with confirmed or suspected infection.[11] They found PCT levels rose significantly in pregnant women with bacterial infection, suggesting a cut-off value of 0.6 ng/mL should be used to diagnose bacterial sepsis.[11]

COVID-19 and PCT

In December 2019 a novel Coronavirus Disease (COVID-19) was discovered and spread rapidly to become a worldwide pandemic. Since then, multiple studies have been published investigating potential biomarkers that may be used to predict severity of disease and poor outcomes. Unfortunately, data for the obstetric population are lacking. Pregnant women with COVID-19 are at increased risk of preterm birth and developing severe disease.[12] The largest cohorts of patients have come from the epicentre of the epidemic and did not specifically focus on pregnant women. One meta-analysis included 5350 patients, elevated PCT levels were associated with severe COVID-19 disease, increased composite poor outcome and mortality.[13] Another meta-analysis evaluated the diagnostic and prognostic value of

PCT levels and other biomarkers in 6320 patients.[14] Cohorts with increased PCT levels had higher odds of progressing to severe disease.[14] Mingchun[15] et al. analysed risk factors for severe COVID-19 disease in 5872 patients, they found significantly elevated PCT levels in those patients with severe disease and possibly secondary bacterial infection. A smaller analysis of 4 studies, found that elevated PCT levels conferred a nearly 5-fold increased risk of severe COVID-19 disease.[16] This meta-analysis concluded that serial PCT levels could be used to predict progression towards severe disease and significant elevations in PCT levels suggests bacterial co-infection.[16]

Aim of the study and justification thereof

The aim of our study was to correlate PCT levels and the qSOFA score in high-risk obstetric patients. We studied those patients admitted to labour ward high care at Chris Hani Baragwanath Academic Hospital (CHBAH). This is a tertiary-level institution in Soweto, South Africa, which serves a population of more than one million people in the immediate surrounding area. The hospital is also a referral centre for primary and secondary level facilities. As mentioned before the qSOFA score and PCT have not yet been extensively studied or validated in pregnant patients, which forms part of the motivation for this study. We aim to contribute to the existing pool of data on the qSOFA score and PCT levels in the obstetric population. The data could be used to encourage the use of an early warning score like the qSOFA, at the bed side, to rapidly identify those patients at risk for poor outcomes. This could prompt earlier intervention or escalation of management and more frequent monitoring. The qSOFA score could be used in conjunction with PCT levels

to guide management of patients with suspected sepsis. This data can also stimulate interest in conducting further larger scale studies to validate these parameters in obstetric patients.

Methods

We devised a prospective study to correlate PCT levels and the qSOFA score in high-risk obstetric patients admitted to labour ward high care at CHBAH. Ethics clearance was obtained from the Human Research Ethics Committee of the University of the Witwatersrand, certificate number M191151 (see Appendix 4). The study was conducted from 1 July 2020 to 31st August 2020. Data collection was briefly interrupted from 17 to 27 July 2020, as the principal investigator contracted COVID-19 and was placed in quarantine for 10 days. After patients gave written consent, we interviewed them to determine baseline demographic data and obtained details on the condition that necessitated their admission to high care. The final diagnosis for these patients is often not established at the time of admission to high care, so we could not allocate cases (those patients with suspected sepsis) and controls (those without suspected sepsis). We chose to collect our data upon the patient's admission to high care to obtain baseline data and scores before significant interventions such as fluid resuscitation or administration of antibiotics could occur, which would potentially alter qSOFA and PCT scores. We calculated the qSOFA score upon admission to labour ward high care using the patients' standard vital signs and drew blood to measure their PCT levels, which was specifically required for the study. Serum was separated immediately using a centrifuge, then PCT levels were measured using a point of care machine sponsored by Biocombiotech. This machine, which has been independently validated (see Appendix 7), was placed directly outside of labour ward high care at CHBAH and determines PCT levels within 15 minutes.

Sample size estimation

As previous authors have experienced, there are no studies to guide sample size calculation to measure PCT levels or the qSOFA score in the obstetric population. The sample size was not based on a calculation, which is a limitation of this study. The sample size was determined by the sponsor generously donating 100 PCT assays.

Inclusion and exclusion criteria

We aimed to include all obstetrics patients admitted to labour ward high care at CHBAH from 1 July 2020 to 31st August 2020. We defined “obstetric” as those patients whose pregnancies were determined to be at viable foetal weight at CHBAH (at least 750 grams), up to the end of the puerperal period (42 days post-partum). At CHBAH, minors are often not accompanied to hospital by their parents or legal guardians, this raised logistical concerns regarding obtaining consent from minors. South African law states that persons under the age of 18 cannot independently consent to participate in research without the consent of their parents or legal guardians, thus we excluded all minors from the study.

Data Analysis

Statistical analyses were conducted using R software (version 4.00; www.R-project.org). The dataset did not meet the assumptions of normality (Shapiro-Wilk’s

test) and non-parametric statistical analyses were used. Tests were two-tailed, and model significance set at 0.05. Data are reported descriptively as counts for categorical data and mean ± SD for continuous data. A Spearman rank test was used to analyze the association between the qSOFA score and the PCT score. Pearson's chi-squared tests (with Yate's correction) were used to analyse the association between PCT and women who had normal vaginal delivery (NVD) or had a surgical intervention and those with Pre-eclampsia.

Results

Summarized in the table below are the clinical parameters of 100 patients studied. Continuous variables are shown as mean ± SD and categorical values are counts.

Table 1. Clinical parameters of women admitted to labour ward high care at CHBAH.

Variable	Values
Respiratory rate (bpm)	19.88±2.48
Non-invasive Systolic blood pressure (mmHg)	135.09±24.57
GCS	All scored 15
Age	28.98±6.40
Parity	1.63±1.41
Gravidity	2.54±1.31
HIV status	Positive 25, Negative 75
CD4 cells/mm^3 (if+)	372.71±253.83
VL copies/mL (if+)	66144*±118559.49
Currently Still Pregnant	64 Yes, 36 No
Gestational age currently or at delivery (in weeks)	34.94±4.53

Diabetic	Yes 9, No 91
Did the patient have a normal vaginal delivery	Yes 22, No 78
Did the patient have an assisted delivery	Yes 2, No 98
Did the patient have a Caesarean Section	Yes 14, No 86
Known source of sepsis	Yes 9, No 91
COVID-19 suspect/confirmed	Yes 5, No 95
Did the patient have pre-eclampsia	Yes 60, No 40

*****In those patients on treatment for HIV, their viral loads were most often lower than detectable limit. The mean is not representative due to two patients who had virological failure and thus very high viral loads.

For statistical analysis we grouped PCT levels into 3 categories, to correlate a continuous variable (PCT) with a categorical variable (qSOFA score). PCT levels less than 0.50 ng/mL were designated as 0, 0.51 ng/mL to 1.00 ng/mL as 1 and more than 1.00 ng/mL as 2. This correlates with bacterial infection being unlikely (0), possible bacterial infection (1) and bacterial infection being likely (2). The Spearman regression between qSOFA and PCT scores was significantly positively correlated (Figure 1), generating a Spearman's rho of 1. All women scored the same values for qSOFA and PCT (i.e., 0 on both scales). Most of the patients scored 0 for both qSOFA and PCT and fewer women scored 1 and 2 for both qSOFA and PCT (Figure 1).

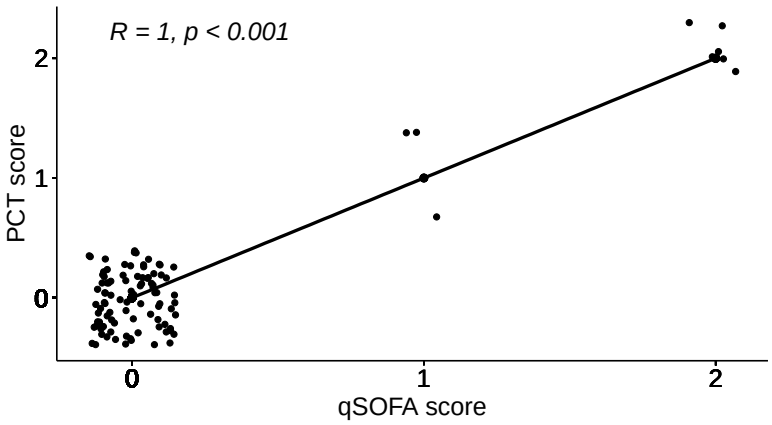

Figure 1. The association between qSOFA and PCT scores in women admitted to labour ward high care at CHBAH. The Spearman regression and statistical output are presented.

The mean PCT and qSOFA scores for the patients in this study was 0 (range 0 to 2). Nine of the patients included in the study scored more than 0 for both PCT and the qSOFA. Bacterial sepsis was confirmed in most of these patients and the most common causes were LRTI and urosepsis, the uterus was the confirmed source of sepsis in two of the patients. Severe COVID-19 disease was confirmed in one patient with elevated PCT and qSOFA scores.

The association between PCT scores and normal vaginal delivery (NVD) was not statistically significant ($\chi^2 = 4.62$, df = 2, p = 0.099). Most patients had a PCT score of 0, regardless of whether they did, or did not have a normal vaginal delivery (Figure 2). This contributes to the existing pool of data in the obstetric population in that NVD does not significantly alter PCT levels, which aids in the effort to establish “normal” reference ranges for PCT levels in the obstetric population.

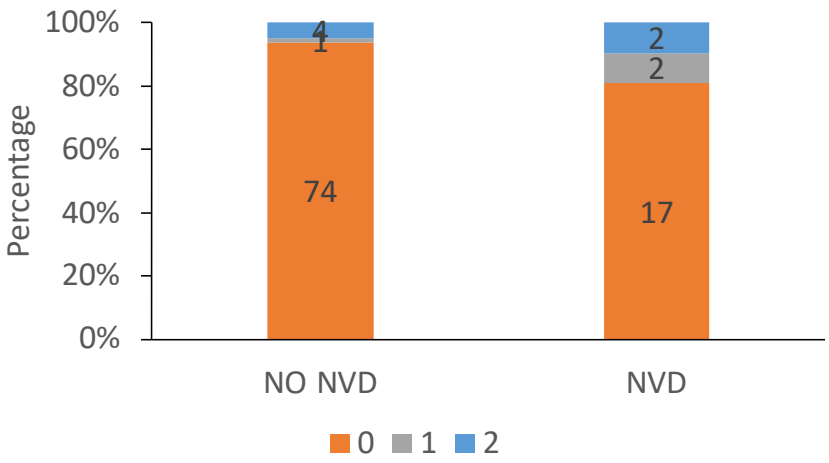

Figure 2. The percentage of women post NVD in relation to PCT score categories (0, 1 and 2), admitted to labour ward high care at CHBAH. The number of women in each category is shown.

The association between PCT scores and surgical intervention was statistically significant ($\chi^2 = 6.85$, df = 2, p = 0.034). Significantly more patients who did not have surgical intervention had PCT scores of 0 (Figure 3).

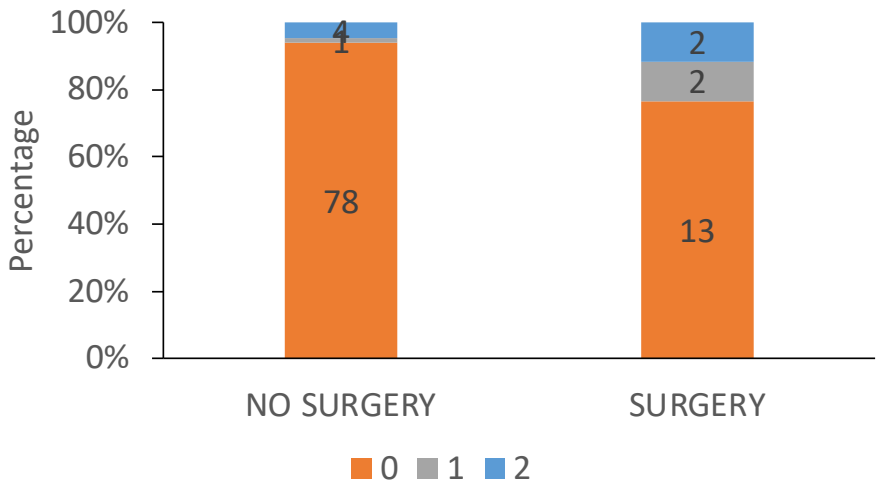

Figure 3. The percentage of women after surgical intervention in relation to PCT score categories (0, 1 and 2), admitted to labour ward high care at CHBAH. The number of women in each category is shown.

Most women with a PCT score of zero did not have a surgical intervention such as a caesarean section, re-look laparotomy or evacuation of the uterus. Factors such as the need for surgical intervention to control bleeding, or laparotomy for source control of suspected sepsis need to be carefully considered when interpreting this data.

The association between PCT scores and pre-eclampsia was statistically significant ($\chi^2 = 6.81$, df = 2, p = 0.033). Significantly more patients who did have pre-eclampsia had PCT scores of 0 (Figure 4). This contradicts previously published opinions that pre-eclampsia can cause falsely elevated PCT levels.[8,10]

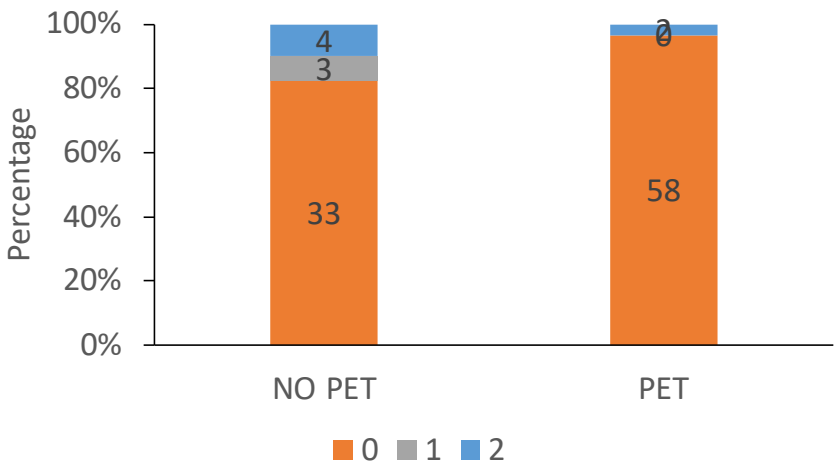

Figure 4. The percentage of women with pre-eclampsia in relation to PCT score categories (0, 1 and 2), admitted to labour ward high care at CHBAH. The number of women in each category is shown.

Discussion

The primary aim of this study was to correlate PCT levels and the qSOFA score in obstetric patients admitted to labour ward high care at CHBAH. A significant positive correlation was found (p value <0.001), with all patients in the study scoring in the same category for PCT and the qSOFA score. The strength of the study lies in that this is the largest study undertaken to measure PCT levels and the qSOFA score in the obstetric population in South Africa. The use of the qSOFA score in this population has not yet been validated, however the data shows that it correlates significantly with PCT levels. Importantly, this study also found that pre-eclampsia did not significantly elevate PCT levels in pregnant patients as previously reported by Agarwa[8,10], et al. and other authors. This indicates that PCT can be safely interpreted in patients with pre-eclampsia.

The United States Food and Drug administration approved the use of PCT to guide antibiotic therapy in patients with acute respiratory infections and sepsis in 2017.[17] Several trials have demonstrated significant decreases in antibiotic exposure when PCT is used to guide duration of treatment in high risk patients, as well as initiation of antibiotics in low risk patients.[17] A meta-Analysis of these studies found a significant decrease in mortality and antibiotic related side-effects when PCT was used in antibiotic stewardship programmes.[17] Unnecessary use of antibiotics, for example in viral bronchitis and prolonged use of antibiotics contributes to the evolution of multidrug-resistant bacteria, which is a global concern.[17] A recent landmark systematic review and meta-analysis of randomized controlled trials focusing on PCT-guided antimicrobial management in critically ill patients, found no

difference in short-term mortality when compared to usual care.[18] However, when PCT levels were used to guide cessation of antibiotic therapy, a statistically significant decrease in mortality was found.[18] Some conditions may cause falsely elevated or decreased levels of PCT.[19] These include: patients with immunosuppression (e.g. HIV); trauma; cystic fibrosis; pancreatitis; high volume transfusions; malaria; renal dysfunction and pregnancy.[19]

The are no large randomized controlled trials investigating the use of PCT in the pregnant population. Our data contributes to the effort to establish reference ranges for PCT levels and the validate the use of the qSOFA score in obstetric patients. We found that PCT levels below 0.5 ng/mL correlated significantly with a qSOFA score of 0 and that these patients were unlikely to have bacterial sepsis. We recommend including the qSOFA score as part of the routine clinical assessment of obstetric patients with suspected sepsis. We stress that neither the qSOFA score, nor PCT levels are meant to be used on their own to diagnose sepsis. Instead, clinicians can utilize these tests in the obstetric population, as part of a holistic assessment, to rapidly identify those patients that may suffer morbidity and mortality due to sepsis.

Limitations of this study include that there was no sample size calculation. We could not allocate patients to a case and control arm, as their final diagnosis was not clearly established on admission to high care, at the time of data collection. We aimed to include all patients admitted to labour ward high care at CHBAH, regardless of their suspected diagnosis. We did not follow-up their final outcomes, morbidity and/or mortality as this was not a longitudinal study. Another limitation is that only 9% of the patients included in the study scored more than 0 for both PCT and the

qSOFA. The study was conducted on all high-risk patients admitted to labour ward high care. We aimed to identify patients at risk of sepsis who may not have shown obvious signs, we did not investigate a cohort with a high suspicion of sepsis. The relatively small sample size limits our ability to draw definitive conclusions.

Conclusion

The study is not large enough to make clinical practice recommendations, however the data does indicate the potential utility of the qSOFA score to predict PCT levels in the obstetric population studied. This may be especially useful outside of the ICU setting where PCT testing may not be available, as the qSOFA score can be easily and repeatedly calculated by clinicians, at the bedside. This simple scoring system can prompt the clinician to rapidly identify those patients who may need additional investigations like PCT levels and possible escalation to a higher level of care. Our data also contributes to the effort to establish normal reference ranges for PCT levels in the obstetric population. A combination tool of the qSOFA and PCT may prove useful in the obstetric population. We recommend further larger scale studies to validate the use of the qSOFA score in the obstetric population and to establish reference ranges for PCT levels in these patients. The ideal cut-off for PCT levels in the obstetric population is still not universally agreed upon, further larger scale studies should try to establish the ideal cut-off.

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APPENDIX 1 – Study information document and participant consent form

Study information document

Study title: Correlation of PCT levels and the qSOFA score in obstetrics patients admitted to labour ward high care at CHBAH**.**

Good day,

My name is Dr Michael Storm, I am doing research on patients admitted to labour ward high care at CHBAH. Research is a process used in seeking new knowledge. In this study I want to learn how a blood test (known as PCT) correlates with a clinical scoring system (known as the qSOFA)

Invitation to Participate: I am asking / inviting you to take part in a research study.

What the study involves. I need to do a simple blood test, collect some of your demographic information and use your vital signs to calculate the qSOFA score. This will take less than 5 minutes of your time, I will need to draw a teaspoon of blood from you, only once. This study will be conducted from 1 January 2020 to 31 March 2020.

Risks of being involved in the study: You should not find the proceedings traumatic, but if you feel the need to talk to someone a social worker or counsellor can be arranged free of charge.

Benefits of being in the study: The result of your blood test (PCT level) may help guide your management during your stay in high care and assist management of other patients in the future.

Participation is voluntary. If you decide not to participate, this will involve no penalty or loss of benefits to which you are otherwise entitled. You may discontinue

participation at any time without penalty, or loss of benefits to which you are otherwise entitled. There is no requirement to provide a reason for withdrawing and any data collected about you will be destroyed unless you consent to retention of this data.

There is NO payment or cost associated with participation.

Confidentiality: Normally personal information will be treated in the strictest confidence and will only be available to myself, the Principal Investigator (PI) and my supervisor. If results are published, this may, exceptionally, lead to cohort, or more rarely, individual identification. All data collected during the study will be securely retained for two (2) years if a scientific publication arises from the study and six (6) years if there is no publication. Thereafter it will be destroyed accordingly.

Anonymity will be maintained as far as possible as I will allocate a study ID to your information and results, which cannot be traced back to you.

Contact details of researcher: Dr Michael Storm Tel: 0114884911, email: 0702450T@students.wits.ac.za

Outputs I am hoping to correlate PCT levels with the qSOFA score to see if I can improve patient management and outcomes.

Contact details of HREC administrator and chair – for reporting of complaints / problems

This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg ("Committee"). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.

If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be

contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for reading this Study Information Sheet.

Participant Consent Form

Title of project: Correlation of PCT levels and the qSOFA score in obstetric patients admitted to labour ward high care at CHBAH

Researcher: Dr Michael Storm

I……, agree to participate in this research project. The research has been explained to me in a language that I understand. I understand what my participation will involve. I agree that my participation will remain anonymous and that the information gathered may be used anonymously by other researchers following this study. I understand that I may withdraw my participation at any time and that such withdrawal will not result in any penalty or loss of benefits.

…… (Signature)

…… (name of participant)

…… (Date)

APPENDIX 2 – Data Collection Sheet

Study ID	Age		Parity		Gravidity
HIV status	Positive	CD4	VL	Negative	
Currently pregnant?	Yes			No	
If currently pregnant, how many weeks gestation by best estimate:			If post-delivery or post re-look laparotomy, how many days:		
Does the patient have hypertension or pre-eclampsia?	Does the patient have diabetes mellitus?		Did the patient deliver vaginally?	Did the patient have a caesarean section?	
Respiratory rate in breaths per minute (bpm)	Less than 22 bpm			More than, or equal to 22bpm	
Systolic blood pressure (mmHg)	Less than, or equal to 100 mmHg			More than 100 mmHg	
Level of consciousness	Alert			Altered	
qSOFA score	0	1		2	3
PCT level:	Date taken:			Time taken:	
	Pre-eclampsia/Eclampsia			Sepsis	

Provisional diagnosis/reason for admission	Ante- or post-partum Haemorrhage/Anaemia	Preterm labour and PROM
	Cardiac Disease/ Venous thromboembolic disease	Other, please specify:
Does the patient have a known source of sepsis	Blood culture	Urine Culture
	Sputum culture	Diagnostic imaging
Was the PCT level useful?	Yes	No

APPENDIX 3 – Approved Research Protocol

1. TITLE

Correlation of Procalcitonin (PCT) levels and the quick Sequential Organ Failure Assessment (qSOFA) score in obstetrics patients admitted to labour ward high care at Chris Hani Baragwanath Academic Hospital (CHBAH).

2. INTRODUCTION

According to the World Health Organization, 303 000 females died from complications of childbirth and pregnancy in 2015.[1] Sub-Saharan Africa accounts for 66% of all maternal deaths worldwide, each year.[1] Women in sub-Saharan Africa face the highest lifetime risk of maternal death in the world.[1] A 15 year-old-girl living in sub-Saharan Africa has a 1 in 36 lifetime risk of dying from complications of pregnancy or childbirth.[1] According to the UNICEF report on trends in maternal mortality, haemorrhage remains the leading cause of maternal deaths in 2015, accounting for 27%. Sepsis accounts for 11% of maternal deaths globally and these are mostly preventable.[1]

Sepsis is a leading cause of morbidity and mortality globally and in South Africa.[2] According to the 7th triennial report on confidential enquiries into maternal deaths in South Africa, there were 263 maternal deaths due to non-pregnancy-related infections in 2016. This remains the leading cause of maternal deaths in South Africa.[2] The final causes of death, in decreasing order of frequency, were respiratory failure (secondary to respiratory tract infection), then immune system failure (HIV-related, including IRIS), followed by septic shock.[2] Healthcare provider factors, that were identified as being avoidable, were mainly due to problems of late recognition

or delayed diagnosis of infection.[2] Recommendations from the confidential enquiry include that the unwell pregnant woman needs appropriate investigation, especially for respiratory tract infection and that referral pathways need to be created for patients who warrant tertiary level expertise or ICU care.[2] The recommendations from the 7th triennial report also emphasised the need for creating obstetric critical care units in tertiary and referral hospitals in South Africa.[2] Pregnancy related sepsis accounted for 71 cases of maternal deaths in South Africa in 2016.[2] A large majority of these deaths could have been prevented, as the severity of the sepsis is often not recognized by healthcare providers, especially in ill post-partum women.[2] Early recognition, adequate resuscitation and administration of broad-spectrum antibiotics with source control, are crucial to improve the outcomes of patients with sepsis.[2]

The third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defines sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection".[3] The consensus describes significant organ dysfunction as a score of 2 or more points on the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) tool.[3] A score of 2 or more is associated with an in-hospital mortality greater than 10%.[3] Application of the SOFA score requires laboratory testing and has a significant measurement burden.[3] The full SOFA score has been shown to predict mortality from sepsis equally well in obstetric, as in non-obstetric populations.[4] Singer[3] et al. 2016, suggest using the bedside q(quick) SOFA score, outside of the ICU setting, to rapidly identify patients with suspected infection who are likely to have poor outcomes. The clinical parameters include alteration in mental status (i.e. any GCS less than 15), systolic blood pressure of 100 mmHg or less and respiratory rate of 22 breaths per minute or greater.[3] Similarly to the SOFA, a score

of 2 or greater on the qSOFA should prompt additional investigation of organ dysfunction, initiation or escalation of intervention, referral to a higher level of care and more intensive monitoring.[3] The appeal of the qSOFA is that it can be applied quickly and repeatedly, although the test is less robust than the SOFA.[3] The qSOFA score may be especially useful in resource-poor settings as a screening tool, where laboratory testing may be limited. However, it is not meant to be used as a singular tool to define sepsis.[3]

A qSOFA score of 2 or more has predictive validity for in hospital mortality, however the recently published SOMANZ guidelines stress that caution should be taken when extrapolating these data to postpartum and pregnant women.[5] Bowyer[5] et al. state that the data from which the qSOFA score was derived, was retrospective and the population used to validate the data was a heterogenous group, half of whom were male, with an average age of 61. No study using the qSOFA score in maternity patients has been published yet.[4] Significant physiological changes occur in pregnancy. The lower limit of the normal range of systolic blood pressure at 15 weeks gestation extends to 92 mmHg and at 37 weeks it can be as low as 87 mmHg.[4] The upper limit of normal for respiratory rates in pregnant women range from 20 breaths per minute in the first trimester up to 22 breaths per minute in the third trimester and within the first 48 hours after delivery.[4] The qSOFA score has not been evaluated in pregnancy and the aforementioned physiological changes in pregnancy may cause false positive results.[4]

Since the introduction of qSOFA, subsequent validation studies have raised concerns of poor sensitivity.[7] None of the criteria used for the qSOFA are specific for

infection.[7] Biomarkers of infectious disease such as procalcitonin (PCT) and C-reactive protein (CRP), have been proven to accurately detect infection and predict mortality.[7] These biomarkers were included as part of the diagnostic criteria in Sepsis-2, however they were excluded in Sepsis-3 definitions as they were not found to be predictive of mortality.[7] A large study from Asia confirmed that qSOFA has high specificity but low sensitivity in predicting mortality from sepsis.[7] This study attempted to incorporate an ordinal scale of PCT into the qSOFA model and their results suggest enhanced sensitivity of combined qSOFA _PCT screening tool.[7]

Procalcitonin is a pro-hormone in the serum, released from many tissues and increases significantly in the presence of severe bacterial infection, particularly gram-negative infections.[8] The most common pathogen in blood cultures grown from patients with severe obstetric infections is gram-negative *E. Coli*.[8] A Scandinavian study concluded that although reference ranges for PCT have not yet been established in the pregnant population, it is likely to be a useful biomarker in obstetric patients.[8] PCT is more sensitive and specific than CRP for bacterial infection, concentrations of PCT increases rapidly within 2-4 hours of severe bacterial infection.[8] Leukocyte count is normally increased during pregnancy which limits its use as a biomarker for infection in the obstetric population.[8] Quantitative estimation of PCT and particularly the change in PCT values is useful to diagnose infection and guide antibiotic management.[8]

A recent systematic review and Meta-Analysis of PCT-guided antimicrobial management in critically ill patients found no difference in short-term mortality when compared to usual care.[18] However, when PCT levels were used to guide cessation

of antibiotic therapy, a decrease in mortality was found.[18] No mortality benefit was observed when using PCT-guided strategy for the initiation of antibiotics.[18]

The Society for Maternal-Foetal Medicine recently published a consult series article on sepsis, in which they emphasized again that the qSOFA does not define sepsis.[6] Instead, it should be used as a rapid method to identify high risk patients who are more prone to develop severe complications.[6] The best early warning system in obstetric patients has yet to be defined, but what is important is that the implementation of an early warning system may decrease maternal risk.[6] The Society for Maternal-Foetal Medicine recommend that sepsis be considered a medical emergency and that early aggressive therapy could improve maternal outcomes.[6]

The aim of this study is to correlate PCT levels and the qSOFA score in obstetric patients. I will study those patients admitted to labour ward high care at Chris Hani Baragwanath Academic Hospital. As mentioned before the qSOFA score has not yet been studied or validated in pregnant patients and this forms part of the motivation for this study. I aim to contribute to the existing pool of data on the qSOFA score and PCT levels in the obstetric population. The data could be used to encourage the use of an early warning score like the qSOFA to identify those patients at risk for poor outcomes. This could lead to earlier intervention or escalation of management and more frequent monitoring. The qSOFA score could be used in conjunction with PCT levels to guide management of patients with suspected sepsis.

3. STUDY OBJECTIVES

The primary aim of this study is to correlate PCT levels and the qSOFA score in obstetric patients admitted to labour ward high care at CHBAH.

4. METHODS

a. **Design**: prospective, descriptive study of 100 patients.

b. **Site of study**: CHBAH labour ward high care area.

c. **Study population:** all obstetric patients (who are at least 18 years or older) that are admitted to labour ward high care at CHBAH, between 1 June 2020 and 31 August 2020.

d. **Sampling:**

i. Sample size is limited by the number of high care admissions during the study period as well as the corporate sponsorship of 100 PCT assays.

ii. I will invite all patients (18 years and older) who are admitted to labour ward high care area, between 1 June 2020 and 31 August 2020, to participate in the study.

iii. Exclusion criteria: due to ethical concerns regarding obtaining consent from minors, all patients under the age of 18 years will be excluded from the study.

e. **Measuring tool or instrument**: I will be correlating patient's qSOFA score with their PCT levels. I will calculate the patient's qSOFA score using their standard vital signs (blood pressure, respiratory rate, and level of consciousness) upon admission to labour ward high care. PCT levels will be determined using a point of care machine supplied by Biocombiotech, which has been independently validated (see appendix 4).

f. **Data collection**:

i. This will be a prospective, descriptive study of the obstetric patients admitted to labour ward high care at CHBAH, from 1 June 2020 and 31 August 2020.

ii. I will attempt to obtain informed consent from every patient (who is at least 18 years old) admitted to labour ward high care during the study period.

iii. Once patients are admitted to labour ward high care, I will give and explain to patients a standard study participant information sheet and consent form (see appendix 1).

iv. If the patient consents to participate, I will collect standard demographic and clinical data that is routine during an admission to high care (see appendix 2).

v. I will calculate the patient's qSOFA score upon their admission to labour ward high care, using their standard recorded vital signs.

vi. The patients routinely have baseline blood tests drawn when they are admitted to high care by intern doctors. I will use some of this plasma for PCT testing, thereby limiting any additional discomfort for the patient.

vii. I will use a point of care PCT assay provided by Biocombiotech, to determine PCT levels. Since I am using a point of care machine, there will be no need to store patient's blood or any samples, as they will be analysed immediately and then discarded.

viii. Each patient will be assigned a Study ID, which will be used to record their demographic and clinical data, along with their PCT levels.

ix. A separate database will be kept linking the patients' Study ID, with their actual hospital number. Only myself and my supervisor will have access to this separate database, thereby ensuring patient anonymity throughout.

x. The information gathered on the data collection sheet will then be captured on Redcap by myself and data analysis will be done with the help of a biostatistician.

xi. Once data analysis is complete, data will be safely retained for the appropriate period and then destroyed.

g. **Pilot study**: no pilot study will be needed.

5. DATA ANALYSIS

The population will consist of all the obstetric patients (18 years and older), admitted to labour ward high care at CHBAH, from 1 June 2020 and 31 August 2020. This will be a descriptive study of 100 patients. Biocombiotech have agreed to sponsor 100 PCT assays for this research. I will use statistical tests to determine associations between PCT (continuous variable) and qSOFA score (categorical variable with more than 2 groups). I will use ANOVA or Kruskal-Wallis tests, depending on if the data are normally or not normally distributed, respectively. I will also be able to correlate PCT (continuous variable) with the qSOFA score (as it is a ranked score) with Pearson or Spearman tests for further analysis.

Objectives	Variables	Type of variable	Test
1. To determine the association between PCT levels and the qSOFA score in obstetric patients admitted to labour	qSOFA PCT	Categorical Continuous	ANOVA test

ward high care at CHBAH			

6. **ETHICS**

No ethical issues are currently anticipated. This protocol has been approved by the internal review committee from the department of Obstetrics and Gynaecology. Institutional permission to conduct the study will be sought from the CEO of CHBAH upon receipt of an ethics clearance certificate from HREC.

7. **TIMING**

The study will be a prospective analysis from 1 June 2020 and 31 August 2020.

8. **FUNDING**

The funding for the necessary equipment (approximately R44206.40) will be provided by a private company, Biocombiotech, who have provided a letter of commitment (see appendix 3). All other work will be completed by the myself. I declare no conflicts of interest; I have no financial or personal interest or affiliation to Biocombiotech.

9. **PROBLEMS**

a. The study may end prematurely if the sponsored PCT assays (100) run out before 31 August 2020.
b. If additional funding is secured OR additional sponsorship from Biocombiotech is provided for more PCT assays, the study may be prolonged after 31 August 2020.

c. For those patients with an impaired GCS on admission to high care, consent will be sought from their partner or relatives, or retrospective consent will be sought once the patient is competent to consent.

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APPENDIX 4 – Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr Michael Storm

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M191151

NAME: (Principal Investigator)	Dr Michael Storm
DEPARTMENT:	Clinical Medicine / Obstetrics and Gynaecology Chris Hani Baragwanath Academic Hospital (CHBAH)
PROJECT TITLE:	Coorelation of Procalcitonin (PCT) levels and the quick Sequential Organ Failure Assessment (qSOFA) score in obstetrics patients admitted to labor ward high care at Chris Hani Baragwanath Academic Hospital (CHBAH)
DATE CONSIDERED:	29/11/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Shastra Bhoora and Prof Guy Richards
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	22/06/2020

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

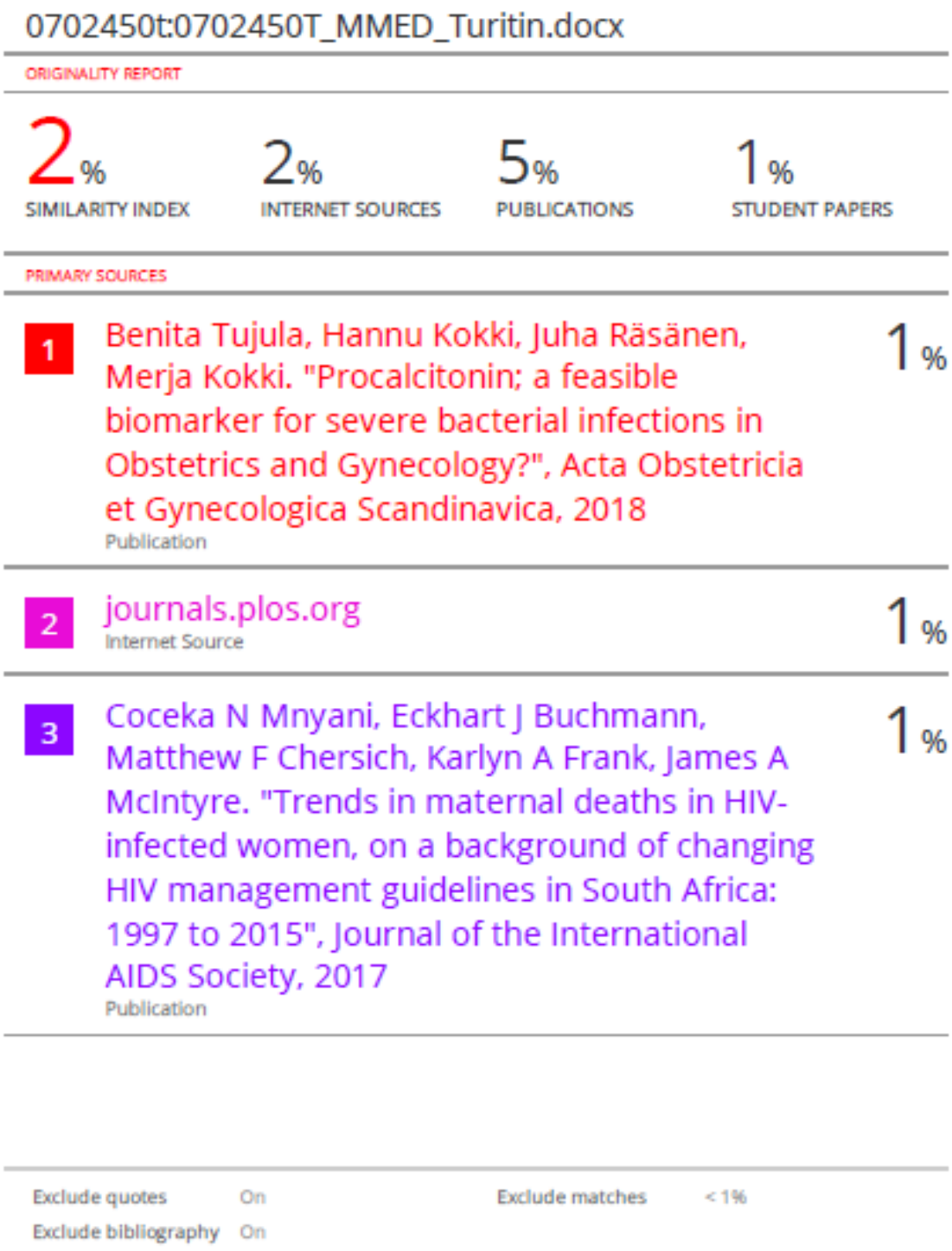
To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore be due in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

30/06/2020.
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 5 – Turnitin Plagiarism Report



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APPENDIX 6 – Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I MICHAEL SERVAAS STORM (Student number: 0302450T) am a student registered for the degree of MMED O&G in the academic year 2021 / YOS: 3

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 30/12/2021

APPENDIX 7 – Point of Care PCT rapid test validation documents

See pdf documents attached:

1. Evaluation Report between CT3 and Cobas e411 for PCT
2. Assessment of analytical performance study report for PCT Rapid Test