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Maternal Stress and Its Effects on Infant Outcomes: A Proposal for Research

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Abstract:*The burden of maternal stressamong HIV positive pregnant women in the Sub Saharan Africa region is a cause for concern. In addition, while Prevention of Mother to Child Transmission of HIV (PMTCT)programmes have reduced HIV transmission to infants, high morbidity and mortality have been documented among the growing population of HIV exposed uninfected (HEU) infants. The reasons for high infant mortality and morbidity among HEU infants has not been fully established. This research proposal is based on a study to improve our understanding onthe prevalence of maternal stress, nature of stressors, the ways adopted by the study participants to cope with stress and the association between maternal stress and infant outcomes.* A nested prospective open cohort study design will be adopted. *A systematic sample of at least 242 participants (121 HIV positive pregnant women and a control group of 121 HIV negative pregnant women) will be enrolled from polyclinics in 3 high density suburbs of Harare, Zimbabwe. At baseline, the participants will be screened for the exposure (maternal stress) using the Perceived Stress Scale. At the time of delivery, the newborn babies will be recruited to form mother – baby pairs. The pairs will be followed up for a 6 month period for various measures such as chronic maternal stress, maternal postnatal depression as well as for the major infant outcomes, namely infant morbidity, infant mortality and infant stress). The Edinburgh Postnatal Depression Scale (EPDS) will be used to measure maternal postnatal depression at 6 weeks post-delivery. Infant stress will be measured through analysis of infant saliva cortisol levels. The Research Electronic Data Capture (REDCap) software package will be used for data analysis. Descriptive statistics will be used to analyze obstetric and sociodemographic data. Calculation of incidence rates of maternal stress and adverse infant outcomes, and estimation of risks (Relative Risk and Attributable Risks) will be done. The Chi square and the t-tests will be used for analysis of variance for statistical significance of differences. Logistic regression will show the different effects of several predictors on infant morbidity, mortality and infant stress.Infant mortality will be determined through survival analysis. For all statistical tests, a p-value of ≤0.05 will be considered statistically significant.The study findings will assist in providing information for a more holistic approach in predicting adverse infant outcomes. Data from this study will also assist in formulation of strategies towards the Sustainable Development Goals (SDGs), particularly SDG 3.2.*

Key Words:*Maternal Stress, Stressors, Ways of coping, infant stress, infant morbidity, infant mortality*

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I. Introduction

Pregnancy is a stressful transition. When HIV infection compounds pregnancy, women seem to suffer additional and unrelieved psychological distress[1]. Such psychological distress occurring before, during or after pregnancy and manifesting as depression, anxiety, and/or perceived stress is referred to as maternal stress[23]. Most studies in Africa have shown maternal stress to be prevalent among HIV positive women. For Ghana 69% HIV positive versus 51% HIVnegative pregnant women were reported to be stressed. In addition, there was a statistically significant association between stress and HIV status[4]. In Uganda, emotional distress was observed to be twice as common in HIV^+ pregnant women[5]. South Africa reported that 62% of pregnant women met the criteria for antenatal depression and 30% even deteriorated to Post Traumatic Stress Disorder[6].

While there is so much evidence on maternal stress, the stressors and ways of coping with maternal stress are equally important but appear to be understudied[7]. In Zimbabwe for example there is paucity of information on maternal stress, stressors and ways of coping with stress as well as effects of maternal stress on both mother and infant outcomes. Studies elsewhere have shown that unrelieved maternal stress poses risks to both maternal and child outcomes [8,9,10]. Of note are the unexplained adverse infant outcomes among the growing

population of HEUinfants[11,12]. HEU infants have a 2.74 greater risk of hospitalization in the first year of life[13]. Worldwide, mortality for HEU infants is higher [18.7% versus 4.3% for HIV unexposed uninfected (HUU) infants][14]. Furthermore, HEU infants have higher morbidity and mortality particularly between 2 and 6 months[15,16]. Reports from South Africa confirm that HEU have increased infectious morbidity and mortality[17,15]. Mortality for HEU infants in Harare, Zimbabwe was found to be 17% as reported in an unpublished thesis by Pasi titled "Spectrum of disease and clinical outcomes of HIV exposed uninfected infants at a tertiary hospital in Harare. The reported mortality far exceeds the 50/1 000 reported in the 2015 Zimbabwe Demographic Health Survey[18]. While the reasons for this high mortality have not been fully established, there is growing evidence that HEU infants have altered immunity[12]. The causes for altered immunity are not fully understood. The present study is proposing that maternal stress could be contributor since there is evidence that stress related disruption of infant immunity begins in utero[1920].

II. Material And Methods

This study is a sub-study within a major University of Zimbabwe College of Health Sciences Birth Cohort (UZCHS-Birth Cohort). The UZ-Birth cohort is recruiting 1200 pregnant women (600 HIV positive pregnant women in the study group and 600 HIV negative pregnant women in the control group) then later follow up mother - baby pairs for an initial 24 month period. During the follow up period, the role of various possible factors associated with increased morbidity and mortality among HEU infants will be established.

Study Design: A nested prospective open cohort study design will be used

Study Location: Three urban polyclinics in the high density suburbs of Glen View, Kuwadzana and Dzivarasekwa in Harare, Zimbabwe will be the study sites.

Study Duration: February 2017 to April 2018.

Sample size: A minimum sample size of 242 participants will be recruited.

Sample size calculation:

Pocock's formula was used to determine sample size (n) required:

$$n = \frac{p_1(1-p_1) + p_2(1-p_2)\left(Z_\alpha + Z_\beta\right)^2}{(p_1 - p_2)^2}$$

Where p_1 and $p_2$are the rates of mortality in population 1 (HIV unexposed) and 2 (HIV exposed) respectively

$Z_\alpha$andZ_β are values of standard normal distribution

α = Significance level

β = Power

Assuming the rate of morbidity and mortality to be up to 5.5% [21] and 17% reported by Pasi for a tertiary hospital in Harare in 2015, among HIV unexposed and HIV exposed respectively, the minimum sample size required at 5% level of significance, 80% power and a 20% adjustment for attrition is 242 (121 HIV unexposed and 121 HIV exposed).

Subjects & selection method:

The study sample will be drawn from the population of 1 200 pregnant women enrolled into the UZCHS – Birth cohort. The list of participants in the UZCHS – Birth cohort will form the sampling frame. The sampling method will be systematic sampling, which requires calculation of the K^{th} number to use as a sampling interval.The K^{th} number will be calculated by dividing the population (600) for each group by the calculated sample size (121) for each group. The calculated K^{th} number will therefore be 5. Therefore every 5^{th}pregnant woman on the sampling frame will be approached and asked to participate in this study.

Inclusion criteria:

1. Consenting pregnant women
2. Maternal age of at least 15 years
3. Pregnancy of at least 28weeks gestation
4. All infants born to mothers enrolled into the cohort study
5. A clinically proven HIV test result
6. Fluency in either English or the local Shona language

Exclusion criteria:

1. Presence of communication barriers such as blindness, deafness and dumbness
2. Maternal disease conditions that raise cortisol levels such as diabetes mellitus and Cushing'sdisease

Variables

The main outcome variables in this study will be infant mortality, infant morbidity and infant stress while the predictor variables will include variables in the participants' obstetric history, sociodemographics, acute and chronic maternal stress, stressors and ways of coping with stress.

Table 1: The variable indicator matrix

Variable	Method of measurement	Description of measurement method	Timing for data collection	Indicator
Obstetric History	Obstetric History Data Collection form	A short form eliciting information on parity, number of pregnancies, gestational age and maternal HIV status	At enrolment	
Sociodemographics	Sociodemographic Questionnaire	A 9-item questionnaire seeking information on age of participant, marital status, age of spouse / sexual partner, religion, educational level, employment status and average monthly income	At enrolment	
Maternal Stress	Perceived Stress Scale (PSS)[22]	A widely used 10 item self - report scale measuring perceived stress in the past month.Each item on this scale is scored on a frequency scale ranging from 0-4. A total score (ranging from 0 to 40) is obtained by summing individual item scores. The higher the score, the more sever the perceived stress. A high score indicates more severe stress. Cut off scores ≥13 have been recommended for the creation of dichotomous variables for perceived stress. A score of ≥13 indicates presence of perceived stress[22].	At enrolment, 6 weeks after delivery and 6 months after delivery. Those participants continuously exhibiting high perceived stress scores at 6 months post - delivery will be classified as having chronic maternal stress	Perceived Stress Scores
	Edinburg Postnatal Depression Scale (EDPS)	A 10- item self – reported scale measuring depressive symptoms in postnatal women. The instrument has been validated in Zimbabwe and scores of ≥11 are considered to indicate presence of postnatal depression[23]	6 weeks after delivery	EPDS scores
Maternal Stressors	The Stressful Life Events Questionnaire	A 26 item questionnaire eliciting data on occurrence of 26 stressful life events 6 months before the current pregnancy (prenatal stressors) and during the course of the current pregnancy	At enrolment	Number of stated stressors
	One open ended question	The open ended question which will be asked at the end of the PSS will elicit data on the participants' opinions on what caused them to experience the thoughts and feelings indicated in the PSS.	At enrolment, 6 weeks after delivery and 6 months after delivery	Number of stated stressors
Ways of Coping with Stress	One open ended question	The open ended question follows the question on stressors at the end of the PSS and seeks information on what the participants did when they experienced the thoughts and feelings in the PSS. The stated ways of coping will be matched and categorized as active ways of coping, avoidance coping and minimizing the situation guided by Smyth and Yarandi's (1996) Ways of Coping 35-item questionnaire[24]	At enrolment, 6 weeks after delivery and 6 months after delivery	The number and nature of the stated ways of coping with stress.
Infant Morbidity	1. Questionnaire to mothers 2. Clinic Records 3. Information from the morbidity diary documented and kept by the mothers	The probability of falling ill within the first year of life	At 6 months after delivery	1. Number of clinic visits 2.Number of illnesses treated with home remedies 3.Number of hospitalizations 4.Length of hospitals stay
Infant mortality	Clinic Records	The probability of dying before first birthday	Throughout the 6 month period after delivery	Number of infants dying
Infant Stress	Elisa assays for infant saliva cortisol	Infant saliva samples will be collected at 6 months post - delivery, stored at -80^{0}C then tested in batches.	At 6 months after delivery	Infant saliva cortisol levels

Procedure

Participants (pregnant mothers) will be enrolled using the sampling criteria. The HIV positive participants will form the study group and the HIV negative participants will be the control group. In addition to collection of data on obstetric history, sociodemographics, stressors and ways of coping with stress, the exposure (maternal stress) will be measured at the time of enrolment. Participants will be categorized by exposure into "stress" and "non - stress" groups. At the time of delivery, all the infants born will automatically be enrolled into the study to form mother- baby pairs. At this stage, the HIV positive mothers, HEU and HIV exposed infected (HEI) infants will form the study group while the control / comparison group will comprise the HIV negative mothers and the HIV unexposed uninfected (HUU) infants. The follow-up period will be 6 months during which presence or absence of outcomes (infant morbidity, infant mortality and infant stress) will be ascertained.

Data collection and specimen handling for infant stress

Infant saliva for cortisol levels will be collected at the 6 month follow up period. Saliva samples will be collected in the homes of all participants so as to avoid environmental conditions that may cause escalation of anxiety and effect on cortisol concentrations. Each mother will be given written instructions and taught on how to use a simple saliva collection device [the SalivaBio Infant's Swab (SIS) by Salimetrics] for infant saliva sample collection. The first sample of saliva will be collected at 20 00 hours in the evening of the day the infant gets seen at the antenatal clinic. The second sample will be collected between 30 and 45 min after baby wakes up (after 0600 hours) the following morning. The specimens will be kept in a sealed plastic packet placed in a container with cold water, then brought to the clinic soon after collecting the morning sample. SMS messages on the phone will be used to remind participants to collect samples as well as bring the samples to the research nurse at the clinic. The specimens will be refrigerated at 4^0C at the clinic until collection for delivery (in cold boxes) to the UZ-CHS Chemical Pathology laboratory for storage at -80^0C. Analysis of cortisol levels will be done using ELISA kits

Ethical considerations

Ethical clearance will be sought from Harare City Health Department, the Joint Research Ethics Committee for The University of Zimbabwe College of Health Sciences and Parirenyatwa Group of Hospitals (JREC) as well as the Medical Research Council of Zimbabwe (MRCZ). Individual written informed consent will be obtained from each participant at the time of recruitment.

Statistical analysis

Raw data will be analyzed using the Research Electronic Data Capture (REDCap) software package. Descriptive statistics (means, frequencies and percentages) will be used for the data on obstetric history, sociodemographics, maternal stress, stressors and ways of coping with stress. Standard cut-off points will be used to assess measured stress and postnatal depression. Incidence rates of maternal stress and adverse infant outcomes (infant stress, infant morbidity and infant mortality) will be calculated and compared among the stress exposed and stress unexposed groups. Estimation of risks (Relative Risk and Attributable Risks) will be doneand calculations made from 2x2 tables. Infant mortality will be determined through survival analysis. The Chi square and the t-testswill be used for analysis of variance for statistical significance of differences. Logistic regression will be used for different effects of several predictors on infant morbidity, mortality and infant stress. For all statistical tests, a p-value of ≤ 0.05 will be considered statistically significant.

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