Protocol

Establishing Gestational Age-Specific Blood Pressure Reference Ranges in Pregnancy and for Hypertensive Disorders among Tribal Women of Andhra Pradesh, India: A Study Protocol

Running Title: Establishing Gestational Age-Specific Blood Pressure References-Protocol

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Abstract

Background: The Tribal health program (ASARA) for tribal women in rural Andhra Pradesh, India, suggests that tribal women who show signs and symptoms of hypertensive disorders have lower blood pressure levels than the standard cut-offs. *Objectives*: In this study, we aim to define the reference ranges of systolic and diastolic blood pressure (before pregnancy, during pregnancy and within 42 days after delivery) correlated with clinically confirmed and self-reported symptoms of hypertensive disorders and their association with other maternal and lifestyle factors among women (15 – 49 years) living in selected tribal blocks of district Vishakhapatnam. *Methodology*: This is a prospective observational cohort study for 18 months duration in three tribal blocks of Vishakhapatnam, Andhra Pradesh. The study has two components: (1) line-listing of all non-pregnant tribal women through a door-to-door survey in selected geographical areas. (2) identification of three hundred tribal women who become pregnant in the first six months and following them up during their entire pregnancy and 42 days after childbirth. Anthropometric (weight), blood pressure measurements and urine albumin testing will be done before pregnancy through the door-to-door survey and during defined pregnancy for selected cohort of pregnant women. *Findings*: We will triangulate maternal, lifestyle, behavioural and sociodemographic data of the pregnant cohort with their blood pressure values and the reported signs and symptoms of hypertensive disorders. *Ethics*: Piramal Swasthya Management and Research Institute ethics committee approved this study. We also took administrative approval from The Integrated Tribal Development Agency and local health administration for field activities.

Keywords: Blood pressure, hypertensive disorder, tribal, pregnancy, reproductive age, prospective

Hypertensive disorders (HTDs) are the second most common, and direct obstetric cause of maternal deaths, accounting for 14% and 14.5% of maternal deaths worldwide and in South East Asia, respectively [1]. Clinically HTDs are three types – preeclampsia, severe preeclampsia and eclampsia. Preeclampsia typically starts after the 20th week of pregnancy, manifested by increased blood pressure (BP) (systolic BP≥140 or diastolic BP≥90mmHg) and elevated urine albumin levels (urinary albumin ≥ 300 mg/24hour). The clinical spectrum of preeclampsia ranges from mild to severe, affecting all organ systems and is far more than high blood pressure or renal dysfunction. Eclampsia is the convulsive phase of the disorder that may appear before, during or after the labour among pregnant pre-eclamptic women [2]. Collectively HTDs pose a significant risk to both mothers and children.

HTDs are associated with a wide range of adverse maternal and child health outcomes. Globally, one in seven maternal deaths, and one in 3,000 deaths in South Asia result from eclampsia [3]. Literature suggests adverse perinatal health outcomes in the form of macerated late fetal deaths, fresh late foetal deaths, and early neonatal deaths among women suffering from HTDs during their pregnancy [4-6].

The incidence of HTDs in India is not uniform and varies within and across states [7]. A recent study using National Family Health Survey data suggested self-reported overall preeclampsia symptoms prevalence of 29% (30% urban; 28% rural), while another study employing clinical investigations, showed a varying prevalence of eclampsia (0.2-5.0%) and preeclampsia (8-10%) in hospital drawn sample population [7-9]. All such estimates are from studies conducted mainly among pregnant women attending antenatal care clinics in secondary or tertiary hospital settings in rural and urban areas. There are no such estimates for tribal women living in isolated and scattered geographical areas.

To address the tribal women's maternal and child health issues including HTDs, Piramal Swasthya Management and Research Institute (a national Non-governmental organization) launched “ASARA” project in the Araku valley of Andhra Pradesh in 2010. The project covers 451 tribal habitations and provides antenatal and nutrition care services to women and children through telemedicine centres and field visits. General physicians at telemedicine centres do the routine health check-up of pregnant women, and field-nursing staff (Auxiliary nursing midwife) identify and track all pregnant women in the project area. Besides, field-nursing staff also motivate pregnant women for early pregnancy registrations, counselling for institutional deliveries, specialist consultations at the telemedicine centre, and arrange for referral and transport services to link high-risk pregnancy cases to the nearest government health facility.

Specifically, ASARA’s telemedicine centres work as a referral unit for those identified with systolic BP >140 of mmHg or diastolic BP >90 of mmHg during pregnancy. However, field observations report episodes of convulsions among pregnant women having lower blood pressure values compared to existing standard guidelines on HTDs during pregnancy. The project staff, therefore, is at risk of missing HTDs cases during pregnancy because of higher clinical cut-offs during routine antenatal care. It, therefore, becomes important to study the BP (systolic and diastolic) levels during pregnancy. In particular, our study has following objectives, (i) To establish the reference ranges of systolic and diastolic

blood pressure (before pregnancy, during pregnancy and within 42 days after delivery); (ii) To establish and correlate systolic and diastolic blood pressure levels consistent with clinically confirmed and self-reported symptoms of hypertensive disorders and (iii) To determine the associated maternal, behavioural, socioeconomic, and demographic risk factors for HTDs among tribal women of reproductive age group (15–49 years).

Methodology

Study Area

Vishakhapatnam is a north-eastern coastal district in the Indian state of Andhra Pradesh. In the district, there are 3265 villages in 43 blocks organized into three-revenue divisions. The district has a total population of 4,290,589; of which nearly 53% reside in the rural areas. Fifteen per cent of the total population is comprised of scheduled tribes (STs), and 26% of STs live in rural areas. Literates form 67% of the population, however, only 48% of rural females are literate [10]. About 70% of the population depends upon agriculture either directly or indirectly [11]. Key health indicators of the district are provided below in Table 1.

Table 1: Key health indicators of the district Vishakhapatnam, Andhra Pradesh, India

Indicator	Value
Infant mortality rate [12]	40 – 45/1000 live birth
Maternal mortality ratio [12]	130 – 137/100000 live birth
High risk pregnancies identified [12]	28% (out of 77,924 registered ANC)
Institutional deliveries (rural) [13]	77%
Immunization (total) [13]	66%
*Hypertension: Women (rural) [14]	9%

*A woman is classified as hypertensive if she had SBP >140 mmHg or DBP >90 mmHg at the time of the survey or is currently taking hypertensive medication to control her BP (existing government of India guidelines)

For the current study, we will focus on three blocks under the ASARA project in the Vishakhapatnam district of Andhra Pradesh. The selected blocks are Araku (population–40381; habitations–181), Chintapelle (population–33458; habitations–135) and Paderu (population–32385; habitations–135). Habitation here refers to a congregate of people belonging to similar tribes living close to each other, also called a hamlet. For the study, we refer to each habitation as a cluster.

Study Participants

Tribal women in their reproductive age group (15–49 years). As per Census 2011 reports, 25% of the total population constitutes women in the reproductive age group [15, 16]. Inclusion Criteria: All women, aged 15–49 years, residents of Araku, Paderu and Chintapelle block covered under project areas. Women already having children, pre-existing hypertension or with history of preeclampsia in previous pregnancy also included. Exclusion Criteria: Women pregnant at the time of identifying eligible participants or have completed family or

undergone tubectomy or husband underwent vasectomy or woman refusing to be part of the study.

Study Sample

We used nMaster2.0 statistical software (https://www.cmc-biostatistics.ac.in/nmaster/) for sample size estimation. Considering the expected proportion of preeclampsia/eclampsia among tribal women 0.15, cluster size 2 (each cluster), between cluster variability 2, within-cluster variability 1, intra-class correlation 0.67, design effect 1.5, precision 5%, confidence interval 95% and target eligible population of 30000, we calculated a sample of 229 women for statistically significant results. Taking into account the nonresponse and loss to follow-up, we extended the final sample to 300. Considering cost implications and time feasibility, we decide to distribute the sample in at least one-third of the total clusters (150 clusters selecting two pregnant women in each cluster).

We will use the multi-stage cluster sampling technique to recruit our sample in the following stages. In stage I, preparing a list of all habitations in three blocks. In stage II, sampling of the clusters will be done applying probability proportional to size (PPS). With sampling interval (SI) of 708 (total population/ number of clusters required in the study) the clusters will then be selected. The first habitation will be selected randomly (random start, RS) using a random number generator. The second habitation will be selected using formula RS + (1*SI). The third habitation will be selected using formula RS + (2*SI), and so on till the 150 clusters are identified. Using PPS and random number generator, Araku block will have 58 clusters, Chintapelle 48 clusters, and Paderu 44 clusters. In the third stage, a line listing of all eligible beneficiaries (15–49 years) will be done from the selected 150 clusters using a household-level door-to-door survey.

In the last stage, we will select 300 women who become pregnant in six month period (taking two pregnant women per cluster) from all eligible women. In case, the desired number of women is not available from the selected cluster (for any reason), we will identify the eligible pregnant women from the next closest cluster.

Study Variables

Outcome Variables: The primary outcome variable is the mean blood pressure values (systolic and diastolic) among normal and hypertensive pregnant women at different stages of pregnancy and 42 days after delivery. Information on the following derived secondary outcome variables will also be collected and coded as the presence of hypertensive disorders as yes/no [17,18].

(1) Clinically diagnosed preeclampsia (two readings of systolic BP 140 mmHg or higher and/or diastolic BP 90 mmHg or higher after 20 weeks of gestation or presence of albumin on dipstick urine test) and eclampsia (convulsions or systolicBP 140 mmHg or higher or diastolic BP 90 mmHg or higher after 20 weeks of gestation or coma (unconscious) and (2) Self-reported symptoms suggestive of eclampsia and preeclampsia during 7th or 8th month of pregnancy, will include questions (yes/no/do not know) such as “During this pregnancy, did you have?–“severe headaches; difficulty with your vision during daylight; severe pain just below the ribs; swelling of the legs, body or face).

Predictor variables: Predictor variables are selected based on our previous knowledge of the factors affecting HTDs during pregnancy. These are- maternal risk factors (age, gravida, parity, birth interval, antenatal care utilization, last pregnancy outcome, delivery type – normal vs. caesarean); behavioural and lifestyle factors, current smoking status, current alcoholic status, and self-reported

history of diabetes or hypertension) and sociodemographic factors (women education, marital status, religion and economic status of family, income, occupation, exposure to various media).

Data Collection, Management and Analysis

Data Collection

Data will be collected as per the below-mentioned schedule to derive the study objectives.

Door-to-door Household Survey

Before Pregnancy: The nursing staff will visit the selected clusters for line listing activity and will identify all eligible participants for the study. An eligible woman is defined as a woman in her reproductive age group (15–49 years), not pregnant and living in the selected habitations at the time of line listing. To rule out pregnancy, we will use the World Health Organization and Centre for Disease Control and Prevention's criteria along with a urine pregnancy test (Table 2). These criteria are highly accurate (negative predictive value of 99%–100%) in ruling out pregnancy among women who are not pregnant [19, 20].

Table 2: WHO and CDC criteria: Pregnancy checklist

1. Did your last menstrual period start within the last seven days? 2. Have you had no sex since your last menstrual period started? 3. Have you been using a reliable birth control method consistently and correctly since your last menstrual period start? 4. Did you have a miscarriage or abortion in the last seven days? 5. Did you deliver in the last four weeks? 6. Did you have a baby in the last six months, fully or nearly breastfeeding now, and have you had no menstruation since then?	
If woman answer 'yes' to anyone or a few of the above six questions, and If there is no sign or symptom of pregnancy	We can safely assume she is not pregnant using the checklist
If a woman answers 'no' to all six questions Then, if required	Pregnancy cannot be ruled out using the checklist. Additional test (urine pregnancy) is required.
A urine pregnancy test will be done: to rule out the final status	

Nursing staff will collect the first record of information from all the eligible women in their pre-pregnancy stage, which are weight, mid-upper arm circumference, BP (diastolic BP and systolic BP) and urine albumin levels. We will follow all eligible women for six months from the day of their identification to check their pregnancy status. For this

activity, the nursing staff will be in touch with local government health staff of a particular cluster daily.

Data Collection from Pregnant Cohort of Tribal Women

We will follow the cohort of 300 pregnant women until delivery and 42 days after childbirth and collect data as per the following stages.

During Gestation Period: In this period, the nursing staff will administer a paper-based questionnaire to each identified pregnant woman documenting their demographic details, lifestyle and behavioural risk factors. This questionnaire section is adapted from the questionnaire used in the National Family Health Survey of India [21, 22]. Questionnaires will be in the native language of the respondent using local, commonly understood terms. We will record clinical information of all enrolled pregnant women during the pregnancy phase at, (i) 1st trimester (2nd month of pregnancy): 2nd recording of BP and weight; (ii) 2nd trimester (4th month of pregnancy): 3rd recording of BP; (iii) 2nd trimester (6th month of pregnancy): 4th recording of BP, 3rd recording of weight and 2nd recording of urine albumin and (iv) 3rd trimester (8th month of pregnancy): 5th recording of BP, 4th recording of weight and 3rd recording of urine albumin. The questionnaire on self-reported symptoms of preeclampsia will be administered between 7th to 8th months of pregnancy [17].

After Gestation Period: Participants in their post-partum period will be followed to collect information at (within 0–2 days of delivery): 6th recording of BP and 4th recording of urine albumin; (within 3–42 days of delivery): 7th recording of BP. The pregnancy outcome (live birth, full-term or preterm birth, stillbirth or abortion will also be captured. Table 3 summarizes the data collected from the pregnant cohort of women.

Table 3: Data collection schedule for the pregnant cohort of tribal women

Recordings	Weight	Blood Pressure	Urine albumin
Pre Pregnancy	√	√	√
First trimester (2nd month)	√	√	
Second trimester (4th month)		√	
Second trimester (6th month)	√	√	√
Third trimester (8th month)	√	√	√
Within 0-2 days of delivery		√	√
Within 3-42 days of delivery		√	

Measurements

All the measurements of the enrolled sample will be taken during the home visit, and the beneficiary will be comfortably seated for at least 5 minutes in her position. A calibrated weighing machine and a BP apparatus based on the oscillometric method will be used. The women will stand on weighing scale (placed on a flat surface) without any support and

barefoot. The BP measurement will be taken in the sitting position. For the study purposes, only the first recording will be taken into account. Urine albumin testing will be done using dipstick testing of spot urine samples at the doorstep. As per the guidelines, staff will collect the spot urine sample in a container and test the presence of albumin by dipping chemically treated strip in it. The dipstick changes colour if albumin is present in urine [23].

The purpose of the study will be explained to participants during the door-to-door survey and before enrolling eligible pregnant women into the study. Written consent will be taken from all participants during the door-to-door survey and audio-video consent taken from the final sample enrolled for the study.

Study Status: The door-to-door household survey is completed. Pregnant women tracking and follow-up is underway. Data collection is likely to complete in October 2020.

Data Management

Nursing staff will collect the data using paper questionnaires. They will also enter the data of all women and identified pregnant women in an excel sheet, transmitted electronically once weekly (every Friday) to Principal Investigator for review and feedback. Additionally, 10% of the entered data shall be randomly checked for data quality monitoring. Thorough data cleaning shall be performed for any missing or incomplete information before analysis. Data obtained from participants after their informed consent will be kept confidential and anonymous. Data files will be encrypted, and access will be limited to investigators.

Data Analysis

The univariate analysis will report descriptive statistics for all variables. Unpaired t-test Pearson's X2 tests will be used. P-value <0.05 will be considered for significant results.

Multiple linear regression will estimate the effect of maternal and lifestyle factors on the blood pressure levels before, during and within 42 days after delivery. Logistic regression will report the odds ratios and significant determinants of HTDs alongside different significant predictor variables. We will use STATA version SE 16 for analysis of data [24].

Discussion

Our study, one of its kind, aims to establish the reference blood pressure levels across pregnancy and in hypertensive disorders to aid clinical interpretation of the repeat antenatal monitoring among tribal women. The study will use an exhaustive door-to-door survey to enlist all eligible women (15–49 years) in the selected clusters giving everyone in a cluster an equal chance of selection into the study. Clinical investigations to confirm hypertensive disorders among pregnant women at the community level is a unique study feature. Non-disclosure of early pregnancy by tribal women poses a significant challenge. To ensure early identification of pregnant women (within the first month), we will work closely with the local government health staff.

Ethical approval

Institutional Ethics Committee of Piramal Swasthya Management and Research Institute (PSMRI) approved the study (letter no: PSMRI/2019/02).

Conflict of Interest

None declared.

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