Tamil Nadu Pregnancy and Heart Disease Registry (TNPHDR): design and methodology

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Abstract

Background: Cardiac disease in pregnancy is a major contributor to maternal mortality in high, middle and low-income countries. Availability of data on outcomes of pregnancy in women with heart disease is important for planning resources to reduce maternal mortality. Prospective data on outcomes and risk predictors of mortality in pregnant women with heart disease (PWWHD) from low- and middle-income countries are scarce.

Methods: The Tamil Nadu Pregnancy and Heart Disease Registry (TNPHDR) is a prospective, multicentric and multidisciplinary registry of PWWHD from 29 participating sites including both public and private sectors, across the state of Tamil Nadu in India. The TNPHDR is aimed to provide data on incidence of maternal and fetal outcomes, adverse outcome predictors, applicability of the modified World Health Organization (mWHO) classification of maternal cardiovascular risk and the International risk scoring systems (ZAHARA and CARPREG I & II) in Indian population and identify possible gaps in the existing management of PWWHD. Pregnancy and heart teams will be formed in all participating sites. Baseline demographic, clinical, laboratory and imaging parameters, data on counselling received, antenatal triage and management, peripartum management and postpartum care will be collected from 2500 eligible participants as part of the TNPHDR. Participants will be followed up at one, three and six-months after delivery/termination of pregnancy to document study outcomes. Predictors of maternal and foetal outcome will be identified.

Discussion: The TNPHDR will be the first representative registry from low- and middle-income countries aimed at providing crucial information on pregnancy outcomes and risk predictors in PWWHD. The results of TNPHDR could help to formulate steps for improved care and to generate a customised and practical guideline for managing pregnancy in women with heart disease in limited resource settings.

Keywords: Pregnancy, Heart disease, Maternal outcome, Mortality, Risk prediction

Background

Cardiac disease in pregnancy presents a great challenge, since it involves a complex interplay of both obstetric and cardiovascular management of the mother and the fetus.

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risk factors, delayed marriage and conception, increased awareness and early diagnosis of genetic conditions and improved survival of women with congenital heart diseases [1, 2].

Recent data show that mortality in WHOHD during pregnancy is increasing, both in high and low-income countries [3]. Cardiac disease is one of the commonest cause of maternal deaths in high-income countries such as the United Kingdom, the United States of America and the Nordic countries [4–6]. With obstetric transition taking place related to improved management of bleeding, infective and hypertensive causes of maternal death, cardiovascular disease is becoming an increasingly important non-obstetric cause of maternal death in low- and middle-income countries (LMICs) [7]. Additionally, pregnant women with heart disease (PWWHD) from LMICs often do not receive optimal pre-conceptional counselling and care [8]. Further, diagnosis of heart disease for the first time during pregnancy and lack of availability / affordability to appropriate care [9–11] contribute to adverse outcomes in pregnancy.

To continue improvement in line with millennium development goals by the World Health Organization (WHO) in reducing global maternal mortality ratio (MMR) [12], each country/state/health care region has to plan its customised steps according to its current position in the obstetric transition, the prevailing health demographics, socio-cultural environment and the available health care infrastructure [7].

India is a nation with 28 states, 8 union territories, 22 official regional languages, [13] and significant political, geographical, cultural and educational diversity, which extends to its health care indicators like MMR and infant mortality rate. Some Indian states are still in stage III of obstetric transition with a MMR as high as 215 per 100,000 live births, while few others have already moved into stage IV [7] with a MMR as low as 43/100,000 live births [14]. States with lower MMR have to shift focus to target reduction of deaths due to heart diseases and other indirect causes, which needs a different set of interventions with multidisciplinary approach [15].

The state of Tamil Nadu in India is moving ahead in the obstetric transition with its MMR dropping from 111 in 2013 to 63 in 2017 [16] to the present level of 57 per 1,00,000 live births in 2019–2020. The contribution from heart disease to maternal mortality, which doubled over the last ten years from 4.56% to 10.36%, is likely to approach that of high-income countries (15–25%) as the state of Tamil Nadu moves into stage IV of obstetric transition. Early identification of heart disease in pregnant women and ensuring appropriate management strategies may improve foetal and maternal outcomes. A recent analysis of maternal deaths from Nordic countries, which have the lowest MMR in the world, suggested that improvements in care could have made a difference in outcomes in at least 32% of maternal deaths due to heart disease [4]. Lack of multidisciplinary care, customised local guidelines, non-uniform distribution of health care facilities and poor awareness (among public, health care providers and policy makers) are the predominant reasons for higher mortality in pregnant women with heart diseases from LMICs. A significant number of maternal deaths due to heart disease could be prevented in LMICs by targeted steps to deliver improved health care. The latest guideline from European Society of Cardiology (ESC) on managing pregnant women with heart disease recognises the potential of surveys and registries in generating answers to crucial questions in management of pregnant women with heart diseases [17]. The Tamil Nadu Pregnancy and Heart Disease Registry (TNPHDR) was initiated to generate essential data for informed and data driven policy changes, introduce appropriately targeted steps for strengthening the healthcare infrastructure, improve capacity for appropriate training of the health care workers, and develop a new customised local guidelines for management of PWWHD. It may facilitate to reduce the contribution of heart diseases to maternal mortality and thus enhance the pace of the obstetric transition to stage IV in this region.

Methods/Design

The TNPHDR is aimed to (i) analyze the socio-demographic and clinical profile of various heart diseases observed during pregnancy, (ii) measure the fetal and maternal outcomes and identify predictors of those outcomes, (iii) examine the applicability of the modified World Health Organization (mWHO) classification of maternal cardiovascular risk [18, 19] (Table 1), and the appropriateness of the available risk prediction scoring systems based on data from high-income countries such as CARPREG I & II score [20, 21] and ZAHARA score [22] (Table 2) in LMICs, (iv) propose a risk scoring system unique for LMIC population, and (v) develop an evidence-based guideline for management of PWWHD in LMIC settings.

Study settings

All public and private hospitals with inhouse cardiology and obstetric services across the state of Tamil Nadu were eligible for enrollment as a participating site in the TNPHDR. The interested sites were requested to form a pregnancy and heart team with members from the departments of obstetrics, cardiology, pediatrics/neonatology and anesthesia to be responsible for the care of those participants enrolled in TNPHDR. The government of Tamil Nadu organized pregnancy and heart teams in
all the eligible 23 government medical college teaching hospitals in Tamil Nadu and ensured their participation in the registry. Additionally, six leading private hospitals in Tamil Nadu also enrolled in the registry (Additional file 1, online supplement). The spread of the selected sites across the state of Tamil Nadu is given in Fig. 1. A premier public hospital at the state capital was chosen as the nodal coordinating center of TNPHDR. The pregnancy and heart team sensitization and TNPHDR sensitization training are conducted at each of the participating sites by the nodal center. Site investigators and co-investigators are chosen from the pregnancy and heart team of the participating sites.

**Enrollment, inclusion, and exclusion criteria**

The TNPHDR is a prospective observational registry enrolling all antenatal women seeking outpatient or inpatient care in any of the participating sites with known or newly diagnosed structural heart disease, cardiac rhythm disorders or aortopathy/vascular diseases from 15th of January 2020 to 31st March 2021 or till at least 2500 eligible participants are enrolled. Antenatal patients will be enrolled at any trimester when they first enter the institution. Women with eligible heart disease seen after delivery will be included in the first six weeks postpartum. Inclusion for women with peripartum cardiomyopathy will be allowed up to six months postpartum. Collected data will be protected for privacy with all standard precautions. For example, each enrolled participant will be assigned a unique autogenerated TNPHDR identification number by which they will be identified subsequently. The unique number will remain the same despite inter-institutional transfer. Patients with pregnancy related complications like gestational hypertension, anemia, eclampsia, and gestational diabetes without structural heart disease will be excluded from the TNPHDR. Patients with trivial / mild regurgitation of the cardiac valves will be excluded, unless associated with other eligible heart diseases.

**Table 1 Modified WHO Classification of heart disease in pregnancy [17, 18]**

| mWHO I | mWHO II | mWHO II-III |
|--------|---------|-------------|
| • Small or mild (Pulmonary stenosis, patent ductus arteriosus, mitral valve prolapse) | • Unoperated atrial septal defect or ventricular septal defect | • Mild LV impairment (EF >45%) |
| • Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage) | • Repaired tetralogy of Fallot | • Hypertrophic cardiomyopathy |
| • Atrial or ventricular ectopic beats-isolated | • Most arrhythmias (supraventricular arrhythmias) | • Native or tissue valve disease not considered |
| | • Turner syndrome without aortic dilatation | WHO I or IV (mild MS, moderate AS) |
| mWHO III | mWHO IV |
| • Moderate LV impairment (EF 30–45%) | • Pulmonary arterial hypertension |
| • Previous PPCM without any residual LV impairment | • Severe systemic ventricular dysfunction (EF <30% or NYHA class III–IV) |
| • Mechanical valve | • Previous PPCM with any residual LV impairment |
| • Systemic RV with good or mildly decreased ventricular function | • Severe MS |
| • Fontan circulation- uncomplicated, stable patient | • Severe symptomatic aortic stenosis |
| • Unrepaired CHD | • Systemic RV with moderate or severely decreased ventricular function |
| • Other complex heart disease | • Severe aortic dilatation (>45 mm in Marfan syndrome or other HTAD, >50 mm in BAV, Turner syndrome ASI >25 mm/m², TOF >50 mm) |
| • Moderate MS | • Ventricular tachycardia |
| • Severe asymptomatic AS | • Pulmonary arterial hypertension |
| • Moderate aortic dilatation (40–45 mm in Marfan syndrome or other HTAD, 45–50 mm in BAV, Turner syndrome ASI 20–25 mm/m², TOF <50 mm) | • Severe systemic ventricular dysfunction (EF <30% or NYHA class III–IV) |
| • Ventricular tachycardia | • Previous PPCM with any residual LV impairment |
| | • Severe MS |

PPCM Peripartum Cardiomyopathy, LV Left Ventricle, RV Right Ventricle, EF Ejection fraction, EDS Ehlers Danlos syndrome, MS Mitral Stenosis, AS Aortic Stenosis, HTAD Heritable Thoracic Aortic Disease, ASI Aortic Size Index, CHD Cyanotic Heart Disease, BAV Bicuspid Aortic Valve
distributed to all participating sites. It will then be converted to an electronic format by using an online CRF web application platform. In addition, an Android/iOS application will be made available with facilities for both online and offline data entry. All the investigators will be provided with a username and password for restricted access to the data application. The nodal center will access, guide and support the online CRF data entry by the participating sites. The TNPHDR data will be stored in an encrypted format. The necessary backup of the database will be done every day in the evening (5 PM) to local servers at the nodal center as an added security measure. A standard operating procedure (SOP) will be formulated and circulated to all the participating centers (Additional file 3, online supplement) to enable understanding of the registry process and CRF entry.

Antenatal triage of cardiac patients
The antenatal patients with cardiac disease will be initially triaged as high-risk cardiac illness and low-risk cardiac illness during their registration based on the mWHO classification of maternal cardiovascular risk (Table 1). Patients belonging to mWHO I and II will be classified as low-risk, and patients belonging to mWHO II-III, III and IV as high-risk groups. More frequent follow up as per existing guidelines [23] will be recommended for high-risk patients including early hospitalization for safe delivery and childbirth as appropriate. However, the frequency and components of follow up will be decided as per the discretion of the participating site investigators or according to the institutional protocol of each participating sites.

Antenatal counseling and management
Antenatal mothers and their families will be counselled about their cardiac condition, its impact on maternal and fetal outcome, the importance of periodic monitoring and pharmacotherapy and the role of healthcare in supporting them through the pregnancy. Termination of pregnancy will be advised for the mWHO IV patients as applicable. However, if the patient chooses to continue the pregnancy against the medical advice, she will be under close monitoring and supervision throughout pregnancy. Details of optimisation of cardiac medications, safe delivery and childbirth in high-risk patients, anticoagulant management of patients with prosthetic valve in the first trimester, management of complications, interventional procedures like valvotomy will be documented.

Peripartum management and counseling and discharge
The intra and postpartum management will be taken care by the respective pregnancy and heart teams. Details of the mode of delivery, the type of anesthesia/analgesia, outcome, complications, and management will be documented for all the patients. Patients will undergo a detailed clinical examination and echocardiographic

### Table 2: Details of risk scores analysed in the TNPHDR (Parameters with points assigned)

| CARPREG I Score [19] | CARPREG II Score [20] | ZAHARA Score [21] |
|----------------------|-----------------------|-------------------|
| Prior cardiac events before pregnancy (HF, Stroke, TIA, or Arrhythmia) | Prior cardiac events or arrhythmia | Mechanical heart valve | 4.5 |
| Baseline NYHA > 2 or cyanosis SPO2 < 90% | Baseline NYHA III-IV or cyanosis | Left heart obstruction | 2.5 |
| Left heart obstruction (MVA < 2 cm2, AVA < 1.5 cm2, LVOT pressure gradient > 30 mm of Hg by echo) | Mechanical heart valve | Prior Cardiac arrhythmia | 1.5 |
| Reduced LV ejection fraction < 40% | Systemic LV dysfunction | Cardiac medication use before pregnancy | 1.5 |
| High risk valve disease | High Risk Valve disease | Cyanotic CHD | 1 |
| Pulmonary hypertension (RVSP > 49 mm of Hg) | NYHA ≥ 2 | 0.75 |
| High Risk Aortopathy | Systemic AV Valve Regurgitation | 0.75 |
| Coronary Artery Disease | Pulmonary AV Valve Regurgitation | 0.75 |
| No prior Cardiac Intervention | Late Pregnancy Assessment | 1 |

* LV ejection fraction < 55%; † Aortic Valve area < 1.5 cm² or subaortic gradient > 30 mm of Hg or Mitral stenosis < 2.0 cm² or moderate to severe mitral regurgitation; ‡ Pressure Gradient > 50 mm of Hg or AVA < 1 cm²

HF Heart Failure, TIA Transient Ischemic Attack, AHA Aortic valve area, LV Left ventricle, RVSP right ventricular systolic pressure, AV Atrioventricular valve, CHD Congenital Heart disease, MVA Mitral Valve Area, LVOT Left Ventricular Outflow Tract
assessment before discharge. Counselling provided will include discussions on need and timing of further follow up, cardiac medications, appropriate contraceptive methods, spacing, breast feeding etc.

**Post-partum care and follow up**

All patients enrolled in the TNPHDR will be actively followed up for a period of 6 months from the date of delivery/termination of pregnancy. During this time data will be collected at one month, three-month and six-month time points either during the clinical visits or by telephonic calls. At least one clinical follow up including an echocardiographic assessment is mandatory during follow up (Fig. 2).

**Trainings and sensitizations**

Initial sensitization cum training program about the TNPHDR and about pregnancy and heart team was conducted for all the site investigators in December 2019. In addition, periodic refresher trainings will be done at the individual sites. The site investigators are encouraged to train their team on data collection and entry in the online
Online pregnancy and heart team groups have been formed for each site, which also includes members from the central coordinating nodal team, to discuss any queries on patient management and data entry.

**Outcome measures**

Primary outcome will be a composite of maternal cardiac events. Cardiac death, resuscitated cardiac arrest, cardiac hospitalization, new or worsening heart failure requiring treatment escalation or hospitalization, new episode of arrhythmia requiring treatment, thromboembolic event, hemorrhagic complications, aortic dissection, endocarditis, acute coronary syndrome, or cardiac intervention during pregnancy and up to 1 week post-delivery will be included as maternal cardiac events. Individual components of composite primary outcome and all-cause mortality will be the secondary outcomes.

We will include both obstetric and fetal outcomes as additional secondary outcomes. Obstetric outcome measures will include gestational diabetes mellitus, gestational hypertension (at least two blood pressure readings above 140/90 measured more than 6 h apart, after 20 weeks of gestation), pre-eclampsia (gestational hypertension with >0.3 g proteinuria in the 24 h urine sample), eclampsia (pre-eclampsia with seizures) / HELLP syndrome (haemolysis, elevated liver enzymes, low platelet count), preterm labour (spontaneous onset of labour<37 weeks of gestation), premature rupture of
membranes (membrane rupture before onset of uterine contractions) and mode of delivery. Fetal loss (abortions defined as fetal death <20 weeks, intra-uterine death defined as fetal death >20 weeks and still births) will be the main fetal outcome considered in the study. We will also include a composite of fetal loss, premature birth before 37 weeks of gestation, intra-uterine growth retardation or small-for-gestational-age (birth weight <10th percentile for gestational age or less than 2.5 kg) and congenital heart disease or anomalies in the newborn as additional secondary fetal outcome.

Data management and analysis
Data uploaded in the TNPHDR server will be verified for accuracy and completeness by the nodal coordinating centre team. Regular assessment will be done to check the appropriateness and completeness of the uploaded data. As required by the International Conference on Harmonisation Good Clinical Practice guidelines (ICH-GCP), the investigator will allow direct access to all registry related medical records to allow the verification of data gathered in the eCRFs and for the review of the data collection process. The nodal center staff will conduct periodic site visits to all participating centers to verify the data by random cross-check of the source documents (10% of all data fields), as part of quality assurance. We will use appropriate summary statistics to present the descriptive data. Multivariate regression models will be employed to study predictors of maternal and fetal outcomes.

Ethical considerations
The TNPHDR follows the ethical principles in line with the current declaration of Helsinki and ‘ethical guidelines for bio-medical research on human participants’ as laid down by the Indian Council of Medical Research (ICMR). Approval for participation in the study was obtained from the Institutional Ethics Committees of the coordinating center and all the participating institutions. The TNPHDR has been registered in the Clinical Trial Registry of India (CTRi/2020/01/022736) and all relevant data will be available in http://www.ctri.nic.in. Information and consent forms will be provided to study participants in a clear, and simple local language. Written informed consent in vernacular will be obtained before enrolment into the registry. All efforts will be made to ensure confidentiality, anonymity and privacy of the information and this shall be assured to all participants and hospital administration.

Study Status
The study started enrolling patients from 15th January 2020. As of 5th November 2021, 2461 eligible patients have been enrolled in TNPHDR. Some participating sites have stopped enrolling, while the other participating sites and nodal site are continuing enrolment. Antenatal observation and active post-natal follow up are ongoing. The 6-month post-natal follow up data collection of all enrolled patients is expected to be completed by early 2023.

Discussion
There is limited data on management of PWWHD from LMICs particularly from Asia. The available studies are small, often retrospective, and limited to small geographic areas. The TNPHDR will add large scale prospective data from a LMIC settings, on pre-pregnancy counselling, fetal and maternal outcomes, and outcome predictors in PWWHD. It will give information on applicability of existing risk scoring systems based on data from high-income countries to PWWHD in LMICs.

The data from this study will be used to bring out a management guideline for PWWHD in LMICs. Identifying the gaps in the existing health care delivery, may facilitate initiation of steps for capacity building and empowerment of health care workers and institutions to ensure delivery of quality cardiac care to antenatal mothers with heart disease and formulation of a practical and applicable guideline for management of PWWHD.

Abbreviations
AHA: Acute Valve Area; AV: Atrio Ventricular valve; CHD: Congenital Heart disease; CRF: Case Report Form; HF: Heart Failure; ICH-GCP: International Conference on Harmonisation—Good Clinical Practice guidelines; ICMR: Indian Council of Medical Research; LMIC: Low- and Middle-Income Countries; LV: Left Ventricile; MMR: Maternal Mortality Ratio; PWWHD: Pregnant Women with Heart Disease; RVSP: Right Ventricular systolic pressure; SOP: Standard Operating Procedure; TIA: Transient Ischemic Attack; TNPHDR: Tamil Nadu Pregnancy and Heart Disease Registry; WHO: World Health Organization; WWHD: Women With Heart Disease; mWHO: Modified World Health Organization classification of maternal cardiovascular risk.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12884-021-04305-3.

Additional file 1: List of participating sites with investigators.
Additional file 2: Case report form booklet.
Additional file 3: Standard operating procedure.

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Authors’ contributions
GJP and SAP contributed to the concept and design of the study and drafting of the manuscript. KSH, PJ and KK contributed to the concept and design of the
study and substantial revision of the initial draft of the manuscript. SS, NJ, RS, SG, NS, VS, PP, VM, SB, GT, MP, EE, RR and VS contributed to the design of the study and substantial revision of the initial draft of the manuscript. All authors read and approved the final manuscript. All authors agree both to be personally accountable for their own contributions and to ensure questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials
Data sharing is not applicable to this article, as it is a protocol paper. Once the study is completed and after the publication of the preliminary results, the data will be made available to interesting researchers upon submission of a formal proposal to the corresponding author. The permission of the Institute Ethics Committee of Madras Medical College, Chennai will be obtained prior to the release of deidentified data.

Declarations

Ethics approval and consent to participate
The Institute Ethics Committee of Madras Medical College, Chennai-60003 approved the study on 11th July 2019 (approval number-0162019). The study protocol is also approved the Institutional Ethical Committee- Government Kilpauk Medical College (approval number—254/2019), Institutional Ethics Committee of Sri Ramachandra Institute of Higher Education & Research (SRIHER) (IEC/19/NOV/135/71), Institutional Ethical & Scientific Committee – Government Vellore Medical College, The Ethics Committee – Dhanapuri Medical College, The Ethics Committee -Madurai Medical College, Institutional Ethics Committee-Government Mohamed Kunaramangalam Medical College & hospital (approval number: GMWMCH&H/4341/IEC/2019–194), Institutional Human Ethics Committee–Coimbatore Medical College (approval number: 0298/2019), Institutional Ethical Committee-Government Theni Medical College (approval number: 97/MEBII/19), Institutional Ethics Committee-KAPV Government Medical College (IEC no: 77/2019), Institutional Ethical Committee-Kanyakumari Government Medical College (Ref No: 3624 / ME2/2019) and Institutional Research Ethics committee-Tirunelveli Medical College, (Ref No. 1588/06/G/2019). We have obtained written informed consent from all the participants before enrolment.

Consent to publish
Not Applicable.

Competing interests
The authors declare that they have no competing interests.

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