RESEARCH ARTICLE

Rheumatic heart disease in pregnancy and neonatal outcomes: A systematic review and meta-analysis

Joshua Liaw1*, Betrice Walker1☯, Leanne Hall1☯, Susan Gorton2☯, Andrew V. White2☯, Clare Heal1☯

1 College of Medicine and Dentistry, James Cook University, Mackay, Queensland, Australia, 2 College of Medicine and Dentistry, James Cook University, Townsville, Queensland, Australia

*These authors contributed equally to this work.
*Joshua.liaw@my.jcu.edu.au

Abstract

Purpose

Associations between rheumatic heart disease (RHD) in pregnancy and fetal outcomes are relatively unknown. This study aimed to review rates and predictors of major adverse fetal outcomes of RHD in pregnancy.

Methods

Medline (Ovid), Pubmed, EMcare, Scopus, CINAHL, Informit, and WHOICTRP databases were searched for studies that reported rates of adverse perinatal events in women with RHD during pregnancy. Outcomes included preterm birth, intra-uterine growth restriction (IUGR), low-birth weight (LBW), perinatal death and percutaneous balloon mitral valvuloplasty intervention. Meta-analysis of fetal events by the New-York Heart Association (NYHA) heart failure classification, and the Mitral-valve Area (MVA) severity score was performed with unadjusted random effects models and heterogeneity of risk ratios (RR) was assessed with the I² statistic. Quality of evidence was evaluated using the GRADE approach. The study was registered in PROSPERO (CRD42020161529).

Findings

The search identified 5949 non-duplicate records of which 136 full-text articles were assessed for eligibility and 22 studies included, 11 studies were eligible for meta-analyses. In 3928 pregnancies, high rates of preterm birth (9.35%-42.97%), LBW (12.98%-39.70%), IUGR (6.76%-22.40%) and perinatal death (0.00%-9.41%) were reported. NYHA III/IV pre-pregnancy was associated with higher rates of preterm birth (5 studies, RR 2.86, 95%CI 1.54–5.33), and perinatal death (6 studies, RR 3.23, 1.92–5.44). Moderate/severe mitral stenosis (MS) was associated with higher rates of preterm birth (3 studies, RR 2.05, 95%CI 1.02–4.11) and IUGR (3 studies, RR 2.46, 95%CI 1.02–5.95).
Interpretation
RHD during pregnancy is associated with adverse fetal outcomes. Maternal NYHA III/IV and moderate/severe MS in particular may predict poor prognosis.

Introduction
The global prevalence of rheumatic heart disease (RHD) is 1%, and is twice as common in women than men, particularly in women of childbearing age [1, 2]. This figure is likely underestimated in developing countries [2]. RHD accounts for approximately 30% of cardiac disease in pregnancy in developed countries, and 90% of cardiac disease in non-industrialized regions [3, 4].

Normal hemodynamic changes of pregnancy impose an additional 30–50% cardiac load. This is well tolerated by a normal heart but can result in morbidity and mortality in women with pre-existing RHD [5–7]. Mitral stenosis (MS) is especially sensitive to cardiac insufficiency in pregnancy [8, 9]. The placental-fetal heart circulation is likely affected [10], and hemodynamic insufficiency poses a risk to the developing fetus. Complications such as intra-uterine growth restriction (IUGR) and prematurity may have lasting developmental effects into childhood and beyond [11].

The New York Heart Association (NYHA) functional classification of heart failure is used worldwide, with four categories (I-IV) based on limitations during physical activity; Class I–no limit, to Class IV- symptoms at rest [12]. In addition, MS severity can be graded using echocardiography based on mitral-valve area (MVA) into mild (>1.5cm²), moderate (1.0–1.5cm²) and severe (<1.0cm²) [13]. Increasing severity of these indicators (NYHA, MVA) is associated with increased frequency of maternal cardiac complications [9]. In contrast, the association with adverse fetal and neonatal outcomes is often unreported.

The purpose of this study was to review rates of adverse fetal and neonatal outcomes for women with RHD in pregnancy and investigate the association between increasing severity of RHD using the NYHA and MVA scales with fetal outcomes. Additionally, the effects of percutaneous balloon mitral valvuloplasty (PBMV) on fetal events is reported.

Methods and analysis
This systematic review and meta-analysis is reported in accordance with the PRISMA guidelines [14], and registered with PROSPERO (CRD42020161529) [15].

Search strategy
An electronic search of Medline (Ovid), Pubmed, EMcare, Scopus, CINAHL, Informit, and WHO ICTRP was performed on 15 July 2020, limited to studies published in English language between 01 January 1990–15 July, 2020.

The complete search strategy (S1 Fig) used combined controlled vocabulary with free-text words related to population, intervention/exposure, and outcome (PICO). Studies were eligible for inclusion if they were conducted at a tertiary centre and reported associations between RHD in pregnancy and one or more pre-specified fetal outcomes. Studies with non-specific pregnancy-related cardiac disease, concordant congenital heart disease, isolated pulmonary or aortic valve involvement were excluded. Randomized controlled trials, intervention studies, cohort studies, case-control studies were eligible for inclusion. Case reports, case series, reviews, and duplicates were excluded.
Titles and abstracts were screened by the primary author (JL) on selection criteria. A second reviewer (BW) screened a sample until agreement reached >0.8 using Cronbach alpha [16]. For all selected articles, the full text were retrieved and evaluated by primary author and independent second reviewer (BW) for eligibility. In case of disagreements, a third reviewer was consulted (CH), and a decision agreed by consensus. Additional studies were identified from a manual search of references of included studies.

**Type of outcome measures**

Studies reporting one or more of the following outcomes were included: preterm birth (live delivery before 37 weeks gestation), low birth weight (LBW) (<2500 grams), small for gestational age (SGA) or intra-uterine growth restriction (IUGR) (estimated weight <10% percentile for gestational age), miscarriage (non-viable products of conception <20 weeks gestation) or perinatal death (including stillbirths (fetal demise after 20 weeks) and neonatal deaths (within the first 28 days of life)).

**Data extraction and risk of bias assessment**

Data were extracted into custom data collection forms by two independent reviewers (JL, BW). Authors were contacted for further information if required. Information extracted included: authors, setting, location, study design, study period and population characteristics (maternal age, gravida, parity, gestational age, rheumatic valvar lesions, mitral valve area severity, baseline NYHA classifications and mode of delivery).

Two authors (JL and BW) independently scored the risk of bias with a modified Quality in Prognostic Studies (QUIPS) tool [17] (S2 Fig). A risk of bias assessment was based on criteria for study participation, study attribution, prognostic factor measurement, outcome measurement, study confounding and statistical analysis. Each category was classified as low, medium, high or unknown risk of bias. Discrepancies were resolved by consensus or by a third reviewer (LH).

**Statistical analysis**

Rates of neonatal outcomes were recorded and compared based on maternal baseline NYHA status and MVA severity at the time of first antenatal visit. The effect of minimal invasive intervention (PBMV) during pregnancy on neonatal outcomes was narratively synthesised. An a-priori decision was made to perform meta-analysis if sufficient data was available. Weight of the studies in the meta-analysis was calculated based on the Mantel-Haenszel test using Revman v5.4 [18]. The random effects model was chosen to account for inter- and intra-study variability [19, 20]. Between-study heterogeneity was assessed using the I² test [21]. Risk ratios (RR) were reported with 95% confidence intervals (CI). Subgroup analysis was conducted based on country and non-PBMV/PBMV cohorts and sensitivity analysis was conducted with exclusion of outliers. Small study bias (including publication bias) was examined using funnel plots and Egger’s test [22] if 10 or more studies were available, with statistical significance set at 10%.

**Evaluating the presented evidence**

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) [23] system was used to evaluate the certainty of evidence across studies regarding clinical significance of NYHA or MVA on fetal outcomes.
Results

The initial database search identified 9719 papers. A further 4 papers were obtained from other sources. After removal of duplicates (n = 3774) and ineligible studies from title and abstract screening (n = 5813) and full text review (n = 114), 22 studies were included in the review (all cohort study designs) (Fig 1), and 11 in the meta-analysis (Table 1).

Study characteristics and risk of bias assessment

The studies, published from 1990–2020, comprising 3928 pregnancies with rheumatic heart disease were conducted across countries including India (7), Israel (2), South Africa (2), Nepal (2), Egypt (2), Canada (1), Australia (3), Brazil (1), Thailand (1). One study involved over 60 countries using the Registry of Pregnancy and Cardiac disease (ROPAC).

Three studies were assessed as high [24–26], 12 moderate [8, 27–37], and 7 low risk [7, 9, 38–42] of bias (Fig 2). Risk of bias was frequently identified in outcome measurements, which often lacked definition, citing information bias towards the null value. Other risk of bias (3 studies) [24–26] identified were study participation. One study [24] had high risk of bias in the prognostic factor measurement (NYHA) with values being recorded post-pregnancy. Most studies were at unknown risk for confounding bias. Eight studies conducted analysis of fetal outcomes by prognostic factors using univariate analyses. Only Van Hagen et al. [9] used multivariate analysis in order to adjust for confounding. As such, results from this review regarding risk index of NYHA and MVA should be interpreted in terms of absolute risk, and meta-analysis is of unadjusted rates.

Preterm birth was the most commonly reported adverse outcome for women with RHD during pregnancy (Table 2) [7–9, 24–35, 37, 38, 40–42]. Incidence ranged from 9.35%-42.97%,
Table 1. Characteristics of included studies.

| Author (year)       | Country and setting | Study design | Sample size (n) | Sample size (n) pregnancies | Population | QUIPS (Risk of bias) | Additional Comments                                                                 |
|---------------------|---------------------|--------------|-----------------|-----------------------------|------------|----------------------|-------------------------------------------------------------------------------------|
| Bhatla et al. (2003) [27] | India, New Delhi    | Retrospective | 183             | Maternal age– 25.66 +/-3.90 | Maternal age– 25.66 +/-3.90 | Moderate | Outcomes were for both RHD and congenital heart disease. Study time frame not specified. |
| Suri V, et al. (2019) [36] | India, Chandigarh   | Retrospective | 309             | NYHA III/IV –14.2%          | Previous surgery–9.4%     | Moderate | Average diagnosis of RHD at 26 weeks GA Education low– 14% illiterate, 10.6% primary school |
| Sawhney H, et al. (2002) [33] | India, Chandigarh   | Retrospective | 500             | Maternal age– 25.27 +/-3.79 | Maternal age– 25.6 +/-3.9 | Moderate | 35 pregnancies lost to follow up. Unclear definitions of perinatal death. |
| Mane SV, et al. (1993) [26] | India, Mumbai       | Retrospective | 51              | Maternal age– not reported   | Maternal age– 25 +/-3.4     | High    | LBW was defined as <2000g. No report on antenatal care, GA, co-morbidities. Unclear timing of NYHA measurement. |
| Pandey U (2014) [31] | India, Varanasi     | Retrospective | 96              | Maternal age– 79% between 21–35 years old | NYHA III/IV = 4.2%         | Moderate | Timing of NYHA measurement was not specified. Unclear definition of preterm birth. |
| Shuchi J (2013) [29] | India, Kolkata      | Retrospective | 48              | Maternal age– 25 +/-3.4      | NYHA III/IV – 25%          | Moderate | Did not report patients with previous cardiac surgery. |
| Brezinov OP, et al. (2019) [8] | Israel, Tel Hasomer | Retrospective | 31              | Maternal age– 30.97 +/-5.59  | NYHA III/IV – 9.7%         | Moderate | 35 pregnancies were lost to follow up. Did not report any comorbidities. |
| Baghel J, et al. (2020) [7] | South India, Puducherry | Retrospective | 820             | Maternal age– 25.3 +/-4.4    | NYHA III/IV – 1.2%         | Low     | 26.3% were diagnosed during pregnancy. Main outcomes were to create a predictor score for adverse maternal cardiac events in pregnancy. |
| Nqayana et al. (2008) [18] | South Africa, Durban | Retrospective | 77              | Maternal age– 21-40         | 28% patients had MS        | Low     | Definition for LBW was <2kg. |

(Continued)
| Author (year)          | Country and setting | Study design | Sample size (n) pregnancies | Population | QUIPS (Risk of bias) | Additional Comments                                                                 |
|-----------------------|---------------------|--------------|----------------------------|------------|----------------------|-------------------------------------------------------------------------------------|
| Desai DK, et al. (2000) [28] | South Africa, Durban | Prospective  | 128                       | Maternal age– 27.00 | Moderate             | 42% new diagnosis in pregnancy.                                                        |
|                       |                     |              |                            | NYHA–NA    |                      | Did not specify exact years of study.                                                |
|                       |                     |              |                            |            |                      |                                                                                      |
|                       |                     |              |                            |            |                      |                                                                                      |
| Sharma P, (2017) [34] | Nepal, Kathmandu    | Prospective  | 85                        | Maternal age– 27.34 | Moderate             | Excluded mitral valve repair/replacement, MVA >1.5cm² and patients that did not receive any antenatal care. |
|                       |                     |              |                            | NYHA III/IV– 20.0% |                      | NYHA was measured throughout pregnancy and unclear which was reported in final report. |
|                       |                     |              |                            | Previous operated– Not reported |                      |                                                                                      |
|                       |                     |              |                            | 60% primipara |                      |                                                                                      |
| Chhetri S, (2014) [25] | Nepal, Eastern Nepal | Prospective  | 45                        | Maternal age– 25 +/- 5 | High                 | <90% presented for first time at labour                                                  |
|                       |                     |              |                            | NYHA III/IV– 33.3% |                      | No inclusion or exclusion criteria, and no record on past surgery, anticoagulation or comorbidities. |
|                       |                     |              |                            |            |                      | Unclear when NYHA was assessed.                                                       |
| Van Hagen et al. (2019) [9] | ROPAC*              | Prospective  | 390 (218 with MS +/- MR)  | NYHA >1–43.6% (of 390) | Low                  | Over 60 countries are involved in this registry.                                      |
|                       |                     |              |                            |            |                      |                                                                                      |
|                       |                     |              |                            |            |                      |                                                                                      |
| Barbosa PJB et al. (2000) [24] | Brazil, Salvador   | Retrospective | 45                        | Maternal age– 28.8 +/- 4.6 | High                 | NYHA was collected on follow up post-pregnancy for 6 patients.                        |
|                       |                     |              |                            | NYHA III/IV– 86.6% |                      |                                                                                      |
|                       |                     |              |                            |            |                      | Did record of past surgery, anticoagulants or RHD specific lesions.                   |
| Sartain JB, et al. (2012) [41] | Australia, Cairns | Retrospective | 74                        | Maternal age–not stated | Low                  | Only 74/94 infant data was available (<80%). No reason for loss of follow up given.   |
|                       |                     |              |                            |            |                      |                                                                                      |
|                       |                     |              |                            |            |                      |                                                                                      |
| Ongzalima C, et al. (2019) [39] | Australia (WA)    | Retrospective | 53                        | Maternal age– 26.9 | Low                  | Aboriginal mothers were younger in age, and have a higher gravida than non-Indigenous mothers. |
|                       |                     |              |                            | RHD severity (AU) – severe– 40.7% |                      |                                                                                      |
|                       |                     |              |                            | Previous operated– 18.5% |                      |                                                                                      |
|                       |                     |              |                            |            |                      |                                                                                      |
| Sullivan EA, et al. (2019) [42] | Australia and New Zealand | Prospective | 314                       | Maternal age 27 (22–32) | Low                  | Aboriginal mothers were younger in age, more likely to smoke in pregnancy, present late to antenatal care, and be in Quintile 1 (most) of social disadvantage. |
|                       |                     |              |                            | NYHA III/IV– 2.3% |                      |                                                                                      |
| Michaelson-Cohen, et al. (2011) [30] | Israel, Jerusalem | Prospective  | 71                        | Maternal age–32 +/- 5.9 | Moderate             | Did not state patients who were on anticoagulants/past surgery.                       |
|                       |                     |              |                            | NYHA III/IV– 25.33% |                      | SGA definition was <5% predicted weight.                                              |
| Thanajira-prapraprai et al. (2009) [37] | Thailand, Bangkok | Retrospective | 133                       | Maternal age– 27.9 +/- 5.8 | Moderate | The most severe NYHA III/IV is recorded                                                |
|                       |                     |              |                            | NYHA III/IV– 15% |                      |                                                                                      |
|                       |                     |              |                            | Previous operated– 20% |                      |                                                                                      |

(Continued)
with substantial intra- and inter-country variation; Australia [39, 41, 42], (10.81%-21.01%), India (12.00% -25.12%) [7, 26, 31, 33, 36], Nepal (15.55%-22.35%) [25, 34], Egypt (9.36%-26.04%) [32, 40] and South Africa (16.88%-41.97%) [28, 38]. Meta-analysis of preterm birth in women with baseline NYHA included 5 studies (n = 936 pregnancies) [9, 30, 32, 34, 40] and showed a clear difference in this outcome between NYHA III/IV and NYHA I/II, with a RR 2.86 (95% CI 1.54–5.33, \( p < 0.001 \)). Heterogeneity was high (I\(^2\) = 64%) (Fig 3). An outlier study from Nepal, Sharma et al [34] reported a RR of 8.67 (3.86–19.45) (Fig 3) in comparison to a RR < 3 in all other studies. A post-hoc sensitivity analysis with removal of this outlier result gave an RR of 2.38 (95% CI 1.56–3.64, \( p < 0.001 \)), and reduced I\(^2\) to 12% (Fig 4).

Preterm birth in women with moderate or severe MS, meta-analysis of 3 studies (n = 329) [8, 9, 35] had a significant unadjusted RR of 2.05 (95% CI 1.02–4.11, \( p = 0.04 \)) (Fig 5).

Incidence of IUGR/SGA was 6.25% -25.00% among 13 studies (Table 2) [7–9, 27–39, 31–33, 35–37, 40]. On meta-analyses of 3 studies (n = 546) [32, 33, 40], NYHA III/IV was not significantly associated with IUGR/SGA (RR 1.53, 95% CI 0.84–2.80, \( p = 0.16 \)) (Fig 6), but moderate/severe MS was significant (3 studies, n = 421, RR 2.46, 95% CI 1.02–5.95, \( p = 0.05 \)) (Fig 7) [8, 9, 35] Subgroup analyses were not undertaken due to the limited number of studies.

Low-birth weight (LBW) rates varied between countries. High rates were seen in India (32.78–39.70%) [27, 29], Egypt (37.44%) [32], and Brazil (22.22%) [24], compared to Australia (14.97%) [42] and South Africa (12.98%) (Table 2) [38]. The ROPAC study\(^9\) reported LBW rates of 17.89% across the multiple countries included in the registry. Meta-analysis of 4 studies (n = 826) [9, 27, 32, 34] found no significant association of NYHA III/IV with LBW (RR 1.74, 95%CI 0.98–3.10, \( p = 0.06 \)) and had high heterogeneity (I\(^2\) = 85%) (Fig 8). Post-hoc sensitivity analysis excluding the outlier study [34] changed the overall significance (RR 1.40, 95% CI 1.07–1.83, \( p = 0.01 \)), and reduced statistical heterogeneity (I\(^2\) = 9%) (Fig 9).

Perinatal death was reported in most studies [7–9, 24–42]. Incidence of intrauterine death (IUD) (or stillbirth) varied (0.00%-9.41%), with the highest rates seen in Nepal (8.89%-9.41%)

| Author (year) | Country and setting | Study design | Sample size (n) pregnancies | Population | QUIPS (Risk of bias) | Additional Comments |
|---------------|---------------------|--------------|-----------------------------|------------|-------------------|---------------------|
| Rezk M, et al. (2015) [40] | Egypt, Meoufia | Prospective | 192 | Maternal age– 23–24 +/- 3,2 | Low | Excluded co-morbidities in cohort. |
| | | | | NYHA III/IV– 41.6% | Previous operated– 62.5% | |
| Pratibha D, et. al (2009) [32] | Egypt, Telangana | Retrospective | 203 | Maternal age– 95% between 20–30 years old | Moderate | No record of previous cardiac surgery. |
| | | | | NYHA III/IV– 27.6% | Previous operated– 3.4% | |
| Silverside C et al. (2003) [35] | Canada, Toronto | Prospective | 80 | Maternal age– 32 +/- 5 | Moderate | No clear definition of fetal outcomes. |
| | | | | NYHA III/IV– 0% | Severe MS– 11% | Previous operated– 34% | Univariate analysis was not conducted for other potential confounders. |

SGA/IUGR- small for gestational age/intra-uterine growth restriction; LBW-low birth weight; NYHA-New York Heart Association; MVA-mitral valve area; MS-mitral stenosis; RHD-rheumatic heart disease; NA-not applicable; GA-gestational age.

https://doi.org/10.1371/journal.pone.0253581.t001

with substantial intra- and inter-country variation; Australia [39, 41, 42], (10.81%-21.01%), India (12.00% -25.12%) [7, 26, 31, 33, 36], Nepal (15.55%-22.35%) [25, 34], Egypt (9.36%-26.04%) [32, 40] and South Africa (16.88%-41.97%) [28, 38]. Meta-analysis of preterm birth in women with baseline NYHA included 5 studies (n = 936 pregnancies) [9, 30, 32, 34, 40] and showed a clear difference in this outcome between NYHA III/IV and NYHA I/II, with a RR 2.86 (95% CI 1.54–5.33, \( p < 0.001 \)). Heterogeneity was high (I\(^2\) = 64%) (Fig 3). An outlier study from Nepal, Sharma et al [34] reported a RR of 8.67 (3.86–19.45) (Fig 3) in comparison to a RR < 3 in all other studies. A post-hoc sensitivity analysis with removal of this outlier result gave an RR of 2.38 (95% CI 1.56–3.64, \( p < 0.001 \)), and reduced I\(^2\) to 12% (Fig 4).

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Perinatal death was reported in most studies [7–9, 24–42]. Incidence of intrauterine death (IUD) (or stillbirth) varied (0.00%-9.41%), with the highest rates seen in Nepal (8.89%-9.41%)
and South Africa (6.25%-6.49%) [28–38], as did neonatal death rates (0.63%-3.10%) (Table 2) [7, 32, 34, 38–40].

Meta-analysis of the association of perinatal death and NYHA III/IV pre-pregnancy in 6 eligible studies (n = 1682) [9, 32–34, 36, 40] gave an unadjusted RR 3.23 (95% CI 1.92–5.44, \( p < 0.001 \)). Heterogeneity was low (I\(^2\) = 0%) (Fig 10). Sharma et al. [28] was a clear outlier with a neonatal mortality rate of 12.94%. Post-hoc sensitivity analysis after exclusion of this study gave an RR of 2.96 (1.74–5.02, \( p < 0.001 \)) (Fig 11).
Table 2. Incidence of fetal events (%).

| Study (Author/Year) | n   | Preterm | SGA/IUGR | LBW (<2500g) | Perinatal Death | Additional findings                                      | Comparator (NYHA, MVA, Both) or NA |
|---------------------|-----|---------|----------|--------------|-----------------|----------------------------------------------------------|----------------------------------|
| Bhatla et al. (2003) [27] | 183 | 25.12%  | 22.40%   | 32.78%       | 1.10%           | 2 congenital malformation (TOF, ASD)–none on anti-coagulants | NYHA                             |
| Suri V, et al. (2019) [36] | 309 | NA      | 25.00%   | Mean BW = 2.4 +/-0.6 | 3.14%          | 1.81% Lower GA at delivery in mild/moderate vs severe MS (P<0.005) | NYHA                             |
| Sawhney H, et al. (2002) [33] | 500 | 12.00%  | 18.20%   | NA           | 2%             | 10 maternal deaths~ 8 in NYHA III/IV, 2 in MVR replacement | NYHA                             |
| Mane SV, et al. (1993) [26] | 51  | 17.64%  | NA       | 17.64%       | NA             | SCU admission~ 13.72% (1 MAS, 6 premature)                  | NA                               |
| Pandey U (2014) [31] | 96  | 12.50%  | 8.33%    | 3.12%        | 1.22%          | NA 0 miscarriage                                          | NA                               |
| Shuchi J (2013) [29] | 48  | 25.00%  | 6.25%    | 35.40%       | 2.10%          | No difference in BW, neonatal death or preterm in those undergone PBMV vs no PBMV in pregnancy. (P>0.05) | NA                               |
| Brezinov OP, et al. (2019) [8] | 31 | 16.10%  | 19.35%   | NA           | 0%             | 1 congenital malformation                                  | MVA                             |
| Baghel J, et al. (2020) [7] | 820 | 20.6%   | 8.4%     | 39.7%        | 1.7%           | 2.1% Total adverse event rate was higher in severe MS when compared to moderate or mild MS (HR 3.15, 95%CI 1.04–9.52) and (HR 4.06, CI 1.14–11.19), P<0.05, respectively. | NA                               |
| Nqayana et al. (2008) [38] | 77  | 16.88%  | NA       | 12.98%       | 6.49%          | 1 congenital malformation–gastrochisis (neonatal death)    | NA                               |
| Desai DK, et al. (2000) [28] | 128 | 42.97%  | 16.41%   | NA           | 6.25%          | 38% had pulmonary oedema                                   | NA                               |
| Sharma P, (2017) [34] | 85  | 22.35%  | NA       | NA           | 9.41%          | 12.94% All neonatal deaths were due to premature birth complications | NYHA                             |
| Chhetri S, (2014) [25] | 45  | 15.55%  | Mean BW = 2.6 +/-0.5 | 8.80% | 15.55% Pulmonary H was in 38% of pregnancies. Emergency caesarean in 31% of deliveries. | NA                               |
| Van Hagen et al. (2019) [9] | 390 | 9.63%   | 9.63%    | 17.89%       | 1.00%          | Miscarriage~ 4.13% Multivariable–fetal adverse outcome - AF–OR 1.63 (0.20–8.90) - Severe MS–OR 3.62 (1.45–9.05) - Severe MR–OR 2.59 (0.83–8.09) Anticoagulation during pregnancy–OR 0.63 (0.15–2.62) | Both                             |
| Barbosa PJB et al. (2000) [24] | 45  | 22.22%  | NA       | 22.22%       | 2.22%          | Miscarriage~ 2.22% 35% of NYHA IV had PBMV during surgery | NA                               |
| Sartain JB, et al. (2012) [41] | 74  | 10.91%  | NA       | NA           | 0.00%          | 9.5% with RHD did not receive antenatal care during pregnancy. | NA                               |
| Ongjalima C, et al. (2019) [39] | 53  | NA      | NA       | NA           | 1.83%          | Antenatal attendance was higher in non-Indigenous population than Aboriginal mothers. P = 0.0078 | NA                               |
| Sullivan EA, et al. (2019) [42] | 314 | 21.01%  | NA       | 14.97%       | 2.22%          | Miscarriage~ 1.85% Higher NICU admission, LBW in Aboriginal mothers (vs Maori and other), p<0.05 Late diagnosis of RHD was associated with low Apgar babies p<0.05 | NA                               |
| Michaelson-Cohen, et al. (2011) [30] | 71  | 25.35%  | NA       | NA           | 0.00%          | Higher preterm deliveries in RHD (25–38%) compared to Congenital disease (13–14%, P = 0.062) | NYHA                             |

(Continued)
Intervention with percutaneous balloon mitral valvuloplasty (PBMV) during pregnancy compared to no intervention was reported in 3 studies [29, 32, 36]. Suri et al. reported lower birth GA [36], and higher perinatal deaths in those with NYHA III/IV who did not undergo PBMV vs those who did; (GA 37.15+/-1.06 vs 43.8+/-3.61, p = 0.002), and (0% perinatal death vs 19.4%, p = 0.08) respectively [36]. Lower preterm births in women who underwent PBMV during pregnancy was also seen in another study [29] but did not reach statistical significance. No meta-analysis was conducted for this outcome.

Incidence of miscarriage in pregnancy with RHD was investigated in 5 studies [7, 24, 28, 31, 42]. Rates varied between 1.85%–4.70% [28]. One study found 4 out of the 6 miscarriages in their cohort were attributed to critical MS <1.0cm² [28]. No studies had a comparator group for meta-analysis. Congenital malformations were rarely reported [27, 29, 38].

High Neonatal Intensive Care Unit (NICU) admission rates (13.70–42.25%) were reported in 3 studies [7, 26, 32]. One study found significantly higher NICU admissions associated with NYHA III/IV pre-pregnancy in women with RHD vs NYHA I/II (42.50% vs 14.20%, P <0.001) [40].

RHD was first diagnosed during pregnancy in 66.5% of patients in one study [32]. High rates were also seen in Australia (14.2%) [42], South Africa (42%) [28] and 24.9% in the ROPAC study [9]. Limited antenatal care in multiple studies [25, 34, 39, 42] was associated with poor fetal outcomes and late optimisation of anticoagulants during pregnancy in select women.

Table 2. (Continued)

| Study (author/Year) | n | Preterm | SGA/IUGR | LBW (<2500g) | Perinatal Death | Additional findings | Comparator (NYHA, MVA, Both) or NA |
|---------------------|---|---------|----------|--------------|-----------------|-------------------|----------------------------------|
| Thanajira-praprapa et al. (2009) [37] | 133 | 11.28% | 6.76% | 9.77% | 0.01% | 1 reported birth asphyxia | NA |
| Rezk M, et al. (2015) [40] | 192 | 26.04% | 19.79% | NA | 2.60% | 3.12% | Higher NICU admission in NYHA III/IV (47.5%) vs NYHA I/II (25.8%), P<0.001 | NYHA |
| Pratibha D, et al. (2009 [32] | 203 | 9.36% | 9.36% | 37.44% | 4.90% | 1.00% | 27.09% admitted to NICU | NYHA |
| Silverside C et al. (2003 [35] | 80 | 21.25% | 7.50% | NA | 2.50% | | MVA |

SGA/IUGR= small for gestational age/intra-uterine growth restriction; LBW=low birth weight; IUD=intrauterine death; NYHA=New York Heart Association; MVA-mitral valve area; TOF-tetralogy of fallot; GA-gestational age; SCU-special care nursery; MV-mitral valve; MR-mitral regurgitation; NICU-neonatal intensive care unit; BW-birth weight, MS-mitral stenosis; RHD = rheumatic heart disease; NA—not applicable; PBMV-percutaneous balloon mitral valvuloplasty.

https://doi.org/10.1371/journal.pone.0253581.t002

Fig 3. Comparison of New York health assessment I/II and New York health assessment III/IV scores for preterm births in women with baseline New York health assessment scores.

https://doi.org/10.1371/journal.pone.0253581.g003
One study [9] conducted adjusted analysis and found severe MS was independently associated with adverse fetal outcomes (OR 3.62, 95% CI 1.45–9.05), when adjusted for atrial fibrillation, severe mitral regurgitation, and anticoagulation during pregnancy. Pre-pregnancy NYHA > 1 did not show univariate significance with adverse fetal outcomes (OR 1.10, 95% CI 0.59–2.02, p = 0.10), but was an independent predictor of maternal cardiac events in women with MS [9].

Funnel plot and Eggers test was not conducted as less than 10 studies were included per meta-analysis. The GRADE system rated the overall certainty of evidence as low for MVA and NYHA as markers for preterm, and very low for NYHA as markers of SGA/IUGR, LBW and perinatal death (Table 3). There was also low certainty for MVA and SGA/IUGR.

Discussion

Evidence from the 22 included studies suggest RHD in pregnancy is associated with high rates of adverse fetal outcomes (preterm birth, LBW, SGA, IUGR, miscarriage and perinatal death). Additional outcomes found high rates of NICU admissions [26, 32, 40] low rates of antenatal care and late diagnosis of RHD in many women.

On meta-analysis, both severe MS and NYHA III/IV were significantly associated with preterm birth. Additionally, NYHA III/IV were also associated with higher rates of perinatal death. A Nepalese study [34] appeared to be an outlier in reporting consistently higher rates of fetal adverse outcomes in their patient cohort. Post-hoc sensitivity analyses excluding this study lowered statistical heterogeneity and reduced the RR. This could indicate that this site in Nepal may have wider health care inequities (low health resources, health access, co-morbidities) compared to other developing countries (India, Egypt etc.).

The association between rheumatic MS during pregnancy and adverse fetal outcomes is biologically plausible. Early pregnancy is associated with a 30–40% increase in cardiac preload [43], decreased systematic vascular resistance and systolic blood pressure. These changes are
poorly tolerated in MS and restricted left ventricular inflow with increasing atrial pulmonary pressures often precipitates cardiac decompensation and pulmonary edema [10]. Adverse fetal outcomes are likely due to uteroplacental insufficiency secondary to left heart obstruction [10]. Poor oxygen and nutrient transfer may lead to stunted fetal growth.

Mitral stenosis carries a high risk of chronic fetal hypoxia and early onset (<32 weeks) IUGR in pregnancy. These fetuses are more likely born preterm, and are high risk of rapid deterioration, fetal demise in-utero and stillbirth [44]. There are also recognised links of IUGR with cardio-vascular remodelling, sub-optimal renal and neurological development, and altered glucose metabolism; collectively known as the fetal origin hypothesis [45]. Such outcomes are currently unexplored in neonates born to mothers with RHD.

The prognostic value of NYHA classification for neonatal outcomes is likely a reflection of the severity of the pressure gradient across the mitral valve and underlying pulmonary edema. As such, it is well established in predicting maternal cardiac events, but less so for adverse fetal events. This review found NYHA class III/IV had significant associations with prematurity and perinatal death, but not LBW or IUGR/SGA. Conversely, mitral valve area (MVA) determined by echocardiogram could more directly indicate cardiac output and uteroplacental perfusion as moderate/severe MS was significantly associated with both SGA/IUGR and prematurity.

RHD remains the predominant form of maternal heart disease in pregnancy in developing nations [3, 4]. In this study, developing countries [46] (India, Nepal, Egypt, South Africa) exhibited relatively higher rates of adverse neonatal outcomes compared to developed countries (Australia, New Zealand). Shortage of health services and delayed access to tertiary centres may be more evident in these developing nations, with further limited capacity of hospitals in surgical intervention [29] and neonatal intensive care [34].

Poorer education among women with RHD was reported in one study in Chandigarh, India [36]; 14% illiterate and 10.6% only receiving a primary school education. Downstream
health behaviours associated with low education status, such as younger maternal age and multiparity are also predictors for adverse perinatal events [47].

Within-country variations in birth outcomes were observed in western developed nations. One study found higher rates of preterm and perinatal death in Aboriginal Australians or Torres Strait Islanders, and Maori or Pasifika mothers compared to non-Indigenous counterparts [42]. Indigenous mothers with RHD were significantly younger, [39, 42] more likely to present >20 weeks to antenatal clinic, be socioeconomically disadvantaged, and smoke during pregnancy compared to non-Indigenous mothers [42]. While the disparity in fetal outcomes is likely a combination of these bio-psychosocial factors, there is evidence of an independent association of RHD in pregnancy. For example, in Australia, one study [42] reported an overall preterm birth rate of 21%; much higher than the overall rate of Australia (9%) and of babies born to Indigenous mothers (14%) [48]. As such, closing the gap between health inequities among disadvantaged populations is a priority in the improvement of global neonatal health, and eradication of RHD among women of child-bearing age.

Antenatal care remains a critical component of neonatal outcomes in RHD patients [49]. Sub-optimal antenatal visits were common among studies with relatively higher adverse fetal events. In one study [25] over 90% of women presented for first time in labour and reported a high IUD rate (6.25%). In Durban South Africa [38] 62% had first cardiac evaluation in 3rd trimester and had 42.97% prematurity deliveries. Greater emphasis on pregnancy planning, particularly after an index pregnancy would be beneficial.

Pregnancy planning and early initial antenatal consultation is also important for women with a surgical valve replacement and on lifelong anticoagulants such as warfarin. Delayed initial antenatal visits and low uptake of contraceptives [50] were reported among this sub-group of women in several studies [34, 38]. This is concerning as warfarin is teratogenic and has strong associations with fetal malformation, abortion and stillbirth. Early optimisation with heparin or low-molecular weight heparin should be a priority in these patients [51].

![Fig 8. Comparison of New York health assessment I/II and New York health assessment III/IV for low birth weight outcome.](https://doi.org/10.1371/journal.pone.0253581.g008)

![Fig 9. Sensitivity analyses—comparison of New York health assessment I/II and New York health assessment III/IV for low birth weight outcome.](https://doi.org/10.1371/journal.pone.0253581.g009)
PBMV remains the treatment of choice for isolated non-calcified MS and is safe to perform during pregnancy, with few adverse maternal or fetal events [52–54]. This systematic review suggests PBMV in women with severe symptoms (NYHA III/IV) is associated with reduced rates of preterm births; however, further comparative studies are required. No long-term effects on child development have been reported to date [52, 55, 56].

Mitral valve surgery involving cardiac bypass was not assessed in this review as such interventions are avoided where possible during pregnancy due to the significantly high associated fetal mortality (ranging from 5–33%) [54, 57].

**Limitations**

Neonatal outcomes are influenced by a complex interplay of known and unknown factors. RHD is associated with socio-economically disadvantage, and many important potentially confounding variables such as smoking, poor antenatal care, chronic disease [58] and extent of RHD-related antenatal services in hospitals of different countries, which were not measured in the included studies. Insufficient reporting on outcomes of women on warfarin during pregnancy also limited analysis of a clinically important sub-group.

Only studies based at tertiary hospitals were included, and it is likely that lower-resourced and rural areas experience even poorer pregnancy outcomes that are underreported.

There is some methodological limitation in this research. First, most studies in this review had moderate risk of bias in multiple domains. In particular, outcome definitions were not clearly explained, and influence of confounders was also uncertain. Second, there is a possibility of publication bias among studies with small samples, particularly in outcomes around perinatal death. Overestimation of the true effect size may have resulted from smaller studies with
non-significant findings not being published. Third, there was clinical and statistical heterogeneity between studies. The overall certainty of the evidence generated from meta-analysis was low or very low (Table 3), although the GRADE system allows a maximum of low-quality evidence for meta-analysis of cohort studies [59].

These findings are important from a national, international, public health policy perspective, highlighting increased perinatal morbidity and mortality in infants born to women with RHD. As our results indicate that moderate or severe MS, symptomatic NYHA, have worse outcomes, we recommend early specialist involvement in these cases. While no definitive management for IUGR exists besides delivery, neonatal USS Doppler could be useful for early identification. PBMV in pregnancy is an effective, low risk procedure for symptom relief in MS during pregnancy but requires further research. Finally, our findings add support to large scale echocardiographic screening of RHD in pregnancy in high-risk populations.

Large, well-designed prospective studies of pregnancy in women with RHD are required. Associations with NYHA and MVA severity on neonatal outcomes need to be calculated based on adjusted rates. One study [9] in this systematic review demonstrated robust methodology that could be modelled in future studies.

Supporting information

S1 Checklist. PRISMA 2009 checklist. (DOC)

S1 Fig. Literature search strategy. (DOCX)

S2 Fig. Risk of bias assessment tool: Modified (QUIPS) template. (DOCX)
Acknowledgments
The authors thank Mr Stephen Anderson, Senior Librarian at the James Cook University, Townsville, for his contribution in the development of the search strategy.

Author Contributions
Conceptualization: Joshua Liaw, Leanne Hall, Clare Heal.
Data curation: Joshua Liaw.
Formal analysis: Joshua Liaw, Betrice Walker, Clare Heal.
Funding acquisition: Clare Heal.
Investigation: Joshua Liaw, Betrice Walker, Andrew V. White, Clare Heal.
Methodology: Joshua Liaw, Betrice Walker, Leanne Hall, Susan Gorton, Andrew V. White, Clare Heal.
Project administration: Joshua Liaw, Leanne Hall, Susan Gorton, Andrew V. White, Clare Heal.
Resources: Joshua Liaw, Leanne Hall, Susan Gorton, Andrew V. White, Clare Heal.
Software: Leanne Hall.
Supervision: Leanne Hall, Susan Gorton, Andrew V. White, Clare Heal.
Validation: Joshua Liaw, Betrice Walker, Leanne Hall.
Visualization: Joshua Liaw, Clare Heal.
Writing – original draft: Joshua Liaw.
Writing – review & editing: Joshua Liaw, Leanne Hall, Susan Gorton, Andrew V. White, Clare Heal.

References
1. Watkins DA, Johnson CO, Colquhoun SM, et al. Global, Regional, and National Burden of Rheumatic Heart Disease, 1990–2015. N Engl J Med. 2017; 377(8):713–722. https://doi.org/10.1056/NEJMoA1603693 PMID: 28834488.
2. Zühlke LJ, Steer AC. Estimates of the Global Burden of Rheumatic Heart Disease. Glob Heart. 2013; 8(3):189–195. https://doi.org/10.1016/j.ghart.2013.08.008 PMID: 25690495.
3. Siu SC, Sermer M, Colman JM, et al. Prospective Multicenter Study of Pregnancy Outcomes in Women With Heart Disease. Circulation. 2001; 104(5):515–521. https://doi.org/10.1161/01.cir.130.12.1003–1008 PMID: 11479246.
4. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis. 2005; 5(11):685–694. https://doi.org/10.1016/S1473-3099(05)70267-X PMID: 16253886.
5. Sanghavi M, Rutherford JD. Cardiovascular Physiology of Pregnancy. Circulation. 2014; 130(12):1003–1008. https://doi.org/10.1161/CIRCULATIONAHA.114.009029 PMID: 25223771.
6. Hameed A, Karapal IS, Tummala PP, et al. The effect of valvular heart disease on maternal and fetal outcome of pregnancy. J Am Coll Cardiol. 2001; 37(3):899–909. https://doi.org/10.1016/s0735-1097(00)01198-6 PMID: 11983767.
7. Baghel J, Keepanasseril A, Pillai AA, Mondal N, Jeganathan Y, Kundra P. Prediction of adverse cardiac events in pregnant women with valvular rheumatic heart disease. Heart. 2020. https://doi.org/10.1136/heartjnl-2020-316648 PMID: 32601124.
8. Perelstein Brezinov O, Simchen MJ, Ben Zekry S, Kuperstein R. Maternal and Neonatal Complications of Pregnant Women with Mitral Stenosis. Isr Med Assoc J. 2019; 21(2):88–93. PMID: 30772958.
9. van Hagen IM, Thorne SA, Taha N, et al. Pregnancy Outcomes in Women With Rheumatic Mitral Valve Disease: Results From the Registry of Pregnancy and Cardiac Disease. Circulation. 2019; 137(8):806–816. https://doi.org/10.1161/CIRCULATIONAHA.117.032561 PMID: 29459466.
10. Tsiraras S, Poppas A. Mitral valve disease in pregnancy: outcomes and management. Obstet Med. 2009; 2(1):6–10. https://doi.org/10.1258/om.2008.080002 PMID: 27582798.
11. Hartkopf J, Schlieger F, Keune J, et al. Impact of Intrauterine Growth Restriction on Cognitive and Motor Development at 2 Years of Age. Front Physiol. 2018; 9:1278–1278. https://doi.org/10.3389/fphys.2018.01278 PMID: 30283344.
12. Dolgin M. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. JAMA. 1940; 114(2):2054. https://doi.org/10.1001/jama.1940.02810200082036
13. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic Assessment of Valve Stenosis: EAE/ASE Recommendations for Clinical Practice. J Am Soc Echocardiogr. 2009; 22(1):1–23. https://doi.org/10.1016/j.echo.2008.11.029 PMID: 19130998.
14. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Medicine. 2009; 6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097 PMID: 23020236.
15. Liaw J, Gorton S, White A, Heal C. Pregnancy outcomes in patients with rheumatic mitral valve disease: A systematic review and meta-analysis: National Institute for health research. PROSPERO. 2020; CRD42020161529.
16. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017; 358:j4008. https://doi.org/10.1136/bmj.j4008 PMID: 28935701.
17. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing Bias in Studies of Prognostic Factors. Ann Intern Med. 2013; 158(4):280–286. https://doi.org/10.7326/0003-4819-158-4-201302190-00009 PMID: 23420236.
18. The Cochrane Collaboration. Review Manager Web. Version 1.22 [software]. 2020 [Cited 2020 Sep 08]. Available from https://revman.cochrane.org/#/myReviews.
19. Mueller M, D’Addario M, Egger M, et al. Methods to systematically review and meta-analysis observational studies: a systematic scoping review of recommendations. BMC Med Res Methodol. 2018; 18(1):44. https://doi.org/10.1186/s12874-018-0495-9 PMID: 29783954.
20. Metelli S, Chairani M. Challenges in meta-analyses with observational studies. Evid Base Ment Health. 2020; 23(2):83. https://doi.org/10.1136/ebmental-2019-300129 PMID: 32139442.
21. Higgins JPT, et al. Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. Chichester (UK): John Wiley & Sons; 2019.
22. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315(7109):629. https://doi.org/10.1136/bmj.315.7109.629 PMID: 9310563.
23. Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. BMJ. 2015; 350:h870. https://doi.org/10.1136/bmj.h870 PMID: 25775931.
24. Barbosa PJ,B, Lopes AA, Feitosa GS, et al. Prognostic factors of rheumatic mitral stenosis during pregnancy and puerperium. Arq Bras Cardiol. 2000; 75(3):215–224. https://doi.org/10.1590/s0066-782x2000000900003 PMID: 11018807.
25. Chhetri S, Shrestha NR, Pilgrim T. Pregnancy complicated by heart disease in Nepal. Heart Asia. 2014; 6(1):26–29. https://doi.org/10.1136/heartasia-2013-010396 PMID: 27326158.
26. Mane SV, Gharpure VP, Merchant RH. Maternal heart disease and perinatal outcome. Indian pediatr. 1993; 30(12):1407–1411. PMID: 8077029.
27. Bhatia N, Lal S, Behera G, et al. Cardiac disease in pregnancy. Int J Gynaecol Obstet. 2003; 82(2):153–159. https://doi.org/10.1016/s0020-7292(03)00159-0 PMID: 12873775.
28. Desai DK, Adanlawo M, Naidoo DP, Moodley J, Kleinschmidt I. Mitral stenosis in pregnancy: a four-year experience at King Edward VIII Hospital, Durban, South Africa. BJOG. 2000; 107(8):953–958. https://doi.org/10.1111/j.1471-0528.2000.tb01039.x PMID: 10955424.
29. Jain S, Maiti TK, Jain M. Fetomaternal outcome among women with mitral stenosis after balloon mitral valvotomy. Int J Gynaecol Obstet. 2013; 121(2):119–122. https://doi.org/10.1016/j.ijgo.2012.11.017 PMID: 23465852.
30. Michaelson-Cohen R, Elstein D, Iscovitch A, et al. Severe heart disease complicating pregnancy does not preclude a favourable pregnancy outcome: 15 years’ experience in a single centre. J Obstet Gynaecol. 2011; 31(7):597–602. https://doi.org/10.3109/01443615.2011.603064 PMID: 21973131.
31. Pandey U. To study the maternal and neonatal outcomes of pregnancies complicated by rheumatic heart disease. Int J Infertility and Fetal Medicine. 2014; 5(3):92–94. https://doi.org/10.5005/jp-journals-10016-1088

32. Pratibha D, Kiranmai D, Rani VU, Vani NG. Pregnancy outcome in chronic rheumatic heart disease. J Obstet Gynaecol India [Internet]. 2009 [cited 2020 June 12]; 59(1):41–46. Available from: https://jogii.co.in/jan_feb_2009/05_0a_pregnancy_outcome.pdf.

33. Sawhney H, Aggarwal N, Suri V, Vasishtha K, Sharma Y, Grover A. Maternal and perinatal outcome in rheumatic heart disease. Int J Gynaecol Obstet. 2003; 80(1):9–14. https://doi.org/10.1016/s0020-7292(02)00029-2 PMID: 12527454.

34. Sharma P. Obstetric outcome in patients with rheumatic heart disease: Experience of a tertiary hospital. Nepalese Heart Journal. 2017; 14(2):31–34. PMID: 619130700.

35. Silversides CK, Colman JM, Sermer M, et al. Cardiac risk in pregnant women with rheumatic mitral stenosis. Am J Cardiol. 2003; 91(11):1382–1385. https://doi.org/10.1016/s0002-9149(03)00339-4 PMID: 12767443.

36. Suri V, Sikka P, Singla R, Aggarwal N, Chopra S, Vijayvergiya R. Factors affecting the outcome of pregnancy with rheumatic heart disease: an experience from low-middle income country. J Obstet Gynaecol India, 2019; 39(6):1087–1092. https://doi.org/10.1080/01434615.2019.1587595 PMID: 31195863.

37. Thanajiraprapa T, Phupong V. Pregnancy complications in women with heart disease. J Matern Fetal Neonatal Med. 2010; 23(10):1200–1204. https://doi.org/10.3109/14767050903410698 PMID: 19903109.

38. Nqayana T, Moodley J, Naidoo DP. Cardiac disease in pregnancy. Cardiovasc J Afr. 2008; 19(3):145–151. PMID: 18568175.

39. Ongzalim CO, Greenland M, Vaughan G, et al. Rheumatic heart disease in pregnancy: Profile of women admitted to a Western Australian tertiary obstetric hospital. Aust N Z J Obstet Gynaecol. 2020. https://doi.org/10.1111/ajo.13102 PMID: 31782139.

40. Rezk M, Gamal A. Maternal and fetal outcome in women with rheumatic heart disease: a 3-year observational study. Arch Gynaecol Obstet. 2016; 294(2):273–278. https://doi.org/10.1007/s00404-015-3990-9 PMID: 26700422.

41. Baschat AA. Planning management and delivery of the growth-restricted fetus. Best Pract Res Clin Obstet Gynaecol. 2018; 49:53–65. https://doi.org/10.1016/j.bpbobgyn.2018.02.009 PMID: 29606482.

42. Development Policy and Analysis Division of the Department of Economic and Social Affairs of the United Nations Secretariat. World Economic Statistical Annex [Internet]. New York: United Nations; 2018 [cited 2020 Sep 08]. Available from https://www.un.org/development/desa/dpd/wp-content/uploads/sites/45/WESP2020_Annex.pdf.

43. Malhotra A, Allison BJ, Castillo-Melendez M, Jenkin G, Polglase GR, Miller SL. Neonatal Morbidities of Fetal Growth Restriction: Pathophysiology and Impact. Front Endocrinol (Lausanne). 2019; 10:55–55. https://doi.org/10.3389/fendo.2019.00055 PMID: 30792696.

44. Teckelab T, Chojenta C, Smith R, Loxton D. The impact of antenatal care on neonatal mortality in sub-Saharan Africa: A systematic review and meta-analysis. PloS one. 2019; 14(9):e0222566–e0222566. https://doi.org/10.1371/journal.pone.0222566 PMID: 31518365.

45. Chang AY, Nabbaale J, Nalubwama H, et al. Motivations of women in Uganda living with rheumatic heart disease: A mixed methods study of experiences in stigma, childbearing, anticoagulation, and contraception. PloS One. 2018; 13(3):e0194030. https://doi.org/10.1371/journal.pone.0194030 PMID: 29590159.

46. Newmire RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. Circulation. 2014; 129(23):e521–e643. https://doi.org/10.1161/CIR.000000000000031 PMID: 24589853.
52. Vinayakumar D, Vinod GV, Madhavan S, Krishnan MN. Maternal and fetal outcomes in pregnant women undergoing balloon mitral valvotomy for rheumatic mitral stenosis. Indian Heart J. 2016; 68(6):780–782. https://doi.org/10.1016/j.ihj.2016.04.017 PMID: 27931546.

53. Ananthakrishna Pillai A, Ramasamy C, V SG, Kottyath H. Outcomes following balloon mitral valvuloplasty in pregnant females with mitral stenosis and significant sub valve disease with severe decompensated heart failure. J Interv Cardiol. 2018; 31(4):525–531. https://doi.org/10.1111/joic.12507 PMID: 29527717.

54. de Souza JAM, Martinez EE, Ambrose JA, et al. Percutaneous balloon mitral valvuloplasty in comparison with open mitral valve commissurotomy for mitral stenosis during pregnancy. J Am Coll Cardiol. 2001; 37(3):900. https://doi.org/10.1016/s0735-1097(00)01184-0 PMID: 11693768.

55. Esteves CA, Munoz JS, Braga S, et al. Immediate and long-term follow-up of percutaneous balloon mitral valvuloplasty in pregnant patients with rheumatic mitral stenosis. Am J Cardiol. 2006; 98(6):812–816. https://doi.org/10.1016/j.amjcard.2006.03.068 PMID: 16950192.

56. Routray SN, Mishra TK, Swain S, Patnaik UK, Behera M. Balloon mitral valvuloplasty during pregnancy. Int J Gynaecol Obstet. 2004; 85(1):18–23. https://doi.org/10.1016/j.ijgo.2003.09.005 PMID: 15050462.

57. Elkayam U, Bitar F. Valvular Heart Disease and Pregnancy: Part I: Native Valves. J Am Coll Cardiol. 2005; 46(2):223–230. https://doi.org/10.1016/j.jacc.2005.02.085 PMID: 16022946.

58. Carapetis JR, Beaton A, Cunningham MW, et al. Acute rheumatic fever and rheumatic heart disease. Nat Rev Dis Primers. 2016; 2:15084–15084. https://doi.org/10.1038/nrdp.2015.84 PMID: 27188830.

59. Cochrane Effective Practice and Organisation of Care. EPOC worksheets for preparing a Summary of Findings (SoF) table using GRADE [Internet]. London: EPOC Resources for review authors; 2017 [cited 2020 Sept 20]. Available from: epoc.cochrane.org/resources/epoc-resources-review-authors.