Review article

Cardiovascular adverse events in pregnancy: A global perspective

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ABSTRACT

Pregnant women with heart disease are vulnerable to many adverse cardiovascular events (AE). AEs during and after pregnancy continue to be important causes of maternal mortality and morbidity worldwide, with huge variations in burden in different countries and regions. These AEs are classified as having direct or indirect causes, depending on whether they are directly caused by pregnancy or due to some pre-existing disease and/or non-obstetric cause, respectively.

The risks continue throughout pregnancy and even after childbirth. Apart from immediate complications during pregnancy, there is increasing evidence of a significant link between several events and the risk of cardiovascular disease (CVD) later in life.

A significant number of pregnancy-related deaths caused by cardiovascular disease are preventable. This prevention can be realized through increasing awareness of cardiovascular AE in pregnancy, coupled with the application of strategies for prevention and treatment. Knowledge of the risks associated with CVD and pregnancy is of extreme importance in that regard.

We discuss the global distribution of cardiovascular maternal mortality, adverse events during and after pregnancy, their predictors and risk stratification. In addition, we enumerate possible solutions, particularly the role of cardio-obstetric clinics.
INTRODUCTION

Pregnant women with heart disease have pronounced vulnerability to adverse cardiovascular events. Diagnosis and treatment of heart disease in pregnancy is difficult due to similarities between disease manifestations and normal physiological changes. Cardiovascular adverse events (AEs), during and after pregnancy continue to be important causes of maternal mortality and morbidity worldwide, with huge variations in burden in different countries and regions. These AEs are classified as having direct or indirect causes, depending on whether they are directly caused by pregnancy or due to some pre-existing disease and/or non-obstetric cause, respectively.

Cardiovascular disease is the single largest cause of indirect maternal mortality, accounting for over 33% of pregnancy-related maternal deaths. Additionally, maternal heart disease complicates up to 4% of pregnancies and up to 16% of pregnancies in women with previous cardiac conditions, with risk depending on the underlying cardiac condition.

Over 50% of maternal deaths occur post-partum. Late maternal mortality is defined as death more than 42 days (and up to one year) after childbirth. Importantly, the currently cited figures almost certainly constitute an underestimate. It is estimated that up to 68% pregnancy-related deaths caused by cardiovascular conditions are preventable. This can be achieved, through increasing awareness, coupled with applying strategies for prevention and treatment. Knowledge of the risks associated with CVD and pregnancy is of extreme importance in that regard.

We discuss the global distribution of cardiovascular maternal mortality, the adverse events during and after pregnancy, their predictors and risk stratification. In addition, we enumerate possible solutions, particularly the role of cardio-obstetric clinics.

Incidence and global distribution of maternal mortality

According to the World Health Organization (WHO) and Global Burden of Disease (GBD), in 2017 there were up to 295,000 maternal deaths globally, leading to an estimated global maternal mortality rate (MMR) of 211 per 100,000 live births. In 2017, every day approximately 810 women died from preventable causes related to pregnancy and childbirth, with 94% of all maternal deaths occurring in low and middle-income countries (LMIC’s). Sub-Saharan Africa alone accounted for roughly two-thirds of the estimated global maternal deaths. In Egypt the number of maternal deaths was 1,316 in 2017 with a MMR of 62 per 100,000 livebirths. The regional distribution and pattern of maternal death reported by the GBD varies considerably around the world.

Causes of maternal mortality and burden of disease

Up to 1990, direct causes accounted for over two-thirds of maternal mortality worldwide. There has been a significant decrease in overall maternal mortality over the years due to progressive drops in direct causes, however, the contribution of indirect and late maternal deaths, as well as maternal hypertensive disorders, has remained unchanged (Figure 2).

Regional and national variation in incidence and causes of maternal mortality

According to the GBD, maternal mortality rate (MMR) varied from 1 to 496 per 100,000 live births (Figure 3) in 2017. The alarmingly high incidence in MMR in some countries continues, with very few exceptions.

The regional incidence and cause of maternal mortality varies considerably from one country to another (Table 1). In addition, the representation of maternal hypertensive
Figure 1. Maternal mortality ratio (MMR; number of deaths per 100,000 livebirths) for countries and territories, GBD 2015.23

Figure 2. Causes of maternal deaths globally, 1990–2017.12 (A) maternal hypertensive disorders: High blood pressure during pregnancy in women who did not already have hypertension, or pre eclampsia in women with preexisting hypertension. (B) Indirect maternal deaths: Deaths due to preexisting conditions made worse by physiologic effects of pregnancy. (C) Late maternal deaths: Deaths due to any cause that occurs six weeks to 12 months after pregnancy. (D) Other maternal disorders: All other direct maternal disorders, including anemia in pregnancy, gestational diabetes and embolism.

disorders, indirect maternal deaths as well as the reported late maternal mortality also differs across countries.

Details of adverse cardiovascular events

Direct maternal adverse cardiovascular events

Hypertensive disorders of pregnancy. Chronic hypertension, gestational hypertension and preeclampsia26 are important causes of maternal and perinatal morbidity and mortality,9,27–31 particularly toward the end of pregnancy (Figure 4). Novel diagnostic methods and therapies have recently been reviewed.32

Gestational hypertension is defined as new-onset hypertension arising after 20 weeks of gestation33,34 and occurs in 10% of women.35 It is associated with acute and chronic
cardiovascular changes leading to an increased risk for hypertension throughout life,\textsuperscript{36,37} and a 4-fold increased risk of future maternal cardiovascular events.\textsuperscript{37–40}

**Indirect maternal adverse cardiovascular events**
Cardiovascular disease is the single largest cause of indirect maternal mortality.\textsuperscript{3,6} Patients who experience complications during pregnancy may also be at higher risk of cardiac events later in life.\textsuperscript{44}

**Arrhythmias**
The altered cardiac anatomy during pregnancy can elicit new onset arrhythmia or prompt the recurrence of preexisting arrhythmias.\textsuperscript{45,46} An increased incidence of cardiac arrhythmias has been reported during pregnancy\textsuperscript{47} in patients with and without identifiable heart disease. Arrhythmias are responsible for complications in 67 per 100,000 pregnancies,\textsuperscript{48–50} mainly in the form of atrial fibrillation (27 per 100,000 pregnancies) and supraventricular tachycardia (22 per 100,000 pregnancies).\textsuperscript{48–50}

**Heart failure**
Heart failure (HF) remains the most common complication during pregnancy among all women with heart disease, regardless of the cardiac pathology.\textsuperscript{42,51} Heart failure can occur during, or immediately after pregnancy (Figure 5). Despite the poor prognosis associated with the diagnosis of HF during pregnancy, and the fact that prevalence of HF among pregnant women has increased over the years - particularly in the post-partum period,\textsuperscript{52} data in the literature are scarce.

**Peri-partum cardiomyopathy**
Peri-partum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricle systolic dysfunction towards the end of pregnancy or in the months following child birth.\textsuperscript{53–56} At diagnosis, the majority of patients have severe symptoms (NYHA III/IV) and LVEF < 35%, with regional variations in presentation and outcomes\textsuperscript{57–59} (Figure 6).

The incidence of PPCM varies markedly from 1–100 per 10,000 live births depending on the region.\textsuperscript{59,61–63} PPCM has the highest mortality rate in pregnancy, with a worldwide mortality of 2.4%,\textsuperscript{57} although it may be underdiagnosed. PPCM leads to substantial maternal and neonatal morbidity and mortality, with less than half of all cases recovering
Table 1  Global distribution in incidence, causes and timing of maternal mortality by MMR (2017).1,2 The reported late maternal deaths represented 21.9% of total maternal mortality in Chile, compared to 0.08% in Iceland.

| Country      | Number of maternal deaths (2017) | MMR (2017) | Top mortality disorder | Maternal hypertensive disorders (% total maternal deaths) | Indirect maternal deaths (% total maternal deaths) | Late maternal deaths (% total maternal deaths) |
|--------------|----------------------------------|------------|------------------------|----------------------------------------------------------|---------------------------------------------------|-----------------------------------------------|
| Globally     | 193,639                          | 140        | Other maternal disorders | 15.17                                                    | 17.61                                             | 1.74                                          |
| Iceland      | 0                                | 1          | Other maternal disorders | 0.08                                                     | 0.03                                              | 0.08                                          |
| Sweden       | 4                                | 3          | Other maternal disorders | 7.25                                                     | 2.50                                              | 7.50                                          |
| Italy        | 37                               | 4          | Other maternal disorders | 7.82                                                     | 1.29                                              | 1.65                                          |
| Spain        | 20                               | 5          | Other maternal disorders | 11.40                                                    | 1.20                                              | 1.50                                          |
| Poland       | 16                               | 5          | Other maternal disorders | 6.31                                                     | 0.88                                              | 6.50                                          |
| Australia    | 15                               | 5          | Other maternal disorders | 5.07                                                     | 1.53                                              | 9.07                                          |
| Japan        | 46                               | 5          | Other maternal disorders | 7.87                                                     | 9.93                                              | 3.50                                          |
| Netherlands  | 11                               | 6          | Other maternal disorders | 11.09                                                    | 2.36                                              | 2.91                                          |
| Croatia      | 2                                | 6          | Other maternal disorders | 5.50                                                     | 7.00                                              | 8.00                                          |
| France       | 52                               | 7          | Other maternal disorders | 11.27                                                    | 9.54                                              | 2.54                                          |
| United Kingdom | 62                          | 8          | Other maternal disorders | 9.11                                                     | 14.56                                             | 6.27                                          |
| Portugal     | 7                                | 8          | Other maternal disorders | 11.14                                                    | 4.29                                              | 0.86                                          |
| Canada       | 31                               | 8          | Other maternal disorders | 6.10                                                     | 12.26                                             | 16.94                                         |
| South Korea  | 42                               | 10         | Other maternal disorders | 10.24                                                    | 6.98                                              | 2.29                                          |
| New Zealand  | 6                                | 11         | Other maternal disorders | 1.33                                                     | 37.00                                             | 12.17                                         |
| Latvia       | 3                                | 14         | Other maternal disorders | 1.67                                                     | 1.67                                              | 5.33                                          |
| China        | 2241                             | 14         | Other maternal disorders | 14.80                                                    | 6.80                                              | 0.98                                          |
| Vietnam      | 213                              | 14         | Maternal hemorrhage     | 14.63                                                    | 13.50                                             | 2.77                                          |
| Russia       | 250                              | 15         | Other maternal disorders | 11.33                                                    | 12.35                                             | 2.08                                          |
| Kazakhstan   | 53                               | 15         | Other maternal disorders | 8.32                                                     | 6.53                                              | 7.66                                          |
| Chile        | 56                               | 23         | Late maternal death     | 17.27                                                    | 19.84                                             | 21.91                                         |
| Iran         | 298                              | 23         | Indirect maternal disease | 10.58                                                   | 33.20                                             | 9.95                                          |
| United States | 1171                          | 30         | Other maternal disorders | 10.12                                                    | 15.65                                             | 17.12                                         |
| Mexico       | 1120                             | 44         | Maternal hemorrhage     | 23.45                                                    | 19.17                                             | 7.22                                          |
| Cuba         | 53                               | 48         | Indirect maternal disease | 7.09                                                    | 21.43                                             | 17.06                                         |
| Colombia     | 427                              | 50         | Indirect maternal disease | 23.16                                                    | 24.17                                             | 11.71                                         |
| Egypt        | 136                              | 62         | Other maternal disorders | 15.76                                                    | 19.68                                             | 3.67                                          |
| Brazil       | 2,054                            | 68         | Maternal hypertensive disorders | 20.93                                                   | 18.23                                             | 6.23                                          |
| Venezuela    | 395                              | 69         | Maternal hemorrhage     | 26.26                                                    | 22.81                                             | 2.83                                          |
| Dominican Republic | 237                             | 109        | Hypertensive disorders  | 26.21                                                    | 17.34                                             | 9.92                                          |
| South Africa | 139                             | 109        | Indirect maternal disease | 15.44                                                   | 35.03                                             | 1.89                                          |
| Uganda       | 375                              | 113        | Indirect maternal disease | 15.22                                                   | 22.27                                             | 0.72                                          |
| India        | 39,428                           | 160        | Other maternal disorders | 11.50                                                    | 13.16                                             | 1.78                                          |
| Indonesia    | 6627                             | 165        | Maternal hemorrhage     | 26.69                                                    | 2.19                                              | 1.41                                          |
| Ethiopia     | 2452                             | 201        | Maternal hemorrhage     | 15.56                                                    | 17.38                                             | 0.73                                          |
| Mozambique   | 2090                             | 212        | Indirect maternal disease | 15.07                                                   | 25.13                                             | 5.29                                          |
| Burkina Faso | 1863                             | 219        | Indirect maternal disease | 12.40                                                   | 28.46                                             | 0.74                                          |
| Nigeria      | 17982                            | 231        | Maternal hemorrhage     | 5.22                                                     | 16.79                                             | 1.68                                          |
| Tanzania     | 4046                             | 247        | Maternal hypertensive disorders | 24.61                                                   | 21.65                                             | 0.79                                          |
| Mali         | 2559                             | 291        | Indirect maternal disease | 6.63                                                     | 31.18                                             | 1.23                                          |

(continued on next page)
Table 1 (continued)

| Country                      | Number of maternal deaths (2017) | MMR (2017) | Top mortality disorder                        | Maternal hypertensive disorders (% total maternal deaths) | Indirect maternal deaths (% total maternal deaths) | Late maternal deaths (% total maternal deaths) |
|------------------------------|----------------------------------|------------|-----------------------------------------------|--------------------------------------------------------|-------------------------------------------------|-----------------------------------------------|
| Niger                        | 2930                             | 291        | Maternal sepsis and other maternal infections | 2.00                                                   | 26.25                                           | 0.87                                          |
| Kenya                        | 3990                             | 292        | Indirect maternal disease                     | 15.70                                                  | 23.88                                           | 1.19                                          |
| Afghanistan                  | 4095                             | 301        | Indirect maternal disease                     | 9.11                                                   | 38.79                                           | 0.66                                          |
| Cote d’Ivoire                | 2631                             | 305        | Indirect maternal disease                     | 9.47                                                   | 28.27                                           | 0.67                                          |
| South Sudan                  | 1410                             | 344        | Maternal hemorrhage                           | 5.95                                                   | 8.82                                            | 0.62                                          |
| Somalia                      | 2363                             | 344        | Maternal hemorrhage                           | 9.10                                                   | 16.98                                           | 0.56                                          |
| Democratic republic of Congo| 10166                            | 349        | Indirect maternal disease                     | 10.99                                                  | 26.59                                           | 0.68                                          |
| Chad                         | 2745                             | 383        | Maternal hemorrhage                           | 6.29                                                   | 14.41                                           | 0.78                                          |
| Congo                        | 572                              | 398        | Indirect maternal disease                     | 11.60                                                  | 26.63                                           | 0.80                                          |
| Guinea                       | 1916                             | 451        | Maternal hemorrhage                           | 8.35                                                   | 25.25                                           | 0.82                                          |
| Papua New Guinea             | 1532                             | 496        | Indirect maternal disease                     | 8.86                                                   | 34.92                                           | 0.59                                          |

Figure 4. Onset of hypertensive disorders at different stages of pregnancy and postpartum (PP) among women without chronic hypertension (adapted from Ramlakhan et al).41,43

Figure 5. Timing of heart failure in women with structural heart disease at different stages of pregnancy and postpartum (PP) (adapted from Ramlakhan et al).41,42
Figure 6. Diagnostic pathway in patients with suspected peripartum cardiomyopathy (PPCM). BNP, B-type natriuretic peptide; ECG, electrocardiogram; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RV, right ventricular.

Figure 7. Time course of left ventricular function (adapted from) (A) Changes in left ventricular ejection fraction (LVEF) from baseline (BL) to 5-year follow-up. Remarkably, LVEF further improves even after 1 year. (B) Proportion of patients with full cardiac recovery constantly increases. At 5-year follow-up, 72% had recovered completely and 23% partially. No recovery was observed in 5%. Death occurs up to 5 years.

full cardiac function (Figure 7). Six-month mortality is around 6%, mainly due to heart failure. Neonatal death is around 5%, although with marked regional variation.

Management follows the guidelines of HF. In non-responsive patients, other pharmacological agents - such as bromocriptine and prolactin-blocking therapy with dopamine D2 receptor agonists - have been tried with variable results.

Contributing factors to PPCM include genetic predisposition as well as auto-immune responses. Using such factors, all be it indirectly, to define phenoclusters - it could be possible to identify novel therapeutic targets to guide personalized medicine in PPCM.

For a small proportion of patients with rapidly-progressive PPCM resistant to conventional therapy, the use of the current generation of left ventricular assist devices can give long-lasting “cures” in some patients (personal experience in Harefield and Aswan series).

Registries on the condition will provide fundamental data on predisposing factors, potential aetiology and regional variations.
Mechanical valve thrombosis
Even with the right care, the incidence of thromboembolism during pregnancy is estimated from 7–23% with half of these cases being mechanical valve thrombosis (MVT), which is associated with 20% mortality. Thrombosis is the most life-threatening complication for women with prosthetic heart valve, during pregnancy. The chance of a successful uncomplicated pregnancy, which depends on the balance between the thrombotic and bleeding risks, is around 57%.

Acute coronary syndromes
The incidence of coronary artery disease (CAD) in women of childbearing age is unclear and varies between countries. CAD, is a major cause of maternal death and accounts for over 20% of maternal cardiac deaths, especially in the form of acute coronary syndromes (ACSs). The estimated incidence of 6.2 per 100,000 deliveries nearly 4 times higher than in non-pregnant women and reflects the growing prevalence of cardiovascular risk factors in the pregnant population.

Risk stratification
Several tools have been developed to estimate morbidity and mortality risk in pregnant women with cardiac disease, such as CARPREG and ZAHARA. However, the best estimate of the risk of cardiovascular events during pregnancy in pre-existing heart disease is the WHO's (Figure 8), as it integrates congenital and acquired heart disease. The risk of cardiac adverse events during pregnancy are significantly increased in mWHO IV compared to mWHO I (Figure 9).

Based on the modified WHO risk classification for milder conditions, where the risk of pregnancy is very low to moderate, the needed care might be limited to a few visits during pregnancy, while in case of high risk of complications, a more frequent follow-up schedule is recommended. Women in the highest risk group (WHO IV) should be advised against pregnancy. More comparative studies should be performed in order to define the most accurate risk index for pregnant women with heart disease.

The role of comprehensive cardio-obstetric clinics
The concept of multidisciplinary cardio-obstetric clinics (Figure 10) has evolved and been applied in several countries, with extremely encouraging results and excellent survival rates of mothers even with complex diseases, and their offspring.

However, the need for cardio-obstetric clinics remains un-met, with most programs to be found in developed countries and with only a few centers continuing follow-up long term.

Although these initiatives might be feasible in large metropolitan areas, smaller towns, rural communities and remote regions are completely neglected. There is an urgent need for action and worldwide implementation of cardio-obstetric clinics, strategically placed, in order to reach the majority of those in need.

Integrated, tailored and dynamic healthcare services responding to current state of disease burden and initiatives are essential. Cardio-obstetric care clinics (COcare) have been initiated in the metropolitan Aswan Heart Center as well as its rural branch in Ballana.

CONCLUSIONS
Preventable maternal cardiovascular adverse events continue to be a global problem with an unacceptably high burden of disease. This requires urgent concerted efforts
### WHO Pregnancy Risk Classification (Risk of pregnancy by medical condition)

| WHO Risk Class I | Cardiovascular Conditions by WHO Risk Class |
|------------------|---------------------------------------------|
| No detectable increased risk of maternal mortality and no or mild increase in morbidity. | • Uncomplicated, small or mild  
  - Pulmonary stenosis  
  - Patent ductus arteriosus  
  - Mitral valve prolapse  
  - Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage)  
  - Atrial or ventricular ectopic beats, isolated |

| WHO Risk Class II (If otherwise well and uncomplicated) | Cardiovascular Conditions by WHO Risk Class |
|----------------------------------------------------------|---------------------------------------------|
| Small increased risk of maternal mortality or moderate increase in morbidity. | • Unoperated atrial or ventricular septal defect  
  • Repaired tetralogy of Fallot  
  • Most arrhythmias |

| WHO Risk Class II or III (Depending on individual) Risk as indicated in Class II (above) or Class III (below) | Cardiovascular Conditions by WHO Risk Class |
|----------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| • Mild left ventricular impairment  
  • Hypertrophic cardiomyopathy  
  • Native or tissue valvular heart disease not considered WHO I or IV  
  • Marfan syndrome without aortic dilatation  
  • Aorta <45 mm in aortic disease associated with bicuspid aortic valve  
  • Repaired Coarctation |

| WHO Risk Class III | Cardiovascular Conditions by WHO Risk Class |
|--------------------|---------------------------------------------|
| Significantly increased risk of maternal mortality or severe morbidity. Expert counseling required. If pregnancy is decided upon, intensive specialist cardiac and obstetric monitoring needed throughout pregnancy, childbirth and the postpartum. | • Mechanical valve  
  • Systemic right ventricle  
  • Fontan circulation  
  • Cyanotic heart disease ( unrepaired)  
  • Other complex congenital heart disease  
  • Aortic dilatation 40-45 mm in Marfan Syndrome  
  • Aortic dilatation 45-50 mm in aortic disease associated with bicuspid aortic valve |

| WHO Risk Class IV (Pregnancy contraindicated) Extremely high risk of maternal mortality or severe morbidity; pregnancy contraindicated. If pregnancy occurs termination should be discussed. If pregnancy continues, care as for class III. | Cardiovascular Conditions by WHO Risk Class |
|----------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| • Pulmonary arterial hypertension of any cause  
  • Severe systemic ventricular dysfunction (LVEF <30%, NYHA III-IV)  
  • Previous peripartum cardiomyopathy with any residual impairment of left ventricular function  
  • Severe symptomatic mitral or aortic stenosis  
  • Marfan syndrome with aorta dilated >45 mm  
  • Aortic dilatation >50 mm in aortic disease associated with bicuspid aortic valve  
  • Native severe Coarctation |

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**Figure 8.** Modified WHO classification of maternal cardiovascular risk: application.92

![Diagram showing risk of cardiac event during pregnancy per mWHO class based on CARPREG II and ROPAC data.

**Figure 9.** Risk of cardiac event during pregnancy per mWHO class based on CARPREG II and ROPAC data. 12,13,93 adapted from.94
from governments, individuals and professionals, who have first-hand experience of the magnitude of the problem. Multidisciplinary cardio-obstetric care should also play an important role.

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