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Epidemiology of the hypertensive disorders of pregnancy

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SYNOPSIS

This chapter provides a review of the literature on incidence and prevalence of the hypertensive disorders of pregnancy including chronic hypertension, gestational hypertension, pre-eclampsia and HELLP syndrome. Estimates are provided for both high-income and low- or middle-income country settings published within the past 10 years. Where possible, we have emphasised population-based data derived from national or regional data sets. Overall, the hypertensive disorders of pregnancy occur in 5–10% of pregnancies worldwide, with limited data suggesting an upward trend in incidence. The most common are gestational hypertension and pre-eclampsia, with pre-eclampsia being the most dangerous as it is associated with the highest prevalence of maternal and perinatal complications. There are many individual disease risk factors for the hypertensive disorders of pregnancy related to demographic, familial, personal medical/obstetric history, or to the current pregnancy; these are discussed in detail in Chapters 5 and 6 as these risk factors are used to identify women at increased risk who warrant enhanced antenatal surveillance and preventative therapy[1].

SEARCH STRATEGY

For this review, two literature searches were performed using the search strategies provided in Appendix 4.1. Publications were included in the review if they were published in English in the past 10 years. For incidence and prevalence estimates, publications were reviewed if they included either a population-based or cross-sectional hospital cohort reporting incidence or prevalence of all combined hypertensive disorders of pregnancy or any one of pre-eclamspia, gestational or chronic hypertension or haemolysis elevated liver enzymes and low platelets (HELLP) syndrome. For morbidity and mortality estimates publications that reported prevalence of any major adverse event known to be associated with a hypertensive disorder of pregnancy (as described in Chapter 3) within a population-based or cross-sectional hospital-based cohort of women with confirmed diagnosis of any hypertensive disorder of pregnancy were reviewed.

THE BURDEN

Combined hypertensive disorders of pregnancy estimates

Determining the true incidence of the hypertensive disorders of pregnancy is complicated by variations in the reported classification of the disorders (as

KEY POINT

The most commonly cited and accepted estimate of hypertensive disorder of pregnancy occurrence is 5–10%[1]

described in Chapter 3) and study design, with few reliable estimates provided by population-based cohorts and inflated estimates of prevalence reported by hospital-based studies. As such, incidence and prevalence estimates vary significantly based on country of origin and quality of available data. Although the definitions of chronic hypertension and gestational hypertension are reasonably standard (i.e., hypertension before or at/after 20 weeks of pregnancy, respectively), the definition of pre-eclampsia is not, and this may contribute to further variation.

In low- and middle-income countries (LMICs), incidence estimates are restricted to hospital-based cross-sectional surveys. Therefore, these are likely to be overestimates owing to the high proportion of births (and disproportionately, normal births) occurring in the home in most LMICs. In the WHO Multicountry Survey on maternal and newborn health, 313,030 women were included who were admitted to 357 health facilities in 29 countries across Africa, Asia, Latin America and the Middle East (2010–2012)[2]. In all 2.7% of the total number of women included in the study were reported to have suffered from chronic hypertension, pre-eclampsia, or eclampsia; gestational hypertension was not included in this estimate. This prevalence estimate ranged between 1.8% in the Middle East and 4.5% in the Americas region. In contrast, smaller single hospital-based surveys have reported higher hypertensive disorder of pregnancy rates, ranging from 4.0% to 12.3%[4–7]; however, even with large numbers, such as the 164,250 women in a single hospital-based cohort study in southern India (1996–2010), estimates must be viewed as potentially inflated owing to selection bias. The mobile health-supported community surveillance activities of the Community-Level Interventions for Pre-eclampsia (CLIP) trials in Mozambique, Pakistan and India will provide accurate population estimates of hypertensive disorders of pregnancy prevalence in these countries (http://www.thelancet.com/protocol-reviews/13PRT-9313)

A hypertensive disorder of pregnancy incidence of 5–10% is supported in high-income countries (HICs) in several large national cohorts that have reported rates of 4.6–9.2% based on publications since 1995[8–11].

Chronic hypertension and gestational hypertension appear to be much less common than pre-eclampsia, although limited population-level estimates exist.

Chronic hypertension (≈1%)

Reliable estimates for LMIC settings for chronic hypertension can be based solely on the WHO multicountry survey described above (of hospital-based cross-sectional data) which found a prevalence of 0.29% in the total cohort ranging between 0.21% in the African region and 0.32% in the Western Pacific region[2].

More reliable estimates are available for HICs. In a national cohort of all hospital deliveries in Canada in all provinces except Quebec (2003–2010), the incidence of chronic hypertension was 0.4%[11]. These data are consistent with 0.6% reported in the Alberta Perinatal Health Registry of all births in the province of Alberta, Canada (2000–2009)[12]. In the American National Inpatient Sample data set, chronic hypertension complicated 1.5% of births (2007–2008)[13], and 0.83–0.85% of births in New York State, USA (1995–2004)[14]. A similar rate of 1.3% was reported in the UK (1996–2010)[15].

Gestational hypertension (≈3%)

We found very limited data on prevalence of gestational hypertension for LMICs and no data giving a reliable estimate of incidence. In a hospital-based cohort of 193,554 births registered in two provinces of Southern China (1993–1996), gestational hypertension occurred at a rate of 9.5%[16]; this was a secondary analysis of data from a study evaluating the impact of folic acid supplementation on the incidence of neural tube defects and there is likely to be selection bias.

Gestational hypertension rates in HICs differ substantially from those described above. In a national cohort of all hospital deliveries in Canada in all provinces except Quebec (2003–2010), the incidence of gestational hypertension was 1.1%[11]. In New York State, USA (1995–2004), gestational hypertension complicated 1.4–2.5% of births (2007–2008)[13].

Pre-eclampsia (≈2–4%)

In the largest hospital-based cohort to report prevalence of pre-eclampsia in LMICs, the WHO Multicountry Survey reported an overall prevalence of 2.2% ranging from 1.4% in the Middle East region

to 3.9% in the African region[2]. Other cohorts reviewed since 1995 reported prevalence estimates ranging from 1.2% to 8.4%[16–19]. In a WHO systematic review of 129 studies covering approximately 39 million women from 40 countries (2002–2010), the crude incidence of pre-eclampsia was 2.3% (4.6% using a model-based estimate to account for lack of data sets from certain regions causing under-representation of countries believed to have higher rates of pre-eclampsia), ranging from 1.2% in the Middle East to 4.2% in the Western Pacific[3]. However, there was substantial regional variation, from 0.7% reported in a small study from Morocco to 15.6% reported in a Turkish data set. If estimates are restricted to those from national cohorts, data were available from seven countries that collectively reported pre-eclampsia rates of 1.4–4.0%[3].

This range has been supported by other reported national population-level cohorts, primarily from HICs. For example, in the Norwegian National Birth Registry (1967–2008), the incidence of pre-eclampsia was 2.8%[20] and 2.2% in another national data set from South Korea (2007–2010)[21]. Regional population-level data sets from Canada, the USA and Australia report incidence estimates between 1.3 and 3.4%[11,12,14,20,22–24].

Early-onset (vs. late-onset) disease Late-onset pre-eclampsia is more common than early-onset disease, the latter usually being defined as onset or delivery prior to 34 weeks. Estimates vary, but early-onset disease appears to represent no more than one-third of pre-eclampsia. In the National Birth Registry of Denmark covering all singleton births (1993–2007), the incidence of early-onset pre-eclampsia was 1.0% and late onset 1.9%[15]. In Washington State, USA among all singleton births (2000–2008), early-onset disease pre-eclampsia incidence was 0.3% and late-onset 2.7%[22,23].

HELLP syndrome (<1% of all births, <50% of women with pre-eclampsia) There are few epidemiological data about the prevalence of HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome, a severe manifestation of pre-eclampsia. No population-based estimates of incidence were identified in the literature. A 2009 review of management of HELLP syndrome quotes a prevalence of 0.5–0.9% of all pregnancies, based on small case series and retrospective hospital- and USA-based cohort studies published in the early 1990s[25]. A more recent, but small, retrospective hospital-based cohort included 5155 women admitted to a tertiary academic centre in Turkey (1997–2004) and found an incidence of HELLP of 0.5%[26]. Other LMIC- and HIC-based cohort studies suggest a higher prevalence of HELLP syndrome ranging from 2.5% to 50%[27–30]. However, some of these studies are tertiary facility-based with cohorts of women selected based on complicated pre-eclampsia. In addition, in settings where expectant management of early-onset pre-eclampsia is not the norm, the opportunity for pre-eclampsia to evolve into HELLP syndrome is abbreviated. Therefore, variability in estimates of HELLP syndrome incidence is likely to have been magnified by differences in study inclusion criteria, study settings and patterns of clinical management, and are not reliable.

Temporal trends in the hypertensive disorders of pregnancy

Data related to temporal trends are limited, but suggest an increase in incidence of all hypertensive disorders of pregnancy and specific disorders over time.

In a prospective cohort from a single hospital in India, the incidence of hypertensive disorders of pregnancy has increased from 10.3% of all births (1996–2004) to 11.8% (2005–2010)[4]. This study did not provide an analysis of significance relating to the temporal trend.

Similar increasing trends in chronic hypertension have been observed in HICs. In the US National Inpatient Sample data set, an increase in chronic hypertension was reported from 0.9% (1995–1996) to 1.5% of births (2007–2008) as discussed above[13]. The rising incidence of chronic hypertension in HIC settings is thought to reflect changing demographics, as pregnant women are tending to be both older and more frequently either overweight or obese.

The incidence of pre-eclampsia appears to be rising in HICs, including the USA (1980–2010)[23] and Norway (1967–2008)[31]. For example, in Washington State, USA, hypertensive disorders of pregnancy complicated 2.9% of all singleton live births in 2000 and increased significantly ($p<0.001$) to 3.1% in 2008[22]. When considering all births in the USA, the rates increased significantly ($p<0.001$) from 2.4% (1987–1988) to 2.9% (2003–2004)[32].

One exception to this trend was reported in a regional dataset from New South Wales in Australia where the hypertensive disorders of pregnancy *decreased significantly* ($p<0.001$) in incidence from 4.6% of all births (2000) to 2.4% (2008)[24]; the authors of this study suggested that earlier intervention and increased use of induction of labour or elective Caesarean delivery at earlier gestational ages for chronic or gestational hypertension were reducing the diagnosis of pre-eclampsia, although this should not have altered the overall rate of hypertension in the population.

Other trends in pre-eclampsia

The risk of having a pregnancy complicated by pre-eclampsia is thought to vary across climates and regions. Higher rates have been associated with rainy seasons in studies from several countries[8,9,33–36]. In addition, pre-eclampsia appears to complicate more commonly the pregnancies of immigrant women, compared with women born in the respective country. According to several large national datasets from HICs in Europe and Canada, women of African, Caribbean, and South and East Asian descent endure higher rates of pre-eclampsia compared with women of European descent[37–40].

RISK FACTORS FOR HYPERTENSIVE DISORDERS OF PREGNANCY OCCURRENCE OR RECURRENCE

Risk factors for pre-eclampsia include a wide array of conditions that reflect the complexity of the disease process[41]. These can be categorised as demographic, familial factors, past medical/obstetric history, current pregnancy history and paternal factors. These factors are used to identify women at increased risk of a hypertensive disorder of pregnancy who warrant enhanced surveillance and/or preventative therapy. As such, these risk factors are discussed in detail in Chapters 5 and 6. As risk markers for recurrence of pre-eclampsia are used in the same way, they too are discussed in Chapter 5.

MORTALITY AND MORBIDITY ASSOCIATED WITH THE DISORDERS OF PREGNANCY

Hypertensive disorder of pregnancy-related mortality and morbidity are to a large extent, but not entirely, owing to pre-eclampsia. A more detailed discussion of complications by type of hypertensive disorder of pregnancy can be found in Chapter 3.

> "I was told upon arriving at the hospital that they had managed to regain a pulse after 25 minutes but that my wife had most likely suffered severe brain damage from the lack of oxygen . . . She never regained consciousness and on August 6, three days after being removed from support, she passed into the arms of her loving Lord. The silence, since then, has been deafening."
>
> Widower of a woman with pre-eclampsia, courtesy of the Preeclampsia Foundation, USA

Maternal mortality

The hypertensive disorders of pregnancy, and particularly pre-eclampsia and eclampsia, are significant contributors to the global burden of maternal and perinatal mortality[42–46], being responsible for an estimated 10.0% of maternal deaths, annually[46]. Pre-eclampsia remains one of the top four causes of maternal mortality (and morbidity) in high-, middle- and low-income countries. Using data from 29 LMICs participating in the WHO Multicountry Survey on maternal and neonatal health, the odds of maternal death associated with the diagnosis of pre-eclampsia (compared with no pre-eclampsia) was 3.73 (95% CI 2.15–6.47) and with eclampsia (vs. no eclampsia) (OR 42.4, 95% CI 25.1–71.4)[2]. Similar results to the pre-eclampsia-related risk were illustrated by data from the UK Obstetric Surveillance System that reported an increased odds of maternal death of 2.4 (95% CI 1.3–4.5) associated with a hypertensive disorder of pregnancy (compared with no hypertensive disorder of pregnancy)[50].

A vastly disproportionate burden of maternal deaths related to the hypertensive disorders of pregnancy is borne by women in LMICs[51–53]; estimated to be >99% of all hypertensive disorder

KEY POINT

The majority of deaths associated with hypertensive disorders of pregnancy occur in LMICs in the absence of a trained health professional

of pregnancy-related maternal deaths. This is believed to be owing primarily to delays in triage (identification through basic blood pressure and urine screening of who is, or may become, severely ill and should seek a higher level of care), transport (getting women to appropriate care), and treatment (provision of appropriate treatment such as magnesium sulphate, antihypertensive therapy and timed delivery)[57,58]. A major contributing factor to the morbidity and mortality associated with pre-eclampsia is the shortage of health workers adequately trained in the detection and triage of suspected cases[60]. The consequences of delayed management are illustrated by Figure 4.1 of an 18-year-old mother brought to hospital after 14 hours of status eclampticus in Dhaka, Bangladesh; she suffered a stillbirth and remained comatose for the 3 days until her death shortly after this image was taken. Her family asked us to use this photograph to emphasise the importance of, and potential tragedy resulting from, pre-eclampsia and eclampsia.

Figure 4.1 This photo was taken in the Eclampsia Ward, Dhaka Medical College Hospital, Dhaka, Bangladesh. The 18-year-old woman lying supine had been admitted 14 hours after the onset of her first seizure in status eclampticus 3 days earlier. She had been delivered of a stillborn infant by Caesarean delivery soon after admission and had remained unresponsive since admission, and remained so until her death. Bed sharing with her is another woman post-eclampsia who had had an unremarkable recovery from her seizures. The 18-year old's hand is being held by her mother with her grandmother in the background. They asked that this image be shared to emphasise the importance of, and tragedy associated with, pre-eclampsia and eclampsia

According to global estimations, there has been a downward trend in hypertensive disorder of pregnancy-related maternal mortality, suggesting an improvement in our ability to care for women with pre-eclampsia. In the 2013 report on maternal deaths from the Global Burden of Disease Study, the absolute number of maternal deaths attributed to the hypertensive disorders of pregnancy was 29,275; this compared favourably with 47,100 deaths in the 2010 report and 69,800 in the 1990 one[46]. This trend towards a reduction in total number of maternal deaths associated with the hypertensive disorders of pregnancy has also been shown by the WHO[43].

Maternal morbidity

For every maternal death, it has been estimated that an additional 20 or 30 women suffer significant morbidity. In the same manner as maternal death, the burden of maternal morbidity is estimated to be highest in LMICs. The term, 'morbidity', covers a wide range of problems of varying severity. WHO has defined 'near-miss morbidity' as the near-death of a woman who has survived a complication (occurring during pregnancy or childbirth, or within 42 days of the termination of pregnancy). 'Severe' pre-eclampsia is a near-miss according to the WHO[61]. Although the definition of 'severe' pre-eclampsia varies by organisation as does the definition of 'pre-eclampsia' itself (as discussed in Chapter 3), the unifying principle is that pre-eclampsia is always potentially life-threatening. As there are women (such as those with hypertension, headache and visual symptoms) who are defined as having pre-eclampsia by some organisations, but gestational hypertension by others, it should not be surprising that 'gestational hypertension' is not a benign condition according to published literature[62–66]. The progression to pre-eclampsia occurs in 15–56% of women who initially present with gestational hypertension[62,65,67], as discussed in detail in Chapter 3.

Several large cohort studies have estimated the contribution of the hypertensive disorders of pregnancy to 'near-miss morbidity' as defined by the WHO[61]. The proportion attributable to the hypertensive disorders of pregnancy appears to be higher in LMICs than in well-resourced settings. In a Brazilian study of 16,243 deliveries in two large obstetric facilities (2011–2012), the hypertensive

disorders of pregnancy were responsible for 1102 (67.5%) near-misses[68]. In a similar study from Abu Dhabi of 122,702 deliveries in all major maternity units across a single province (2000–2006), 553 (59.5%) of all near-miss cases were attributed to the hypertensive disorders of pregnancy[69]. These estimates are in contrast to a large hospital-based cohort study in the USA of 115,502 deliveries (2008–2011) that found that 68 (20.5%) of near-miss cases were attributable to the hypertensive disorders of pregnancy[70]. It is probable that women in Abu Dhabi presented later in the course of their disease compared with women with greater antenatal surveillance and earlier diagnosis in the USA where expectant management of early-onset pre-eclampsia is not a uniform standard of care.

Maternal morbidities associated with the hypertensive disorders of pregnancy are thought to be a result of excessive inflammation and endothelial damage[71] and include virtually all end-organ complications. Estimates of complications that are most feared (such as hepatic haematoma/rupture or central nervous system complications of eclampsia, stroke, retinal detachment and blindness), most common (such as HELLP syndrome, pulmonary oedema, or placental abruption), or most easily recognised (such as acute renal failure)[64–73] come mainly from hospital-based studies, with the exception of eclampsia.

As observed with incidence estimates for the hypertensive disorders of pregnancy, most studies of morbidity rates are based on either cross-sectional or prospective cohorts collected in hospital after a diagnosis of pre-eclampsia has been made and may not be representative of the hypertensive disorder of pregnancy population as a whole. Rates of hypertensive disorder of pregnancy-related morbidity reported in LMICs tend to be higher (10–20%)[68,69,72–80] than those reported in HICs (5–9%)[22,30,50,70,81]. In addition, higher morbidity rates are reported in association with 'severe' pre-eclampsia, however defined[82–85].

KEY POINT

Rates of hypertensive disorder of pregnancy-related morbidity reported in LMICs tend to be higher (10–20%) than those reported in HICs (5–9%). Higher rates are also reported in association with 'severe' pre-eclampsia, however defined

The two large, multicountry, but facility-based, PIERS (Pre-eclampsia Integrated Estimate of RiSk) studies highlight the disparity in maternal outcomes between high- and low-resourced settings that probably reflect differences in health care resource access and underlying social determinants of health. The PIERS research programme has published a list of relevant maternal morbidities associated with the hypertensive disorders of pregnancy (see Chapter 3). This list was developed by an International Delphi consensus group[30] consisting of experts in obstetrics, paediatrics, anaesthesia, neonatology, medicine, global health and epidemiology from 19 high-, middle- and low-resourced countries. Two cohorts of women were collected as part of the PIERS project. The fullPIERS cohort included data from 2023 women admitted with a diagnosis of pre-eclampsia in a participating hospital in Canada, the UK, Australia or New Zealand; maternal morbidity, as defined by the Delphi group was 5.0% within 48 hours of admission and 13.0% at any time after admission. This is in contrast to the miniPIERS cohort that included data from 2081 women admitted with any hypertensive disorder of pregnancy to one of seven participating hospitals in Brazil, Uganda, South Africa, Pakistan or Fiji; maternal morbidity was 12.5% within 48 hours of admission and 19.3% at any time after admission.

Eclampsia

Estimates of eclampsia incidence have been refined by efforts to reduce the global burden of disease using magnesium sulphate, an agent that is effective for eclampsia prophylaxis and treatment. According to the WHO Multicountry Survey, eclampsia occurs in 1.0–2.0% of pregnancies[2]. The incidence is lower in HICs, with published estimates from population-level data below 1% (ranging from 2–8.6/10,000 live births)[24,38,86–91].

Stroke

In the USA, hypertensive disorder of pregnancy-related stroke, particularly postpartum, appears to be on the rise, with a reported 5-fold increase in incidence from 1994 to 2011[92]. Severe systolic hypertension (i.e., ≥160 mmHg) appears to be a particular risk factor for hypertensive disorder of pregnancy-related stroke[93,94].

Perinatal mortality and morbidity

Adverse outcomes for both mother and fetus tend to cluster around the diagnosis of pre-eclampsia whether defined traditionally (as gestational hypertension and proteinuria) or broadly (as gestational hypertension with end-organ dysfunction)[95].

Adverse perinatal outcomes associated with the hypertensive disorders of pregnancy include stillbirth, neonatal death, oligohydramnios, bronchopulmonary dysplasia and fetal growth restriction[71,96,97].

Of perinatal deaths (i.e., stillbirth or neonatal death), an estimated 9–20% are reported to be directly related to the hypertensive disorders of pregnancy in several large multi-country cohort studies[98–100]. In the WHO Multicountry Survey study, women with pre-eclampsia or eclampsia had an odds ratio of perinatal death of 3.0 (95% CI 2.7–3.3) and 4.9 (95% CI 4.1–5.9), respectively, compared with women without a hypertensive disorder of pregnancy[2]. In the Nationwide Inpatient Sample study of all deliveries reported in the USA, 7.5% of all stillbirths were in association with pre-eclampsia[101].

Adverse perinatal outcomes, including stillbirth, are modified by gestational age. The risk of stillbirth is higher at earlier gestational ages. In the Norwegian Medical Birth Registry (1999–2008), the RR of fetal death among women with pre-eclampsia was 86 (95% CI 46–142) at 26 weeks' gestation, 7.3 (95% CI 3.3–11.0) at 34 weeks, and 3.0 (95% CI 1.7–4.1) at 38 weeks[102]. Pre-eclampsia is recognised as a significant contributor to iatrogenic preterm birth and associated neonatal morbidity[103–108]. A secondary analysis of data from the WHO Global Survey data set, including 172,461 deliveries from 145 facilities across 22 low-resourced countries, determined that pre-eclampsia was associated with 8 times the odds of provider-initiated preterm birth[109].

Although most studies reporting complications focus on a diagnosis of pre-eclampsia, chronic hypertension (compared with normal blood pressure) has been associated with an increased risk of preterm birth[110,111] (RR 2.7, 95% CI 1.9–3.8)[112] and perinatal death (RR 4.2, 95% CI 2.7–6.5)[112], as well as congenital malformations (whether women were treated with antihypertensive therapy (OR 1.3, 95% CI 1.2–1.5) or not 1.2 (95% CI 1.1–1.3))[113].

> "I would not wish the days that followed on anyone. Leaving the hospital with a teddy bear and an urn instead of a sweet little baby is unthinkable. Having your daughter's milk come in without the baby grandson for whom it was intended was heart-wrenching."
>
> Rita C, courtesy of the Preeclampsia Foundation, USA

PRIORITIES FOR FUTURE RESEARCH

With regards to the epidemiology of pre-eclampsia, the main priorities for future research include development of consistent definitions of hypertensive disorder of pregnancy types, and robust population-level surveillance systems incorporating across multiple country settings. Particularly in LMICs where the burden, and health consequences, of these disorders is thought to be greatest, population-level surveillance is required in order to properly ascertain the effectiveness of interventions and public health programmes aimed at improving maternal health. These improved surveillance systems should include information related to risk factors that would improve our knowledge of how risk factors may vary based on classification of the disorder and other subgroups of pregnant women.

As populations of pregnant women continue to experience demographic shifts worldwide, other priorities will be to understand the contribution of these changes to disease burden and complication rates.

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