
Navigating the Perfect Storm: Confronting the Epidemic of Hypertensive Disorders in Pregnancy

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Abstract:

Hypertensive Disorders in Pregnancy (HDP) are leading causes of immediate and long-term maternal and fetal morbidity and early mortality. While a generation ago these conditions affected 6-8% of all pregnancies, in recent years about one in eight pregnant women are affected, a rate that translates into more than one-half million new cases each year in North America alone. This article discusses the history, presentations and changing incidence rates of HDP. In addition, it identifies and describes the social and biological changes that account for the increases. For example, because risks for developing HDP increase with advanced maternal age, nulliparity, and multiple gestations, modern trends such as delayed childbearing, smaller family size, and in vitro fertilization procedures that increase multi-gestational pregnancies all contribute to the growing incidence of HDP. Rising levels of obesity evidenced by high-pre-pregnancy body mass index and metabolic abnormalities also add to the HDP epidemic. The article concludes with some recommendations regarding how this knowledge can impact healthcare in the 21st century.

Keywords: hypertensive disorders in pregnancy, preeclampsia, obesity, metabolic disorders

**Resumen:****Navegando la tormenta perfecta: confrontando la epidemia de trastornos de hipertensión durante el embarazo**

Los trastornos relativos a la hipertensión en el embarazo (HDP) son las causas principales de la mortandad inmediata y a largo plazo de las mujeres y los fetos y la prematura mortalidad. Hace una generación estas condiciones afectaban de 6 a 8% de todos los embarazos, pero en años recientes afectan una de cada ocho mujeres embarazadas, una tasa que representa más de medio millón de nuevos casos sólo en los Estados Unidos. Este artículo trata la historia, incidencias y cambios en las tasas de HDP. Además, identifica y describe los cambios sociales y biológicos que explican los aumentos. Por ejemplo, debido a que el riesgo de desarrollar HDP aumenta con la avanzada edad materna, la nuliparidad y los embarazos múltiples, las tendencias modernas de procreación tardía, menor tamaño familiar y la fertilización in vitro que aumentan los embarazos múltiples contribuyen a la creciente incidencia de HDP. Los crecientes niveles de obesidad, manifestados en el índice de masa corporal pre-embarazo y las anomalías metabólicas, contribuyen a la epidemia de HDP. El artículo concluye con unas recomendaciones sobre la manera en que estos conocimientos pueden afectar la atención médica en el siglo XXI.

Palabras claves: trastornos relativos a la hipertensión en el embarazo, preeclampsia, obesidad, trastornos metabólicos.

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Introduction

Seizures in pregnant women or “eclampsia” have been and continue to be a leading cause of maternal and fetal mortality. The etiology of the word “eclampsia” is controversial, but according to some distant sources, the term was originally used in the 4th century BCE by Hippocrates, the so-called “father of Western medicine,” to reference the susceptibility of pregnant women to convulsions and their subsequent adverse prognoses (Lindmeimer, Roberts, & Cunningham, 2009, p. 2-6). The word “eclampsia” is a derivative of the Greek word for “lightning or shining forth,” and may refer to the “sparkling” in the eyes of its victims, which according to James Coudon, the first American to write on the subject, is one of the most prominent features of the disease (Coudon, 1813, p. 2).

Even if the tradition that associates eclampsia with Hippocrates is apocryphal, this pregnancy-specific seizure disorder was well known throughout the ancient world. Famous physicians like Celsus described it in the first century, as did the renowned Galen in the second century CE (Lindmeimer et al, 2009, p. 2-3). Knowledge of the disorder, however, was slow in evolving. For the next fifteen centuries, eclampsia generally was mistakenly known as a form of epilepsy that affected pregnant women. In 17th century France, male physicians entered the field of obstetrics and began to study and publish information on eclamptic patients. Within a century, specialists recognized that first-time pregnant mothers (nulliparous) were more susceptible to convulsions than previously pregnant women, that women carrying twins were more at risk than those with singleton pregnancies, and that swelling of the face and extremities (“dropsy” or edema) often was a precursor to the eclamptic convulsion. By the mid-19th century, physicians suspected that eclampsia might cause “chronic nephritis,” a disease associated with the loss of kidney function and the appearance of protein in the urine. In response to this insight, scholars hypothesized that eclampsia was caused by uremic poisoning that followed deficient renal excretion, and used the term “nephritic toxemia” to describe the two conditions that lead to imminent eclampsia: proteinuria and edema (Woods, 1902, p. 659-64; Chesley, 1984, p. 801-20).

By the 1890s, after technological advancements made it possible to measure blood pressure noninvasively, physicians were able to investigate the association between high blood pressure (hypertension) and renal disorders. Soon researchers recognized that the presentation of hypertension and protein in the urine (proteinuria) in pregnancy increased the risk of eclamptic seizures and the high rates of mortality associated with the disorder (Pond, 1903, p. 184-6; Roberts, Pearson, Cutler, & Lindheimer, 2003, p. 437-45). Believing that hypertension, not chronic nephritis, was likely the cause of the seizures, in the 1930s some



researchers concluded that “the toxemias of pregnancy are probably not toxemias” (Herrick, 1932, p. 210-20).

As the medical community shifted its focus from eclampsia to the set of symptoms that presented before the appearance of the eclamptic convulsions, greater attention was given to what has been labeled “preeclampsia.” During the second half of the 20th century, medical authorities from numerous national settings debated and proposed a variety of definitions for preeclampsia and other hypertensive disorders of pregnancy. At this time most medical authorities understood preeclampsia as a disease defined by the presentation after 20 weeks of gestation of at least two of the following symptoms: hypertension, proteinuria, and/or edema. Controversies remained over the optimal methods for measuring blood pressure (BP), and over whether hypertension should be defined by absolute readings above a designated level or by a rise in BP from an established baseline (Report of the National High Blood Pressure Education Program Working Group, 2000, p. S1-S22). In 1996 and 2002, the American College of Obstetricians and Gynecologists (ACOG) adopted more stringent guidelines that more precisely separated preeclampsia from gestational hypertension, a less severe hypertensive disorder of pregnancy that presents without proteinuria or other multiorgan failure. The new guidelines eliminated edema as a determinate for diagnosis and embraced absolute BP readings over 140 systolic or 90 diastolic rather than a rise in BP over baseline as the standard criteria for hypertension. Most international health agencies currently accept the ACOG classifications.

According to current ACOG standards, preeclampsia is diagnosed when a woman with a fetus of at least 20 weeks receives two BP readings at least four hours apart above 140 systolic or 90 diastolic and presents with protein in the urine (≥ 300 mg in a 24-hour urine collection). Eclampsia is defined as seizures in a setting of preeclampsia without an alternate explanation. Gestational hypertension refers to a milder disorder characterized by the appearance of hypertension during the second half of pregnancy in the absence of proteinuria. Chronic hypertension designates women with hypertension before the 20th week of gestation, and superimposed preeclampsia includes chronic hypertensive patients who then develop proteinuria during the pregnancy. Hypertensive Disorders in Pregnancy (HDP) is the umbrella term that comprises all of these disorders.

Advances and setbacks in the struggles against HDP morbidities

During the last century, advances in medical knowledge have successfully reduced the rate at which preeclamptic symptoms advance to eclamptic seizures. As a result, the number of



maternal and fetal deaths associated with eclampsia have declined dramatically. For example, at the turn of the 19th century more than one in four women who suffered from eclamptic convulsions did not survive delivery. By the 1970s, the case fatality from eclampsia at advanced medical centers had dropped to under 1% (Davies, 1979, p. 373-86). In the United States, much of this decline took place during the middle decades of the 20th century. A population-based analysis of births in Michigan between 1950 and 1971 found a ten-fold drop in maternal death rates due to preeclampsia (toxemia) during these decades (Schaffner, Federspiel, Fulton, Gilbert, & Stevenson, 1977, p. 821-9). Similar rates of reduction were found in another population-based study of maternal deaths in Massachusetts between 1954 and 1985 (Sachs, et al., 1988, p. 671-5). Rapid reductions in the rates of eclamptic seizures also were reported during these decades throughout the world (Douglas & Redman, 1994, p. 1395-1400; Corkill, 1961, p. 428-34). Currently in developed countries eclampsia affects only 0.1% of all pregnancies (Wagner, Barac, & Garovic, 2007, p. 560-6).

Success in curtailing the mortalities associated with eclampsia, however, has not arrested the onset or the morbidities associated with preeclampsia and the other less severe hypertensive disorders in pregnancy. To the contrary, in recent decades both the number and percentage of women suffering from these disorders have been escalating rapidly. A generation ago, it was estimated that hypertensive disorders affected between 6 to 8% of all pregnancies (Rochat, Koonin, Atrash, & Jewett, 1988, p. 91-7; Zhang, Meikle, & Trumble, 2003, p. 203-12). By the early years of the 21st century, studies indicated that about one in ten pregnant women were so affected, a percentage which translated into more than one-half million new cases each year in North America alone (Lydon-Rochell, et al., 2005, p. 125-34; Wagner, 2007, p. 560-6). More recent data suggests that the percentage of pregnant women suffering from hypertensive disorders has risen to 12-18% worldwide (Huda, Freeman, & Nelson, 2009, p. 1581-94; Rath & Fischer, 2009, p. 733-8). Despite changes in the diagnostic guidelines for preeclampsia that logically should have reduced the diagnosis of this disease, during the last fifteen years the incidence rates of preeclampsia have grown at an even more rapid pace than that of the less severe forms of HDP. Notwithstanding the significant medical advances of the last century, according to a 2006 report of the World Health Organization, HDP are responsible for 16% of all maternal deaths in developed countries and 26% in developing countries (Khan, Wojdyla, Say, Gulmezoglu, & Van Look, 2006, p. 1066-74).

This recent trend is alarming because a growing body of evidence confirms that the impact of hypertensive disorders on public health extends beyond the immediate increased maternal morbidity and mortality risks. Because the onset of preeclampsia can strike even before the fetus is viable, and the only known cure for the disease is delivery of the placenta,



neonates of preeclamptic mothers often are pre-term and of low birth weight. Each of these conditions is associated with increased risks for these children in psychomotor/intellectual impairment, diabetes, obesity, cardiovascular disease morbidity and early mortality (Puga B, Puga PG, De Arriba, Armendariz, Labarta, & Longas, 2009, p. 358-70; Smith, et al., 1997, p. 1189-93; Hovi, Andersson, Raikonen, Strang-Karlsson, Jarvenpaa, & Eriksson, 2010, p. 54-59 e1; Cooper, Atherton, & Power, 2009, p. 235-44; Pulver, Guest-Warnick, Stoddard, Byington, & Young, 2009, p. e1072-7; Reinehr, Kleber, & Toschke, 2009, p. 579-84).

Equally disturbing are the latent maternal risks associated with hypertensive disorders of pregnancy, in particular the more severe forms of preeclampsia. Recent studies have shown that women with a preeclamptic history have more than double the risk of early cardiac, cerebrovascular, and peripheral arterial disease and more than triple the risk of cardiovascular mortality than women of normotensive pregnancies of similar age (McDonald, Malinowski, Xou, Yusuf, & Devereaux, 2008, p. 918-30). Meanwhile, the relative risk for hypertension is about four times greater among women with a history of preeclampsia than women of similar age without this history. Preeclamptic patients in comparison with non-preeclamptic women also had about twice the future risk for ischemic heart disease, about twice the later risk for venous thromboembolism, and about 1.5 times the future risk of all-cause-mortality. Even more alarming, women who contracted preeclamptic symptoms before 37 weeks gestation suffered an eightfold increased risk for future ischemic heart disease over non-preeclamptic women (Bellamy, Casas, Hingorani, & Williams, 2007, p. 974-86).

The subsets of women who develop preeclampsia in second or later pregnancies and in subsequent pregnancies also carry more adverse health outcomes than preeclampsia among first-time mothers. For example, according to a 2009 study based on more than one million deliveries, nulliparous women with preeclampsia are about twice as likely as normotensive mothers to develop hypertension, ischemic heart disease, and congestive heart failure within a mean followup time of less than fifteen years after first delivery. These risks expand to triple the normotensive rates among women inflicted with preeclampsia in their second pregnancy. For women suffering from preeclampsia in both their first *and* second pregnancies, the future risks are six times greater than for women experiencing healthy pregnancies. Women with preeclampsia who delivered before 37 weeks gestation (early-onset preeclampsia) when compared with those with uncomplicated pregnancies also had seven- to eight-fold higher risks for developing hypertension and diabetes mellitus (Lykke, Langhoff-Ross, Sibai, Funai, Triche, & Paidas, 2009, p. 944-51), and a six fold greater risk for developing end-stage renal disease among women with one versus no preeclamptic pregnancies. For mothers with two or more preeclamptic pregnancies the relative risk of developing end-stage renal disease soared to over



fifteen times of those with uncomplicated pregnancies (Vikse, Irgens, Leivestad, Skjaerven, & Iversen, 2008, p. 800-9).

This brief summary of recently published evidence suggests consistency in the direction and magnitude of risks between forms of hypertensive disorders in pregnancy and a wide variety of future cardiovascular disorders. Depending on the presentation, frequency, and onset of these hypertensive disorders, women with complicated pregnancies are two to eight times more likely to experience adverse cardiovascular events within two decades of first-deliveries than women without this history. Preeclamptic women delivering before 37 weeks gestation, and mothers with recurring preeclampsia in multiple pregnancies carry the greater risks. These sex-specific risks are of similar magnitude to many traditional cardiovascular disease risk factors, including smoking, obesity, and chronic hypertension (Padwal, Straus, & McAlister, 2001, p. 977-80).

Understanding the rise in HDP cases and morbidities

Although the mechanisms that cause these disorders remain controversial, epidemiological studies, such as the ones stated above, clearly identify a number of risk factors that predispose women to the disease. For centuries we have known that nulliparous and multigestational pregnancies are at higher risk for eclampsia/preeclampsia. Other identified risk factors include advanced maternal age, smoking, high pre-pregnancy body mass index (BMI), black ethnicity, family history of preeclampsia, and the presence of a number of preexisting conditions, including chronic hypertension, diabetes, and renal disease.

Some of these risks are biologically determined and therefore are largely beyond the control of human populations. For example, first-time pregnant mothers are two to four times more likely to suffer from preeclampsia than mothers previously pregnant. Therefore, if humans are to procreate, nature requires all first-time mothers to accept the increased morbidity risks associated with nulliparous pregnancies. In addition, mothers with multigestational pregnancies carry greater risks of complicated pregnancies. As a result, short of selective abortion, society also cannot reduce this additional risk to pregnant women who carry more than one fetus.

Even these largely uncontrollable biological risk factors, however, can be influenced by cultural and personal decision-making. To illustrate, in developed countries the average size of the family unit has been decreasing for a number of decades as large households have become less common. In 1970, for example, when more than one in five US households contained five or more family members, the average number of children under 18 in a US family was 1.27. By



2009, this average had dropped by 34 percent to 0.84 children per family unit as the proportion of large family units declined to about one in ten (Rawlings, n.d.; US Census Bureau, n.d.). Such familial decisions to reduce family size resulted in a higher percentage of nulliparous births, a demographic that in turn raises the risk of morbidities associated with hypertensive disorders in pregnancy.

Similarly, advances in in-vitro fertilization (IVF) techniques, while providing millions of women with an opportunity to enjoy motherhood, inadvertently results in a larger percentage of multigestational deliveries. In recent years, for example, children of multiple births account for more than 4 percent of all births in the United States, which is about twice the percentage of multigestational children born forty years ago (National Vital Statistics Reports, 2009). As the proportion of lower risk singleton deliveries decreases, the prevalence of preeclampsia will simultaneously rise.

Other HDP risk factors are even more directly influenced by cultural decisions. The decision of modern family units to delay childbearing, for example, adversely impacts the rates of preeclamptic pregnancies by raising the proportion of births to higher risk mothers of more advanced age. Between 1970 and 2006, the average age of first-time US mothers increased 3.6 years, from 21.4 to 25.0 years. This increase occurred in every state, although it was particularly pronounced in the northeast and west. During this time the proportion of US mothers aged 35 years and over increased nearly eight times (Mathews & Hamilton, 2009). In recent decades many other developed nations have observed similar increases in the average maternal age and in the numbers of women of advanced age giving birth. In Canada, for example, between 1970 and 2005 the average age at first-birth increased from about 24 years to over 28 years, while the proportion of first-time pregnant women over 30 years of age increased about 300% (Report on the Demographic Situation in Canada, 2005 and 2006, 2008). Similarly, by 2006 the average age of first-birth in the nations of the European Union had reached 27.7 years; in Japan the average age of first-birth reached even higher levels at 28.7 years (Vienna Institute of Demography, 2008).

Another social factor influencing the prevalence of preeclampsia is smoking habits. Although smoking is detrimental to many health outcomes for both mother and fetus and thus should be avoided, nonetheless, a smoking history actually lowers the risk of preeclampsia by approximately 33 percent (England & Zhang, 2007, p. 2471-83). In the last several decades, public health anti-tobacco campaigns have attempted to reduce smoking rates. Although the success of these effects vary widely by world region, in most nations smoking rates have declined during the last four decades (European Commission, 2006, p. 3-17, 57-60). For example, whereas in 1970 about 45% of women in the United Kingdom were smokers, by 2007



this percentage was cut in half to only 21% (Smoking--Statistics, 2009). Meanwhile, whereas about 34% of women in the United States were smokers in 1965, by the turn of the century this number was reduced to about 22%. This decline was even more substantial among African-American women. Currently, only 13% of pregnant US women are smokers (Women and Smoking: A Report of the Surgeon General, 2002; Women's Health USA 2009: Smoking During Pregnancy, 2009). Although these decreases are welcome news for public health educators, ironically, whatever gains have been made in counseling pregnant women to avoid tobacco have paradoxically resulted in higher rates of preeclampsia.

Culturally sensitive dietary and lifestyle choices also directly impact several other major and interrelated HDP risk factors: high pre-pregnancy BMI and preexisting metabolic abnormalities. Obesity and metabolic disorders associated with it (i.e. diabetes, chronic hypertension) have tripled around the industrialized world in less than two generations. To illustrate, in the 1970s the median BMI in the United Kingdom was a healthy 23, a level that was similar to the median BMI of that nation when MA Quetelet first created this "measurement of fatness" in 1842. By the late 1990s, however, the median BMI in the UK had risen to 26, indicating that more than 60% of the adult population was overweight (Wilkin & Voss, 2004, p. 511-20).

Numerous factors have contributed to the rising worldwide obesity epidemic. Modern changes in the processing of food and in the availability of low-cost high-caloric foods and drinks, coupled with the growing reliance on the automobile for personal transport and the replacement of labor intensive employment with more sedentary occupations, have contributed to sudden and often unhealthy alterations in the human anatomy. As Terence Wilkin and Linda Voss (Wilkin & Voss, 2004, p. 512) have noted, "equipped with genes ideally suited to—and expressly selected for—the storage of fat, modern man now inhabits a land of plenty. Worse still, we do not possess genes to control obesity, because weight excess was never until now a pressure on survival". Whereas in previous times infection was the number one public health enemy, today the metabolic syndrome is emerging as the world's primary cause of morbidity and mortality. According to the World Health Organization, overnutrition, not undernutrition, is now the principal cause of global malnutrition. As rates of the metabolic syndrome and its adverse consequences continue to rise, it is not surprising to find the rates of preeclampsia are rising with it.



Conclusions

Because risks for developing HDP increase with nulliparity, multiple gestations, advanced maternal age, decreased smoking, high-pregnancy BMI, and a history of metabolic disorders such as diabetes and chronic hypertension, modern trends such as delayed childbearing, smaller family size, IVF procedures, and the rising incidence of high-caloric malnutrition all contribute to the growing incidence of hypertension in pregnancy (Duckitt & Harrington, 2005, p. 565; Chen, Bottomley, Smith, Leader, & Walker, 2009, p. 1-12; Luo, An, Larante, Audibert, & Fraser, 2007, p. 36-45). The contemporary world community is confronting a perfect storm that threatens the future health of millions of women and their offspring.

Given the enormity of the storm, finding effective ways to navigate through it is a difficult task because many HDP risk factors cannot be addressed in socially responsible ways. For example, it would neither improve overall health nor be ethically appropriate to attempt to reduce HDP incidence rates by forbidding IVF techniques to infertile women, by promoting smoking in pregnancy, or by encouraging through tax incentives younger maternal ages at first-births and larger family units.

On the preventive side, screening females for a history of preeclampsia should become as commonplace as inquiring about tobacco use, and its presence should constitute one variable in evaluating a patient for future cardiovascular disease. Physicians should take careful histories, including obstetrical histories, of all their female patients. Just as best practice protocols require counseling and regular screening for hypertension during pregnancy because it is a marker of dangerous multi-organ syndromes, it is reasonable to expect physicians to provide counseling and care for at risk women subsequent to their deliveries. Greater public attention can and should be given to interventions designed to control the health problems associated with excess weight gain. Despite the difficulties of navigating through this stormy crisis, implementing such preventive interventions have the potential to slow or arrest the HDP epidemic that is endangering the health of the global community.



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Notes

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