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Author manuscript

Biochem Pharmacol. Author manuscript; available in PMC 2021 December 01.

Published in final edited form as:

Biochem Pharmacol. 2020 December ; 182: 114247. doi:10.1016/j.bcp.2020.114247.

Comparative Risks and Predictors of Preeclamptic Pregnancy in the Eastern, Western and Developing World

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Abstract

Preeclampsia (PE) is a complication of pregnancy characterized by hypertension (HTN-Preg), and often proteinuria. If not managed promptly, PE could lead to eclampsia and seizures. PE could also lead to intrauterine growth restriction (IUGR) and prematurity at birth. Although PE is a major cause of maternal and fetal morbidity and mortality, the underlying mechanisms are unclear. Also, there is a wide variability in the incidence of PE, ranging between 2 to 8% of pregnancies in the Eastern, Western and Developing world, suggesting regional differences in the risk factors and predictors of the pregnancy-related disorder. Several demographic, genetic, dietary and environmental factors, as well as maternal circulating biomarkers have been associated with PE. Demographic factors such as maternal race and ethnicity could play a role in PE. Specific genetic polymorphisms have been identified in PE. Maternal age, parity, education and socioeconomic status could be involved in PE. Dietary fat, protein, calcium and vitamins, body weight, and environmental factors including climate changes and air pollutants could also play a role in PE. Several circulating cytoactive factors including anti-angiogenic factors and cytokines have also been associated with PE. Traditional midwifery care is a common practice in local maternity care units, while advanced perinatal care and new diagnostic tools such as uterine artery Doppler velocimetry have been useful in predicting early PE in major medical centers. These PE risk factors, early predictors and diagnostic tools vary vastly in different regions of the Eastern, Western and Developing world. Further understanding of the differences in the demographic, genetic, dietary and environmental factors among pregnant women in different world regions should help in designing a region-specific cluster of risk factors and predictors of PE, and in turn provide better guidance for region-specific tools for early detection and management of PE.

Keywords

endothelium; hypertension; placenta; preeclampsia; pregnancy

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Conflict of Interest

None

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Introduction

Preeclampsia (PE) is a pregnancy-related disorder characterized by hypertension (HTN-Preg) and often proteinuria. If untreated preeclampsia could lead to eclampsia and seizures. PE could also be associated with intrauterine growth restriction (IUGR), premature labor, and low newborn birth weight for gestational age. Although PE is one of the leading causes of maternal and perinatal morbidity and mortality [1], the underlying pathophysiological mechanisms are not clearly understood [2, 3]. Also, the incidence of PE shows a wide range between 2 and 8% of pregnancies worldwide [4, 5], and shows further variability in different countries and world regions [5]. The wide variability in the incidence of PE could be partly related to differences in the risk factors and predictors of PE in different parts of the world. Studies have suggested several demographic, genetic, dietary, environmental, and maternal circulating factors as potential risk factors and predictors of PE [6, 7]. Maternal demographic factors such as race and ethnicity could affect the incidence of PE. Certain maternal genes have been proposed to increase the risk of PE. Maternal age, parity, education and socioeconomic status could contribute to the risk of PE [5, 8]. For instance, pregnant women at very young/older age have higher risk of PE. Dietary fat, protein, calcium and vitamins, body weight, and environmental factors such as climate change and air contaminants could also affect the incidence of PE. For example, pregnant women with higher body mass index (BMI) may be more prone to PE. Importantly, while traditional midwifery care is the main health resource in local maternity units, cutting-edge perinatal care, new diagnostic tools, advanced laboratory tests, and ultrasonography are available in major medical centers. Advanced diagnostic tools have been useful in detecting increased levels of circulating bioactive factors such as anti-angiogenic factors, cytokines, angiotensin receptor antibodies and reactive oxygen species (ROS) in women with PE [9, 10]. Also, Doppler velocimetry often shows uterine artery notching in late PE women. The reliance on these PE risk factors and predictors, and the availability of advanced PE diagnostic tools vary greatly in the Eastern, Western and Developing world.

In this review, we used reports from Pubmed, Medline and the World Health Organization to discuss the incidence and different risk factors and predictors of PE in the Eastern, Western and Developing world. We will first compare the pregnancy outcome data from representative countries in the Eastern world including China and Japan, the Western world including USA and Europe, and the Developing world including the Middle East, Africa and Latin America. We will discuss data gathered from the representative countries by studies conducted between the years 2000 and 2017 and included data from as early as 1967 until 2017, and use these data to compare the average incidence of PE in different regions of the world. We will describe how demographic, genetic, dietary and environmental factors vary among pregnant women in the Eastern, Western and Developing world. We will also describe the various PE biomarkers and diagnostic tools used in clinical practice and in experimental animal models of hypertension in pregnancy (HTN-Preg). We will finally discuss how further understanding of the differences in the demographic, genetic, dietary and environmental factors, and in the availability of advanced diagnostic tools could help in the design of a region-specific cluster of risk factors and predictors of PE, and in turn provide guidance for region-specific tools for early detection and management of PE.

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1. Regional Differences in the Incidence of PE

Clinical and epidemiological studies have assessed the incidence of PE among pregnant women in different countries and regions of the world (Fig. 1). Studies from the years 2000 to 2017 that included data from as early as 1967 until 2017, were conducted in different cohorts of pregnant women, and determined the number of PE cases in these cohorts. The incidence of PE was then calculated as the number of PE cases divided by the number of pregnant women in the respective cohort (Fig. 1). In 4 different studies in Eastern countries, the incidence of PE appeared to be lowest in Vietnam (0.2 to 1.19%) and highest in the Philippines (3.6 to 6.3%). In the Western world, 4 studies showed the lowest PE incidence in Spain (0.7 to 1.6%) and the highest incidence in Finland (3.6 to 8.1%). In the Middle East, 4 studies showed that the lowest incidence of PE was in Saudi Arabia (0.9 to 1.3%), the highest incidence was in Iran (3.3 to 7.8%), and the greatest variability in the incidence of PE in Jordan (0.9 to 6.8%). In Africa, 4 studies showed almost similar incidence of PE in most countries (2 to 4%), with the most dramatic variability in DR-Congo (0.8 to 8.5%), and the highest incidence in Africa and among all countries of the world in Ghana (4.4 to 11.8%). In Latin America, the incidence of PE appeared to be high in most of the countries studied, with the most apparent variability in Brazil (1.5 to 8.2%) and the highest incidence in Ecuador (3.5 to 9.6%). Thus while the incidence of PE appears to be somewhat consistent among different studies in Eastern and Western countries, the highest incidences and greatest variability are observed in Developing countries. The large variability in the incidence of PE among different studies makes it important to not rely on only one study, but to study the trends and average incidence of PE from multiple studies.

We calculated the average incidence of PE from the aforementioned 4 different studies using two approaches. In the first approach, we divided the sum of the number of PE cases from the 4 different studies by the sum number of pregnant women in the 4 respective cohorts (Fig. 2A, 2C, 2E and 2G). In the second approach, we averaged the 4 reported incidences of PE from the 4 different studies to calculate the means±SEM, which allowed us to statistically compare the average incidence of PE in different countries and regions (Fig. 2B, 2D, 2F and 2H). The cumulative data from these 2 different approaches supported the notion that among the Eastern countries the average incidence of PE was lowest in Vietnam and highest in the Philippines. Among Western countries, the average incidence of PE was lowest in Spain (1%) and highest in Finland (5.58%). The calculated incidence of PE in Europe and USA appeared to conform with the general estimates that PE complicates 2 to 5% of pregnancies in the Western world, but showed some differences in specific countries. For example, a previous study has shown that the overall incidence of PE in Norway is 3.5% [11], while the calculated average from 4 different studies suggests that the incidence of PE in this Northern European country is higher (3.97%). In Middle Eastern countries, the average incidence of PE was lowest in Saudi Arabia and highest in Iran. In Africa, the average incidence of PE was almost similar in different countries with an apparent spike in Ghana. Among Latin American countries, the average incidence of PE appeared to be low in Chile, and was largely not statistically different among different countries, except between Mexico and Argentina.

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When the average incidence of PE was compared by region, the Eastern world appeared to show the lowest incidence (2.27%), with a stepwise increase in the Western world (3.3%) and Middle East (3.22%), and further increase in Africa (4.18%) and Latin America (4.65%) (Fig. 2G, 2H). This is consistent with studies demonstrating that Asian-Chinese, New Zealand-Chinese and Asian-American women have a lower incidence of PE compared with their European, Native American and African-American counterparts [12–14].

A cursory look at the incidence of PE suggests that it is higher in countries with low and middle income populations [15, 16]. Although some studies have suggested that the incidence of PE is higher in countries with low and middle income, the variability observed in these studies and presented in this review does not support such a correlation. For instance, the per capita income in Philippines is higher than that in Vietnam, while PE incidence shows the opposite, with the average incidence of PE lowest in Vietnam and highest in the Philippines. Likewise, in Africa, Ghana shows the highest average incidence of PE at 7.2% and the DR-Congo shows an average PE incidence of 5.1%, but the per capita income is higher in Ghana ($4,650) compared with DR-Congo ($900). Also, Finland has a much higher per capita income ($45,580) and is ranked the 12th country in the Human Development Index (HDI), a summary measure of average achievement in key dimensions of human development including a long and healthy life, being knowledgeable, and having a decent standard of living. Yet, Finland has an average 5.6% incidence of PE, which is much higher than the 0.65% PE incidence in Vietnam with 118th HDI ranking. Additionally, all developing countries in Latin America have a much higher per capita income than any developing country in Africa, yet the PE incidence is almost the same in the two continents. Moreover, the reported incidences of PE do not take into consideration the different regions in each country. For example, in large countries, like Brazil, variation of PE incidence ranging from 1.5% to 8.2% can be related to different levels of development in different regions of the country that are dependent not only on family income, but also healthcare accessibility. These observations suggest the contribution of other factors beyond socioeconomics.

The higher incidence of PE in Africa and Latin America compared with Eastern and Western countries, makes it important to further examine the causes of such disparity. One main reason for the incidence of PE to be as high as 10% of pregnancies in Developing countries could be related to inadequate maternal and prenatal care [4]. This could also be partly related to inadequate keeping of medical records, limited resources and diagnostic tools, and decreased confidence in reported data from clinical and epidemiological studies in Developing countries. Specific demographic, genetic, dietary and environmental factors in the Developing world including maternal age, education, lack/surplus of certain nutrients in diet and BMI could also place pregnant women at higher risk of having PE [6, 9] (Fig. 3). Of note, socioeconomics can influence lifestyle and other demographic factors differently depending on the region and country, and these factors could be superimposed. In the following sections, we will discuss the risk factors and predictors of PE in different countries and world regions, which should help to understand the reasons of the variability in the incidence of PE, and shed further light on the predisposing factors and underlying mechanisms of PE.

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2. Demographic and Genetic Factors in PE

2.1 Maternal and Paternal Race—The incidence of PE varies among women of different race, with a higher incidence in African-American (5.2%) than Caucasian, Hispanic (4.0%) and Asian women (3.5%), when controlled for maternal age, parity, education, and gestational age [13] (Fig. 4). Overall, Hispanic and Asian women show a decreased risk while non-Hispanic black women show more severe PE compared with non-Hispanic White women during their first pregnancy [17]. Also, while the overall incidence of HTN-Preg in Asian-American women is 2.72%, Filipino-American women are more likely to experience PE than other Asian ethnic groups [18]. Among Asian-American groups, the incidence of PE is 5.30% in Filipino, 2.80% in Asian-Indian, 2.34% in Korean, 2.21% in Vietnamese, 2.19% in Japanese, 1.41% in Chinese, and 2.98% in other Asian ethnic groups [19]. Also, the rates of PE are higher in Filipinos, Native Hawaiians and other Pacific Islanders, but lower in Chinese and other Asian groups compared with Whites, and this is likely related to maternal age, obesity, and multiple pregnancy [20]. Collectively, while the contribution of race to PE could be better evaluated in more homogenous populations such as in Asia, Africa and the Middle East, the role of race is more difficult to evaluate in a multi-racial and multi-cultural society such as the USA. Therefore, while the average incidence of PE in Asian and African countries could be representative of the whole society, the average incidence of PE in USA should be considered with caution as it may not reflect the racial and ethnic diversity in the society.

Paternal ethnicity could also play a role in the incidence of PE (Fig. 4). Studies have shown that Asian paternity was associated with the lowest rate of PE (odds ratio [OR] 0.76, 95% confidence interval [CI] 0.68 – 0.85), with an increase in the rate of PE (OR 1.13, 95% CI 1.02–1.26) among parents with different ethnicity compared with those with the same ethnicity [13]. Because of the diverse demographic, cultural, socio-economic characteristics and the different geographic location and environment for different segments of the population in the USA, evaluating the role of paternal ethnicity could be even more complex when compared with a more homogeneous society such as China.

2.2 Hereditary and Genetic factor—Maternal、fetal and paternal genes may play a role in PE [9]. Women and men born from PE pregnancies have higher risk of PE in their own or their partner’s pregnancy, suggesting inheritance of PE susceptibility genes [21]. Differences in the incidence of PE among different races have also supported a role of genes in the racially disparate incidence of PE. Several genes have been implicated in PE including those involved in thrombophilic, vasoactive, immune and metabolic processes as well as cell signaling, and racial differences in genetic variants of PE have been reported [22–24]. Polymorphisms in the methylene tetrahydrofolate reductase 677T, and factor V Leiden mutations among White and Indonesian mothers have been associated with PE [25]. Fetal HLA-C is a major inhibitory ligand for maternal killer cell immunoglobulin-like receptor (KIR) that regulates the cytotoxic activity of natural killer (NK) cells in the placenta. In sub-Saharan Africans, White, and Chinese Han populations, different interactions between maternal KIR gene variants and the genes encoding fetal HLA-C have been associated with PE [26, 27]. The KIR AA genotype is a risk factor for PE in both Europeans and sub-Saharan Africans populations, while different KIR B genotypes were found to protect

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against PE in both populations [28]. In Caucasian subjects, studies have shown a relation between the frequency of *CORIN* gene variations and PE [29]. Also, studies in a subset of early onset and severe PE placentae have shown racially disparate expression of the cardiovascular developmental transcription factor Nkx2–5 with Caucasians > African-Americans [30]. Nkx2–5 expression was highly correlated with the mRNA expression of the PE marker sFlt-1, and this correlation was significant in Caucasian, but not African-American women [30]. In Japanese subjects, the TT genotype of angiotensinogen (AGT), heterozygosity of the Glu298Asp variant and homozygosity of the Glu298 genotype of the endothelial nitric oxide synthase (*NOS3*) gene are independently associated with HTN-Preg [31]. Also, in Dutch women, a M235T polymorphism is associated with a history of elevated blood pressure during pregnancy [32, 33]. In Brazil, the T allele of the rs1319501 of the nicotinamide phosphoribosyl transferase gene is associated with PE [34]. In the Chinese Han population, the G allele of rs-2228570 of the Vitamin D receptor gene、IL-10 −1082A/G and −819T/C、IL-27 rs153109, rs17855750 variants, 11β-HSD2 and KIR genetic variations have been related to PE [35–37]. In contrast, COX2–1195A homozygosity、and variant GAS6+1332 T allele are associated with a decreased risk for PE in the Han Chinese population [38–40].

Although several genes have been linked to high or low incidence of PE, it is not clear how these genes could affect BP and vascular function. Further studies of these genes in different races and in different world regions will further clarify their role in PE.

2.3 Maternal age—PE is more likely to occur at the extremes of reproductive age. The incidence of PE is higher with advanced maternal age [41–43], and is also common in women younger than 20 years of age [44]. Maternal age varies markedly in the Eastern, Western and Developing world (Fig. 5). The maternal age at childbirth has shown substantial increase in many Western countries [45]. The proportion of first births for women aged over 35 years has increased in the United States and Europe (Table 1). The mean age of women at childbirth in Western countries increased from 29.3 years in 2003 to 29.8 years in 2009 [46]. The proportion of women with maternal age ≥35 years is less in Eastern than Western countries. In China, the overall average maternal age is 28.4 years [47]. The relatively young maternal age could partly explain the lower incidence of PE in the Eastern world. However in Developing countries, there is a high teenage pregnancy, which is also associated with higher risks of PE and preterm labor [48]. According to the World Health Organization (WHO) 2010–2011 Multi-country Survey, the percentage of mothers age <20 years old is 14.4% in DR-Congo and 14.6% in the Philippines [49].

In recent years, pregnancy has been postponed in Asian cultures and maternal age over 35 years for the first child is not uncommon in Japan [50], Korea [51], and even China [52]. This is attributable to the recent increase in women's participation in the work force in Eastern countries. On the other extreme, teen pregnancies are common in some Western cultures particularly USA, thus increasing the risk of PE in this young segment of the population.

2.4 Parity—Nulliparity is a risk factor for PE [53], and the incidence of PE is higher in primiparous than multiparous women [19, 54, 55]. Parity varies markedly in the Eastern,

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Western and Developing world (Fig. 6). In China, due to the one child policy, most pregnant women were nulliparous, which could adversely affect the incidence of PE. In October 2015, China's one-child policy was changed to a two-child policy, and a large number of women became multiparous, although the maternal age also increased. In comparison, the parity in the Western world has been consistent in the range of 1 to 3. This is because most Western women pursue a career, and the large expense of child-care limits the number of pregnancies. In marked contrast, in some cultures such as the Middle East and Africa, maternal fertility and child-bearing is valued and even rewarded by the society.

2.5 Singleton vs multiples pregnancy—Women with multiples pregnancy, e.g. twins, are more likely to develop PE than women with singleton pregnancy [56, 57] (Fig. 7).The relative risk of PE is ~2.8 fold in multifetal over singleton pregnancies [58], and the risk is directly correlated with the number of babies [59]. This could be related, in part, to placental efficiency (i.e. the ratio of fetal weight to placental weight). Also, women who conceive multiples pregnancy through Assisted Reproductive Technologies have a 2.1-fold higher risk of PE than those who conceive naturally [60].

The reliance of women on Assisted Reproductive Technologies to improve fertility could be related to socio-demographic factors. For instance, Caucasian and older women are more likely to seek Assisted Reproductive Technology. A study in California found that Caucasian and Asian women comprised most (90%), whereas Hispanic women comprised only 8% of all Assisted Reproductive Technology pregnancies [61].

2.6 Maternal Education—The relationship between maternal education and pregnancy outcome has shown marked variability in different regions [62–64]. Post-secondary education is more common in the Western world compared to the Eastern and Developing world (Fig. 8). This is largely because of the marked difference in the standard of living, and the lower income and decreased affordability of higher education in the Developing world. Although the relation between the level of maternal education and the incidence of PE has not been directly studied, maternal higher education may be associated with a lower risk of HTN-Preg [65].

2.7 Number of Partners—In women without a history of PE, a change of partner is thought to increase the risk of PE [66, 67]. Because of cultural differences, Eastern women may have fewer partners than Western women. For instance, the majority of Chinese women maintain a stable sexual relationship for more than a year before becoming pregnant, and they usually have a long-lasting sexual relationship with the same partner.

3. Dietary and Environmental Risk Factors in PE

3.1 Diet—The incidence of PE may be affected by dietary patterns and nutritional factors. High total energy, high salt, and low dietary magnesium and calcium intake during pregnancy have been related to HTN-Preg [68, 69]. In support, pregnant rats on a high fat diet demonstrate aberrant lipid metabolism and PE-like manifestations. In comparison, diets high in fiber and potassium and plant-derived food seem to reduce the risk of PE [70, 71]. Studies in China and Norway suggest that vegetarian diet is associated with decreased risk

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of PE [72, 73]. A study among Australian women has shown that implementation of a Mediterranean diet with large vegetable components before pregnancy could help in the prevention of HTN-Preg [74].

Dietary patterns vary markedly in different world regions. The Western diet is higher in salt and sugar compared with that in Eastern countries. In USA, the “meat” dietary pattern is common among Hawaiians, while the “bean” pattern is more common among women with Chinese and Japanese background [75]. Differences in dietary pattern have been found between Chinese and European communities living in the same country [76]. Compared to Caucasians, Chinese migrants have lower energy and fat dietary intakes and consume higher amounts of soy, grains, vegetables and fish, and lower amounts of meat, dairy products, sweets and alcohol than Caucasians. One study has shown that the energy-adjusted total fat intake is at least 10% lower in Chinese and Japanese women than African, Caucasian and Hispanic women [77]. The differences in caloric, salt and meat intake between different ethnic groups may contribute to the differences in the incidence of PE.

Other nutrition factors have shown effects in animal models of HTN-Preg and could play a role in PE. In an animal model of HTN-Preg, a maternal diet containing high levels of folate, vitamin B12 and docosahexaenoic acid (DHA) reduced the risk for cognitive disorders in the adult offspring [78]. Also, a combined supplementation of folic acid, vitamin B12, and omega-3 fatty acid improved placental levels of the anti-inflammatory cytokine IL-10 in a rat model of HTN-Preg, and decreased the levels of the inflammatory cytokine TNF-α in livers of 3 month old offspring [79].

Low dietary calcium less than 700 mg increases the risk of PE, and calcium supplementation for women with low dietary calcium could reduce the risk of PE by 30% to 50% [80]. The potential role of dietary calcium and vitamin D in reducing the incidence of PE has been highlighted in WHO reports (Table 2). Following nutrition data, the WHO issued a recommendation that pregnant women should have calcium supplements to prevent PE. The guidelines recommend daily administration of supplemental calcium and vitamin D from 20 week of gestation. However, these recommendations should be adopted with caution, as the incidence of PE is higher in Western than Eastern countries although diets rich in calcium are more common in Western countries. Also, the recommended dietary intake of vitamin D for pregnant and lactating women may need to be adjusted in different countries. For instance, deficiency in the intake of calcium and antioxidant vitamins is more common and may be responsible for the higher incidence of PE in the Developing world compared to the Western and more developed countries [81]. Pregnant women in Asia, the Middle East, Africa and Latin America are at risk of vitamin D deficiency [82]. A study in Ecuador showed that pregnant women in Ecuador’s Andean area consumed only 60% of the calcium intake recommended by WHO [83]. Thus, if used adequately in different world regions, calcium and vitamin D could be a relatively affordable supplement to reduce the incidence of PE.

3.2 Obesity—Obesity is a major risk factor for cardiovascular and metabolic disorders. Increased body mass index (BMI) have been associated with late-onset PE, and studies have suggested that obesity increases the risk of PE [84–87]. The prevalence of overweight and

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obesity has been increasing in the population of many developed countries particularly USA (Fig. 9). Of note, in USA, obesity varies in different ethnic groups with the largest proportion of obesity among African-American, followed by Latinas and White women [88]. In comparison, overweight and obesity are less common and amount to only 21.2% of pregnant women in mainland China [89].

Weight gain during the course of pregnancy also varies with race. A study found that weight gain during pregnancy was less in Asians and Blacks than Caucasians [90]. Another study found that white women experienced excessive gestational weight gain (54%), which was more than that in Asian (43%) and Hispanic women (46%) [91]. Women in USA and Western Europe have higher pre-pregnancy BMI and higher rates of gestational weight gain, often surpassing healthy guidelines when compared with women in East Asia [92]. These observations highlight the importance of further studying the interrelationship between obesity, ethnicity, and pregnancy outcomes.

3.3 Exercise—Because overweight and obesity increase the risk of PE, prenatal exercise could reduce gestational weight gain and in turn the incidence of PE. Studies have shown that regular exercise during pregnancy decreases the risk of developing PE [93–96]. Exercise during pregnancy has been suggested to improve placental angiogenesis and endothelial function, and reduce the risk of vascular dysfunction during pregnancy and PE [97].

The benefit of physical activity before and during pregnancy has also been reported in animal models of HTN-Preg [98–100]. Physical activity has been shown to decrease BP and improve the angiogenic profile and placental efficiency in both normal pregnancy and in a rat model of placental ischemia and reduced uterine perfusion pressure [99].

The practice of exercise is different among races. Some studies suggest that black adolescents have less physical activity compared with their white counterparts [101]. Physical activity was lower in non-Hispanic Black or women of other race/ethnic groups than non-Hispanic white women [102, 103]. Some studies in Brazil suggest that pregnant women have low level of physical activity [104]. In China, physical activity is low among pregnant women, likely due to psychological factors such as fear of miscarriage and fatigue. Also, threatened abortion and preterm labor are common in China, which has led many pregnant women to prefer bed rest. Thus in general, Chinese women are more sedentary during pregnancy compared with women in Western countries

3.4 Climate—Seasonal variation in the incidence of PE has been reported in many countries [105–108]. Most studies suggest that women who give birth in Winter are at higher risk of developing PE than women who give birth in warmer seasons. A study from Tygerberg Hospital in South Africa showed that PE occurred in 11.5% of all admissions (1,329/11,585), with the highest incidence in Winter (13.6%) [107]. Women admitted in Winter had a higher risk of developing PE than those admitted in Summer. The risk of developing PE in June (Winter in South Africa) was higher than in February (Summer in South Africa). There was also a correlation between the number of PE cases and the minimum daily temperature [107]. In Europe, countries with colder climate such as Finland and Norway have higher incidence of PE than countries with warmer climate. There could

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also be an interrelationship between climate and race. A study found that while the incidence of PE decreased in white women during the Summer months, that pattern was not observed in black women [109].

3.5 Air pollution—Exposure to air pollution has been associated with systemic inflammation and oxidative stress, which could affect vascular remodeling and function during pregnancy [110]. Studies found that exposure to certain environmental contaminants may adversely affect cytotrophoblasts and contribute to PE [111]. Exposure to fine particulate matter <2.5 microns, particulate matter <10 microns, and nitrogen dioxide was associated with increased risk of gestational hypertension and PE [112, 113]. A study in China has suggested that prenatal exposure to particulate matter <10 microns and sulfur dioxide increases the risk of PE, and that these effects could be exacerbated by humidity [114]. However, in a large Norwegian pregnant women cohort, no statistically significant associations were found between moderate to low levels of nitrogen dioxide exposure during pregnancy and HTN-Preg or PE [115]. Environmental noise pollution may also be another risk factor for PE [116].

4. Prenatal care and minimizing complications of pregnancy

Prenatal care could minimize complications of pregnancy including PE, gestational diabetes and preterm birth. Guidelines for prenatal care have developed over the years and are now highly recommended for health pregnancy. Advocates for prenatal care recommend integrated maternal and fetal care, screening for diabetes, blood factors, iron deficiency anemia, vaccination history, tobacco or drug use, bacterial infection and sexually-transmitted disease, medical care, vitamins and folic acid supplementation, and counseling and psychosocial support. The number of women receiving prenatal care has steadily increased in the United States and other Western countries. On average, women in Western countries have between 7 to 12 prenatal visits to their family physician or obstetrician [117]. To minimize the incidence of PE, BP is monitored at each prenatal visit, and women are counseled on warning signs of PE. Women with history of chronic hypertension or PE in a previous pregnancy have additional measurements of baseline urine protein, uterine artery Doppler velocimetry, and other laboratory tests for biomarkers of PE [80].

Prenatal care is not well-adopted in developing countries partly because prenatal facilities are either absent or inadequate. Despite the dire economic conditions in many developing countries, pregnant women should be encouraged to use the existing facilities to their best advantage, and governments should provide resources and access to maternal care facilities. Unfortunately, even when prenatal facilities are adequate they are often underutilized because they are very distant or expensive, or due to widespread illiteracy or ignorance. Even literate women may not use prenatal services due to traditional and cultural beliefs and prejudices. Health Departments in developing countries should educate the population about the importance and availability of prenatal programs. With further education, access to information, and collaboration with the developed world, these prejudices should gradually disappear. Pregnant women attitude towards prenatal care could also be improved by further training of already existing and entrusted local traditional birth attendants or midwives, and their integration in the healthcare system [118].

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5. Predictors and markers of PE

Apart from delivery of the baby and placenta, there is no effective treatment for PE, making primary and secondary prevention of PE a major public health objective. Screening for women at high risk of PE and providing them with adequate care, could substantially improve the maternal and perinatal outcomes. The International Federation of Gynecology and Obstetrics (FIGO) encourages all countries to adopt and promote PE prediction strategies. The predictive methods range from basic diagnostic tools to advanced biomarkers. Clinical history of PE is an important risk factor of PE. There is also a large number of bioactive factors in the circulation and amniotic fluid that can be used as biomarkers of PE (Fig. 10). Some of these biomarkers have also shown similar pattern in animal models of HTN-Preg (Fig. 10). Uterine artery Doppler can also be used to predict PE. The reliance on these different methods in predicting PE varies in Western countries compared to Eastern and Developing countries.

5.1 Clinical history and early diagnosis of PE—

History of PE in a previous pregnancy is a risk factor of PE. A study found that the risk of recurrent PE is 14.7% in the second pregnancy and 31.9% in the third pregnancy among women with a history of PE [119]. Family history of PE or a cardiovascular disease is also a risk for PE. History of chronic hypertension, renal disease and diabetes mellitus is also considered in determining the risk of PE. As described above, other genetic, demographic and lifestyle factors such as maternal age and weight, different partners, and high salt diet could also be considered in PE risk prediction. If a pregnant woman is positive for these predictors, additional signs and symptoms are needed for early diagnosis of PE.

According to the guidelines of the American College of Obstetric and Gynecology (ACOG), the following signs and symptoms could be used for early diagnosis of PE:

1. Systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg on 2 occasions at least 4 hours apart after 20 weeks of gestation.
2. Proteinuria (≥300 mg per 24 hour urine collection, protein/creatinine ratio ≥0.3, or dipstick reading of 1+).
3. With high BP alone and even in the absence of proteinuria, PE can still be diagnosed if any of the following conditions is present. Evidence of other maternal organ dysfunction, including new development of renal insufficiency, liver involvement with or without right upper quadrant or epigastric abdominal pain; neurological complications (e.g. eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata); hematological complications; or uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth).

These guidelines for PE have evolved over the years and could vary among different countries. In 2010, The National Institute for Health and Care Excellence in the United Kingdom introduced evidence-based guidelines on the diagnosis and management of HTN-Preg, birth, and the postnatal period (www.nice.org.uk/guidance/cg107). In USA, the classification scheme of HTN-Preg adopted by ACOG in 2013 comprised four categories,

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i.e. chronic HTN that predates pregnancy, PE-eclampsia, chronic HTN with superimposed PE, and nonproteinuric gestational HTN [120]. In 2014, the Society of Obstetricians and Gynecologists of Canada released revised recommendations for HTN-Preg on the basis of literature reviews and criteria from the Canadian Task Force on Preventative Health Care [121]. The Society of Obstetric Medicine of Australia and New Zealand has expanded its definition of chronic HTN [122].

While these guidelines are readily available from various health agencies, they have not been fully implemented in different countries and world regions. As described in WHO's 2014 consultation on quality of maternal and newborn care: "… there has been limited progress in improving maternal and pediatric outcomes because of a major gap between coverage and the quality of care provided in health facilities". For instance, despite the issuance of these PE diagnosis criteria, the adoption of these guidelines is low in some African countries. In sub-Saharan African countries, a survey found less than a quarter (24%) of women admitted to labor and delivery services were asked about signs of PE or eclampsia, ranging from 11% in Mozambique to 34% in Kenya and Ethiopia. Only 77% had their BP checked upon admission, and less than half (46%) underwent testing for proteinuria [123].

5.2 Biomarkers and biochemical profile of PE—Studies have suggested multiple screening biomarkers for PE including angiogenic and antiangiogenic factors involved in placental development, markers of endothelial dysfunction, inflammatory cytokines, and angiotensin receptor antibodies [124, 125] (Fig. 10). Some of the biochemical indexes closely related to the onset of PE include increased sFlt-1/PlGF ratio, soluble fms-like tyrosine kinase-1 (sFlt-1) levels, free vascular endpothelial groth factor (VEGF), soluble endoglin (sEng), and cell-free fetal DNA (cffDNA), and decreased placental growth factor (PlGF), placental protein 13 (PP13) and pregnancy-associated plasma protein A (PAPP-A) [126–128]. Maternal circulating sFlt-1 and sEng are increased and free PlGF is decreased several weeks prior to the signs and symptoms of PE [129–131]. Among these biochemical factors, the sFlt-1/PlGF ratio shows certain accuracy in predicting PE [132, 133]. Some of the biomarkers of PE in human show a similar pattern in HTN-Preg rodents [6] (Fig. 10).

The levels of circulating biomarkers could show some racial/ethnic differences. A study found that the associations between low levels of PlGF and high levels of sEng and early-onset PE were stronger in Whites and Hispanics than in Blacks. Higher sFlt-1 (or sVEGFR-1) levels were associated with increased risk of early-onset PE only in Hispanic and White women [134]. Racial/ethnic differences have also been reported in tumor necrosis factor-α (TNF-α). A pro-inflammatory pattern with increased TNF-α biological activity was more common among African-American compared to Caucasian women [135].

5.3 Uterine artery Doppler velocimetry (notching)—Uterine artery Doppler waveform analysis has been proposed as a predictive marker for late PE and fetal growth restriction. PE is predicted from either the presence of bilateral uterine artery early diastolic notches or a mean pulsatility index above 95% for gestational age (Fig. 11). Although uterine artery Doppler is a convenient and noninvasive tool, its use as the sole predictive test for PE has shown poor accuracy [136]. On the other hand, predictive models combining

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first-trimester uterine artery Doppler waveform analysis with maternal characteristics and biochemical markers, can achieve a detection rate of over 90% for early-onset PE [137].

5.4 Brachial artery flow-mediated dilation (FMD)—Brachial artery FMD has been used for evaluation of endothelial cell function in healthy subjects and individuals with cardiovascular disease. Because systemic endothelial dysfunction has been identified as one of the main pathophysiological events in PE, FMD could be used to predict PE [138]. FMD is a cost-effective, convenient and non-invasive method to measure endothelial function in PE women. A study has reported that the use of FMD to assess endothelial dysfunction in patients with PE and as a tool to predict the clinical onset of the disorder have shown promising results [139].

5.5 Cell-free fetal RNA/DNA—Amniotic fluid cell-free RNA (cff-RNA) has been used widely in diagnosing chromosome abnormalities. Recent research suggests potential predictive value of analyzing the amniotic fluid transcriptome in PE. Studies have demonstrated that RNAs associated with the ribosome pathway, insulin-like growth factor B, and ubiquitin C are upregulated more than 10-fold in PE compared with control pregnant women [140], suggesting that these genes could be used as predictive biomarkers for PE in early pregnancy.

Cell-free fetal DNA (cffDNA), a product of normal placental apoptosis, has also been evaluated as a screening tool for PE. Increased levels of cffDNA have been observed in patients before the onset of symptoms of PE, purportedly from increased placental hypoxia and apoptosis [141]. A disadvantage of cffDNA analysis is that it may be reliable only from the beginning of the second trimester. Also, the procedure may not gain popularity among patients and healthcare practitioners due to its invasive nature.

Considering the complexity of the pathogenesis of PE, it is not possible to use a single predictor or biomarker to predict the disorder, and a combination of these factors could provide more accurate prediction. The use of clinical risk factors combined with biochemical profile and biomarkers can improve their predictive value in PE [142]. Among the different biomarkers, the sFlt-1/PlGF ratio is considered a clinically useful predictor of the risk of PE. Studies have also recommended a combined and feasible test that includes evaluation of maternal history and risk factors, measurement of mean arterial pressure, measurement of biomarkers such as serum PlGF, and assessment of uterine artery pulsatility index [143].

6. Complications and management of PE

If not managed properly, PE could lead to eclampsia with severe hypertension, headache, visual disturbances and seizures. Because the pathophysiology of PE is not clearly understood, prevention and management of PE have eluded healthcare practitioners for decades.. Interestingly, the rate of recurrent PE among women with a history of PE decreased by 30% after the release of the US Preventive Services Task Force recommendation of aspirin for PE prevention [144]. However, the use of aspirin as preventive measure of PE is not universally accepted. Instead, management of PE is usually focused on control of acute HTN, prevention of seizures, and timely delivery of the fetus. In

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patients with late-onset PE, delivery is an effective way to treat the disorder [145]. Patients with early-onset PE need further evaluation and weighing of available options. The risk of wait-and-see approach versus rapid delivery of the baby must be carefully balanced. These options may have different weights and may be considered differently in various regions and countries.

Most of the PE patients in China deliver by Caesarean section compared to induced labor in Western countries. This is likely because in China and the Eastern world especially in rural areas, pregnant women do not have adequate education or financial resources with limited access to prenatal care. In many instances, Eastern women do not have prenatal care and plan to give birth at home with the help of the local midwife. Eastern women usually do not go to the hospital unless they feel sick, with symptoms such as headache, upper abdominal pain, or visual disturbances, suggesting advanced stages and complications of PE. In comparison, pregnant women in the Western world have a better healthcare system and better access to perinatal care. Thus while the overall incidence of PE is higher in the Western than the Eastern world, due to advanced perinatal care the complications of PE are less common in Western countries with the PE maternal fatality rate at 1% or less.

Magnesium sulfate ($MgSO_4$) has been recommended internationally as the first-line drug for treatment of severe PE and eclampsia. WHO and other international organizations recommend two $MgSO_4$ regimens for eclampsia prophylaxis, intramuscularly and intravenously [146]. However, the use of $MgSO_4$ in clinical practice for prevention and treatment of eclampsia varies widely. One survey including 147 health facilities in 15 countries across Africa, Latin America and Asia has shown that intramuscular maintenance regimens were more commonly used in the African region (45.7%) than in Latin American (3.0%) and Asian regions (22.9%), whereas intravenous maintenance regimens were used more often in Latin American (94.0%) and Asian regions (60.0%) than in the African region (21.7%) [147].

The availability of $MgSO_4$ in health facilities also varied in different countries [123]. In a study of health facilities, the labor and delivery wards that carried $MgSO_4$ were 16% in Ethiopia and 55% in Madagascar. Also, the availability of $MgSO_4$ in health centers varied, from 4% in Rwanda to 96% in Mozambique. The causes of these variabilities could be related to the specific Ministry of Health policy which did not allow the use of $MgSO_4$ at lower level facilities in Ethiopia and Rwanda. Also, a study in Pakistan found that health care workers, in particular older generation physicians, felt that using $MgSO_4$ outside facilities with intensive care units was unsafe [148].

7. Other Considerations

Despite the variability in the incidence, risk factors and predictors of PE highlighted in this review, certain limitations should be considered. First, the review evaluated the incidence of PE in representative countries in the Eastern, Western and Developing world. Inclusion of a larger number of countries could be more representative of the incidence of PE in a specific world region. Second, the incidence of PE in different countries was evaluated in different years and time periods. This is particularly limiting because the incidence of PE is expected to change with the economic development and advances in medicine and technology over

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time. Ideally, evaluation of the incidence of PE in different countries and world regions should be compared over the same period of time. Third, although we have attempted to provide a complete picture of the incidence of PE in different countries, data from some countries have been incomplete, inadequate or not reliable. While the incidence and predictors of PE have been extensively studied and well-documented in the Western world, access to adequate maternal data is somewhat limited in developing countries and in rural areas. The PE data could also be limited in non-English speaking countries, where scientific data are published mainly in local journals with limited access to world-wide readers.

8. Perspective

The incidence of PE varies in different world regions and in different countries of the same region, and the causes of this variability involve multiple demographic, genetic, dietary and environmental factors. Generally, the incidence of PE is less in the Eastern than the Western and Developing world. In the Eastern World, the incidence of PE is highest in the Philippines likely due to the advanced maternal age and variants of the *VEGF-A* and *VEGFR1* gene [149]. In the Western World, the incidence of PE is higher in Norway and Finland possibly due to the seasonal extremes in both temperature and hours of daylight as these countries are stretched north-south over a vast span of latitudes, and far from the equator [150]. The incidence of hypertensive disorders of pregnancy and PE is higher in Africa and Latin America likely due to early pregnancies, maternal anemia and infections, low socioeconomic status, limited access to healthcare services, and lack of advanced tools and capabilities to predict and diagnose PE in pregnant women at high risk and at early stages of the disorder [151, 152].

Several approaches are needed to reduce the incidence of PE. Because of the high incidence of PE in low income countries, greater efforts should be made in these countries to raise awareness of the benefits of early prenatal visits, improve maternal education, enhance the hospitals perinatal care, and provide advanced technologies to collect and analyze PE data and risk factors. Also, significant efforts should be made to enhance the perinatal life style and promote low-salt diet, calcium supplementation, exercise, and appropriate weight gain in pregnancy, and treat any underlying health conditions such as cardiovascular, metabolic, and kidney diseases. Additionally, diagnostic guidelines and criteria and advanced diagnostic tools should be made available in different regions particularly in rural areas. Baseline screening measures should include evaluation of various maternal risk factors, and measurements of mean arterial pressure, and should be confirmed with serum PlGF, and uterine artery pulsatility index. Future research should further examine the relationship between gene polymorphisms, maternal lifestyle and demographic and environmental factors risk factors of PE. These efforts should help design region-specific clusters of risk factors, diagnostic tools and approaches for prevention and management of PE

Acknowledgements

This work was supported by BRI Fund to Sustain Research Excellence from Brigham Research Institute, and grants from National Heart, Lung, and Blood Institute (HL65998, HL111775, R56HL147889, R01HL147889-A1). Dr. Ning Zhang was a visiting scholar from Department of Obstetrics and Gynecology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong Province, P. R. China. Dr. Jing Tan was a visiting scholar from School of Acupuncture, Moxibustion & Tuina, Hunan University of Chinese Medicine, Changsha, China. Dr. HaiFeng Yang

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was a visiting scholar from Department of Neurosurgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China. We thank Elizabeth Hiebert, Bonnie Liu, Tejas Shah, Mayuri Venkatesh, and Jacob Zinner for critically reviewing, proof-reading, and editing the manuscript.

List of Abbreviations:

AT_1-AA	angiotensin type 1 receptor agonistic autoantibody
BP	blood pressure
COX	cyclooxygenase
eNOS	endothelial nitric oxide synthase
ET-1	endothelin-1
HO	hemeoxygenase
HIF	hypoxia-inducible factor
HTN-Preg	hypertension in pregnancy
IL	interleukin
IUGR	intrauterine growth restriction
NO	nitric oxide
NOS	nitric oxide synthase
PE	preeclampsia
PGI_2	prostacyclin
PlGF	placental growth factor
ROS	reactive oxygen species
sEng	soluble endoglin
sFlt-1	soluble fms-like tyrosine kinase-1
TGF-β	transforming growth factor-β
TNFα	tumor necrosis factor-α
VEGF	vascular endothelial growth factor
VEGFR	VEGF receptor

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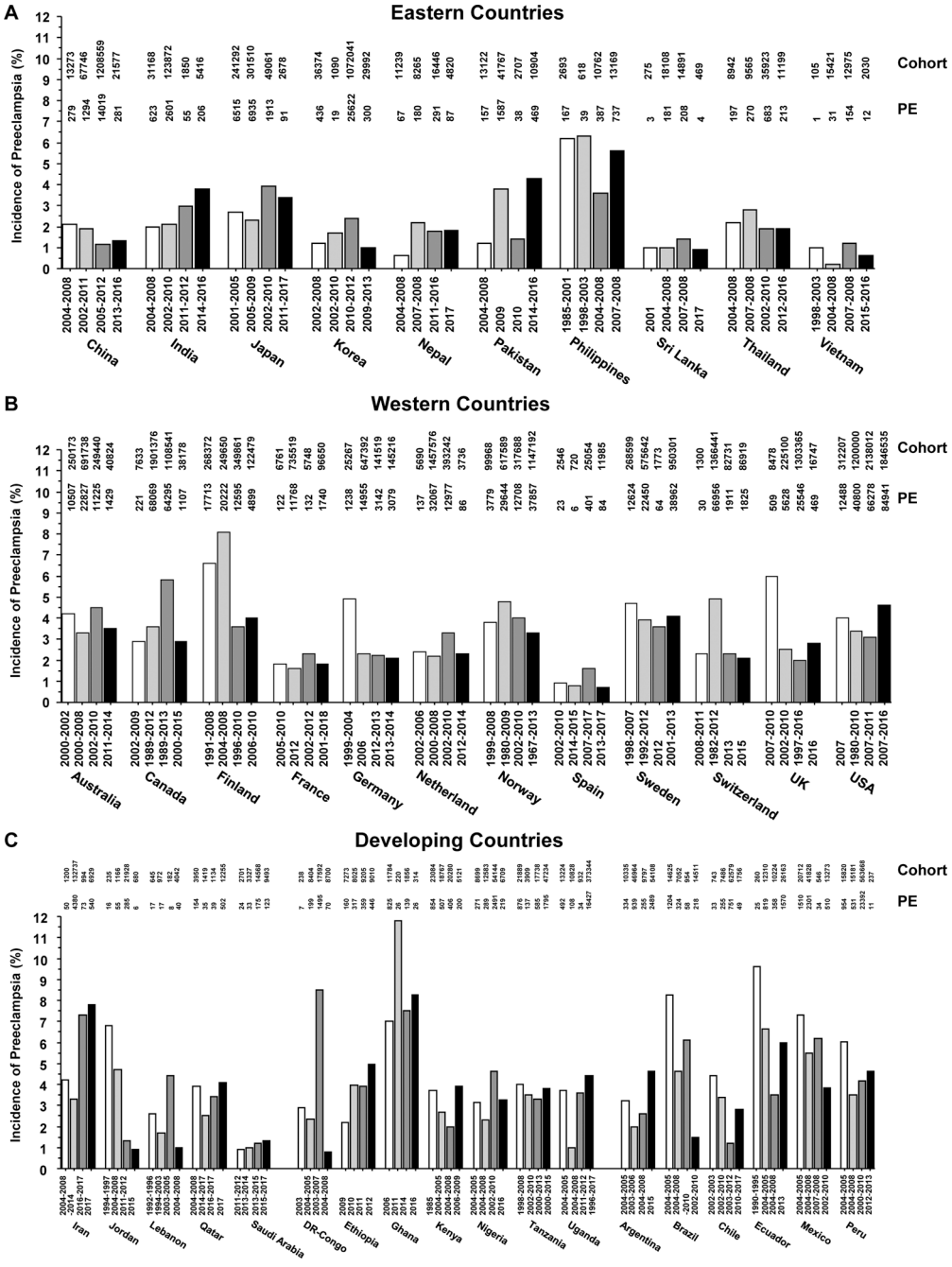

Fig. 1.

Incidence of PE in representative countries of the Eastern Western and Developing world. The incidence of PE, number of cases of PE, and the number of pregnant women in the cohort from 4 different studies performed between the years 1985 to 2017 in representative countries from the Eastern, Western and Developing world are presented.

References: [5, 47, 86, 114, 155–249]

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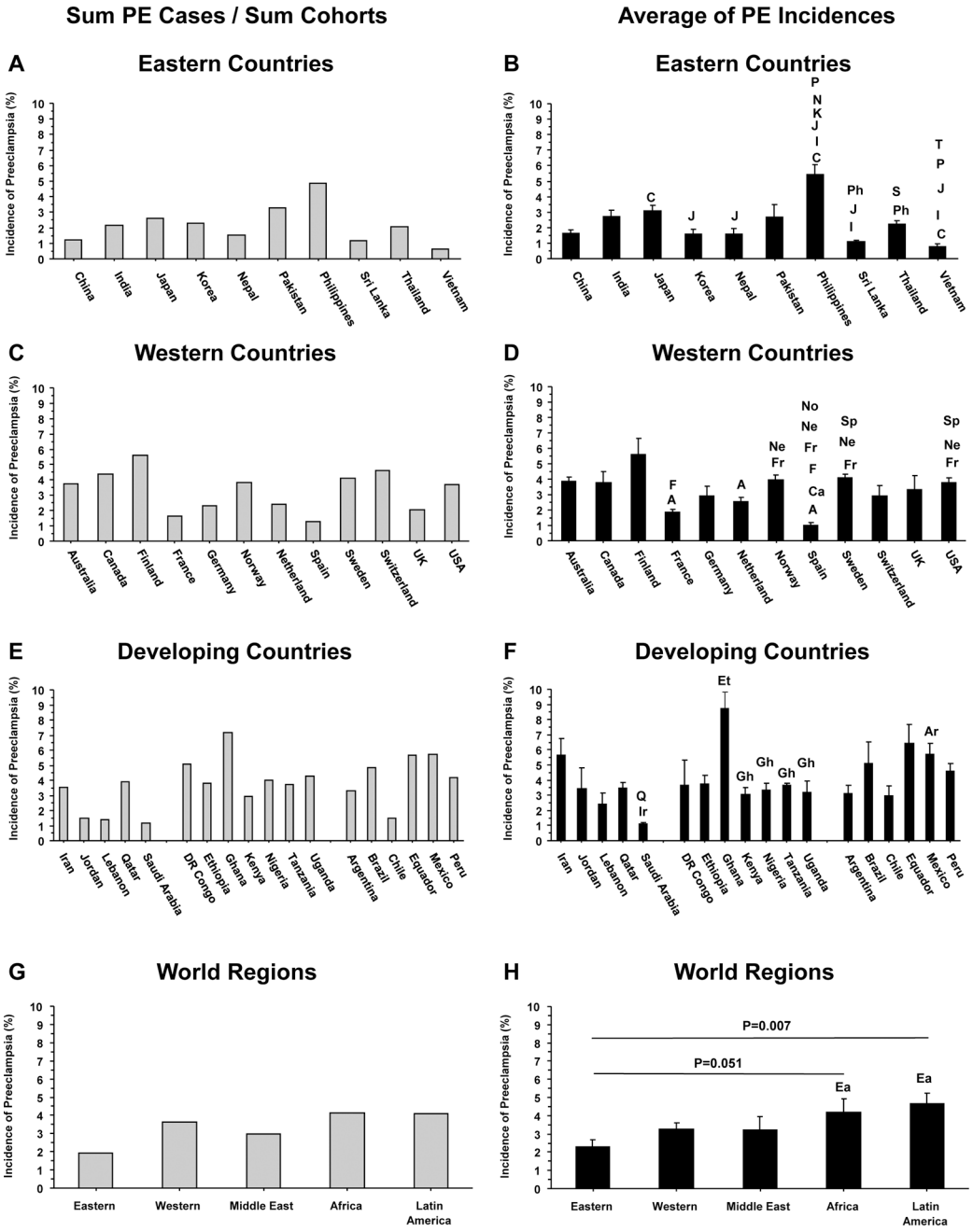

Fig. 2.

Average incidence of PE in representative countries and in the Eastern Western and Developing world. Data from the 4 studies presented in Figure 1 were used to calculate the average incidence of PE in representative countries and world regions by dividing the Sum number of PE cases by the Sum number of pregnant women in the different cohorts (A, C, E and F), or by calculating the means±SEM of the incidences of PE from the 4 different studies, which allowed statistical comparison of different countries and regions (B, D, F and H). Letters on columns indicate significantly different ($p<0.05$) from C (China), I (India), J (Japan), K (Korea), N (Nepal), P (Pakistan), Ph (Philippines), S (Sri Lanka), and (T)

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Thailand in Eastern Countries (B); significantly different ($p<0.05$) from A (Australia), Ca (Canada), F (Finland), Fr (France), Ne (Netherland), No (Norway), Sp (Spain) in Western Countries (D); significantly different ($p<0.05$) from Ir (Iran), and Q (Datar) in the Middle East, from Et (Ethiopia), and Gh (Ghana) in Africa, and from Ar (Argentina) in Latin America (F); and borderline ($p=0.051$) or significantly different ($p=0.007$) from Ea (Eastern world) in different world regions (H).

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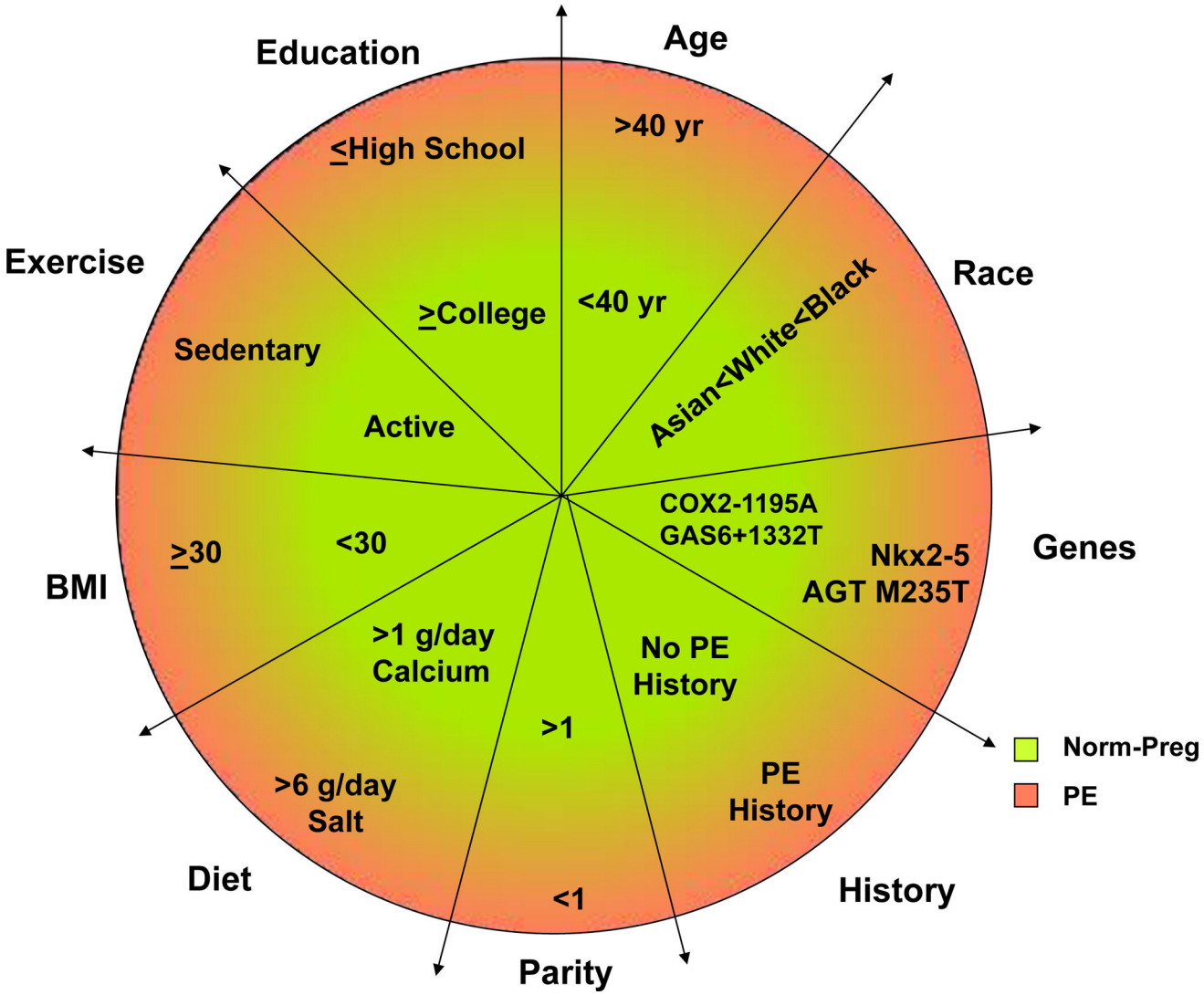

Fig. 3.

Risk factors of PE. Comparison of demographic, environmental and socioeconomic factors in normal pregnancy (Norm-Preg) and preeclampsia (PE).

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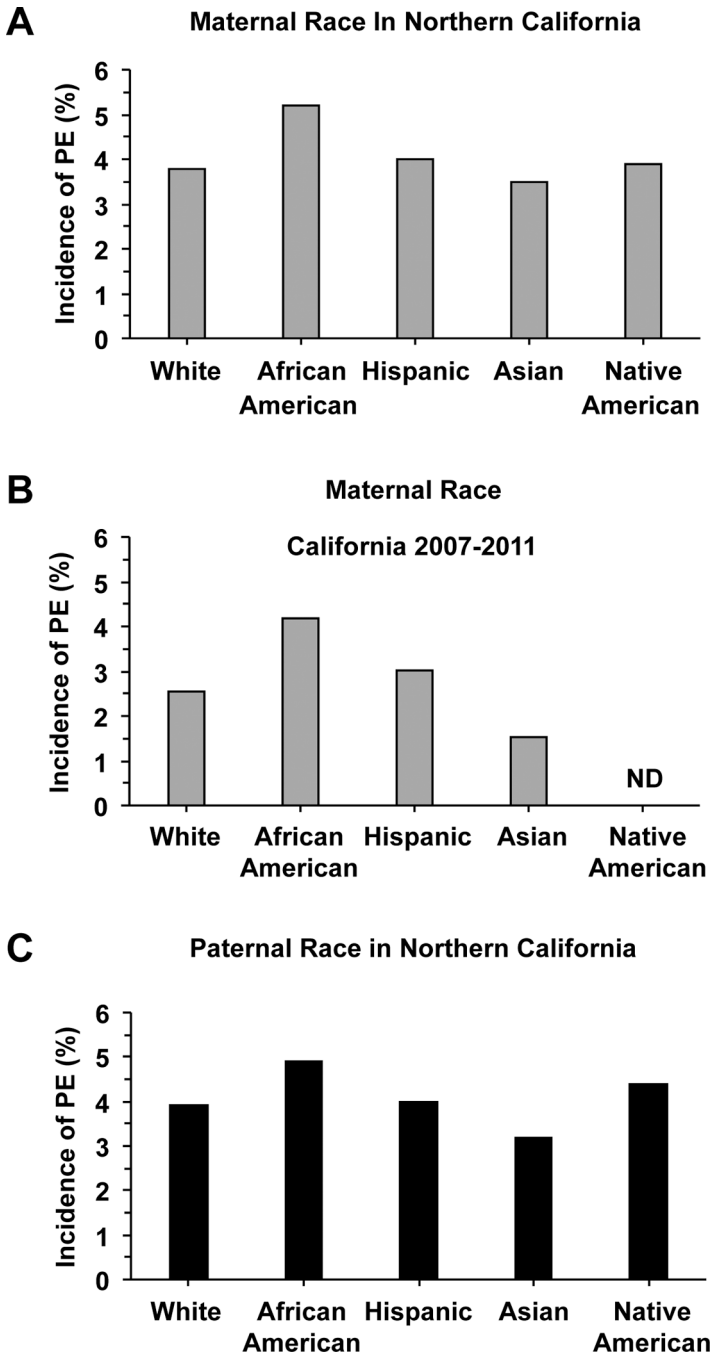

Fig. 4.

Maternal and paternal ethnicity and the incidence of PE. Comparison of the incidence of PE n different maternal (A, B) and paternal ethnic groups (C) in California, USA. ND, Not determined.

References: [13]

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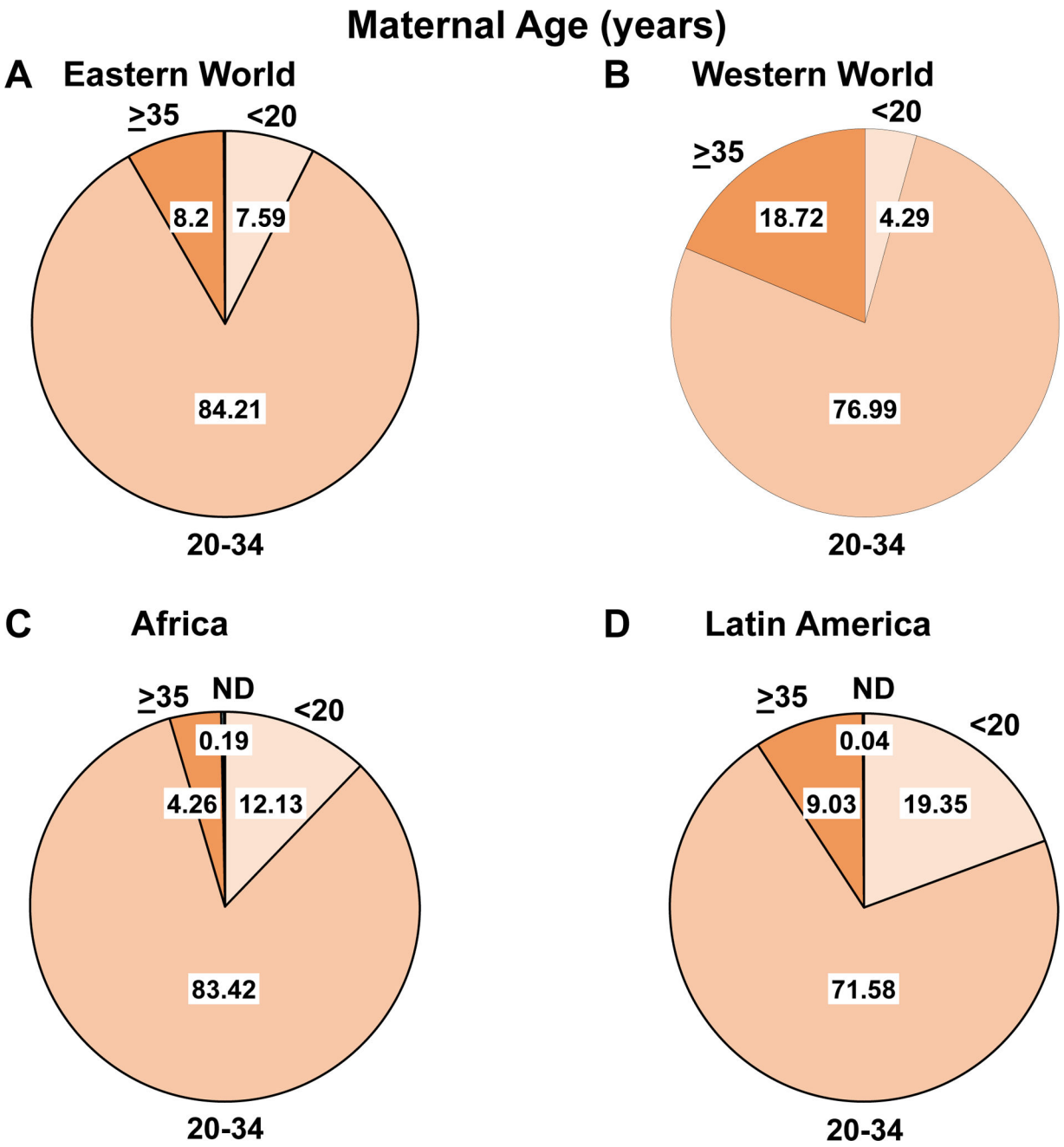

Fig. 5.

Maternal age in different world regions. Comparison of maternal age in Eastern world (A), Western world (B), Africa (C), and Latin America (D). ND, Not determined.

References: Eastern World and Latin America [250], Western World [153], Africa [237]

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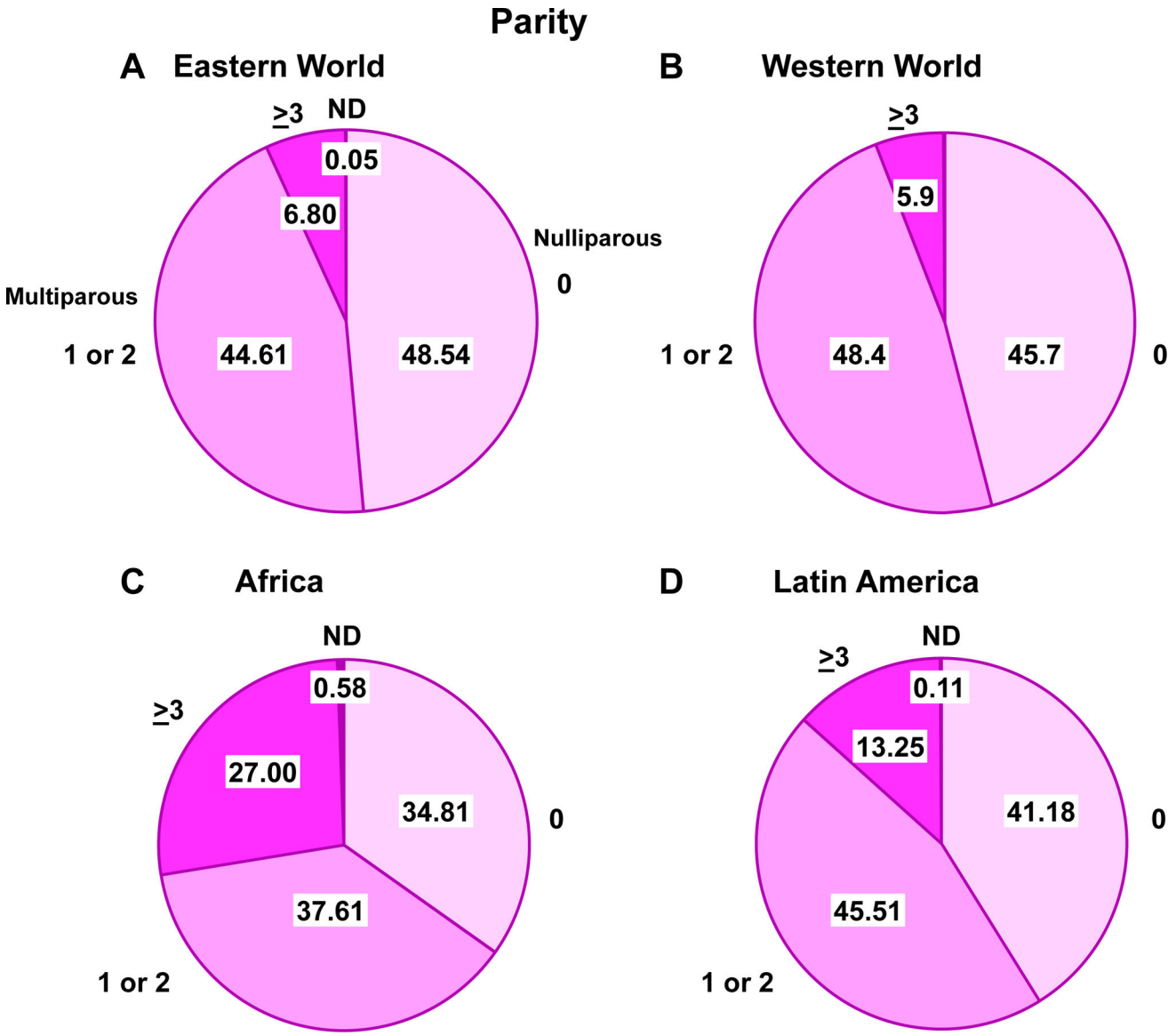

Fig. 6.

Parity in different world regions. Comparison of the number of pregnancies among women in Eastern World (A), Western World (B), Africa (C) and Latin America (D). ND, Not determined.

References: Eastern World, Africa and Latin America [250], Western World [251]

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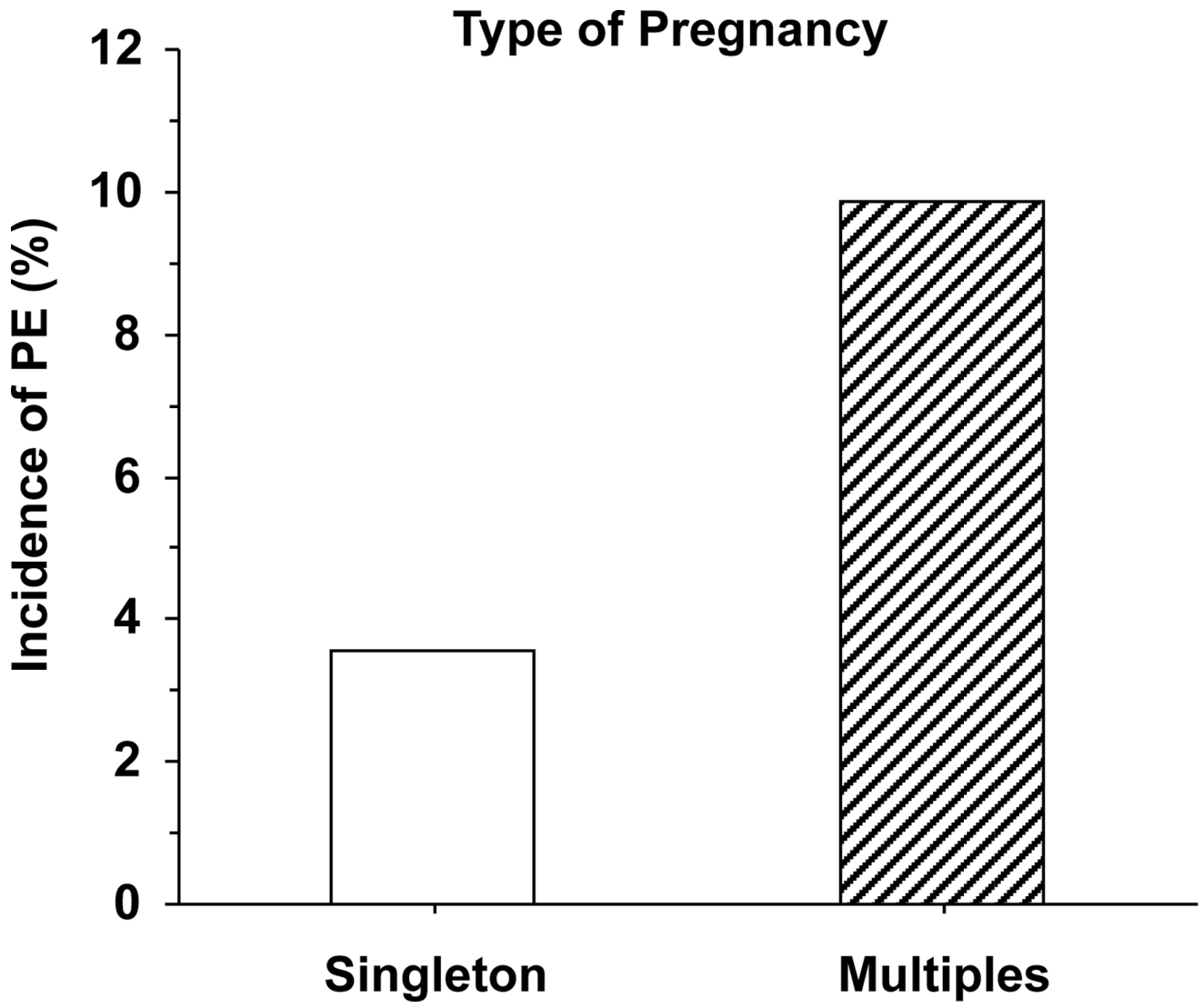

Fig. 7.
Incidence of PE in singleton versus multiples pregnancy.
Reference: [58]

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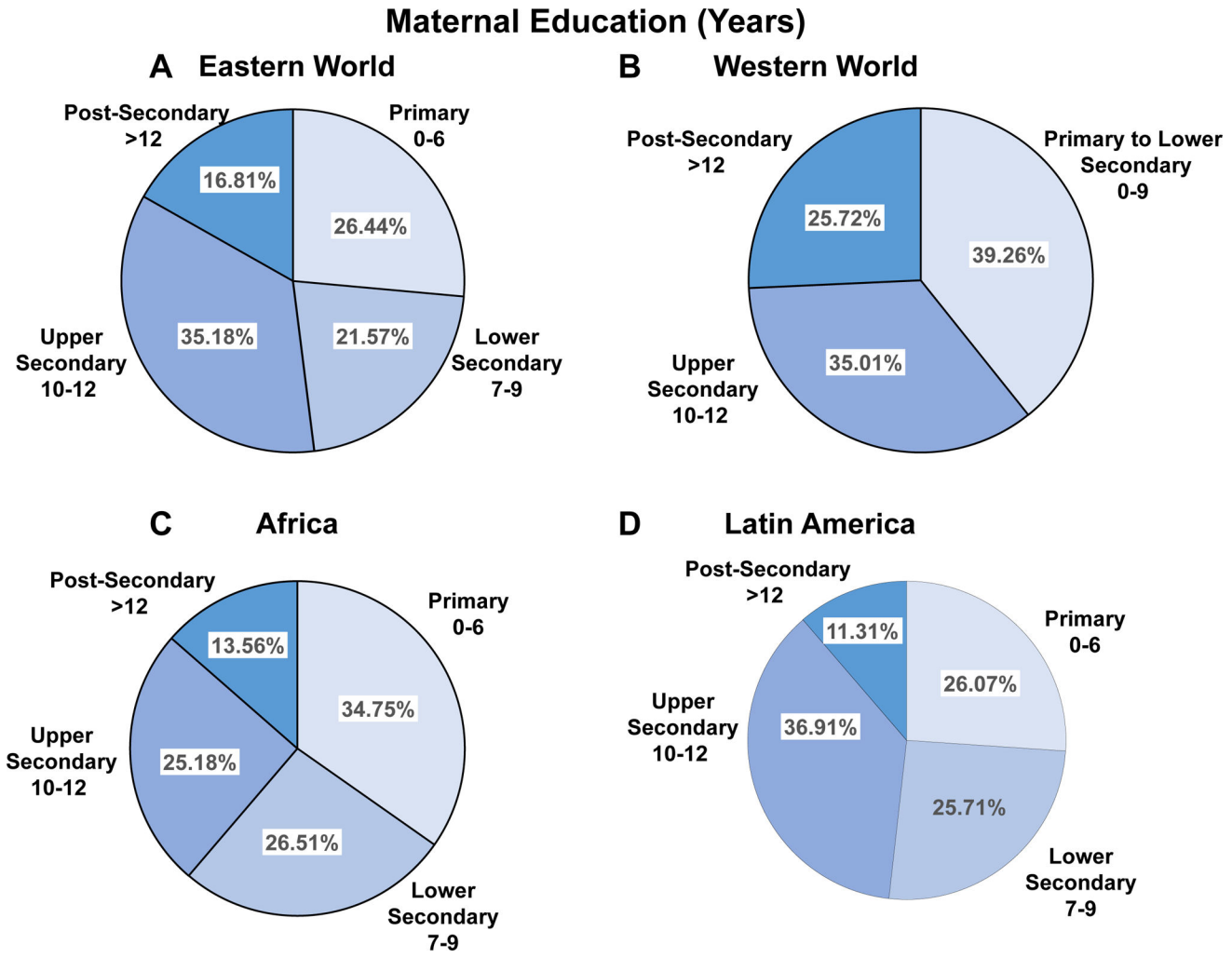

Fig. 8.

Education level of pregnant women in different world regions. Comparison of the number of years of education among pregnant women in Eastern World (A), Western World (B), Africa (C) and Latin America (D).

References: Eastern World, Africa and Latin America [252], Western World [253]

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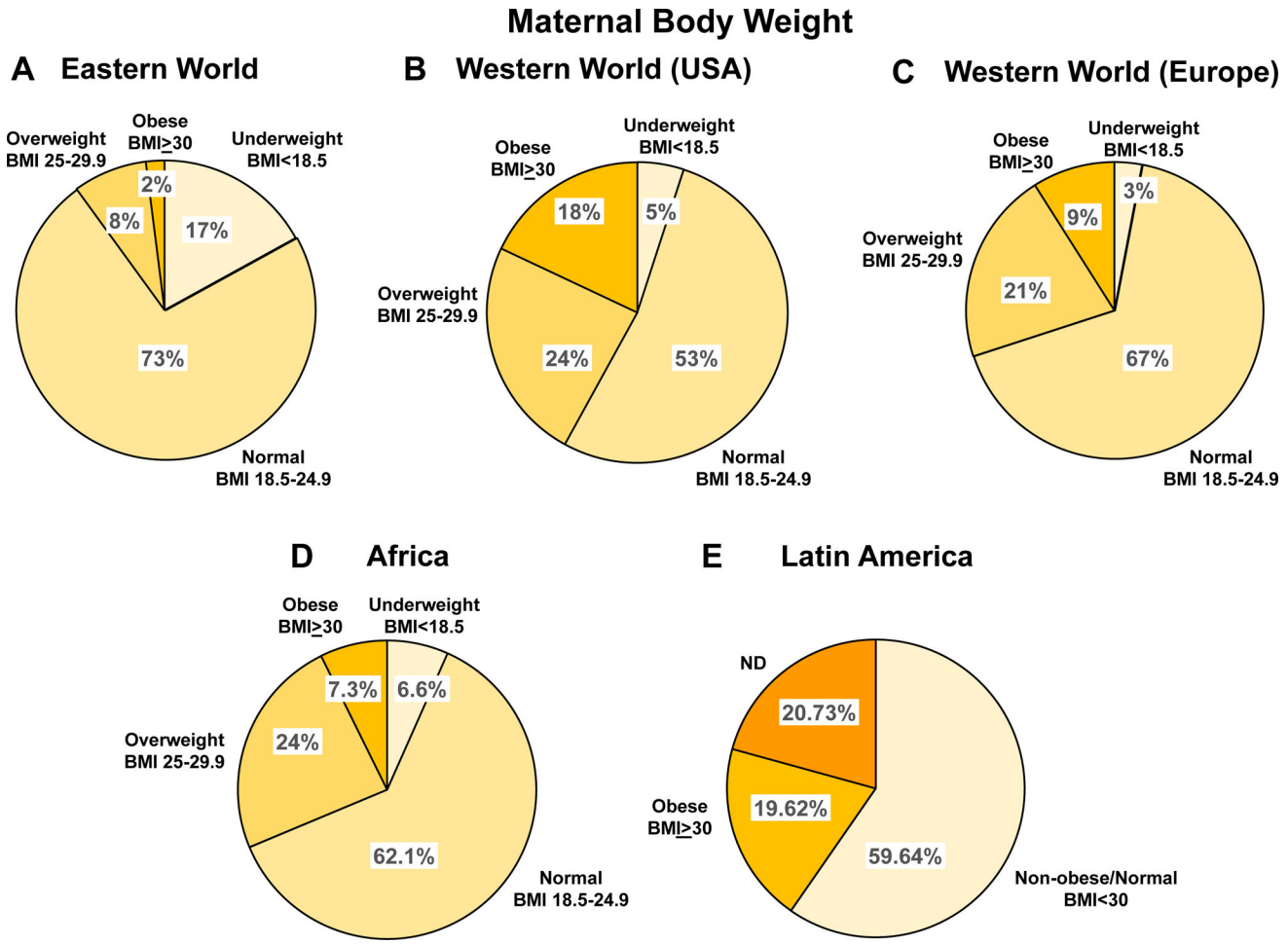

Fig. 9.

Maternal body weight in different world regions. Comparison of maternal body weight among pregnant women in Eastern World (A), USA (B), Europe (C), Africa (D) and Latin America (E).

References: Eastern and Western World [92], Africa [237], Latin America [250]

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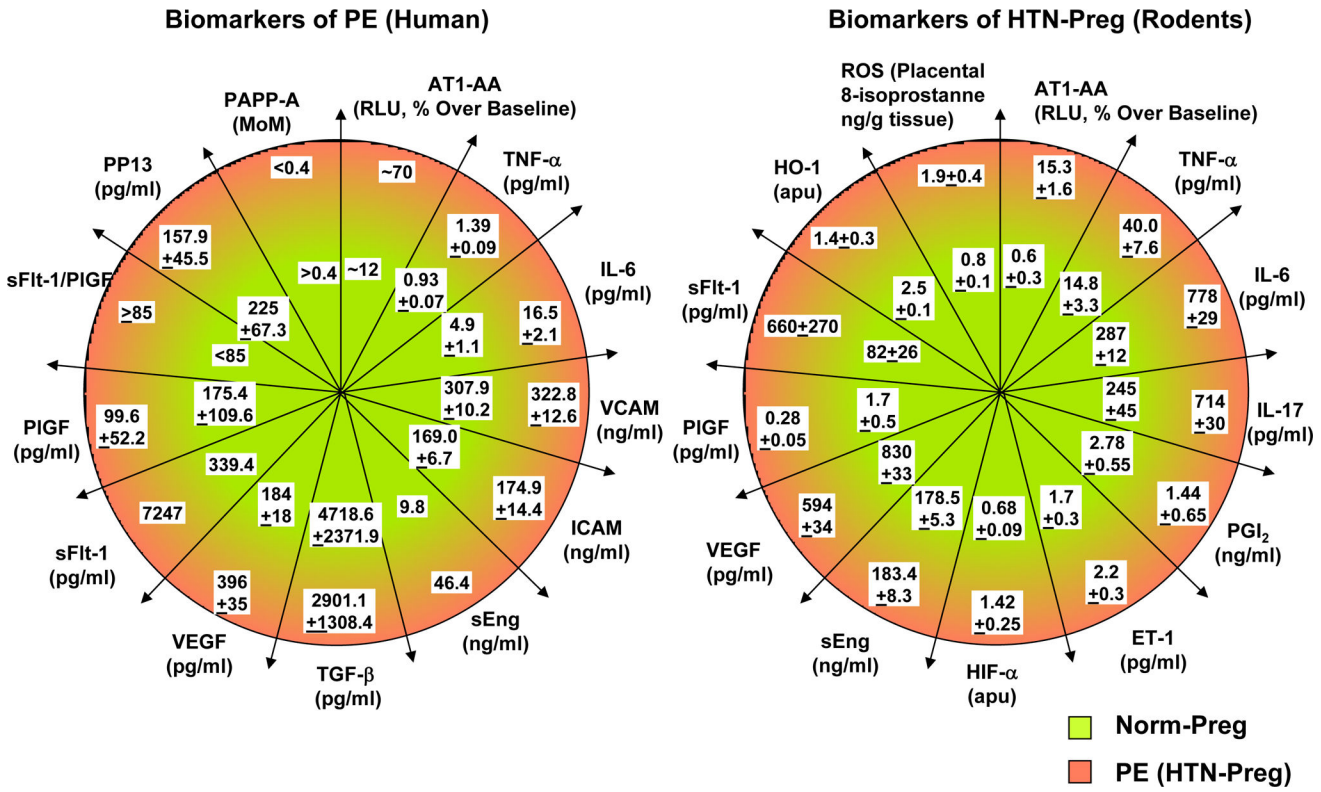

Fig. 10.

Biomarkers of PE and HTN_Preg. Comparison of biomarkers in Norm-Preg and PE women (A), and in Norm-Preg and HTN-Preg rodents (B).

AT1-AA, angiotensin type 1 receptor agonistic autoantibody; ET-1, endothelin-1; HIF-α, hypoxia inducible factor-α; HO-1, hemeoxygenase 1; ICAM, intercellular adhesion molecule; IL-6, interleukin-6; MoM, multiple of the median; PAPP-A, pregnancy-associated plasma protein-A; PGI_2, prostacyclin; PlGF, placental growth factor; PP13, placental protein 13; sEng, soluble endoglin; ROS, reactive oxygen species; sFlt-1, soluble fms-like tyrosine kinase-1; TGFβ, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor,

References; [6, 7, 9, 254–257]

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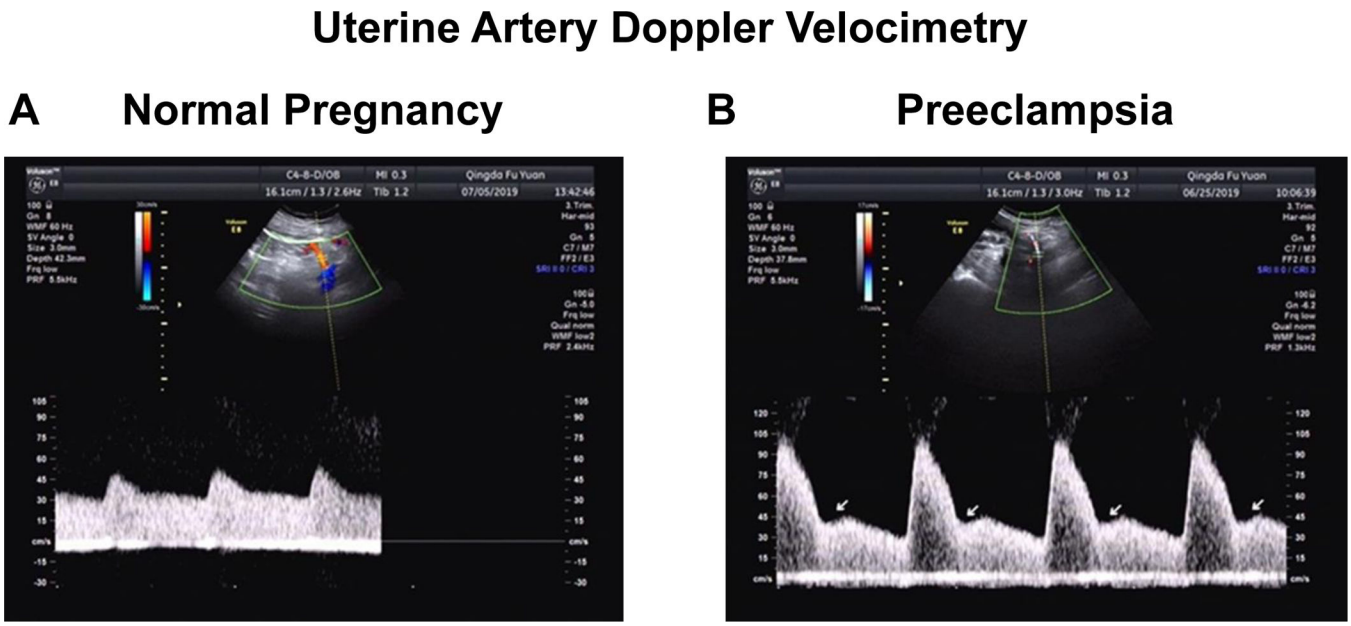

Fig. 11.

Uterine artery Doppler velocimetry in normal versus preeclamptic pregnancy. Representative uterine artery Doppler velocimetry obtained from normal pregnant (A) and preeclamptic women (B) in the second trimester. PE is suspected by either the presence of bilateral uterine artery early diastolic notches (arrows) or a mean pulsatility index above the 95th percentile for gestational age.

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Table 1.

Percentage of pregnant women with maternal age ≥35 years in representative Eastern and Western countries

Eastern Countries	% Pregnant women age ≥35 years	Western Countries	% Pregnant women age ≥35 years
China (2010–2011)	9	Australia (2000–2005)	20.2
India (2010–2011)	3	Canada (2002–2007)	14.7
Nepal (2010–2011)	3	Norway (1999–2006)	15.9
Philippines (2010–2011)	15	Sweden (1997–2006)	18.1
Thailand (2010–2011)	15	UK (1997–2006)	17.1
Vietnam (2010–2011)	10	USA (1998–2007)	22.0
Average	9.2±2.2	Average	18.0±1.1 *

* Average % of pregnant women with maternal age ≥35 years is significantly greater ($p<0.05$) in Western versus Eastern countries. References: [149, 153]

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Table 2.

Recommended dietary intake of vitamin D (IU) for pregnant and lactating women by different agencies in different countries and conglomerates of countries

Country/Region	Recommending Agency	Pregnancy	Lactation
Australia and New Zealand	NHMRC 2006	200	200
China	Chinese Nutrition Society 2013	400	400
Austria-Germany- Switzerland	DACH 2012	800	800
Nordic Countries	Nordic nutrition recommendations, Nordic Council of Ministers 2012	200	200
Central Europe	Polish Scientific Committee on Vitamin D 2013	1500–2000	1500–2000
Europe	EC 1993	400	400
USA	Endocrine Society 2010	600–2000	600–2000
USA and Canada	IOM 2010	600	600
Worldwide	WHO/FAO 2012/2014	200	200

DACH, Joint Nutritional Society of Germany, Austria and Switzerland; EC, European Commission; FAO: Food and Agriculture Organization of the United Nations; IOM, Institute of Medicine; NHMRC: National Health and Medical Research Council of Australia; Nordic countries, Denmark, Finland, Iceland, Norway and Sweden; WHO, World Health Organization.

Reference: [154]