

# The evolution of the diagnostic criteria of preeclampsia-eclampsia



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## Introduction

Preeclampsia has a long history. It is a major cause of maternal and perinatal morbidity and mortality worldwide, preceding complications ranging from eclampsia and stroke to fetal growth restriction, prematurity, and stillbirth. As clinicians' understanding of the disease has evolved, so too have the criteria by which we diagnose the syndrome. The so-called classic triad of hypertension, proteinuria, and edema has been superseded with hypertension and organ dysfunction, be it renal, hepatic, hematological, neurologic, or placental, and it is now sufficient for a diagnosis. However, in recent guidelines, the diagnostic criteria for preeclampsia have commonly been updates of previous guidelines, often based on expert opinion and consensus. Ideally, diagnostic categories should be based on facts that help answer questions such as the following: which characteristics contribute to the patient's prognosis?

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As the understanding of the pathophysiology of preeclampsia has improved, its diagnostic criteria have evolved. The classical triad of hypertension, edema, and proteinuria has become hypertension and organ dysfunction—renal, hepatic, neurologic, hematological, or uteroplacental. However, the most recent definitions have largely been based off consensus and expert opinion, not primary research. In this review, we explore how the criteria have evolved, particularly through the second half of the 20<sup>th</sup> and the beginning of the 21st century and offer a critical appraisal of the evidence that has led the criteria to where they stand today. Some key themes are the following: the debate between having a simple and convenient blood pressure cutoff vs a blood pressure cutoff that accounts for influencing factors such as age and weight; whether a uniform blood pressure threshold, a rise in blood pressure, or a combination is most discriminatory; whether existing evidence supports blood pressure and proteinuria thresholds in diagnosing preeclampsia; and whether using flow-charts and decision trees might be more appropriate than a single set of criteria. We also discuss the future of a preeclampsia diagnosis. We challenge the move toward a broad (vs restrictive) diagnosis, arguing instead for criteria that directly relate to the prognosis of preeclampsia and the response to treatments.

**Key words:** criteria, diagnosis, history, hypertensive disorders, management, preeclampsia

And which therapeutics do we have to improve that prognosis? In this review, we explore the history of preeclampsia and eclampsia and critically appraise the evidence that brought us to the current diagnostic criteria. We discuss how preeclampsia might be diagnosed in the future and how ongoing and future research should be structured to best answer the 2 key questions of prognosis and treatment.

## Pre-20th Century

Hippocrates, who lived between 460 BC and 370 BC, said that headaches, drowsiness, and convulsions were of serious significance in pregnancy.<sup>1</sup> “Eclampsia” comes from the Greek “ἐκλαμψις” which means a “light burst,” and it is thought to have been first documented by the physician Johannes Varandeuus in 1619.<sup>2</sup> In the 1700s, it was recognized that delivery was crucial for recovery, whereas eclampsia and epilepsy were distinguished by the middle of the century, with headaches identified as a

prodromal symptom of the former.<sup>3</sup> By the end of the century, a link between edema and eclampsia was described, followed in the mid-1800s by the association of proteinuria and eclampsia.<sup>3</sup>

## The Early 20th Century

In the late 19th and early 20th centuries, there was much speculation as to the etiology of preeclampsia. It was thought to be a renal disorder; compression of the uterus; epilepsy; or a bacterium coined as *Bacillus eclampsiae*, which turned out to be *Proteus vulgaris*.<sup>4</sup> Ahlfeld from Germany, in 1894, was perhaps the first to propose that preeclampsia was because of toxins produced in the placenta. The clinical presentation indicated as much, with Allbutt from Cambridge remarking in *The Lancet* in 1897 that the “vomiting,....nervous disturbance,....albuminuria, then enlargement of the heart” that are typical of preeclampsia would, if seen in a nonpregnant person, lead to the conclusion that “there is a circulating

toxin in the body.”<sup>5</sup> As DeLee reflected in 1905, “...eclampsia is the disease of theories....only one point seems to be generally conceded, that eclampsia is because of the action of a toxin in the blood upon the nerve centres.”<sup>4</sup>

By 1938, toxemia in pregnancy had been divided into mild preeclampsia, preeclampsia, and eclampsia, whereas nephritic toxemia remained a part of but separate to the rest of the spectrum.<sup>6</sup> Headache, vertigo, visual disturbances, retinal change, albuminuria, edema, and hypertension had been identified as manifestations, whereas convulsions indicated eclampsia and renal failure nephritic toxemia. The common feature was hypertension, defined “by convention” as a systolic blood pressure of  $\geq 140$  mm Hg and/or a diastolic pressure of  $\geq 90$  mm Hg.<sup>6</sup>

Because of the “lack of uniform terminology,” the American Committee on Maternal Welfare (ACMW) in 1940 developed a classification for the toxemias of pregnancy.<sup>7</sup> The classification separated disorders not “peculiar” to pregnancy, which are, hypertensive and renal disease, from those “peculiar” to pregnancy, which are, preeclampsia and eclampsia. Preeclampsia was divided into mild and severe subtypes. Mild preeclampsia was characterized by hypertension  $\geq 140/90$  mm Hg, with slight or absent edema, and proteinuria of  $< 6$  g/L (equivalent to 2+). Two of hypertension, proteinuria, and edema were required. Two or more of moderate to severe edema, a blood pressure  $\geq 160/100$  mm Hg, or proteinuria greater than 6 g/L (3–4+) constituted severe preeclampsia.

### 1950s

The Toxemias of Pregnancy by William J Dieckmann,<sup>3</sup> Professor at the University of Chicago, is a textbook published in 1952 that explores in detail the toxemias of pregnancy. Interestingly, Dieckmann<sup>3</sup> rejected the notion of a circulating toxin, stating that “the term toxemia is not well chosen because it suggests a circulating toxin which is probably not correct.”

The textbook reproduces the “widely accepted” classification of the toxemias of pregnancy from the AC MW. The

“general consensus” was that the blood pressure must be  $\geq 140/90$  mm Hg or more “for some time.” The textbook offers no source for this. However, there is debate about whether a uniform cutoff is appropriate. Dieckmann<sup>3</sup> references a 1943 study from Master et al<sup>8</sup> from Mount Sinai Hospital, which found that both increasing age and weight were associated with higher blood pressure measurements. Master et al<sup>8</sup> proposed that there should not be a single blood pressure cutoff to define hypertension but that it should be a statistical definition: a reading of 2 standard deviations or more from the mean, given a certain age and weight.

Dieckmann<sup>3</sup> notes that this means that a uniform cutoff for hypertension in pregnancy will unnecessarily diagnose women, particularly older mothers, with preeclampsia or hypertensive disease. “Systolic and diastolic blood pressure level for classification of toxemia cannot be an arbitrary one, but must be adjusted to the patient’s age and weight.”<sup>3</sup>

He suggests that proteinuria of more than 0.3 g per 24 hours for 3 or more days is abnormal. It is unclear where this threshold originated. In a 1940 paper, he asserts that “usual qualitative tests reveal no protein in the urine of normal pregnancy patients, but a quantitative determination will yield 0 to 0.3 g per 24 hours.” Edema was considered abnormal if it extended to the face and/or hands, or the ankles and/or tibia, despite being in bed.

Dieckmann<sup>3</sup> acknowledges that this set of criteria identifies women—those with only slight hypertension, or only a trace of proteinuria—as having preeclampsia, when they “should be classified as having pseudopreeclampsia.” However, for simplicity’s sake, he proposes that these women be included in the mild preeclampsia group.

Simplicity continued to be valued in the following years. Nelson, from Aberdeen Maternity Hospital, in a 1955 paper titled A Clinical Study of Pre-eclampsia,<sup>9</sup> proposed the following definition of preeclampsia that would still be in use 3 decades later: a rise in the diastolic blood pressure to 90 mm Hg or more on 2 separate occasions

separated by at least a day. Neither proteinuria nor edema were required. The presence of proteinuria raised the classification to “severe.” He defended the “extreme simplicity” of this schema, as “any investigation...which is almost entirely retrospective, must be kept to a simple set of rules which can be rigidly applied so that there is no temptation for the investigator to use their ‘judgment’”, which could cause “inconsistencies of diagnosis and grading.”

Future research sought to evaluate the associations between blood pressure, proteinuria, and perinatal mortality. MacGillivray,<sup>10</sup> from the University of Aberdeen, in 1961, concluded that an increase in the diastolic blood pressure after 20 weeks’ gestation of as little as 5 mm Hg was associated with increased perinatal mortality, and that the likelihood of developing proteinuria was associated with a diastolic blood pressure level of  $\geq 90$  mm Hg and not with a change in blood pressure. Women with a higher blood pressure early in pregnancy had a high likelihood of developing proteinuria. He thus supported Nelson’s diastolic blood pressure cutoff of 90 mm Hg for diagnosing preeclampsia.

### 1970s

The American College of Obstetricians and Gynecologists (ACOG) published a comprehensive definition of preeclampsia in 1972. As reported by Chesley,<sup>11</sup> preeclampsia required the development of hypertension ( $\geq 140/90$  mm Hg or a rise of  $\geq 30/15$  mm Hg) and significant proteinuria or edema after 20 weeks’ gestation. However, the source of this threshold, *Obstetric-Gynecologic Terminology* by Edward Hughes,<sup>12</sup> does not offer any primary data in support. In the ensuing years, these criteria were only taken up intermittently.

Friedman and Neff,<sup>13</sup> in 1976, from Harvard Medical School, attempted to define the criteria for diagnosing hypertensive disorders of pregnancy that were based on “objective data” by developing thresholds that correlated with a risk of complications. In a cohort of 38,636 pregnancies, a maximum diastolic blood pressure of 75 to 84 mm Hg

during pregnancy correlated with the lowest rate of fetal mortality. Fetal mortality increased with a maximum diastolic blood pressure of 85 to 94 mm Hg, and above this level, there was a more marked increase. Fetal mortality was also increased with 2+ or more proteinuria, independent of blood pressure.

Increased blood pressure and proteinuria had a synergistic effect. A diastolic blood pressure of  $\geq 95$  mm Hg plus trace or less proteinuria, or a diastolic blood pressure of 84 mm Hg combined with 2+ or more proteinuria, were associated with an approximately 4-fold increased risk of fetal death. A diastolic blood pressure  $\geq 85$  mm Hg and proteinuria of at least 1+ was associated with a 7-fold increased risk of fetal mortality. The authors concluded that these findings “provide the basis for a proposed classification of hypertensive states in pregnant women.” However, this did not lead to a widely accepted set of criteria.

A review by Davies<sup>14</sup> published in 1979 for the World Health Organization provided updated classifications from the ACMW. This classification differed from the existing ACOG criteria, chiefly because it “accepts hypertension or significant proteinuria or edema of the face and arms,” whereas the ACOG guidelines required hypertension plus proteinuria or edema. Issues with this “babel of schemata,” as Davies<sup>14</sup> described the conflicting criteria, were being noted, with a British Perinatal Mortality Survey, showing that 6.1% to 35.3% of women developed preeclampsia, depending on the criteria utilized.<sup>14</sup>

### 1980s

In 1986, the ACOG updated their 1972 criteria of Pregnancy-Induced Hypertension (PIH). As reported by Dildy and Cotton,<sup>15</sup> the diagnostic criteria were unchanged, including hypertension—either absolute or relative—and significant proteinuria or edema (Table 1). This guideline introduced the following criteria for severe PIH: involving significant hypertension (systolic  $\geq 160$  mm Hg or diastolic  $\geq 110$  mm Hg) or hypertension combined with organ dysfunction.

A 1987 World Health Organization guideline study group report<sup>17</sup> reiterated a diastolic blood pressure of 90 mm Hg as a “reasonable” cutoff for the diagnosis of hypertension in pregnancy. This was based off data from Friedmann and Neff,<sup>13</sup> as 90 mm Hg is halfway between 85 mm Hg (associated with perinatal mortality when seen with proteinuria) and 95 mm Hg (associated with perinatal mortality regardless of proteinuria) and off data from MacGillivray, as it is also associated with the later development of proteinuria.<sup>10</sup> However, if proteinuria is to remain part of the diagnostic criteria, why should a blood pressure threshold be chosen on the basis that it predicts proteinuria? It is more relevant to identify a blood pressure level that predicts adverse maternal and/or perinatal outcomes.

Conflicting proposals for the diagnosis of preeclampsia were published in April 1988. Davey and MacGillivray,<sup>18</sup> from the University of Cape Town, published theirs in the *American Journal of Obstetrics & Gynecology*, and Redman and Jefferies,<sup>19</sup> from John Radcliffe Hospital, Oxford, published in *The Lancet*.

Davey and MacGillivray's<sup>18</sup> guidelines had been approved by the International Society for the Study of Hypertension in Pregnancy (ISSHP) and by the International Committee of ISSHP in 1986 and also by the International Federation of Gynecology and Obstetrics in 1985. They considered the spectrum of hypertensive disorders to include gestational hypertension without proteinuria, gestational proteinuria without hypertension, and gestational proteinuric hypertension (preeclampsia).

They defined hypertension as a diastolic blood pressure  $\geq 90$  mm Hg on 2 consecutive readings, at least 4 hours apart, or a single reading  $\geq 110$  mm Hg. The use of a rise in blood pressure was abandoned, as “a rise of...30 or 40 mm Hg may ... fall within the normal statistical range,” and “the absolute level of blood pressure provides the best guide to fetal and maternal prognosis and the development of proteinuria.” The threshold of 90 mm Hg was given for 3

reasons. First, “simplicity, precision and convenience;” second, “it corresponds with defined statistical limits: 3 standard deviations above the mean in early pregnancy; 2 standard deviations above the mean between 34 and 38 weeks; and 1.5 standard deviations above the mean at term;” and third, “It corresponds to the point of inflection of the curve relating diastolic blood pressure to mortality.”

There is some nuance to these conclusions. Firstly, as described by Master,<sup>8</sup> statistical limits are influenced by maternal characteristics such as age and body mass index. Secondly, the point of inflection of the curve relating diastolic blood pressure to mortality, according to Friedmann and Neff who the authors cite, is strictly speaking, between 75 and 84 mm Hg. Finally, this curve is heavily influenced by the development of proteinuria. In sum, the criteria are not firmly rooted in either the prognosis or the management of preeclampsia.

Davey and MacGillivray rejected suggestions that different cut-offs for hypertension should be used at different stages of pregnancy or different populations, as it would “confus(e) and vitiate (spoil or impair the quality of) comparison of results.” They conclude that it is better to have 1 diagnosis with various interpretations in different populations, stages of pregnancy and clinical circumstances, as opposed to various diagnoses with one interpretation.<sup>18</sup>

In contrast, Redman and Jefferies<sup>19</sup> attempted to devise a classification that not only identified women at an elevated risk of adverse outcomes, but it also did so in such a way that accounted for the fact that preeclampsia is a disease predominantly, but not exclusively, seen in nulliparous women.

The authors proposed that a classification should focus on diastolic blood pressure, as nulliparous women tended to have a higher systolic, but not diastolic, blood pressure at booking than did multiparous women. In a cohort of 15,000 women, they found that when women had a large increase in diastolic blood pressure, those with a lower booking blood pressure were more likely to be nulliparous. Similarly, among

**TABLE 1**  
**Brief summary of the evolution of various diagnostic criteria for preeclampsia**

Author	Year	Definition of preeclampsia	Hypertension criteria	Proteinuria/edema criteria
Dieckmann <sup>3</sup>	1952	One of edema, proteinuria, hypertension, symptoms	$\geq 140$ mm Hg systolic and/or $\geq 90$ mm Hg diastolic	
Nelson <sup>9</sup>	1955	Gestational hypertension	$\geq 90$ mm Hg diastolic	
ACOG <sup>12</sup>	1972	Gestational hypertension plus proteinuria	Rise of 30 mm Hg Systolic or 15 mm Hg diastolic or $\geq 140/\geq 90$	Proteinuria—0.3 g/L in 24-h urine collection
Davies <sup>14</sup>	1979	Gestational hypertension or significant proteinuria or edema of the face and arms, or any 2	$+\geq 30/15$ or $\geq 140/90$	Edema: edema of the face and arms Proteinuria: 2+ on dipstick
ACOG <sup>16</sup>	1986	Gestational hypertension plus edema and/or proteinuria	$+\geq 30/15$ or $\geq 140/90$	Edema: $\geq 1+$ pitting edema after 12 h of bedrest; weight gain of $\geq 5$ pounds in 1 week Proteinuria: $\geq 300$ mg in a 24-h collection; urine protein concentration $\geq 1$ g/L
WHO <sup>17</sup>	1987	Gestational hypertension plus proteinuria	$\geq 140/90$	Proteinuria: 300 mg in a clean-catch or midstream specimen or in a 24-h collection
Davey and MacGillivray <sup>18</sup>	1988	Gestational hypertension plus proteinuria	$\geq 90$ diastolic	Proteinuria: $\geq 300$ mg per 24 h, or 2 dipstick x2
Redman and Jefferies <sup>19</sup>	1988	Gestational hypertension plus rise in blood pressure	$+\geq 25$ to $\geq 90$ diastolic, from a booking $< 90$	Nil
NHBPEWG <sup>20</sup>	1990	Gestational hypertension plus proteinuria	$+\geq 30/15$ ; if no reading from early in pregnancy available, $\geq 140/90$	Proteinuria: 0.3 g or more in a 24-h specimen or 1+ dipstick in a random urine determination
ASSHP <sup>21</sup>	1993	Gestational hypertension; Severe preeclampsia = severe hypertension $\pm$ organ dysfunction	$+\geq 25/15$ or $\geq 140/90$ Severe preeclampsia: $\geq 170/110$	
CHSC <sup>22</sup>	1997	Gestational hypertension plus proteinuria	$\geq 90$ Diastolic	Proteinuria: $\geq 0.3$ g in 24-h urine collection
NHBPEWG <sup>23</sup>	2000	Gestational hypertension plus proteinuria	$\geq 140/90$	Proteinuria: 1+ dipstick or 0.3 g in 24 h
ASSHP <sup>24</sup>	2000	Gestational hypertension plus organ dysfunction	$\geq 140/90$	Table 2
ISSHP <sup>25</sup>	2001	Research definition: Gestational hypertension plus proteinuria Clinical definition: Gestational hypertension plus organ dysfunction	$\geq 140/90$	Proteinuria: urinary excretion of 0.3 g protein or higher in a 24-h urine specimen
ACOG <sup>26</sup>	2002	Gestational hypertension plus proteinuria	$\geq 140/90$	Proteinuria: Urinary excretion of 0.3 g protein or higher in a 24-h urine specimen

Tanner. Evolution of the diagnosis of preeclampsia. Am J Obstet Gynecol 2022.

(continued)

**TABLE 1**  
Brief summary of the evolution of various diagnostic criteria for preeclampsia (continued)

Author	Year	Definition of preeclampsia	Hypertension criteria	Proteinuria/edema criteria
ACOG <sup>27</sup>	2013	Gestational hypertension plus organ dysfunction	≥140/90	Proteinuria: Urinary excretion of 0.3 g protein or higher in a 24-h urine specimen, or 1+ dipstick
ISSHP <sup>28</sup>	2014	Gestational hypertension plus organ dysfunction	≥140/90	Table 2
ACOG <sup>24</sup>	2018	Gestational hypertension plus organ dysfunction	≥140/90	Table 2
ISSHP <sup>29</sup>	2018	Gestational hypertension plus organ dysfunction	≥140/90	Table 2

+≥30/15 means a rise in systolic blood pressure of 30 mm Hg systolic or diastolic of 15 mm Hg; ≥140/90 means an absolute systolic blood pressure of ≥140 mm Hg systolic or 90 mm Hg diastolic.  
 ACOG, American College of Obstetricians and Gynecologists; ASSHP, Australasian Society for the Study of Hypertension in Pregnancy; CHSC, Canadian Hypertension Society Conference; ISSHP, International Society for the Study of Hypertension in Pregnancy; NHBPEWG, National High Blood Pressure Education Working Group; WHO, World Health Organization.  
 Tanner. Evolution of the diagnosis of preeclampsia. *Am J Obstet Gynecol* 2022.

women who recorded a high maximum diastolic blood pressure, those with a greater increase were also more likely to be nulliparous. Nulliparity was thus associated with both a higher rise in *and* maximum diastolic blood pressure. Any subsequent classification of hypertensive disorders should thus involve both.

They found that perinatal mortality and the rate of proteinuria increased significantly among women, with a rise in the diastolic blood pressure of at least 30 mm Hg; and that birthweight, but not gestational age at delivery, was lower in those with a rise of >25 but <29 mm Hg. Thus, they suggested that a rise in the diastolic blood pressure of at least 25 mm Hg, from a booking diastolic blood pressure of <90 mm Hg to >90 mm Hg, should be diagnostic of preeclampsia. No proteinuria would be required.

The authors applied this to a second dataset of 15,000 women. Compared with Nelson's criterion, this criterion diagnosed preeclampsia in fewer women (11.5% vs 26.3%). The extra women diagnosed by Nelson's criteria were older, heavier, developed less proteinuria, and delivered at a later gestation; their babies had higher birthweights and lower mortality. Overall, the new criterion identified a more severe form of disease. However, the authors did not compare their criterion against the more specific 1972 ACOG classification. Nelson's criterion had already received criticism for offering too broad a definition.

The debate over the appropriate classification of preeclampsia prompted an editorial in *The Lancet* in 1989,<sup>30</sup> which challenged the idea that the hypertensive disorders of pregnancy required labeling and classification. "It is sufficient to know the risks and appropriate treatment of the various manifestations of hypertension in pregnancy," the editorial argues. It suggests that flow diagrams and decision analysis, with their use of data at the time of decision-making and their incorporation of the probability of adverse outcomes, are more pragmatic for management than strictly assigning women to having preeclampsia or not. Davey and MacGillivray<sup>31</sup> rejected the idea that a classification precludes the

use of flow diagrams, decision analysis, and further observations, arguing that classifying preeclampsia was “the first step ensuring that doctors and nurses mean the same things by the same words.”

### 1990s

The 1990s saw consensus reports on hypertension in pregnancy from a range of groups, including the National High Blood Pressure Education Working Group (NHBPEWG) in 1990<sup>20</sup>; The Australasian Society for the Study of Hypertensive Disorders in Pregnancy (ASSHP) in 1993,<sup>21</sup> The American College of Obstetricians and Gynecologists (ACOG) in 1996<sup>16</sup>; and The Canadian Hypertension Society Conference (CHSC) in 1997.<sup>22</sup> Table 1 summarizes the similarities and differences.

The NHPEWG report defined hypertension as a rise in blood pressure of  $\geq 30/15$  mm Hg or an absolute blood pressure of  $\geq 140/90$  mm Hg. The ASSHP defined hypertension as a rise of  $\geq 25/15$  mm Hg, or an absolute level  $\geq 140/90$  mm Hg. The ACOG's 1996<sup>1</sup> guidelines used  $\geq 140/90$  mm Hg, and the CHSC only a diastolic  $\geq 90$  mm Hg. They also differed in the definition of preeclampsia. The NHPEWG and CHSC required gestational hypertension plus proteinuria; the ASSHP, only gestational hypertension, with organ dysfunction (including proteinuria) leading to a diagnosis of severe preeclampsia. The ACOG did not define preeclampsia but defined only PIH with organ dysfunction and/or severe hypertension, warranting a diagnosis of severe PIH.

### 2000s

New and updated guidelines from the NHBPEWG, the ASSHP, the ACOG, and the ISSHP followed in the early 2000s.

A few key changes were introduced to the NHBPEWG Report of 2000.<sup>23</sup> It abandoned the use of a rise in blood pressure as sufficient to diagnose hypertension. This followed work by North et al<sup>32</sup> in 1999, and Levine et al,<sup>33</sup> in 2000, who determined that women who experienced a rise in blood pressure of  $\geq 30/15$  mm Hg to a level  $< 140/90$  mm Hg, were not at a higher risk of

complications than normotensive women without such a rise. Edema too was abandoned because of its high prevalence among healthy pregnant women.

The ASSHP consensus statement of 2000 was the first to offer a clinical diagnosis of preeclampsia, which included organ dysfunction beyond proteinuria (Table 1). Renal, hepatic, neurologic, hematological, and uteroplacental dysfunction were considered to be diagnostic of preeclampsia. This guideline maintained a 140/90 mm Hg cutoff for diagnosing hypertension in pregnancy, as it was “outside 2 standard deviations of the blood pressure mean in the normal pregnant population.”

The ISSHP in 2001<sup>25</sup> concluded that further research comparing maternal and fetal outcomes between a “restrictive” definition of hypertension and proteinuria and an “inclusive” definition of hypertension and other organ dysfunction was warranted and that the criteria should remain restrictive. The ACOG's 2002 criteria<sup>26</sup> were based off the NHBPEWG report from 2000, defining preeclampsia as elevated blood pressure plus significant proteinuria. Organ dysfunction was still considered a feature of “severe preeclampsia.”

A decade later, there was a shift toward the “inclusive” definition of preeclampsia. The ACOG's 2013 guidelines abandoned the reliance on proteinuria for diagnosing preeclampsia, with other organ dysfunction now sufficient.<sup>27</sup> The ISSHP's updated recommendations in 2014<sup>28</sup> followed suit. An important distinction was that ISSHP considered uteroplacental dysfunction, such as fetal growth restriction, as diagnostic, whereas the ACOG did not. Conversely, pulmonary edema was included in the ACOG's but not the ISSHP's guidelines. Other differences were minor, such as cut-offs for platelet counts ( $< 100,000/\mu\text{L}$  for ACOG,  $< 150,000/\mu\text{L}$  for ISSHP) and liver enzymes (transaminases  $\geq$  twice the upper limit of normal for ACOG,  $\geq 40$  IU/L for ISSHP). Table 2 summarizes the criteria for organ dysfunction. In 2018, both the groups published updated guidelines,<sup>34,29</sup> which remained largely unchanged.

### Subtypes of Preeclampsia

Preeclampsia is commonly classified into an early-onset or a late-onset disease (arising before or after 34 weeks gestation). The 2 subtypes have been described as “qualitatively different.”<sup>35</sup> Early-onset preeclampsia is associated with a high-resistance, low-output hemodynamic state, whereas late-onset disease demonstrates a low-resistance, high-output state.<sup>36</sup> They share some but not all risk factors, and the effect of each risk factor differs. Angiogenic biomarkers that have prognostic value are higher in early- than late-onset disease,<sup>37</sup> and maternal and perinatal outcomes are worse in early-onset disease.<sup>38</sup>

However, these differences exist on a spectrum. The earlier preeclampsia develops, the more severe the angiogenic imbalance and the worse the outcomes are. The ASpirin for evidence-based PREEclampsia prevention trial showed that aspirin reduces the incidence of preterm preeclampsia but has no influence on term disease.<sup>39</sup> However, it is not clear whether this reflects a protective effect, or whether aspirin delays the onset of preeclampsia, meaning women give birth before it develops.

No clear pathologic evidence differentiates early- and late-onset preeclampsia. There is an ongoing debate as to whether preeclampsia is a placental disorder that leads to disruption of the maternal endothelial system or if placental dysfunction is secondary to suboptimal maternal cardiovascular adaptation to pregnancy.<sup>40</sup> Both are likely true, and so it is the varying extent to which each process occurs that leads to disparate prognoses. Gestation at onset is a useful heuristic for judging the likely prognosis of preeclampsia, but it must be remembered that 34 weeks is not a hard cutoff.

### Summary and Future Directions

The criteria defining preeclampsia have not changed significantly in recent years, but the evidence underpinning them has.

### Blood Pressure

The evidence underpinning blood pressure thresholds in the most recent ACOG

and ISSHP criteria can be retraced through guidelines to the 2000<sup>23</sup> and 1990<sup>20</sup> NHBPEWG reports and to a 1988 report from the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure<sup>41</sup> that focused on the nonpregnant population. This report has been superseded by the 2017 American Heart Association/American Cardiology Society guidelines, which lowered the threshold for stage 1 hypertension to 130 mm Hg systolic and/or 80 mm Hg diastolic, instead of 140 and 90 mm Hg, respectively. Recent evidence for pregnant women, too, suggests that 130/80 mm Hg is the threshold above which the risk of perinatal complications begins to rise.<sup>42,43</sup> This raises the question whether 140/90 mm Hg is an outdated threshold.

### Proteinuria

Despite occasional protestations to the contrary,<sup>44</sup> the prognostic significance of proteinuria in preeclampsia remains unclear. A 24-hour protein  $\geq 300$  mg is, as the ISSHP criteria from 2018 reflects, “more a time-honored value than one with scientific proof.”<sup>34</sup> In justifying this threshold, the ACOG’s 2018 guideline<sup>28</sup> cites the 2000 NHBPEP working group report (a consensus report)<sup>23</sup>, a meta-analysis studying the relationship between significant proteinuria on spot urine protein-creatinine ratio (PCR) and 24 hour<sup>45</sup>, and a cohort study that determined among pregnant women 95th and 99th centile cut-offs for proteinuria.<sup>46</sup> None is based on a relationship with the prognosis.

A 2009 meta-analysis concluded that proteinuria was “a poor predictor of either fetal or maternal complications in women with preeclampsia,”<sup>47</sup> and prospective research has shown that significant proteinuria is common without developing preeclampsia.<sup>48</sup> Although some studies suggest that proteinuria in preeclampsia is associated with more severe disease,<sup>49</sup> these should be interpreted carefully, as a higher blood pressure is associated with more proteinuria. Thus, any relationship between proteinuria and complications may be better explained by blood pressures (the collider bias<sup>50</sup>).

**TABLE 2**

### Differences in the definitions of organ dysfunction in the diagnostic criteria for preeclampsia

Criterion or organ system	ASSHP, <sup>24</sup> 2000, Brown et al, <sup>25</sup> 2001	ACOG, <sup>27</sup> 2013; ACOG, <sup>34</sup> 2018	Tranquilli et al, <sup>28</sup> 2014; Brown et al, <sup>29</sup> 2018
Proteinuria	300 mg/24 h or spot urine PCR $\geq 30$ mg/mmol	300 mg/24 h; urine PCR $\geq 0.3$ ; dipstick 1+ [2013], 2+ [2018]	1+, 30 mg/dL; urine PCR $\geq 30$ mg/mmol (0.3 mg/mg)
Other renal	Creatinine $\geq 0.09$ mmol/L [90 $\mu$ mol/L] or oliguria	Serum creatinine $> 1.1$ mg/dL; doubling of serum creatinine in absence of other renal disease	Creatinine $\geq 90$ $\mu$ mol/L (1 mg/dL)
Hepatic	Raised serum transaminases and/or severe epigastric/right upper quadrant pain	Liver transaminases $\geq$ twice the normal concentration	Alanine aminotransferase or aspartate aminotransferase $\geq 40$ IU/L
Neurologic	Convulsions; hyperreflexia with clonus; severe headaches with hyperreflexia; persistent visual disturbances	Cerebral or visual symptoms	Eclampsia; altered mental status; blindness; stroke; clonus; severe headaches; persistent visual scotomata
Hematological	Thrombocytopenia; disseminated intravascular coagulation; hemolysis	Platelets $< 100,000/\mu$ L	Platelets $< 150,000/\mu$ L; disseminated intravascular coagulation, hemolysis
Other	Fetal growth restriction	Pulmonary edema	Uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, stillbirth)

ACOG, American College of Obstetricians and Gynecologists; ASSHP, Australasian Society for the Study of Hypertension in Pregnancy; ISSHP, International Society for the Study of Hypertension in Pregnancy; Urine PCR, urine protein: creatinine ratio. Tanner. Evolution of the diagnosis of preeclampsia. Am J Obstet Gynecol 2022.

Finally, measuring proteinuria is challenging. A 24-h collection is considered as gold-standard but is “frequently inaccurate”<sup>51</sup>. Urine PCR is also imperfect. Two meta-analyses suggest that a cutoff of 0.26–0.30 has a sensitivity of 81% to 83% and specificity of 76% for detecting proteinuria >300 mg in a 24-hour collection.<sup>45,52</sup> However, even if these tests were perfect, sparse to nonexistent data ties proteinuria to outcomes from preeclampsia.

### Other Organ Dysfunction

Research into links between organ dysfunction and complications is also limited. Reddy et al<sup>53</sup> showed that women meeting the ACOG’s 2018 thresholds for low platelets and elevated liver enzymes had odds ratios (OR) for complications of 3.70 (95% confidence interval [CI], 1.98–6.89) and 2.32 (95% CI, 1.39–3.87), respectively. Women meeting the ISSHP’s less restrictive thresholds had lower ORs, of 2.09 (95% CI, 1.34–3.24) and 1.66 (95% CI, 1.04–2.67). Symptoms such as headache were not associated with complications. Future research should take a follow a similar approach.

### Future Criteria

The diagnostic criteria of preeclampsia are again becoming a “babel of schemata”<sup>14</sup>, and once more, there is debate about what the goals of a preeclampsia diagnosis should be.

A recurring theme in prospective studies<sup>54,55</sup> is that compared with a narrow definition (ie, hypertension and proteinuria), a broad definition has a higher sensitivity for identifying women who suffer complications but a lower specificity. Authors have supported this, as “the purpose of classification is to identify groups of women who require specific care,”<sup>55</sup> such as closer monitoring.

This makes sense. However, it implies that if a woman does not meet the diagnostic criteria, they would not require closer monitoring. However, preeclampsia represents a spectrum of disease. Those who fall immediately on either side of the criteria’s dividing line are similar. Clinical judgment should be applied, and the lack of a diagnosis

should not exclude a woman from closer surveillance.

There are other implications to broadening the criteria. Evidence-based guidelines are only useful insofar as the population they are applied to reasonably mimics the population they were developed in. If women are diagnosed with preeclampsia without meeting a strict research definition, the guidelines will be less applicable. Varying definitions also make it difficult to compare the incidence, outcomes, and prognosis between studies. There are also economic implications—closer monitoring of women at a low risk of complications stretches the resources of hospitals and clinicians.

The diagnosis and classification of preeclampsia should instead be rooted in a relationship with prognosis and treatment. Prognostic studies and randomized controlled trials should be developed around the following 2 questions: what is the natural course of preeclampsia, and how can treatment alter it?

Angiogenic biomarkers are potentially valuable here.<sup>56,57</sup> However, much work has focused on a diagnosis of preeclampsia and not its complications as the outcome.<sup>56,58</sup> Ruling out a diagnosis of preeclampsia in the ensuing weeks may reduce unnecessary interventions and admissions but has limited bearing on prognosis. Knowing the likelihood of a woman suffering a serious complication in the coming weeks is far more important. This is where research should focus.

Research into treatments should focus on how women respond and why. The Control of Hypertension in Pregnancy Study trial<sup>59</sup> showed that in women with hypertension in pregnancy, tight blood pressure control was not associated with better outcomes than less-tight control. But as Lees and Ferrazzi remarked “Would it not have been instructive...to understand the underlying differences in womens’ cardiovascular status and in this light the response to treatment?”<sup>60</sup>

This reflects a difference in how we think in the clinical and research settings. Clinicians make a diagnosis such as preeclampsia, then move to treatment, deciding (for example) whether

induction of labor or expectant management is best. This leads to a descriptive criteria for preeclampsia, as we identify and record how the disease manifests. In contrast, research begins with the intervention, then identifies those who respond to it. Consider the HYPITAT trial, which found that induction at 37 weeks improves maternal outcomes for women with mild hypertensive disease.<sup>61</sup> Treatment first, then the population who benefit.

How we diagnose and manage preeclampsia will continue to evolve in the future, but it should always be guided by following the most important questions in medicine: what is the prognosis of this patient? What can we do about it? ■

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