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The definition of severe and early-onset preeclampsia. Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP)

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ABSTRACT

Objective: There is discrepancy in the literature on the definitions of severe and early-onset pre-eclampsia. We aimed to determine those definitions for clinical purposes and to introduce them in the classification of the hypertensive disorders of pregnancy for publication purposes.
Methods: We circulated a questionnaire to the International Committee of the International Society for the Study of Hypertension in Pregnancy focusing on the thresholds for defining severe preeclampsia and the gestation at which to define early-onset preeclampsia, and on the definition and inclusion of the HELLP syndrome or other clinical features in severe preeclampsia. The questions were closed, but all answers had space for more open detailed comments.
Results: There was a general agreement to define preeclampsia as severe if blood pressure was >160 mmHg systolic or 110 mmHg diastolic. There was scarce agreement on the amount of proteinuria to define severity. The HELLP syndrome was considered a feature to include in the severe classification. Most investigators considered early-onset preeclampsia as that occurring before 34 weeks.
Conclusions: A definition of pre-eclampsia is paramount for driving good clinical practice. Classifications on the other hand are useful to enable international comparisons of clinical data and outcomes. We used the results of this survey to update our previous classification for the purposes of providing clinical research definitions of severe and early onset preeclampsia that will hopefully be accepted in the international literature.

Introduction

When reading articles on 'severe' preeclampsia, we often note discordance among the criteria used to define this condition. Authors use different blood pressure (BP) thresholds, different (if any) proteinuria thresholds, include the partial or total HELLP syndrome, or clinical symptoms and/or fetal–placental parameters.

The same occurs for the definition of early onset preeclampsia, with thresholds ranging from 28 to even 37 weeks gestation.

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This is why during the last World and European congresses a group of researchers was committed by the International Society for the Study of Hypertension in Pregnancy (ISSHP) to refine those criteria, for publication but not for clinical purposes. These refinements were begun by a consensus of experts, whose statements are subject to the International Council and then to the General Assembly. It is anticipated that through this procedure, the results may finally serve as a publication guideline for all journals when addressing the issues of 'severe' or 'early onset' pre-eclampsia.

With this work we have expanded on our earlier publication [1] by being clearer on a scientific research diagnosis to be used in the international literature. We do this so that only women with the correct disorder are included in scientific research. If a clinician is submitting clinical research, describing patient outcomes in general, then these definitions of 'severe' or 'early onset' pre-eclampsia can apply if they wish to report on those aspects; if a scientist is submitting laboratory or physiology research, stringent definitions should apply in all cases.

Methods

We circulated a questionnaire to the International Committee of the ISSHP and analyzed the results, prepared a consensus document to submit to the Council and the General Assembly during the Geneva meeting 2012 and obtained the approval and endorsement of the International Society. This procedure was already experienced in 2000 at the Paris Congress ISSHP, followed by publication in 2001 of the classification we endorsed [1].

The questionnaire was focused on the thresholds for severe preeclampsia and the gestation at which to define early-onset preeclampsia; we also asked about the definition and inclusion of the HELLP syndrome or other clinical features to be included in severe preeclampsia. Those questions were closed, but all answers had space left open for more detailed comments.

The questions were as follows.

1. For severe preeclampsia: the thresholds considered for Systolic Blood Pressure (SBP) in mmHg (>160, >170, >180, or other); Diastolic Blood Pressure (DBP) in mmHg (>100; >110; >120, or other); proteinuria in g/l (>2; >3; >5, or other).

The investigators were also asked if they would include the HELLP syndrome in the definition of severe preeclampsia, and if they would use Sibai's criteria for 'atypical' pre-eclampsia [2].

Furthermore they were asked if they would include other clinical signs (headache, epigastric pain and visual disturbances) in the classification of severe preeclampsia and if they would define "impending eclampsia".

1. For early-onset preeclampsia: the gestational age in weeks at onset (<28; <30; <32; <34; <37, or other). The investigators were also asked if they agreed to define as "preterm preeclampsia" that occurring before 37 weeks.

The questionnaire was sent to 26 members of the International Committee: 22 responded (11 with the form and comments, 10 with the form only, 1 with only comments).

Results

Systolic Blood Pressure: 82.0% considered 160 mmHg as the threshold to define severe preeclampsia; 9.0% considered 170 mmHg; 9.0% considered 180 mmHg.

Diastolic Blood Pressure: 86.4% considered 110 mmHg as the threshold to define severe preeclampsia; 13.6% considered 100 mmHg.

Proteinuria: 36.3% considered 5 g/l as the threshold to define severe preeclampsia; another 36.3% considered 3 g/l, 9.2% considered 2 g/l. Three investigators suggested to not consider proteinuria for defining severe preeclampsia.

Seventy-seven percent agreed to include the HELLP syndrome in the classification, and 73% agreed on the definition of "impending eclampsia".

For early-onset preeclampsia: 73.0% considered it as occurring before 34 weeks; 18.0% considered 32 weeks; 9.0% chose 28 weeks. Seventy-three percent agreed to define preterm preeclampsia as that occurring before 37 weeks.

Comment

Definitions of 'severe' preeclampsia are all arbitrary. The need for a consensus is therefore clear. A common classification does not necessarily impose mandatory clinical decisions, but at least it is the tool to compare a series in the scientific literature and speak the same international language.

The results of this survey indicate that even among renowned international clinicians and scientists in the field there is still some discordance on how to define and classify severe or early onset forms of preeclampsia. This is also evident from guidelines where some discrepancy exists even in the same country (e.g. 170 mmHg systolic BP as a threshold level for RCOG [3] but 160 mmHg for NICE [4], both from the United Kingdom).

There is a general consensus that the factors determining severity and indication to expedite delivery are the difficulty in controlling blood pressure and the deteriorating clinical conditions (HELLP syndrome, impending eclampsia, worsening thrombocytopenia, or worsening fetal growth restriction) while there is less concern on the meaning of increased proteinuria: the degree of which, except at extremes, is not considered a reliable marker of pre-eclampsia severity nor seems to predict clinical outcome [5].

From the survey of our Society, there is a general agreement that blood pressure has to be considered severely elevated when it is >160 mmHg systolic or >110 mmHg diastolic.

One issue that emerged concerned with how many BP readings to measure before establishing the diagnosis of hypertension in pregnancy. We agreed not to rely on a single reading because a single BP might be an error in

measurement, but on the other hand in the case of severely elevated BP not to wait for "6 h apart", because this position would endorse that the disease cannot be severe by BP criteria until 6 h after the first severe BP, a position that might lead to poor clinical outcome. After a first severely elevated BP, we recommended to measure BP frequently, (e.g. every 15 min and then every 30 min in the initial phase of assessment, consistently with the Canadian guidelines [6]), and make decisions on the trend and preponderance of blood pressures. We did not address which device to use to measure BP but suggest mercury sphygmomanometry when available or sphygmomanometry using a liquid crystal device [7]. If an automated device is to be used then it should have been validated for use in pregnancy.

For the HELLP syndrome there have been some comments on which platelet level has to be considered as being low. We agreed that the value of <100,000/dl has served well, and higher values, such as Martin's class 3 of <150,000 are mostly intended to alert clinicians that such counts are not normal and significant hypertensive disease could be progressing [8]. We also agree that ALT or AST elevations of twofold the upper limit of normal seems reasonable, although elevations of this level may persist for some time without clinical deterioration and of course may be due to other conditions in pregnancy. The issue of hemolysis in the HELLP syndrome was raised. Some commented that in their experience, hemolysis is rarely so significant to destabilize the patient or require transfusion. When it does, the other criteria are almost always strongly positive, so it really does not drive care. The diagnosis is controversial because very few examine a peripheral smear for hemolysis, whereas most use elevated LDH (twofold the upper reference limit or >650 IU/l). Whichever method is used, we believe that this is a feature of severe disease and should be noted.

Although there was good (73%) agreement on the definition of "impending eclampsia" the reasons against including it *tout court* in the classification of 'severe pre-eclampsia' were that this cluster of signs and symptoms is already included in the organ-based system of classification and this term will confuse rather than clarify thinking and should not prove useful in research.

The issue of proteinuria is fairly critical, not only because there was no agreement of what amount could be 'severe', but because some strongly disagreed with the inclusion of heavy proteinuria in the definition of severe pre-eclampsia. Some of our investigators confirmed that in their experience proteinuria at levels higher than those for the diagnosis of preeclampsia does not predict clinical outcome. Some guidelines already do not recommend to repeat and followup the amount of proteinuria, once it has been found [4]. Also, the techniques used to detect or measure proteinuria are unreliable to some extent: dipstick is considered useful for alerting clinicians to an initial diagnosis; 24/h urine has been more frequently used but has pitfalls in clinical practice and is time consuming; a spot urine protein/creatinine ratio > 30 mg/mmol was felt to be the optimal measurement to confirm proteinuria.

There is no clear consensus on the amount of proteinuria to be considered 'severe', although the majority rely on values between >3 and 5 g/l. From our results, the amount of proteinuria should not be a criterion of severity.

As for the time of onset of pre-eclampsia there was a more general agreement that early-onset would be labeled when preeclampsia presents before 34 weeks.

It was felt reasonable to call "preterm preeclampsia" that occurring from 34 + 1 but before 37 + 0 weeks and consequently label as "term preeclampsia" that occurring after 37 + 1 weeks.

Clinical considerations

In this survey, the investigators agreed that the purpose of classifying pre-eclampsia as 'severe' is to identify women at increased risk of adverse maternal/fetal outcomes and/or requiring more urgent treatment and to highlight for clinicians 'red flags' that need immediate attention and care (e.g. extremely high BP, neurological signs, etc.).

Many of the investigators considered early-onset as a part of the severity, because it reflects on maternal and especially neonatal outcome and may express a specific form of the preeclampsia syndrome [9], though this remains controversial and there is no doubt that women can present at term with features of severe pre-eclampsia.

Another issue dealt with the use of 24-h automated ambulatory BP recording. At this stage, we can consider the method extremely useful to diagnose white-coat hypertension in the early stages of pregnancy [10], but any further use in pregnancy should be the subject of further study and a future consensus from this Society.

Another issue is the attention that now has to be given to those less common forms of preeclampsia [2,6,11], such as 'non-proteinuric' pre-eclampsia, which occurs in about 25% of cases, and has an intermediate outcome profile between that of pre-eclamptic women with proteinuria and those with non-proteinuric gestational hypertension and other "preeclamptic" features, including those with hypertension and fetal growth restriction in the absence of proteinuria [1,12].

In conclusion, clinicians worldwide have become increasingly convinced that preeclampsia is much more than "pregnancy-induced hypertension" [13]. In accordance with good clinical practice ISSHP has defined an 'inclusive' definition of pre-eclampsia that should drive good clinical diagnoses erring on the side of not missing cases of this important disorder; this will be described in a further statement from the Society.

For scientific research and publication purposes we have been deliberately more restrictive and now provide the International Society's definitions of 'severe' and 'early onset' pre-eclampsia. It is hoped that these definitions will become uniform and to this end the ISSHP will work with a range of journal editors to discuss such an approach.

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