Thieme

Assessing Severity and Need for Delivery in Early Onset Preeclampsia Before 32 Weeks of Gestation: a Delphi Consensus Procedure

Einschätzung des Schweregrads und der Dringlichkeit einer Entbindung bei Präeklampsie im Frühstadium vor der 32. Schwangerschaftswoche: ein Delphi-Konsensus-Prozess

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ABSTRACT

Background
Preeclampsia is a potentially life-threatening hypertensive pregnancy disorder that carries an acute risk of an unfavorable outcome of the pregnancy but also has consequences for the long-term health of the mother. Women who develop the early form of pre-eclampsia before the 32 nd week of pregnancy have the highest risk and are also the most difficult to treat. The severity of pre-eclampsia is not characterized uniformly in Germany, so that the indication for delivery is rather individualized. The aim of this study was to reach a consensus on parameters that could serve as criteria for describing the severity of pre-eclampsia based on the urgency of delivery. To this end, a Delphi procedure was used to present a scenario in which a woman was admitted for preeclampsia before 32 gestational weeks and after completion of antenatal steroid therapy.

Methods
Clinicians specialized in maternal-fetal medicine from German-speaking countries completed five rounds of a modified Delphi questionnaire. Presented parameters were selected by the section “Hypertensive Pregnancy Diseases and Fetal Growth Restriction” of the German Society of Gynecology and Obstetrics after reviewing the literature. These included objectifiable laboratory or clinical parameters as well as subjective symptoms of the patient. In addition, nine fetal parameters were taken into account. The clinicians were asked to rate presented parameters as an indication for delivery on a Likert scale from 0 to 4 (no indication to absolute indication without delay). For each item, the predefined cut-off for group consensus was ≥ 70 % agreement.

Results
A total of 126 experts were approached. Sixty-nine experts (54.8 %) took part in the first round; of those 50 completed the entire Delphi procedure. A consensus was reached on 14 parameters to be considered rapid preparation for delivery without delay (4 points on the Likert scale). These were among others hepatic hematoma or liver capsule rupture, acute liver failure with fulminant coagulation disorder or disseminated intravascular coagulation, eclampsia, pathologic findings in imaging (e.g. cMRI) or electrocardiogram arranged for new onset of headache or retrosternal pain, respectively. Twenty-six parameters were rated as factors that should be considered in the decision without being absolute (1 to 3 points), and 13 parameters should have no influence on the decision to deliver (0 points). No consensus on severe hypertension as an indication for delivery could be reached for blood pressure values below 220/140 mmHg.

Conclusion
A consensus was reached on whether to deliver in preeclampsia typic clinical findings and symptoms. The results can serve as guidance for current clinical practice and for the definition of clinical endpoints in intervention studies. Nevertheless, the isolated criteria are a theoretical construction since the combined deterioration or summation of several factors rather than a single factor most likely influences the decision to deliver and reflect the severity of preeclampsia. Moreover, the degree of hypertension as an indication for delivery remains controversial, unless the patient suffers additionally from complaints. Future research should be enforced to incorporate long-term risks for the mother into a decision aid.

ZUSAMMENFASSUNG

Hintergrund
Präeklampsie stellt eine potenziell lebensbedrohende hypertensive Schwangerschaftserkrankung dar, die mit einem akuten Risiko für ein ungünstiges Schwangerschaftsoutcome und mit Konsequenzen für die langfristige Gesundheit der Mutter verbunden ist. Das höchste Risiko haben Frauen, welche die Frühform von Präeklampsie vor der 32. Schwangerschaftswoche entwickeln, und die Behandlung dieser Frauen ist auch am schwierigsten. Der Schweregrad der Präeklampsie wird in Deutschland nicht einheitlich eingestuft. Das bedeutet, dass die Indikation zur Entbindung eher individuell erfolgt. Ziel dieser Studie war es, einen Konsens hinsichtlich der Parameter zu erreichen, die, basierend auf der Dringlichkeit der Entbindung, als Kriterien zur Beschreibung des Schweregrads der Präeklampsie dienen könnten. Es wurde dazu eine Delphi-Studie durchgeführt, die ein Szenario beschreiben sollte, bei der eine Frau wegen Präeklampsie vor der 32. Schwangerschaftswoche und nach Abschluss einer antenatalen Steroidtherapie stationär aufgenommen wird.

Methoden
Fachärzte und -ärztinnen für mütterliche-fetale Medizin aus deutschsprachigen Ländern nahmen an 5 Runden einer modifizierten Delphi-Befragung teil. Die vorgestellten Parameter wurden von der Sektion Hypertensive Schwangerschaftserkrankungen und fetale Wachstumsrestriktion der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe nach Durchsicht der Literatur ausgewählt. Die Liste der Parameter umfasste objektivierbare Laborparameter und klinische Parameter sowie subjektive Symptome von Patientinnen. Es wurden auch 9 fetale Parameter berücksichtigt. Die Fachärzte und -ärztinnen wurden gebeten, die vorgestellten Parameter als Indikation für eine Entbindung auf einer Likert-Skala von 0 bis 4 (keine Indikation bis absolute Indikation ohne Verzug) zu bewerten. Für jeden Punkt war der vorgegebene kritische Wert für ein Gruppenkonsens eine Zustimmung ≥ 70 %.

Ergebnisse
Insgesamt wurden 126 Fachärzte und -ärztinnen angeschrieben. Es nahmen 69 Fachärzte und -ärztinnen (54,8 %) an der 1. Runde teil; davon haben 50 den gesamten Delphi-Prozess abgeschlossen. Ein Konsens wurde für 14 Parameter erreicht, die als Hinweise für eine schnelle Entbindung eingestuft wurden (4 Punkte auf der Likert-Skala). Dazu zählten u. a. Leberhämatom bzw. Leberkapselruptur, akutes Leberversagen mit fulminanter Gerinnungsstörung oder disseminierter intravasaler Gerinnung, Eklampsie, pathologische Befunde in der Bildgebung (z. B. cMRI) oder beim Elektrokardiogramm, das wegen erneutem Auftreten von Kopfschmerzen bzw. Brustbeinschmerzen durchgeführt wurde. 26 Parameter wurden als Faktoren eingestuft, die bei einer Entscheidung zur Entbindung berücksichtigt werden sollten, ohne dass sie absolut eine Entbindung erfordern (1 bis 3 Punkte); bei 13 Parametern war der Konsens, dass diese keinen Einfluss auf die Entscheidung zur Entbindung haben sollten (0 Punkte). Hinsichtlich des Punktes „schwerer Bluthochdruck als Indikation für eine Entbindung“ konnte kein Konsens erreicht werden, wenn die Blutdruckwerte unter 220/140 mmHg lagen.

Schlussfolgerung
Es wurde ein Konsens hinsichtlich der typischen klinischen Befunde und Symptome für eine dringliche Entbindung erreicht. Die Ergebnisse können als Anleitung für die aktuelle klinische Praxis und bei der Definition von klinischen Endpunkten in Interventionsstudien dienen. Dennoch stellen diese isolierten Kriterien ein theoretisches Konstrukt dar, da in der Praxis die Entscheidung zur Entbindung auf einer kombinierten Verschlechterung bzw. auf der Summierung mehrerer Faktoren anstelle eines einzigen Faktors beruht, da diese Konstellation eher den Schweregrad der Präeklampsie reflektiert. Hinzu kommt noch, dass die Schwere der Hyper-

tonie als Indikation für eine Entbindung immer noch kontrovers diskutiert wird, es sei denn, dass die Patientin auch unter anderen Beschwerden leidet. Die zukünftige Forschung sollte auch mütterliche Langzeitrisiken in die Entscheidungshilfe integrieren.

Introduction

Pregnancy-related hypertensive disorders (PIH), in particular preeclampsia, is one of the most common causes of maternal and fetal morbidity and mortality [1]. Preeclampsia is defined by elevated blood pressure with the newly involvement of at least one other organ [2]. Though any organ can be affected, the kidneys, liver, and the placenta are most commonly involved [2]. This can acutely lead to short-term maternal complications, such as cerebrovascular bleeding, retinal detachment, HELLP syndrome and eclampsia [3].

Impaired placental development early in pregnancy and consequent release of several placenta-derived factors into the maternal circulation that lead to generalized maternal endothelial dysfunction is the leading hypothesis of pathogenesis [4, 5, 6]. However, there is increasing evidence that suboptimal maternal cardiovascular performance is likely to be causative for placental dysfunction in preeclampsia [7]. This may be one explanation for the known long-term consequences for women with preeclampsia especially regarding the cardiovascular system [8, 9], the renal system [10], thromboembolism [11], and neurocognitive impairment [12, 13]. Yet, it is controversial whether preeclampsia can be regarded as the pathological insult that causes the long-term consequences or whether the development of preeclampsia reveals a (previously unknown) risk condition prior to pregnancy [4, 14].

Early-onset preeclampsia before 32 weeks of pregnancy accounts for 0.7% to 1.0% of all births [15]. The timing of delivery demands balancing maternal risks of acute or chronic disease, intrauterine fetal demise, and sequelae of neonatal preterm birth. International guidelines differ in their recommendations for the delivery of early-onset preeclampsia before 32 weeks' gestation. The Swiss-Austrian-German Guideline for the treatment of women with preeclampsia states: "Before 34 weeks' gestation, a primarily conservative approach can be considered depending on the severity of preeclampsia." However, the definition of "severe preeclampsia" is not only inconsistent in the literature [16, 17, 18, 19, 20, 21, 22], international societies like the International Society for the Study of Hypertension in Pregnancy (ISSHP), Society of Obstetric Medicine of Australia and New Zealand (SOMANZ), European Society of Cardiology (ESC), and the Swiss-Austrian-German Guideline on Hypertension in Pregnancy (German Society of Gynecology and Obstetrics [DGGG]) refrained from defining "severe preeclampsia" in their guidelines [2, 23, 24]. Furthermore, the decision to deliver is complex and depends on many aspects, especially as the presentation of preeclampsia and its complications is heterogeneous. The indication for delivery therefore remains an individual decision, and the term "severe preeclampsia" is very often used in clinical language to justify an indication for delivery without a clear definition of the term.

The aim of the present study was to define "severe early-onset preeclampsia" based on consent among obstetricians from Germany, Switzerland, and Austria about the indication for mandatory preterm birth for imminent maternal complications. This can be considered a thought experiment. We have assumed that prolongation of pregnancy up to 32 weeks' gestation to improve fetal maturity is justified until acute or imminent complications threaten the mother. Consequently, since delivery is the only cure, we define a finding that forces the obstetrician to suggest delivery as "severe preeclampsia". With this in mind, we asked obstetricians for their opinion on various scenarios and constellations of preeclampsia. By grading these findings for necessary delivery on a Likert scale from 0 to 4, results of this study may also be used in preparation of future observational studies to challenge a severity score of preeclampsia.

Methods

Delphi study design

To address the study aim, we used the classic asynchronous Delphi consensus methodology. This is an iterative technique based on evaluating a series of structured statements. After revision, this is communicated to the participants and repeated in increasing detail in several rounds until a consensus can be reached [25, 26]. The classic asynchronous Delphi design anticipates the development of unwanted group dynamics. This prevented the development of trends and tendencies in opinions that could potentially interfere with good estimates. Furthermore, the individual online surveys made it easier and safer to reach the experts. This made it possible to address a larger group of experts.

For the development of questionnaires international clinical practice guidelines were reviewed for clinical features, symptoms, and laboratory findings related to preeclampsia. In detail, the practice guidelines of the International Society for the Study of Hypertension in Pregnancy (ISSHP) 2018, the American College of Obstetricians and Gynecologists (ACOG) 2013, the Society of Obstetricians and Gynaecologists of Canada (SOGC) practice guideline on hypertensive disorders in pregnancy 2014, the National Institute for Health and Care Excellence (NICE) 2019, and the German Society of Gynecology and Obstetrics (DGGG) 2019 was used [2, 23, 24, 27, 28, 29].

Identified parameters were structured into four categories: (i) 19 maternal parameters that can be measured and ordered on a metric scale, like oxygen saturation, blood pressure, weight gain, creatinine concentration, proteinuria, platelet count, and others; (ii) eight maternal clinical diagnoses that can be determined objectively by the physician but can be coded binary. This includes pulmonary edema, any heart disease (e.g. low ejection fraction, myocardiac ischemia), hepatic hematoma, hyperreflexia and other; (iii) 13 maternal symptoms that are subjective to the pa-

tient's perception but impair the patient's well-being, and that can be categorized in binary terms, like nausea, headache, dizziness, abdominal or thoracal pain. It has been specified that symptoms last over several hours; (iv) nine fetal parameters assessed by ultrasound or cardiotocography.

A case was then constructed for all Delphi rounds to query delivery criteria and their weighting: a pregnant woman between 24 + 0 and 31 + 6 weeks' gestation with diagnosed pre-eclampsia according to the AWMF criteria (German Guideline for gynecology and obstetrics) [2]. The treatment with antenatal corticosteroids for fetal lung maturity has already been completed [30, 31]. In the first round of the Delphi procedure, participants were asked about their confidence in suggesting delivery for this case and for each of the 49 parameters in categories (i) to (iv). For metric scales, obstetricians were asked to indicate a specific cut-off value at which they would recommend delivery. For the binary parameters, participants were asked to rate on a Likert scale according to whether they considered it as no (0 points), mild, moderate, severe, or absolute delivery criterion (4 points), where "absolute" refers to delivery without any delay. During each round, participants could provide feedback on existing items or suggest additional ones for each category. Finally, participants were asked for demographic characteristics, clinical and academic background. The questionnaires were initially critically examined within the section "Hypertensive Pregnancy Diseases and Fetal Growth Restriction" of the German Society of Gynecology and Obstetrics. The predefined cut-off for group consensus on an item or group of related answers was ≥ 70 %.

Panel selection

The selection of potential panel members was based on their recognized expertise as heads of the tertiary perinatal centers in Germany, Austria, and Switzerland. In addition, clinical experts were identified who attended the congress of the German-Austrian-Swiss branch of the International Society for the Study of Hypertension in Pregnancy in Bern, Switzerland, in 2019. In total 126 participants were invited to participate. In the Delphi process, the votes of all committee members are weighted equally. Experts who did not participate in a particular round were not invited to participate in subsequent rounds. Ethical approval was obtained from University Medical Centre of Kiel (D 404/21). All participants provided informed consent before commencing the first round, and they were reminded of their right to withdraw before each subsequent round.

Data collection and analyses

The Delphi process started with round one in 11/2019 followed by round two from 12/2020 to 02/2021, round three from 02/2021 to 04/2021, round four from 05/2021 to 08/2021, and round five from 09/2021 to 11/2021. The first round of the Delphi process involved a questionnaire sent by post. The remaining four rounds were conducted online. The questionnaires were completed using the online tool SurveyMonkey (https://de.surveymonkey.com). In each round, a unique link (token-secured) to the questionnaire was sent to the panel members via email. The results of the questionnaires for each round were shared with the participants in the next round. The results were presented anonymously at the group level. Those who did not respond received reminder emails every 10 to 14 days until 8 weeks. Withdrawal from the proceedings was offered at any time.

Delphi rounds

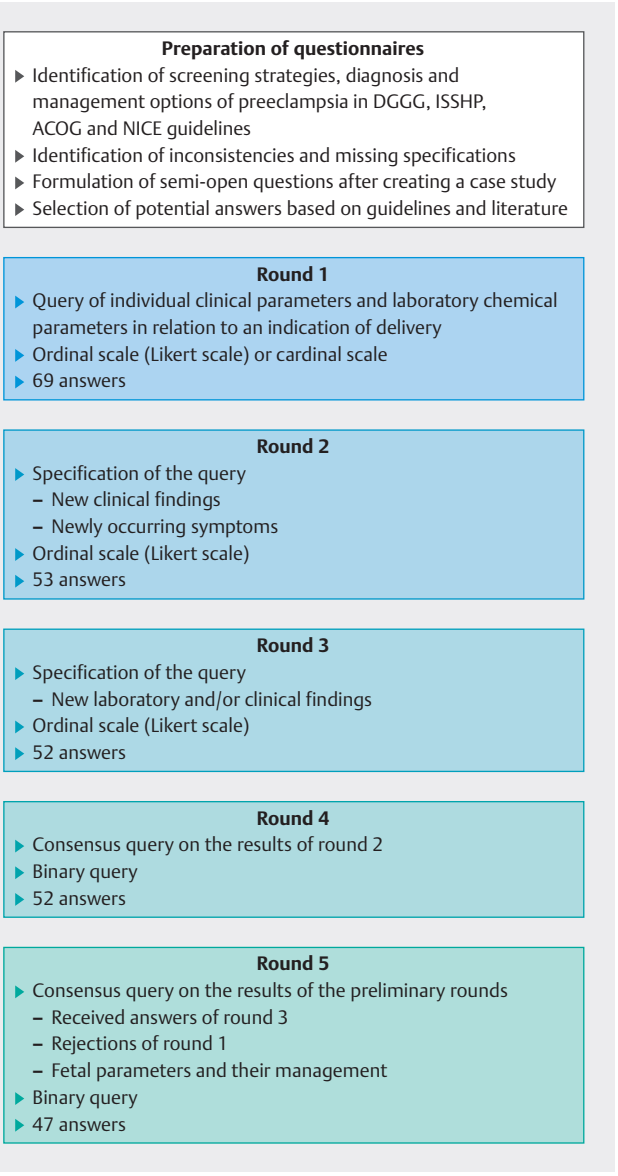
After the first round, all examined 49 parameters were evaluated descriptively. If ≥ 70 % of respondents agreed or rejected a value or parameter as an indication of delivery, it was accepted or rejected. The parameters without consensus were checked for relevance and, if necessary, the question was reformulated or made more precise. All further rounds were conducted via an online survey tool. In the second round, a precision of category (ii) (newly occurring clinical finding) and category (iii) (newly occurring clinical symptom) from round one was carried out. The respective finding or symptom was described in more detail to achieve a better assessment. In round three, parameters from category (i) have been specified and dynamic changes have been added. By defining cut-offs based on the participants' feedback a purely categorical query was carried out on a 5-point Likert scale. In round four, the parameters from category (ii) and (iii) which still failed to reach consensus were examined again. The classification into the respective categorical query, based on the majority opinion from the previous surveys, was presented. The panel was asked whether they agreed or disagreed. In round five, categories (i) and (iv) were reassessed. The classification into the respective categorical query, based on the majority opinion from the previous surveys, was presented. The panel was asked whether they agreed or disagreed. For various fetal parameters (category [iv]), it was checked whether the wording of the current national guideline on fetal growth restriction "delivery should be considered" was equivalent to a "more serious relative delivery criterion" in the opinion of the panel.

Within the five Delphi rounds, seven additional parameters were included by clarifying the parameters and questions and through feedback from the participants, so that a total of 56 parameters finally were considered as an indication for delivery. A flowchart of the development, the process and the participation per Delphi round is shown in ▶ **Fig. 1**.

Results

Participants

Sixty-nine of 126 experts (54.8 %) responded to the invitation and took part in the first round. Of these, 54 agreed to be contacted for further Delphi rounds. The response rates for round two were 53/54, for round three 52/53, for round four 52/52, and round five 50/52. Thus, 72.2 % (50/69) of participants who began the Delphi procedure completed the entire procedure. Of all initial 69 participants, 97.1 % were senior obstetricians, of whom 53 (76.8 %) had a recognized perinatal sub-specialization on maternal-fetal medicine, an optional additional qualification in the German-speaking area. The majority of experts regularly deal with the issue in scientific and/or in training aspects; 94.2 % of the experts work in a tertiary maternal and perinatal care center or University hospitals.



▶ **Fig. 1** The Delphi procedure. A flowchart of the development, the process and the participation per Delphi round. DGGG = German Society of Gynecology and Obstetrics, ISSHP = International Society for the Study of Hypertension in Pregnancy, ACOG = American College of Obstetricians and Gynecologists, NICE = National Institute for Health and Care Excellence

On average, experts were 48 years of age, 45% were female (▶ **Table 1**).

Delphi rounds

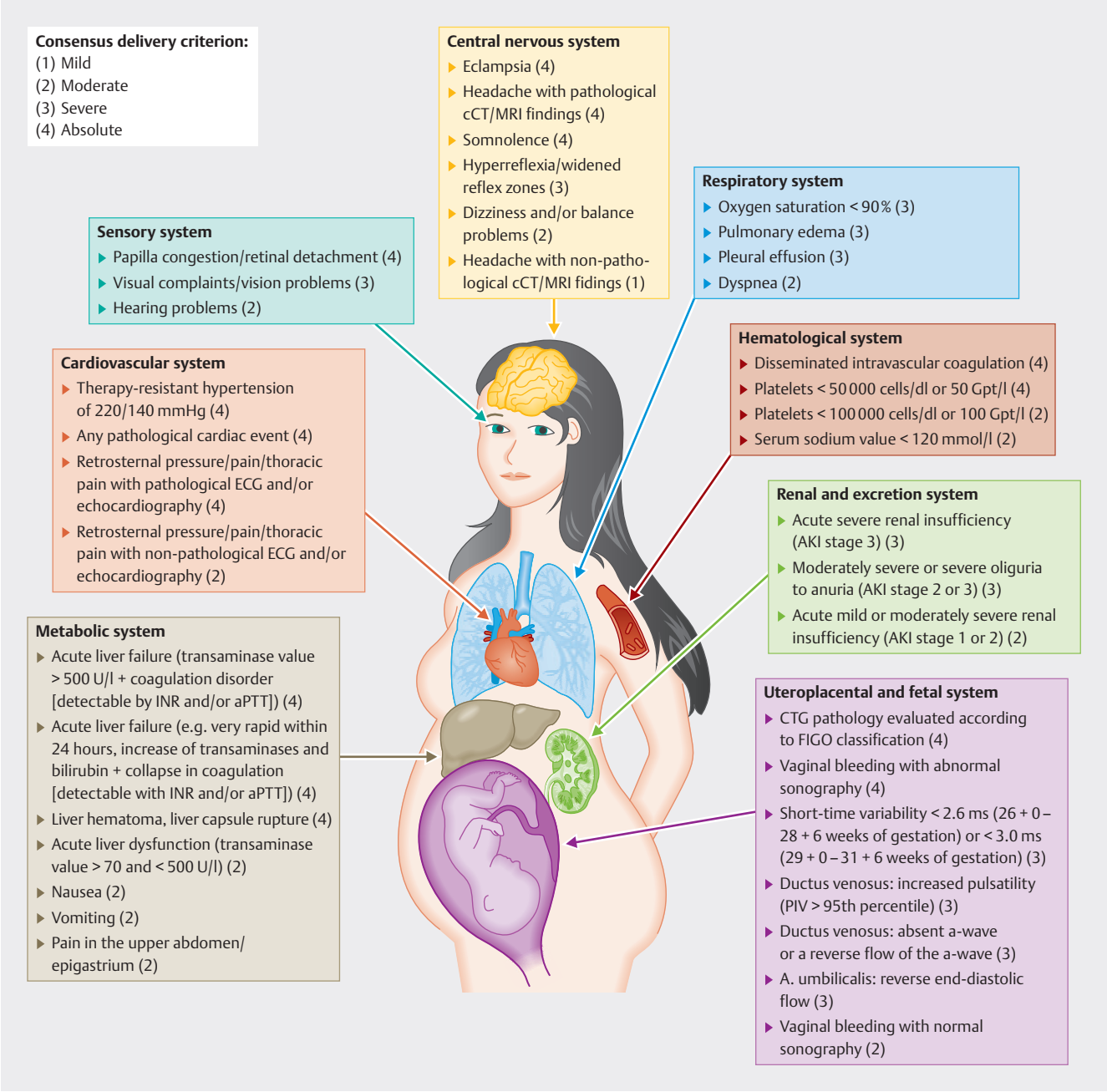
In the first round, a new hepatic hematoma or liver capsule rupture as well as disseminated intravascular coagulation led to a consensus of 100% and 94.2%, respectively, that these findings represent an absolute indication of delivery. Eclampsia was considered as an absolute indication of delivery by 87.0% of the panel, as was suspected fetal status in cardiotocography, evaluated according to FIGO classification (76.1%). The laboratory parameters albumin (86.8%), leukocytes (86.6%), uric acid (75.0%) and serum PlGF

▶ **Table 1** Demographic and baseline characteristics of respondents (mean ± SD or n [%]).

Characteristic	Respondents (n = 69)
Age, years	47.6 ± 8.4
Gender	
Female	31 (45%)
Male	38 (55%)
Region of practice	
Germany	67 (97%)
Austria	1 (1.5%)
Switzerland	1 (1.5%)
Operating level	
Head of department	19 (27.5%)
Head of obstetrics	22 (31.9%)
Consultant	26 (37.7%)
Resident physician	2 (2.9%)
Level of experience	
Specialist in obstetrics	53 (76.8%)
Consultant	10 (14.5%)
Resident physician	2 (2.9%)
Level of care	
Tertiary obstetric center or University	65 (94.2%)
General/routine obstetric center	3 (4.3%)
Primary care	1 (1.5%)
Deliveries per year	
> 3000	14 (20.3%)
2000–3000	27 (39.1%)
1000–2000	27 (39.1%)
< 1000	1 (1.5%)

(93.7%) as well as the symptom weight gain (73.1%) reached a consensus as not being an indication for delivery. No consensus was reached in the assessment of the remaining parameters in the first round. The committee proposed additional parameters and cut-offs for assessing an indication of delivery in preeclampsia, which were included in the next rounds. Furthermore, the wish was expressed to assume that all conservative measures had been exhausted for some criteria without any improvement to be able to assess the indication of delivery more easily. In the next rounds, individual laboratory parameters and clinical findings were clustered to form groups (e.g. acute liver failure, acute kidney failure).

In the second round, consensus was reached regarding new-onset headache with pathologic cCT/MRI, leading to an immediate indication of delivery. 82.4% of the panel agreed. Furthermore, 74.0% of the panel were in favor of immediate delivery if there was retrosternal pain in combination with a pathological finding in ECG.



▶ **Fig. 2** Results of delphi consensus presented by organ systems and delivery criterion. The delivery criteria for each organ system which reached a consensus are ordered according to the urgency of the delivery indication from mild (1) to absolute (4).

In the third round, therapy-resistant hypertension of 220/140 mmHg or higher achieved a consensus for immediate indication of delivery (71.2 %) after no agreement could be reached in the previous rounds at lower blood pressure values. The same applied to acute liver failure with fulminant coagulation disorder (80.8 %), while liver failure with mild changes in coagulation did not achieve consensus.

In round four and five, the parameters which still failed to reach consensus were examined again. The classification into the respective categorical query, based on the majority opinion from the previous surveys, was presented. The panel was asked whether they agreed or disagreed. For various fetal parameters, it was checked whether the wording of the current national guideline on fetal growth restriction "delivery should be considered" was equivalent to a "more serious relative delivery criterion" in the opinion of the panel.

There was consensus that an oxygen saturation < 90 %, an acute severe renal insufficiency, a moderately severe to severe oliguria (AKI stage 2 and 3), a pulmonary edema, a pleural effusion, a hyperreflexia, visual complaints, and fetal parameters as low short-time-variability, increased pulsatility in ductus venosus flow, and reverse end-diastolic flow of A. umbilicalis are severe delivery

criterions. In this round, no consensus was reached on indication of delivery for pain in the lower and middle abdomen, therapy-resistant hypertension of 160/110 mmHg, mild oliguria, and absent a-wave in the ductus venosus. The results of the individual rounds can be reviewed as supplements (Supplemental **Table S1–S5**, online).

All delivery criteria for each organ system, ordered according to the urgency of the delivery indication from mild (1) to absolute (4) are shown in ▶ **Fig. 2**, ▶ **Table 2** (ordered by organ systems) and ▶ **Table 3** (ordered by relevance of delivery). Consensus and assessment of relevance regarding an indication of delivery presented by domains is shown in Supplemental **Table S6**.

Discussion

The term "severe preeclampsia" is not universally defined, nor is the indication for a mandatory delivery in preeclampsia. Particularly in the case of very early pre-eclampsia before 32 weeks' gestation, the decision to deliver is often made by an interdisciplinary team based on individual factors and circumstances, including fetal maturity, maternal symptoms and clinical picture, but also logistical aspects and personal opinions. The term "severe preeclampsia" is then often used as a justification for delivery without a more precise definition. The aim of the present study is to reach a consensus among German-speaking obstetricians experienced in the management of women with preeclampsia before 32 weeks' gestation to define "severity" by the need for delivery for acute maternal reasons with impending complications. To this end, a Delphi procedure was conducted in which participants were asked for their opinion on when delivery should take place in a particular case with different constellations of pre-eclampsia. Fifty experts finished all five Delphi rounds. Consensus was reached on 53 parameters. Of these 14 were considered absolute criteria, i.e. rapid preparation for delivery without any delay, 26 parameters were rated as factors that should be considered in the decision without being absolute, and 13 parameters should have no influence on the decision to deliver. On three parameters a consensus was not reached. Most interesting, "blood pressure values" was one of these. Depending on the height of blood pressure, obstetricians either agreed that this only mildly influences decision to deliver, or it was difficult to get any consent. In contrast to the expected threshold of 160/110 mmHg, which generally defines severe hypertension in national guidelines, consent was only

▶**Table 2** Results of delphi consensus presented by organ systems.

System/organ	Parameter	Consensus
Central nervous system	Headache with pathological cCT/MRI findings	Absolute delivery criterion
	Eclampsia	Absolute delivery criterion
	Somnolence	Absolute delivery criterion
	Hyperreflexia/widened reflex zones	Severe delivery criterion
	Dizziness and/or balance problems	Moderate delivery criterion
	Headache with non-pathological cCT/MRI findings	Mild delivery criterion
Cardiovascular system	Retrosternal pressure/pain/thoracic pain with pathological electrocardiogram and/or echocardiography	Absolute delivery criterion
	Any pathological cardiac event	Absolute delivery criterion
	Therapy-resistant hypertension of 220/140 mmHg	Absolute delivery criterion
	Retrosternal pressure/pain/thoracic pain with non-pathological electrocardiography and/or echocardiography	Moderate delivery criterion
	Therapy-resistant hypertension of 160/110 mmHg	No consensus
Respiratory system	Oxygen saturation < 90 %	Severe delivery criterion
	Pulmonary edema	Severe delivery criterion
	Pleural effusion	Severe delivery criterion
	Dyspnea	Moderate delivery criterion
Haematological system	Disseminated intravascular coagulation	Absolute delivery criterion
	Platelets < 50 000 cells/dl or 50 Gpt/l	Absolute delivery criterion
	Platelets < 100 000 cells/dl or 100 Gpt/l	Moderate delivery criterion
	Serum sodium value < 120 mmol/l	Moderate delivery criterion
	Leukocytes	No delivery criterion
	Serum sodium value < 135 mmol/l	No delivery criterion
	Serum potassium	No delivery criterion

▶**Table 2** continued

System/organ	Parameter	Consensus
Renal and excretion system	Acute severe renal insufficiency (AKI stage 3)	Severe delivery criterion
	Moderately severe oliguria (AKI stage 2)	Severe delivery criterion
	Severe oliguria to anuria (AKI stage 3)	Severe delivery criterion
	Acute mild renal insufficiency (AKI stage 1)	Moderate delivery criterion
	Acute moderately severe renal insufficiency (AKI stage 2)	Moderate delivery criterion
	Proteinuria	No delivery criterion
	Serum uric acid	No delivery criterion
	Edema/swelling of the hands/face	No delivery criterion
	Weight gain	No delivery criterion
	Mild oliguria (AKI stage 1)	No consensus
Metabolic system	Liver hematoma, liver capsule rupture	Absolute delivery criterion
	Acute liver failure (transaminase value > 500 U/l + coagulation disorder (detectable by INR and/or aPTT))	Absolute delivery criterion
	Acute liver failure (e.g. very rapid within 24 hours, increase of transaminases and bilirubin + collapse in coagulation (detectable with INR and/or aPTT))	Absolute delivery criterion
	Acute liver dysfunction (transaminase value > 70 and < 500 U/l)	Moderate delivery criterion
	Nausea	Moderate delivery criterion
	Vomiting	Moderate delivery criterion
	Pain in the upper abdomen/epigastrium	Moderate delivery criterion
	LDH serum concentration	No delivery criterion
	Bilirubin serum concentration	No delivery criterion
	Serum albumin	No delivery criterion
	Serum haptoglobin	No delivery criterion
	Pain in the lower and middle abdomen	No consensus
Sensory system	Papilla congestion/retinal detachment	Absolute delivery criterion
	Visual complaints/vision problems	Severe delivery criterion
	Hearing problems	Moderate delivery criterion
Uteroplacental and fetal	CTG pathology evaluated according to FIGO classification	Absolute delivery criterion
	Vaginal bleeding with abnormal sonography	Absolute delivery criterion
	Short-time variability < 2.6 ms (26 + 0–28 + 6 weeks of gestation) or < 3.0 ms (29 + 0–31 + 6 weeks of gestation)	Severe delivery criterion
	Ductus venosus: increased pulsatility (PIV > 95 th percentile)	Severe delivery criterion
	Ductus venosus: absent a-wave or a reverse flow of the a-wave	Severe delivery criterion
	A. umbilicalis: reverse end-diastolic flow	Severe delivery criterion
	Vaginal bleeding with normal sonography	Moderate delivery criterion
	Serum sFlt-1/PlGF ratio	No delivery criterion
	Serum PlGF	No delivery criterion

Results of delphi consensus presented by organ systems. Consensus = ≥ 70 % of panelists agree to absolute, severe, moderate or no delivery criterion.

▶**Table 3** Results of delphi consensus presented by relevance of delivery criterion.

Consensus	Parameter
Absolute delivery criterion	Headache with pathological cCT/MRI findings
	Eclampsia
	Somnolence
	Retrosternal pressure/pain/thoracic pain with pathological electrocardiogram and/or echo-cardiography
	Any pathological cardiac event
	Therapy-resistant hypertension of 220/140 mmHg
	Disseminated intravascular coagulation
	Platelets < 50 000 cells/dl or 50 Gpt/l
	Liver hematoma, liver capsule rupture
	Acute liver failure (transaminase value > 500 U/l + coagulation disorder (detectable by INR and/or aPTT))
	Acute liver failure (e.g. very rapid within 24 hours, increase of transaminases and bilirubin + collapse in coagulation (detectable with INR and/or aPTT))
	Papilla congestion/retinal detachment
	CTG pathology evaluated according to FIGO classification
	Vaginal bleeding with abnormal sonography
Severe delivery criterion	Hyperreflexia/widened reflex zones
	Oxygen saturation < 90 %
	Pulmonary edema
	Pleural effusion
	Acute severe renal insufficiency (AKI stage 3)
	Moderately severe oliguria (AKI stage 2)
	Severe oliguria to anuria (AKI stage 3)
	Visual complaints/vision problems
	Short-time variability < 2.6 ms (26 + 0–28 + 6 weeks of gestation) or < 3.0 ms (29 + 0–31 + 6 weeks of gestation)
	Ductus venosus: increased pulsatility (PIV > 95 th percentile)
	Ductus venosus: absent a-wave or a reverse flow of the a-wave
	A. umbilicalis: reverse end-diastolic flow
Moderate delivery criterion	Dizziness and/or balance problems
	Retrosternal pressure/pain/thoracic pain with non-pathological electrocardiogram and/or echocardiography
	Dyspnea
	Platelets < 100 000 cells/dl or 100 Gpt/l
	Serum sodium value < 120 mmol/l
	Acute mild renal insufficiency (AKI stage 1)
	Acute moderately severe renal insufficiency (AKI stage 2)
	Acute liver dysfunction (transaminase value > 70 and < 500 U/l)
	Nausea
	Vomiting
	Pain in the upper abdomen/epigastrium
	Hearing problems
	Vaginal bleeding with normal sonography
Mild delivery criterion	Headache with non-pathological cCT/MRI findings
No delivery criterion	Leukocytes
	Serum sodium value < 135 mmol/l
	Serum potassium
	Proteinuria
	Serum uric acid
	Edema/swelling of the hands/face
	Weight gain
	LDH serum concentration
	Bilirubin serum concentration
	Serum albumin
	Serum haptoglobin
	Serum sFlt-1/PlGF ratio
	Serum PlGF
No consensus	Mild oliguria (AKI stage 1)
	Therapy-resistant hypertension of 160/110 mmHg
	Pain in the lower and middle abdomen

Results of delphi consensus presented by relevance of delivery criterion. Consensus = ≥ 70 % of panelists agree to absolute, severe, moderate or no delivery criterion.

reached at therapy-resistant blood pressure values that permanently exceed 220/140 mmHg.

Most international and national guidelines provide indications for delivery, independent of gestational age. Uncontrollable or worsening hypertension and eclampsia were most advocated [2, 19, 32]. A specific upper limit of blood pressure at which delivery should take place is not specified in the current guidelines, which apply to most of the experts involved [2]. However, there is a general agreement that severe hypertension at or above 160/110 mmHg is associated with increased risk for the mother to suffer from stroke and other acute cardiovascular or neurologic complications [2, 33]

Antihypertensive medication should therefore be considered at the latest if blood pressure consistently exceeds this threshold [2, 34]. It has been suggested if severe hypertension persists despite adequate antihypertensive therapy, delivery should be attempted after maternal stabilization [35]. It was therefore rather surprising that no consensus could be reached in favor of a delivery in this situation. Since delivery is the only causative cure of preeclampsia, the decision to end pregnancy aims at reducing short-term morbidity of the mother including stroke and eclampsia. However, one may also consider delivery at a certain point of persistent high blood pressure values since preeclampsia is associated with long-term risks on maternal health [8, 9, 10, 11, 12, 13]. Whether these long-term consequences may be influenced by timely delivery (i.e. by shortening the exposure to a preeclamptic condition) is a matter of debate.

In contrast to blood pressure, other parameters were clearly regarded by the panel as absolute indications for delivery. Most parameters belong to the group of HELLP syndrome, which is excluded in most published studies on expectant management of severe preeclampsia, as these abnormalities are generally considered an indication for delivery [34, 36, 37]. A large systematic review by Magee et al. examined the frequency of expectant management complications in HELLP syndrome before 34 weeks of gestation [38]. Complications included severe hypertension, abruptio placentae and eclampsia, subcapsular hepatic hematoma, stroke, stillbirth, and neonatal death. The panel's assessment of these parameters as an absolute indication for delivery is therefore plausible. Likewise, acute moderate to severe renal insufficiency (AKI stage 2 and 3) is regarded as absolute indication for delivery. This is compatible with the available studies, which compared conservative treatment to immediate delivery [34, 36, 37, 39]. A high risk of increasing severe renal insufficiency was found for expectant vs. interventionist care (RR 3.33) [38]. In addition, prolonged exposure to placental ischemia impairs postpartum maternal renal function [40, 41]. Beside maternal complications, non-assurance of fetal well-being by Doppler ultrasound or cardiotocogram is generally accepted for timing of birth. Several randomized multicenter studies in recent years have addressed the management and monitoring of early severe fetal growth restriction, which is often a concomitant condition of preeclampsia. For pregnancies before 32 weeks of gestation, the TRUFFLE study showed that a combination of monitoring using computerized CTG and Doppler of the ductus venosus is most suitable for estimating the correct time of delivery [42, 43]. However, in a third of the women included in the TRUFFLE study, maternal factors such as severe preeclampsia, rather than the results of fetal monitoring, led to the decision to deliver. This emphasizes the need for clear maternal delivery indications regardless of the fetal situation. However, a fetal assessment should be carried out and fetal well-being should be considered during management [39, 44, 45, 46].

A limitation of the study is that the invited senior obstetricians primarily derive from German-speaking countries (Germany, Austria, Switzerland). The answers given must therefore be interpreted in the context of the respective national healthcare system and cannot necessarily be generalized. Moreover, though skilled for the management of high-risk pregnancies in a clinical setting the participants overall may not necessarily have a scientific focus in the treatment of preeclampsia. Therefore, the consent achieved may rather reflect clinical practice than expert opinion. Additionally, the Delphi output quality reflects the contemporary interpretation of the actual state of the art, which may rapidly change over time. Another potential bias is the Delphi consensus design in which results have been presented to the participants in subsequent rounds. Participants might have re-considered their initial views and the views of the majority are agreed upon [47]. A further limitation is that the questionnaire asked about single events or parameters that occurred in connection with a specific case. In the clinical context, however, the decision is usually based on a summation of several factors. For example, severe hypertension, even if resistant to treatment, is often only considered an indication for delivery if other symptoms such as headaches, nausea, or abdominal tenderness occur. It therefore remains to be investigated whether a combination of characteristics or a summation of the mild to moderate indications for delivery identified here can change the decision.

Another weakness of this Delphi procedure is that we did not incorporate gestational age as an independent factor. For simplification of the questionnaire, and hence for feasibility of the Delphi procedure we rather assumed that between 24 to 32 weeks' gestation decision will not be influenced by dynamics in neonatal outcome. However, gestational age at preterm birth is inversely correlated to adverse medical and neurodevelopmental outcomes, including motor, neurosensory, cognitive, and behavioral deficits [48, 49, 50]. Therefore, the criteria for delivery are relative since at more than 30 weeks most clinicians would be more liberal to deliver than at the limit of viability. Likewise, we specifically asked for criteria for delivery after completion of antenatal steroid therapy. The reason for this is that when designing the study, we primarily aimed at defining endpoints for the treatment of women with preeclampsia in multicenter, randomized, controlled intervention trials. In these, completed antenatal steroid therapy was considered a compulsory inclusion criterion [51, 52, 53, 54, 55]. For general clinical practice it would also be of interest how the experts would have decided without having completed antenatal steroid therapy. This issue should be investigated in future observational studies that can now be based on the here presented findings. The restriction to a clear case of preeclampsia can also be regarded as an advantage of the study. Preeclampsia is characterized by many variants in additional risk factors and multivariate expression. It was therefore important to create a uniform picture of pre-eclampsia that could be presented to the participating experts. Another strength of the study was the recruitment of a large and diverse panel of clinicians in the field. Once having completed the first round of the Delphi procedure, dropout rate was low. As the clinicians were obstetricians from different perinatal centers all over Germany (and Austria and Switzerland) with different specialties, local infrastructure, and resources, the data presented here can be considered a good average of current clinical practice. We are aware that in other countries the indication for delivery may be made by an interdisciplinary team, usually obstetrics, neonatology, anesthesia, internal medicine, and others. In Germany, however, the final decision to recommend delivery to women and to balance the maternal risks against the fetal benefits of prolongation lies with the obstetrician (subspecialized in mater-

nal and fetal medicine). Therefore, only obstetricians have been invited to participate. Finally, an already established Delphi method was used in this study [56, 57, 58]. To maximize the possibilities for consensus, a modification was used to reformulate questions or define parameters more precisely after rounds had ended. By doing this, we achieved consensus in 53 of 56 questions and scenarios.

In conclusion, whether to prolong pregnancy in preeclampsia and when to deliver is not uniformly defined and varies from clinic to clinic and case to case. This makes it difficult for clinical interventional studies to use the time from admission to delivery, or the duration of prolongation, respectively, as primary endpoints [52, 54]. Since the non-standardized assessment of disease severity and the different indications for delivery between study sides, involved staff, and other individual patient's factors call into question the prolongation of pregnancy until delivery as a primary endpoint, consensus-based diagnostic criteria may be helpful by integrating into prospective study designs. By generating a consensus within a panel of clinical experts working in the field, we stimulated a discussion on how to define "severe preeclampsia" by the need of delivery for acute or imminent maternal complications of preeclampsia in Germany. Although our study aimed to develop objective degrees of severity indicating prompt delivery in pregnancies with early-onset preeclampsia, the partly high cut-off values for consensus were rather surprising. This might be because the disease is characterized by many variants in additional risk factors and multivariate expression. In addition, the population served by the experts might show such variation in severity that the experience of serious outcomes is rather small also because long-term follow-up is not realized. As with neonatal outcomes, quality of life and health of mothers throughout their life cycle are equally important and must be considered when timing delivery.

Supplementary Material

- Supplemental **Table S1**. Results of round 1.
- Supplemental **Table S2**. Results of round 2.
- Supplemental **Table S3**. Results of round 3.
- Supplemental **Table S4**. Results of round 4.
- Supplemental **Table S5**. Results of round 5.
- Supplemental **Table S6**. Consensus and assessment of relevance regarding an indication of delivery presented by domains.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Roberts JM. Preeclampsia: what we know and what we do not know. Semin Perinatol 2000; 24: 24–28. DOI: 10.1016/s0146-0005(00)80050-6

[2] Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V. (DGGG). S2k-Leitlinie Hypertensive Schwangerschaftserkrankungen: Diagnostik und Therapie [Hypertensive Pregnancy Disorders: Diagnosis and Therapy. Guideline of the German Society of Gynecology and Obstetrics (S2k-Level, AWMF-Registry No. 015/018)]. 2019 . Accessed July 21, 2024 at: https://register.awmf.org/de/leitlinien/detail/015–018

[3] US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, Curry SJ et al. Screening for Preeclampsia: US Preventive Services Task Force Recommendation Statement. JAMA 2017; 317: 1661–1667. DOI: 10.1001/jama.2017.3439

[4] Burton GJ, Redman CW, Roberts JM et al. Pre-eclampsia: pathophysiology and clinical implications. BMJ 2019; 366: l2381. DOI: 10.1136/bmj.l2381

[5] Maynard SE, Min JY, Merchan J et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest 2003; 111: 649–658. DOI: 10.1172/JCI17189

[6] Cockell AP, Learmont JG, Smarason AK et al. Human placental syncytiotrophoblast microvillous membranes impair maternal vascular endothelial function. Br J Obstet Gynaecol 1997; 104: 235–240. DOI: 10.1111/j.1471-0528.1997.tb11052.x

[7] Melchiorre K, Giorgione V, Thilaganathan B. The placenta and preeclampsia: villain or victim? Am J Obstet Gynecol 2022; 226: S954–S962. DOI: 10.1016/j.ajog.2020.10.024

[8] Arnadottir GA, Geirsson RT, Arngrimsson R et al. Cardiovascular death in women who had hypertension in pregnancy: a case-control study. BJOG 2005; 112: 286–292. DOI: 10.1111/j.1471-0528.2004.00396.x

[9] Hassdenteufel K, Muller M, Gutsfeld R et al. Long-term effects of preeclampsia on maternal cardiovascular health and postpartum utilization of primary care: an observational claims data study. Arch Gynecol Obstet 2023; 307: 275–284. DOI: 10.1007/s00404-022-06561-w

[10] Goetz M, Muller M, Gutsfeld R et al. An observational claims data analysis on the risk of maternal chronic kidney disease after preterm delivery and preeclampsia. Sci Rep 2021; 11: 12596. DOI: 10.1038/s41598-021-92078-2

[11] Wilson BJ, Watson MS, Prescott GJ et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. BMJ 2003; 326: 845. DOI: 10.1136/bmj.326.7394.845

[12] Aukes AM, De Groot JC, Wiegman MJ et al. Long-term cerebral imaging after pre-eclampsia. BJOG 2012; 119: 1117–1122. DOI: 10.1111/j.1471-0528.2012.03406.x

[13] Postma IR, Bouma A, Ankersmit IF et al. Neurocognitive functioning following preeclampsia and eclampsia: a long-term follow-up study. Am J Obstet Gynecol 2014; 211: 37.e1–37.e9. DOI: 10.1016/j.ajog.2014.01.042

[14] Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ 2002; 325: 157–160. DOI: 10.1136/bmj.325.7356.157

[15] Rolnik DL, Wright D, Poon LCY et al. ASPRE trial: performance of screening for preterm pre-eclampsia. Ultrasound Obstet Gynecol 2017; 50: 492–495. DOI: 10.1002/uog.18816

[16] Anonymous. WHO Recommendations for Prevention and Treatment of Pre-Eclampsia and Eclampsia. Geneva: World Health Organization; 2011.

[17] Mounier-Vehier C, Amar J, Boivin JM et al. Hypertension and pregnancy: expert consensus statement from the French Society of Hypertension, an affiliate of the French Society of Cardiology. Fundam Clin Pharmacol 2017; 31: 83–103. DOI: 10.1111/fcp.12254

[18] Borghi C, Ferri C, Sechi L et al. Clinical management of hypertension in pregnancy. Practical recommendations from the Italian Society of Hypertension (SIIA). [corrected]. High Blood Press Cardiovasc Prev 2013; 20: 123–127. DOI: 10.1007/s40292-013-0019-y

[19] ACOG Committee on Practice Bulletins–Obstetrics. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol 2002; 99: 159–167. DOI: 10.1016/s0029-7844(01)01747-1

[20] Sibai BM, Stella CL. Diagnosis and management of atypical preeclampsia-eclampsia. Am J Obstet Gynecol 2009; 200: 481.e1–481.e7. DOI: 10.1016/j.ajog.2008.07.048

[21] Tranquilli AL, Brown MA, Zeeman GG et al. The definition of severe and early-onset preeclampsia. Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Pregnancy Hypertens 2013; 3: 44–47. DOI: 10.1016/j.preghy.2012.11.001

[22] Pettit F, Brown MA. The management of pre-eclampsia: what we think we know. Eur J Obstet Gynecol Reprod Biol 2012; 160: 6–12. DOI: 10.1016/j.ejogrb.2011.09.049

[23] Brown MA, Magee LA, Kenny LC et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis management recommendations for international practice. Pregnancy Hypertens 2018; 13: 291–310. DOI: 10.1016/j.preghy.2018.05.004

[24] Lowe SA, Bowyer L, Lust K et al. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. Aust N Z J Obstet Gynaecol 2015; 55: e1–e29. DOI: 10.1111/ajo.12399

[25] Sinha IP, Smyth RL, Williamson PR. Using the Delphi technique to determine which outcomes to measure in clinical trials: recommendations for the future based on a systematic review of existing studies. PLoS Med 2011; 8: e1000393. DOI: 10.1371/journal.pmed.1000393

[26] Murphy MK, Black NA, Lamping DL et al. Consensus development methods, and their use in clinical guideline development. Health Technol Assess 1998; 2: i–iv

[27] Webster K, Fishburn S, Maresh M et al. Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance. BMJ 2019; 366: l5119. DOI: 10.1136/bmj.l5119

[28] Magee LA, Pels A, Helewa M et al. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary. J Obstet Gynaecol Can 2014; 36: 416–441. DOI: 10.1016/s1701-2163(15)30588-0

[29] Anonymous. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013; 122: 1122–1131. DOI: 10.1097/01.AOG.0000437382.03963.88

[30] Berger R, Abele H, Bahlmann F et al. Prevention and Therapy of Preterm Birth. Guideline of the DGGG, OEGGG and SGGG (S2k-Level, AWMF Registry Number 015/025, September 2022) - Part 1 with Recommendations on the Epidemiology, Etiology, Prediction, Primary and Secondary Prevention of Preterm Birth. Geburtshilfe Frauenheilkd 2023; 83: 547–568. DOI: 10.1055/a-2044-0203

[31] Berger R, Abele H, Bahlmann F et al. Prevention and Therapy of Preterm Birth. Guideline of the DGGG, OEGGG and SGGG (S2k Level, AWMF Registry Number 015/025, September 2022) - Part 2 with Recommendations on the Tertiary Prevention of Preterm Birth and on the Management of Preterm Premature Rupture of Membranes. Geburtshilfe Frauenheilkd 2023; 83: 569–601. DOI: 10.1055/a-2044-0345

[32] Royal College of Obstetricians & Gynaecologists. Severe Pre-eclampsia/Eclampsia, Management (Green-top Guideline No. 10A). 2006. Accessed July 21, 2024 at: https://www.rcog.org.uk/guidance/browse-all-guidance/green-top-guidelines/severe-pre-eclampsiaeclampsia-management-green-top-guideline-no-10a/

[33] Judy AE, McCain CL, Lawton ES et al. Systolic Hypertension, Preeclampsia-Related Mortality, and Stroke in California. Obstet Gynecol 2019; 133: 1151–1159. DOI: 10.1097/AOG.0000000000003290

[34] Sibai BM, Barton JR. Expectant management of severe preeclampsia remote from term: patient selection, treatment, and delivery indications. Am J Obstet Gynecol 2007; 196: 514.e1–514.e9. DOI: 10.1016/j.ajog.2007.02.021

[35] Publications Committee, Society for Maternal-Fetal Medicine, Sibai BM. Evaluation and management of severe preeclampsia before 34 weeks' gestation. Am J Obstet Gynecol 2011; 205: 191–198. DOI: 10.1016/j.ajog.2011.07.017

[36] Sibai BM, Mercer BM, Schiff E et al. Aggressive versus expectant management of severe preeclampsia at 28 to 32 weeks' gestation: a randomized controlled trial. Am J Obstet Gynecol 1994; 171: 818–822. DOI: 10.1016/0002-9378(94)90104-x

[37] Odendaal HJ, Pattinson RC, Bam R et al. Aggressive or expectant management for patients with severe preeclampsia between 28–34 weeks' gestation: a randomized controlled trial. Obstet Gynecol 1990; 76: 1070–1075

[38] Magee LA, Yong PJ, Espinosa V et al. Expectant management of severe preeclampsia remote from term: a structured systematic review. Hypertens Pregnancy 2009; 28: 312–347. DOI: 10.1080/10641950802601252

[39] Bombrys AE, Barton JR, Nowacki EA et al. Expectant management of severe preeclampsia at less than 27 weeks' gestation: maternal and perinatal outcomes according to gestational age by weeks at onset of expectant management. Am J Obstet Gynecol 2008; 199: 247.e1–247.e6. DOI: 10.1016/j.ajog.2008.06.086

[40] Paauw ND, Joles JA, Spradley FT et al. Exposure to placental ischemia impairs postpartum maternal renal and cardiac function in rats. Am J Physiol Regul Integr Comp Physiol 2017; 312: R664–R670. DOI: 10.1152/ajpregu.00510.2016

[41] Paauw ND, Luijken K, Franx A et al. Long-term renal and cardiovascular risk after preeclampsia: towards screening and prevention. Clin Sci (Lond) 2016; 130: 239–246. DOI: 10.1042/CS20150567

[42] Bilardo CM, Hecher K, Visser GHA et al. Severe fetal growth restriction at 26–32 weeks: key messages from the TRUFFLE study. Ultrasound Obstet Gynecol 2017; 50: 285–290. DOI: 10.1002/uog.18815

[43] Lees C, Marlow N, Arabin B et al. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). Ultrasound Obstet Gynecol 2013; 42: 400–408. DOI: 10.1002/uog.13190

[44] Oettle C, Hall D, Roux A et al. Early onset severe pre-eclampsia: expectant management at a secondary hospital in close association with a tertiary institution. BJOG 2005; 112: 84–88. DOI: 10.1111/j.1471-0528.2004.00262.x

[45] Hall DR, Odendaal HJ, Kirsten GF et al. Expectant management of early onset, severe pre-eclampsia: perinatal outcome. BJOG 2000; 107: 1258–1264. DOI: 10.1111/j.1471-0528.2000.tb11617.x

[46] Chammas MF, Nguyen TM, Li MA et al. Expectant management of severe preterm preeclampsia: is intrauterine growth restriction an indication for immediate delivery? Am J Obstet Gynecol 2000; 183: 853–858. DOI: 10.1067/mob.2000.109049

[47] Turner ME, Pratkanis AR. Twenty-Five Years of Groupthink Theory and Research: Lessons from the Evaluation of a Theory. Organ Behav Hum Decis Process 1998; 73: 105–115. DOI: 10.1006/obhd.1998.2756

[48] Behrman RE, Butler AS (eds.). Preterm Birth: Causes, Consequences, and Prevention. Washington, DC: The National Academies Press; 2007. DOI: 10.17226/11622

[49] Rogers EE, Hintz SR. Early neurodevelopmental outcomes of extremely preterm infants. Semin Perinatol 2016; 40: 497–509. DOI: 10.1053/j.semperi.2016.09.002

[50] Gibson AT. Outcome following preterm birth. Best Pract Res Clin Obstet Gynaecol 2007; 21: 869–882. DOI: 10.1016/j.bpobgyn.2007.03.008

[51] Winkler K, Lorey C, Contini C et al. Comparison of double-filtration plasmapheresis (DFPP) versus heparin-mediated extracorporeal LDL-precipitation (HELP)-apheresis in early-onset preeclampsia. Pregnancy Hypertens 2024; 36: 101128. DOI: 10.1016/j.preghy.2024.101128

[52] Contini C, Putz G, Pecks U et al. Apheresis as emerging treatment option in severe early onset preeclampsia. Atheroscler Suppl 2019; 40: 61–67. DOI: 10.1016/j.atherosclerosissup.2019.08.028

[53] Contini C, Winkler BS, Maass N et al. Concomitant intrauterine growth restriction alters the lipoprotein profile in preeclampsia. Pregnancy Hypertens 2019; 15: 154–160. DOI: 10.1016/j.preghy.2018.12.006

[54] Winkler K, Contini C, Konig B et al. Treatment of very preterm preeclampsia via heparin-mediated extracorporeal LDL-precipitation (H.E.L.P.) apheresis: The Freiburg preeclampsia H.E.L.P.-Apheresis study. Pregnancy Hypertens 2018; 12: 136–143. DOI: 10.1016/j.preghy.2018.04.007

[55] Contini C, Jansen M, Konig B et al. Lipoprotein turnover and possible remnant accumulation in preeclampsia: insights from the Freiburg Preeclampsia H.E.L.P.-apheresis study. Lipids Health Dis 2018; 17: 49. DOI: 10.1186/s12944-018-0698-4

[56] Gordijn SJ, Beune IM, Thilaganathan B et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol 2016; 48: 333–339. DOI: 10.1002/uog.15884

[57] Khalil A, Beune I, Hecher K et al. Consensus definition and essential reporting parameters of selective fetal growth restriction in twin pregnancy: a Delphi procedure. Ultrasound Obstet Gynecol 2019; 53: 47–54. DOI: 10.1002/uog.19013

[58] Johnson S, Gordijn S, Damhuis S et al. Diagnosis and Monitoring of White Coat Hypertension in Pregnancy: an ISSHP Consensus Delphi Procedure. Hypertension 2022; 79: 993–1005. DOI: 10.1161/HYPERTENSIONAHA.121.18356