The prediction of preeclampsia: the way forward

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Despite intensive investigation, we still cannot adequately predict, treat, or prevent preeclampsia. We have gained awareness that preeclampsia is a syndrome not a disease and is heterogeneous in its presentation and pathophysiology, which may indicate differing underlying phenotypes, and that the impact extends beyond pregnancy per se. Effects on the fetus and mother extend many years after pregnancy, as evidenced by fetal programming of adult disease and increased risk of the development of maternal cardiovascular disease. The increased occurrence of preeclampsia in women with preexisting risk factors suggests that the stress of pregnancy may expose subclinical vascular disease as opposed to preeclampsia damaging the vasculature. The heterogeneity of preeclampsia has blighted efforts to predict preeclampsia early in gestation and has thwarted success in attempts at therapy with treatments, such as low-dose aspirin or global antioxidants. There is a critical need to identify the phenotypes to enable their specific prediction and treatment. Such studies require considerably larger collections of patients than employed in past and current studies. This does not necessarily imply much larger patient numbers in single studies but can be facilitated by the ability to easily combine many smaller studies. This can be accomplished by agreeing on a priori standardized and harmonized clinical data and biospecimen collection across new studies. Such standards are being established by international groups of investigators. Leadership by international organizations, perhaps adopting a carrot and stick approach, to overcome investigator, institutional and funder reticence toward data sharing is required to ensure adoption of such standards. Future studies should include women in both low- and high-resource settings and employ social media and novel methods for data collection and analysis, including machine learning and artificial intelligence. The goal is to identify the pathophysiology underlying differing preeclampsia phenotypes, their successful prediction with the design, and the implementation of phenotype-specific therapies.

Key words: angiogenic factor, antioxidant, aspirin, blood pressure, Combined Antioxidant and Preeclampsia Prediction Studies, hemolysis, elevated liver enzymes, and low platelet count syndrome, placental growth factor, prediction, preeclampsia, Screening for Pregnancy Endpoints, syndrome

Introduction

The societal and economic costs, estimated at $2.18 billion within the first 12 months of delivery in the United States,[1] of preeclampsia, which is the leading cause of maternal morbidity and responsible for 75,000 maternal deaths worldwide each year,[2] remain unabated despite a substantial and ongoing amount of work attempting to describe the mechanistic underpinnings of the disorder, prediction of its occurrence, and therapeutic approaches. Most of this work was performed in developed countries where pregnant women have good access to antenatal care and advanced healthcare facilities and where morbidity and mortality are limited by prompt delivery of women with preeclampsia, which is accompanied by iatrogenic delivery of preterm neonates. In comparison, only 1% of the perinatal research expenditure but 99% of the 600,000 annual maternal deaths occur in low- and middle-income countries,[2] where women have limited access to healthcare. Although improved access to care is necessary for alleviating the burden of preeclampsia in developing countries, there is still a role for predicting preeclampsia in that setting and in developed countries to alleviate the consequences.

Where are we now?

Over the past 30 years, there has been a general acceptance that preeclampsia is a syndrome and not a disease[3] and that preeclampsia presents with different phenotypes. These can be described clinically as mild vs severe and early- vs late-onset preeclampsia, although these are not dichotomous variables but rather continuous variables with arbitrary but clinically relevant definitions. Further clinical phenotypes include the presence or absence of growth restriction and variants, such as the HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome and superimposition of preeclampsia on chronic hypertension. The knowledge that there is varying involvement of different organ systems in the clinical presentation of preeclampsia,[4,5] together with the large number of cross-sectional studies measuring different analytes in women with preeclampsia and the growing number of discovery-type "omics" studies,[6–9] has supported the concept of different biochemical phenotypes.[4,5,10] This concept was instrumental in the design of the Combined Antioxidant and Preeclampsia Prediction Studies (CAPPS)[11] and the Screening for Pregnancy Endpoints (SCOPE)[12] studies, which both measured a range of biomarkers longitudinally across gestations

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in what were thought at the time to be relatively large numbers (2500 and 5623, respectively) of low-risk nulliparous women. Disappointingly, neither of these studies could identify early pregnancy predictors of preeclampsia; however, both studies made a point that the heterogeneity of preeclampsia contributed to the failure to identify early predictors with clinical utility. However, as these were studies of low-risk nulliparous women, most of those who developed preeclampsia developed late-onset preeclampsia, a condition alleviated by prompt delivery of the patient with relatively low fetal morbidity and mortality. There was also growing acceptance of the concept that early-onset preeclampsia is primarily related to failure of trophoblast invasion and adaptation of uterine spiral arteries[13] leading to a relative placental ischemia and that late-onset preeclampsia, in which two-thirds of women do not display increased uterine artery vascular impedance,[14] is related to increased maternal susceptibility to the vascular and metabolic stress of pregnancy[15] or to advancing placental senescence[16] that releases damaging vasoactive factors into the maternal circulation.

An important finding from both CAPPS and SCOPE was that although they could not identify the biomarkers with clinical utility for first-trimester prediction of preeclampsia, measurement of changes in biomarkers from first to early or late second trimester of pregnancy[17] increased the sensitivity for detecting preeclampsia, that is, the later in gestation, the better the ability to predict. Subsequently, these findings have been capitalized on with second[18] and third trimesters[19] measurement of angiogenic factors being shown to have high diagnostic accuracy for predicting subsequent development of preeclampsia and other adverse outcomes and assignment of women to appropriate clinical care pathways, indeed being introduced into routine clinical practice in the United Kingdom.[20] First-trimester screening using a combination of ultrasound measurement of uterine artery pulsatility index, maternal risk factors, mean arterial pressure, and placental growth factor has now been recommended for predicting early-onset preeclampsia,[21] that is, the placental disease. It is recommended that low-dose aspirin be administered to these women before 16 weeks' gestation, reducing the incidence of early-onset preeclampsia by more than 60%.[22] Although this is a significant step forward, early-onset preeclampsia only affects <1% of the pregnant population with up to 80% of preeclampsia being late onset where both mother and fetus are still at risk of adverse outcomes with only increased surveillance and delivery available to prevent adverse events. We are now aware that exposure to an adverse intrauterine environment, such as that presented by growth restriction or preeclampsia, results in fetal programming of adult diseases, including cardiovascular, metabolic, and neurodevelopmental disorders[23,24]; hence, instead of leaving the fetus exposed throughout gestation, early prediction of the potential development of preeclampsia and implementation of a therapy could prevent these programming effects. Similarly, there is now increasing awareness of the association of adverse pregnancy outcomes, including preeclampsia, with the development of long-term cardiovascular and metabolic diseases in women.[25] Whether this is the result of preeclampsia damaging the maternal vasculature or whether the stress of pregnancy exposes women with preexisting subclinical vascular disease is currently being investigated. However, early prediction and institution of a prophylactic therapy to prevent the development of preeclampsia may be beneficial in preventing long-term consequences.

Caveats for prediction studies and therapeutic trials

If we accept that early prediction of late-onset (and early-onset) preeclampsia may be of benefit for both the mother and offspring, how do we achieve it against the background of heterogeneity of the syndrome that has blighted previous efforts? The overall incidence of preeclampsia and the incidence of severe preeclampsia are increased in certain high-risk groups of patients, for example, multifetal gestation, previous preeclampsia, chronic hypertension, and pregestational diabetes,[26] which may point to different underlying causes, for example, placental or endothelial dysfunction. These patient groups may present enriched populations for study, but most preeclampsia cases in developed countries occur in clinical practice in low-risk nulliparous women, leading to this group being selected in many studies, for example, CAPPS and SCOPE. However, among nulliparous women, up to 5% will have chronic hypertension, multifetal gestation, or pregestational diabetes, and the increased incidence of preeclampsia associated with these high-risk conditions means that up to 14% of preeclampsia in nulliparous women will be associated with these conditions (Levine and Myatt unpublished). Similarly, in multiparous women, a group also including those with previous preeclampsia, up to 9% will have a high-risk condition, and close to 100% of their preeclampsia will be associated with these preexisting high-risk conditions. The association of preeclampsia with high-risk conditions and the mendelian pattern of inheritance in some families suggest that preeclampsia is a complex genetic disorder occurring as a result of numerous common variants at different loci that contribute to an individual's susceptibility to the disease.[27] Because no single cause or genetic variant will account for all preeclampsia cases, large patient numbers across many different populations are required to unravel this complexity.[28,29]

Beyond predicting which women are likely to develop preeclampsia, prediction studies would be useful for identifying women who might benefit from some sort of therapy if it was available. Although the deviation in biomarker levels or profiles from those seen in normotensive patients with good outcomes is used to identify those developing preeclampsia and indicate potential pathophysiologic pathways, we have to be cautious as the placenta and maternal systems may adapt to the pathophysiologic insult and display this adaptive response rather than display the evidence of the causative pathway. A therapeutic action targeted at these pathways may worsen the condition and threaten

maternal and fetal well-being by ameliorating the adaptive response rather than inhibiting a causative pathway.

What lessons have we learned?

The rate of occurrence of preeclampsia (5%−7%) means that even in large studies, such as CAPPS (n=2500) and SCOPE (n=5623), only relatively small numbers of patients actually develop preeclampsia with most cases being late-onset mild preeclampsia and a proportion of these cases associated with preexisting conditions. Obviously, a larger number of patients have to be enrolled to achieve meaningful numbers of women with preeclampsia to allow the dissection of biomarker profiles, risk factors, etc., necessary to reveal different known, suspected, and unknown phenotypes of preeclampsia. This may be beyond the resources of single centers or even networks. It is not surprising that many current studies still employ small patient numbers and are cross-sectional in nature, limiting the utility and knowledge gained. The differences in study design, patient selection, and clinical data collection make it extremely difficult to combine these studies even in meta-analyses.[30] A major failure is poor definition and clinical phenotyping of patients, leading to the concept of the 1 million dollar test but the 5 cent diagnosis.[31] Although useful in clinical practice, where the objective is not to miss patients at high risk of adverse outcome, use of the recently more inclusive clinical diagnosis[32] for research studies may include many patients with weak phenotypes. What strategy can then be employed? Regardless of their size, studies must collect sufficient clinical data (not just blood pressure and proteinuria) to enable adequate phenotyping of patients. The data should be compatible with data collected from other studies, allowing them to be easily compared and combined if necessary. The need for data standardization and harmonization across studies has been clearly recognized and operative in, for example, the cancer field for many years and has been clearly mentioned as advantageous in study of preeclampsia.[33] Collection of data across many studies into a database with a priori agreed data fields will allow easy combination of large numbers of smaller studies to quickly achieve the patient numbers needed to encompass the different phenotypes of preeclampsia each in adequate numbers.[34] The patient numbers have to be large enough to achieve statistical power necessary to define the contribution of factors, such as ethnicity, geography and environmental exposures, genetics, preexisting conditions, and confounders, such as obesity and fetal gender. It is realized that the collection of extensive and detailed clinical data is difficult in resource-poor areas; however, in this case, all efforts should be made to collect at least a minimal agreed standardized data set[33] (Supplemental Table 1) compatible with data that are collected in resource-rich areas.

What data to collect to really understand preeclampsia

Traditionally, preeclampsia studies have collected data in cross-sectional studies from patients diagnosed with preeclampsia, and these have been the basis for our current understanding of the pathophysiology and therapeutic approaches. Recently, a few longitudinal sample and data collections have been made, with both their expense and the incidence of preeclampsia (5%−7%) ultimately limiting the numbers of women in such studies who will develop preeclampsia. Our realization of the long-term consequences of adverse pregnancy outcome on the mother and offspring now indicates that we should collect pregnancy and postpregnancy data in the same women. Deep phenotyping of women during pregnancy has recently been suggested to offer an opportunity to not only improve pregnancy outcomes but also define the antecedents of lifelong health and wellness.[35] The understanding that preexisting risk factors, exposed by pregnancy and leading to preeclampsia, may play a major role in the pathophysiology suggests that prepregnancy studies are also important. Hence, comprehensive studies of the reproductive life course may need to be undertaken to truly understand the antecedents, incidence, and consequences of preeclampsia. This Herculean long-term undertaking is perhaps beyond the capacity of even major philanthropic organizations but can be aided by agreed upon types and standards for data collection. Leadership to encourage adoption of such standards should perhaps come from authoritative international organizations; a top-down approach linked to grant support may aid in the adoption of standards. This does not mandate large multicenter international studies; individual investigator-initiated studies can still occur, but adoption of data collection standards allows the facility to easily aggregate data if desired and overcome the previously mentioned issues of data combination.[30] Where will such data come from? Obviously, medical records are a major source but standards and ease of access vary across the globe. Efforts must be made to again standardize and get ease of access. Furthermore, in the United States, the major driver of electronic medical record design was for accurate billing with little attention to accumulating data to understand diseases. There is also an abundance of data generated and gathered on social media, through patient advocacy sites and via commercial tests, for example, genetic ancestry, that can be incorporated into preeclampsia studies. Again, the quality and disease identification from such data are of widely varying quality. A similar concern related to the variation in the collection of clinical data applies to the collection of biospecimens into biobanks. Various organizations have presented standardized methods for the collection and storage of materials, for example, the placenta;[36] however, these need to be widely adopted to ensure consistency across studies.

Research studies will usually have high-quality clinical data and associated biomaterials that are carefully collected but are limited by the number of subjects in any study. This raises the issue of data sharing, in which investigators can combine many such studies to achieve a large data set. However, data sharing is currently associated with several challenges. These include the mindset of investigators, academic institutions, and

funders for whom sharing has not been of high priority. Furthermore, collecting necessary data and identifying and including relevant outcomes sufficient for sharing and data formats and dictionaries that do not impede sharing present major problems.[37] It is encouraging that funders, academic institutions, and individual investigators are beginning to recognize the importance of sharing. For preeclampsia, the Global Pregnancy Collaboration (CoLab) has presented data fields that are necessary to collect data for preeclampsia research, including a minimal and an optimal set of variables[33] (Supplemental Table 1, Supplemental Table 2), whereas the International Collaboration to Harmonize Outcomes in Pre-eclampsia (iHOPE) is attempting to standardize outcomes collected in preeclampsia studies.[38] The iHOPE initiative builds on the efforts of 80 journals participating in the Core Outcomes in Women's and Newborn Health (CROWN) initiative, which encourages researchers to develop core outcome sets, that is, minimum collections of outcomes with standardized measurement and prioritized reporting in clinical trials to facilitate synthesis and dissemination of results in systematic reviews. The CoLab has also prepared a harmonized preeclampsia database available to all investigators at nominal or no charge in which data can be securely stored with access only to the investigator (https://pregnancycolab.tghn.org/collect/).[34] However, if sharing is chosen, data are easily shared with others who are using this database.

Data Analysis

A powerful illustration of the heterogeneity of preeclampsia is the wide scatter seen in data presented from studies of biomarkers. Often, this is presented as mean and standard deviation and hides the considerable overlap between patients with and without preeclampsia; furthermore, patients with preeclampsia often have analyte values similar to patients without preeclampsia.[39,40] Beyond this, data analyses have been routine and depend on receiver operating characteristic curve analysis to identify the predictors. The recent interest in the use of dynamical modeling, machine learning, and artificial intelligence that more comprehensively studies the interaction of various factors offers some hope in studying the interaction of clinical and biochemical factors and may also be useful in being applied retrospectively to previous data sets.

Therapeutic approaches

In retrospect, it is perhaps easy to determine why previous therapeutic trials with low-dose aspirin[26,41] or antioxidants[42] aimed at reduction in overall preeclampsia have failed in large-scale trials. Given the heterogeneity of preeclampsia, any beneficial effect on 1 or more phenotypes of patients may have been obscured by the lack of effect on other phenotypes within the population. Furthermore, these treatments were chosen on the basis of empirical observations in cross-sectional studies of women with established disease. So were deficiencies in antioxidant defenses seen as a cause or consequence of preeclampsia? We now have more knowledge of the cell and subcellular specific sites of synthesis and action of different pro- and antioxidants[43,44] that it is not surprising that a global antioxidant did not work. The use of low-dose aspirin in women who are predicted to be at high risk of early-onset preeclampsia[21] where large numbers of women need to be treated to prevent 1 case of preeclampsia[22] is defended by the low-risk profile of low-dose aspirin, although recently aspirin use in pregnancy has been associated with increased postpartum bleeding and hematoma.[45] Novel therapeutic approaches currently being investigated include targeting the complement system,[46] proangiogenesis,[47] and the use of pravastatin, metformin, proton-pump inhibitors, and micronutrients.[48] These trials may suffer the same consequences as previous ones related to the heterogeneity of preeclampsia. Obviously, the identification of different phenotypes of preeclampsia and application of therapies specific to that phenotype are the way forward.

Summary: How to Move Forward

Despite preeclampsia being described over 15 centuries ago and with tremendous energy and resources being expended in the second half of the 20th century in attempting to define the underlying pathophysiology and limited success in predicting and preventing the less frequently occurring early-onset form we still, in the 21st century, lack the overall ability to predict, prevent other than by delivery, or effectively treat preeclampsia. The impact of preeclampsia extends beyond risks to the mother and fetus in pregnancy per se, as the adverse intrauterine environment programs the fetus for disease in adult life and women with preeclamptic pregnancy are at increased risk of cardiovascular disease in later life. The prepregnancy antecedents of preeclampsia may also contribute to its development, illustrating that the condition is related to health across the lifespan. We now accept that preeclampsia is a syndrome and not a disease and that the considerable heterogeneity in its presentation and associated pathology implies that the condition has several phenotypes that has yet to be clearly defined beyond their associated temporal or clinical appearance. This heterogeneity has blighted our attempts to predict who will develop preeclampsia at a time when intervention may be useful to prevent adverse outcomes and has shown that global therapeutic approaches do not work and therapies tailored for individual phenotypes may be necessary. Hence, there is a need to identify the different phenotypes of preeclampsia, develop methods for their prediction, and design and test phenotype-specific interventions. The burden of overall maternal morbidity and mortality and of preeclampsia in low-resource settings mandates that increasing attention is paid to the study of preeclampsia in those countries where currently only 1% of research occurs and the antecedents, development, and consequences may differ. To define the phenotypes of preeclampsia, a much larger number of patients than have been employed in studies to date is needed. This does not necessarily imply that larger single studies, the use of agreed upon standardized and harmonized clinical data, and biospecimen collection

will allow aggregation of many small studies to achieve large numbers by overcoming previous barriers to data combination. Novel methods of data collection emerging in the digital age and on social media should be incorporated together with machine learning and artificial intelligence in data analysis. These efforts have to be led by international organizations and may need to involve a "carrot and stick" approach to overcome investigator, institutional, and funder resistance to collaboration. Such collaborative investigator-led efforts are emergent but need the support of funding bodies to achieve their potential. If we can define the differing underlying phenotypes of preeclampsia and hence identify phenotype-specific predictors, we can then start phenotype-specific therapies rather than continue the one-size-fits-all approach previously adopted where any potential success is obscured by the background of nonresponders. ■

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Supplemental Material

SUPPLEMENTAL TABLE 1
Minimal data set for studies on preeclampsia

Maternal data
Physical, anthropologic, and ethnographic data
Age
Self-described ethnicity (white, black, Asian, Hispanic, unknown, or other [mixed])
Country of birth
Parents' country of birth
Parity
Gravidity
Measured height, measured weight (prepregnancy or before 14 wk) and BMI
Years of schooling or other indicator of socioeconomic status
Smoking history
Cigarette or cigar smoker
Snuff user
Chews tobacco or takes nicotine
For each choice, check ≥1 of the following:
Never used
Irregularly used
Regularly used
Gave up before pregnancy
Gave up during pregnancy
Uses currently in this pregnancy
Medical history (reported)
Hypertension
Renal disease
Diabetes mellitus (type I or type II)
Collagen vascular disease (eg, Sjogren, antiphospholipid syndrome, systemic lupus erythematosus)
Previous preeclampsia
Previous gestational diabetes
Obstetrical history (indicate numbers and gestational age at occurrence)
Miscarriage
Stillbirth
Induced abortion
Gestational hypertension
Preeclampsia
Eclampsia
HELLP
SGA and IUGR
Gestational diabetes mellitus requiring treatment with insulin or oral hypoglycemic agents
Preterm delivery (<37 wk)
Neonatal death

Myatt. The prediction of preeclampsia. Am J Obstet Gynecol 2022. *(continued)*

SUPPLEMENTAL TABLE 1
Minimal data set for studies on preeclampsia *(continued)*

Present pregnancy
BP at first visit (booking)
Singleton or multifetal pregnancy
Hydatidiform mole
Hydropic placenta
Antihypertensive use in this pregnancy
For preeclampsia
For essential hypertension
Other medications
Magnesium sulfate
Corticosteroids for lung maturation
Low-dose aspirin
Thyroid supplements
Antithyroid treatment for thyrotoxicosis
Other (list)
Diagnosis of preeclampsia
Highest recorded systolic and diastolic BPs within 2 wk of delivery (do not use values during labor)
Choose available or not available
Highest intrapartum BP
Highest BP within 48 h after delivery
Proteinuria (dipstick/24 h urine/PC ratio)
Choose available or not available
Multisystem involvement (platelets, liver enzymes, serum creatinine, seizures, indicated preterm birth, IUGR, fetal, or neonatal death)
Choose yes, no, or unavailable
Maternal outcome
Length of stay in hospital predelivery (d)
Mode of delivery (vaginal and cesarean deliveries with or without labor or with or without induction)
$MgSO_4$ use in this pregnancy (before, during, or after delivery)
Maternal outcome (healthy, PIH, preeclampsia, eclampsia, abruption, HELLP, GDM, death)
Infant data
Survival (yes or no)
Intrauterine fetal death (before admission or after admission)
Neonatal death
Gestational age at delivery in completed wk and d (if possible; calculated using LMP and ultrasound)
Sex
Newborn weight

BMI, body mass index; *BP*, blood pressure; *GDM*, gestational diabetes mellitus; *HELLP* syndrome, hemolysis, elevated liver enzymes, and low platelet count; *IUGR*, intrauterine growth restriction; *LMP*, last menstrual period; *PC*, protein-creatinine; *PIH*, pregnancy-induced hypertension; *SGA*, small for gestational age.

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Myatt. The prediction of preeclampsia. Am J Obstet Gynecol 2022.

SUPPLEMENTAL TABLE 2

Optimal data set for studies on preeclampsia

Maternal data (data from minimal data set plus the following)
Clinical history
Gestational age at start of documented maternity care
Number of prenatal visits (doctor, midwife, or hospital in present pregnancy)
Blood transfusions
In life time
In present pregnancy
Fertility history
Assisted reproductive technology
Present pregnancy
Any previous attempted pregnancy
IVF
ICSI
Artificial insemination
Partner or donor sperm
Egg recipient
Embryo recipient
Age at menarche
Birthweight of the pregnant woman
Duration of preconception sexual intercourse with biologic father of child (months [list as zero if donor semen])
Previous pregnancy outcomes (indicate numbers, and if with same partner or a previous partner and gestational age at occurrence)
Miscarriage
Stillbirth
Induced abortion
Recurrent spontaneous pregnancy loss
Gestational hypertension
Preeclampsia
Eclampsia
HELLP
SGA and IUGR
Gestational diabetes mellitus requiring treatment with insulin or oral hypoglycemic agents
Preterm delivery (<37 wk)
Neonatal death
Relevant maternal family history
Mother, sister, or cousin with preeclampsia
Validated or self-reported
Family history (siblings, parents, and grandparents) of cardiovascular disease (none, hypertension, CHD, stroke, and actual age [y] at occurrence)
Family history (siblings, parents, and grandparents) of diabetes mellitus

Myatt. The prediction of preeclampsia. Am J Obstet Gynecol 2022. *(continued)*

SUPPLEMENTAL TABLE 2
Optimal data set for studies on preeclampsia *(continued)*

- Relevant paternal family history
  - Has he fathered a preeclamptic pregnancy? (This mother or other mother)
  - Mother, sister, or cousin with preeclampsia
  - Validated or self-reported
  - Family history (siblings, parents, and grandparents) of cardiovascular disease (none, hypertension, CHD, stroke, and actual age [y] at occurrence)
- Nicotine history
  - Cigarette or cigar smoker
  - Snuff user
  - Chews tobacco or takes nicotine
  - None of above used ever
  - Used irregularly or regularly only before pregnancy
  - Continues (number of cigarettes/d: 1–10, 11–20, >20; number of cigars/d: 1, 2–5, >5)
  - In the third trimester of pregnancy (28–36 wk), stopped since early pregnancy, restarted since early or before pregnancy, continued to smoke [number])
- Alcohol use
  - At baseline (never or gave up before pregnancy or gave up during pregnancy or this pregnancy)
    Number of units/wk
  - In the third trimester of pregnancy (stopped since early pregnancy, restarted since early or before pregnancy, continued to drink)
    Number of units/wk
- Recreational drugs or drug abuse (yes or no)
  - Cannabis (yes or no)
  - Cocaine (yes or no)
  - Opiates (heroin, morphine, codeine, or methadone; yes or no)
  - Methamphetamine
  - Ecstasy or other central stimulating drugs? (Specify)
  - At baseline (never, gave up before pregnancy, gave up during pregnancy, or this pregnancy)
  - In the third trimester of pregnancy (stopped since early pregnancy, restarted since early or before pregnancy, continued to use)
- Clinical data
  - Blood pressures
    - First blood pressure (and gestational age)
      - Two highest systolic and diastolic blood pressures at each visit (can be at different times) or each wk if visit lasts >1 wk)
      - At diagnosis of preeclampsia
      - 2 highest systolic blood pressures within 2 wk of delivery
      - 2 highest diastolic blood pressures within 2 wk of delivery
  - Urine protein values (at each visit)
    - First urinalysis (and gestational age)
    - 24 h or timed collections
    - Protein-to-creatinine ratio
  - Weight gain during pregnancy
  - Weight gain since last delivery
  - Growth by ultrasound

Myatt. The prediction of preeclampsia. Am J Obstet Gynecol 2022. *(continued)*

SUPPLEMENTAL TABLE 2
Optimal data set for studies on preeclampsia *(continued)*

- Constant (above, below, or on curve)
- Falling off with increasing gestation
- Macrosomia

Uteroplacental blood flow indices at midgestation (16–25 wk), performed or not performed

- Notching (yes or no)
  - Unilateral (yes or no)
  - Bilateral (yes or no)
- Pulsatility index (mean of bilateral measurements)

Umbilical blood flow indices if clinical suspicion of FGR or documented FGR (done or not done)

- Gestational age at which performed
- Pulsatility index (value) and resistance index (value)
- Absent end diastolic flow (yes or no)
- Reversed end diastolic flow (yes or no)

Fetal growth ultrasound

- 12 wk
- 18–20 wk
- 28 wk
- 36 wk
- If clinical indication of FGR or documented FGR

Labor (active phase, yes or no; labor defined as uterine contractions, which result in cervical dilatation and effacement)

- Spontaneous (yes or no)
- Induced (yes or no)
- Induction indicated for hypertensive disorder (yes or no)
- Cesarean delivery (yes or no)
- Cesarean delivery indicated for hypertensive disorder (yes or no)

Medical conditions before pregnancy (in addition to those in minimal data set)

- Select either
  - In pregnancy alone
  - Before pregnancy
  - Before and continuing during pregnancy
- Other endocrine disease
- Thyroid disease
- Adrenal disease
- Liver disease
- Hematologic disorder, including alloimmune or isoimmune
- Epilepsy or seizure disorder
- Heart disease
- Cancer
- Metabolic syndrome (any 3 of the 5 criteria described in Alberti et al[49] are present before pregnancy)
- PCOS (≥2 of the following 3 features are present)
  - Oligo- and anovulation

Myatt. The prediction of preeclampsia. Am J Obstet Gynecol 2022. *(continued)*

SUPPLEMENTAL TABLE 2
Optimal data set for studies on preeclampsia *(continued)*

- Clinical and biochemical signs of hyperandrogenism
- Polycystic ovaries and exclusion of other pathogeneses (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing syndrome)
- Infectious disease
  - Malaria
    - Placental (yes or no), laboratory diagnosis (yes or no)
  - HIV
    - CD4 count
  - TB
    - Active or inactive
  - Schistosomiasis
  - Hepatitis B
  - STD
    - Gonorrhea
    - Syphilis
    - Chlamydia
    - Herpes
    - Trichomoniasis
    - Genital warts
    - Other
  - Urinary tract infection
    - Antibiotics (yes or no)
- Other infectious disease

Medications before and during pregnancy

- Select either
  - In pregnancy alone (Which wk started?)
  - Before pregnancy
  - Before and continuing during pregnancy
- Vitamins
  - Vitamin C
  - Vitamin D
- Vitamin E
- Other
- Multivitamins
- Folate
- Fortified foods available in country of residence (yes or no)
  - List additives used for fortification
  - Aspirin
  - Platelet-active drugs
- Antioxidants
  - High dosages of vitamin C (>500 mg)

Myatt. The prediction of preeclampsia. Am J Obstet Gynecol 2022. *(continued)*

SUPPLEMENTAL TABLE 2
Optimal data set for studies on preeclampsia *(continued)*

- High dosages of vitamin E (>400 IU)
- β-carotene
- Resveratrol
- Selenium
- Coenzyme Q10
- Other (specify)

Fish oil
Calcium (specify amount)
Iron supplements (specify)
Diuretics (specify)
Antihypertensive agents (specify)
Antibiotics (specify)
Anticoagulants (specify)
Anticonvulsants
$MgSO_4$
- Other (specify)

Antidepressants (SSRIs; specify)
Antiglycemic agents
- Insulin
- Metformin
- Other (specify)

Long-term immunosuppressants
Thyroid supplements
Antithyroid treatment for thyrotoxicosis
Other (specify)

Postnatal maternal care
- Length of stay in hospital (d)

Infant data (data from the minimal data set plus the following)
- Length
- APGAR scores (1, 5, and 10 min if recorded)
- Umbilical cord gases
- Admitted to NICU (yes or no)
- Length of stay in NICU (d)
- Outcome at discharge from the NICU
  - IVH
  - BPD
  - RDS
  - NEC
  - Hypoxic-ischemic encephalopathy
  - Convulsions

Myatt. The prediction of preeclampsia. Am J Obstet Gynecol 2022. *(continued)*

SUPPLEMENTAL TABLE 2
Optimal data set for studies on preeclampsia *(continued)*

Placenta data
Weight
Cord insertion
Number of vessels in cord
Pathology report (if sent for pathology)
Photograph against a scale bar

Appendix for other important information is presented.

BPD, bronchopulmonary dysplasia; *CD4*, cluster of differentiation 4; *CHD*, coronary heart disease; *FGR*, fetal growth restriction; *HELLP syndrome*, hemolysis, elevated liver enzymes, and low platelet count; *ICSI*, intracytoplasmic sperm injection; *IUGR*, intrauterine growth restriction; *IVF*, in vitro fertilization; *IVH*, intraventricular hemorrhage; *NEC*, necrotizing enterocolitis; *NICU*, neonatal intensive care unit; *PCOS*, polycystic ovary syndrome; *RDS*, respiratory distress syndrome; *SGA*, small for gestational age; *SSRI*, selective serotonin reuptake inhibitor; *STD*, sexually transmitted disease; *TB*, tuberculosis.

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