Strategy for Standardization of Preeclampsia Research Study Design

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Abstract—Preeclampsia remains a major problem worldwide for mothers and babies. Despite intensive study, we have not been able to improve the management or early recognition of preeclampsia. At least part of this is because of failure to standardize the approach to studying this complex syndrome. It is possible that within the syndrome there may be different phenotypes with pathogenic pathways that differ between the subtypes. The capacity to recognize and to exploit different subtypes is of obvious importance for prediction, prevention, and treatment. We present a strategy for research to study preeclampsia, which will allow discrimination of such possible subtypes and also allow comparison and perhaps combinations of findings in different studies by standardized data and biosample collection. To make studies relevant to current clinical practice, the definition of preeclampsia can be that currently used and accepted. However, more importantly, sufficient data should be collected to allow other diagnostic criteria to be used and applied retrospectively. To that end, we present what we consider to be the minimum requirements for a data set in a study of preeclampsia that will facilitate comparisons. We also present a comprehensive or optimal data set for in-depth investigation of pathophysiology. As we approach the definition of phenotypes of preeclampsia by clinical and biochemical criteria, adherence to standardized protocols will hasten our understanding of the causes of preeclampsia and development of targeted treatment strategies **(*Hypertension*. 2014;63:1293-1301.)** ● **Online Data Supplement**

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Preeclampsia remains a major problem worldwide for mothers and babies. It is estimated that yearly 50 000 women die in developing countries from preeclampsia.[1] Careful maternal observation for the signs of preeclampsia and delivery of women with increasingly severe preeclampsia is the cornerstone of management (as it has been for the past 100 years). Maternal mortality is, therefore, much less in developed countries with the capacity for careful perinatal observation, but morbidity is considerable and remains the leading cause of admissions to intensive care for pregnant women.[2] Also, the appropriate delivery of women who develop increasingly severe preeclampsia early in gestation accounts for 8% of all preterm births.[3]

Why No Advances in Clinical Management?

During the past 20 years, there has been an explosion in our knowledge of preeclampsia. The recognition of inflammation, including endothelial dysfunction as potential unifying pathophysiological concepts and the appreciation of the multisystemic nature of preeclampsia, has directed attention away from blood pressure as the sole or even most important pathophysiological issue of preeclampsia.[4] This concept has resulted in recognition of other origins of organ dysfunction. Despite this, we have not managed to affect the management or early recognition of preeclampsia with this information. Large, well-designed multicenter, clinical intervention trials have, at best, demonstrated a minimal effect on outcome except in perhaps the highest risk cases. Attempts to use factors implicated in the pathophysiology of the disorder to predict preeclampsia have also not as yet provided adequate sensitivity and specificity to be adopted for use in routine clinical practice.[5]

Is There >1 Subtype of Preeclampsia?

Why is this? A recurring theme is success in small studies of prediction, prevention, or treatment of preeclampsia, and failure in larger adequately powered multicenter trials. This

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is often interpreted as a result of publication bias. However, an alternative explanation is that the important difference between small and large studies is that small studies are usually within homogeneous populations, whereas large multicenter studies include a much more heterogeneous group of women. Furthermore, another explanation for the poor predictive power of studies guided by proposed pathogenic factors is that none of these factors can be demonstrated in all women with preeclampsia (Figure S1 in the online-only Data Supplement). These findings lead to the hypothesis that not all preeclampsia is the same, that subtypes may be present.

This is supported by clinical and epidemiological data. Most preeclampsia occurs in the last month of pregnancy; however, the 10% of earlier cases are strikingly different than those occurring at term. The excess of small for gestational age deliveries that occurs in preeclampsia is associated with disease presenting before 37 weeks of gestation when preeclampsia tends to be more severe.[6] Epidemiological data indicate major differences in the risk of later life cardiovascular disease with the risk with earlier onset preeclampsia 8- to 10-fold[7,8] versus a doubling when preeclampsia occurs close to term.[9] A similar increased cardiovascular risk is present with recurrent preeclampsia. Clinically, preeclamptic women at any gestational age may present with fulminant preeclampsia that goes from recognition to life-threatening disease over hours to days or the syndrome may be indolent with little progression in the same time frame.

This hypothesis predicts that no 1 test will predict and no 1 treatment will prevent preeclampsia. However, to offer encouragement, this also means that if we could identify subtypes of preeclampsia, appropriate predictors could more successfully predict, and the appropriate treatment more effectively prevents the different subtypes of preeclampsia.

What Should We Do Differently?

Study designs that aggregate what might be different forms of preeclampsia, resulting from different pathophysiological pathways, are part of the problem. Amalgamation of the less obvious heterogeneous phenotypes is compounded by studies that combine obviously dissimilar subsets. Considering all causes of increased risk of preeclampsia as resulting in a group of homogeneous high-risk subjects is one such obvious error. Should it be surprising that a preeclamptic woman with a large placenta, as present with multiple gestations or diabetes mellitus, would not respond to the same preventive therapy as a woman with chronic hypertension or previous preeclampsia? Also important differences between recurrent and first pregnancy preeclampsia are often ignored and early and late onset preeclampsia are usually combined for analysis. Another discrimination, the difference between preeclampsia with proteinuria and gestational hypertension with no obvious systemic changes is often not made. It is likely that some cases of gestational hypertension are early preeclampsia. It is also possible that others reflect chronic hypertension, masked in early pregnancy by the physiological decrease in blood pressure that occurs at that time. Gestational hypertension without systemic involvement could also be a distinct and unrelated phenotype. In most settings, the findings with gestational hypertension are intermediate between normal pregnancy and preeclampsia. However, the increasing certainty that gestational hypertension is not a manifestation of a multisystemic syndrome (absence of hyperuricemia and markers of endothelial dysfunction) suggests that it generally is of more benign origin with outcomes for mother and baby not different than in normal pregnancy.[10,11] There may, therefore, be a form of new onset hypertension in pregnancy, which has minimal effect on mother or baby.

The capacity to recognize and to exploit different subtypes is of obvious importance for prediction, prevention, and treatment. As an analogy, our progress in the successful management of diabetes mellitus would have been far less if all patients with carbohydrate intolerance were thought to be insulinopenic.

What Might Be the Subtypes of Preeclampsia?

Obvious subtypes of preeclampsia are early and late onset, recurrent and nonrecurrent, and preeclampsia with the different types of high-risk pregnancies. Clinically it is also possible that severe and mild preeclampsia and preeclampsia with and without intrauterine growth restriction could be different (see online-only Data Supplement). In addition, preeclampsia seems to have a different target in different cases. The primary organ involvement may be hepatic, renal, cardiovascular, or placental. Do these define different subtypes in which prediction and prevention may require different strategies?

Another interesting subclassification could exploit the differences in pathophysiological biomarkers associated with preeclampsia. In this regard, the most valuable findings would be those present before clinically evident disease. Once disease is established, the biochemical consequences of multiple organ involvement will mask causal pathways. However, we know that not all subjects manifest the same early markers, so should we begin to redefine preeclampsia on the basis of, for example, inflammatory, antiangiogenic, oxidative stress, or endoplasmic stress-mediated subtypes? Some caution is required here, however, because some biochemical clusters may reflect different steps in a common pathway. Nonetheless, the common strategy of amalgamating all is increasingly undermined by the current evidence base. To achieve progress in prediction and prevention inevitably demands recognition of subtypes (see online-only Data Supplement). Although the hypothesis of several subtypes of preeclampsia to explain the discrepant findings and outcomes in preeclampsia is attractive, it has also recently been proposed that true preeclampsia is only present when excess antiangiogenic or deficient angiogenic factors are present. Without these findings, preeclampsia is a misdiagnosis.[12] The argument is that the most dangerous features of new onset gestational hypertension with proteinuria or other organ involvement are much more common when angiogenic imbalance is evident from laboratory findings. These abnormal angiogenic findings are also more prevalent in early onset, the most serious form of this disorder. To a certain extent this concept is not without potential risk if applied to current clinical practice. Most deaths from preeclampsia are in developing countries with late onset preeclampsia, which is less likely to be accompanied by these laboratory findings, Nonetheless the understanding of preeclampsia regardless of semantics will be aided by more standardized definitions and data and biological sample collection.

It is with this goal of translating current and emerging understanding to define, treat, and prevent disease that we make the following proposal for the investigation of preeclampsia.

Proposal

Appreciation of Preeclampsia as a Syndrome

The current definition of preeclampsia requires renal (proteinuria) and cardiovascular (blood pressure) dysfunction. These were established historically as the first signs preceding what at the time was considered a pregnancy-specific seizure disorder, eclampsia.[13] They were not selected as sensitive or specific indicators of maternal or fetal morbidity. However, in combination they predict increased risk for mother and baby and indicate that preeclampsia affects many organ systems. This is confirmed by the increased risk associated with gestational hypertension when accompanied by other systemic involvement, even without proteinuria.[14–16] Thus, a key feature in studying preeclampsia is recognizing the fact that it is a syndrome and that it can occur in the absence of proteinuria.

Identification of Preeclampsia Subtypes

Identifying possible preeclampsia subtypes is clearly an important goal in translating findings of preeclampsia research into effective modifications of clinical care. We have presented obvious candidates. How do we modify current research strategies to address this goal? Either we must examine homogenous groups of women—only nulliparas, only obese women, only women with previous preeclampsia, only early onset preeclampsia, etc—or the study population should be of an adequate size to enable separate study of these obviously different groups. There should, at the very least, be an effort to look at results in relation to these different possible subtypes (and allow readers to also make these comparisons), given the problems of inadequate power in smaller studies. The solution to this quandary is big science that is the merging of data and biological samples from several centers. This is a major goal of the Global Pregnancy CoLaboratory, which has authored this article because data and biosample sharing can only be successful with standardized data and sample collection.

We present a strategy for research to study preeclampsia and suggest that further large multicenter trials be deferred until rigorous exploration for subtypes of preeclampsia has been attempted.

Approach

Comparisons and interpretation of the data generated in the many studies of preeclampsia remain complicated because of differences in study sizes, study designs, definition of patient groups, and outcomes measured. There is a need for standardization of study design, including patient selection, data collection, and definition of outcome, to allow comparable studies and trials to be performed and allow comparison of data sets and integration for meta-analyses. To facilitate comparison of studies or trials, at a minimum, the patient groups selected, information collected, and definitions used need to be similar. Critical components of this approach are unambiguous and unbiased definitions. With this in mind, we recommend collecting the clinical and laboratory information necessary to make the diagnosis that is then examined retrospectively in a blinded manner by impartial observers rather than relying on clinical diagnoses made by care providers.

We offer here an outline that can be used for study design and clinical trials. We also present what we think are the minimum requirements for a data set in a study of preeclampsia that will facilitate comparisons (Table 1). Subsequently, we define a comprehensive or optimal data set (Table 2) together with recommendations for collection of biological materials (Table 3). This, we consider, would provide all that is needed for in-depth investigation of pathophysiology.

Key Definitions

For studies to be relevant to current clinical practice, the definition of preeclampsia can be that currently used and accepted. However, diagnostic criteria change. Thus, sufficient data should be collected (Tables 1 and 2) to allow retrospective analysis not only to satisfy new diagnostic recommendations but also to facilitate the development of novel and improved methods of diagnosis (see online-only Data Supplement). Defining the syndrome by only traditional criteria is too limited and does not facilitate progress.

Gestational Age

Gestational age should be determined using information from the last menstrual period, if known, and first or second trimester ultrasounds with standardized criteria for resolving discrepancies between menstrual history and ultrasound findings[17] or, if last menstrual period is not known, preferably by first trimester ultrasound (Table S1, online-only data supplement). Gestational age should be recorded by completed weeks and days.

Fetal Variables

A proportion of pregnancies complicated by preeclampsia is also associated with intrauterine growth restriction. In all cases, birth weight and gestational age data should be recorded to determine whether the fetus is small for gestational age. Population-specific birth weight centiles adjusted for gestational age, ethnicity, and sex should be calculated.

Control Subjects

Mechanistic Studies

Parity, age, race, ethnicity, smoking, and body mass index are all recognized to influence the incidence of preeclampsia and patients in case control studies should, therefore, be carefully matched for each of these factors. Also, in these studies, it is appropriate to compare women with preeclampsia with women with normal outcomes to identify the specific pathophysiology of preeclampsia. In case control studies, case and controls should be matched for gestational age and parity.

Prediction Studies

For studies of predictors, it is not appropriate to compare women with preeclampsia with women with normal outcomes. This will inevitably falsely enhance the predictive capability. When a predictive test is used in the real world, it will attempt to identify women with preeclampsia as distinct from all other outcomes, both normal and abnormal. Therefore, the use of the test in this scenario should always be evaluated. Any information not known at the times of testing (eg, eventual pregnancy outcome) must not influence the selection of controls. It is equally inappropriate to combine high-and low-risk women in a prediction study; populations

Table 1. Minimal Data Set for Studies on Preeclampsia

- Maternal data
  - Physical, anthropological, 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/cigar smoker
      - Snuff user
      - Chews tobacco/takes nicotine
        - For each choice check ≥1 of
          - 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
  - Obstetric 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
  - Present pregnancy
    - Blood pressure 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 blood pressure within 2 wk of delivery (do not use values during labor)
      - Choose available/not available
    - Highest intrapartum BP
    - Highest BP within 48 h postpartum
    - Proteinuria (dipstick/24 h urine/PC ratio)
      - Choose available/not available
    - Multisystem involvement (platelets, liver enzymes, serum creatinine, seizures, indicated preterm birth, IUGR, fetal, or neonatal death)
      - Choose yes/no/unavailable
  - Maternal outcome
    - Number of days in hospital predelivery
    - Mode of delivery (vaginal, cesarean section with or without labor, 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/no)
  - Intrauterine fetal death (before admission/after admission)
  - Neonatal death
  - Gestational age at delivery in completed weeks and days (if possible; calculated as in Table S1 using LMP and ultrasound)
  - Sex
  - Newborn weight

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

should be predefined according to the risk status. Eventually, after such trials of defined risk subjects, clinical data and biomarkers can be combined for prediction.

Clinical Trials

Low-Risk Subjects

Standardization of studies of low-risk subjects should use the following exclusion criteria at recruitment:

1. Two or more blood pressures with systolic pressure ≥135 mm Hg or diastolic blood pressure ≥85 mm Hg during this pregnancy. If the screening blood pressure is the only blood pressure that exceeds this cutoff, a repeat blood pressure should be taken within 30 to 60 minutes. If this second blood pressure remains ≥135 mm Hg systolic or ≥85 mm Hg diastolic, the patient is excluded.

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 at doctor/midwife/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/donor sperm
          - Egg recipient
          - Embryo recipient
      - Age at menarche
      - Birth weight of the pregnant woman
      - Duration of preconception sexual intercourse with biological 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
    - Relevant paternal family history
      - Has he fathered a preeclamptic pregnancy? (this mother/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

(*Continued*)

Table 2. Continued

- Cigarette/cigar smoker
- Snuff user
- Chews tobacco/takes nicotine
  - None of above used ever
  - Used irregularly/regularly only before pregnancy
  - Continues (no. of cigarettes/d: 1–10, 11–20, >20 per day, no. of cigars 1, 2–5, >5 per day)
  - In third trimester (28–36 wk), Stopped since early pregnancy, restarted since early/before pregnancy, continues to smoke [no.])
- Alcohol use
  - At baseline (never/gave up before pregnancy/gave up during pregnancy/this pregnancy) number of units/wk
  - In third trimester (stopped since early pregnancy, restarted since early/before pregnancy, continues to drink) number of units/wk
- Recreational drugs/drug abuse (yes/no)
  - Cannabis (yes/no)
  - Cocaine (yes/no)
  - Opiates (heroin/morphine/codeine/methadone; yes/no)
  - Methamphetamine
  - Ecstacy/other central stimulating drugs? (specify)
    - At baseline (never/gave up before pregnancy/gave up during pregnancy/this pregnancy)
    - In third trimester (stopped since early pregnancy, restarted since early/before pregnancy, continues 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 week if visit lasts >1 wk)
    - At diagnosis of preeclampsia
    - Two highest systolic blood pressures within 2 wk of delivery
    - Two 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/creatinine ratio
  - Weight gain during pregnancy
  - Weight gain since last delivery
  - Growth by ultrasound
    - Constant (above, below, or on curve)
    - Falling off with increasing gestation
    - Macrosomia
  - Uteroplacental blood flow indices at mid gestation (16–25 wk), performed/not performed
    - Notching (yes/no)
      - Unilateral (yes/no)
      - Bilateral (yes/no)
    - Pulsatility index (mean of bilateral measurements)
  - Umbilical blood flow indices if clinical suspicion of FGR or documented FGR (done/not done)
    - Gestational age at which performed
    - Pulsatility index (value) and resistance index (value)

(*Continued*)

Table 2. Continued

- Absent end diastolic flow (yes/no)
- Reversed end diastolic flow (yes/no)

Fetal growth ultrasound
- 12 wk
- 18–20 wk
- 28 wk
- 36 wk
- And if clinical indication of FGR or documented FGR

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

Spontaneous (yes/no)

Induced (yes/no)

Induction indicated for hypertensive disorder (yes/no)

Cesarean section (yes/no)

C section indicated for hypertensive disorder (yes/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[21] are present before pregnancy)
- PCOS (≥2 of the following 3 features are present)
  - oligo- and anovulation
  - 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/no, laboratory diagnosis yes/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/no)
  - Other infectious disease

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

(*Continued*)

Table 2. Continued

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/no)
Length of stay in NICU, d
Outcome at discharge from NICU
IVH
BPD
RDS
NEC
Hypoxic ischemic encephalopathy
Convulsions
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

BPD indicates bronchopulmonary dysplasia; CD4, cluster of differentiation 4; CHD, coronary heart disease; FGR, fetal growth restriction; HELLP, hemolysis elevated liver enzymes low platelets; ICSI, intra-cytoplasmic 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; STD, sexually transmitted disease; SSRI, selective serotonin reuptake inhibitor; Vit, vitamin; and TB, tuberculosis.

2. Proteinuria as exhibited by either of the following:
   a. A spot urine protein/creatinine ratio of >30 mg/mmol at any time during this pregnancy.
   b. A 24-hour urine collection of ≥300-mg protein, or the equivalent from a timed collection, at any time during this pregnancy.

   (Dipstick protein values should not be used unless no other measurement is available, then two readings of 1+ would exclude the individual)
3. History or current use of antihypertensive medication (including diuretics).
4. Pregestational diabetes mellitus
5. Current pregnancy as a result of in vitro fertilization.
6. Regular use (more than once a week) of platelet active drugs (eg, heparin) or nonsteroidal anti-inflammatory agents affecting platelet activity (eg, ibuprofen, aspirin, Cox-1 and Cox-2 inhibitors). The use of platelet active drugs or nonsteroidal anti-inflammatory agents affecting platelet activity within 7 days (168 hours) before randomization for all studies.
7. Known fetal abnormalities (eg, neural tube defect), known chromosomal or major malformations, fetal demise, or planned termination.
8. Documented uterine bleeding within a week of screening. Unobserved self-reported bleeding with confirmed intact pregnancy on ultrasound after the bleeding episode is not an exclusion.
9. Uterine malformations

Table 3. Collection of Biological Materials

Timing of samples (preferably coordinate with clinical examination/visit)
8–10 wk
16–20 wk (fasting)
28 wk
36 wk
At delivery before labor
At discharge from hospital (list time after delivery)
6–24 mo postpartum (maternal sample)
Type of samples (blood samples should be taken from vein without ongoing intravenous infusion)
Maternal plasma (EDTA and heparinized)
Maternal serum
Maternal urine
Maternal and paternal residual whole blood for DNA
Cord arterial and venous blood (plasma and serum as above)
Cord residual whole blood for DNA
Umbilical cord tissue for DNA
Cord blood white blood cell count
Maternal nail clippings
Maternal and neonatal bucchal swab for DNA
Meconium
Placenta (see below for recommended method)
Amniotic fluid at delivery (if can be obtained in sterilized manner)—save both pellets and supernatant
Conditions of collection and storage
Blood: processed within 30 min of draw, in freezer by 1 h (times from draw to processing to freeze should be recorded). Store in 0.5-mL aliquots at –80°C
Urine: centrifuge 25 mL, 5-mL aliquots of supernatant, store at –80°C
Residual whole blood for DNA: store at –80°C
Placenta
Photograph the placenta from the chorionic and basal aspects against a scale bar
Take a piece of umbilical cord
Take a membrane roll 2-cm wide from the rupture site to the placental margin
Weigh the placenta after trimming the membranes and umbilical cord to 1 cm
Place the placenta with the basal plate uppermost, overlay a transparent grid with ≥4 sampling sites. At each site remove the basal plate by trimming with a pair of scissors. Then cut out a grape-sized piece of the exposed villous tissue, avoiding areas of infarction or other gross pathology. Wash thoroughly but gently in PBS at 4°C. Quickly divide with scissors or scalpel into pieces for metabolomics, mitochondrial respirometry, electron microscopy, RNA, protein and DNA, immunohistochemistry, and frozen sections.[22]
Tissue should be processed within 30 min of delivery (10 min for RNA) and record time to sampling

10. History of medical complications such as the following:
    a. Cancer (including melanoma but excluding other skin cancers)
    b. Endocrine disease, including thyroid disease and adrenal disease
    c. Renal disease with altered renal function (creatinine >78.6 μmol/L [0.9 mg/dL] or proteinuria [as above])

d. Epilepsy or other seizure disorder
e. Any collagen disease (lupus erythematosus, scleroderma, etc)
f. Active or chronic liver disease (acute hepatitis, chronic active hepatitis, persistently abnormal liver enzymes)
g. Hematologic disorder, including alloimmune and isoimmune thrombocytopenia but excluding mild iron deficiency anemia (Hb>90 g/L)
h. Chronic pulmonary disease, including asthma requiring regular the use of medication
i. Heart disease except mitral value prolapse not requiring medication

12. Illicit drug or alcohol abuse during current pregnancy
13. Participating in another intervention study that influences maternal and fetal morbidity and mortality or participation in this trial in a previous pregnancy.

High-Risk Subjects

Studies of women who are at high risk for development of preeclampsia should be sufficiently powered to determine the efficacy of therapy or prediction on obviously disparate risk groups separately.

Confounding Factors to be Considered in All Studies

Obesity

Obesity has a profound effect on the incidence of preeclampsia with the incidence typically doubling with each 5 to 7 kg/m^2 increase in prepregnancy body mass index.[18] Indeed the dramatic increase in obesity in the United States for the past 10 years means that obesity has become a major pathophysiologic factor, probably via its associated inflammatory milieu, in the development of preeclampsia. Because obesity is also more prevalent in black and Hispanic populations, it needs to be taken into account as a confounding factor in studies. If possible, prepregnancy body mass index should be recorded together with body mass index in the first trimester and at delivery. Weight gain throughout pregnancy should be calculated.

Smoking

The incidence of smoking is decreasing slowly in the United States but varies by region and by socioeconomic status. Paradoxically smoking exerts a protective effect on the development of preeclampsia[19] although preeclampsia that develops in smokers is usually more severe. Data on whether the patient was ever or never a smoker should be obtained as well as whether the patient smoked during the index pregnancy.

Sex of the Fetus

There is a strong influence of sexual dimorphism across many aspects of reproductive physiology, particularly those involving inflammatory mechanisms. There is a well-known association of a male fetus with adverse perinatal outcomes, particularly those related to delivery at early gestational age.[20] The presence of a male fetus (and a male placenta) is associated with a slightly greater overall risk (1.02) of development of preeclampsia than that of a female fetus.[20] However, preeclampsia that develops early in gestation is predominantly more associated with a female rather than that with a male fetus (relative risk, 0.7 at 26 weeks).[20] Whether this effect is because of a disproportionate delivery of male fetuses for other causes at this time that removes them from the population that will develop preeclampsia remains unknown. However, the presence of a sexually dimorphic effect means fetal sex should be recorded.

Outcomes

The outcome variables recorded for studies will be dependent on whether the study is a clinical trial of an intervention or whether it is a study evaluating a predictor. In addition, for clinical intervention studies, demographic factors will influence the outcome studied. In developing countries, the focus is on maternal outcomes, whereas in developed countries the focus will be more on fetal outcomes. With this in mind outcomes on both mother and fetus should be collected, and composite outcomes combining fetal and maternal outcomes are discouraged.

Standardized Data Collection

The value and strength of any clinical study is proportional to the amount and quality of data collected. We provide in Table 1 the minimum data set we consider necessary for collection in a study of preeclampsia. This would allow combination and comparison with other data sets to enable meta-analyses to be performed. In Table 2, we provide the optimal data set that could be collected in a comprehensive approach when studies involving determination of pathophysiologic mechanisms are proposed. Guidelines for specifying date and time using International Standard ISO 8601 and for the use of SI units are presented in the in the online-only Data Supplement.

Perspective

Despite many years of clinical and basic science studies and of many small-scale and several large-scale interventional studies, we have not been able to predict, prevent, or treat preeclampsia. There is now a growing realization that under the umbrella of the preeclampsia syndrome, there may be several different phenotypes that may be predicted by distinct biomarkers, presented with different features, and potentially treated by different therapies. Previously, using a standard clinical definition of preeclampsia, these phenotypes have been merged within large cohorts contributing to the lack of success in predicting and treating preeclampsia. The lack of standardization in study design and clinical data acquisition has prevented combination of studies. We offer here an outline that can be used for study design and clinical trials. In addition, we present the minimum requirements for a data set that will facilitate comparisons, whereas collection of a more comprehensive or optimal data set will allow in-depth investigation of pathophysiology. We are now at the point of being able to define phenotypes of preeclampsia by clinical and biochemical criteria and thus tremendously increase our understanding of pathophysiology. Knowledge of distinct pathophysiologies will to lead to more specific therapeutic approaches.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This study presents a strategy for adherence to standardized protocols to study preeclampsia
- This may allow identification of subtypes of the syndrome and allow comparison and combination of different studies by standardized data and biosample collection.

What Is Relevant?

- Because preeclampsia remains a major problem worldwide for mothers and babies, with no improvement in management or early recognition, there is a need to standardize the approach to study the complex syndrome.

Summary

We present the minimum requirements for a data set to facilitate comparisons in a study of preeclampsia together with a comprehensive or optimal data set to allow in-depth investigation of pathophysiology. In addition, standards for sample collection are presented.